Diploma Thesis

Hypertrophic Cardiomyopathy

The Examination of Contemporary Insights with Regard to Genetic Aspects, Various Implications, Morphologic Variants, and Therapeutic Intervention

Submitted by

Calin Gabriel Demian

In Fulfillment of the Requirements for the Degree of

Doctor Medicinae Universae

(Dr. med. univ.)

At the

Medical University of Graz

Conducted at the

Department of Internal Medicine

Division of Cardiology

Under the Supervision of

Univ. Ass. Dr. med. univ. Klemens Ablasser

Priv. Doz. Dr. med. univ. Nicolas Dominik Verheyen

Linz, January the 20th, 2021

Affidavit

Herewith I declare to have written the present Diploma Thesis independently on my own as well as in absence of any assistance proceeding from third parties. Furthermore, I confirm to not have utilized in the preparation of the Thesis sources other than those specified as well as to have indicated the sources, cited or in terms of content, as such.

Linz, January the 20th, 2021 Calin Gabriel Demian, m. p.

List of Contents

List of Contents II
List of Abbreviations IX
List of Figures X
List of Tables XIII
Zusammenfassung XIV
Abstract XV
1 Introduction 1
1.1 The Fascination of the Heart 1
1.2 Historical Perspectives 1
1.3 Definition 2
1.4 Epidemiology 3
1.5 Etiology 4
2 Methods 6
3 Results 7
3.1 Genetic Aspects 7
3.1.1 The Cardiac Sarcomere 7
3.1.2 Implicated Genes and Distribution 8
3.1.3 Types of Mutation 10
3.1.4 Mutational Hot Spots 11
3.1.5 Phenocopies 11
3.1.6 Genotype-Phenotype Correlation 12
3.1.7 Penetrance 13
3.1.7.1 Interrelationship of Penetrance and Age 13
3.1.7.2 Interrelationship of Penetrance and Gender 14
3.1.7.3 Interrelationship of Penetrance and Involved Genes 14
3.1.8 Phenotype Modifying Factors 14

3.1.8.1 Presence of Complex Genotypes 14
3.1.8.2 Modifier Genes 15
3.1.8.3 Epigenetics 16
3.1.8.4 Environmental Factors 17
3.2 Pathomorphological Implications 17
3.2.1 Macroscopic 17
3.2.2 Microscopic 19
3.2.3 Electron-Microscopic 20
3.3 Clinical Presentation 21
3.4 Physical Examination 21
3.4.1 Carotid Pulse 21
3.4.2 Jugular Pulse 21
3.4.3 Apical Impulse 22
3.4.4 Cardiac Auscultation 22
3.5 Diagnostic Aspects 22
3.5.1 Electrocardiography 22
3.5.2 Chest X-Ray 23
3.5.3 Echocardiography 23
3.5.4 Transesophageal Echocardiography 24
3.5.5 Cardiac Magnetic Resonance Imaging 24
3.5.6 Nuclear Imaging 25
3.5.7 Cardiac Catheterization 26
3.6 Pathofunctional Implications 26
3.6.1 Systolic Anterior Motion 26
3.6.2 Left Ventricular Outflow Tract Obstruction 27
3.6.3 Mitral Valve Regurgitation 28
3.6.4 Systolic Dysfunction 28
3.6.5 Diastolic Dysfunction 28

3.7 Complicative Aspects 29
3.7.1 Atrial Fibrillation 29
3.7.2 Infective Endocarditis 30
3.7.3 Heart Failure 30
3.7.4 Sudden Cardiac Death 31
3.8 Morphologic Forms 32
3.8.1 Asymmetric Form 32
3.8.1.1 Historical Perspectives 32
3.8.1.2 Asymmetric Septal Hypertrophy 33
3.8.1.2.1 Definition 33
3.8.1.2.2 Epidemiology 33
3.8.1.2.3 Medical History within the Family 34
3.8.1.2.4 Genetic Aspects 34
3.8.1.2.5 Clinical Aspects 34
3.8.1.2.6 Diagnostic Aspects 35
3.8.1.2.7 Complicative Aspects and Prognosis 36
3.8.1.2.8 Comorbidities 36
3.8.1.2.9 Aspects According to the Morphologic Form of the Septum 36
3.8.1.2.9.1 Asymmetric Sigmoid Form 36
3.8.1.2.9.2 Reverse Septal Contour 37
3.8.1.2.9.3 Neutral Septal Form 38
3.8.2 Concentric Form 39
3.8.2.1 Historical Perspectives 39
3.8.2.2 Definition 40
3.8.2.3 Epidemiology 40
3.8.2.4 Genetic Aspects 40
3.8.2.5 Characteristics of Concentric Hypertrophic Cardiomyopathy 41

3.8.2.6 Differentiation between Concentric Hypertrophic Cardiomyopathy and Other Conditions 41
3.8.2.6.1 Athlete's Heart 42
3.8.2.6.2 Hypertension 42
3.8.2.6.3 Aortic Stenosis 44
3.8.2.6.4 Infiltrative and Deposition Diseases 44
3.8.2.6.4.1 Amyloidosis 44
3.8.2.6.4.2 Anderson-Fabry Disease 46
3.8.2.6.4.3 Cardiac Sarcoidosis 46
3.8.3 Apical Form 48
3.8.3.1 Historical Perspectives 48
3.8.3.2 Definition 48
3.8.3.3 Epidemiology 49
3.8.3.4 Genetic Aspects 49
3.8.3.5 Clinical Aspects 50
3.8.3.6 Diagnostic Aspects 51
3.8.3.7 Complicative Aspects and Prognosis 52
3.8.3.8 Comorbidities 53
3.8.4 Midventricular Form 53
3.8.4.1 Historical Perspectives 53
3.8.4.2 Definition 54
3.8.4.3 Epidemiology 54
3.8.4.4 Genetic Aspects 54
3.8.4.5 Clinical Aspects 54
3.8.4.6 Diagnostic Aspects 55
3.8.4.7 Complicative Aspects and Prognosis 55
3.8.4.8 Comorbidities 56

3.8.4.9 Hypertrophic Cardiomyopathy with Midventricular Obstruction and Left Ventricular Apical Aneurysm 56
3.8.4.9.1 Definition 56
3.8.4.9.2 Epidemiology 57
3.8.4.9.3 The Formation of Left Ventricular Apical Aneurysm 57
3.8.4.9.4 Clinical Aspects 58
3.8.4.9.5 Diagnostic Aspects 58
3.8.4.9.6 Complicative Aspects and Prognosis 59
3.8.5 Mass-Like Hypertrophic Cardiomyopathy 59
3.8.5.1 Diagnostic Aspects 60
3.8.6 Right Ventricular Involvement 62
3.8.6.1 Definition 62
3.8.6.2 Epidemiology 63
3.8.6.3 Genetic Aspects 63
3.8.6.4 Morphologic Aspects 64
3.8.6.5 Right Ventricular Outflow Tract Obstruction 64
3.8.6.6 Clinical Aspects 65
3.8.6.7 Diagnostic Aspects 65
3.8.6.8 Complicative Aspects and Prognosis 67
3.8.6.9 Comorbidities 68
3.8.7 Genotype Positive Phenotype Negative Hypertrophic Cardiomyopathy 68
3.8.7.1 Historical Perspectives 68
3.8.7.2 Definition 69
3.8.7.3 Genetic Aspects 69
3.8.7.4 Clinical Aspects 70
3.8.7.5 Diagnostic Aspects 70
3.8.7.5.1 Electrocardiography 70
3.8.7.5.2 Echocardiography 71

3.8.7.5.3 Magnetic Resonance Imaging 72
3.8.7.5.3.1 Myocardial Crypts 72
3.8.7.5.3.2 Other Structural Abnormalities 73
3.8.7.6 Alteration of Calcium Homeostasis 75
3.8.7.7 Alteration of Myocardial Energetics 76
3.9 Therapeutic Intervention 77
3.9.1 General Measures 77
3.9.2 Pharmacological Measures 77
3.9.2.1 Hypertrophic Cardiomyopathy with Left Ventricular Outflow Tract Obstruction 78
3.9.2.1.1 The Application of β-Adrenoceptor Blocking Agents 78
3.9.2.1.2 The Class IV Antiarrhythmic Agents Verapamil and Diltiazem 80
3.9.2.1.3 The Class Ia Antiarrhythmic Agent Disopyramide 81
3.9.2.2 Nonobstructive Hypertrophic Cardiomyopathy 82
3.9.2.2.1 Heart Failure 82
3.9.2.2.2 Angina Pectoris 84
3.9.3 Invasive Therapeutic Interventions of Left Ventricular Outflow Tract Obstruction 84
3.9.3.1 Procedural Indication 84
3.9.3.2 Ventricular Septal Myectomy 85
3.9.3.2.1 Historical Perspectives 85
3.9.3.2.2 Clinical Aspects 85
3.9.3.2.3 Complicative Aspects and Prognosis 85
3.9.3.2.4 Element of Consideration 87
3.9.3.3 Alcohol Septal Ablation 87
3.9.3.3.1 Historical Perspective 87
3.9.3.3.2 Clinical Aspects 88
3.9.3.3.3 Complicative Aspects and Prognosis 89

3.9.3.3.4 Elements of Consideration 89
3.9.4 Cardiac Pacing 91
3.9.4.1 Pacing Location 92
3.9.4.2 Biventricular Pacing 92
3.9.5 Cardiac Transplantation 93
4 Discussion 96
4.1 General Considerations 96
4.2 Genetic Aspects 97
4.3 Various Condition Related Implications 99
4.4 Morphologic Forms 103
4.4.1 Asymmetric Septal Hypertrophy 103
4.4.2 Concentric Form 105
4.4.3 Apical Form 108
4.4.4 Midventricular Form 110
4.4.5 Mass-Like Hypertrophic Cardiomyopathy 112
4.4.6 Right Ventricular Involvement 113
4.4.7 Genotype Positive Phenotype Negative Hypertrophic Cardiomyopathy 114
4.5 Therapeutic Intervention 116
4.6 Conclusion 121
5 References 128

List of Abbreviations

ACCF	American College of Cardiology Foundation
AF	Atrial Fibrillation
AHA	American Heart Association
CI	Confidence Interval
ECG	Electrocardiogram
EF	Ejection Fraction
LVOTO	Left Ventricular Outlflow Tract Obstruction
LVOT	Left Ventricular Outflow Tract
LVWT	Left Ventricular Wall Thickness
MRI	Magnetic Resonance Imaging
NYHA	New York Heart Association
SAM	Systolic Anterior Motion
SCD	Sudden Cardiac Death
NSVT	Non-Sustained Ventricular Tachycardia

List of Figures

Figure 1: Global political map depicting nationalities with presence of Hypertrophic Cardiomyopathy …… 4

Figure 2: Etiologic subjacency of Hypertrophic Cardiomyopathy and attendant proportions of mutations in involved genes according to the European Society of Cardiology …… 5

Figure 3: Composition of the cardiac sarcomere accompanied by inter alia a selection of protein formations affected within Hypertrophic Cardiomyopathy ……... 8

Figure 4: Findings of an ordinary heart at post mortem ……... 18

Figure 5: Heart of a 14-year-old boy presenting Hypertrophic Cardiomyopathy with the asymmetric morphologic variant ……. 18

Figure 6: Transverse section of either cardiac ventricles of an individual subject to Hypertrophic Cardiomyopathy …….. 19

Figure 7: Myocyte disarray with myocytes exhibiting an arrangement perpendicular or oblique to each other surrounding a focus of connective tissue …… 20

Figure 8: Myocyte disarray demonstrating a “herring-bone” pattern ……... 20

Figure 9: Intramural artery exhibiting hypertrophy of the media and narrowing of the vessel lumen ……... 20

Figure 10: Increase of interstitial firbosis ……. 20

Figure 11: Echocardiographic image of the heart of a 20-year-old male athlete demonstrating Hypertrophic Cardiomyopathy holding a positive mutational subjacency with regard to the sarcomere ……. 24

Figure 12: Three-Chamber View of the heart in assistance of Steady State Free Precession Cine MRI …….. 25

Figure 13: Heart via MRI exhibiting the asymmetric phenotypic expression of Hypertrophic Cardiomyopathy …….. 25

Figure 14: Entity of SAM of the mitral valve complex presented in assistance of M-Mode Echocardiography …… 26

Figure 15: Two-Dimensional Echocardiographic image of Hypertrophic Cardiomyopathy presenting with obstruction …….. 27

Figure 16: Utilization of the Continuous-Wave Doppler technique in order to attain an estimation of the obstruction encountered in Hypertrophic Cardiomyopathy …….. 27

Figure 17: Turbulent flow in the outflow tract with a jet directed posteriorly within context of Mitral Regurgitation and SAM ……. 28

Figure 18: Heart of an individual via MRI with Hypertrophic Cardiomyopathy presenting the asymmetric morphologic form ……. 34

Figure 19: Asymmetric Septal Form of Hypertrophic Cardiomyopathy …….. 37

Figure 20: Reverse Septal Contour of Hypertrophic Cardiomyopathy …… 38

Figure 21: Neutral Septal Form of Hypertrophic Cardiomyopathy …….. 39

Figure 22: Long-Axis Two Chamber View of the heart of a 54-year-old individual in assistance of Steady State Free Precession MRI demonstrating the concentric variant of Hypertrophic Cardiomyopathy …….. 41

Figure 23: Histologic assessment of a post mortem heart with presence of Amyloidosis …….. 45

Figure 24: Image of a post mortem cardiomyocyte affected by Anderson-Fabry Disease at 6000-fold magnification in assistance of the Electron Microscope ……... 46

Figure 25: Image of Cardiac Sarcoidosis at a 100-fold magnification ……. 47

Figure 26: Four-Chamber View of the heart via MRI of an individual presenting Apical Hypertrophic Cardiomyopathy …… 49

Figure 27: Electrocardiogram of an individual subject to Apical Hypertrophic Cardiomyopathy …….. 52

Figure 28: Four-Chamber View of the heart of a female individual at the age of 51 years in assistance of Steady State Free Procession MRI exhibiting Midventricular Hypertrophic Cardiomyopathy …….. 55

Figure 29: Heart of a person at the age of 55 years as a Three-Chamber View in assitance of Steady State Free Precession MRI exhibiting Midventricular Hypertrophic Cardiomyopathy with Left Ventricular Apical Aneurysm ……... 57

Figure 30: Short-Axis View of the heart of a female person at the age of 51 years via MRI presenting Mass-Like Hypertrophic Cardiomyopathy with hypertrophy located in the left ventricular free wall ……. 60

Figure 31: Images of the heart of a 51-years-old female individual in assistance of MRI in Short-Axis View attained at five succesive trigger delays exhibiting a mass simulating hypertrophy in the left ventricular free wall …….. 61

Figure 32: Hypertrophy encountered in the right ventricle while left ventricle is as well affected by hypertrophy ……. 63

Figure 33: Short-Axis View of the heart via MRI with hypertrophy within the right ventricle …….. 64

Figure 34: Image of a heart in end diastole in assistance of MRI in Long-Axis View of an asymptomatic genotype positive girl at the age of 17 years demonstrating no left ventricular hypertrophy …….. 73

Figure 35: Long-Axis View of a heart via MRI of a person subject to a mutation in the gene MBPC3 yet with an ordinary LVWT ……... 74

Figure 36: Image of the heart of a genotype positive phenotype negative individual at the age of 19 years in assistance of MRI presenting an ordinary maximal LVWT …….. 75

Figure 37: Image of the heart of a genotype positive phenotype negative individual demonstrating increased trabeculation ……. 76

Figure 38: Algorithm for the treatment of Hypertrophic Cardiomyopathy according to the ACCF/AHA collaboration ……... 79

Figure 39: Treatment algorithm for individuals presenting Heart Failure within Hypertrophic Cardiomyopathy according to the ESC …… 83

Figure 40: Possible proceeding within Ventricular Septal Myectomy ……. 86

Figure 41: Demonstration of Alcohol Septal Ablation ……. 88

List of Tables

Table 1: Identified genes with a mutation holding possibility of a subsequent phenotypic expression of Hypertrophic Cardiomyopathy …… 9

Zusammenfassung

Einführung: Die Relevanz der Erkrankung Hypertrophe Kardiomyopathie, mit ihrer klinischen Erkennung vorhanden in insgesamt 122 Ländern der Welt, ist von globalem Ausmaß. Der Krankheit ätiologische Basis, im Ausmaß von bis zu 60% der Personen in ihrem Adoleszenten- oder Erwachsenenalter, wird von Mutationen angetroffen in Genen, die für kardiale sarkomerische Proteine kodieren, dargestellt.

Methoden: Die vorliegende Diplomarbeit stellt das Resultat von Literaturrecherche dar. Literatur vorhanden in Lehrbüchern, Studien und Reviews wurden in Anspruch genommen. Des Weiteren wurde die Ressource PupMed® und medizinische Platform Ovid® angewendet.

Ergebnisse: Eine Genotyp-Phenotyp Korrelation der Krankheit, auch wenn nicht eindeutig ersichtlich, wird diskutiert während eine inkomplette und Alters assoziierte Penetranz erwiesen als auch Determinanten wie Komplexe Genotypen und Modifizierende Gene einen Einfluss auf das Leiden ausüben. Des Weiteren wurden Epigenetik als auch Umweltfaktoren in Erwägung gezogen die Hypertrophe Kardiomyopathie zu beeinflussen.

Die Hypertrophe Kardiomyopathie besitzt eine Variabilität an morphologischer Expression mit verschiedenen hypertrophischen Mustern. Die Manifestation der Hypertrophie weist eine erhebliche interindividuelle Variation bezüglich des Ausmaßes als auch der Verteilung auf. Die Möglichkeit die Krankheit in eine asymmetrische, konzentrische, apikale und midventrikuläre Form als auch in eine Masse-ähnliche Manifestation, rechts ventrikuläre Beteiligung und einen Genotyp positiv Phenotyp negativen Umstand zu unterteilen, ist vorhanden.

Die therapeutische Intervention beinhaltet unter anderem die Implementation von allgemeinen Maßnahmen und einen pharmakologischen Ansatz hinsichtlich beider, Gruppen, die eine Linksventrikuläre Ausflusstrakt Obstruktion aufweisen, als auch Individuen in Abwesenheit der Entität. Im Falle von Personen die eine Linksventrikuläre Ausflusstrakt Obstruktion aufweisen, stellen die Prozeduren der Ventrikulären Septalen Myektomie und Alkoholisch Septalen Ablation invasiv therapeutische Möglichkeiten dar. Während das Anwenden eines kardialen Schrittmachers als therapeutische Maßnahme nicht eindeutig etabliert ist, ist die Option der Herztransplantation für eine Untergruppe von sich eignenden Individuen vorhanden.

Conclusio: Das Leiden Hypertrophe Kardiomyopathie war Gegenstand eines erheblichen Ausmaßes an Personen, die ihr ihre Aufmerksamkeit widmeten. So viel Information wie bis zur gegenwärtigen Zeit gesammelt wurde, gänzliche Aufklärung einer zum Teil Frage aufwerfenden Erkrankung wurde nicht erlangt.

Abstract

Introduction: The relevance of the ailment Hypertrophic Cardiomyopathy, with its clinical identification in existence in collectively 122 countries of the world, is of global scale. The disease's etiologic basis in the extent of up to 60% of persons within their adolescence or adulthood represents mutations encountered in genes encoding for cardiac sarcomeric proteins.

Methods: The present Diploma Thesis constitutes the result of Literature Research. Literature contained in Textbooks, Studies, and Reviews were utilized. Furthermore, the resource PubMed® and medical research platform Ovid® were applied.

Results: A condition's Genotype-Phenotype Correlation, even though not unequivocally evident, is discussed while an incomplete and age associated Penetrance has been demonstrated as well as determinants such as Complex Genotypes and Modifier Genes exert influence on the condition. Furthermore, Epigenetics as well as environmental factors have been taken into consideration of influencing Hypertrophic Cardiomyopathy.

Hypertrophic Cardiomyopathy is encountered with a variability in morphologic expression, holding different hypertrophic patterns. Its manifestation of hypertrophy presents a substantial interindividual variation with regard to its extent as well as distribution. Possibility of a disease's subdivision into an asymmetric, concentric, apical, and midventricular form as well as a mass-like manifestation, right ventricular involvement and genotype positive phenotype negative conjuncture, is existent.

Therapeutic intervention includes inter alia the implementation of general measures and a pharmacological approach in reference to either, collectives subject to Left Ventricular Outflow Tract Obstruction and individuals in absence of the entity. In case of persons presenting Left Ventricular Outflow Tract Obstruction, invasive therapeutic contingencies constitute the procedures of Ventricular Septal Myectomy and Alcohol Septal Ablation. While Cardiac Pacing as a therapeutic measure is not unequivocally established, the option of Cardiac Transplantation in a subdivision of individuals presenting affirmative eligibility, is available.

Conclusion: The condition of Hypertrophic Cardiomyopathy has been subject of a considerable extent of persons directing their attention to. As much information as has been gathered up until present time, entire elucidation of this in part question raising ailment has not been attained.

1 Introduction

1.1 The Fascination of the Heart

From times of ancient Egypt to Greece, Roman civilization, and the Medieval Era (1) up until into the contemporary century (2), the heart has represented the entity of astonishment numerous persons directed their attention to. Not only science, but as well as literature and the arts (3) addressed this wonder surrounded place. (3) Biblical Scriptures inter alia associate it with the "cognitive, affective, and volitional elements of personal life" (4). (4) Yet the corporal constituent is not inaccessible to ailment as once thought. (3, 1)

1.2 Historical Perspectives

Apparently, in the year of 1868, Vulpian may have provided a publication in description of the condition Hypertrophic Cardiomyopathy. (5, 6) As well apparently, the subsequent year, Liouville (5, 7) and Hallopeau (5, 8) may have imparted findings resembling those by antecedent author in assistance of the Medical Gazette of Paris. (5, 7, 8)

In the year of 1957, Brock reported about three cases presenting left ventricular hypertrophy either at post mortem examination or within context of electrocardiographic findings, yet overall associated the occurrences with Hypertension. (5, 9) The subsequent year, Robert Donald Teare, practicing at the Department of Pathology at the St. George Hospital (10) in London (5), imparted his findings with regard to eight post portem examined individuals presenting an asymmetric hypertrophy of the heart. (5, 10) Titled as "Asymmetrical Hypertrophy of the Heart in Young Adults" (10) the publication comprised inter alia the pathomorphological delineation of "asymmetrical hypertrophy or muscular hamartoma of the heart" (10). Seven of aforementioned eight cases were subject to the incident of Sudden Cardiac Death [SCD], with the exception having deceased subsequent to an intervention of Mitral Valvotomy. (10) Teare's histopathologic investigation revealed a "[d]isordered arrangement of muscle bundles" (10) alongside with "hypertrophy of individual muscle fibres and their nuclei" (10). (10)

In 1963, Braunwald and Aygen, delineated 14 patients presenting "clinical, electrocardiographic, and angiographic evidences of left ventricular hypertrophy" (11), yet an absence in hemodynamically observable Left Ventricular Outflow Tract Obstruction [LVOTO], thereby providing the primary description of nonobstructive Hypertrophic Cardiomyopathy. (5, 11) The subsequent year, Morrow et al. reported in respect to the

performing of Ventricular Septal Myectomy, representing a contingent surgical intervention for patients subject to Hypertrophic Cardiomyopathy. (5, 12) The publication by Moreyra et al. in 1969 (13), assessing 16 individuals echocardiographically, constitutes the primary description of the condition in assistance of the imaging method. (5, 13)

In the year of 1989, Jarcho et al. were the first to conclude, with regard to a certain kindred the location of the causal gene for Familial Hypertrophic Cardiomyopathy to represent chromosome 14 band q1. (14, 15) The subsequent year, Geisterfer-Lowrance et. al., reported a missense mutation with regard to exon 13 of the cardiac ß-Myosin Heavy Chain gene, exchanging an arginine with a glutamine, to be carried by all persons subject to Familial Hypertrophic Cardiomyopathy found within a kindred (16), thereby describing for the first time a causal mutation for the condition of Hypertrophic Cardiomyopathy (3).

1.3 Definition

In principal, the designation of "Cardiomyopathy" relates to a collective of ailments holding its preeminent deficiency within the myocardium and presenting an alteration in the structure and/or function of myocytes. (3) It is denoted that hypertrophy constitutes an ordinary cardiac reaction in response to any form of injury or stimuli. (3) Hypertrophic Cardiomyopathy is defined as the presence of left ventricular hypertrophy without an elicitation attributable to unordinary loading conditions or hemodynamic aspects (by way of example, hypertension or aortic valve disease), or the manifestation of systemic infiltrative or storage diseases. (3, 17, 18) The extent of ≥15 mm in left ventricular wall thickness [LVWT] encountered in at least one of its segments visualized in assistance of medical imaging techniques is regarded as diagnostic threshold. (17) Within circumstance of an ambiguous approaching magnitude of 13-14 mm diagnose necessitates supportive evidence proceeding from within family history, presence of non-cardiac symptoms and signs, electrocardiographic abnormalities, laboratory testing, or multimodality imaging procedures. (17) In children the diagnose is performed in case of LVWT surpassing the extent of two standard deviations above the corresponding mean (designated as z-score). (17)

Of note, authors have historically utilized more than 75 (19) designations with regard to the condition of Hypertrophic Cardiomyopathy (19, 20). Antecedent obsolete denotations include "Idiopathic Hypertrophic Subaortic Stenosis" (21), "Functional Hypertrophic Subaortic Stenosis" (22), "Idiopathic Myocardial Hypertrophy" (11), "Familial [H]ypertrophic [C]ardiomyopathy" (23), and "Functional Aortic Stenosis" (24).

Aforementioned titular names are considered to partially represent the result of the disease's clinical heterogeneity. (25) Even though being aware of the term "[H]ypertrophic [C]ardiomyopathy" (20) to contingently not constitute the resultant ailment of an isolated single etiologic causality (20), preference to the designation is given by its virtue of encompassing the overall conditional spectrum (25). It does not perceive LVOTO as a sine qua non in reference to the diagnosis of Hypertrophic Cardiomyopathy (25) and is regarded as contemporarily the most applicable appellation (19).

1.4 Epidemiology

The prevalence of Hypertrophic Cardiomyopathy has been within analysis of echocardiographically acquired data, considering its phenotypic manifestation, initially placed at 1:500. (26) On basis of including more recent findings, genotypic positive individuals yet with an absence in clinical expression, the more sensitive detection modality of Cardiac Magnetic Resonance Imaging [MRI], as well as the disease's familial essence, the aforementioned estimation rises to 1:200. (27)

Hypertrophic Cardiomyopathy has been reported from various regions of the world, including the United States of America (26), the United Kingdom (28), France (29), Germany (30), Brazil (31), the Republic of South Africa (32), China (33), as well as Japan (34), with China and Japan denoting similar rates of antecedently mentioned phenotypic prevalence, videlicet 1:622 (33) and 1:584 (34), respectively. Clinical identification of the ailment is in existence in collectively 122 countries of the world. (35)

The formation of left ventricular hypertrophy has been denoted to regularly concur with episodes of accelerated somatic growth. (3) Yet, the possibility of de novo occurrences is existent for the entire time lapse from infancy to grandevity. (3)

The disease has been reported as predominantly affecting male individuals with a proportion of 59.4%. (36) Of note, 33.4% of Hypertrophic Cardiomyopathy diagnoses resulted from routine examinations, with female patients being less frequently diagnosed within such assessments, noted with 41% for men and 23% for women (p value of <0.001). (36)

Furthermore, African American individuals were found to represent an under-diagnosed ethnicity in relation to Hypertrophic Cardiomyopathy. (37) While 54.9% of competitive athletes with an incident of SCD related to Hypertrophic Cardiomyopathy were represented by African American, the occurrence was encountered in 41.2% of white individuals (p value of 0.002). (37) Nevertheless, clinically identified persons were represented by 89.8% of white individuals,

Figure 1: Global political map depicting nationalities with presence of Hypertrophic Cardiomyopathy. (35) Affected nationalities are designated by red. (35) Image from (35).

while as few as 8% were African American, with either ethnical collectives presenting similar values of attested preparticipation assessments (98.6% compared to 97.3%, with a nonsignificant *p* value). (37)

1.5 Etiology

The etiologic basis in the extent of up to 60% of individuals within their adolescence or adulthood subject to the condition of Hypertrophic Cardiomyopathy represents mutations in genes encoding for cardiac sarcomeric proteins. (17)

Additionally, the proportion of 5-10% of incidents in adult subjects identified as carrying Hypertrophic Cardiomyopathy represent cases with other causal ailments of genetic or non-genetic nature, such as metabolic (by way of example, Anderson-Fabry Disease), neuromuscular (Friedreich's Ataxia), infiltrative (Cardiac Amyloidosis), or endocrine (Pheochromocytoma) disorders. (17) Further instances include mitochondrial cardiomyopathies and malformation syndromes (Noonan Syndrome). (17)

The extent of 25-30% of individuals subject to Hypertrophic Cardiomyopathy hold an unidentified causality of the condition. (17)

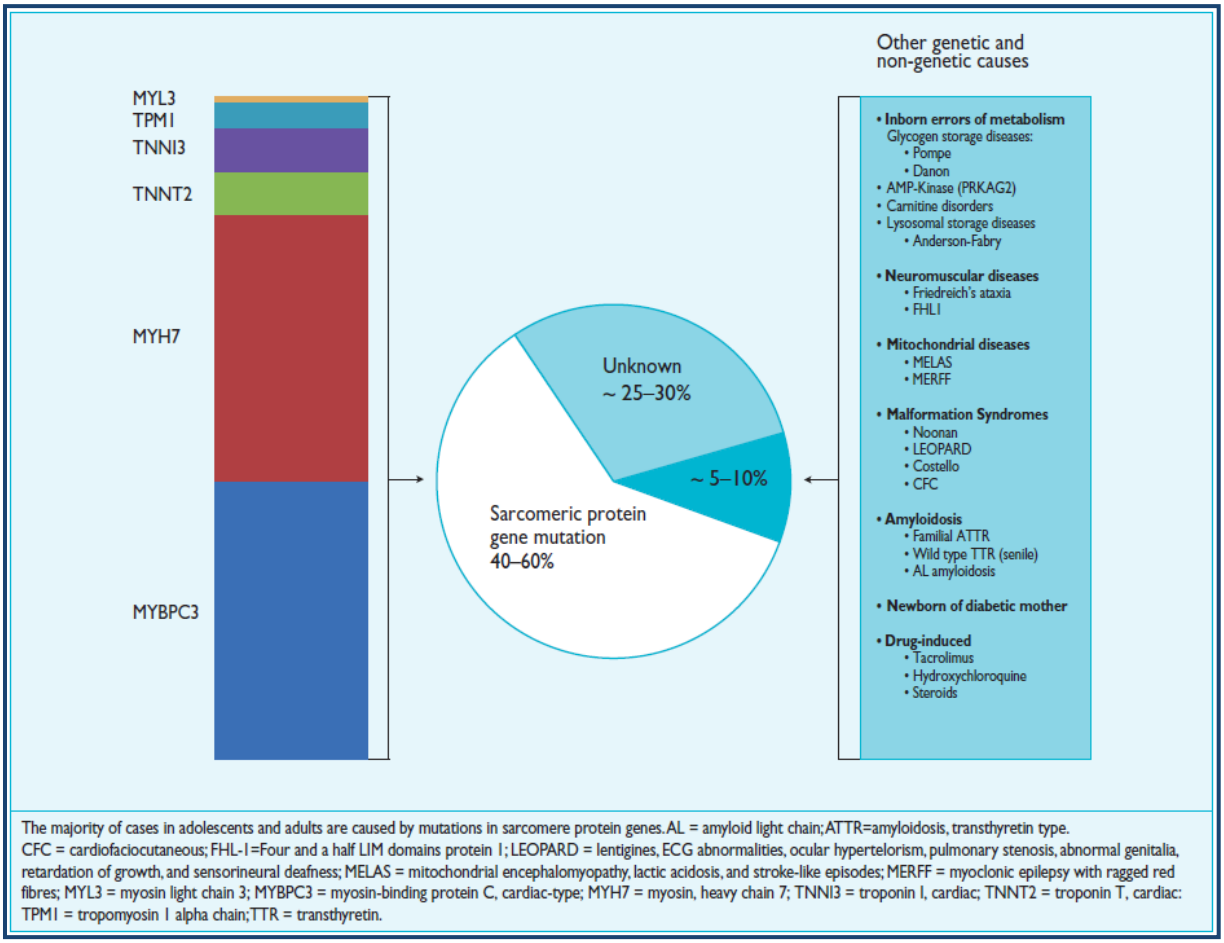

Figure 2: Etiologic subjacency of Hypertrophic Cardiomyopathy and attendant proportions of mutations in involved genes according to the European Society of Cardiology [ESC]. (17) Image modified from (17).

2 Methods

The present Diploma Thesis represents the result of Literature Research. Literature within Textbooks, Studies and Reviews were utilized. Furthermore, research was conducted in assistance of the resource PubMed® as well as the medical research platform Ovid®.

3 Results

3.1 Genetic Aspects

On basis of the initial insight of Hypertrophic Cardiomyopathy to hold a genetic connotation, originating in consequence of the discovery of a missense mutation at the exon 13 in the gene responsible for the cardiac β Myosin Heavy Chain published by Geisterfer-Lowrence et al. in the year of 1990 (16), as well as the ensuing detection of hundreds of further gene mutations resulting in the condition (38), placement of Hypertrophic Cardiomyopathy as an ailment of cardiac sarcomeric proteins has been voiced. (38)

Hypertrophic Cardiomyopathy has been denoted to hold a mutational locus as well as allelic heterogeneity. (39) Its mode of inheritance is designated as most frequently presenting autosomal dominant, yet with unusual forms noted as possessing an autosomal recessive, mitochondrial, or X-linked trait. (40) Furthermore, it demonstrates an elevated frequency in individual de novo mutations (39), a variability in expressivity, as well as an age associated and contingently incomplete penetrance (41).

3.1.1 The Cardiac Sarcomere

Cardiac myocytes contain myofibrils in a lengthwise distribution within the cell holding transverse segmentations, nominally "sarcomeres" (42). (42) These constitute contractile entities and contain the structures of thick and thin myofilaments. (42) The former comprises approximately 300 myosin molecules, in turn each consisting of either two β-Myosin Heavy Chain or α-Myosin Heavy Chain proteins as well as additional four Myosin Light Chains. (42) The thin myofilaments comprise an accumulation of Actin proteins and the presence of Troponin complexes in a connection to α-Tropomyosin. (42) Aforementioned Troponin complex consists of Troponin T, Troponin I, and Troponin C. (42) Furthermore, Myosin Binding Protein C is involved in the interaction of actin and myosin as well as kinetics associated with cross-bridges. (42)

The sarcomere holds several topographic zones, with its middle constituting the M-Band. (42) The I-Band comprises no thick myofilaments, while the H-Zone is characterized by an absence of cross-bridges. (42) The Z-Disks delineated the sarcomere's lateral margins. (42)

Muscular contraction is apprehended to occur by means of actin sliding by myosin. (42) The myosin head supposedly effectuates a binding to actin, a subsequent contraction and eventually disconnects from actin with an ensuing initiation of a further cycle. (42) This process

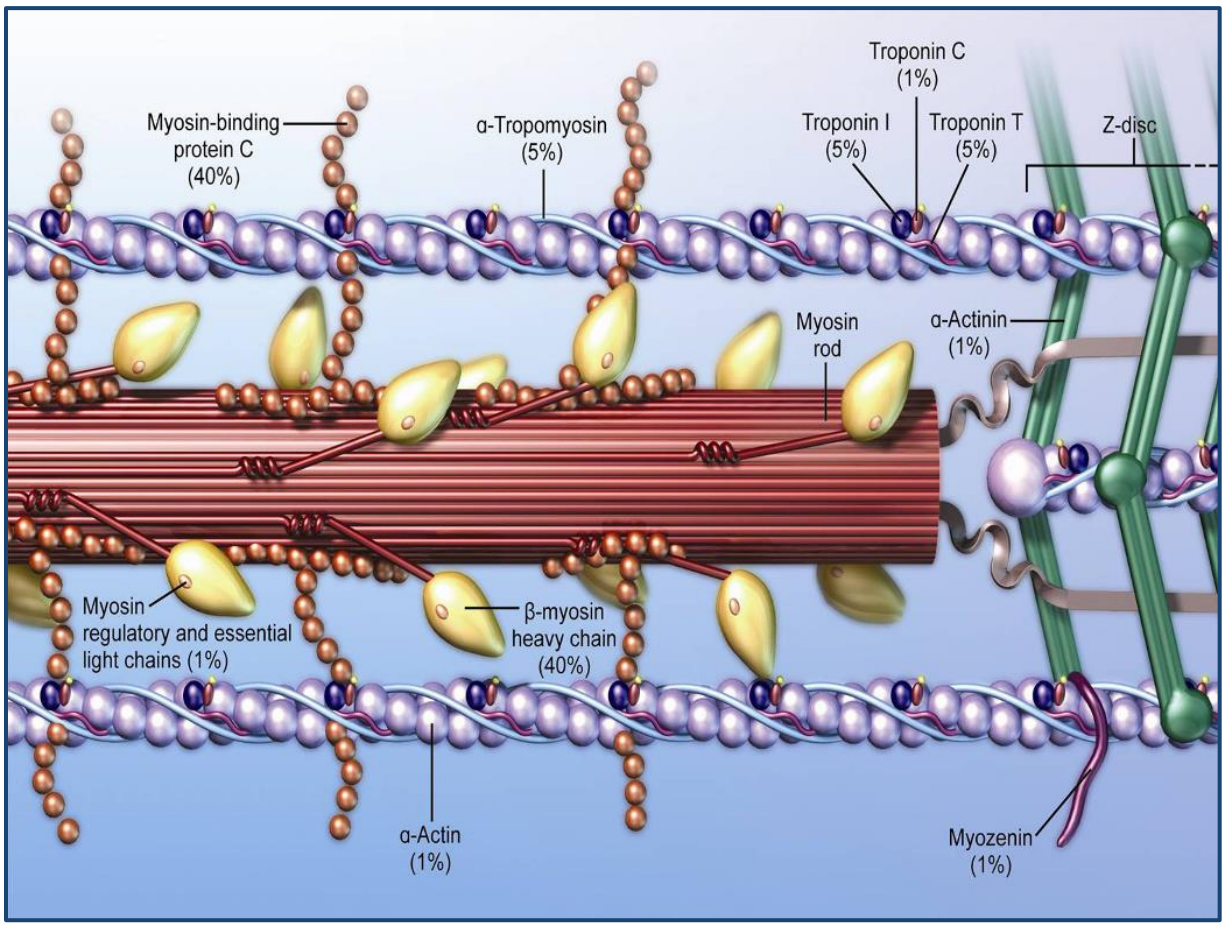

Figure 3: Composition of the cardiac sarcomere (43) accompanied by inter alia a selection of protein formations affected within Hypertrophic Cardiomyopathy. (43) The percental proportions of involved protein structures are denoted according to Maron (43). Image from (43).

necessitates the Hydrolysis of Adenosine Triphosphate while cardiac contraction is associated with intracellular Calcium movement. (42)

3.1.2 Implicated Genes and Distribution

The genetic heterogeneity of Hypertrophic Cardiomyopathy emerges apparent inter alia within context of >1,500 denoted mutations resulting in the phenotypic expression of the condition. (44) Furthermore, mutations are reported to be encountered in at the minimum 45 genes presenting at least an association with the ailment of Hypertrophic Cardiomyopathy. (39, 3, 18)

The preponderance of individuals subject to Hypertrophic Cardiomyopathy demonstrate mutations related to the sarcomeric genes MYH7 or MYBPC3 holding the chromosomal locations of 14q12 and 11p11, respectively and encoding for the proteins of β-Myosin Heavy Chain and Myosin Binding Protein C 3, respectively. (39) Collectively, mutations in aforementioned genes in one publication accounted for as much as up to 82.3% of cases (29).

Table 1: Identified genes with a mutation holding the possibility of a subsequent phenotypic expression of Hypertrophic Cardiomyopathy. (39, 3, 18) Table according to (39, 3, 18).

Genes	Proteins	Proportion of Individuals Identified with a Mutation in Affected Gene
Enconding for Sarcomeric Proteins		
MYH7	β-Myosin Heavy Chain	40-44%
MYBPC3	Myosin Binding Protein C	35-40%
TNNT2	Troponin T	5-15%
TNNI3	Troponin I	5%
TPM1	Tropomyosin 1	3%
TTN	Titin	<3%
MYL2	Myosin Light Chain 2	1-2%
MYL3	Myosin Light Chain 3	1%
ACTC1	Actin α-Cardiac Muscle 1	1%
TNNC1	Troponin C1	<1%
TRIM63	E3 Ubiquitin-Protein Ligase	<1%
MYH6	α-Myosin Heavy Chain	
Encoding for Z-Disk Proteins		
LDB3	LIM Domain Binding 3	1-5%
ACTN2	Actinin α 2	<1%
ANKRD1	Ankyrin Repeat Domain 1	<1%
CSRP3	Cysteine And Glycine Rich Protein 3	<1%
MYOZ2	Myozenin 2	<1%
TCAP	Telethonin	<1%
VCL	Vinculin	<1%
NEXN	Nexilin F-Actin Binding Protein	<1%
FLNC	Filamin C	<1%
Other Involved Genes		
DES	Desmin	<1%
FHL1	Four And A Half LIM Domains 1	<1%
CAV3	Caveolin 3	
ALPK3	α Kinase 3	
Genes Involved in Calcium-Handling		
PLN	Phospholamban	<1%
CALR3	Calreticulin 3	<1%
CASQ2	Calsequestrin 2	<1%
JPH2	Junctophilin 2	<1%
Phenocopies		
PRKAG2	Protein Kinase AMP-Activated Non-Catalytic Subunit γ 2	
GAA	Glucosidase α Acid	
GLA	Galactosidase α	
LAMP2	Lysosomal Associated Membrane Protein 2	
KRAS	KRAS Proto-Oncogene GTPase	
SOS1	SOS Ras/Rac Guanine Nucleotide Exchanger Factor 1	
PTPN11	Protein Tyrosine Phosphatase Non-Receptor Type 11	
RAF1	Raf-1 Proto-Oncogene Serine/Threonine Kinase	
TTR	Transthyretin	
FXN	Frataxin	
MOY6	Unconventional Myosin 6	
DMPK	DM1 Protein Kinase	
DMWD	DM1 Locus WD Repeat Containing	

MT-TG	Mitochondrially Encoded tRNA Glycine	
MT-TI	Mitochondrially Encoded tRNA Isoleucine	

Particularly, mutations in the gene MYH7 are noted to be encountered in 40-44% of patients subject to the disease, while individuals present mutations in the gene MYBPC3 in the extent of 35-40% of cases. (39) Further mutation detected sarcomeric genes include TNNT2 and TNNI3, on the chromosomal locations of 1q32 and 19q13, respectively, with a proportion of 5-15% and 5%, respectively. (39) The genes TPM1 and MYL2 are specified to be affected in 3% and 1-2%, respectively. (39)

The most mutation affected gene encoding for a protein of the Z-Disk is represented by LDB3, chromosomal located at 10q22, encountered in the extent of 1-5% of cases. (39) Further Z-Disk related genes presenting a mutation include ACTN2, ANKRD1, and CSRP3, with a proportion of <1%, each. (39)

Mutations causative of a conditional phenotype of Hypertrophic Cardiomyopathy are found as well in genes responsible for proteins involved in the cellular Calcium Handling. (39) These genes include PLN, CALR3, CASQ2, and JPH2, detected in the amount of 1% of individuals, each. (39)

Additionally, other mutation affected genes resulting in Hypertrophic Cardiomyopathy constitute DES and FHL1, encoding for the proteins Desmin and Four and a Half LIM Domain Protein 1, respectively, encountered in the extent of 1% of cases, each, (39) as well as CAV3 (3) and ALPK3 (18), responsible for the proteins Caveolin 3 and α-Kinase 3, respectively.

3.1.3 Types of Mutation

The extent of 90% of mutations involved in Hypertrophic Cardiomyopathy are denoted as missense mutations (41), consisting of an exchange of a single amino acid for another (45). The result constitutes a change in the encoded protein's structure and function. (45) These include, according to Marian the preponderance of mutations in the genes MYH7, TNNT2, TNNI3, TPM1, as well as ACTC1. (38) An exception of aforementioned represent mutations in reference to the gene of MYBPC3, holding a proclivity towards mutations with an insertion or deletion of at least one nucleic acid. (44, 45) In consequence, the process of Translation experiences a frameshift with the result of an unordinary process of mRNA Splicing. (45) Additionally, the occurrence of a frameshift contingently leads to proteins exhibiting a premature truncation. (45) The mutant mRNA is subject to the Nonsense Mediated mRNA Decay, experiencing a degradation. (45) Alongside, proteins affected by premature truncation

encounter the Ubiquitin-Proteasome System undergoing degradation as well, with a consequent haploinsufficiency as ultimate result. (45)

Inter alia, frameshift mutations in principal are considered to hold an increased severity in clinical manifestation. (45)

3.1.4 Mutational Hot Spots

The frequency in repeatedly occurring mutations in Hypertrophic Cardiomyopathy presents diminished (38), with the preponderant proportion constituting nominally “private” (46) mutations, signifying to be encountered exclusively in at the utmost a few families (46).

Nevertheless, mutational “hot spots” (46) have been denoted, with mutations being repeatedly detected in an increased extent of families presenting no relation to each other. (46) These include the mutations Arg403Gln, Arg453Cys and Arg663His in the gene MYH7, Arg92Gln, Arg92Trp, and Arg104Val in the gene TNNT2, as well as Arg502Trp, c.1928-2A>G, and Arg495Gln in the gene MYBPC3. (46, 47)

The mutation p.Arg502Trp in the gene MYBPC3 has been denoted to occur in approximately 1.5-3% of individuals subject to the condition of Hypertrophic Cardiomyopathy. (44) Furthermore, the mutation p.Val762Asp in aforementioned gene is specified to be demonstrated by the amount of 3.9% of individuals within Japan. (44)

Nevertheless, according to Marian and Braunwald, the possibility of the elevated frequency of the two aforementioned mutations to be as well attributable to a founder effect, is existent. (44)

3.1.5 Phenocopies

A distinct subdivision of conditions within the spectrum of Hypertrophic Cardiomyopathy represent Hypertrophic Cardiomyopathy Phenocopies, exhibiting the manifestation of cardiac hypertrophy yet, in comparison to the ailment, holding a different pathogenesis. (3) In consequence, Hypertrophic Cardiomyopathy Phenocopies are regarded as to phenotypically mimic the condition of Hypertrophic Cardiomyopathy. (3)

Even though not with certainty expressible, the prevalence of Hypertrophic Cardiomyopathy Phenocopies has been estimated at approximately 5-10% of all clinically diagnosed Hypertrophic Cardiomyopathy occurrences in adults. (3) Examination of individuals with Hypertrophic Cardiomyopathy at the age of <18 years revealed a presence of inherited metabolic conditions, malformation syndromes, and neuromuscular diseases in 8.7%, 9%, and

7.5% of cases, respectively (48), allowing the conclusion of Phenocopies to be more frequent in children (3).

Hypertrophic Cardiomyopathy Phenocopies include especially storage diseases (3), by way of example Anderson-Fabry Disease, Danon Disease, and Amyloidosis (46), evoked by mutations in the genes of GLA, LAMP2, and TTR, respectively (46). Further Phenocopies are represented by the Wolff-Parkinson-White Syndrome (46), encountered with mutations in the gene PRKAG2, and Cardiomyopathies with causal mutations in mitochondrial genes (46), such as MT-TG and MT-TI (3).

Further affected genes resulting in Hypertrophic Cardiomyopathy Phenocopies constitute GAA, FXN, KRAS, and PTPN11. (39)

Anderson-Fabry Disease represents an X-linked recessive inherited (49) ailment within the collective of Lysosomal Storage Disorders (50) with a mutation in the gene GLA (39) holding a consequential deficiency in the activity of the lysosomal enzyme α-Galactosidase A (50) with the result of an accumulation of Glycosphingolipids in lysosomes and a subsequent cardiac hypertrophy (50). The extent of patients presenting left ventricular hypertrophy in consequence of Anderson-Fabry Disease within Hypertrophic Cardiomyopathy was found with 0.5%. (51)

3.1.6 Genotype-Phenotype Correlation

Patients subject to Hypertrophic Cardiomyopathy are denoted to exhibit a substantial variability in the ailment's phenotypic manifestation. (3) This includes the extent in hypertrophy. (3)

Even though denoted molecularly to not be comprehended in its entirety (3), the range in phenotypic expression is mentioned to had been perceived as partially the result of the condition's genetic heterogeneity (46).

Mutations in the gene of TNNT2 have been reported to hold a moderate severity in cardiac hypertrophy up to a subclinical manifestation. (46, 52) Conversely, Hypertrophic Cardiomyopathy with causal mutations in the gene TNNT2 is associated with an elevated incidence in SCD. (46, 52) Furthermore, in comparison to the Val606Met mutations in the gene MYH7, deceases related to Hypertrophic Cardiomyopathy were found to be encountered more frequently in individuals with the mutations Arg249Gln, Arg403Gln, or Arg453Cys in aforementioned gene. (46, 53) In utilization of Kaplan-Meier analysis, the cumulative survival rates for the genes MYH7 and MYBPC3 at the ages of 50 and 60 were determined with 62%

and 23% as well as 95% and 76%, respectively, accounting for a more favorable prognosis in the latter gene (*p* value of <0.0001). (46, 54)

According to Van Driest et al. individuals with multiple mutations presented in comparison to other study participants with the most increased phenotypic severity. (55) Nevertheless, Girolami et al. denote a relatively moderate extent in left ventricular hypertrophy with regard to two out of four individuals presenting multiple mutations, noted with 17 mm and 16 mm. (56)

According to Fujita et al., utilization of Cox Regression analysis revealed individuals subject to Hypertrophic Cardiomyopathy with a causal mutation in a sarcomeric gene in comparison to persons exhibiting the disease yet with no detected mutation in a sarcomeric gene to hold an elevated risk in cardiovascular incidents, with a hazard ratio of 3.031 (95% Confidence Intervall [CI]: 1.183-7.764, *p* value of 0.021) (46, 57)

Nevertheless, Ho et al. state, that at the present time with regard to the preponderance of mutations, correlations are not unequivocally evident. (46)

3.1.7 Penetrance

The condition of Hypertrophic Cardiomyopathy demonstrates an incomplete and age associated penetrance. (18, 46)

3.1.7.1 Interrelationship of Penetrance and Age

According to Charron et al., among genetically detected individuals, penetrance presented with an extent of 68.9%. (46, 58) Examination of the disease's penetrance in relation to age revealed, with the exception of the sixth decade (100%), a gradual increment from encountered 25% at the age of 10 years reaching 100% with regard to the eighth decade. (46, 58) Subdivision into three collectives related to age, videlicet the ages of 10-29, 30-49, and >50 years, resulted in values of penetrance noted with 54.2%, 74.2%, and 95%, respectively. (46, 58)

Jensen et al. denote, the amount of 5.6% of phenotypically negative children to had developed Hypertrophic Cardiomyopathy within a follow-up time period of 12 ± 1 years. (59)

According to Vermeer et al., additionally to initially detected phenotypic positive individuals within a genotype positive collective at the age of <18 years (4.2%), patients developing Hypertrophic Cardiomyopathy during a mean follow-up time period of 6.9 ± 3.8 years were noted with three, presenting the ages of 16.3, 25.7, and 30.4 years, respectively. (60)

3.1.7.2 Interrelationship of Penetrance and Gender

Charron et al. specify Hypertrophic Cardiomyopathy to had demonstrated a penetrance in relation to male individuals of 77.5% with a mean age of 33.6 ± 17 years and 58.5% with a mean age of 37.9 ± 16 years for the female population. (58) Comparison between male and female individuals determined an odds ratio in relation to penetrance with an adjustment for age of 3.98 (95% CI: 1.34-11.48, *p* value of 0.011). (58)

3.1.7.3 Interrelationship of Penetrance and Involved Genes

Even though not reaching a statistically significant difference between assessed mutations, according to Charron et al. penetrance in reference to individuals presenting a causal mutation in the genes MYH7, MYBPC3, and TNNT2 was determined with the extents of 67.3%, 67%, and 100%, respectively. (58)

Individuals subject to a mutation in the gene MYH7, despite not holding statistical significance, were found in comparison to persons with a mutation in MYBPC3 presenting an elevated penetrance, with 62% and 41%, respectively. (54) According to Niimura et al., individuals at the age of <50 years identified with a mutation in the gene MYBPC3 manifesting hypertrophy were determined with 58.1%. (61) Maron et al. denote a penetrance related to age in reference to patients demonstrating a mutation affected gene of MYBPC3 with left ventricular hypertrophy, to had been present at the ages of <20 and >50 years in the amount of 30.8% and 83.3% of individuals, respectively. (62)

3.1.8 Phenotype Modifying Factors

The variability in clinical expression within context of a sarcomeric elicited Hypertrophic Cardiomyopathy presents with a spectrum ranging interindividually from an absence of symptoms to the extent of severe manifestations such as Heart Failure or SCD. (46) Even within context of an identical mutation encountered in persons in the same family, the phenotypic expression may vary from not impaired to afflicted. (46) In consequence, the approach of Hypertrophic Cardiomyopathy to constitute an invariably monogenic ailment, with the attempt of explaining its manifestation exclusively by principals of Mendel, presents insufficient. (46)

3.1.8.1 Presence of Complex Genotypes

Double heterozygous mutations were demonstrated to hold an increased severity in clinical manifestation of Hypertrophic Cardiomyopathy, as encountered in a pedigree including

individuals being subject to the mutations p.Arg633His in the gene MYH7 and p.Tyr18GInfsX194 in the gene CRSP3. (63) While probands holding both mutations (index person and his brother) exhibited a more severe phenotype and clinical manifestation, with an echocardiographically determined maximal LVWT of 25 mm and 21 mm, respectively, as well as a present New York Heart Association [NYHA] functional class of II-III and III, respectively (63), relatives subject to only one of aforementioned mutations were found with a maximal septal hypertrophy of 14 mm and 17 mm, respectively and either asymptomatic or presenting palpitations (MYH7 mutation carriers) as well as a maximal wall thickness of 12 mm and asymptomatic (CSRP3 mutations carrier). (63) Of note, the index person's daughter (19 years old), subject to either mutations, presented asymptomatic and a LVWT of 8 mm. (63) This might be explained on account of the disease's reduced age-related penetrance.

According to Van Driest et al., study participants subject to the condition of Hypertrophic Cardiomyopathy caused by multiple sarcomeric mutations, including compound heterozygosity, were found as having the most elevated degree in hypertrophy, determined with a mean of 25.2 ± 12 mm, with 20% presenting a LVWT of ≥30 mm, in comparison to inter alia collectives with thick filament mutations or thin filament mutations, with a hypertrophy of at mean 23.5 ± 7 mm and 21.5 ± 4 mm, respectively and a LVWT of ≥30 mm in 14.8% of individuals and no cases, respectively (Analysis of Variance *p* value of 0.01). (55) Nevertheless, no statistical significant differences were determined with regard to gradients of the left ventricular outflow tract [LVOT]. (55)

Ingles et al. denote compound mutation carriers (affected gene constituted MYBPC3) to had presented, in comparison to individuals subject to only one mutation, a statistically significant more increased LVWT, with 30.7 ± 3.1 mm and 24.4 ± 7.4 mm (*p* value of <0.05), respectively. (64)

3.1.8.2 Modifier Genes

Individuals detected with a mutation in the Arg403 codon in reference to the gene of MYH7 holding different genotypes of the Angiotensin I Converting Enzyme were found with various extents in the thickness of the interventricular septum. (65) Mutation affected persons presenting an Angiotensin I Converting Enzyme genotype of DD, ID, and II were determined with a septal thickness of 19.3 ± 2.7 mm, 13.4 ± 1.3 mm, and 11 ± 0.9 mm (*p* value of 0.017), respectively. (65)

In persons subject to Hypertrophic Cardiomyopathy with mutations in the gene MYBPC3, the Angiotensin I Converting Enzyme genotype DD demonstrated in comparison to the genotypes DI and II to hold an increased LVWT, with 25.8 ± 5 mm, 21.8 ± 4 mm, and 20.8 ± 5 mm (*p* value of 0.01), respectively. (66)

Furthermore, carriers of the A allele (found in 25% as compared to the G allele) of the gene END1, encoding for Preproendothelin, were identified to hold, in comparison to individuals in absence of the A allele, an elevated median Left Ventricular Hypertrophy Score, with 7.0 and 5.0 (*p* value of 0.034), respectively. (67)

Individuals holding the AA genotype of the gene TNF-α (encoding for the protein Tumor Necrosis Factor-α), even though demonstrating an age of approximately 13 years younger than study participants with other genotypes related to aforementioned gene, were found, in comparison to the genotypes GG and GA, to present an elevated mean Left Ventricular Mass Index, with 191.8 ± 59.5 g/m², 139.1 ± 47.3 g/m², and 132.1 ± 34.3 g/m² (*p* value of 0.004), respectively. (68)

According to Maron et al. the proportion of 56.4% of echocardiographically examined children, with a family history or the evidence of Hypertrophic Cardiomyopathy, exhibited within a mean follow-up time period of 4 years (2.5-6.8 years) an increase in preexisting or the initial formation of left ventricular hypertrophy noted with a LVWT from 6 to 23 mm, constituting an increase of 101% ± 62% in comparison to the physiologic ordinary process of growth with 13% ± 10% (*p* value of <0.001). (69) Possibility of aforementioned findings to coincide with the natural increased serum concentrations of Insulin-Like Growth Factor 1 during the time period of adolescence (70), is existent. Additionally, Marian proposes in individuals with Hypertrophic Cardiomyopathy an upregulation of inter alia Insulin-Like Growth Factor 1 concentration in consequence of an elevated cell stress within the condition. (3, 71)

3.1.8.3 Epigenetics

According to Egger et al., Epigenetics denotes “all meiotically and mitotically heritable changes in gene expression that are not coded in the DNA sequence itself” (72). (72)

Generally, primary mechanisms exerting an epigenetic modulation are represented by Methylation of CpG islands, the alteration of histone proteins, and the intervention of microRNAs. (46) In result of aforementioned processes, surrounding conditions hold an influence on the expression of similar existing information. (46) The activation or silencing of genes constitute the subsequent consequence. (46)

Ucar et al. identified 26 microRNAs expressed by rat cardiomyocytes with a hypertrophy associated effect, detected by a cardiomyocyte size increase of >20%. (73) The overexpression of microRNA 122 held the result of most hypertrophy. (73)

3.1.8.4 Environmental Factors

The phenotypic expression proceeding from sarcomeric genes is denoted to be possibly influenced by physical activity, dietary aspects, the presence of comorbidities, as well as loading conditions resulting from within Hypertension and Valvular Heart Disease. (46)

According to Olivotto et al., multivariate analysis determined a BMI of 25-30 kg/m² and >30 kg/m² to hold an independent relationship to a left ventricular mass of >120 g/m² in comparison to individuals exhibiting an ordinary corporal weight, with a hazard ratio of 1.65 (95% CI: 0.73-3.74, *p* value of 0.22) and 3.1 (95% CI: 1.42-6.86, *p* value of 0.004), respectively. (74)

Nevertheless, individuals in absence of clinically evident cardiovascular conditions are reported to present a left ventricular hypertrophy as well as an enlargement of the left ventricular cavity. (74, 75) It is questionable if hypertrophy as a result of Obesity might represent inter alia a consequence mediated by the same hemodynamic and neurohormonal interventions encountered in the general population who exhibits cardiac hypertrophy as a secondary development. (74) Conversely, in principal, the possibility of Obesity to hold a direct influence on Hypertrophic Cardiomyopathy as a genetic modifier cannot be discarded. (74) Yet, the latter is regarded as conveying a considerably reduced probability. (74)

Additionally, the condition of Hypertension was demonstrated to hold with regard to the left ventricular mass of >120 g/m² a hazard ratio of 2.2 (95% CI: 1.1-4.5, *p* value of 0.026). (74) Nevertheless, akin to Obesity, Hypertension as well presents per se an association with left ventricular hypertrophy, regardless of the ailment of Hypertrophic Cardiomyopathy. (76–78)

3.2 Pathomorphological Implications

3.2.1 Macroscopic

Macroscopically, the condition of Hypertrophic Cardiomyopathy presents with cardiac hypertrophy regarded as affecting principally the left ventricle. (79) Nevertheless, involvement of the right ventricle, as a biventricular condition (80), or the isolated occurrence of right ventricular hypertrophy (81), is existent. Left ventricular hypertrophy in principal finds possibility of a subdivision into an asymmetric or concentric involvement. (79) Additionally,

further possible partition by hypertrophic patterns include the Apical (76, 82) and the Midventricular Form (76, 83). The left ventricular cavity dimension characteristically presents diminished, yet as well with the possibility of a dilatation subsequent to an extended period of Heart Failure. (84)

Furthermore, within inclusion of the papillary muscles, their structure has inter alia been denoted as holding an enlargement with rounded ends. (84) In comparison to ordinary control study participants, individuals subject to Hypertrophic Cardiomyopathy presented an elevated mitral valve leaflets area, with 8.7 ± 2 cm² and 12.9 ± 3.7 cm² (p value of <0.001), respectively. (85) Furthermore, aforementioned area increase in persons subject to the disease was substantially effectuated by the elongation of the anterior mitral valve leaflet, with 2.2 ± 0.5 cm in persons with Hypertrophic Cardiomyopathy and 1.8 ± 0.3 in ordinary study participants (p value of <0.001). (85)

Concurrent dislocation of the papillary muscles and the mitral valve leaflets towards the anterior has been denoted. (86) Additionally, the mitral valve leaflets have been mentioned with a coaptation ensuing rather at the corpora than their tips. (86) In consequence of the repeated collision

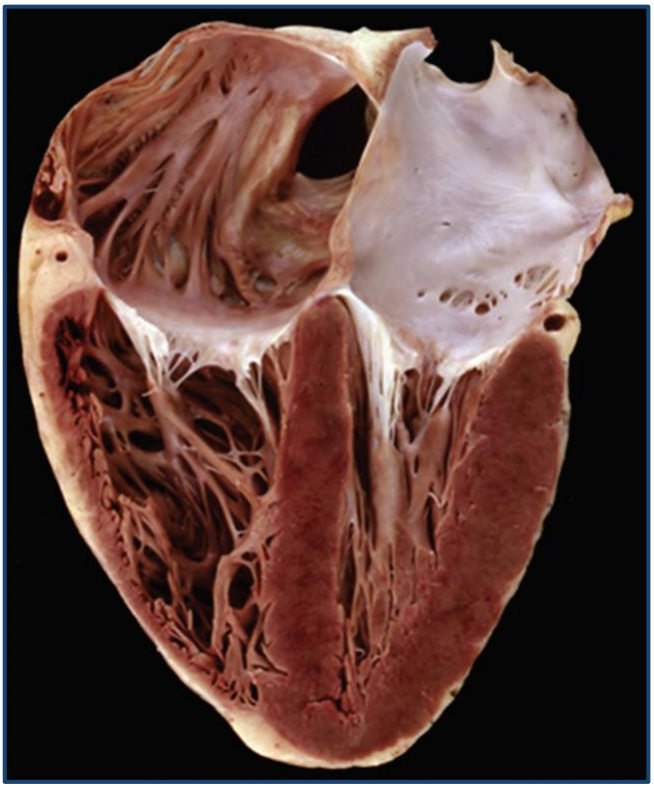

Figure 4: Findings of an ordinary heart at post mortem. (76) Image modified from (76).

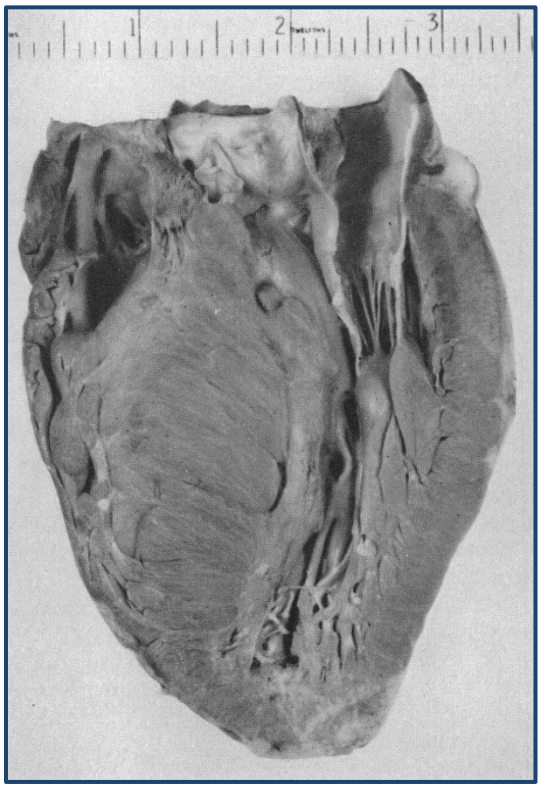

Figure 5: Heart of a 14-year-old boy presenting Hypertrophic Cardiomyopathy with the asymmetric morphologic variant. (10) Direct attention to the increased extent of the interventricular septum. (10) Image modified from (10).

of the mitral valve's anterior leaflet and chordae tendineae with the septum, occurring subjacent to the aortic valve, the affected location exhibits the formation of an endocardial fibrosis. (86) Further structural abnormalities within Hypertrophic Cardiomyopathy include the direct insertion of one or both papillary muscles of the left ventricle into the anterior leaflet of the mitral valve (12.8%) (87) and myocardial clefts (10).

Figure 6: Transverse section of either cardiac ventricles of an individual subject to Hypertrophic Cardiomyopathy. (86) Direct attention to the hypertrophy affected interventricular septum and left ventricular free wall (86) as well as the diminution of the left ventricle's cavity. Image modified from (86).

3.2.2 Microscopic

The ordinary dimension of a single cardiac myocyte constitutes a diameter of 10-15 µm and a length noted with up to 100 µm. (86) Cardiac myocytes in persons subject to Hypertrophic Cardiomyopathy principally present hypertrophied. (88) The most elevated in significantly differing measurements with regard to the diameters of single cardiac myocytes between control subjects and individuals exhibiting the condition were determined in reference to the intraventricular septum, left ventricular free wall, and right ventricular free wall with 16.3 ± 2 µm and 20.5 ± 3 µm, 15 ± 2 µm and 16.8 ± 2.1 µm, as well as 21.1 ± 3.7 µm and 16.9 ± 1.2 µm (each with a p value of <0.05), respectively. (88)

Another feature encountered in Hypertrophic Cardiomyopathy constitutes the disarray of myocytes. (89) Cardiomyocytes have been described as deformed and arranged surrounding a focus of connective tissue. (89) Additionally, disorder is reported as well with regard to extensive bundles of myocytes resulting in a nominally "herring-bone" (89) pattern. (89) Histologic classification of cardiomyocyte disarray has been undertaken (90, 91), including Type I-A (perpendicular or oblique arrangement of cardiac myocytes), Type I-B (perpendicular or oblique organization of cell bundles), Type II-A (lengthwise cut cell bundles with the intersection of transversely arranged cell bundles), and Type II-B (in comparison to Type II-A presence of an elevated linearity among cell bundles). (90, 91)

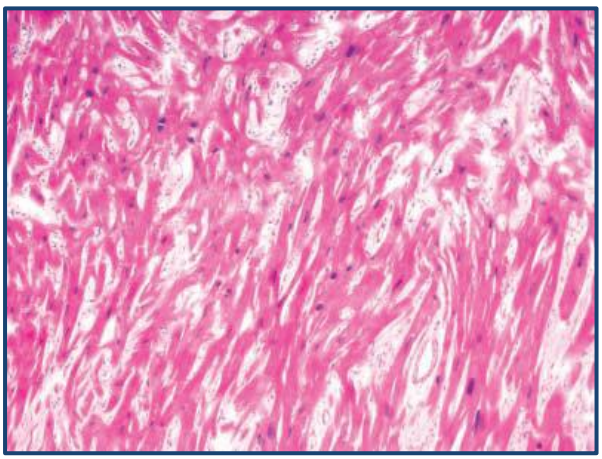

Figure 7: Myocyte disarray with myocytes exhibiting an arrangement perpendicular or oblique to each other surrounding a focus of connective tissue. (86) Image modified from (86).

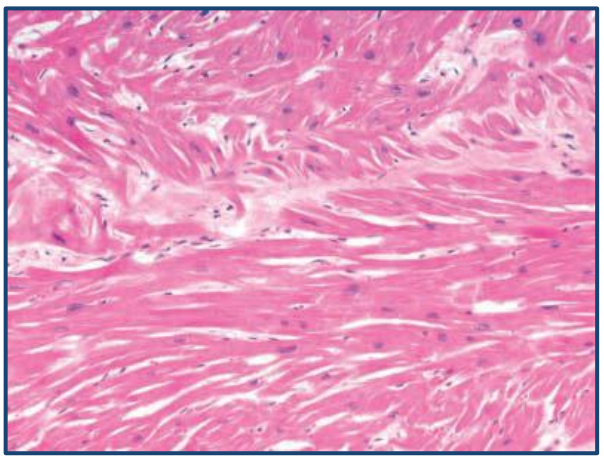

Figure 8: Myocyte disarray demonstrating a "herring-bone" (86) pattern. (86) Image modified from (86).

Furthermore, Hypertrophic Cardiomyopathy has been described with intramyocardial coronary arteries presenting the alterations of thickened walls and constricted blood vessel lumens (92), nominally designated as "Small Vessel Disease" (86). Additionally, presence of fibrotic tissue is elevated within context of the ailment. (86)

3.2.3 Electron-Microscopic

In assistance of Electron-Microscopy, myofibrils exhibit a varying density while being described as short and uncommonly thin. (93) Disorganization is mentioned as well with regard to the myofibril structure. (93) Furthermore, broadening of Z-lines is present frequently, while

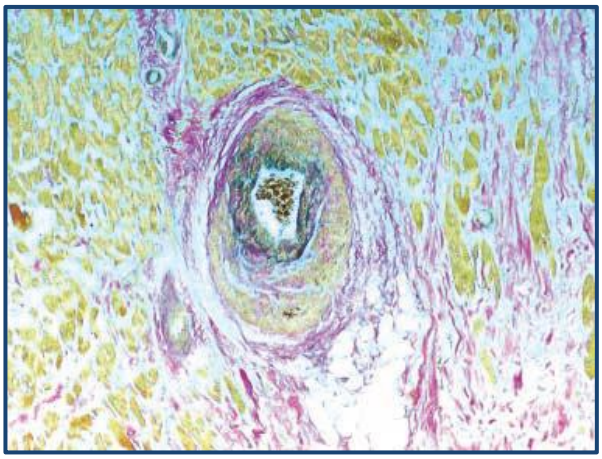

Figure 9: Intramural artery exhibiting hypertrophy of the media and narrowing of the vessel lumen. (86) Image from (86).

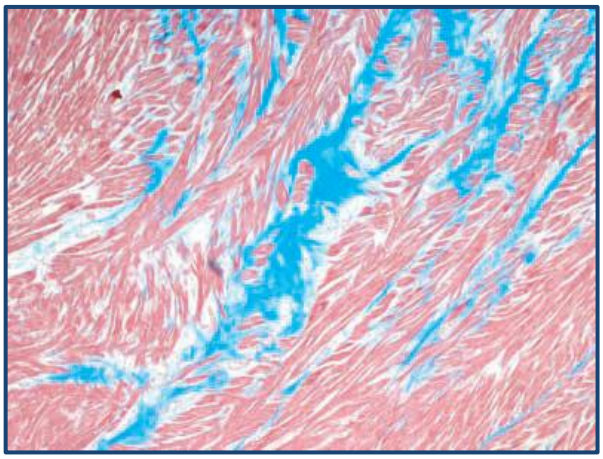

Figure 10: Increase of interstitial fibrosis. (86) Affected regions presenting blue. (86) Image from (86).

the amount of mitochondria is denoted as increased. (93) Partially, nuclei demonstrate a deformity and muscle fibers are found with unordinary ramifications. (93)

Hypertrophic Cardiomyopathy is denoted to present no microscopically as well as electron-miscroscopically determinable difference in reference to the obstructive or nonobstructive form. (93)

3.3 Clinical Presentation

The preponderance of individuals subject to Hypertrophic Cardiomyopathy present asymptomatic. (17) The possibility of a symptomatic manifestation at an early age or after the life time of decades, is existent. (94) Furthermore, development of symptoms might take place years after an electrocardiographically or echocardiographically detectable presence of left ventricular hypertrophy. (17) The most frequently encountered symptoms are inter alia represented by intolerance to exertional physical activity, Angina, Dyspnea, Dizziness, and Syncopes. (94) Further manifestations include Fatigue and Palpitations. (17) Symptoms are denoted with the possibility of a daily variation as well as an exacerbation within circumstance of weather presenting with increased temperature and humidity, the concomitant presence of anemia, or fever. (3) Furthermore, temporary aggravation of symptoms may as well result subsequent to the intake of abundant meals and consumption of alcohol. (3)

3.4 Physical Examination

3.4.1 Carotid Pulse

The carotid pulsation is regarded as most frequently presenting brisk, denoting a “spike-and-dome” (3) appearance. The percussion wave holds an accelerated ascending amplitude, exhibiting a drop in concurrence with mid-systole with the ensuing tidal wave. (3) The pathomorphologic entity corresponding with aforementioned temporary pulsatile decline during mid-systole represents Systolic Anterior Motion [SAM] of the mitral valve complex. (3)

3.4.2 Jugular Pulse

With the exception of a contingently eminent *a* wave, the jugular pressure presents for the most frequent extent ordinary. (3) The abnormal deviation may be the result of right ventricular hypertrophy, pulmonary hypertension, or the presence of a RVOTO. (3)

3.4.3 Apical Impulse

Most frequently, the apical impulse exhibits a constant thrust in concurrence with most of the phase of systole. (3) Furthermore, in consequence of an energetic systole of the atrium, aforementioned process may present bifid or in case of an obstruction comprise three impulses. (3) Additionally, systolic thrill may be existent in context of Mitral Valve Regurgitation at the cardiac apex and as a consequence of obstruction at the left inferior sternal region. (3)

3.4.4 Cardiac Auscultation

The first heart sound is denoted to present as either ordinary or loud, while the second heart sound demonstrates a physiological split. (3) Nevertheless, a paradoxical split may be encountered within context of a Left Bundle Branch Block or LVOTO. (3) Additionally, the condition is mentioned with the existence of a fourth heart sound. (3) This is the case in particular with regard to hypertrophy of severe extent. (3)

The entity of LVOTO usually demonstrates a crescendo-decrescendo murmur. (3) It is mainly encountered at the region of the left sternum and ceases prior to the second heart sound. (3) Furthermore, its radiation is found both, at the cardiac base and apex. (3) Yet, radiation to the carotid arteries is usually not existent. (3)

Within context of Mitral Valve Regurgitation, presence of an additional murmur is possible. (3) It is denoted to exhibit a rather holosystolic sound and to be located at the cardiac apex. (3)

3.5 Diagnostic Aspects

3.5.1 Electrocardiography

An abnormal Electrocardiogram [ECG] is encountered in the extent of 91.8-96.9% (95–98) of individuals subject to Hypertrophic Cardiomyopathy, with 84.8% of the nonobstructive and 98.5% of the obstructive form (95). The most prevalent ECG abnormalities constitute ST-T alterations, present in 81.8% of persons demonstrating the condition, with a ST-segment depression and T-wave inversion found in 66.4% and 50.2% of individuals, respectively. (97) While a positive Romhilt-Estes score is encountered in 63.7% of persons (95), the amount of 36.4% of individuals (97) present a positive Sokolow-Lyon Index. A left axis deviation and Q-waves abnormalities are found in 12.1% (97) and 32.8-34.8% (95, 97) of persons, respectively. Paroxysmal Atrial Fibrillation [AF] is present in 17.6% of individuals with an abnormal ECG

(96), while a Complete Left Bundle Branch Block and Complete Right Bundle Branch Block are encountered in 4.5% and 6.5% of persons with Hypertrophic Cardiomyopathy (97).

In comparison to patients presenting Hypertrophic Cardiomyopathy with a normal ECG, individuals subject to the condition found with an abnormal ECG demonstrated a more elevated pressure gradient within resting conditions (29.1 ± 33 mm Hg compared to 42.4 ± 43 mm Hg, with a *p* value of <0.001) and septal wall thickness (17.3 ± 4 mm compared to 19.8 ± 6 mm, with a *p* value of <0.001). (96)

Of note, the proportion of individuals exhibiting Hypertension was found to be increased within the collective of persons with Hypertrophic Cardiomyopathy demonstrating a normal ECG, with 48.9% and 31.5% (*p* value of <0.001), respectively. (96)

3.5.2 Chest X-Ray

Within the diagnostic modality of Chest X-Ray, generally, the cardiac contour presents with an up to moderate aggrandizement. (3) While the left ventricular shape is denoted to be found with a rounding, the left atrium demonstrates an expansion. (3) The right ventricle as well as atrium most frequently are detected with common dimensions. (3)

3.5.3 Echocardiography

Two-Dimensional Echocardiography is regarded as the most accessible investigative method with regard to diagnosing Hypertrophic Cardiomyopathy. (25) In consequence of the possibility of hypertrophic tissue to occur at any ventricular region, the echocardiographic examination should include a cross-sectional imaging with multiple viewings. (17) Attention should be directed to the presence, distribution and magnitude of hypertrophy. (17)

In reference to diagnosis performing of Hypertrophic Cardiomyopathy, maximal LVWT represents the most important parameter (17), with the end of diastole constituting the moment of measurement to be effectuated. (17) Alignment to orthogonal planes ensures overestimation of thickness to be excluded, while a short-axis view serves as the projection of choice. (17)

Of note, the parameter of Ejection Fraction [EF] in Hypertrophic Cardiomyopathy frequently presents preserved or even supernormal. (3, 99) In contrast, the examination of the mitral annular motion in assistance of Doppler Tissue Imaging is most frequently encountered to be unordinary. (3)

A further echocardiographically detectable entity represents LVOTO. (17)

Additionally, in case of nonsuccess of examining a ventricular segment appropriately, the possibility of a contrast agent application, is existent. (17)

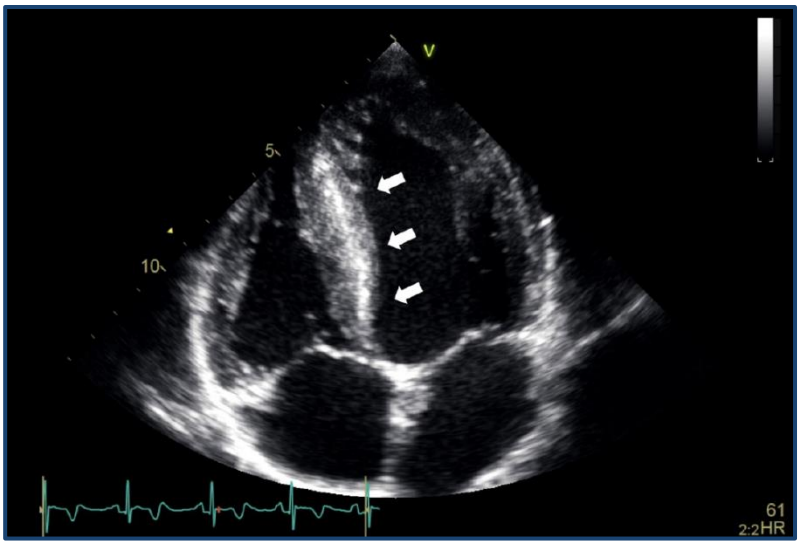

Figure 11: Echocardiographic image of the heart of a 20-year-old male athlete demonstrating Hypertrophic Cardiomyopathy holding a positive mutational subjacency with regard to the sarcomere. (100) Direct attention to the hypertrophy affected basal, medial and apical regions of the interventricular septum (designated by white arrows). (100) Furthermore, the cardiac atria present enlarged, while the left ventricular chamber demonstrates no aggrandizement. (100) Image modified from (100).

Echocardiographic examination revealed individuals subject to Hypertrophic Cardiomyopathy to present a mean transverse left atrial dimension of 43 ± 9 mm. (101) In comparison to individuals found in NYHA functional class I and II, patients presenting a functional class of III and IV, were identified holding an increased dimension, with 42 ± 9 mm and 48 ± 9 mm (p value of <0.001), respectively. (101) In assistance of univariate analysis, every 5 mm increase in left atrial dimension was determined to hold a risk for decease from any causality with a hazard ratio of 1.2 (p value of <0.0001). (101)

3.5.4 Transesophageal Echocardiography

Transesophageal Echocardiography constitutes an alternative or additional imaging modality to Cardiac MRI within context of limited diagnostic opportunity by means of transthoracic Echocardiography. (17) It is considered beneficial inter alia with regard to the examination of the mitral valve complex in patients holding a not ascertained causality of LVOTO as well as a perioperative assisting method within Ventricular Septal Myectomy. (17)

3.5.5 Cardiac Magnetic Resonance Imaging

In comparison to a common assessment in assistance of Two-Dimensional Echocardiography, Cardiac MRI constitutes a superior diagnostic modality. (17) Aforementioned includes the identification of apical as well as anterolateral hypertrophy of the left ventricle, the presence of

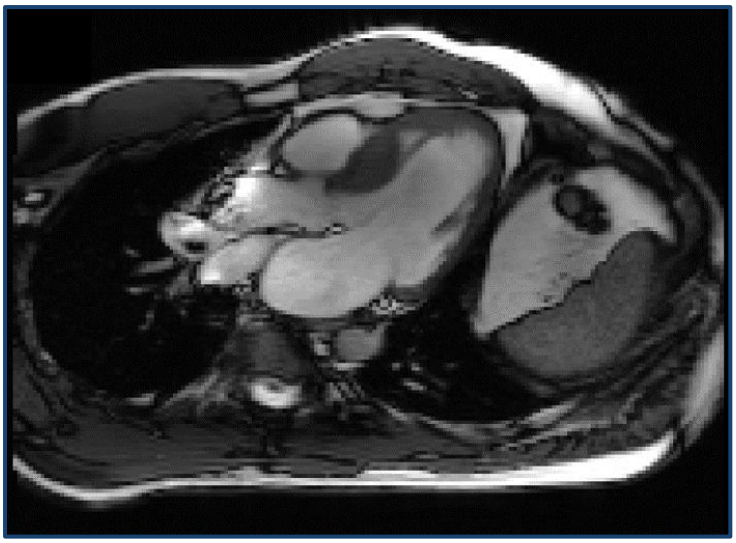

Figure 12: Three-Chamber View of the heart in assistance of Steady-State Free Precession Cine MRI. (102) The heart is visualized at the center of the image. (102) Image modified from (102).

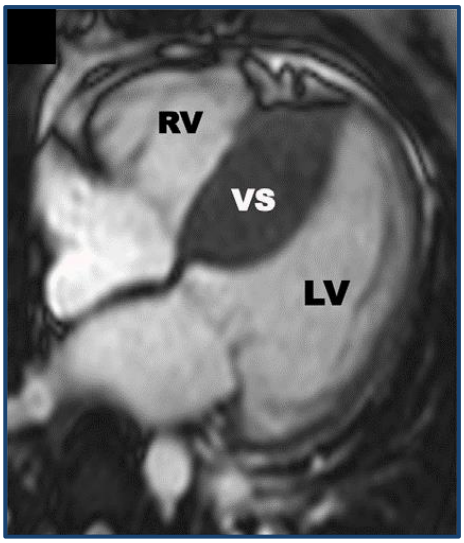

Figure 13: Heart via MRI exhibiting the asymmetric phenotypic expression of Hypertrophic Cardiomyopathy. (41) Direct attention to the hypertrophic interventricular septum. (41) The abbreviations RV, VS, and LV designate Right Ventricle, Ventricular Septum, and Left Ventricle, respectively. (41) Image modified from (41).

aneurysms, thrombi, myocardial crypts, as well as unordinary formations of papillary muscles. (17) Even though considering the relatively small study population of 48 patients, Rickers et al. demonstrated 6.3% of individuals, previously examined in assistance of Echocardiography, to be diagnosed with Hypertrophic Cardiomyopathy subsequent to an additional assessment via MRI, denoting a LVWT in the anterolateral free wall region of 17-20 mm. (103)

According to Chan et al., the incidence of SCD per 1000 person-years was directly related to the existent proportion of LGE, with 4 incidents in absence of LGE (95% CI: 2-8), 10 in context of ≤10% of LGE (95% CI: 6-18), 18 with 11-19% of LGE (95% CI: 7-39), as well as 24 in case of ≥20% of LGE (95% CI: 9-51) (*p* value of 0.001 with regard to the trend). (104)

3.5.6 Nuclear Imaging

Nuclear imaging modalities assist in the assessment of myocardial perfusion in patients with Hypertrophic Cardiomyopathy. (17) The utilization of Single-Photon Emission Tomography with ^{99m}Tc and ^{201}Tl tracers contingently identifies persistent as well as reversible perfusion impairments. (99) This can be effectuated even in absence of epicardial Cardiovascular Disease. (99) Furthermore, Positron Emission Tomography, applying the tracers of ^{13}N ammonia and ^{15}O water enables the determination of myocardial blood flow specified as ml/min/gr. (99)

3.5.7 Cardiac Catheterization

With regard to cardiac function, utilization of Cardiac Catheterization has experienced a decline in favor of noninvasive imaging modalities. (17) Consideration of intracavitary pressure examination in assistance of Cardiac Catheterization is existent within context of noninvasive methods not reaching the required investigative elucidation. (17)

3.6 Pathofunctional Implications

3.6.1 Systolic Anterior Motion

In utilization of Echocardiography Shah et al. encountered in Hypertrophic Cardiomyopathy an abnormal motion of the mitral valve, demonstrating its incipience in concurrence with the initiation of ventricular ejection and its maximum simultaneously with the primary peak of arterial pulse. (106) A contact between leaflet and ventricular septum was existent in the extent of 60% of the ejection time. (106) Although once thought to represent a pathognomonic abnormality of obstructive Hypertrophic Cardiomyopathy (107), echocardiographic detection of SAM of the mitral valve complex was as well reported in patients in absence of hypertrophy, exhibiting a common outflow tract (108), as a result of hypovolemia and anemia (109), as well as in acute perioperative cases of Hypotension (110), demonstrating a presence of the feature outside of Hypertrophic Cardiomyopathy.

Of note, the average length of the anterior leaflet in Hypertrophic Cardiomyopathy is noted with 34 mm in comparison to 24 mm with regard to ordinary individuals (111), with coaptation ensuing rather at the corpora of the leaflets than their tips. (112) On the basis of a narrow LVOT (112, 5), in turn the result of hypertrophy of the ventricular septum as well as the anterior dislocation of collectively, the papillary muscles and mitral cusps (112), SAM is considered to eventuate in consequence of

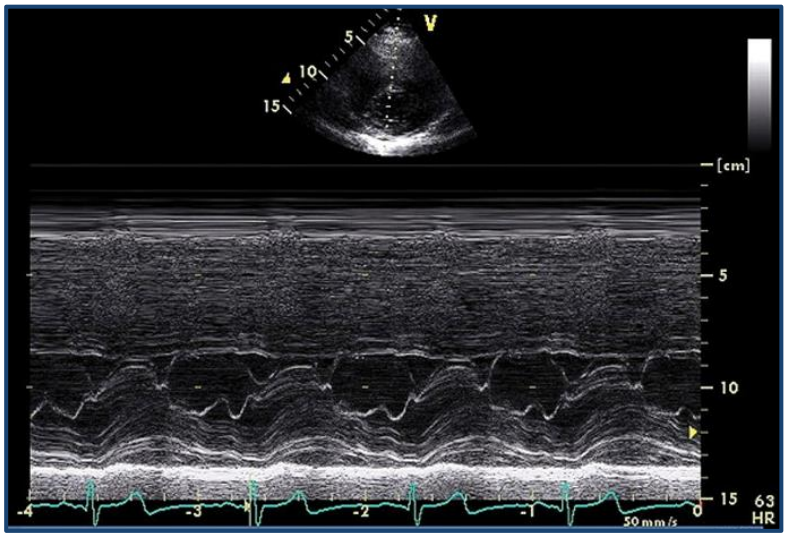

Figure 14: Entity of SAM of the mitral valve complex presented in assistance of M-Mode Echocardiography. (105) Image modified from (105).

Venturi and/or drag forces (112) effectuated on the region of the anterior mitral leaflet distal to coaptation (112).

In detail, SAM is eventuated in 58% of cases by the anterior as well as posterior mitral leaflets, with preponderant involvement of the anterior cusp. (113) The entity of SAM solely elicited by the posterior or anterior leaflet is present in 31% and 10% of cases, respectively. (113) The proportion of 1.6% of patients exhibit the manifestation primarily on basis of a chordae tendineae implication. (113)

3.6.2 Left Ventricular Outflow Tract Obstruction

In context of Hypertrophic Cardiomyopathy, presence of a LVOTO of ≥30 mm Hg within resting conditions is encountered in the proportion of 24.8-31.4% (114, 115) of individuals. (114, 115) Additionally, while the amount of 37.1% of patients subject to the condition demonstrate a LVOTO of ≥50 mm Hg at resting conditions, additional 23.6% of individuals are found with the same extent of gradient within exertional testing. (116) The entity of LVOTO is considered to be effectuated at least by means of the hypertrophy at the septal base and the occurrence of SAM of the mitral valve. (5)

In principal, a maximal pressure gradient of ≥30 mm Hg detected in assistance of Doppler technique within resting conditions or physical provocation for instance by means of Valsalva Maneuver, standing, or exertional activity is regarded as defining for LVOTO. (17) Nevertheless, a hemodynamic relevance in reference to the disease is acquired at the

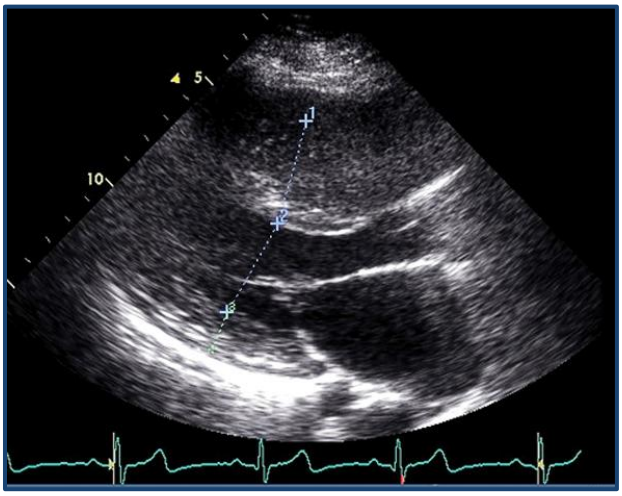

Figure 15: Two-Dimensional Echocardiographic image of Hypertrophic Cardiomyopathy presenting with obstruction. (105) Image modified from (105).

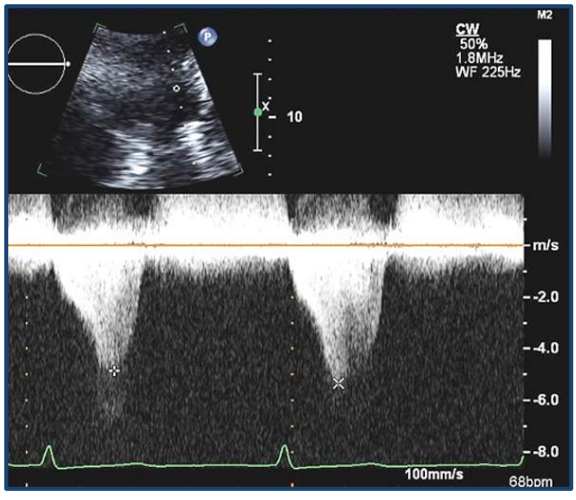

Figure 16: Utilization of the Continuous-Wave Doppler technique in order to attain an estimation of the obstruction encountered in Hypertrophic Cardiomyopathy. (105) Image modified from (105).

threshold of ≥50 mm Hg. (17) The gradient may be subject to alteration over the course of time with its elevation or general appearance as well as its diminution or cessation. (117) While 33.3% of patients exhibit a constant continuity of clinical expression, 66.6% of individuals experience conditional exacerbation. (117)

The presence of LVOTO was found reduced in patients subject to thin filament mutations in comparison to persons with thick filament mutations, with 19% and 34%, respectively. (118)

3.6.3 Mitral Valve Regurgitation

Despite of all individuals presenting coaptation of the mitral leaflets within the initial phase of systole (119), in 56.3% of patients with obstructive Hypertrophic Cardiomyopathy coaptation in mid-systole is absent. (119) The aforementioned represents the consequence of SAM of the anterior mitral cusp, resulting in a regurgitant jet at the mitral valve detected in assistance of Transesophageal Echocardiography. (119) While 28.1% of patients present mild Mitral Valve Regurgitation, a moderate or severe extent of the entity is encountered in 38.5%, each. (120)

3.6.4 Systolic Dysfunction

Impairment in the coronary vasodilator reserve together with myocardial ischemia with an ensuing decay of cardiac muscle cells and a resulting process of replacement firbrosis have been proposed as factors leading to a left ventricular cavity enlargement with a concomitant wall thinning. (121) Collectively, aforementioned measures are suggested to contribute to a process of left ventricular remodeling leading to the progressive formation of systolic dysfunction and the end result of Heart Failure. (121)

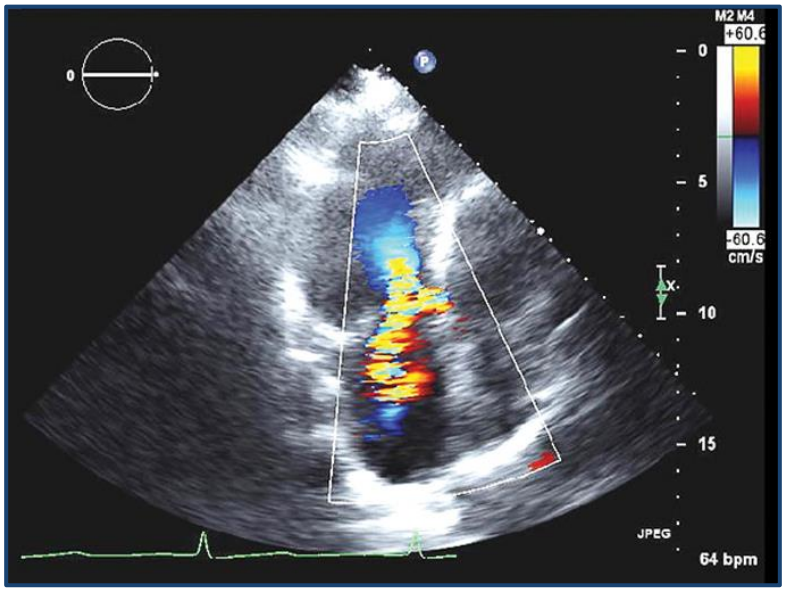

Figure 17: Turbulent flow in the outflow tract with a jet directed posteriorly within context of Mitral Regurgiation and SAM. (105) The utilized technique constitutes Echocardiographic Color Flow Imaging. (105) Image modified from (105).

3.6.5 Diastolic Dysfunction

In individuals subject to Hypertrophic Cardiomyopathy a deterioration of the left ventricle in reference to its relaxation, filling, and

compliance is existent. (122) The amount of 82% of persons presenting the condition were found with an affected left ventricular diastolic function. (122)

In comparison to control study participants, patients with Hypertrophic Cardiomyopathy presented a prolongation of both, isovolumic relaxation and early diastolic peak flow velocity, with 78 ± 12 compared to 94 ± 24 ms and 220 ± 28 compared to 244 ± 55 ms (*p* value of <0.001), respectively. (122) Furthermore, individuals subject to the condition were identified with a diminution in deceleration and maximal flow velocity in the early phase of diastole, with 3.4 ± 1.4 compared to 4.9 ± 1.3 m/s² as well as 0.5 ± 0.2 compared to 0.6 ± 0.1 m/s (*p* value of <0.001), respectively. (122)

3.7 Complicative Aspects

3.7.1 Atrial Fibrillation

The entity of AF is regarded as a sequela in patients with Hypertrophic Cardiomyopathy (123) presenting a prevalence of 22.5% (95% CI: 20.1-24.8%) and an incidence of 3.1% (95% CI: 2.6-3.5%), with both including paroxysmal as well as permanent AF (124). While the proportion of 57.8% exhibit paroxysmal AF, persistent AF is found in 42.2% of individuals. (125)

Univariate analysis determined the female gender and NYHA functional class III or IV in patients with Hypertrophic Cardiomyopathy as predictors of AF with a hazard ratio of 1.27 (CI: 1.10-1.47) and 2.96 (CI: 2.37-3.69), respectively (125) while Cox regression analysis and Kaplan-Meier procedure revealed the left atrial dimension of ≥40 mm and an age of >45 to be predictive (126). Furthermore, AF is more prevalent in patients exhibiting a nonobstructive phenotype as well as in individuals with an EF of <50%. (123) Multivariate analysis detected AF as an independent predictor for Hypertrophic Cardiomyopathy related mortality with an odds ratio of 3.7, 95% CI: 1.7-8.1. (127)

Additionally, variation in the gene MYH7 represents in comparison to the variation in MBPC3 and with the inclusion of the variates age, probands, gender, diameter of the left atrium, peak LVOT pressure gradient within resting conditions, as well as maximal LVWT a significant predictor for the new-onset of AF with a hazard ratio of 1.7, 95% CI: 1.1-2.6. (128)

3.7.2 Infective Endocarditis

Although once considered to be preponderantly present in patients with LVOTO (129), the proportion of 44% of individuals with Hypertrophic Cardiomyopathy complicated by Infective Endocarditis was found in absence of LVOTO (130). Analyses of pathogens reveals a result resembling the one in the general population with Infective Endocarditis. (131) The amount of 80% of patients are affected by staphylococcal or streptococcal species (130), while the most involved valve is represented by the mitral valve in 53-71% (131, 130) of incidences. Patients with Infective Endocarditis present a concentric or asymmetric septal phenotypic expression in 38% and 29% of cases, respectively. (130) The cumulative probability of Infective Endocarditis formation in persons with the obstructive form within the time period of 10 years is 4.3%. (129)

According to the guidelines of The American Heart Association, the administration of antibiotics as a preventive measure finds in exclusion of material prohibiting endothelialization, no recommendation with regard to surgical procedures related to Hypertrophic Cardiomyopathy, nor within elevated life time risk of developing Infective Endocarditis as single causality. (132) The ESC recommends the prophylactic application of antibiotics in reference to a prior incidence of Infective Endocarditis as well as within involvement of prosthetic material to the extent of six months subsequent to the procedure. (133)

3.7.3 Heart Failure

Heart Failure represents aside of SCD one of the causalities of premature decease in patients with Hypertrophic Cardiomyopathy. (134) Delineation of End Stage Hypertrophic Cardiomyopathy exclusively by the factor of EF presenting <50% demonstrates 3.5% of individuals subject to Hypertrophic Cardiomyopathy to be situated within this circumstance. (135) Additionally, the amount of 4.9% of patients progress to an end-stage form of Hypertrophic Cardiomyopathy, including the determinants of an EF of <50% as well as hypokinesia and the dilation of the left ventricular cavity. (136) Harris et al. denote the time lapse between the onset of Hypertrophic Cardiomyopathy related symptoms and the determination of the condition's end-stage to had been 14 ± 10 years. (135) Additionally, the proportion of 45% of patients with End Stage Hypertrophic Cardiomyopathy were found at the age of ≤40 years. (135)

Heart Failure is the consequence of Systolic Dysfunction in 30% of cases, while in 22% of patients the subjacent cause is found in LVOTO. (137) The amount of 48% of patients present Heart Failure in context of no obstruction and preserved EF. (137) Contribution to Heart Failure

formation within aforementioned groups is found by AF in 64%. (137) One causality of ventricular enlargement as well as the eventual condition of Heart Failure represents transmural infarction. (138)

The proportion of 17% of individuals with Hypertrophic Cardiomyopathy develop NYHA functional class III or IV. (137)

3.7.4 Sudden Cardiac Death

The incident of SCD is defined as an occurrence in nature unexpected as well as not in consequence of a traumatic experience manifesting within less than one hour subsequent to the incipience of symptoms. (139) Absence of severe symptoms prior to the event is regarded as precondition. (139)

The rate of SCD in patients with Hypertrophic Cardiomyopathy per year amounts to 1%. (140) The predominant mediating condition for the event is ascribed to Ventricular Fibrillation. (141) In turn, the disarray of myocytes as well as the process of fibrosis possibly represent the basis of variant pathways of cardiac conduction, suspected to hold partial responsibility for the precipitation of Reentry and Ventricular Fibrillation. (142) Additionally, the sensitization of myofilaments to Ca^{2+} in mutant mice models revealed a susceptibility to Ventricular Arrhythmia. (143)

In one publication, the incident of a “sudden and unexpected” (144) decease was found with increased occurrence among first degree relatives with Hypertrophic Cardiomyopathy. (144) In assistance of Cox multivariable proportional hazards regression family history with regard to SCD was determined as an independent predictor for the incident with a hazard ratio of 1.22 (95% CI: 1.08-1.34). (145) Furthermore, multivariate analysis identified family history of SCD as a predictor for the incident with a Relative Risk of 1.88 (95% CI: 1.0-3.5). (115)

Furthermore, the extent in LVWT correlates directly with the risk for SCD, with 0/1000 person-years (95% CI: 0-14.4/1000 person-years) in reference to a wall thickness of ≤15 mm and 18.2/1000 person-years (95% CI: 7.3-37.6/1000 person-years) for a wall thickness of ≥30 mm. (146) Multivariate analysis determined abnormal blood pressure response within exercise with a risk ratio of 1.8 (95% CI: 0.7-4.4). (147) Presence of Non-Sustained Ventricular Tachycardia [NSVT] resulted with regard to individuals at the age of ≤30 years in an odds ratio of 4.35 (95% CI: 1.54-12.28) for SCD and 2.16 (95% CI: 0.82-5.69) for persons at the age of >30 years. (148)

Certain mutations in the gene encoding for Troponin T while found to present with comparatively mild hypertrophy, hold an elevation in the incidence of SCD. (52)

3.8 Morphologic Forms

Despite of Hypertrophic Cardiomyopathy denoted to present with a characteristically asymmetric phenotypic manifestation of left ventricular hypertrophy (149) and the interventricular septum to be affected with varying severity (76), the condition is as well encountered holding different hypertrophic patterns (76).

The possibility of a subdivision into an asymmetric, concentric, apical, and midventricular form as well as a mass-like manifestation, right ventricular involvement and genotype positive phenotype negative situational condition, is existent. (76)

The ailment's hypertrophic expression acts as an enigmatic characteristic (150), as it holds a substantial interindividual variation with regard to its extent as well as distribution. (151) Principally, the deviation in structure and alignment of myofibrils from the ordinary occurrence finds consideration as a subjacent pathologic layer for the macroscopically observable hypertrophic phenotype. (89)

The substantial heterogeneity in clinical manifestation and disease course is regarded to had represented a restrain to the endeavor of an ailment's entire apprehension. (36) Contemporarily, genetic, epigenetic, as well as environmental factors at least find consideration of exerting an influence on the disease's morphology. (152)

3.8.1 Asymmetric Form

3.8.1.1 Historical Perspectives

In 1958, titled as "Asymmetrical Hypertrophy of the Heart in Young Adults" (10), Teare, a pathologist practicing at the St. George's Hospital (10) in London (5), published his findings with regard to eight individuals demonstrating an "asymmetrical hypertrophy or benign tumour of the heart" (10) in the British Heart Journal (10). Seven out of aforementioned eight individuals were noted the causality of decease to had constituted SCD. (10) Histopathologic examination inter alia disclosed a "[d]isordered arrangement of muscle bundles".

Cognizance of Liouville (7) as well as Hallopeau (8) to probably have described individuals subject to Asymmetric Septal Hypertrophy in the year of 1869, has been voiced. (153, 7, 8) In 1907, Schmincke reported in reference to two individuals found demonstrating left ventricular

hypertrophy at post mortem examinations. (153, 154) In 1952, Davies published his findings concerning a family with “cardiac enlargement” (155) in the adult members and “fibrosis of myocardium and subaortic stenosis” (155) at autopsy concerning a woman at the age of 38 years. (153, 155) In the year of 1957, Brock reported with regard to three cases demonstrating the presence of left ventricular hypertrophy either at post mortem examination or in assistance of Electrocardiography. (153, 9) Nevertheless, findings comprised within the publication were overall associated with Hypertension. (9)

Although possibility of inter alia aforementioned authors to have reported in reference to Asymmetric Septal Hypertrophy prior to Teare’s writings, Epstein et al. voice the consideration of Teare’s publication in the year of 1958 (10) to represent the ailment’s “first unequivocal description” (153). (153) According to Epstein et al., even though Brock’s publication eventuated in the 4th quarterly issue of Guy’s Hospital Reports in 1957 (9), in light of the consideration Brock’s operation (second mentioned case within the report, a 63 years aged woman) to have taken place subsequent to the receiving of Teare’s denotations by the journal’s office (British Heart Journal) in January the 7th, 1957 (10), conferring Teare the attribution of the condition’s primary anatomic characterization and Brock the first presentment in terms of its “functional nature” (153), presents as appropriate. (153)

In 1983, Emanuel et al. denoted inter alia isolated asymmetric septal hypertrophy to represent a constituent entity of the clinical spectrum of the condition Familial Hypertrophic Cardiomyopathy. (156)

3.8.1.2 Asymmetric Septal Hypertrophy

3.8.1.2.1 Definition

Asymmetric Septal Hypertrophy is defined by an interventricular septum demonstrating a thickness of ≥15 mm (77, 76, 157) or the presence of a septum to left ventricular posterior wall ratio of >1.5 (77, 76). Williams et al. note the ratios of >1.3 in normotensive individuals and >1.5 for patients subject to Hypertension. (157)

3.8.1.2.2 Epidemiology

The proportion of the variant of Asymmetric Septal Hypertrophy within the entirety of phenotypic expressions encountered in Hypertrophic Cardiomyopathy has been reported with the range of 44.7-90% (158–160, 79). The mean age of individuals presenting the form has been noted with 48.2 ± 14 years, while 70.6% of persons are represented by men. (159)

3.8.1.2.3 Medical History within the Family

The proportion of 4.4% of patients presenting Asymmetric Septal Hypertrophy are found with a family history of the condition of Hypertrophic Cardiomyopathy. (159) At least one incident of SCD within the family is reported by 8.8% of individuals subject to the morphologic variant. (159)

3.8.1.2.4 Genetic Aspects

The examination of the myofilament genes MYBPC3, MYH7, MYL2 (which encode for sarcomeric thick filament proteins), TNNT2, TNNI3, TPM1 (responsible for thin filament proteins), as well as MYL3 (encoding for the essential light chain), revealed mutations in genes encoding for thick filament proteins to result to the extent of 94% in an asymmetric phenotypic expression of Hypertrophic Cardiomyopathy with an involvement of the interventricular basal septum as well as anterior wall. (118)

3.8.1.2.5 Clinical Aspects

The extent of 24.4% of individuals subject to Asymmetric Septal Hypertrophy are reported to be asymptomatic. (159)

Additionally, Chest Pain is encountered in the proportion of 32.5-52.9% (159, 158) of patients with the morphologic form, while 37.5-47.1% (159, 158) of persons demonstrate Dyspnea. Presence of Palpitations is found in 9.4-39.5% (159, 158) of individuals with Asymmetric Septal Hypertrophy.

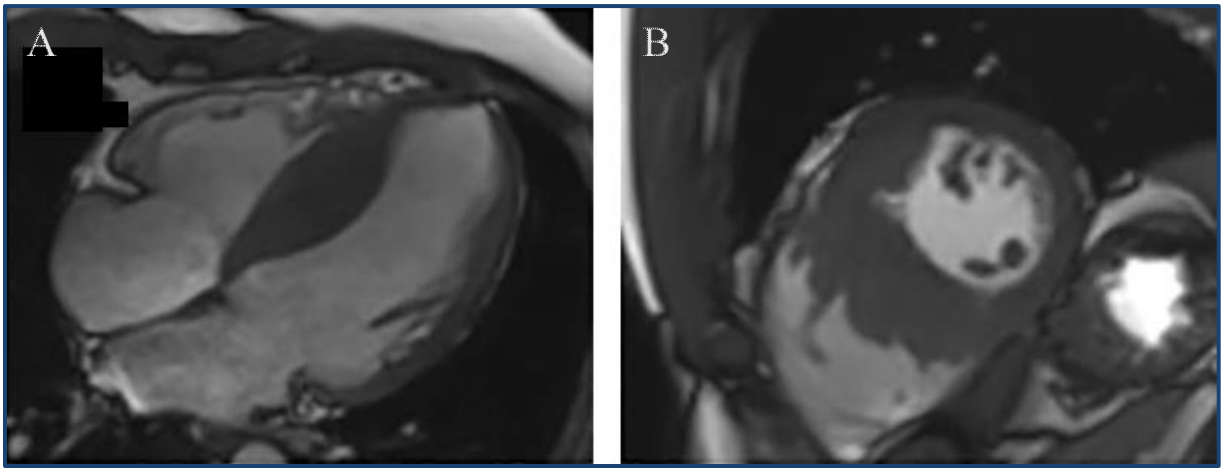

Figure 18: Heart of an individual via MRI with Hypertrophic Cardiomyopathy presenting the asymmetric morphologic form. (161) A: Four-Chamber View of the heart. (161) Direct attention to the hypertrophy affected interventricular septum. (161) B: Identical heart within Two-Chamber View. (161) Images modified from (161).

A NYHA functional class of ≥III at initial presentation is encountered in the amount of 17.1% of patients subject to the phenotypic expression. (159)

3.8.1.2.6 Diagnostic Aspects

The proportion of 41.2% of patients with Asymmetric Septal Hypertrophy demonstrate a heart murmur. (158)

Abnormal electrocardiographic findings are demonstrated by 58.8-90.6% (158, 159) of individuals, with 58.9% of persons holding a Rhomhilt-Estes Score of >5 points and 70.6% individuals being detected with ST wave alterations denoting left ventricular hypertrophy. (158) A QRS axis of ≥30° or a QRS duration of ≥90 msec is encountered in 47.1% and 59.9% of patients subject to Asymmetric Septal Hypertrophy, respectively, while 41.2% of individuals demonstrate the presence of a P wave terminal force. (158)

Examination in assistance of Two-Dimensional Echocardiography revealed 48% of persons to exhibit a hypertrophy involvement of the entire septum reaching from its base to the apex. (79) An involvement of hypertrophy confined to the one third of the septum at the basal region or two thirds of the septal base down towards the papillary muscles are found in 25% and 27% of cases, respectively. (79) According to Klues et al. the subdivision of the left ventricle into 16 possible patterns revealed 25% of persons with the variant to exhibit hypertrophy affecting the anterior portion of the septum, while hypertrophy in the posterior ventricular septum was encountered in as few as 1.3%. (149)

The extent of 33.8-57.1% (159, 160) of individuals with Asymmetric Septal Hypertrophy present SAM of the mitral valve. According to Shapiro and McKenna 57.1% of individuals with the entity, in comparison to a moderate form, are detected with a severe manifestation. (160) Midsystolic aortic valve closure is exhibited by 47.9% of persons. (160) Furthermore, hypertrophy of at least one papillary muscle is found in 95.9%, with 66% of the aforementioned demonstrating a severe degree compared to a moderate extent. (160)

Yang et al. note the mean in EF of individuals presenting Asymmetric Septal Hypertrophy with 64.4% ± 7.3%. (159)

According to Helmy et al., the entity of LVOTO in individuals presenting Asymmetric Septal Hypertrophy is encountered in 58.8%. (158)

3.8.1.2.7 Complicative Aspects and Prognosis

According to Yang et al., presence of AF at initial presentation was encountered in the proportion of 10% of persons subject to Asymmetric Septal Hypertrophy, while 5.6% demonstrated AF as a new-onset manifestation. (159) The conditions of Ventricular Tachycardia or Ventricular Fibrillation were displayed by 1.2%. (159)

Furthermore, Yang et al. note the proportion of individuals with Asymmetric Hypertrophic Cardiomyopathy developing Congestive Heart Failure with 1.2%. (159)

Within a follow-up time period of 32.0 ± 37.2 months, 25.5% of individuals with Asymmetric Septal Hypertrophy experienced an incidence of cardiovascular nature. (159) Furthermore, in assistance of the Kaplan-Meier procedure, the rate of event-free survival of cardiac causality for the time period of 5 years was determined with 72.0% ± 5.6%. (159)

3.8.1.2.8 Comorbidities

The amount of 19.4% of patients with Asymmetric Septal Hypertrophy present the condition of Hypertension. (159) Stroke as part of the patient's medical history is encountered in 1.3% of cases, while the incident was found in the proportion of 5% of individuals subsequent to their initial presentation. (159)

3.8.1.2.9 Aspects According to the Morphologic Form of the Septum

3.8.1.2.9.1 Asymmetric Sigmoid Form

The Asymmetric Sigmoid Form constitutes a distinct subtype of the ventricular septum's morphologic expression. (162) The left ventricular chamber presents ovoid, while the septum takes a concave shape holding an enlargement at its basal portion. (162) The phenotypic variant is present in 27.2% of elderly individuals at the age of ≥65 years with the condition of Hypertrophic Cardiomyopathy. (163) Classifying into a sigmoid, reverse, and neutral septal form as well as apical hypertrophy, reveals 38% of persons at the age of <50 years to be subject to the sigmoid septal variant, while the morphologic expression is found in the amount of 67% at the age of ≥50 years. (162)

Observation of patients presenting with an angle of down to 90° between the Ascending Aorta and the LVOT is existent. (164) Additional left ventricular hypertrophy might lead to an exacerbation of the condition. (164) While suggestion of a deflection of the aortic root as a consequence of hypertrophy is existent (164), it is rejected as an explanatory attempt for

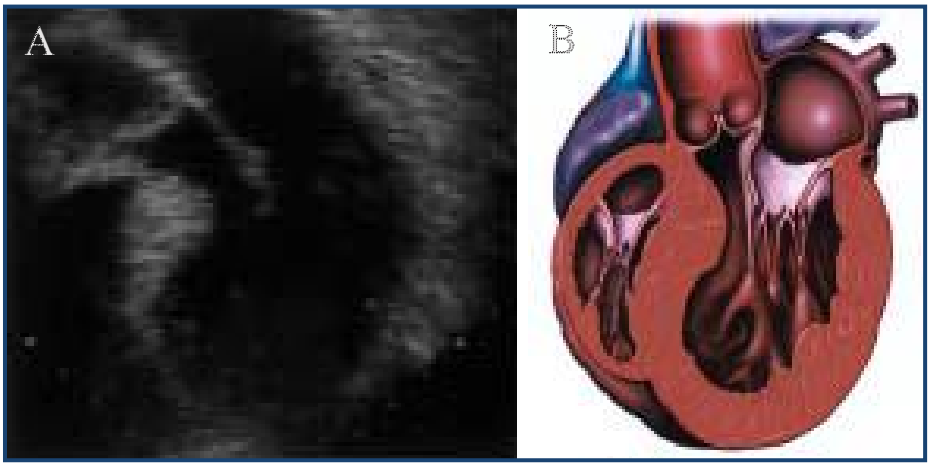

Figure 19: Asymmetric Sigmoid Form of Hypertrophic Cardiomyopathy. (162) A: Echocardiographic Long-Axis View at end diastole (162). B: Image depicting the morphologic subtype. (162) Images modified from (162).

subaortic stenosis (164). Generally, aortic structural alterations related to the process of aging are existent. (165) Yet correlation between the aortic angle and age as an exclusive eliciting factor is based on the condition's finding in individuals at the ages of 48 and 38 not evident. (164)

The reduction in angle leads to a concomitant diminution in left ventricular subaortic space. (164)

A mutation related to the condition of Hypertrophic Cardiomyopathy is found in 8.3-14% (162, 166) of patients with the sigmoid septal variant. (166) Mutation free individuals exhibit differences in clinical manifestation based on gender, with female patients conveying an increased amount of obstruction and Hypertension as well as elevated LVOT gradients at rest. (166)

The maximal LVWT among patients with Asymmetric Sigmoid Form presents with a mean of 19.5 ± 5 mm, while the mean gradient in reference to the LVOT within resting conditions is noted with 55.8 ± 41 mm Hg. (162)

A family history of Hypertrophic Cardiomyopathy or the incident of SCD are encountered in 21% and 9.9% of persons exhibiting the Asymmetric Sigmoid Form, respectively. (162)

Of note, in the extent of 91.7% of individuals with the form, detection of gene mutations was not existent. (162) Encountered mutations within the Asymmetric Sigmoid Form concern the genes MYBPC3 (5%), MYH7 (2.2%), TNNT2 (0.6%), and TNNI3 (0.6%). (162)

3.8.1.2.9.2 Reverse Septal Contour

The Reverse Septal Contour is defined as the ventricular septum demonstrating a convexity preeminently located at its middle portion while the left ventricular chamber is denoted to

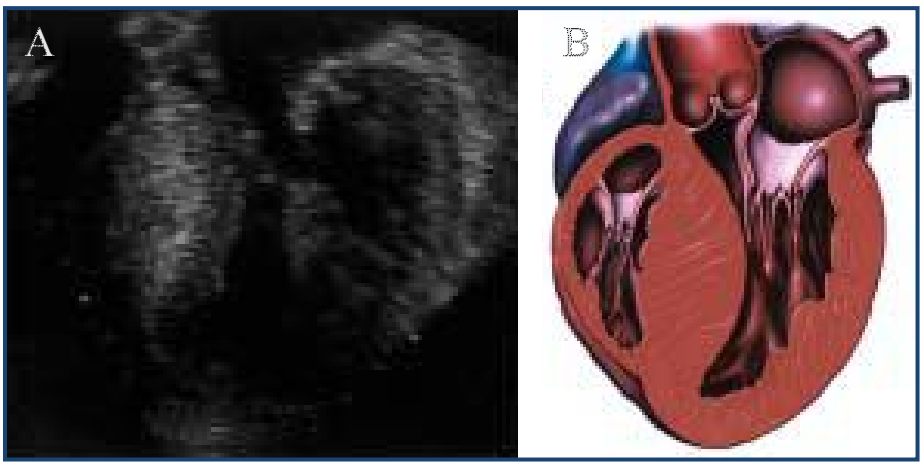

Figure 20: Reverse Septal Contour of Hypertrophic Cardiomyopathy. (162) A: Long-Axis View of the heart at end-diastole via Echocardiography. (162) B: Image of the phenotypic subtype. (162) Images modified from (162).

resemble a crescent. (162) Subdivision into a sigmoid, reverse, and neutral septal morphology as well as apical hypertrophy, exhibits 45% of individuals at the age of <50 years to present a Reverse Septal Contour, while the variant is encountered in 13% of person at the age of ≥50 years. (162) Furthermore, utilizing aforementioned partitioning 73% of individuals detected with a myofilament mutation present a Reverse Septal Contour morphology. (162)

Maximal LVWT in persons with Reverse Septal Contour is found with a mean of 24.5 ± 7 mm, while the mean gradient of the LVOT at resting conditions is noted with 44.0 ± 43.0 mm Hg. (162)

A family history of the condition of Hypertrophic Cardiomyopathy or the incident of SCD is encountered in 45.5% and 18.9%, respectively. (162)

Most identified mutations are found in reference to the genes MYBPC3 (34.1%) and MYH7 (28.8%). (162) Mutations in the genes MYL2, TNNT2, and TNNI3 are present in 3.8%, 3%, and 2.3%, respectively. (162) The amount of 5% of persons with Reverse Septal Contour present multiple mutations. (162)

3.8.1.2.9.3 Neutral Septal Form

The Neutral Septal Form presents a principally linear septal shape holding no eminent convex or concave curvature. (162) Partitioning into a sigmoid, reverse, and neutral septal morphologic form as well as apical hypertrophy, exhibits the Neutral Septal Form to be found in 9% of individuals at the age of <50 years, while the form is presented by 8% of persons at the of ≥50 years. (162)

The mean maximal LVWT was found with 21.3 ± 7 mm, while the patients with the morphologic expression demonstrate a mean gradient of LVOT within resting conditions of 51.5 ± 41.0 mm Hg. (162)

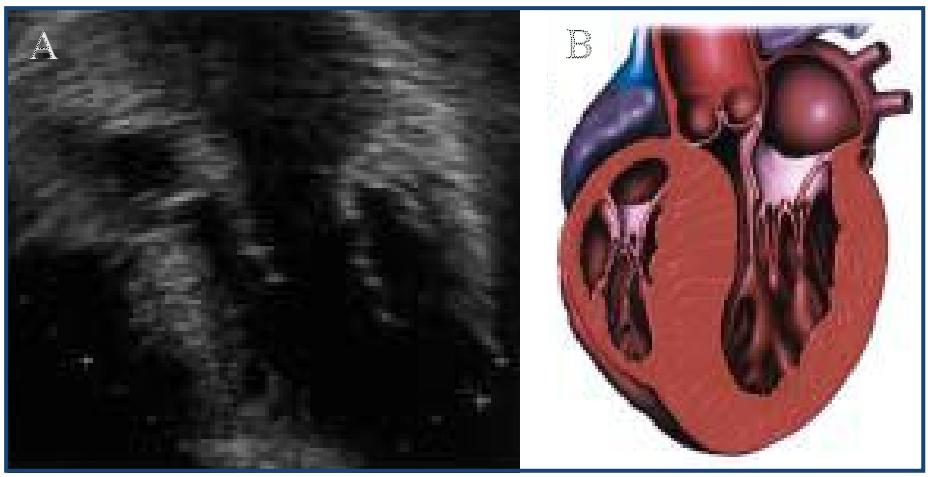

Figure 21: Neutral Septal Form of Hypertrophic Cardiomyopathy. (162) A: Echocardiographic Long-Axis View of the heart at the end-diastole. (162) B: Image of the heart with the morphologic subtype. (162) Images modified from (162).

A family history of Hypertrophic Cardiomyopathy is found in the proportion of 34.4% of persons with the Neutral Septal Form, while 15.6% of individuals present an incident of SCD within their family. (162)

Akin to the morphologic variant Reverse Septal Contour, the Neutral Septal Form comprises individuals predominantly exhibiting mutations regarding the genes of MYBPC3 and MYH7, with the proportions of 18.8% and 12.5%, respectively. (162) Mutations in the genes MYL2 and TNNI3 are found in 3.1% of individuals, each. (162) Furthermore, multiple mutations are detected in 3.1% of patients. (162)

3.8.2 Concentric Form

3.8.2.1 Historical Perspectives

In 1974, Rossen et al. described five patients subject to the condition of Hypertrophic Cardiomyopathy. (167) While four were noted to present an asymmetric phenotypic expression, a fifth individual was limned with the manifestation of a left ventricular “symmetric (concentric)” (167) form of hypertrophy. (167) The 16 years old girl demonstrated a septum to posterior wall thickness ratio of 1.0 with a left ventricular hypertrophy of 20 mm in absence of hypertension, the presence of subaortic obstruction noted with a systolic peak pressure gradient of 30 mm Hg within resting conditions as well as SAM of the mitral valve. (167)

3.8.2.2 Definition

The concentric form has been described as exhibiting diffuse left ventricular hypertrophy (76, 149) with each ventricular segment demonstrating a comparable hypertrophic involvement (149) in concurrence with a diminution of intraventricular dimension (76). (76, 149) According to Williams et al., the presence of a septum to posterior wall thickness ratio of >1.3 in normotensive individuals as well as a ratio of >1.5 within context of Hypertension is considered as threshold delineating asymmetry. (157)

3.8.2.3 Epidemiology

The proportion of the concentric form encompassed within the entirety of Hypertrophic Cardiomyopathy's phenotypic expressions varies according to authorship from 0.8% to 42% (168, 149, 79, 160, 89).

Aforementioned variance in extent of prevalence might be inter alia attributable to the utilization of different standards in terms of morphology (149) or the investigative method (160, 89).

Shapiro and McKenna denote the ratio of <1.5 in wall thickness with reference to various regions of the left ventricle and a difference of <20% with regard to the conducted measurements of wall thickness, as criteria for the determination of concentricity. (160) Furthermore, attention is directed to discrepancy of measurement results between utilization of M-Mode and Two-Dimensional Echocardiography. (160) Alternatively, Davies and McKenna present the proportion of Concentric Hypertrophic Cardiomyopathy as a result of pathologic investigation. (89)

Antithetic data with regard to the correlation between the concentric variant and age is existent from two publications (169, 170), with one reporting an elevated prevalence of the concentric phenotypic expression among elderly individuals (75%) in comparison to 71% of young persons presenting Asymmetric Septal Hypertrophy (169) and conversely, the other noting the proportion of elderly study participants exhibiting an anteroseptal left ventricular hypertrophy with 79% (170).

3.8.2.4 Genetic Aspects

The assessment of mutations in the genes MYBPC3, MYH7, and MYL2 (encoding for the sarcomeric thick filaments), TNNT2, TNNI3, TPM1, and ACTC (encoding for thin filaments), as well as MYL3 (encoding for the essential light chain), demonstrated the circumstance of thin

filament mutations to result to the extent of 31% in less common phenotypic manifestations of Hypertrophic Cardiomyopathy. (118) These involved aside of Apical Hypertrophic Cardiomyopathy the concentric morphologic form. (118) The amount of 11.3% of individuals with thin filament mutations were found with concentric hypertrophy, while the variant was present in 1.3% of persons with mutations concerning thick filaments. (118)

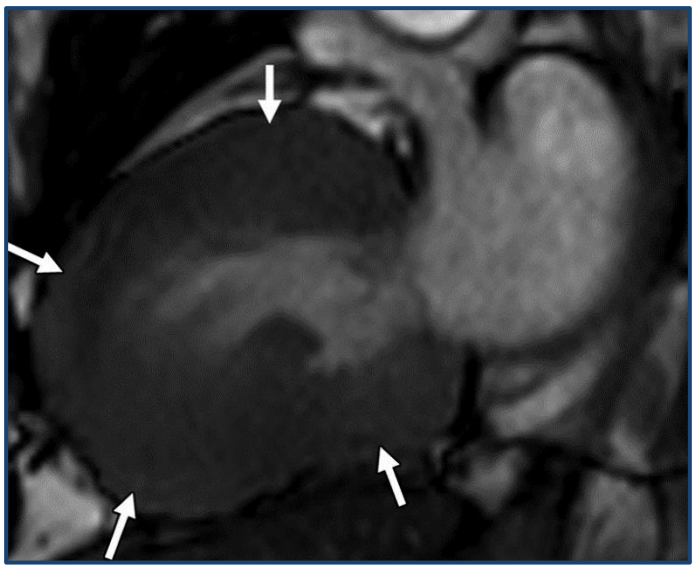

Figure 22: Long-Axis Two-Chamber View of the heart of a 54-year-old individual in assistance of Steady-State Free Precession MRI demonstrating the concentric variant of Hypertrophic Cardiomyopathy. (76) The hypertrophy is designated by arrows. (76) Image from (76).

Furthermore, the extent of 41% of patients with mutations in the gene TNNI3 exhibit either an apical or concentric variant of Hypertrophic Cardiomyopathy. (118) The mutation Glu497Asp, while found to express an apical variant of HCM, has as well been reported with a concentric hypertrophy of 29 mm measured at the interventricular septum. (171)

3.8.2.5 Characteristics of Concentric Hypertrophic Cardiomyopathy

The spectrum in LVWT was found ranging from 14-45 mm (160), with the variance in measurements obtained from different echocardiographic projections resembling normal individuals. (160). A difference of diastolic left ventricular cavity dimension between the concentric form and Asymmetric Septal Hypertrophy is not existent. (160)

The amount of 39% of individuals present SAM of the mitral valve complex (160) while 66% of persons were noted with midsystolic aortic valve closure (160) and 96.4% with hypertrophy of at least one papillary muscle (160).

3.8.2.6 Differentiation between Concentric Hypertrophic Cardiomyopathy and Other Conditions

Baxi et al. state, that within the context of Concentric Hypertrophic Cardiomyopathy, the distinguishing of the aforementioned condition from a hypertrophy as a result of the situation

within Hypertension as well as the condition of Athlete's Heart, represents a challenging circumstance. (76)

3.8.2.6.1 Athlete's Heart

In principal, Athlete's Heart presents with a minor concentric aggrandizement of the left ventricle. (172) The extent of hypertrophy remains <15 mm, while Diastolic Function is noted to display as common. (172)

The range of 13-15 mm in septal wall thickness has been described as a ground of ambiguity in consequence of an overlap between the condition of Hypertrophic Cardiomyopathy and Athlete's Heart. (173, 174)

A LVWT of ≥13 mm in athletes is present to the extent of as few as 1.7%. (175) All of individuals encompassed within the aforementioned proportion were found to be represented by men as well as engaged in the sports of rowing and canoeing. (175) A wall thickness of 16 mm represented the most increased value and was exhibited by one individual. (175)

An echocardiographically assessed intraventricular dimension of >55 mm at end diastole as well as a Maximal Oxygen Capacity of >45 ml/kg/min have been suggested as determinants indicative of Athlete's Heart. (173) Nevertheless, 33.3% of male athletes present a chamber space of >55 mm. (176) In contrast, uncommon distribution of hypertrophy, a ventricular dimension of <45 mm, unusual electrographic findings, abnormal Diastolic Filling, female gender, as well as cases of Hypertrophic Cardiomyopathy within family, direct to the condition of Hypertrophic Cardiomyopathy. (173)

Within context of deconditioning of trained athletes, a demise in left ventricular hypertrophy to the extent of 2-5 mm within the time lapse of three months is possible. (176) Alongside of the echocardiographically assisted examination of Diastolic Filling, the aforementioned procedure has been proposed as a measure serving the differentiation between Hypertrophic Cardiomyopathy and Athlete's Heart. (174) Genetic Testing, although not commonly accessible, has been taken into consideration in this regard. (174)

3.8.2.6.2 Hypertension

The increase in LVWT within the context of Hypertension as a compensatory response to elevated afterload conditions is possible. (76, 77) In principal, the induced hypertrophy presents with a LVWT of <15 mm up until a maximum of 16 mm and rather a concentric left ventricular pattern than asymmetry. (172) Nonetheless, even though considering the utilization of various

left ventricular reference regions and extents concerning ratios determining asymmetry as well as different degrees of Hypertension severity, overall presence of Asymmetric Septal Hypertrophy in individuals with Hypertension has been identified ranging from none up until the extent of 70%. (177–181)

With either study participant collectives in comparison to control subjects, persons with Hypertension were found to exhibit a reduction in EF as well as an elevation in End Diastolic Volume and Left Ventricular Wall Stress, while individuals subject to Hypertrophic Cardiomyopathy displayed a supernormal EF as well as a diminution in End Systolic Volume and Left Ventricular Wall Stress. (182) Furthermore, in assistance of Binary Logistic Regression, determined as identifiers for each collective, were the elevation in Left Ventricular Wall Stress for individuals with Hypertension with an odds ratio of 1.2 and the diminution of the Total Longitutinal Strain rate for persons with Hypertrophic Cardiomyopathy. (182) In comparison to each other, individuals with Hypertension demonstrate increased values of LVWT at the basal anteroseptal and mid anteroseptal segments, while LVWT in persons with Hypertrophic Cardiomyopathy presents raised at the basal inferoseptal and basal inferior as well as mid inferoseptal and mid inferior segments. (182, 183) In addition, a negative correlation is displayed between the score of global LGE and EF ($r = -0.5$) in reference to persons with Hypertrophic Cardiomyopathy. (182) Nevertheless, with regard to the antecedent, Baxi et al. state, that in reference to hypertrophy of the left ventricle resulting from the context of Hypertension, EF presents in most of individuals ordinary. (76)

In comparison to persons subject to Hypertension, the proportion of individuals with Hypertrophic Cardiomyopathy exhibiting LGE was found elevated, with 50% and 72%, respectively. (184) While persons with Hypertension demonstrated no specific localization of fibrotic processes, LGE in individuals with Hypertrophic Cardiomyopathy was primarily present at the junctional regions between the septum and left ventricle. (184) Furthermore, a correspondence between region of fibrosis and segment of maximal wall thickness was found in the amount of 84% of individuals subject to Hypertrophic Cardiomyopathy presenting LGE. (184)

A ratio between the wall thickness of the interventricular septum and left ventricular posterior of 1.3 as well as a Systolic Strain of -10.6 were determined with regard to the differentiation between Hypertrophic Cardiomyopathy and the condition of Hypertension as most advantageous cutoff values. (185) The accuracy of distinguishing between the two ailments within simultaneous application of the two parameters was noted with 96.1%. (185)

Individuals with Hypertrophic Cardiomyopathy were found to present in comparison to either, persons subject to Hypertension or control study participants an elevated value of Free Carnitine in the serum, with 52.5 ± 9.5 nmol/ml, 46.6 ± 6.4 nmol/ml, and 42.3 ± 5.5 nmol/ml, respectively. (177) Conversely, in context of Hypertrophic Cardiomyopathy the value of serum Acylcarnitine displayed reduced in comparison to persons with Hypertension or control study participants, with 10.1 ± 4.0 nmol/ml, 14.5 ± 4.9 nmol/ml, and 13.2 ± 3.9 nmol/ml, respectively. (177)

3.8.2.6.3 Aortic Stenosis

Left ventricular hypertrophy as a mechanism of compensation is as well available in the condition of Aortic Stenosis. (77)

In patients subject to Aortic Stenosis, Cardiac Cine MRI reveals a turbulent jet at the traverse region of the aortic valve. (76) Concomitantly, the systolic Aortic Valve Area presents declined. (76) In contrast, patients with Hypertrophic Cardiomyopathy demonstrate, as a result of wall thickening at the basal anterior septum, a jet turbulence located subjacent to the aortic valve. (76) Furthermore, the amount of 62% of individuals with left ventricular hypertrophy and Aortic Stenosis were found to display LGE, yet with no correlation between LGE occurrence and the severity of Aortic Stenosis. (184)

3.8.2.6.4 Infiltrative and Deposition Diseases

Ailments involving inter alia a diffuse hypertrophic manifestation of the left ventricle constitute the infiltrative and deposition diseases Amyloidosis, Fabry-Anderson Disease and Sarcoidosis. (76)

3.8.2.6.4.1 Amyloidosis

Aggregation of proteins presenting with impaired folding and/or composition and tertiary structure give rise to the formation of stiff and linear fibrils with an extracellular deposition. (186) The resulting cardiac rigidity, decline in intraventricular dimension as well as diastolic atrial malfunction lead to an eventual systolic as well as diastolic impairment. (186) The left ventricular hypertrophic expression manifests most frequently concentric. (187)

Although within incipient stages possibly not existent, Amyloidosis has been described with a left ventricular contraction demise, while contraction in Hypertrophic Cardiomyopathy is considered energetic. (188) The interatrial septum thickness in Amyloidosis was found with 8.7

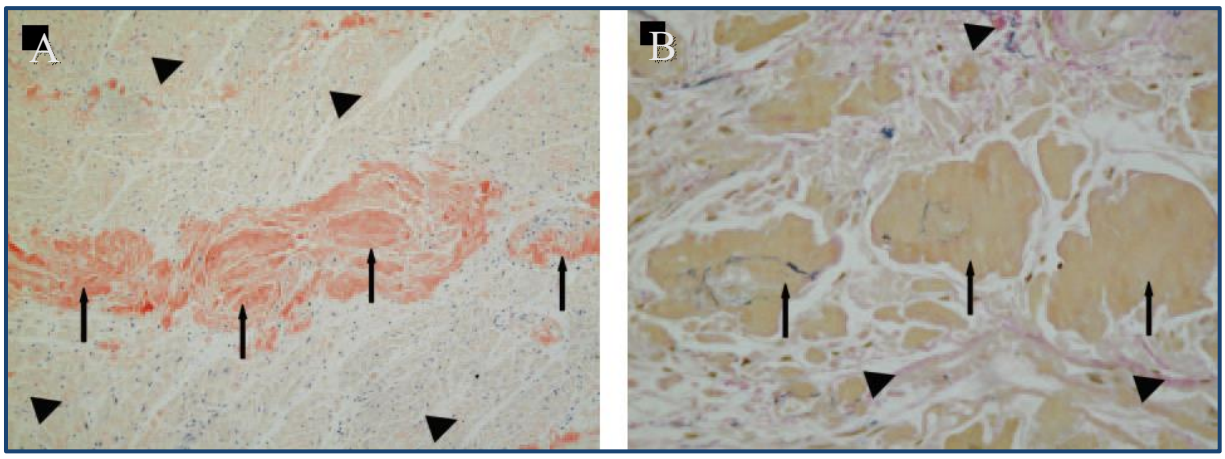

Figure 23: Histologic assessment of a post mortem heart with presence of Amyloidosis. (189) A: Congo Red staining exhibiting amyloid deposition (designated by straight arrows). (189) Furthermore, presence of infiltration into the interstitium (indicated by arrowheads). (189) B: Elastin Van Gieson staining attains a confirmation of the extensive constitutents to represent amyloid (yellow, designated by straight arrows). (189) Collagen presents as darkened pink (indicated by arrowheads). (189) Images modified from (189).

± 2.7 mm, while the one in individuals subject to Hypertrophic Cardiomyopathy presented with 5.3 ± 0.8 mm with no person surpassing 6 mm. (190) The proportion of individuals with Amyloidosis demonstrating Pericardial Effusion in comparison to persons with Hypertrophic Cardiomyopathy was found elevated with 42% and 10%, respectively. (190) Individuals subject to Amyloidosis exhibited Pleural Effusion in 50% of cases, in contrast to no incident in patients with Hypertrophic Cardiomyopathy. (190)

Scintigraphy detected cardiac Transthyretin Amyloidosis in the setting of a radionuclide uptake equal or above the degree of bone tissue accompanied by a missing of monoclonal proteins, confirmed in assistance of a serum and urine Immunofixation Electrophoresis and a Serum Free Light Chain assay, with a specificity of 100%. (191)

Recommendation of amyloid staining the totality of all specimens resulting from within context of Ventricular Septal Myectomy with regard to individuals beyond the age of 65 years, is existent. (86)

Furthermore, the performing of endmyocardial biopsies in refernce to Hypertrophic Cardiomyopathy is equivocally advocated. (86) Nevertheless, its implementation finds essential consideration in respect to the elucidation of a possible presence of ailments capable of mimicking Hypertrophic Cardiomyopathy, such as Amyloidosis. (86)

3.8.2.6.4.2 Anderson-Fabry Disease

Anderson-Fabry Disease exhibits, as a result of mutations, a demise in activity of α-Galactosidase A. (50) As a consequence, lysosomes undergo an accumulation in Glycosphingolipids, with the majority being represented by Globotriaosylceramide. (50)

The amount of 3% of patients presenting with left ventricular hypertrophy at a cardiovascular division in Japan were found with a reduction in the activity of Plasma α-Galactosidase, resulting in the diagnosis of Anderson-Fabry Disease. (192)

A definitive substantiation of the presence of Anderson-Fabry Disease may be achieved by means of a measurement of the Plasma α-Galactosidase activity in suspected individuals. (192)

Nevertheless, Cataracts, Corneal Opacities, Sensorineural Surdity, Paresthesia, as well as Angiokeratoma include comorbidities which should direct attention to Anderson-Fabry Disease. (194) Accordingly, the presence of a reduced electrocardiographic PR interval, Preexcitation, as well as Proteinuria solely or accompanied by a reduced Glomeruleric Filtration Rate should accentuate the possibility of Anderson-Fabry Disease as causality. (194)

Echocardiographic findings indicative of Anderson-Fabry Disease include an aggrandizement in thickness of the atrioventricular valves and right ventricular free wall as well as global Hypokinesia solely or accompanied by left ventricular dilatation. (194)

Furthermore, patients with Anderson-Fabry Disease exhibit LGE in 50% of cases, with 92% of aforementioned individuals demonstrating LGE in the inferolateral wall of the heart's base. (195)

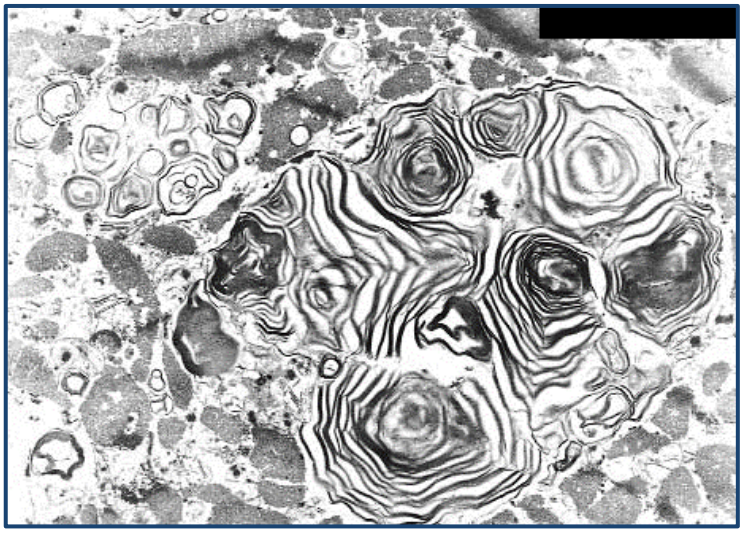

Figure 24: Image of a post mortem cardiomyocyte affected by Anderson-Fabry Disease at 6000-fold magnification in assistance of the Electron Miscroscope. (193) Direct attention to the aggregation of membraneous glycolipid bodies in a concentric arrangement encountered within a lysosome. (193) Image modified from (193).

3.8.2.6.4.3 Cardiac Sarcoidosis

Sarcoidosis represents a disease with a multisystemic involvement and noncaseating granulomas (196), with the status of an unidentified etiology (197). It was found with a cardiac involvement in

26-27% (198, 199). In general, clinically manifest individuals subject to Sarcoidosis overall present inter alia an affliction of the organs lung (95%), skin (21%), liver (16%), and eye (10%). (198) An isolated affliction of the heart by the condition of Sarcoidosis is encountered in 31.6% of cases. (200)

Diagnosis of Cardiac Sarcoidosis via right ventricular endomyocardial biopsy in individuals substantially suspected, engaging a mean of 4.0 ± 1.2 samples per patient, resulted in an eventual confirmation of the disease, holding histologically noncaseating granulomas, in relatively as few as 19.2% of persons. (201)

The cardiac conduction system presents with increased predisposition for the ailment (196), with as few as 8.3% of patients exhibiting a normal ECG (203). Cardiac manifestations as a result of the presence of Sarcoidosis include Premature Ventricular Contractions (37.1%), Complete Heart Block (28.1%), Complete Bundle Branch Block (25.8%), Ventricular Tachycardia (21.3%), and Atrial Arrhythmia (16.9%). (204) Congestive Heart Failure was found in the amount of 39.3%. (204)

An abnormal echocardiographic finding is present in the extent of 30.1% of patients (205). Two-Dimensional Echocardiography in individuals with Sarcoidosis revealed a mean ventricular septal and posterior wall thickness of 9.0 ± 1.7 mm and 9.4 ± 1.0 mm, respectively. (203) The left ventricular diameter was determined with 50 ± 12 mm in Systole and 63 ± 12 mm in Diastole, while the dimension of the left atrium presented with 44 ± 10 mm. (203) The parameter of EF is found reduced with a mean of 39 ± 11%, while 16.7% of cases present Pericardial Effusion. (203)

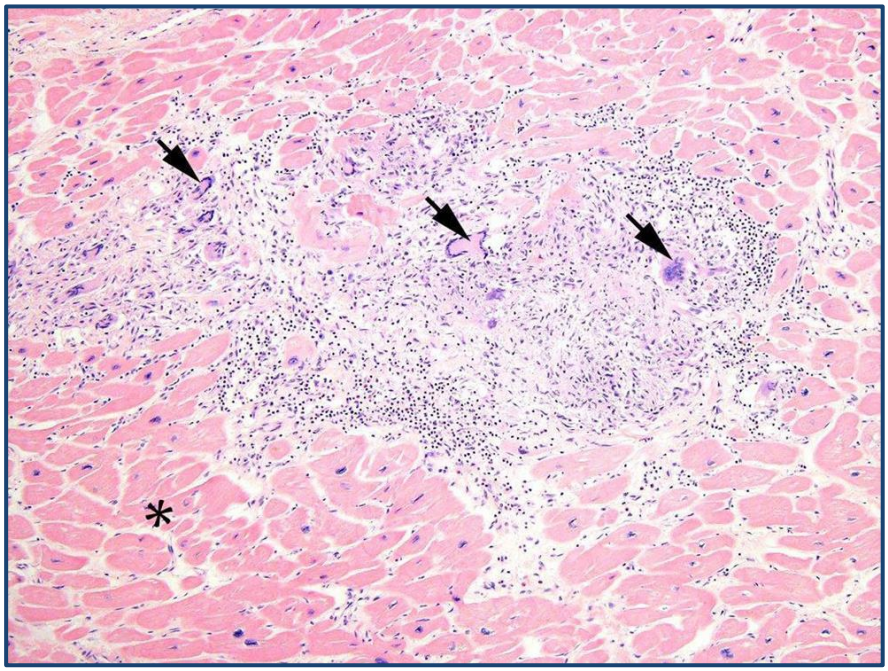

Figure 25: Image of Cardiac Sarcoidosis at a 100-fold magnification. (202) Direct attention to granulomas consisting of multinucleated giant cells (designated by arrows) (202) as well as presence of mononuclear cells within the myocardium (designated by asterisk). (202) Image modified from (202).

Cardiac MRI in assistance of T2-Weighing allows the identification of ongoing inflammatory processes. (206) It is regarded as the prevailing sequence with regard to the assessment of Sarcoidosis. (196) Furthermore, visualization of fibrotic tissue and wall motion abnormalities is made possible via LGE. (206, 197) In the extent of 11% of individuals, MRI assessment identified Sarcoidosis to hold a left ventricular involvement, not revealed in assistance of ECG, Echocardiography, or Scintigraphy. (197) Although further investigation in respect to benefits of MRI application within context of Sarcoidosis is advocated, the imaging technique finds consideration as a helpful measure with regard to the most beneficial moment for the initiation of a medical treatment. (197)

3.8.3 Apical Form

3.8.3.1 Historical Perspectives

In the year of 1976, Sakamoto et al. published their findings in reference to nine individuals of the Japanese population presenting with inverted exceeding amplitudes of electrocardiographic T waves, detected in the precordial leads of V_4-V_6. (207) While a subjacent cause was previously not determined, performing of Echocardiography revealed a substantial hypertrophy at the region of the heart's apex. (207) Sakamoto et al. denoted a correlation between the hypertrophy and electrocardiographic findings. (207)

Two subsequent years, Yamaguchi et al. reported about 30 individuals in which electrocardiographic T wave aspects resembled those accounted by Sakamoto et al. (207). (208) The average of apical hypertrophy with regard to persons affected was noted with a thickness of 24.8 ± 6.6 mm in comparison to normal individuals demonstrating a thickness of 9.4 ± 3.1 mm. (208)

The Apical Form of Hypertrophic Cardiomyopathy finds as well appellation as "Yamaguchi syndrome" (76). (76)

3.8.3.2 Definition

Apical Hypertrophic Cardiomyopathy has been delineated with the characteristics of left ventricular hypertrophy presenting with primary restriction to the region of the cardiac apex demonstrating a maximal wall thickness of ≥15 mm. (82) The ratio between apical and posterior maximal wall thickness regarded as determining is noted with ≥1.5, while exclusion of other conditions of cardiac or systemic nature with the potential of effectuating similar results, is existent. (82)

3.8.3.3 Epidemiology

The variant apparently seems to exhibit in respect to its prevalence a geographical inhomogeneous dispensation. (209, 210) Persons subject to Hypertrophic Cardiomyopathy present the apical phenotypic expression in the proportions of 37.7% (211) of cases within the Republic of Korea, 15% (212) of the Japanese population and as few as 1.9-3% (213, 212) within the United States of America.

A difference of the mean age at diagnosis is aside of the findings within the population of the Republic of Korea not existent (61 ± 11 years) (211), with data ranging from 49 ± 18 to 52.2 ± 12.4 years. (212, 82) While findings concerning gender distribution among the variant seemed more balanced in the United States of America (57%) (212), in Asian countries men represented 69-73% (212, 211, 82) of afflicted population.

3.8.3.4 Genetic Aspects

The amount of 25% of patients with the apical variant investigated for mutations in ACTC1, MYBPC3, MYH7, MYL2, MYL3, TNNT2, TNNI3, TNNC1, as well as TPM1, were found to present at least one mutation in aforementioned genes. (215) The genes of MYBPC3 and MYH7 presented preponderantly afflicted by mutations, either one with a proportion of 33.3%. (215) Furthermore, mutations in the genes TNNI3 and TNNC1 were found with 11,1% and 5.6%, respectively. (215) While one individual (5.6%) exhibited a mutation in both, the gene MYBPC3 and MYH7, one further person was subject to a double mutation in MYBPC3. (215)

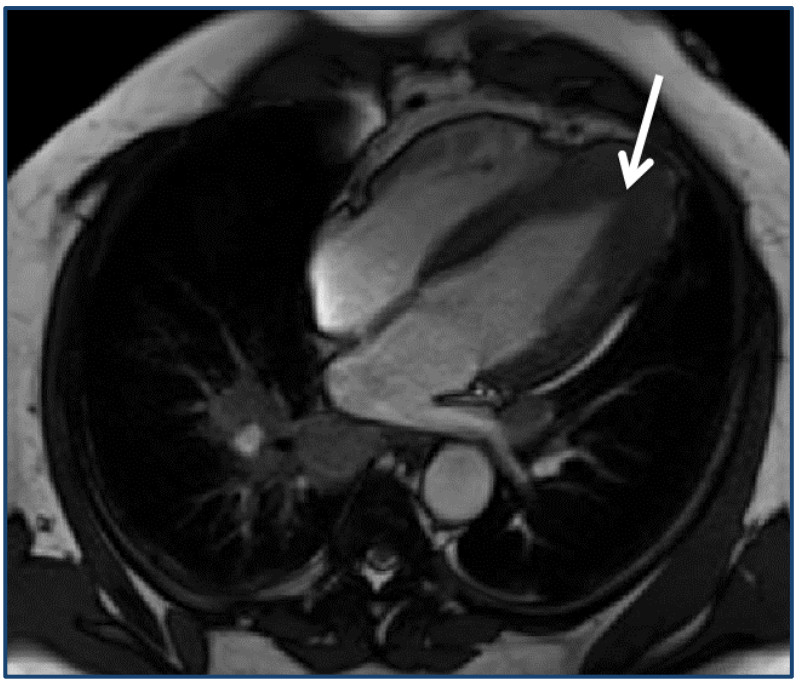

Figure 26: Four-Chamber View of the heart via MRI of an individual presenting Apical Hypertrophic Cardiomyopathy. (214) The hypertrophy at the cardiac apical region is designated by an arrow. Image modified from (214).

Another publication notes the amount of individuals within the apical variant presenting mutations in the gene encoding for the β-Myosin Heavy Chain with 43%. (171) While the

Lys183 deletion in reference to Troponin I as well as the missense mutations Phe110Ile and Arg102Leu in Troponin T were found to result in either the apical or different morphologic variants, the mutation Glu101Lys concerning cardiac Actin was found to exhibit Apical Hypertrophic Cardiomyopathy in 100% of cases. (171) Additionally, Met149Val, a mutation of the sarcomeric Light Chain was detected to express either an apical, midventricular or common form. (171) While in reference to two individuals, the mutation ACTC E101 was found to produce the disease's apical form (171), it has been reported to be as well involved in the formation of Left Ventricular Noncompaction (216).

Minor differences between mutation positive and mutation negative individuals included the age at diagnosis, with 44.2 ± 13 and 49 ± 16 years, respectively. (215) Patients with the detection of a mutation held a family history of Hypertrophic Cardiomyopathy in 39% of cases in comparison to 26% of individuals without detection. (215)

In comparison to mutation negative patients, mutation positive patients presented an elevated proportion of individuals within NYHA functional class ≥III, with 20% and 35%, respectively. (215) In constrast, cases of decease of cardiac causality were increased in undetected persons, with 5.9% (including one case of SCD) and no incidents within the detected collective. (215)

Furthermore, Arrhythmia in comparison to detected persons was more common in mutation negative individuals, with 29.4% and 43.1%, respectively. (215) Both collectives presented one case of Left Ventricular Aneurysm, representing 2% of mutation negative and 5.9% of mutation positive persons. (215)

Proposal of Apical Hypertrophic Cardiomyopathy representing the result of at least one modifier gene, which in turn presents cumulated with regard to populations frequently expressing the variant, is existent. (171)

Additionally, morphologic expression of an apical variant was as well diagnosed in patients with an absence of mutations in genes responsible for β-Myosin Heavy Chain, essential or regulatory Myosin Light Chains or certain reported mutations in genes of Myosin-Binding Protein C, α-Tropomyosin, or Troponin T. (213)

3.8.3.5 Clinical Aspects

In exclusion of abnormal ECG findings, within the apical variant the extent of 43% of patients are found with an absence of symptoms. (217) Chest Pain and Exertional Dyspnea represent

the predominant symptoms exhibited by 57.3% and 33.2% of patients, respectively. (217) Palpitations are encountered with regard to 13.7% of individuals. (217)

The amount of 2.9% of persons present Syncope, while 31% are found within a NYHA functional class of ≥II. (128)

3.8.3.6 Diagnostic Aspects

Eminent negative electrocardiographic T waves are considered to represent a characteristic of the variant. (76) Sakamoto et al. reported of a "deeply inverted T wave" (207) in left precordial leads with an average of 1.63 mV. (207) Modern descriptions of the entity define the nominally "giant negative T wave" (207) with an amplitude of ≥10 mm (218).

Electrocardiographic T-wave inversions are present to the extent of 89.8-91.3% (218, 82) of patients, with 10.8-28.8% holding Giant Negative T-waves (218, 82). The majority of individuals present negative T-waves in the Precordial Lead V_4 (62%). (217) Inverted T-waves in lead V_5 and V_6 are found to the extent of 31% and 10.6%, respectively. (217) While Sakamoto et al. denote continuity in electrocardiographic findings with regard to 74.2% (219) of individuals, aforementioned is paralleled by cases presenting within long-term observation with electrocardiographic alterations, including inter alia progression, incipience, as well as regression of T wave inversion. (219)

In principal, durations of electrocardiographic intervals present within normal ranges, with a mean of 169 ± 26 ms for the PR interval, 96 ± 12 ms for the QRS complex, and 439 ± 30 ms for the cQT interval. (128)

Echocardiographic findings include a mean maximal apical thickness of 17.5 ± 2.8 mm, an EF of 66.4 ± 9.3% - 69 ± 7% (82, 128), and an E/E' ratio of 14.3 ± 5.3. (128) A mean maximal LVWT of ≤20 mm is found in 55% of the US American population and 60% of individuals in Japan, while 9% of persons in USA and 6% of patients in Japan demonstrate a mean thickness of ≥30 mm. (212) The entities of LVOTO as well as Mitral Valve Regurgitation are not encountered in this variant. (220) The ratio between the left ventricular apical and left ventricular posterior wall thickness is noted with 2.1 ± 0.8. (82) while Diastolic Dysfunction is present to the extent of 79%. (218) Furthermore, peak apical rotation in individuals with Apical Hypertrophic Cardiomyopathy in comparison to normal subjects was found diminished, with 12 ± 4.3° and 19.5 ± 5°, respectively. (221) In consequence, peak left ventricular twist presented reduced with 18.1 ± 5° for persons exhibiting the condition compared to 22.6 ± 5.5° in control subjects. (221)

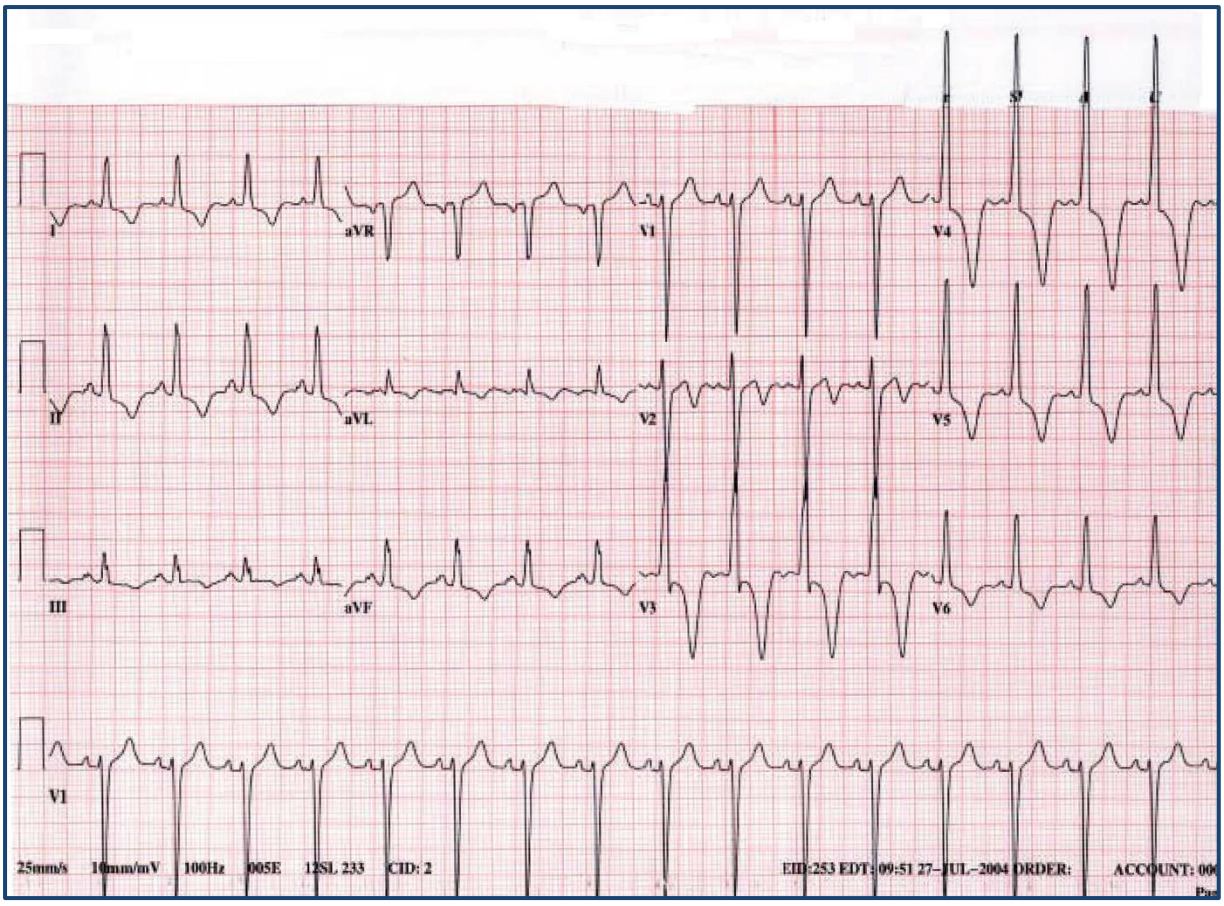

Figure 27: Electrocardiogram of an individual subject to Apical Hypertrophic Cardiomyopathy. (222) Direct attention to the findings of left ventricular hypertrophy (222), extensive QRS voltages (222), and giant T-wave inversions (222) in the precordial leads of V_3-V_5. Image modified from (222).

Assessment via Echocardiography in comparison to MRI results in nonsuccess of diagnosing Apical Hypertrophic Cardiomyopathy in 8.6% of cases. (223) Manifestation of LGE was exhibited by 40.6% of individuals subject to the condition, with its presence confined to the cardiac apex. (224)

3.8.3.7 Complicative Aspects and Prognosis

The condition of AF is exhibited by the extent of 25.2% of persons, with 46.8% of aforementioned individuals, Apical Hypertrophic Cardiomyopathy being diagnosed as a result of a presence in AF. (128) Furthermore, AF is related to a sixfold increased risk for ischemic strokes. (128) In the extent of 46.7% of patients subject to AF and experiencing Stroke, AF is diagnosed subsequent to the incidence of Stroke. (128) As few as 1.6% of patients demonstrate NSVT. (128) Myocardial Infarction is reported in 2.9-10.5% (128, 223) of persons with Apical Hypertrophic Cardiomyopathy, with 81.8% (223) of aforementioned individuals demonstrating the incident at the cardiac apex. Even though not reaching statistical significance, the presence

of AF correlated with a lower amount of Myocardial Infarction, with 3.1% of AF patients and 2.6% of individuals without AF experiencing the incident, with a *p* value of 0.596. (128)

Overall survival rates observed at the time periods of 5, 10, and 20 years presented in one publication slightly unfavorable, with 86%, 70%, and 47%, respectively. (218) Another publication denoted an overall survival at 15, 20, and 25 years of 95% ± 3%, 87% ± 5%, and 79% ± 7%, respectively. (223) The 15-year survival rate of Apical Hypertrophic Cardiomyopathy affected persons in the latter of aforementioned studies was found resembling the expectancy of the general population corresponding to age and gender (Ontario, Canada), with 95% ± 3% and 95% ± 1%, respectively. (223) Additionally, incidences of SCD were not observed while the annual cardiovascular mortality was noted with 0.1%. (223) Analysis of several studies demonstrated a proportion of SCD of 2.5% of individuals and the rate of Congestive Heart Failure of 0.8% of persons. (225) In assistance of Univariate Cox Regression analysis the factors Female Gender, Chronic AF at initial assessment, as well as the presence of Heart Failure at initial assessment were determined as unfavorable predictors, with the hazard ratios of 3.23 (95% CI: 1.88-5.56), 3.82 (95% CI: 1.82-8.03), and 3.24 (95% CI: 1.56-6.70), respectively. (218)

3.8.3.8 Comorbidities

The most encountered comorbidity within the apical phenotypic expression is represented by Hypertension, found ranging from 39-61%. (217, 128) Dyslipidemia and Heart Failure are exhibited by 40% and 33%, respectively. (128) While the extent of 8.7-28% of persons present Diabetes Mellitus, Coronary Artery Disease is found in 15.9-19% of individuals. (128)

3.8.4 Midventricular Form

3.8.4.1 Historical Perspectives

In 1976 Falicov et al. reported on the findings in respect of two individuals presenting with cardiovascular symptoms. (226) The first case presented with dyspnea induced within demanding physical activity and communicated Dizziness in concurrence with a change of position and the presence of a heart murmur since juvenility. (226) The second case, a woman at the age of 44, related the ensuing of retrosternal pain and dyspnea within context of common exercise as well as incidences of vertigo. (226) She was subject to hypertension and experienced syncopes. (226)

Cardiac catheterization revealed with regard to either cases an irregularity in morphology of the left ventricle, with the first case demonstrating a constringence at the midventricular region and a left ventricular gradient of 80 mm Hg and the second case a restriction located amidst the ventricle's center and its blood flow tracts. (226) Falicov et al. denote, furthermore with regard to the second case the formation of an apical aneurysm. (226)

3.8.4.2 Definition

Midventricular Hypertrophic Cardiomyopathy has been described as a variant of the obstructive medical condition, holding the region of stricture at the level of mid-cavity as a result of a hypertrophied septum in apposition with the left ventricular wall, with a possible involvement of, at least, the anterior papillary muscle. (226) The left ventricular aspect has been noted as resembling an "hour-glass" (83). (83) A gradient detected at the center of the left ventricle was regarded as an essential diagnostic constituent (83), while the pressure of ≥30 mm Hg is considered as defining (227, 228).

3.8.4.3 Epidemiology

The proportion of persons exhibiting the midventricular variant within the population subject to Hypertrophic Cardiomyopathy presents with the range of 2.9-9.4% (229, 228, 227) while the mean age at the time of diagnosis has been reported from 40.2 ± 15 - 53.2 ± 14.7 years (229, 228, 227). The eventual extent of male individuals presenting the morphologic form is noted with 47.1-75% (228, 227, 229).

3.8.4.4 Genetic Aspects

Aside being existent within Apical Hypertrophic Cardiomyopathy and other morphologic manifestations of Hypertrophic Cardiomyopathy, the mutation Met149Val was found to as well lead to the midventricular phenotypic expression. (171)

3.8.4.5 Clinical Aspects

The amount of 96.7-97.1% (229, 228) of patients are subject to symptoms within initial assessment, with Dyspnea representing with a proportion of 44-83.3% (228, 229) the manifestation most frequently encountered. Further symptoms constitute Chest Pain, Dizziness as well as Amaurosis Fugax found in 43.3%, 31.7%, and 26.7% of individuals, respectively. (229) An Unexplained Syncope was communicated by 21.7% of persons. (229)

The preponderance of patients subject to Midventricular Hypertrophic Cardiomyopathy (58.8-67.4%) (228, 227) exhibit a NYHA functional class of II while a functional class of ≥III is found with regard to 4.3-36.7% (227–229) of individuals.

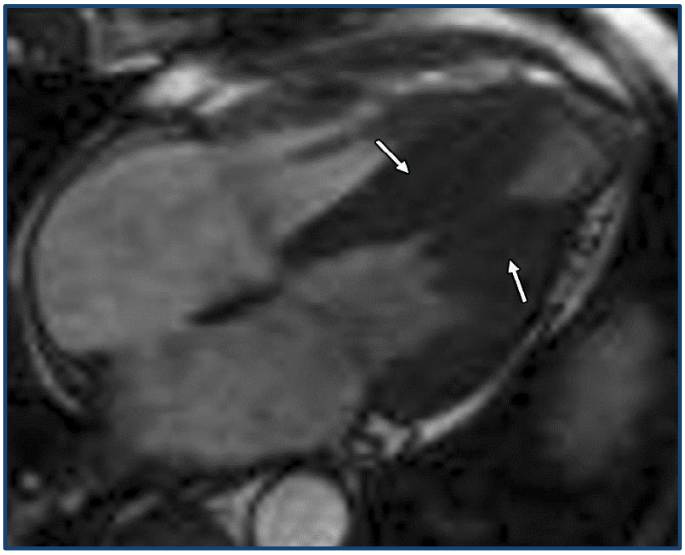

Figure 28: Four-Chamber View of the heart of a female individual at the age of 51 years in assistance of Steady-State Free Precession MRI exhibiting Midventricular Hypertrophic Cardiomyopathy. (76) Direct attention to the hourglass appearnace of the left ventricular cavity (designated by arrows) and the thinning of the cardiac apex. (76) Image from (76).

3.8.4.6 Diagnostic Aspects

As few as 2.9% of persons afflicted by the condition's midventricular variant are noted to present a regular ECG. (228)

In assistance of Echocardiography, the maximal LVWT was determined ranging from 19.1 ± 4.3 mm – 22 ± 7 mm (227, 228) while a thickness of ≥30 mm was found to be present with regard to the proportion of 10% (229) of individuals. A left ventricular gradient within resting conditions was detected with a mean of 65.6 ± 31.1 – 70.4 ± 29.8 mm Hg (228, 229) in concurrence with 75% of individuals being noted to present a peak pressure gradient of ≥50 mm Hg (229).

3.8.4.7 Complicative Aspects and Prognosis

The two most encountered complications are represented by NSVT (20.6-31.7%) (228, 227, 229) and AF (16.7-41.2%) (229, 227, 228). An incident of Stroke or Myocardial Infarction is found in the extent of 6.7-10.9% (229, 228, 227) and 6.7% (229) of individuals, respectively, while 11.8-16.7% (228, 227, 229) of patients are reported to develop Progressive Heart Failure.

An event of decease among persons subject to the midventricular variant associated with Hypertrophic Cardiomyopathy is noted with 23.9% (227), while decease in correlation to the midventricular form is encountered in 15% (229) of individuals, within a follow up time period of 10.4 ± 8.2 (227) and 7.1 ± 6.3 (229) of years, respectively. The occurrence of SCD ranges from 1.7-8.8% (229, 227, 228), while the presence of ≥2 risk factors for the incident was found to be in comparison to persons exhibiting nonobstructive Hypertrophic Cardiomyopathy and

individuals with LVOTO, among persons with midventricular obstruction elevated, with 8.6%, 18.1%, and 29.4%, respectively (228).

According to the Kaplan-Meier procedure, the estimates of survival for the time period of 5 years was found with 86 ± 6.0% and for 10 years noted with 77.0 ± 8.0%. (229) The presence of midventricular obstruction in comparison to patients presenting Hypertrophic Cardiomyopathy without obstruction as well as individuals subject to a LVOTO, was found to have an unfavorable impact on the survival rate for the time period of 5 years with regard to deceases as a result of cardiovascular nature, with 93.5% (95% CI: 89.1-97.9%), 98.9% (95% CI: 98.2-99.4%), and 96.2% (95% CI: 92.4-99.9%), respectively. (228)

A maximal LVWT of ≥30 mm as well as Unexplained Syncope were found to represent in a multivariate analysis with the technique of Cox Regression, independent predictors in reference to decease of cardiovascular causality with a hazard ratio of 3.19 (95% CI: 1.17-10.05) and 4.59 (95% CI: 2.40-15.78), respectively. (229)

3.8.4.8 Comorbidities

The extent of 36.7% of individuals presenting Midventricular Hypertrophic Cardiomyopathy are found to be subject to the condition of Hypertension with mean medicated pressures of systolic 132 ± 13.5 mm Hg and diastolic 80 ±9.8 mm Hg. (229) Hyperlipidemia is existent in 30% of patients with midventricular obstruction, in concurrence with 13.3% exhibiting Coronary Atherosclerotic Heart Disease. (229) Diabetes Mellitus is encountered in 1.7% of individuals with the variant. (229)

Additionally, the majority of patients (80%) with the formation of a segmental or generalized left ventricular Hypokinesia has been reported to be represented by individuals exhibiting a midventricular obstruction. (230)

3.8.4.9 Hypertrophic Cardiomyopathy with Midventricular Obstruction and Left Ventricular Apical Aneurysm

3.8.4.9.1 Definition

Apical Aneurysm of the left ventricle has been described as a separate segment located at the cavity's most distal region. (231) It presents with a connection to the chamber while exhibiting a thin wall alongside with Dyskinesia or Akinesia. (231)

3.8.4.9.2 Epidemiology

The development of Left Ventricular Apical Aneurysm has been reported in the population subject to Hypertrophic Cardiomyopathy with 0.3%. (228) The entity has been apprehended as a distinct constituent of patients presenting the midventricular variant of the condition (228), with the proportion of 20.0-28.3% (229, 228, 227) exhibiting a formation of Left Ventricular Apical Aneurysm. The median age of persons with Midventricular Hypertrophic Cardiomyopathy and Left Ventricular Apical Aneurysm has been reported with 58.05 ± 11.76 years. (232) The extent of 59.6% of individuals are represented by men. (232)

3.8.4.9.3 The Formation of Left Ventricular Apical Aneurysm

In consequence of midventricular obstruction and the increase in pressures within the chamber in systole, the myocardium at the cardiac apex as well is exposed to an elevated pressure load. (229) Simultaneously the left ventricle experiences a greater wall stress. (229) The aforementioned are regarded as preceding the formation of Left Ventricular Apical Aneurysm. (229) Yan et al. determined the presence of a peak pressure gradient of ≥70 mm Hg to represent an independent predictor for the entity's development. (229) Additionally, cardiac intramural arteries presenting with thickened walls and confined lumens are considered to comprise the causalities for a diminution in Coronary Flow Reserve as well as Ischemia. (229)

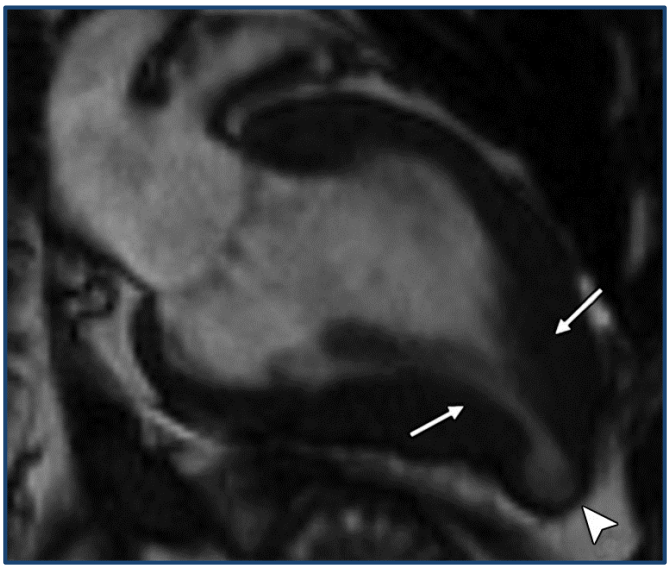

Figure 29: Heart of a person at the age of 55 years as a Three-Chamber View in assistance of Steady-State Free Precession MRI exhibiting Midventricular Hypertrophic Cardiomyopathy with Left Ventricular Apical Aneurysm. (76) The midventrcular hypertrophy is desiganted by arrows, while the Left Ventricular Apical Aneurysm is indicated by the large arrowhead. (76) Image from (76).

According to Yan et al., in case of Left Ventricular Apical Aneurysm, the diagnostic method of ^{99m}Tc Methoxy Butyl Nitrile Single-Photon Emission Computerized Tomography demonstrated an elevated uptake in the septum and a diminution in uptake with regard to the midventricular inferior wall. (229) This is indicative of a perfusion inconsistency. (229) In assistance of ^{18}F Fluorodeoxyglucose Positron Emission Tomography, the midventricular

myocardium was detected presenting a perfusion/metabolism mismatch. (229) Either diagnostic techniques revealed an uptake deficiency in respect to the left ventricular apical region, with ^{99m}Tc Methoxy Butyl Nitrile Single-Photon Emission Computerized Tomography exhibiting a severe perfusion impairment and ^{18}F Fluorodeoxyglucose Positron Emission Tomography identifying a perfusion/metabolism match. (229)

Nevertheless, reports of patients with midventricular obstruction and Left Ventricular Apical Aneurysm demonstrating no deficiency in perfusion with regard to the region of the cardiac apex, are existent. (233, 234)

The implication of genetic components in the formation of Left Ventricular Aneurysm is demonstrated by the publications of cases of related individuals presenting the entity. (235, 236) Identical twins being subject to the same left ventricular morphology (235) as well as three related persons, two sisters and a daughter (236), were identified with Left Ventricular Aneurysm.

Echocardiography revealed a turbulent signal of great velocity within diastole with its origin being located at the cardiac apex. (237) The manifestation endured even despite the incipience of diastolic filling. (237) Its flow exhibited an acceleration when traversing the distal confined portion of the ventricle with a subsequent deceleration approaching the LVOT. (237) The aforementioned echocardiographic occurrence was termed as “Paradoxic [J]et [F]low” (237) and regarded as indicative of an elevated diastolic pressure at the cardiac apex. (237) Appearance of Parradoxical Jet Flow holding a possible correlation to Left Apical Aneurysm formation has been proposed as subject matter of investigation. (237)

3.8.4.9.4 Clinical Aspects

The amount of 11.1% of patients exhibit symptoms within initial assessment (228) while Dyspnea was reported to represent the most frequently encountered manifestation with a proportion of 40.4%. (232) The extent of 26.5% of persons present Chest Pain while Syncope was found in 23.4% of patients. (232)

3.8.4.9.5 Diagnostic Aspects

A negative T wave as well as a ST elevation of ≥1 mm have been defined as characteristic electrocardiographic attributes of Midventricular Hypertrophic Cardiomyopathy presenting with Left Ventricular Apical Aneurysm, with a manifestation in 13.8% and 9.5% of cases,

respectively. (232) A ST depression with a fraction of 3.2% has been described as both, nonspecific as well as nonsensitive for a Left Ventricular Apical Aneurysm diagnosis. (232)

Echocardiographic findings included a mean EF of 53.9 ± 12.3% as well as a Paradoxical Jet Flow traversing the obstruction in 29.7% of cases. (232) A gradient of ≥70 mm Hg has been determined in assistance of a univariate Cox Regression procedure as representing a predictor for the formation of Left Ventricular Apical Aneurysm. (229)

In assistance of cardiac MRI, a detection of a transmural LGE of the Left Ventricular Apical Aneurysm, was existent with regard to 20.2% of individuals. (232)

3.8.4.9.6 Complicative Aspects and Prognosis

The amount of 22.2-58.3% (228, 227, 229) of individuals subject to Midventricular Hypertrophic Cardiomyopathy with Left Ventricular Apical Aneurysm present NSVT while AF has been reported in 23.1%-55.6% of cases (227, 229, 228). Presence of a mural intraaneurysmal Thrombus was found with regard to 33.3% of patients (229) while the amount of 9.5% experience Stroke (232) and 15.4-44.4% exhibit Progressive Heart Failure (227, 229, 228).

The rate of decease associated with Hypertrophic Cardiomyopathy was found to present 2.1-fold more elevated in individuals subject to the midventricular variant with Left Ventricular Apical Aneurysm compared to persons in the absence of the entity, with the proportions of 38.5% and 18.2%, respectively. (227) In assistance of Cox Regression multivariate analyses the presence of Left Ventricular Apical Aneurysm in patients with the midventricular phenotypic expression was found to represent a predictor for decease associated with Hypertrophic Cardiomyopathy (adjusted hazard ratio of 3.47, 95% CI: 1.38 to 8.73). (227)

The presence of Left Ventricular Apical Aneurysm leads to an unfavorable 5-year survival rate with regard to deceases resulting from HF as well as related to HF in comparison to persons in absence of the entity, with 74.1% (95% CI: 58-90.2) and 88.9% (95% CI: 78.4-99.4), respectively. (228)

3.8.5 Mass-Like Hypertrophic Cardiomyopathy

Mass-Like Hypertrophic Cardiomyopathy is regarded as a variant of Hypertrophic Cardiomyopathy (76) and is described as demonstrating an extensive thickening as a focus within the left ventricle (76). Neoplasia represent differential diagnoses with regard to the expansion. (77)

3.8.5.1 Diagnostic Aspects

While tissue originating from within the condition of Hypertrophic Cardiomyopathy is considered to present with different degrees of contractility, neoplastic entities are apprehended as holding no part demonstrating contraction. (238)

Within MRI in assistance of radio frequency saturation a labeling of myocardial tissue by means of altering its magnetization prior to the process of imaging is enabled. (239) The result constitutes hypointense stripes. (239) These markings of tissue endure for the time lapse of 60-450 milliseconds. (239) In consequence acquisition of images of the complete cardiac contraction phase within a cardiac cycle, is capacitated. (239) The deformation of the "tags" (239) concurrently with the heart's contraction allows a tracking of the cardiac motion. (239) This includes its translation, rotation, as well as twist. (239)

In 1991, Bouton et al. utilized aforementioned technique within MRI to differentiate a cardiac rhabdomyoma from ordinary tissue of the heart in a three days old neonate. (240) The girl presented an extensive cardiac contour and a compressing of the left lung within X-Ray assessment. (240) In consequence of an identical intensity of the myocardium and the tumefaction, distinction between the two tissues was impossible within either, T1 as well as T2 weighed MRI procedures. (240) Assistance in differentiation was as well not provided within context of Spin-Echo or Gradient-Echo imaging. (240)

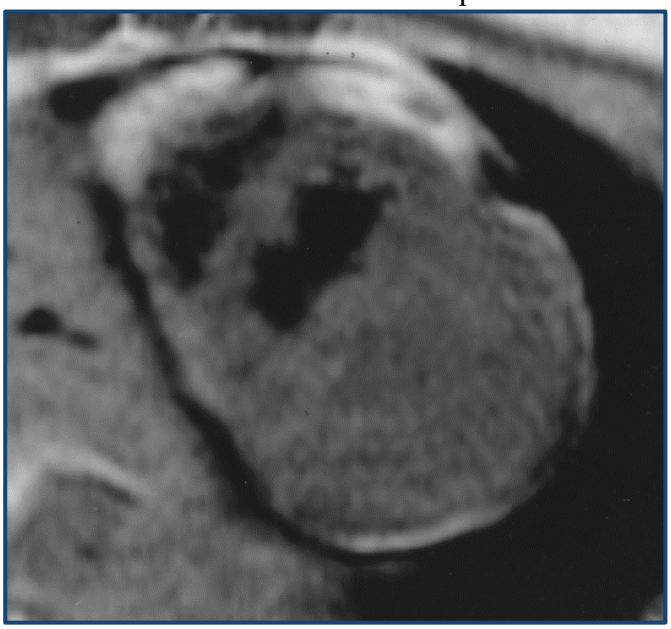

Figure 30: Short-Axis View of the heart of a female person at the age of 51 years via MRI presenting Mass-Like Hypertrophic Cardiomyopathy with hypertrophy located in the left ventricular free wall. (241) Image from (241).

Within utilization of antecedent mentioned technique, marking of the patient's chest by means of 2 mm wide saturation pulses in a star resembling pattern was achieved. (240) Imaging ensued using a multiphase Spin Echo MRI procedure with T1 weighing and Cardiac Gating. (240) While tags located in reference to the chest exhibited no motion, dislocation of tags on the cardiac tissue ensued in consequence of the heart's twisting movement. (240) Furthermore, the contractile part of the myocardium involved a distortion of tag

lines, while contraction with regard to the neoplasm was absent resulting in a preservation of the tag lines' shape. (240) In consequence aforementioned enabled a differentiation between ordinary cardiac tissue and tumefaction. (240) The separation of tag lines at the region between myocardium and pericardium effectuated by the cardiac twisting motion together with the neoplasm's translocation concurrently with myocardial tissue, provided evidence for the mass to have emerged from within the myocardium. (240)

Bergey and Axel describe two cases of patients subject to Mass-Like Hypertrophic Cardiomyopathy in which the utilization of the technique of Spatial Modulation of Magnetization within MRI assisted in determining the condition. (241) The first case exhibited a focal thickening with regard to the free wall of the left ventricle, with a dislocation and a distortion of applied tags in the thickened area as well as the surrounding tissue. (241) Performing of biopsy revealed myocardial fibers demonstrating hypertrophy and presence of fibrotic alterations. (241) Tissue denoting tumefaction was not existent. (241) In the second case the thickening was observed at the interventricular septum with a concurrent protrusion at the region of the RVOT. (241) Dislocation and distortion of tags in reference to the region of thickening was found as well in this patient. (241) Contraction was encountered in all septal portions. (241)

Çoban et al. reported of a boy at the age of twelve years with a focal thickening in the left ventricular superior wall revealed within CT assessment. (242) In assistance of MRI tags in the region of thickening presented dislocated and distorted, in alignment with the findings as well encountered in the patient's ordinary myocardial tissue. (242)

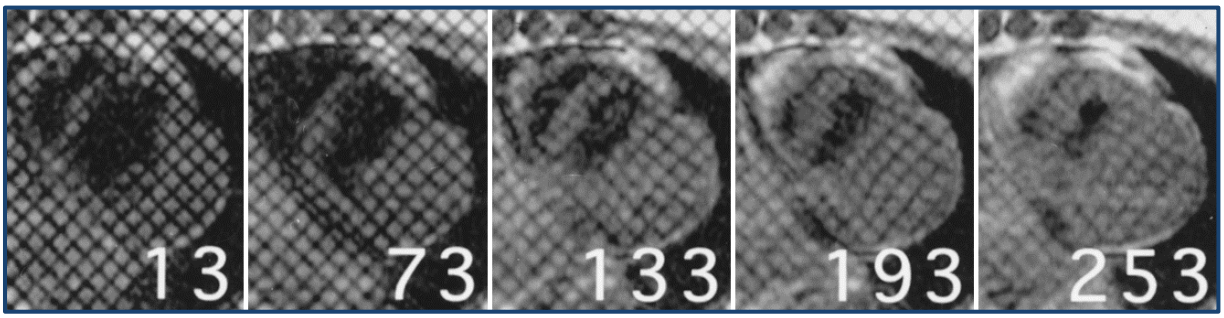

Figure 31: Images of the heart of a 51-year-old female individual in assistance of MRI in Short-Axis View attained at five succesive trigger delays exhibiting a mass simulating hypertrophy in the left ventricular free wall. (241) The tagging technique demonstrates the displacement and distortion of tags localized over the region of hypertrophy. (241) The trigger delays are designated in milliseconds by numbers at the right lower area, each. (241) Images modified from (241).

Nevertheless, it is considered, that the procedure of tagging necessitates further testing. (238, 241, 242) Differentiation between neoplasia and small contractile areas of persisting myocardium within context of infiltrative conditions necessitates elevated assessing caution. (238) This might be the case with regard to Lymphoma, Amyloidosis, or Sarcoidosis. (238)

Hansen and Merchant propose the examination of the myocardium by means of Double Inversion Recovery or the application of different weighings in context of Spin Echo MRI to possibly constitute a more favorable approach in the distinction between Mass-Like Hypertrophic Cardiomyopathy and neoplastic tissue. (238) The implementation of the techniques of First Pass Perfusion and Delayed Enhancement might add assistance in aforementioned consideration. (238) Hansen and Merchant base their suggestion on the signal proceeding from tissue of Mass-Like Hypertrophic Cardiomyopathy, presenting homogeneous, as well as the condition's perfusion to be found with a fairly resemblance of the surrounding intact myocardium. (238) In contrast, the signal with regard to neoplastic tissues is denoted as heterogeneous, demonstrating an alteration within context of Gadolinium application. (238) Furthermore, in comparison to intact tissue, perfusion in tumefactions presents distinct. (238)

3.8.6 Right Ventricular Involvement

In principal, ailments of the left ventricle exert influence on the function of the right ventricle intermediated by the alteration of afterload, immediate transfer of an injury, or the interventricular relationship. (243)

3.8.6.1 Definition

The definition of right ventricular hypertrophy has yet to experience the event of standardization. (244) According to the European Association of Cardiovascular Imaging and Saudi Heart Association, a right ventricular wall thickness of <5 mm is considered as ordinary within echocardiographic assessment in subcostal or parasternal long-axis projections acquired at the height of the chordae tendineae of the tricuspid valve at the end of diastole. (99) Similar notion is shared by other societies. (245)

Considering physiologic value of right ventricular wall thickness in adult individuals to vary contingent upon region from 2 to 7 mm (246), Foale et al. draw attention to measurements of ≥7 mm (246), while accepted to represent abnormal findings, to be reconsidered in case of isolated occurrences or detections with regard to the wall of the lateral or adjacent to the diaphragm. (246)

One further diagnostic approach constituted the presence of right ventricular hypertrophy ≥2 standard deviations in comparison to control individuals. (247) McKenna et al. engaged a subdivision of wall thickness, with ≤8 mm regarded as a mild manifestation, 9 to 12 mm as moderate, and >12 mm as severe hypertrophy (248), while Guo et al. utilize the threshold of ≥10 mm with regard to the anterior, free, or apical wall at end-diastole to delineate severity (249).

3.8.6.2 Epidemiology

The proportion of individuals subject to Hypertrophic Cardiomyopathy presenting an involvement of the right ventricle is noted within histopathologic assessment with 17.6% (89), while imaging modality revealed an extent ranging from 28.3-53.5% (251, 247, 248, 252).

The mean age of persons with right ventricular involvement constitutes 41 ± 17 to 61.0 ± 17.8 years (248, 252, 251), with 47.2-63.3% (252, 248, 251) being represented by male individuals.

3.8.6.3 Genetic Aspects

The amount of 90.9% of persons presenting with a RVWT of ≥10 mm were detected to hold one or more mutations in genes of the sarcomere identified with an association to the condition of Hypertrophic Cardiomyopathy, with 85.2% representing de novo mutations. (249) Mutations in the gene TTN were encountered the most frequent extent with 81.8%, while mutations with regard to the genes MYH7, MYBPC3, and ACTN2 were present in 54.5%, 36.4%, and 36.4% of cases, respectively. (249) Further mutations were found in reference to the genes MYH6, MYOM1 and MYL2 with 9.1% each. (249)

The proportion of 81.8% of individuals were identified as being subject to multiple mutations in sarcomeric genes. (249) Furthermore, presence of mutations in genes holding an association to Cardiomyopathies other

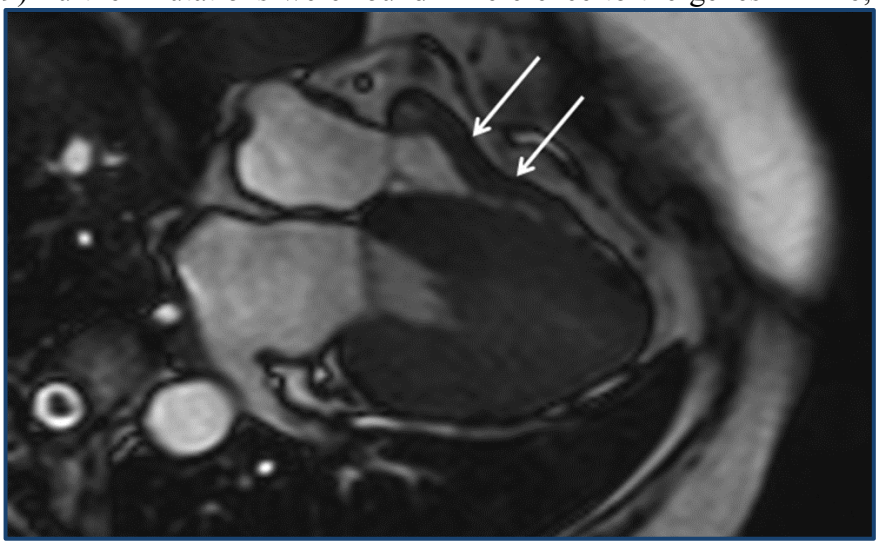

Figure 32: Hypertrophy encountered in the right ventricle while left ventricle is as well affected by hypertrophy. (250) Hypertrophy in the right ventricle is indicated by arrows. (250) Image modified from (250).

than Hypertrophic Cardiomyopathy or conditions with a relationship to Ion-Channels, was detected in 72.7% of persons. (249)

3.8.6.4 Morphologic Aspects

Right ventricular hypertrophy is existent as both, with a biventricular involvement (80) as well as a manifestation isolated to the right ventricle (81).

Patterns of right ventricular hypertrophy present resembling occurrences in the left ventricle. (253) Hypertrophy ranges from demonstrating a right ventricular concentric manifestation to an involvement of the apex, mid septum, basal septum, and/or free wall. (253) Furthermore, report of right ventricular hypertrophy presenting with right ventricular aneurysm, is existent. (254)

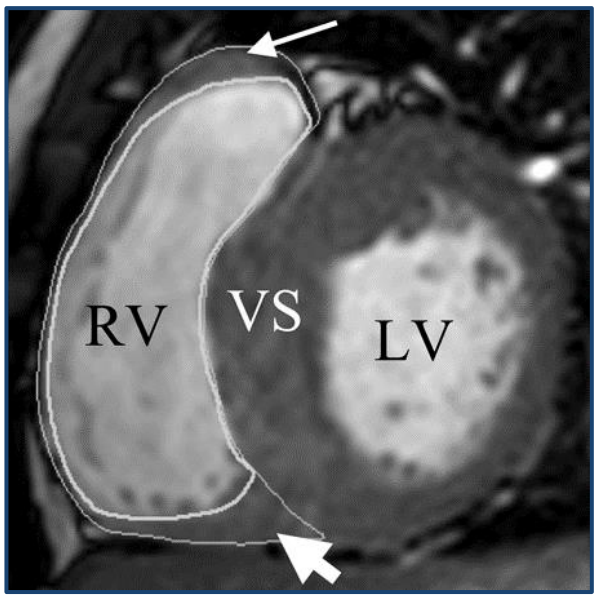

Figure 33: Short-Axis View of the heart via MRI with hypertrophy within the right ventricle. (247) Direct attention to the increase in wall thickness of the right ventricle at the superior region (designated by thin arrow) concurrently with the inferior region being encountered with substantial hypertrophy (indicated by extensive arrow). (247) The abbreviations RV, VS, and LV designate right ventricle, ventricular septum, and left ventricle, respectively. (247) Image modified from (247).

3.8.6.5 Right Ventricular Outflow Tract Obstruction

According to Frank and Braunwald, Right Ventricular Outflow Tract Obstruction has been considered present within circumstance of a pressure gradient of ≥10 mm Hg. (255) The entity was exhibited by 15.9% of individuals subject to Idiopathic Hypertrophic Subaortic Stenosis. (255)

Assessment of severely affected patients (exhibiting a systolic peak pressure gradient of the right ventricle of >50 mm Hg) revealed anatomic structures regarded as to be involved in the elicitation of RVOTO to be represented by the Crista Supraventricularis, the Moderator Band, or trabeculae, with each subject to hypertrophy. (80)

Generally, an obstruction with regard to the right ventricle was found at the level of right ventricular outflow tract in 64.3%, while an impediment at the mid-basal septum or apical trabeculae presented in 14.3% and 21.4% of cases. (256)

3.8.6.6 Clinical Aspects

The extent of 15.6% (248) of patients subject to Hypertrophic Cardiomyopathy and right ventricular hypertrophy experience Presyncope, while Syncope manifests in the amount of 3.3-15.1% (251, 248, 252) of individuals. Presence of angina is demonstrated by 20.8% of persons with a right ventricular involvement. (252)

While 64.2% of individuals are found within NYHA functional class I and II, functional class III and IV is exhibited by 32.1% and 3.8% of persons, respectively. (252)

3.8.6.7 Diagnostic Aspects

The extent of LVWT in individuals subject to right ventricular involvement presents with a mean of 20 ± 5 mm – 23.2 ± 5.1 mm (248, 252, 251) while RVWT is found with a mean of 6.5 ± 2.1 mm - 7.8 ± 1.8 mm (248, 252, 251). The mean basal right ventricular diameter constitutes 30 ± 4 mm (252). A study conducted by Nagata et al. identified persons with left ventricular hypertrophy to display LVOTO in 6.5% of cases, while LVOTO in individuals with right ventricular involvement was noted with 16.6%. (251) In comparison to persons with hypertrophy confined to the left ventricle, individuals with a right ventricular involvement exhibit elevated values of Brain Natriuretic Peptide, with 225.3 ± 254.5 pg/ml and 461.6 ± 669.8 pg/ml, respectively. (251)

While 75% of individuals demonstrate a right ventricular hypertrophy of ≤8 mm, the proportion of persons with a hypertrophy of 9-12 mm and >12 mm constitutes 21.9% and 3.1%, respectively. (248)

Division of the right ventricular wall into a superior, anterior, and inferior region, revealed the amount of 66.6% of individuals to present the maximal RVWT within the inferior right ventricular wall. (251) Maximal RVWT was exhibited by 26% of persons in the superior and 6.6% of individuals in the anterior section of the ventricular wall. (251)

The partition into nine regions, with the superior, anterior, and inferior sides being subdivided into basal, middle, and apical segments, maximal RVWT was manifested by the majority of individuals (33.3%) at the inferior basal region and by 20% of persons at the superior middle section. (247)

Right ventricular EF in individuals with or in absence of right ventricular involvement was found with 58.1% ± 17.5% and 53.4% ± 13.3%, respectively (p value of 0.11). (251) Furthermore, values for Tricuspid Annular Plane Systolic Excursion and right ventricular

Fractional Area Change present no statistical significant difference between persons subject to or without right ventricular hypertrophy, with 23.3 mm ± 3.5 mm compared to 24.3 mm ± 3.3 mm (*p* value of 0.32) and 47.7% ± 8.8% compared to 47.5% ± 6.7% (*p* value of 0.98), respectively. (252)

Yet, in comparison to persons in absence of right ventricular hypertrophy and control subjects, patients with right ventricular involvement demonstrated a lower value of Global Longitudinal Strain, with -22.4 ± 3.5, -23.8 ± 2.7, and -17.0 ± 3.6 (*p* value of <0.001), respectively. (252) Eminent relevance is accorded to aforementioned in consideration of 80% of the right ventricular Stroke Volume being accomplished as a result of longitudinal contraction. (252)

Compared to control study participants, in individuals with Hypertrophic Cardiomyopathy right ventricular -E/A ratio was found to be diminished with 1.30 ± 0.28 and 1.01 ± 0.40 (*p* value of <0.04), respectively. (257) Furthermore, persons subject to Hypertrophic Cardiomyopathy compared to control subjects exhibited a prolongation in right ventricular isovolumetric relaxation time and right ventricular deceleration time, with 170 ± 72 ms compared to 32 ± 23 ms (*p* value of <0.001) and 160 ± 58 ms compared to 118 ± 35 ms (*p* value of <0.01), respectively. (257)

Severino et al. found individuals with Hypertrophic Cardiomyopathy in comparison to normal study participants to demonstrate a reduction in the right ventricular relaxation index of the myocardium, with 34.9% ± 21.7% and 82.6% ± 20.9% (*p* value of <0.00001), respectively. (243) According to Suzuki et al., utilizing Cine Nuclear MRI and the Simpson Rule algorithm, in comparison to ordinary study subjects, individuals with Hypertrophic Cardiomyopathy were found with a diminution in either, right ventricular peak filling rate as well as filling fraction, with 305 ± 50 ml/s compared to 176 ± 46 ml/s (*p* value of <0.01) and 74.5% ± 13.3% compared to 39.5% ± 13.8% (*p* value of <0.01), respectively. (258)

Correlation of the maximal RVWT and left ventricular Mass Index was found to be existent, with a r^2 of 0.22 and a *p* value of <0.0001. (251)

The process of LGE within the right ventricle, while not being displayed by individuals subject to Hypertrophic Cardiomyopathy confined to the left ventricle, was evident in 33.3% of patients with right ventricular involvement. (251)

3.8.6.8 Complicative Aspects and Prognosis

The proportion of 70% (248) of individuals subject to Hypertrophic Cardiomyopathy with a right ventricular involvement exhibit Supraventricular Arrhythmia while manifestation of AF is in 26.6-30.2% (251, 252) of persons existent. Presence of Ventricular Tachycardia is noted in the extent of 46.7% (248) of individuals with a right ventricular involvement, in concurrence with 22.6% (252) demonstrating NSVT.

The extent of 23.3% of persons are detected with uniform while 63.3% exhibit multiform Premature Ventricular Contractions. (248) Couplets are presented by 53.3% of individuals, while the amount of 13.3% of persons manifest >30 incidents of Premature Ventricular Contractions within one hour. (248)

Regarded as the presence of progressive dilatation of the left ventricle in concurrence of systolic dysfunction, End Stage Hypertrophic Cardiomyopathy was identified in 16.6% of individuals with right ventricular involvement. (251)

With regard to the presence of hypertrophy of the right ventricle, mean LVWT as well as Supraventricular Arrhythmias were determined in assistance of stepwise logistic regression to represent independent risk factors. (248) Multivariate logistic regression detected RVWT as an entity correlating with NSVT exhibiting an odds ratio of 2.02, 95% CI: 1.28-3.19. (252) In assistance of a Receiver Operating Characteristic Curve analysis RVWT was identified as being able to differentiate individuals with the presence or the absence of NSVT with an area under the curve of 0.78, 95% CI: 0.64-0.92. (252) The extent of RVWT of 6.5 mm was determined as representing the most favorable distinguishing threshold. (252)

Denoting the Risk SCD score with a mean of 3.3 ± 2.3% and the limits of 0.83-15.90%, the score in reference to individuals demonstrating hypertrophy of the right ventricle in comparison to persons without right ventricular involvement presents with 3.8 ± 2.6% and 2.6 ± 1.6% (*p* value of 0.005), respectively. (252) Furthermore, the elevation in right ventricular hypertrophy was found demonstrating a correlation with the calculated score for the SCD risk with r = 0.52 and a *p* value of <0.001. (252)

Right Ventricular Hypertrophy was determined in assistance of a multivariate Cox proportional hazards regression model with the adjusted cova253riates gender and age as an independent predictor with regard to incidents of cardiovascular nature with a hazard ratio of 8.69, (95% CI: 2.68-28.1, *p* value of 0.0003). (251) The adjustment of gender, age, left ventricular EF, and

Mass Index of the left ventricle, identified RVWT with a hazard ratio of 5.35, (95% CI: 1.17-24.4, *p* value of 0.03). (251)

Although not clearly evident, a the more increased degree of RVWT correlated with a the more elevated NYHA functional class, with r = 0.20 and a *p* value of 0.04. (252) Furthermore, although in absence of statistical significance, presence of right ventricular hypertrophy resulted in an elevated amount of individuals exhibiting a NYHA functional class of ≥III, with 36% and 22% (*p* value of 0.12), respectively, as well as paroxysmal AF, with 31% and 17% (*p* value of 0.11), respectively. (252)

An analysis utilizing multivariate Cox regression in respect to individuals presenting a right ventricular hypertrophy of ≥10 mm determined a NYHA functional class of ≥III and an age of ≤18 years to constitute independent predictors for decease as a result of cardiovascular nature, with the hazard ratios of 8.68 (95% CI: 1.43-52.87, *p* value of 0.019) and 5.45 (95% CI: 1.24-28.36, *p* value of 0.026), respectively. (249)

3.8.6.9 Comorbidities

The condition of Hypertension is found in 37.9-43.4% (251, 252) of individuals presenting right ventricular involvement, while Dyslipidemia is existent in the proportion of 60.4% (252) of persons. Diabetes Mellitus is encountered in 7.5% of individuals. (252)

3.8.7 Genotype Positive Phenotype Negative Hypertrophic Cardiomyopathy

3.8.7.1 Historical Perspectives

In 1990, McKenna et al. reported on the findings concerning five individuals with uncommon cardiac specifics within two families. (259)

The first family demonstrated a frequent occurrence of SCD, with four relatives being subject to the incident. (259) Postmortem examination revealed with regard to all four cases a macroscopic ordinary cardiac semblance. (259) Heart weights within the first family were available from three persons ranging from 292-374 g. (259) Furthermore, LVWT as well as dimensions of the left ventricle presented common. (259)

In contrast, histologic examination revealed fibrotic alterations as well as elevated presence of myocyte disarray in respect to each family member. (259) While individual one, two, and four exhibited Type I myocyte disarray, with the proportions of 61.3%, 32.8, and 47%, respectively, myocardial disorganization in patient three was found of Type II, with an extent of 36%. (259)

The fifth patient, member of a different family, presented in assistance of echocardiographic assessment a ventricular septal thickness of 12 mm and a posterior LVWT of 13 mm. (259) Ventricular end systolic and diastolic expanses were found with 29 mm and 41 mm, respectively. (259) The woman was subject to a major Myocardial Infarction and deceased. (259) Within context of autopsy, the cardiac weight was determined with 325 g; in relation to the female person's corporal weight regarded to had been situated within ordinary confines. (259)

Histologically, atria's tissue was affected by interstitial fibrosis, while myocyte disarray was noted as Type I and being present with a proportion of 25.6%. (259)

Even if perhaps not clearly evident with respect to the fifth case, McKenna et al. eventually conclude along their lines: "[…] hypertrophic cardiomyopathy may exist without hypertrophy […]" (259). (259)

3.8.7.2 Definition

The emergence of genetic testing, effectuated the circumstance of individuals representing carriers of a mutation in a gene relevant to Hypertrophic Cardiomyopathy, yet with an absence in phenotypic expression. (260) The aforementioned is regarded as a subdivision in reference to the condition. (260, 261) The designations "genotype positive-phenotype negative" (261, 260), "preclinical" (260), "subclinical" (262), as well as "pre-hypertrophic" (263) find their utilization interchangeably. (260, 261, 263, 262)

3.8.7.3 Genetic Aspects

According to Lakdawala et al. the majority of genotype positive phenotype negative individuals present a mutation relevant to Hypertrophic Cardiomyopathy in the genes MYH7 and MYBPC3, with 52.6% and 36.8%, respectively. (264) Mutations in the gene TNNT2 are found in the amount of 6.6% of persons, while 3.9% of individuals are detected with a mutation in the gene TNNI3. (264) In this publication none of the persons where found with a TPM1 mutation. (264)

Findings by Ho et al. resemble antecedent distribution with mutations found in the genes MYH7, MYBCP3, TNNT2, and TNNI3 with the proportions of 50%, 36.8%, 8.8%, and 4.4%, respectively and no mutation detected with regard to the gene TPM1. (265)

Gray et al. report genotype positive phenotype negative individuals to present with a proportion of 62.5% predominantly mutations in the gene MYBPC3, while mutations in MYH7 were

encountered in 18.6% of cases. (261) Mutations in the genes TNNI3 and ACTN2 were detected in 12.5% and 6.3% of persons, respectively. (261) While mutations in the genes MYH7 and TNNI3 were equally present in respect to individuals with the age of ≤18 and >18 years, with 18.8% and 12.5%, respectively, mutations in MYBPC3 were found preponderantly in persons >18 years (68.8% compared to 56.3%) in concurrence with the entirety of mutations in the gene ACTN2 being exhibited by individuals with the age of ≤18 years. (261)

In spite of consideration of multiple mutations to implicate an elevated severity in morphologic manifestation (55, 64, 29), cases of genotype positive phenotype negative individuals simultaneously representing carriers of multiple mutations have been denoted (261, 266).

3.8.7.4 Clinical Aspects

Publications with regard to genotype positive phenotype negative persons denote the vast majority of individuals to present either asymptomatic (265, 267), with no administration of cardiac medication (265), or to be found within NYHA functional class I (265, 268).

Carolyn Y. Ho et al. (265) and Jennifer E. Ho et al. (268) note the entirety of their genotype positive study participants yet with an absence in left ventricular hypertrophy to had been found within NYHA functional class I (265, 268). According to Gray et al., while no genotype positive phenotype negative persons experienced Syncopes, NYHA functional class II was identified in reference to one individual at the age of ≤18 years. (261)

3.8.7.5 Diagnostic Aspects

Barry J. Maron et al. state, that to a frequent extent, detection of abnormalities are existent in assistance of 12 Lead Electrocardiography. (269) The assessment of the heart within the context of Two Dimensional Echocardiography as well as MRI yet, provide to a frequent extent, no affirmation. (269) Barry J. Maron et al. state, that the validation concerning the utilization of Cardiac Magnetic Resonance is existent on basis of an absence regard disadvantages in reference to wall thickness determination, as it is, by way of example, the case within the context of Echocardiography. (269)

3.8.7.5.1 Electrocardiography

According to Ryan et al., while 32% of individuals with a presence of left ventricular hypertrophy present abnormal Q waves, the electrocardiographic findings are exhibited by as many as 67% of persons with an either clinically or genetically ascertained diagnosis of

Hypertrophic Cardiomyopathy yet in absence of an increase in LVWT. (98) Lakdawala et al. reported of 18.4% of genotypic positive individuals without expression of LVWT compared to 2.5% of control study participants to had presented abnormal Q waves. (264) Additionally, while being absent in the entire collective of control subjects, a depression of the ST segment or an inversion of the T wave was found in the extent of 5.3% each of genotype positive persons without left ventricular hypertrophy. (264) Presence of abnormal Q waves, inversion of T waves, and/or depression of the ST segment in genotype positive relatives without left ventricular hypertrophy of affected persons had a specificity of 98%, yet with a sensitivity of as low as 25%. (264)

Orientating on the criteria set by Charron et al. (270, 271), Konno et al. state, that utilizing the delineations of a Q wave with an amplitude of >3 mm and/or a duration of >40 milliseconds encountered with regard to at least two leads with the exception of aVR, the amount of 27.6% of genotype positive clinically nonmanifest individuals were detected with abnormal Q waves. (270) Genotype negative individuals exhibiting within aforementioned electrocardiographic descriptions abnormal Q waves were noted with 5.4%. (270) The specificity and sensitivity in respect to persons at the age of ≥30 years was noted with 97% and 29%, respectively. (270) Individuals at the age of <30 years held a specificity of 90% and a sensitivity of 50%. (270)

3.8.7.5.2 Echocardiography

Examining persons subject to the mutation of c.3330+2T>G in the gene MYBPC3, yet with an absence in left ventricular hypertrophy, De et al. denote no major difference in Global Longitudinal Strain rate between genotype positive phenotype negative individuals and control study participants, with 20.3% ± 2.1% and 19.8% ± 1.8% (*p* value of 0.36), respectively. (272) In contrast, the assessment of left ventricular regions revealed inter alia a diminution in the strain rate concerning the basal septum. (272) While control subjects exhibited a strain rate of 19.0% ± 4.0%, genotype positive individuals without left ventricular hypertrophy had a strain rate of 16.8% ± 3.1% (*p* value of 0.02). (272) Conversely, in comparison to control subjects genotype positive individuals in absence of left ventricular hypertrophy were found with an elevation in the strain rate of the basal posterior wall (17.9% ± 5.2% compared to 22.5% ± 5.2%, *p* value of 0.001) as well as mid posterior wall (18.2% ± 3.0% compared to 21.8% ± 4.7%, *p* value of 0.001). (272)

Individuals with a ß-Myosin Heavy Chain mutation, both with and without left ventricular hypertrophy were found in comparison to control study participants to hold an elevation in left ventricular EF, with 75% ± 5%, 71% ± 6%, and 64% ± 5% (*p* value of <0.0001, determined for

both former groups collectively), respectively. (273) Additionally, genotype positive persons with and without a manifestation of left ventricular hypertrophy presented in comparison to control subjects a reduction in average early diastolic velocity, with 9.3 ± 1.8 cm/s, 13.7 ± 1.6 cm/s, and 16.6 ± 3.0 cm/s (*p* value of <0.0001, for each of former denoted groups), respectively. (273)

In assistance of a Receiver Operating Characteristic curve evaluation, the average early diastolic velocity of ≤13.5 cm/s was identified as the most beneficial value predictive of genotype positive persons, with a specificity of 86% and a sensitivity of 75%. (273) Additionally, the most favorable left ventricular EF value represented >68% being specific in 81% and sensitive in 77%. (273) The cutoff value of a left ventricular EF of ≥68% together with an average early diastolic velocity of <15 cm/s resulted in identifying genotype positive persons holding a specificity of 100% and a sensitivity of 44%. (273)

In a study by Ho et al., genotype positive phenotype negative persons were found to present in comparison to control study participants no statistically significant differences with regard to values of Global Systolic Strain (longitudinal, circumferential, and radial) and the longitudinal strain of the septum as well as lateral, anterior, and inferior wall. (265) In contrast, compared to control subjects, genotype positive phenotype negative individuals exhibited a diminution in global early diastolic mitral annular velocity, with 14.2 ± 0.3 cm/s and 12.3 ± 0.3 cm/s (*p* value of <0.0001), respectively, constituting a distinctness of 13%. (265)

3.8.7.5.3 Magnetic Resonance Imaging

3.8.7.5.3.1 Myocardial Crypts

Myocardial Crypts have been described inter alia as discrete blood containing fissures (274) demonstrating a depth of ≥50% (262, 275) or ≥30% (276) within an integral left ventricular myocardium (274) and holding the possibility of an interventricular communication yet in absence of an achievable blood exchange during systole (10). In 1958, Teare denoted myocardial clefts in reference to cases one and three as a result of post mortem investigation. (10) The myocardial structural entities have been encountered in healthy individuals (277) as well as in persons presenting Hypertrophic Cardiomyopathy (278, 279, 275), Hypertension (277), Dilated Cardiomyopathy (274), Aortic Valve Stenosis (279), Fallot Tetralogy (277), or Congenital Pulmonary Stenosis (277), with the latter two subsequent to surgical treatment (277).

The proportion of 32.9-81.3% of genotype positive phenotype negative individuals has been reported to exhibit at least one myocardial crypt. (262, 275, 276, 280)

Persons subject to a mutation in the gene MYBPC3 were found to demonstrate an approximately twofold increased presence in at least one crypt in comparison to individuals with a mutation in the genes MYH7, TNNT2, TNNI3, MYL3, and ACTC1 collectively, with 47% and 23% (odds ratio 2.9, 95% CI: 1.1-7.9, *p* value of 0.045), respectively. (262) According to Captur et al. the displaying of ≥1 crypt holds a correlation to the presence of sarcomere mutations with a β Coefficient of 2.5, 95% CI: 0.5-4.4, *p* value of 0.014, while relationship between ≥2 crypts and sarcomere mutations is existent demonstrating a β Coefficient of 3.0, 95% CI: 0.8-7.9, *p* value of 0.004. (262) Brouwer et al. denote one crypt to be indicative for a mutation in the genes of MYBPC3 or TPM1 with a specificity of 88% (95% CI: 83-91%) and a sensitivity of 70% (95% CI: 54-82%). (276) Additionally, presence of ≥3 crypts demonstrates an association with mutations in aforementioned genes with a specificity of 99% (95% CI: 96-100%) and a sensitivity of 40% (95% CI: 25-56%). (276)

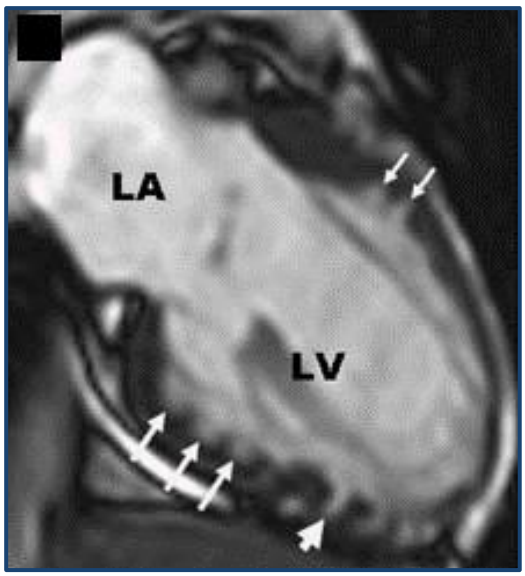

Figure 34: Image of a heart in end diastole in assistance of MRI in Long-Axis View of an asymptomatic genotype positive girl at the age of 17 years demonstrating no left ventricular hypertrophy. (275) Direct attention to the extensive crypts located within the basal inferior wall of the left ventricle, affecting almost more than the half of its transmural thickness (designated by large arrows). (275) Furthermore, two crypts are found within the anterior wall (indicated by small arrows). (275) One crypt, affecting close upon the entire of its thickness, is located within the inferior wall (275) (designated by the large arrowhead). The abbreviations LA and LV indicate left atrium and left ventricle, respectively). (275) Image modified from (275).

In comparison to control study participants, genotype positive phenotype negative individuals presented an elevated value in the crypts' maximal depth within the myocardium, with 59% ± 22% and 74% ± 21% (*p* value of <0.01), respectively. (276)

3.8.7.5.3.2 Other Structural Abnormalities

In comparison to corresponding control study subjects, genotype positive persons in absence of left ventricular hypertrophy exhibited increased longitudes of the anterior mitral valve leaflets, with 18 ± 3 mm and 21 ± 3 mm (*p* value of <0.01), respectively. (267) Of note, longitudes of

the posterior mitral valve leaflets held no eminent distinctness between aforementioned collectives (10 ± 2 mm compared to 11 ± 2 mm, *p* value of 0.17). (267)

Gruner et al. identified in persons subject to Hypertrophic Cardiomyopathy accessory muscle bundles within the left ventricle compared to control subjects to present more frequently. (209) These structural entities were found ranging from the cardiac apex inserting into the basal anterior septum or the anterior free wall. (209) While 63% of individuals with phenotypic manifesting Hypertrophic Cardiomyopathy display an "apical-basal muscle bundle" (209), the entity is found in 60% of genotype positive phenotype negative persons and 9.5% of control study subjects. (209)

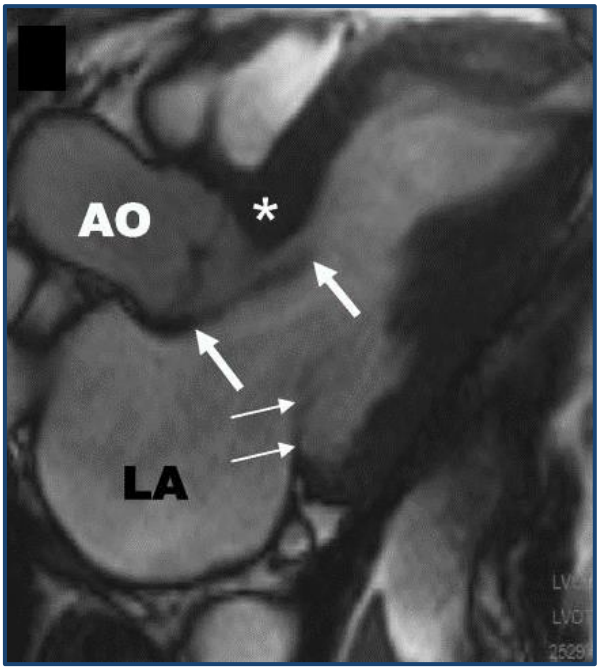

Figure 35: Long-Axis View of a heart via MRI of a person subject to a mutation in the gene MBPC3 yet with an ordinary LVWT. (267) The LVWT measures 9 mm (designated by the asterisk). (267) Direct attention to the elongated anterior mitral valve leaflet with an extent of 25 mm (267) (indicated by large arrows). The posterior mitral valve leaflet presents ordinary (267) (designated by thin arrows). The abbreviations AO and LA indicate aorta and left atrium, respectively (267). Image modified from (267).

In assistance of Fractal Analysis, Captur et al. determined the trabecular complexity of the left ventricle utilizing endocardial margins. (266) The global trabecular complexity of genotype positive phenotype negative individuals in comparison to control study participants presented elevated, with a fractal dimension of 1.176 ± 0.06 and 1.149 ± 0.03 (*p* value of 0.012), respectively. (266) The trabecular complexity between the two collectives was found not differing with regard to the ventricle's basal region. (266) In contrast, the maximal apical fractal dimension for genotype positive phenotype negative persons and control subjects was noted with 1.249 ± 0.07 and 1.199 ± 0.05 (*p* value of 0.001), respectively. (266)

As a consequence, trabecular complexity might assist in the identification of mutation carriers presenting no phenotypic manifestation.

The most beneficial maximal apical fractal dimension serving as a threshold in differentiating between genotype positive phenotype negative individuals and control study participants was determined with ≥1.241. (266)

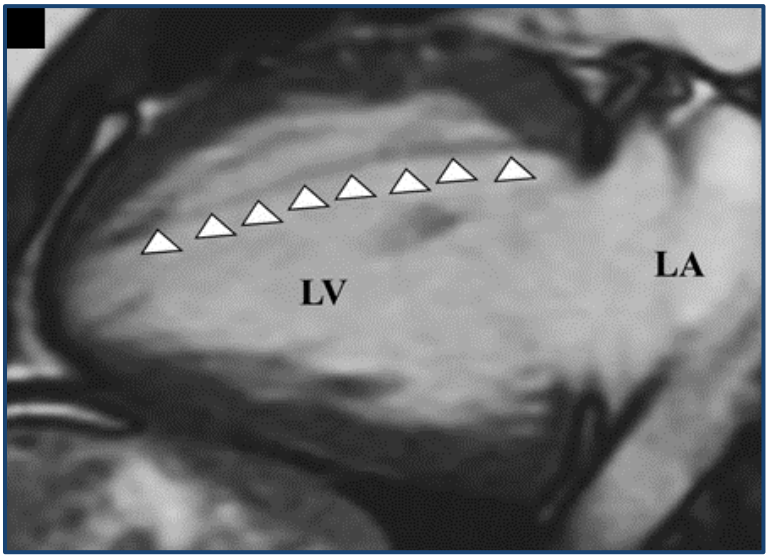

Figure 36: Image of the heart of a genotype positive phenotype negative individual at the age of 19 years in assistance of MRI presenting an ordinary maximal LVWT. (209) The mutation was identified in the gene MYH7 while the LVWT measured 9 mm. (209) Direct attention to the accessory muscle bundle reaching from the left ventricular apex to the cavity's base (indicated by arrowheads). (209) The abbreviations LV and LA designate left ventricle and left atrium, respectively. (209) Image modified from (209).

Within extracellular synthesis of Type I Collagen that assembles fibrils, the propeptide at the carboxy terminal is separated with its subsequent liberation into the blood circulation. (281) In comparison to control subjects, genotype positive individuals with an absence in left ventricular hypertrophy demonstrate an elevation in serum carboxy terminal propeptide, with 82.16 ± 3.03 µg per liter and 107.73 ± 4.65 µg per liter (*p* value of <0.001), respectively, constituting an extent of 31%. (282) The aforementioned is associated with a profibrotic circumstance. (282)

According to a study conducted by Carolyn Y. Ho et al., in comparison to control subjects, genotype positive persons with no manifestation in left ventricular hypertrophy demonstrated an expansion in extracellular volume, noted with 0.27 ± 0.01 and 0.33 ± 0.01 (*p* value of ≤0.001), respectively. (283)

Carolyn Y. Ho et al. denoted presence of LGE to had not been encountered in reference to genotype positive persons without left ventricular hypertrophy (283). In contrast, Rowin et al. reported of four cases of genotype positive phenotype negative individuals subject to the mutations of Asp175Asn in the gene TPM1 (found in two persons), Arg1228Cys in MYBPC3, as well as Arg663His in MYH7 to have presented regions of LGE. (284)

3.8.7.6 Alteration of Calcium Homeostasis

Holding a missense mutation of Arg403Gln in the gene encoding for cardiac α Myosin Heavy Chain, $\alpha MHC^{403/+}$ mice represent a genetic model in reference to human Familial Hypertrophic Cardiomyopathy, with a comparability in terms of the heart's histopathology as well as its dysfunction within the condition. (285)

According to Fatkin et al., the application of Minoxidil or Cyclosporin A to myocytes of wildtype mice in comparison to αMHC$^{403/+}$ mice results to a more pronounced elevation in diastolic Ca^{2+} concentration, with approximately 30% and <10%, respectively. (286) In consequence, Fatkin et al. draw the conclusion, that in myocytes of αMHC$^{403/+}$ mice a suboptimal management of Ca^{2+} concentration is existent. (286) As a result, the aforementioned would hold the implication of identical circumstances in reference to the disease of Hypertrophic Cardiomyopathy in human conditions.

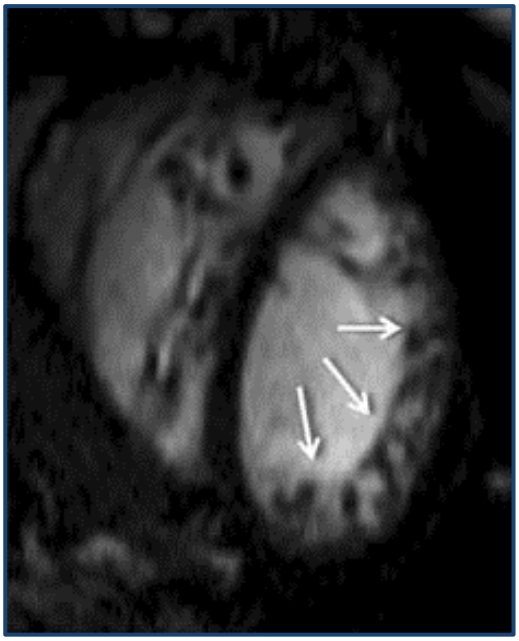

Figure 37: Image of the heart of a genotype positive phenotype negative individual demonstrating increased trabeculation. (266) The trabeculation is designated by arrows and holds a fractal dimension of 1.318. (266) Image modified from (266).

Application of Cyclosporin A, FK506, and Minoxidil to αMHC$^{403/+}$ mice resulted in the formation of left ventricular hypertrophy. (286) Of note, while Cyclosporin A application in αMHC$^{403/+}$ mice exhibited an almost twofold increase in left ventricular hypertrophy, hypertrophy development in wild type mice was not exceeding a moderate extent. (286)

The agent Diltiazem represents an inhibitor of L-Type Ca^{2+}-Channels. (286) Its application to αMHC$^{403/+}$ mice for the time period of two weeks prior to a three week simultaneous administration of either Cyclosporin A, FK506, or Minoxidil resulted in a blocking of the effects of the latter agents, with a LVWT, hypertrophy of myocytes, as well as a fibrotic state corresponding to αMHC$^{403/+}$ mice in absence of any treatment. (286)

According to Fatkin et al., the aforementioned serves to substantiate the affirmation of suboptimal Ca^{2+} concentration management in αMHC$^{403/+}$ mice to participate in the formation of hypertrophy. (286)

3.8.7.7 Alteration of Myocardial Energetics

In assistance of Phosphorus-31 Magnetic Resonance Spectroscopy, Crilley et al. demonstrated a diminution in the ratio between cardiac Phosphocreatine and Adenosine Triphosphate with regard to individuals subject to a mutation in genes encoding for β-Myosin Heavy Chain, Cardiac Troponin T, or Myosin Binding Protein C compared to control study participants. (287)

While the entire collective of mutation carriers exhibited a ratio of 1.70 ± 0.43, control subjects were found with a ratio of 2.44 ± 0.30 (p value of <0.001), constituting a difference of 30%. (287) Reduction in the cardiac Phosphocreatine to Adenosine ratio was as well present in genotype positive persons exhibiting a maximal left ventricular hypertrophy of <13 mm, with 1.57 ± 0.60 (compared to 2.44 ± 0.30 in control subjects, demonstrating a p value of <0.001). (287)

3.9 Therapeutic Intervention

3.9.1 General Measures

General Measures with regard to asymptomatic individuals subject to the condition of Hypertrophic Cardiomyopathy include the recommendation of nonparticipation in effortful physical activity as well as competitive athletics. (288)

Within consideration of concomitant severe epicardial Coronary Artery Disease in individuals at the age of ≥21 years to represent an influencing factor for unfavorable survival (288, 289), the reduction of risk factors involved in the process of Atherosclerosis constitutes an explicitly advised proceeding. (288) In regard to adequate cardiovascular condition, the performing of moderate aerobic activity is considered appropriate. (288)

Presence of LVOTO implies the avoidance of dehydration (17, 288), consumption of alcohol in an excessive conduct (17), or other measures holding the consequence of a vasodilatation (288).

Furthermore, the reduction of corporal weight is to be pursued. (17) Presence of AF concomitant to LVOTO is on basis of symptom aggravation subject of immediate sinus rhythm instauration or initiates the procedure of a monitoring of the ventricular rate. (17)

Generally, on basis of its positive cardiac inotropy, the administration of Digoxin in presence of LVOTO is not recommended. (17)

3.9.2 Pharmacological Measures

According to the ESC (290), as for the time period of the year 1950 up until 2011, the existence of studies enclosing the involvement of a pharmacological agent within the context of Hypertrophic Cardiomyopathy was considered to extent to the amount of 45, comprising 2,121 individuals subject to the ailment. (290) Olivotto et al. state, the contemporary approach of therapeutic intervention to rely on the overall scarcely available amount of clinical studies, the

medical practitioner's empirically acquired experience, or the projecting deduction resulting from within other diseases of cardiac nature. (291)

Generally, the circumstance of a deficiency in extensive clinical studies directs to principal objectives of pharmacological interaction to consist of an elevation of cardiac functional ability, amelioration of symptoms, as well as the possibly contingent discontinuation of the disease's progression. (17)

3.9.2.1 Hypertrophic Cardiomyopathy with Left Ventricular Outflow Tract Obstruction

With regard to the entire subset of individuals presenting Hypertrophic Cardiomyopathy with LVOTO, aside of applying general measures, pharmacological intervention constitutes the primary approach. (292) Provided that correct intake is conducted, the managing of the condition's gradients as well as symptoms might be attained for the time period of years. (292)

3.9.2.1.1 The Application of β-Adrenoceptor Blocking Agents

According to both, the ACCF/AHA collaboration (288) as well as the ESC (17), in principal, the administration of β-Adrenoceptor Blockers in individuals subject to Hypertrophic Cardiomyopathy and presence of LVOTO is to be considered as the initial pharmacological approach. (288, 17) In general, the beneficial effects of β-Adrenoceptor Blocking Agents within context of Hypertrophic Cardiomyopathy are regarded to proceed partially from the impediment of eventualities mediated by catecholamines. (290, 293) The latter inlcude the elevation in cardiac frequency, the ventricle's contractility, and rigidity. (293) The results of the collective effects of β-Adrenoceptor Blocking Agents represent the improvement of the ventricle's relaxation as well as the elevation of the time lapse of diastolic filling. (293) In consequence, the left ventricular pressure at end-diastole and perfusion find improvement. (293)

Propranolol, Atenolol, Nadolol, Metoprolol, as well as Bisoprolol represent agents engaged in the pharmacological treatment of Hypertrophic Cardiomyopathy and the presence of LVOTO, with the latter four contemporarily applied with increased frequency. (292) Even though elevated doses are denoted as necessity, their tolerance is regarded as admissible. (292) The desideratum within the procedure of titration constitutes the utmost elevated dose still tolerated, with the entities of symptoms, cardiac frequency, as well as blood pressure assisting as reference features. (292)

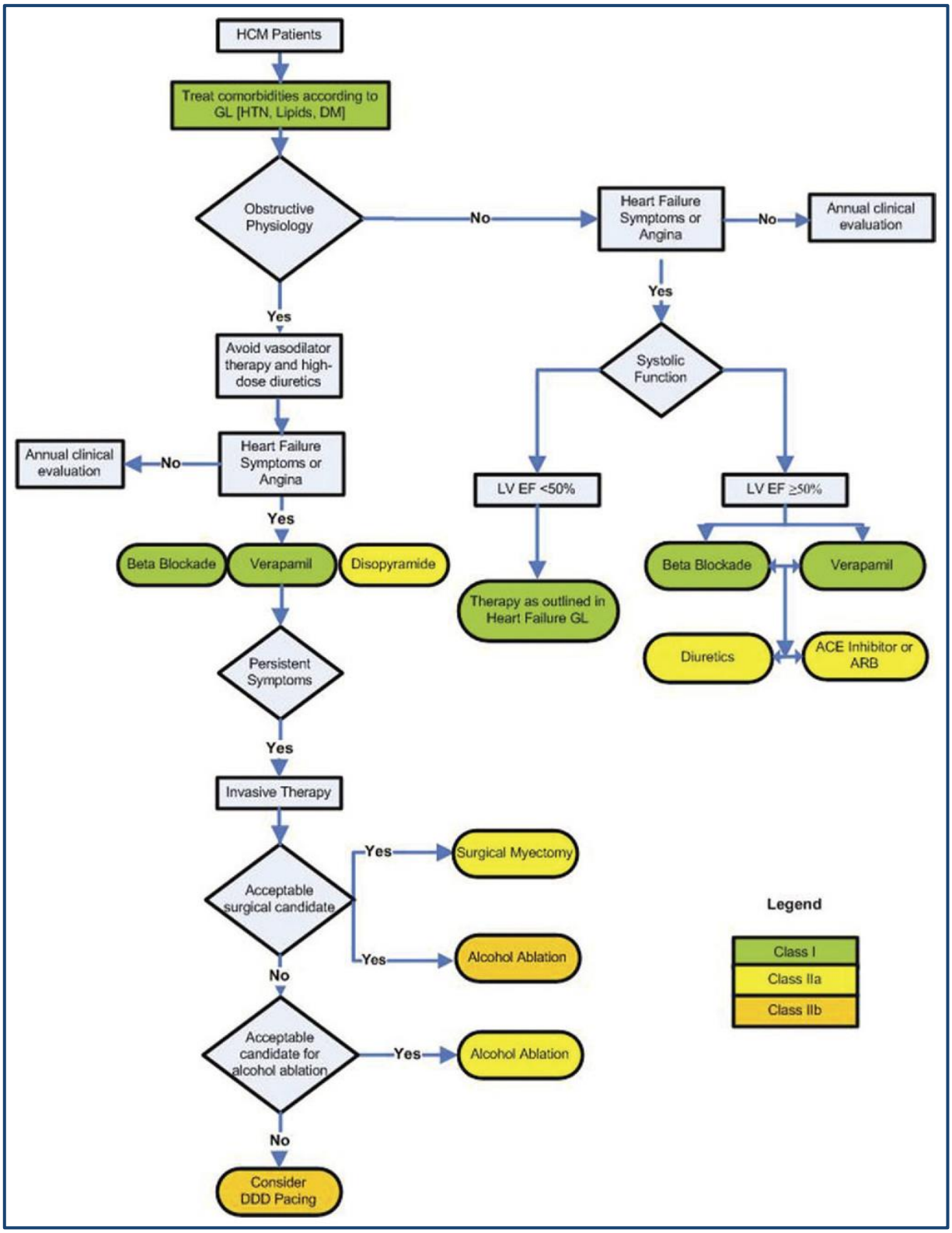

Figure 38: Algorithm for the treatment of Hypertrophic Cardiomyopathy according to the ACCF/AHA collaboration. (288) The abbreviations ACE, ARB, DM, GL, HCM, HTN, and LV designate Angiotensin Converting Enzyme, Angiotensin Receptor Blocker, Diabetes Mellitus, Guidelines, Hypertrophic Cardiomyopathy, Hypertension, and left ventricular respectively while Class I indicates a benefit extensively above possible risk, Class IIa a benefit above possible risk and Class IIb a benefit above or equal to possible risk. (288) Image modified from (288).

3.9.2.1.2 The Class IV Antiarrhythmic Agents Verapamil and Diltiazem

Beneficial effects of Verapamil and Diltiazem withinin the condition of Hypertrophic Cardiomyopathy are considered to proceed in part from their negative inotropy and chronotropy as well as partially from their improvement of the myocardium's diastolic properties. (290, 293)

The Class IV Antiarrhythmic Agent Verapamil (294) finds recommendation (288) or the consideration (17) of its application within the context of Hypertrophic Cardiomyopathy as a secondary option subsequent to β-Adrenoceptor Blocking Agents demonstrating ineffectiveness, unwanted secondary effects, or contraindications by either, the ACCF/AHA collaboration (288) as well as ESC (17). In consequence of a possible eventual Pulmonary Edema formation, increased observance is advised in presence of an obstruction exhibiting a gradient of $\geq$100 mm Hg or an elevated systolic Pulmonary Artery Pressure. (17)

According to Rosing et al., intravenous Verapamil application resulted with regard to patients exhibiting LVOTO in a diminution of the basal gradient from a mean of 94 ± 14 mm Hg to 49 ±14 mm Hg. (17, 295) Reduction in gradients was encountered as well within Valsalva Maneuver, Amyl Nitrite, or Isoprotenerol application, with 76 ± 5 mm Hg to 63 ± 13 mm Hg, 69 ± 15 to 39 ± 13 mm Hg, and 108 ± 29 to 70 ± 21 mm Hg, respectively. (295)

Even though with regard to individuals with or in absence of LVOTO collectively, oral Verapamil administration resulted in an increase of exercise capacity with a mean of 26 ± 8% (p value of <0.005). (296)

Elevated gradients, progressed Heart Failure, or Sinus Bradycardia represent circumstances a Verapamil administration is advised to be conducted with elevated attention. (288)

Furthermore, within context of Systemic Hypotension or a severe degree of Dyspnea within resting conditions, Verapamil application in patients exhibiting an obstruction may hold a detrimental effect. (288)

The agent Diltiazem is considered applicable either principally as an alternative to Verapamil (288) or within pharmacological intolerance or contraindication of β-Adrenoceptor Blocking Agents or Verapamil intake (17).

Diltiazem was found in comparison to Verapamil with no significant differences in reference to clinical and diagnostic findings except for the values of diastolic blood pressure, amplitude of T waves, and maximal cardiac frequency within exercise testing. (17, 179) In contrast,

according to Toshima et al., Verapamil application held secondary effects of a more severe nature. (179) Three study participants decided for a discontinuation of Verapamil intake. (179)

According to Betocchi et al., the administration of Diltiazem resulted in a systemic vasodilatation, with a Cardiac Index of previously 3.4 ± 1.0 to subsequently 4.0 ± 1.0 L/m/m^2 (*p* value of 0.003) and an aortic systolic blood pressure alteration from 116 ± 16 mm Hg to 107 ± 19 mm Hg (*p* value of 0.007). (290, 297) Additionally, while LVOT gradients experienced a diminution in reference to 36.4% of individuals, with a range of 7-10 mm Hg, in the opposite proportion of study participants Diltiazem application induced a gradient elevation extending from 4-68 mm Hg. (297)

The application of Verapamil or Diltiazem is advised to be undertaken in individuals presenting a severe degree of LVOTO in concurrence with the circumstance of an elevation in Pulmonary Artery Occlusion Pressure and diminution in systemic blood pressure with increased attention. (288) Aforementioned recommendation results in consequence of blood pressure diminution possibly inducing an elevation in LVOTO. (288) Subsequently, Pulmonary Edema formation may ensue. (288) The supplementation of either Verapamil or Diltiazem to β-Adrenoceptor Blocking Agents might result in a High-Grade Atrioventricular Block. (288) Furthermore, within concurrent application of β-Adrenoceptor Blocking Agents with either one of aforementioned Antiarrhythmic Agents, titrating the most beneficial dose of the former might encounter impediment on basis of the bradycardia inducing properties of Verapamil and Diltiazem. (288)

3.9.2.1.3 The Class Ia Antiarrhythmic Agent Disopyramide

Principally, either one, the ESC as well as the ACCF/AHA collaboration take the additional application of Disopyramide in patients with LVOTO into consideration in case of ameliorative nonsuccess of sole β-Adrenoceptor Blocking Agents or Verapamil administration. (17, 288)

Disopyramide is regarded as an Antiarrhythmic Agent of Class Ia. (17, 294) Aforementioned results by virtue of the agent exerting a velocity diminution of the action potential's ascending amplitude in Phase 0 as well as a prolongation of the repolarization period. (298, 299) The agent is denoted to hold the property of an ample negative inotropy. (300)

Its first application within the context of Hypertrophic Cardiomyopathy was published by Charles Pollick, in 1982. (298, 301) Intravenous application of Disopyramide resulted in a cessation of the basal pressure gradients and a decrease of pressure gradients within provocation in all patients. (301) Administered orally as maintenance treatment, all study participants

exhibited an enhanced physical tolerance within exercise testing as well as a clinical amelioration, with all individuals found in NYHA functional class I. (301)

According to Sherrid et al., Disopyramide application resulted in a diminution of the average peak LVOT gradient of close to 50% within a time period of ≥3 years. (17, 300)

Patients subject to LVOTO with and in absence of Disopyramide application demonstrate no statistically significant difference with regard to the annual rate of deceases resulting from any cardiac causality, with 1.4% and 2.6% (*p* value of 0.07), respectively. (300) Furthermore, statistically significant distinction between the two collectives is as well not existent in reference to the annual rate of SCD incidents, with 1% and 1.8% (*p* value of 0.08), respectively. (300)

Disopyramide is not to be titrated over the dosage of its properties effectuating a surpassing of a QTc interval of 480 ms. (17) Further confinement in its applicability is found on basis of its anticholinergic effects. (292)

Disopyramide demonstrates a long-term pharmacological tolerative adaptation, with the apprehension of contingently representing an agent for the duration of transition to a surgical therapeutic approach being present. (292)

On basis of an atrioventricular conduction increment and its consequential elevation in ventricular frequency, Disopyramide application in patients with AF or the predisposition for it is recommended to be performed with increased alertness. (17) Furthermore, avoidance of a simultaneous administration of Disopyramide with other agents holding an elongation of the QT interval is to be retained at one's attention. (292)

3.9.2.2 Nonobstructive Hypertrophic Cardiomyopathy

Symptoms in patients presenting Nonobstructive Hypertrophic Cardiomyopathy and a left ventricular EF of ≥50% might result in consequence of Diastolic Dysfunction or Microvascular Ischemia. (292)

3.9.2.2.1 Heart Failure

In general, objectives of pharmacological therapeutic intervention in patients subject to Heart Failure holding a left ventricular EF of ≥50% and concurrently with the presence of LVOTO being excluded (whether at resting conditions or with provocation), constitute the diminution in diastolic pressures within the left cavity and enhancement of its filling process. (17)

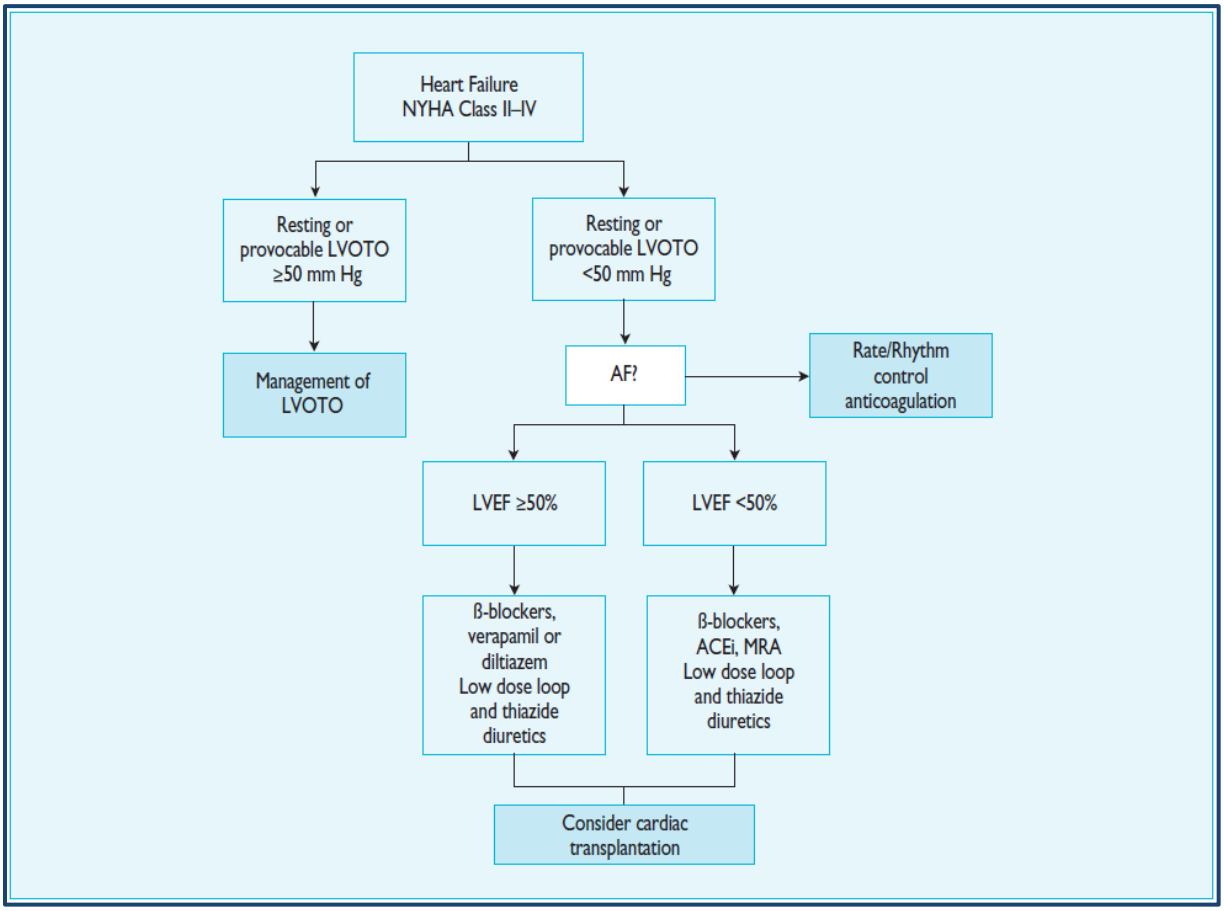

Figure 39: Treatment algorithm with regard to individuals presenting Heart Failure within Hypertrophic Cardiomyopathy according to the ESC. (17) The abbreviations ACEi, LVEF, MRA, and NYHA designate Angiotensin Converting Enzyme Inhibitor, left ventricular Ejection Fraction, Mineralocorticoid Receptor Antagonist, and New York Heart Association, respectively. (17) Image modified from (17).

The application of β-Adrenoceptor Blocking Agents, Verapamil, Diltiazem, as well as Loop Diuretics, represents the pharmaceutical attempt in attaining aforementioned desideratum. (17)

The formation of signs and symptoms related to Heart Failure in individuals subject to Hypertrophic Cardiomyopathy presenting a preserved EF is existent in the extent of 10-15%. (292)

In case of a left ventricular EF of <50% as well as a symptomatic manifest Heart Failure, the ESC regard Diuretics, β-Adrenoceptor Blocking Agents, Angiotensin Converting Enzyme Inhibitors, Angiotensin Receptor Blockers as well as Mineralocortiocoid Receptor Antagonists as applicable pharmaceuticals. (17) In patients subject to Hypertrophic Cardiomyopathy, either one, the ESC as well as the ACCF/AHA collaboration, principally advice within context of Heart Failure and left ventricular EF presenting <50%, a proceeding in accordance with guidelines concerning the condition of Heart Failure, with the ESC specifying the utilization of

aforementioned medications consonantly to its guidelines published in the year of 2012 (302). (17, 288, 302)

Even though, in principal within presence of LVOTO not recommended, on the basis of regulating the individual's cardiac frequency, the application of sparse doses of Digoxin in case of no LVOTO as well as presence of a NYHA functional class II-IV, a left ventricular EF of

<50%, and Permanent AF, might be performed. (17) The aforementioned is contingent with Digoxin as the sole medication or concomitant with β-Adrenoceptor Blocking Agents. (17)

3.9.2.2.2 Angina Pectoris

In context of individuals subject to Hypertrophic Cardiomyopathy experiencing Angina Pectoris resembling pain within physical exercise or as extended periods, in case of an ascertained exclusion of LVOTO (within resting conditions or provocation) or an obstructive Coronary Artery Disease, the ESC recommends the application of β-Adrenoceptor Blocking Agents or Calcium Antagonists. (17) Furthermore, within aforementioned situational condition, the ameliorating intervention by means of oral Nitrates might be attentively performed. (17)

The agent Ranolazine has been noted to convey anti-ischemic as well as antianginal properties. (303) One of its possible mode of action is to deflect the synthesis of Adenosine Triphosphate from the process of Beta Oxidation to Carbohydrate Oxidation. (304) The transfer to the latter, holding a lower oxygen consumption, eventually leads to a reduction in cardiac oxygen demand. (304) According to Ammirati et al., even though with interindividual variance, Ranolazine administration holds the potential of ameliorating Angina Pectoris. (292)

3.9.3 Invasive Therapeutic Interventions of Left Ventricular Outflow Tract Obstruction

3.9.3.1 Procedural Indication

Regarding its entire applicable spectrum, the ESC generally recognizes an application of a LVOTO diminution in assistance of invasive procedures, in case of the determinants of a gradient presenting ≥50 mm Hg, a NYHA functional class III to IV and/or repeatedly occurring incidents of Syncope within physical activity. (17) Aforementioned finds consideration within context of an antecedent pharmacological attempt with utmost elevation of its agents' doses within tolerance. (17)

3.9.3.2 Ventricular Septal Myectomy

3.9.3.2.1 Historical Perspectives

Based on the techniques of Subaortic Ventriculomyotomy (305), Morrow et al. performed the surgical procedure of Ventricular Septal Myectomy (12) by means of enhancing aforementioned intervention via exchanging the single incision with two parallel Myotomies at the distance of 1 cm. (305, 12) Subsequent to manually deepening the incisions to the extent of 2-3 cm, resection of the intermediate tissue ensues, with Morrow et al. noting the resectates' weight with 1-2.5 g. (12)

Messmer extended the initial procedure by Morrow et al. inter alia by additional resections at the regions of septum's encounter with the anterior as well as inferior wall at midventricular level, as nomenclatural considered by the AHA (183). (306) Additionally, Messmer implemented a mobilization of the papillary muscles and their optional trimming. (306) Minakata et al. enhanced the procedure by Morrow et al. inter alia by resecting towards the mitral valve, the papillary muscles's ground, and apical third located at the septum dextral as well as severing abnormal papillary muscle attachments and dividing or removing unordinary formation of cords or fibrous connections. (307)

3.9.3.2.2 Clinical Aspects

According to the ESC, the procedure of Ventricular Septal Myectomy attains an entire elimination or an extensive diminution in the gradient resulting from LVOTO in the amount of >90% of patients. (17) A meta-analysis conducted by Liebregts et al. revealed within context

of Ventricular Septal Myectomy a median reduction in LVOTO gradient in patients subsequent to the procedure of 77% (69-90%). (308)

The ESC denotes Ventricular Septal Myectomy to accomplish a sustained improvement of symptoms in 70-80% of patients. (17)

Individuals with performed Ventricular Septal Myectomy exhibit a median decrease in NYHA functional class of 45% (44-48%). (308) The amount of patients subsequent to the surgical procedure found within NYHA functional class III or IV is noted with 4.5% (4.5-12%). (308)

3.9.3.2.3 Complicative Aspects and Prognosis

An incident of Stroke or Cardiac Tamponade in context of Ventricular Septal Myectomy are according to a meta analysis conducted by Osman et al. periprocedurally exhibited by the

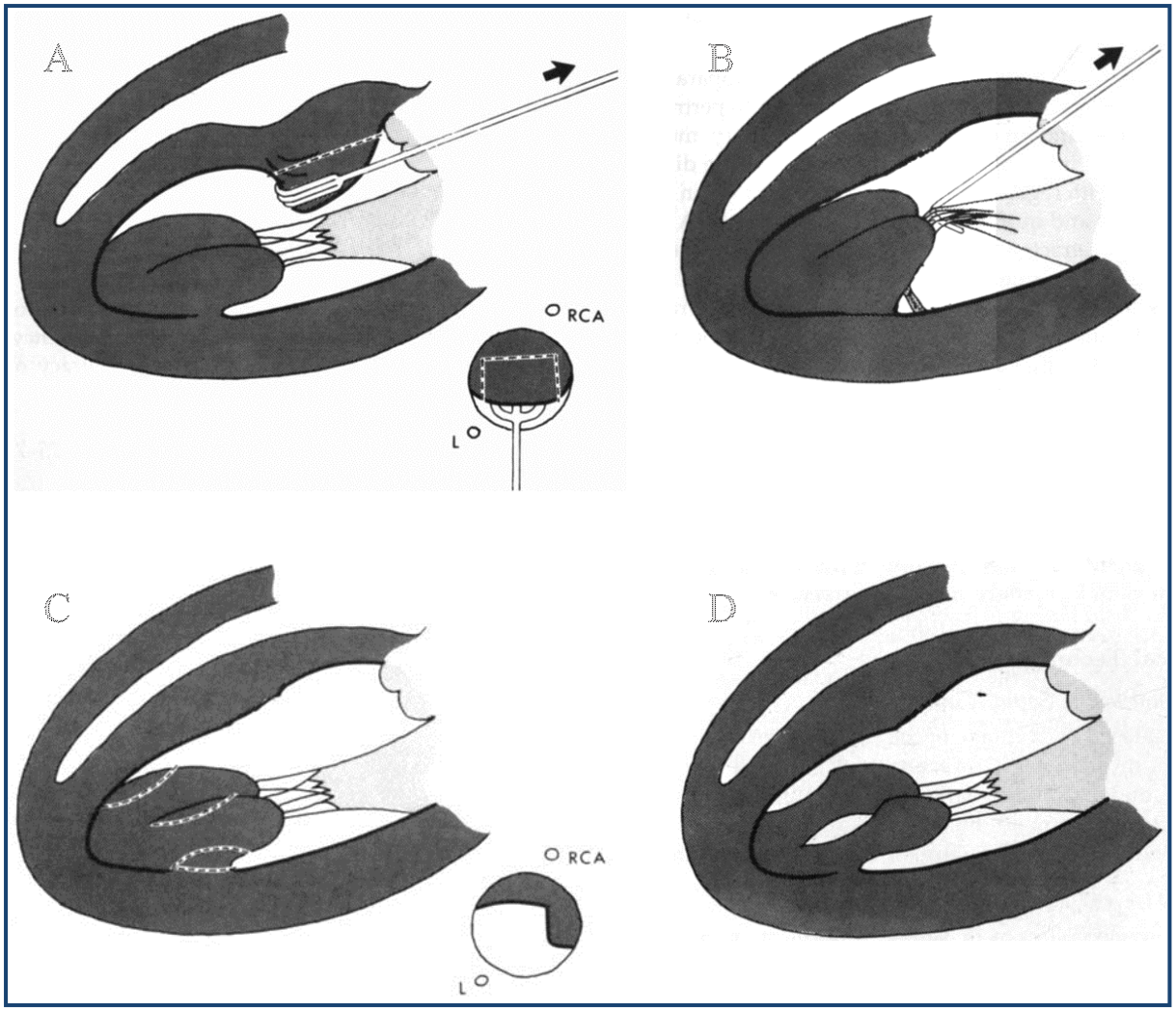

Figure 40: Possible proceeding within Ventricular Septal Myectomy. (306) A: Utillization of a sharp retractor attains the complete resection of the excessive muscular tissue located at the ventricular septum. (306) B: Traction at the chordae tendinae eventuated in assistance of a nerve hook reveals the possible existence of unordinary attachments at the papillary muscles affected by hypertrophy. (306) C: Attachments are removed while fixtures of the papillary muscles with the left ventricular cavity are eliminated. (306) In case of necessity, the hypertrophied papillary muscles are trimmed. (306) D: Eventual state of the heart attained subsequent to the procedure. (306) The abbreviations RCA and L indicate Right Coronary Artery and Left Coronary Artery. (306) Images modified from (306).

proportions of 1.5% (95% CI: 1-2.3%) and 1.8% (95% CI: 0.8-3.6%) of patients, respectively. (309) The amount of 4.2% of individuals are found with a necessity of pace maker implantation in consequence of a Third Degree Atrioventricular Block (309). According to Fitzgerald and Kusumoto, the extent of 50-100% of individuals having performed the procedure of Septal Myectomy present a Left Bundle Branch Block formation. (310) The occurrence of a Right Bundle Branch Block within the context of Septal Myectomy is noted with 0-1%. (310)

A periprocedural decease within Ventricular Septal Myectomy is encountered in 1.8% (95% CI: 1.4-3.1%) of cases. (309)

Overall, the pooled rate of all-cause mortality in context of Ventricular Septal Myectomy is noted with 1.1% per person year, while the pooled rate of deceases resulting from a cardiovascular causality presents with 0.5% per person year. (309)

Furthermore, the pooled rate with regard to the incident of SCD is found with 0.3% per person year. (309)

Ommen et al. denotes findings of overall survival rates for the time periods of 1, 5, and 10 years presenting with 98%, 96%, and 83%, respectively, to resemble rates encountered within the general white population of the United States of America corresponding according to age and gender, with 98%, 95%, and 88%, respectively. (311)

Additionally, Barry J. Maron et al. directs attention to the situational condition of a low in postoperative mortality, in context of Ventricular Septal Myectomy being performed in dedicated Hypertrophic Cardiomyopathy centers conveying an elevated number in patients. (312) Within the time period of the year 2000 until 2014, effectuating Ventricular Septal Myectomy in reference to the extent of 3.695 of patients, at five centers located in North America regarded to conduct the procedure at an increased number, the cases of deceases within the 30 postoperative days, are reported with 17, constituting 0.46%. (312)

3.9.3.2.4 Element of Consideration

According to Osman et al., the proportion of individuals with the requirement of a reintervention subsequent to the procedure of Ventricular Septal Myectomy is noted with 1.5%. (309)

3.9.3.3 Alcohol Septal Ablation

3.9.3.3.1 Historical Perspective

In 1995, Ulrich Sigwart reported about the diminution of myocardial hypertrophy in assistance of a catheter in order to conduct a subsequent injection of absolute alcohol with the intention of producing an infarction. (313, 314) With regard to the first and second patient the balloon catheter was placed at the first principle divarication within the septum of the Anterior Interventricular Artery. (314) In reference to individual number three, after a process of exploration with nonsuccess in temporarily diminishing the pressure gradient subsequent to

inflation, the catheter was placed at a voluminous divarication within the septum. (314) Subsequent to inflation, all individuals presented a decrease of the pressure gradient in reference to the LVOT. (314) Eventually, the injection of 3 ml or 5 ml, respectively, of absolute alcohol was effectuated. (314) It is denoted, that patient three exhibited the transient occurrence of a Complete Heart Block. (314) With regard to all three patients, the attainment of an elimination of pressure gradient was reported. (314)

3.9.3.3.2 Clinical Aspects

Utilizing the Euro-ASA registry, Veselka et al. report a decline in NYHA functional class from 2.9 ± 0.5 to 1.6 ± 07 subsequent to the procedure of Alcohol Septal Ablation. (315) According to Nagueh et al., employing a registry of nine centers in North America, while 78% of individuals with Hypertrophic Cardiomyopathy demonstrated NYHA functional class III or IV prior to the intervention, proportions of NYHA functional class I, II, III, and IV subsequently to Alcohol Septal Ablation were found with 72.5%, 23%, 3.9%, and 0.65%, respectively. (316)

Furthermore, according to Veselka et al., reduction in CCS class prior and subsequent to Alcohol Septal Ablation was accomplished from 1.3 ± 1.2 to 0.7 ± 0.8. (315) While 43% of patients in North America presented CCS class III or IV prior to the intervention, CCS class I, II, III, and IV after Alcohol Septal Ablation was encountered in 89%, 8%, 0.9%, and none of individuals, respectively. (316)

Reduction in the gradient of LVOTO in assistance of Alcohol Septal Ablation within the Euro-ASA registry was accomplished from 67 ± 36 mm Hg to 16 ± 21 mm Hg (315) and within resting conditions from 70 ± 38 mm Hg to 35 mm Hg (316) reported in the

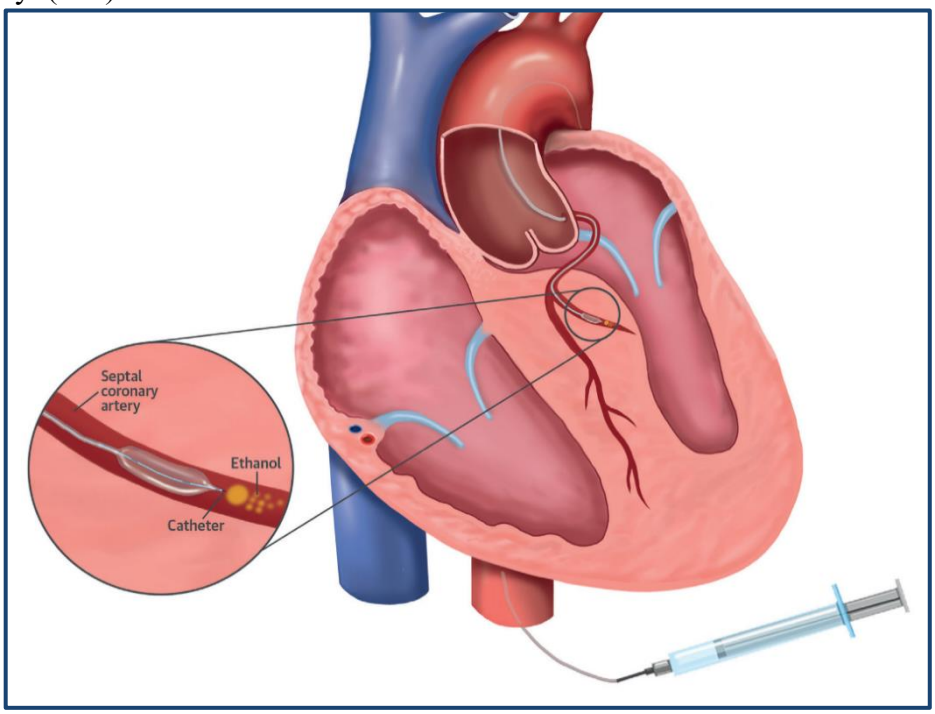

Figure 41: Demonstration of Alcohol Septal Ablation. (317) Image modified from (317).

registry pertaining to North America.

3.9.3.3.3 Complicative Aspects and Prognosis

According to Osman et al., the periprocedural occurrence of Stroke or Cardiac Tamponade within the context of Alcohol Septal Ablation are noted with regard to 0.8% (95% CI: 0.5-1.3%) and 1.3% (95% CI: 0.9-1.7%) of cases, respectively. (309) The imperative in implantation of a permanent pacemaker as a result of a Third Degree Atrioventricular Block is encountered in 5% of patients undergoing the intervention. (309) Of note, Veselka reports of a temporal periprocedural Third Degree Atrioventricular Block occurring within 30 days subsequent to the intervention in the proportion of 36.7%, while implantation of a permanent pacemaker was conducted in 11.8% of individuals encompassed by the study. (315) According to Fitzgerald and Kusumoto Right Bundle Branch Block is encountered in 37-70% of patients, while 2-6% of individuals exhibit a Left Bundle Branch Block. (310)

The extent of 1.6% of individuals are reported to exhibit Ventricular Arrhythmia immediately after Alcohol Septal Ablation. (315)

The pooled rate of all-cause mortality with regard to individuals undergoing Alcohol Septal Ablation presents with 1.5% per person year, while pooled rate of mortality of cardiovascular nature is found with 0.4% per person year. (309) While Veselka et al. note the rate of mortality within the first 30 days subsequent to the procedure with 1% (315), Nagueh et al. mentions within the collective of 874 individuals six cases of decease presenting an immediate association with the intervention, constituting 0.69% (316).

Individuals with the procedure of Alcohol Septal Ablation exhibit a pooled rate of SCD of 0.3% per person year. (309)

In assistance of multivariate analysis, the determinant of NYHA functional class was detected as an independent predictor in reference to all-cause mortality, with a hazard ratio of 1.5 (95% CI: 1.00-2.10, *p* value of 0.047). (315)

3.9.3.3.4 Elements of Consideration

While performing of Alcohol Septal Ablation may find consideration with regard to a patient, locating of a vessel appropriate for its effectuating is not guaranteed. (318) According to Batzner et al., detection of an appropriate blood vessel within the septum was achieved in respect to 93.9% of patients. (318) Additionally, an amount of up to the extent of five blood vessel branches were assessed in order to attain a vessel considerable for the procedure's

application. (318) Possibility of effectuating the procedure with regard to the first examined blood vessel branch, was existent in the extent of 83% of persons. (318) Furthermore, accomplishment of the procedure within two attempts as a result of an interruption with detailed examination of acquired angiographic images within first attempt, was conducted with regard to 3.4% of patients. (318)

Veselka et al. denote, that while the increase in amount of applied alcohol resulted in a more extensive diminution in LVOT gradient, it as well held a more frequent manifestation of a Third Degree Atrioventricular Block, with an odds ratio of 1.19, 95% CI: 1.05-1.35 and a *p* value of 0.006. (315) The median of utilized alcohol doses was found with 2.2 ml ± 0.9 ml. (315) As to assure a sufficient therapeutic result, yet maintain an appropriate patient's safety, Veselka et al. endorse a volume of injected alcohol of 1.5-2.5 ml. (315)

The diminution in LVOT gradient at the time period of >3 months subsequent to Alcohol Septal Ablation for patients undergoing the intervention with an amount of alcohol of ≤2 ml in comparison to >2 ml, was found with 86% ± 25% and 95% ± 21% (*p* value of <0.001), respectively. (319) Akin, the residual extent in LVOT gradient for aforementioned time lapse in reference to individuals having performed the procedure with an alcohol dose of ≤2 ml presented with 11 ± 18 mm Hg, while patients with an amount of >2 ml were found with 6 ± 20 mm Hg (*p* value of <0.001). (319)

Long term All-cause mortality within a median follow-up time period of 6.3 ± 3.7 years was found with regard to an application of an alcohol dose of ≤2 ml in comparison to >2 ml, with 12% and 17.4% (*p* value of 0.2), respectively. (319)

Of note, the amount of 58.3% of patients with a performed Alcohol Septal Ablation demonstrate additionally to immediate postprocedural outcome a further diminution in LVOT gradient at examination three months subsequent to the intervention. (320) Akin, 4.2% of individuals are found with a de novo emerged LVOT gradient at aforementioned time period. (320) According to Seggewiss et al., the supplemental decrease in gradient might be attributable to an eventuating process of cardiac remodeling (resembling the occurrence encountered after an incident of Myocardial Infarction) and/or progressive decline in SAM. (320)

Spirito et al. draw attention to Alcohol Septal Ablation's inability to eliminate a LVOT gradient within conjuncture of being extensively elicited by means of mitral valve complex abnormalities. (321)

Additionally, experience accumulation within the procedure is to be considered. (322) Drawing comparison between three patient collectives, Van der Lee et al. report a substantial decline in deficient clinical end results and residual LVOTO, with the requirement of a reintervention, subsequent to the first collective consisting of 43 performed procedures. (322) In comparison to an extent of 20.9% in the first collective, the subsequent two collectives demonstrated aforementioned situational conditions with a proportion of 2.3% and 4.4%, respectively. (322) Van der Lee et al. denote interventional insufficiencies to extent at an amount of 20 procedures per center and per year to an extent of 4%. (322)

Mateo and Gimeno state cardiac remodeling to ensue subsequent to either therapeutic procedure, Ventricular Septal Myectomy as well as Alcohol Septal Ablation. (313) This occurrence holds as well a diminution in the thickness of other segments and left atrial dimension. (313) Aforementioned result by virtue of the attained more favorable hemodynamic circumstance. (313)

3.9.4 Cardiac Pacing

In 1997, one of the first three randomized studies in reference to cardiac pacing within the context of Hypertrophic Cardiomyopathy, conducted by Nishimura et al., was published. (17, 323, 324) It comprised 63% of individuals reporting of a subjectively apprehended amelioration of symptoms in relation to DDD Pacing. (324) Nevertheless, denoted are the extent of 42% of patients who remarked an equal sensation in reference to AAI Pacing with the programming of 30 beats/min as backup. (324)

Noting the initial extent in LVOT gradient with a mean of 76 ± 61 mm Hg, patients undergoing DDD Pacing demonstrated a diminution in gradient to 55 ± 38 mm Hg, while individuals within AAI Pacing were noted with a gradient of 83 ± 59 mm Hg. (324) It is stated, that within context of the entire study, substantial alterations in cardiac frequency or blood pressure were not existent. (324)

The ESC denotes an absence in the entire elucidation of Cardiac Pacing in patients subject to Hypertrophic Cardiomyopathy to hold an absolute beneficial effect. (17) Aforementioned medical approach may find consideration in patients demonstrating inter alia a LVOTO with a gradient of ≥50 mm Hg present at resting conditions or within context of physical provocation. (17)

According to a study conducted by Kappenberger et al., DDD Pacing induced a diminution in LVOT gradient examined subsequent to one year of pacing from initial 59 ± 36 mm Hg to 30

± 25 mm Hg (*p* value of <0.001). (17, 323, 325) While overall assessment of endurance within exercise testing with regard to all study participants demonstrated no difference with or in absence of pacing, DDD Pacing in individuals with an initial physical capacity of <10 min extended the exertional duration by the amount of 21% (*p* value of 0.008). (325) The extent of 85.7% of patients initially found within NYHA functional class III exhibited an improvement with pacing. (325) Similarly, 45.9% of individuals presenting NYHA functional class II were noted with an amelioration, with 2.7% of patients found with a deterioration. (325)

Generally, the attempts to describe the possible improvement within Atrioventricular Sequential Pacing, even though confirmation not being existent with regard to all, consider the theories of negative inotropy, diminution in left ventricular hypercontractility, inversed activation of the septum, decrement in SAM, influence on left ventricular filling, and a reverse myocardial remodeling. (323)

3.9.4.1 Pacing Location

The reduction in LVOT gradient was demonstrated to hold a variance contingent upon region of pacing. (323, 326) According to Gadler et al., pacing at the right ventricular apex resulted in a diminution of LVOT gradient of >30% in all study participants noted from a mean of 96 ± 33 mm Hg to 38 ± 24 mm Hg. (326) Lead placement at the high septum presented a gradient reduction of >30% in the extent of 20% of study participants, while conversely, the amount of 13.3% of individuals were found with a gradient increase of >30%. (326) Gadler et al. denote with regard to the remaining patients no gradient diminution surpassing 30%. (326)

Furthermore, in aforementioned proportion of 20% of individuals with a gradient decrease of >30% within lead placement at the high septum, pacing performed at the apical region resulted in a further diminution of LVOT gradient. (326)

3.9.4.2 Biventricular Pacing

According to Berruezo et al. Biventricular Pacing led to a decrement of LVOT gradient within resting conditions from initial 74 ± 23 mm Hg to 40 ± 26 mm Hg at the time period of three months (*p* value of <0.05) and 28 ± 17 mm Hg at one year (*p* value of <0.05). (323, 327) Furthermore, it is denoted, that a decline in left ventricular mass within pacing occurred from initial 356 ± 110 g to 315 ± 70 g subsequent to a time period of three months (*p* value of 0.13) and 284 ± 42 g detected at one year (*p* value of <0.05). (327)

Additionally, NYHA functional class within Biventricular Pacing declined from 3.2 ± 0.4 within initial assessment to 1.9 ± 0.3 after three months (*p* value of <0.05) and 1.4 ± 0.5 at one year (*p* value of <0.05). (327) Akin, patients demonstrated an improvement in a six minutes walking test from initial 349 ± 116 m to 454 ± 144 m subsequent to three months of pacing (*p* value of <0.05) and 517 ± 206 m at one year (*p* value of <0.05). (328)

Within a study conducted by Lenarczyk et al., application of Cardiac Resynchronization Therapy Defibrillators attained within a time period of six months a decrease in peak and mean LVOT gradients from 84 to 33 mm Hg (*p* value of <0.05) and 38 to 13 mm Hg (*p* value of <0.05), respectively. (328) Peak and mean LVOT gradients subsequent to a median of 36 months were found in comparison to values at six months exhibiting a further diminution, with 8 mm Hg and 4 mm Hg (*p* value of <0.05), respectively. (328)

According to Lenarczyk et al., patients exhibited different LVOT pressure gradients contingent upon pacing configuration. (328) The pacing settings included right ventricular only and left ventricular only, while biventricular pacing comprised the preexcitation of the right ventricle of 40 ms, the concurrent pacing of either ventricles, as well as the prior excitation of the left ventricle of 40 ms. (328) In the extent of 66.7% of individuals, the configuration of Biventricular Pacing was found to present most beneficial. (328) Aforementioned included the mode of a preceding left ventricular pacing of 40 ms in 66.7% of patients, a prior right ventricular excitation of 40 ms in 16.7%, as well as a concurrent pacing of the left and right ventricle in 16.7% of individuals. (328) With regard to the remaining study participants, the most favorable setting constituted the sole pacing of the left ventricle. (328)

According to Lenarczyk et al., the pacemaker configuration regarded postprocedurally as most beneficial, presented matching aforementioned consideration, at the examination after a follow up of a median of 42 months, in the extent of 44.4% of patients. (328)

While patients initially were found with a median in NYHA functional class of II, subsequent to six months of pacing clinical manifestations presented diminished with a median in NYHA functional class of I. (328)

3.9.5 Cardiac Transplantation

According to the ESC, the performance of an orthotopic Cardiac Transplantation finds consideration in eligible individuals within context of a left ventricular EF of <50% and presence of a NYHA functional class III-IV. (17) The aforementioned applies in case of a nonsuccess of an antecedent pharmacological approach or presence of therapy-resistant

Ventricular Arrhythmia. (17) A preserved EF of ≥50% as well as a NYHA functional class of III-IV elicited by diastolic dysfunction and resistant to a pharmacological therapy may collectively represent an indication for the surgical procedure. (17) The ACCF/AHA collaboration considers Cardiac Transplantation to be performable within context of advanced Heart Failure, absence of an obstruction and an EF of ≤50%, with an antecedent nonsuccess of a pharmacological application. (288) On occasion the procedure in case of a preserved EF is to be considered. (288) With regard to children, the ACCF/AHA collaboration finds consideration of Cardiac Transplantation within context of a presence in symptoms, a restrictive physiology, as well as unresponsiveness or ineligibility in reference to other therapeutic interventions. (288)

According to Maron et al., the overall cardiac transplant survival rates subsequent to performed Cardiac Transplantation at the time periods of 1, 5, and 10 years presented with 85%, 75%, and 61%, respectively. (329) In comparison, patients receiving Cardiac Transplantation not in consequence of Hypertrophic Cardiomyopathy (with Ischemic Cardiomyopathy, Dilated Cardiomyopathy, and Restrictive Cardiomyopathy as causal diseases) demonstrated no significantly different rates for aforementioned time periods, with 82%, 70%, and 49%, respectively (Logrank Test *p* value of 0.05). (329)

As survival rates in reference to patients undergoing the surgical procedure as a result of Ischemic Cardiomyopathy for aforementioned time periods were presented with 82%, 69%, and 48%, respectively, the collective of persons previously diagnosed with Hypertrophic Cardiomyopathy, in comparison, demonstrated a more favorable outcome (Logrank Test *p* value of 0.02). (329) Compared to patients undergoing Cardiac Transplantation in consequence of Hypertrophic Cardiomyopathy, individuals receiving the intervention as a result of Dilated Cardiomyopathy demonstrated no difference in survival rates, with 87%, 71%, and 52% (Logrank Test *p* value of 0.08), respectively. (329) Akin, difference in survival between the former aforementioned collective and individuals undergoing Cardiac Transplantation in consequence of Restrictive Cardiomyopathy was based on the rates of 84%, 70%, and 67% (Logrank Test p value of 0.25), respectively, not existent. (329)

According to Kato et al., the 1 and 5 years survival rates of individuals being subject to Cardiac Transplantation in consequence of Hypertrophic Cardiomyopathy, in comparison to persons undergoing the procedure as a result of Ischemic Heart Disease, presented more favorable, with 90.1% and 85.8% as well as 83.9% and 67.1% (*p* value of 0.0359), respectively. (330) Yet, the former of aforementioned collective compared to the collective of persons subject to Cardiac

Transplantation with other heart diseases as causality, revealed no significant difference (*p* value of 0.1771). (330)

Biagini et al. denote the 7 years survival rate of persons undergoing Cardiac Transplantation in consequence of Hypertrophic Cardiomyopathy to had presented with 94%, demonstrating, subsequent to the adjustment for age, no difference to patients receiving the surgical procedure as a result of Idiopathic Dilated Cardiomyopathy (Logrank Test *p* value of 0.66). (331)

4 Discussion

4.1 General Considerations

Hypertrophic Cardiomyopathy is defined by the presence of left ventricular hypertrophy not elicited in consequence of unordinary loading conditions or hemodynamic aspects (such as Hypertension or Aortic Valve Disease), or the manifestation of systemic infiltrative or storage diseases. (3, 17, 18) In principal, the extent of ≥15 mm of left ventricular hypertrophy encountered in at least one segment represents the substitute for a condition's diagnosis. (17) The surpassing of aforementioned defining threshold apparently has been agreed upon by consensus to represent an abnormal left ventricular hypertrophic magnitude. Intriguing issues related to this aspect, yet to be resolved, comprise the questioning of which extent in hypertrophy reaches a hemodynamic relevance or results in a patient's clinical manifestation.

The prevalence of Hypertrophic Cardiomyopathy, while echocardiographically, initially being placed at 1:500 (26), presents within inclusion of more recent findings, genotypic positive individuals yet with an absence of clinical expression, the superior assessment modality of cardiac MRI, as well as the disease's familial essence, with an estimation of 1:200 (27). As such, as declared by The European Parliament and The Council of The European Union (332), defining the threshold of rarity at the prevalence of 1:2000 (332), or The Senate and House of Representatives of The United States of America (333), delineating rarity with a prevalence of approximately 1:1438 (333, 334), at an estimated population of the United States of America of approximately 287,676,000 persons in the year of 2002 (334), Hypertrophic Cardiomyopathy does not constitute a rare disease.

As reports of the condition are available proceeding from various regions of the world, including the United States of America (26), the United Kingdom (28), France (29), Germany (30), Brazil (31), the Republic of South Africa (32), China (33), and Japan (34) as well as clinical identification being available from collectively 122 countries of the world (35), possibility of Hypertrophic Cardiomyopathy to be regarded as a global disease, is existent.

Even though the etiologic causality of the ailment being ascertained as of genetic nature in relatively as few as 60% of individuals encountered in their adolescence or adulthood (17), placement of Hypertrophic Cardiomyopathy as a condition of cardiac sarcomeric proteins has been voiced (38).

4.2 Genetic Aspects

Of note, the condition's mode of inheritance is not denoted as being singular. (40) While designated to present most frequently as autosomal dominant, it has in reference to rare forms as well been noted as autosomal recessive, mitochondrial, or X-linked. (40) Nevertheless, it exhibits as well an elevated frequency in individual de novo mutations. (39) The condition's genetic heterogeneity emerges apparent inter alia in context of >1,500 mutations eventually resulting in the phenotypic expression of Hypertrophic Cardiomyopathy (44) as well as at the minimum 45 genes reported to be affected, holding at least an association with the disease (39, 3, 18).

The preponderance of individuals have been identified with mutations in the sarcomeric genes of MYH7 or MYBPC3, with the proportions of 40-44% and 35-40%, respectively. (39) Of note, this weighting in affected genes is akin as well encountered in the morphologic form of Apical Hypertrophic Cardiomyopathy (215) and genotype positive phenotype negative individuals (264, 265, 261). Aforementioned genes are reported to have accounted collectively for as much as up to 82.3% of cases of genetically elicited Hypertrophic Cardiomyopathy. (29)

The diverse subjacency of the disease is anew accentuated as, nevertheless, mutations phenotypically effectuating Hypertrophic Cardiomyopathy are as well encountered in genes with an involvement in cellular Calcium Handling, by way of example PLN and CALR3, or other proteins, such as Desmin or Four And A Half LIM Domain Protein 1, with the genes of DES and FHL1, respectively, (39), with genes of Hypertrophic Cardiomyopathy Phenocopies (39, 3) excluded.

With the majority of mutations (90%) in Hypertrophic Cardiomyopathy constituting missense mutations (41) and the circumstance of not every missense mutation leading to an effect on biological outcome, individuals might represent carriers of mutations in disease related genes with still no outbreak of the condition. Mutations in the gene of MYBPC3, with a proclivity for an insertion or deletion of at least one nucleic acid, represent exceptions to the aforementioned (44, 45). Of note, inter alia, frameshift mutations in principal hold the consideration of being related to an elevated severity in clinical manifestation. (45) As hypertrophy constitutes a common response to any injurious instance of the heart (3) this principle might be applied to the extent of severity of the mutational process implicated in the elicitation of the disease. This represents an aspect encouraged by the circumstance of complex genotypes reported to involve an increased hypertrophic severity (63, 55, 64).

While the frequency in repeatedly occurring mutations in Hypertrophic Cardiomyopathy presents diminished (38), nominally mutational “hot spots” (46) detected in an increased extent of families demonstrating no relation to each other have been identified (46). These include inter alia the mutations Arg403Gln, Arg453Cys and Arg663His in the gene MYH7, Arg92Gln, Arg92Trp, and Arg104Val in the gene TNNT2, as well as Arg502Trp and Arg495Gln in the gene MYBPC3 (46, 47). By way of example, the mutation p.Arg502Trp in the gene MYBPC3 has been noted with an occurrence of 1.5-3% of cases of Hypertrophic Cardiomyopathy. (44)

Nevertheless, probability of aforementioned increased mutational occurrences to be as well encountered in consequence of a founder effect has been voiced. (44)

Amidst all clinically diagnosed occurrences of Hypertrophic Cardiomyopathy in adults, the proportion of approximately 5-10% are estimated to be represented by Phenocopies (3), constituting a distinct subdivision of the disease (3) elicited by mutations inter alia in the genes of GLA, LAMP2, and TTR, associated with the conditions of Anderson-Fabry Disease, Danon Disease and Amyloidosis, respectively (46). This classification might present advantageous as inter alia Phenocopies may involve as well corporal structures or organs other than the heart as it is with aforementioned Infiltrative Diseases.

The range in the phenotypic manifestation of Hypertrophic Cardiomyopathy has been perceived as partially representing the result of its genetic heterogeneity. (46) Aforementioned has been substantiated by investigation suggesting a moderate hypertrophic severity up to a subclinical manifestation in relation to mutations in the gene of TNNT2 (46, 52) and correspondence of an increased phenotypic severity with presence of multiple mutations (55). Additionally, deceases related to Hypertrophic Cardiomyopathy were more frequently encountered in individuals subject to the mutations Arg249Gln, Arg403Gln, or Arg453Cys in the gene of MYH7, as in comparison to the mutation Val606Met in the identical gene. (46, 53)

Influence on the phenotypically expressed severity in Hypertrophic Cardiomyopathy is exerted by the condition’s manifested incomplete penetrance (18, 46). Aforementioned genetic entity demonstrates in Hypertrophic Cardiomyopathy an interrelationship to age (in principal observed gradual increment) (46, 58–60), gender (increased in male individuals) (58), as well as (in consideration of not reaching statistical significance) probably involved genes (58, 54). Charron et al., even though statistically not significant, detected individuals with a mutation in the gene MYH7, in comparison to an affected MYBPC3 gene, to exhibit an elevated penetrance, with 62% and 41%, respectively. (54) Penetrance, per se, as a genetic entity, adds to the apparent complex genetic situational condition of Hypertrophic Cardiomyopathy.

Overall, as persons subject to the identical mutation or encountered within the same family may demonstrate a phenotypic expression varying from no impairment to affliction, the manifestation of Hypertrophic Cardiomyopathy to be exclusively explained by principals of Mendel presents as not conclusive. (46) The aforementioned is substantiated inter alia by the context of presence of Complex Genotypes to implicate an increased severity in the disease's morphologic manifestation (55, 64). These include multiple sarcomeric mutations (55) and compound mutations (64). This is exemplified by the circumstance of compound mutation carriers to had held in comparison to individuals presenting one mutation a more increased LVWT, with 30.7 ± 3.1 mm and 24.4 ± 7.4 mm (p value of <0.05), respectively (64).

Furthermore, alteration in phenotypic expression is encountered as well within context of Modifier Genes. (65, 66) Different genotypes of the Angiotensin I Converting Enzyme with a mutation in the Arg403 codon with regard to the gene of MYH7 (65) or mutations in the gene MYBPC3 (66) demonstrate an influence on the manifesting morphology of Hypertrophic Cardiomyopathy (65, 66), supporting the conception of the condition representing the result of processes beyond explanations within a mendelic approach.

Generally, an epigenetic modulation is encountered within processes such as Methylation of CpG islands, alteration of histone proteins, and the intervention of microRNAs. (46) This might have been existent within the conjuncture of microRNA 122 overexpression to have been encountered with consequential hypertrophy of rat cardiomyocytes. (73)

Additionally, environmental factors, videlicet, physical activity, dietary aspects, the presence of comorbidities, as well as loading conditions effectuated by Hypertension and Valvular Heart Disease are instanced as possibly exerting an influence on the eventual phenotypic manifestation proceeding from sarcomeric genes. (46) This might have been existent within the circumstance of individuals holding an increased BMI (25-30 kg/m² and >30 kg/m²) in comparison to an ordinary corporal weight were determined presenting an independent relationship to a left ventricular mass of >120 g/m², with the hazard ratio of 1.65 (95% CI: 0.73-3.74, p value of 0.22) and 3.1 (95% CI: 1.42-6.86, p value of 0.004), respectively (74). These findings, nevertheless might be inter alia mediated by the same processes encountered in cases with hypertrophy as a secondary occurrence. (74)

4.3 Various Condition Related Implications

Generally, hypertrophy may in principal involve the left cardiac ventricle (79), yet isolated right ventricular (81) or biventricular manifestation has been denoted as well (80). As the

aforementioned is by simple causal means not explainable, it serves as an exemplification of the enigmatic implications in the condition of Hypertrophic Cardiomyopathy. While the cavity of the left ventricle characteristically presents a diminished dimension, possibility of its dilatation as a consequence of an extended time period of Heart Failure, is existent (84), leading to the necessity of an attentive examination with regard to either extremes on the spectrum of left ventricular dimensions. Principal histopathologic findings represent myocyte disarray (89), the nominally "Small Vessel Disease" (86), comprising thickened coronary walls and constricted blood vessel lumens (92), as well as the increased presence of fibrotic tissue (86).

As the preponderance of affected individuals present asymptomatic (17), as well as most frequent symptoms in Hypertrophic Cardiomyopathy constitute inter alia the intolerance to exertional physical activity, Angina, Dyspnea, Dizziness, and Syncopes (94), an identification of the disease on basis of symptoms might not eventuate or presents complicated by the unspecificity of these. Cardiac Auscultation inter alia detects the second heart sound demonstrating a physiological split, a crescendo-decrescendo murmur within context of LVOTO (with the cessation prior to the second heart sound), and the possible occurrence of an additional murmur (rather holosystolic) in the presence of Mitral Valve Regurgitation. (3)

The difficulty of the condition's identification is attenuated by the circumstance of 91.8-96.9% of individuals subject to Hypertrophic Cardiomyopathy to demonstrate an unordinary ECG (95–98), with ST-T alterations representing the most encountered abnormalities (81.8%) (97). Of note, on basis of presence of hypertrophy being detected assessed in assistance of the Romhilt-Estes score in 63.7% of individuals exhibiting the condition (95), in comparison to only 36.4% of persons determined by means of the Sokolow-Lyon Index (97), within context of Hypertrophic Cardiomyopathy the former assessing mean in reference to the electrocardiographic determination of hypertrophy, is, in principal, to be favored.

Even though, Echocardiography is regarded as the most accessible diagnostic method with regard to Hypertrophic Cardiomyopathy (25), attention is to be directed to the circumstance of the parameter of EF frequently presenting preserved or even supernormal within the condition (3, 99). This conjuncture may find compensation by affected individuals being assessed in observance of mitral annular motion, as this entity is most frequently found unordinary in patients with Hypertrophic Cardiomyopathy (3) and may assist in the detection of the condition.

Cardiac MRI represents within context of Hypertrophic Cardiomyopathy, in comparison to a common Two-Dimensional Echocardiography examination, the superior diagnostic modality. (17) Aforementioned is exemplified by the circumstance of 6.3% of individuals with

Hypertrophic Cardiomyopathy, even though undergoing a previous echocardiographic assessment, to had been diagnosed with the condition only subsequent to an additional applied examination via MRI. (103) This emerges a fortiori remarkable, as the involved patients were encountered with a LVWT at the anterolateral region of the free wall of 17-20 mm (103).

A remarkable entity patients with Hypertrophic Cardiomyopathy may present, constitutes SAM of the mitral valve complex (106). Yet, although once considered to represent a pathognomonic abnormality of obstructive Hypertrophic Cardiomyopathy, SAM of the mitral valve complex has as well been reported within the circumstances of an absent hypertrophy and with a common outflow tract (108), presence of hypovolemia and anemia (109), as well as acute perioperative cases of Hypotension (110), leaving the condition anew with no specific diagnostic characteristic.

Individuals subject to Hypertrophic Cardiomyopathy may as well be encountered with LVOTO. (114–116) While in principle, a pressure gradient of ≥30 mm Hg (at resting conditions or within physical provocation) is regarded as defining for LVOTO, conditional hemodynamic relevance, nevertheless, is attained at the extent of ≥50 mm Hg. (17) A LVOTO of a gradient of ≥50 mm Hg is present in the proportion of 37.1% of patients at resting conditions, while additional 23.6% of individuals develop aforementioned gradient within exertional testing. (116) Of note, LVOTO may exhibit alteration over the course of time, including its elevation, general appearance, diminution, or cessation (117), inducing the necessity of repeatedly occurring intervallic examinations of the patient.

Another entity encountered in Hypertrophic Cardiomyopathy constitutes Mitral Valve Regurgitation (119), eventuated by means of an absence of mitral leaflets coaptation within the phase of mid-systole, present in 56% of patients subject to the ailment (119). Nevertheless, as the feature is contingently as well present in other conditions, such as Rheumatic Heart Disease, Myocardial Infarction, and Dilated Cardiomyopathy, possibility of regarding it as pathognomonic in reference to Hypertrophic Cardiomyopathy, is not existent.

The extent of 82% of persons subject to Hypertrophic Cardiomyopathy demonstrate an affected left ventricular diastolic function. (122), constituting it a significant diagnostic entity for the condition.

A sequela of Hypertrophic Cardiomyopathy represents AF (123), prevalent in 22.5% (95% CI: 20.1-24.8%) of patients subject to the disease. Its association with Thromboembolism is well established (335), while studies presenting its interrelationship with Dementia (336–338), are

existent, with the odds ratio adjusted for age and, if applicable, gender of 2.3 (95% CI: 1.4-3.7) (337) and an adjusted hazard ratio for all-cause dementia of 1.38 (95% CI: 1.10-1.73) (adjustment for gender, education, Diabetes Mellitus, Hypertension, Systolic as well as Diastolic Blood Pressure, Stroke, Coronary Heart Disease, Congestive Heart Failure) (338). Di Nisio et al. encountered the prevalence of Vascular Dementia to be increased in individuals presenting AF in comparison to control subjects, with 21.4% and 10.7% (*p* value of 0.014, utilizing the Chi-Squared Test with Dementia constituting the reference category and *p* value of 0.024 in adjustment for Smoking, Arterial Hypertension, Heart Failure, and Cerebrovascular Disease), respectively. (336, 339)

Infective Endocarditis, although once considered to be preponderantly encountered in patients with LVOTO (129), the amount of 44% of individuals subject to the complication was found to demonstrated no LVOTO (130). Furthermore, the proportion of 38% with Infective Endocarditis exhibit concentric hypertrophy, while 29% of persons are found with an asymmetric septal phenotypic expression. (130) Either of aforementioned circumstances demonstrate no necessary proclivity towards Infective Endocarditis elicited by structural or morphologic abnormalities. As positions on the antibiotic treatment as a prophylactic measure in reference to Infective Endocarditis present antithetic (132, 133), as to minimize the complication's contingent occurrence, application of aforementioned antibiotic measure may appear more supportable.

Heart Failure constitutes aside of SCD one of the causalities of premature decease in persons presenting Hypertrophic Cardiomyopathy. (134) Of note, overall 3.5-4.9% of individuals are found with at least an EF of <50% (135, 136), delineating a state of end-stage within Hypertrophic Cardiomyopathy (135, 136) - with the extent of 4.9% of persons being additionally characterized by factors such as hypokinesia and the dilation of the left ventricular cavity (136) - as well as contrasting the circumstance of individuals with the ailment to frequently present a preserved or even supernormal EF (3, 99).

Direct influnence of LVOTO on the condition of Hypertrophic Cardiomyopathy is observed as 22% of individuals develop Heart Failure as a consequence of LVOTO (137).

One of the most incisive encounter within Hypertrophic Cardiomyopathy constitutes the incident of SCD, amounting to a rate of 1% of individuals subject to the disease per year (140). As the predominant mediating condition is ascribed to Ventricular Fibrillation (141), it represents an objective of medical intervention. Of note, the extent in LVWT correlates directly with the risk for SCD. (146) This is exemplified by a wall thickness of ≤15 mm to present a

SCD rate of 0/1000 person years (95% CI: 0-14.4/1000 person-years), while a dimension of ≥30 mm is found with a rate of 18.2/1000 person-years (95% CI: 7.3-37.6/1000 person-years). (146) Furthermore, genetic aspects to hold influence on the incident of SCD may present presumable, as certain mutations in the gene encoding for Troponin T find association with an elevated incidence of SCD (52). This may be evoked by several structural abnormalities on the molecular level, implicated with mutations in aforementioned gene and not present in other gene mutations.

4.4 Morphologic Forms

Even though Hypertrophic Cardiomyopathy is denoted presenting a characteristically asymmetric phenotypic manifestation with regard to left ventricular hypertrophy (149) and the region of interventricular septum to be affected with varying severity (76), the ailment is as well found with different hypertrophic patterns (76) serving as an enigmatic component of the ailment's entirety as it directs to the cogitation of the emergence of these.

4.4.1 Asymmetric Septal Hypertrophy

One encountered phenotypic variant of Hypertrophic Cardiomyopathy is represented by Asymmetric Septal Hypertrophy, defined by the interventricular septal thickness of ≥15 mm (77, 76, 157) or in principal a septum to left ventricular posterior wall ratio of >1.5 (77, 76). Differentiation in reference to the ratio is made by Williams et al. denoting a ratio of >1.3 for normotensive and >1.5 for Hypertension demonstrating patients. (157)

As this variant is present in 44.7-90% of individuals with Hypertrophic Cardiomyopathy (158–160, 79), it constitutes the most frequently encountered morphologic form within the condition.

Of note, as mutations in the genes MYBPC3, MYH7, MYL2, encoding for thick filament proteins have been determined to result in the proportion of 94% of cases in an asymmetric phenotypic expression of the condition (118), evidence for a disease's varying eventual morphologic manifestation contingent upon involved sarcomeric structures, is provided.

As the proportion of 24.4% with the variant are denoted to be asymptomatic and 17.1% of individuals within initial presentation are encountered in a NYHA functional class of ≥III (159), the form presents two relatively considerable extremes on the spectrum of clinical manifestation. Abnormal electrocardiographic findings are present in 58.8-90.6% (158, 159) of patients, providing a relatively increased probability of an initial detection via ECG within context of clinical routine assessments. Of note, the extent of as few as 48% of individuals are

echocardiographically found with hypertrophy involving the entire septum, from base to apex (79). Akin to patients with Hypertrophic Cardiomyopathy, in general, to frequently demonstrate a preserved or even supernormal EF (3, 99), this circumstance is as well reflected within the form of Asymmetric Septal Hypertrophy, with individuals exhibiting a mean EF of 64.4% ± 7.3% (159).

Of interest, the amount of 25.5% of persons subject to the variant demonstrated within a follow-up time period of 32 ± 37.2 months an incidence of cardiovascular nature. (159)

Asymmetric Septal Hypertrophy finds possibility of a further subdivision according to the morphologic form of the cardiac septum. Aforementioned includes the Asymmetric Sigmoid Form, the Reverse Septal Contour, and Neutral Septal Form (162). The classification into a sigmoid, reverse, and neutral septal form as well as apical hypertrophy, reveals 67% of individuals at the age of ≥50 years to demonstrate the morphologic expression of Asymmetric Sigmoid Form. (162) This is consistent with the overall impression voiced by Noureldin et al. the Asymmetric Sigmoid Form to constitute a morphologic variant encountered preponderantly in the elderly population subject to Hypertrophic Cardiomyopathy. (340) Yet, antithetically, Noureldin et al. denote aforementioned form to frequently as well demonstrate an absence of causal mutations related to Hypertrophic Cardiomyopathy. (340)

Of note, while the suggestion of an aortic root deflection in consequence of hypertrophy, is existent (164), in addition, generally, structural alterations of the aorta related to the process of aging per se has been mentioned as well (165). The latter finds substantiation as according to Binder et al., the proportion of 91.7% of persons demonstrating the Asymmetric Sigmoid Form were identified to hold no mutation (162). Yet, as a decreased aortic angle has been reported in individuals at the ages of both, 48 as well as 38 years, correlation between an aortic root deflection and age as the single eliciting factor is not evident. (164)

These two antithetic positions might find resolution within the conception of both circumstances representing distinct entities with an observable morphologic overlap, eventuating a difficult differentiation between these. Mutations related to Hypertrophic Cardiomyopathy as well as processes of deterioration associated with advanced age, might affect the same subjacent structures leading to morphologically resembling conditions.

The antecedently mentioned subdivision into a sigmoid, reverse, and neutral septal morphology as well as apical hypertrophy, demonstrates 73% of individuals holding a myofilament mutation to be encountered within the collective exhibiting a Reverse Septal Contour. (162) As most

frequent mutations in this form concern the genes MYBPC3 and MYH7, with 34.1% and 28.8%, respectively (162) and most encountered mutations in the Neutral Septal Form affect the genes MYBPC3 and MYH7, with 18.8% and 12.5%, respectively (162), both, the Reverse Septal Contour as well as Neutral Septal Form are in accord with the findings of most mutations overall in Hypertrophic Cardiomyopathy to be detected in the genes MYH7 and MYBPC3 (39, 29).

Additionally, as the amount of 45.5% of individuals with a Reverse Septal Contour present a family history of Hypertrophic Cardiomyopathy (162), genetic testing or echocardiographic assessment of related family members might present of eminent importance.

4.4.2 Concentric Form

Concentric Hypertrophic Cardiomyopathy has been delineated presenting diffuse left ventricular hypertrophy (76, 149), while each ventricular segment is found with a comparable hypertrophic involvement (149) concurrently with a diminution of the intraventricular dimension (76).

Two publications present antithetic data with regard to the relationship between the concentric morphologic form and age (169, 170). While one denotes the concentric phenotypic expression to be encountered in the proportion of 75% of elderly individuals and 71% of young persons to present Asymmetric Septal Hypertrophy (169), the other reports the amount of 79% of elderly study participants to had exhibited anteroseptal left ventricular hypertrophy (170). An approach to explain the aforementioned circumstance might reside in the different geographical regions of the study populations, with Litovsky et al. conducting their study in the United States of America (169) and the study location of Lai et al. being found in Japan (170). Akin to Apical Hypertrophic Cardiomyopathy to be encountered with varying prevalence contingent upon geographical regions (211–213), difference in prevailing morphologic form in the elderly population might have been encountered with varying international terrenes. Furthermore, of note, either authorships of the studies utilize different thresholds for defining the elderly collectives (169, 170). While Litovsky et al. apply the age of >60 years for the elderly population (169), Lai et al. utilize the threshold of ≥85 years of age (170).

Mutations in genes encoding for thin myofilaments exhibit in 31% of cases the manifestation of less usual phenotypic expressions of Hypertrophic Cardiomyopathy, including the concentric form. (118) Additionally, 41% of individuals with a mutation in the gene TNNI3 are found demonstrating either an apical or concentric morphologic expression. (118)

An essential task represents the differentiation between Concentric Hypertrophic Cardiomyopathy and other conditions with the possibility of a left ventricular concentric hypertrophic manifestation. Aforementioned include, the Athlete's Heart (172), Hypertension (76, 77), Aortic Stenosis (77), and Infiltrative and Deposition Diseases, such as Amyloidosis (77), Anderson-Fabry Disease (77), or Cardiac Sarcoidosis (77).

Of note, an extent in LVWT of ≥13 mm in individuals presenting Athlete's Heart is encountered in as few as 1.7%, in concurrence with the magnitude of 16 mm to had been determined with regard to only one person. (175) An echocardiographically determined intraventricular dimension of >55 mm at end diastole found consideration of representing a contingent factor suggestive of Athlete's Heart. (173) As the proportion of as few as 33.3% of male athletes are encountered with aforementioned extent, a chamber magnitude of >55 mm to remain exclusively an indicative factor appears as appropriate. On basis of hypothetically myocardial tissue in Hypertrophic Cardiomyopathy to allow the assumption of presenting in comparison to hearts of healthy individuals more impaired, the proposal of a Maximal Oxygen Capacity of >45 ml/kg/min as an indicative determinant of Athlete's Heart (173) may cautiously be taken into consideration.

As the cessation of athletic activity includes a possible remission of left ventricular hypertrophy to the extent of 2-5 mm within the time lapse of three months (176), eventuating of aforementioned occurrence provides a relative assurance of trained individuals possibly being subject to Athlete's Heart. This might be substantiated by a negative result obtained within context of Genetic Testing. (174) Yet, as certainty of all causal gene mutations to already have been identified, is not provided, Genetic Testing might not administer a definitive result.

In the interest of differentiating the disease of Hypertrophic Cardiomyopathy and Hypertension, the parameters of EF, Left Ventricular Wall Stress as well as End Systolic Volume or End Diastolic Volume, respectively (contingent upon condition), might constitute entities of orientation. This is eventuated by the circumstance of Hypertrophic Cardiomyopathy while being encountered with a supernormal EF as well as a demise in End Systolic Volume and Left Ventricular Wall Stress, individuals subject to Hypertension to demonstrate a reduction in EF as well as an increase in End Diastolic Volume and Left Ventricular Wall Stress. (182)

Within context of direct comparison, aforementioned intention of distinction may find substantiation by virtue of 50% of individuals with Hypertrophic Cardiomyopathy exhibiting LGE, while the diagnostic entity was encountered in 72% of persons subject to Hypertension. (184) As the difference between the collectives does not present abundant, the diagnostic

measure might find consideration of being collectively implemented with other parameters for the purpose of aiding in the intention of distinguishing the two diseases.

In individuals with Hypertrophic Cardiomyopathy in comparison to either, persons with Hypertension and control subjects, Free Carnitine in the serum presented elevated, with 52.5 ± 9.5 nmol/ml, 46.6 ± 6.4 nmol/ml, and 42.3 ± 5.5 nmol/ml, respectively. (177) Conversely, serum Acylcarnitine in persons with Hypertrophic Cardiomyopathy compared to individuals with Hypertension or control study participants, was encountered reduced, with 10.1 ± 4.0 nmol/ml, 14.5 ± 4.9 nmol/ml, and 13.2 ± 3.9 nmol/ml, respectively. (177) The combination of either aforementioned objective blood values, aligned with antecedent entities of EF, Left Ventricular Wall Stress, as well as End Systolic Volume or End Diastolic Volume, might be implemented in the interest of differentiating between the condition of Hypertrophic Cardiomyopathy and Hypertension.

In the interest of distinguishing Aortic Stenosis from Hypertrophic Cardiomyopathy, the presence of a turbulent jet at the traverse region detected in assistance of Cardiac Cine MRI has been identified in the former of the two conditions. (76) In contrast, in consequence of wall thickening at the basal anterior septum, within context of Hypertrophic Cardiomyopathy, a jet turbulence is encountered subjacent to the aortic valve. (76)

Of interest, in the intention of differentiating Amyloidosis from Hypertrophic Cardiomyopathy, the former ailment was encountered with an interatrial septum thickness of 8.7 ± 2.7 mm, while the latter demonstrated a thickness of 5.3 ± 0.8 mm. (190) Of note, no person subject to Hypertrophic Cardiomyopathy surpassed the magnitude of 6 mm. (190) The aforementioned accompanied by the circumstance of 42% of individuals with Amyloidosis (190) demonstrating Pericardial Effusion in comparison to 10% with Hypertrophic Cardiomyopathy (190) as well as 50% of persons subject to Amyloidosis (190) presenting Pleural Effusion compared to none within the collective demonstrating Hypertrophic Cardiomyopathy (190), might collectively provide to some extent an orientation with regard to the present of the two diseases.

Of interest, the specificity of the diagnostic method of Scintigraphy to detect cardiac Transthyretin Amyloidosis in the setting of a radionuclide uptake equal or above the degree of bone tissue accompanied by a missing of monoclonal proteins, confirmed by means of a serum and urine Immunofixation Electrophoresis and a Serum Light Chain assay, was denoted with 100%. (191) Such or a resembling result might be attained with regard to other circumstances, holding the accuracy at an elevated level.

With regard to the differentiation of the conditions Hypertrophic Cardiomyopathy and Anderson-Fabry Disease, even though, individuals subject to the latter may present with Cataracts, Corneal Opacities, Sensorineural Surdity, Paresthesia, Angiokeratoma, the possibility of a reduced electrocardiographic PR interval, Preexcitation, as well as Proteinuria (194), definitive assurance of an Anderson-Fabry Disease presence is effectuated in assistance of determining the α-Galactosidase activity (192) in persons suspected of being affected by the ailment.

In the interest of distinguishing Hypertrophic Cardiomyopathy and Cardiac Sarcoidosis, the latter is eventually confirmed by means of endmyocardial biopsy of the right ventricle in substantially suspected patients, with a mean of 4.0 ± 1.2 samples per person as well as demonstrating the histologic evidence of noncaseating granulomas, in relatively as few as 19.2% of individuals (201). In consequence of the aforementioned, other relevant aspects directing to the diagnosis of Cardiac Sarcoidosis are to be involved, including the involvement of other possibly afflicted organs clinically manifest, as individuals subject to Sarcoidosis present the disease inter alia in the lung (95%), skin (21%), liver (16%), and eye (10%) (198). Nevertheless, antecedent mentioned approach is complicated by the circumstance of 31.6% of cases with Sarcoidosis demonstrating an isolated affliction of the heart (200).

While the parameter of EF in individuals with Hypertrophic Cardiomyopathy frequently presents preserved or even supernormal (3, 99), persons subject to Sarcoidosis were encountered with a reduced EF, with a mean of 39 ± 11% (203). Nevertheless, the aforementioned does not serve as a basis in differentiating the ailments of Hypertrophic Cardiomyopathy and Sarcoidosis. Of some aid might be the circumstance of Cardiac MRI, with the utilization of T2-Weighing, to allow a detection of ongoing inflammatory processes (206).

4.4.3 Apical Form

The form of Apical Hypertrophic Cardiomyopathy has been described as left ventricular hypertrophy demonstrating primary restriction to the cardiac apex with a maximal wall thickness of ≥15 mm. (82) The aforementioned magnitude is in accordance with the general diagnostic threshold delineated for Hypertrophic Cardiomyopathy. (17)

An apparent peculiarity of Apical Hypertrophic Cardiomyopathy represents its inhomogeneous distribution in relation to geographical region (209, 210), with different rates of prevalence (211–213). This accentuates the possibility of an interference on the condition’s phenotypic manifestation on the part of epigenetic factors as well as environmental aspects.

Akin to the overall impression of Hypertrophic Cardiomyopathy to be genetically with predominance elicited by mutations in the genes of MYH7 or MYBPC3 (39, 29), the apical variant of the ailment follows this basic principle, with either of aforementioned genes being afflicted in 33.3% of cases, each (215). Arad et al. denote the implication of MYH7 gene mutations in the variant even rising to the proportion of 43%. (171)

Of note, Arad et al. report the mutation of Glu101Lys in cardiac Actin to had demonstrated Apical Hypertrophic Cardiomyopathy in the extent of 100% of individuals. (171)

Further evidence for influence on the morphologic manifestation to be exerted by factors beyond mendelian principles, is provided by the circumstance of the mutation ACTC E101 to elicit in two individuals the apical form of Hypertrophic Cardiomyopathy (171) and additionally to present involvement in the condition of Left Ventricular Noncompaction (216).

Arad et al. voice the proposal of Apical Hypertrophic Cardiomyopathy to constitute the result of at least one modifier gene, presenting cumulated in populations frequently encountered with the disease's form. (171) This circumstance might as well be in effect with regard to factors pertaining to the environment.

Electrocardiographically, eminent negative T waves are regarded as a characteristic of Apical Hypertrophic Cardiomyopathy (76), contemporarily defined as holding an amplitude of ≥10 mm (218). Of note, while generally, T wave inversions are present in the extent of 89.8-91.3% of individuals (218, 82), relatively as few as 10.8-28.8% of persons hold Giant Negative T waves (218, 82). Nevertheless, as Giant Negative T waves represent remarkable findings, identification of Apical Hypertrophic Cardiomyopathy in assistance of an ensuing echocardiographic examination presents probable.

A further peculiarity in Apical Hypertrophic Cardiomyopathy represents the absence of LVOTO as well as Mitral Valve Regurgitation. (220) As hypertrophy in the apical variant involves in comparison to other morphologic forms a relatively modest extent of the ventricle, LVOTO might correlate with the degree of severity encountered in Hypertrophic Cardiomyopathy.

Furthermore, in the variant peak apical rotation in affected individuals compared to normal persons presents diminished, with 12 ± 4.3° and 19.5 ± 5°, respectively. (221) As a result, peak left ventricular twist as well was encountered reduced, with 18.1 ± 5° for individuals subject to the variant and 22.6 ± 5.5° in control study participants. (221) These represent alterations

attributable to Apical Hypertrophic Cardiomyopathy, yet might be present as well overall in morphologic forms affecting the region of the cardiac apex.

Of note, the echocardiographic examination of individuals in comparison to the utilization of MRI, demonstrates no successful diagnosis of Apical Hypertrophic Cardiomyopathy in 8.6% of cases. (223) As such, presence of ECG alterations with no evidence for the disease in assistance of echocardiography should direct to the assessment via MRI.

Further of note, the extent of 46.8% of individuals with Apical Hypertrophic Cardiomyopathy are diagnosed with the condition as a result of a presence of AF, rendering the abnormal heart rhythm as one of the diagnostically most substantial entities in the variant. (128)

Relatively antithetic data is available with regard to overall survival rates in reference to the variant, with one publication noting a 5, 10 and 20 year survival rate within the condition of 86%, 70% and 47%, respectively (218) and the other presenting an overall survival at 15, 20, and 25 years of 95% ± 3%, 87% ± 5%, and 79% ± 7%, respectively. (223) Of note, the latter specifies a 15-year survival rate for individuals subject to the disease resembling the expectancy of the general population (Ontario, Canada) corresponding to age and gender, with 95% ± 3% and 95% ± 1%, respectively. (223) This demonstrates the possibility of to some extent equalized survival rates over an relatively extensive time period between healthy and affected persons and might be attained for further periods. The decline of survival rate subsequent to the time period of 15 years might be investigated in reference to causal factors.

4.4.4 Midventricular Form

Midventricular Hypertrophic Cardiomyopathy has been described presenting a region of stricture at the level of mid-cavity, constituting the result of a hypertrophied septum in apposition with the left ventricular wall, in possible concurrence of the involvement of at least the anterior papillary muscle. (226) The pressure of ≥30 mm Hg is regarded as defining. (227, 228)

The mutation Met149Val, while being encountered within the variant of Apical Hypertrophic Cardiomyopathy, has been reported to as well present the midventricular phenotypic expression of Hypertrophic Cardiomyopathy. (171) This demonstrates the implication of additional accompanying factors aside of the causal mutation, exerting influence not only on the eventuating condition per se, by way of example the apical variant of Hypertrophic Cardiomyopathy or Left Ventricular Noncompaction (171, 216), but the final phenotypic form of Hypertrophic Cardiomyopathy.

Contrary to the general consideration the predominant proportion of persons with Hypertrophic Cardiomyopathy to present asymptomatic (17), 96.7-97.1% of individuals subject to the midventricular variant exhibit symptoms within the initial examination. (229, 228) Furthermore, a regular ECG is present in as few as 2.9% of persons with the Midventricular Hypertrophic Cardiomyopathy, holding an elevated probability of patients being directed to further diagnostic investigation. (228)

Patients with Midventricular Hypertrophic Cardiomyopathy demonstrate NSVT and AF as the most encountered complications, present in the proportions of 20.6-31.7% (228, 227, 229) and 16.7-41.2% (229, 227, 228) of individuals, respectively.

Of note, the mere presence of midventricular obstruction was associated with an unfavorable impact on the 5 year survival rate in reference to deceases as a result of cardiovascular nature, in comparison to both, Hypertrophic Cardiomyopathy without obstruction as well as presenting LVOTO, with 93.5% (95% CI: 89.1-97.9%), 98.9% (95% CI: 98.2-99.4%), and 96.2% (95% CI: 92.4-99.9%), respectively. (228) As such, deficient prognosis is associated with the variant per se.

As the extent of 80% of patients exhibiting a segmental or generalized left ventricular Hypokinesia are reported to be represented by individuals exhibiting a midventricular obstruction (230), the variant of Midventricular Hypertrophic Cardiomyopathy demonstrates to be associated with an increased degree of functional deterioration.

Possibility of patients with Midventricular Hypertrophic Cardiomyopathy presenting the formation of Left Ventricular Apical Aneurysm, is existent. (232) The entity has been delineated as a separate segment at the cavity's most distal region. (231) It demonstrates a connection to the chamber as well as a thin wall presenting with Dyskinesia or Akinesia. (231)

While Left Ventricular Apical Aneurysm has been reported in the overall population of Hypertrophic Cardiomyopathy with a proportion of 0.3% (228), the entity is present in 20.0-28.3% (229, 228, 227) of patients demonstrating the midventricular variant. In consequence, even though description of the entity is existent within context of the apical variant of Hypertrophic Cardiomyopathy (220), Efthimiadis et al. apprehend Left Ventricular Apical Aneurysm to represent a distinct constituent of midventricular hypertrophy (228).

Of note, according to Yan et al. the presence of a peak pressure gradient of ≥70 mm Hg represents an independent predictor in reference to the development of Left Ventricular Apical Aneurysm. (229) This is to be retained with regard to persons in absence of the entity, as timely

pressure gradient reduction might avert the potential formation of Left Ventricular Apical Aneurysm.

Of interest, a Paradoxical Jet Flow traversing the obstruction is present in 29.7% of individuals with Midventricular Hypertrophic Cardiomyopathy with Left Ventricular Apical Aneurysm. (232) As such, the entity might hold relevance in reference to diagnostic aspects.

Of note, while midventricular obstruction per se already increases the probability of a decease (228), the additional presence of Left Ventricular Apical Aneurysm in patients subject to Midventricular Hypertrophic Cardiomyopathy is associated in comparison to individuals in absence of the entity with a 2.1-fold elevation in the rate of deceases related to Hypertrophic Cardiomyopathy, with 38.5% and 18.2%, respectively. (227)

4.4.5 Mass-Like Hypertrophic Cardiomyopathy

Mass-Like Hypertrophic Cardiomyopathy presents an extensive thickening as a focus within the left ventricle. (76) The most essential circumstance within context of this variant represents the necessity to differentiate the expansion from neoplasia (77). This is effectuated on basis of the conception of, in principal, tissue pertaining to the condition Hypertrophic Cardiomyopathy to be regarded demonstrating different degrees of contractility, while neoplastic entities are apprehended as holding no part presenting contraction. (238) The aforementioned yet, might constitute an oversimplification of in nature encountered circumstances. As the infiltration of neoplastic tissue contingently might not eventuate in an orderly manner, but occur with regions of healthy myocardium or even inclusions of these, exact demarcation of affected tissue may demonstrate difficult or might even be disguised by the presence of healthy contractile myocardial portions. (238) Hansen and Merchant direct attention to the complicated differentiation between neoplastic tissue and small areas of contraction from persisting myocardium within context of infiltrative conditions. (238) According to aforementioned authors, this includes Lymphoma, Amyloidosis, or Sarcoidosis. (238)

The technique of radio frequency saturation within context of MRI enables the labeling of myocardial tissue via alteration of its magnetization prior to the process of imaging. (239) These “tags” (239), constituting hypointense stripes, allow a tracking of the heart’s motion (including translation, rotation, as well as twist). (239) In theory, the aforementioned technique should assist in the undertaking of a differentiation between neoplastic tissue and Hypertrophic Cardiomyopathy. Nevertheless, it is voiced, that the procedure of tagging is in need of further testing. (238, 241, 242) The differentiation between neoplastic tissue and small contractile

regions of persisting myocardium as encountered in infiltrative conditions necessitates increased assessing caution. (238)

4.4.6 Right Ventricular Involvement

The definition of right ventricular hypertrophy has been noted to have yet to experience the event of standardization. (244) Yet, according to the European Association of Cardiovascular Imaging and Saudi Heart Association a right ventricular wall thickness of <5mm finds consideration as an ordinary extent. (103) A similar notion to the aforementioned is shared by other societies. (251)

Patients with Hypertrophic Cardiomyopathy holding a right ventricular involvement range from 17.6-53.5% (89, 251, 247, 248, 252), occurring with a more elevated prevalence than the midventricular form (2.9-9.4%) (229, 228, 227) and apical variant encountered within the region of the United States of America (1.9-3%) (213, 212).

In patients presenting a RVWT of ≥10 mm, mutations in the gene TTN were determined in the extent of 81.8% of cases (249), deviating from the usually most encountered mutations in the genes MYH7 and MYBPC3 in context of left ventricular hypertrophy (39, 29). Individuals with aforementioned RVWT demonstrated mutations in the genes MYH7, MYBPC3, and ACTN2 in 54.5% and 36.4% of cases, respectively. (249)

Hypertrophic patterns in the right ventricle hold a resemblance of those occurring in the left ventricle (253), with report of right ventricular aneurysm being existent (254) and Right Ventricular Outflow Tract Obstruction (being defined as a pressure gradient of ≥10 mm) (255). This demonstrates the coherence between the condition encountered with regard to the left and right ventricle, sharing contingently the same subjacent processes leading to their phenotypic expressions.

According to McKenna et al. 75% of persons with right ventricular involvement demonstrate a hypertrophy of the right ventricle with an extent of ≤8 mm. (248) Repeatedly, the extent of right ventricular hypertrophy reaching relevance in hemodynamic aspects and inducing potential clinical manifestation represent domains of possible investigation.

Global Longitudinal Strain in patients with right ventricular involvement was detected presenting decreased in comparison to individuals without right ventricular hypertrophy or control study participants, with -17.0 ± 3.6, - 22.4 ± 3.5 and -23.8 ± 2.7, respectively. (252)

Aforementioned holds eminent relevance in consideration of 80% of the right ventricular Stroke Volume being effectuated in consequence of longitudinal contraction. (252)

Of note, 70% of patients with Hypertrophic Cardiomyopathy and right ventricular involvement demonstrate Supraventricular Arrhythmia. (248) As such, the aforementioned constitutes a substantial entity in the morphologic form.

As a multivariate Cox proportional hazards regression model, with the adjusted covariates of gender and age, determined right ventricular hypertrophy as an independent predictor of incidents of cardiovascular nature, with a hazard ratio of 8.69 (95% CI: 2.68-28.1, *p* value of 0.0003) (251), its presence is associated with an eminent risk for affected patients. Even though attenuated, it remained elevated even subsequent to the adjustment for gender, age, left ventricular EF, and Mass Index of the left ventricle, with a hazard ratio of 5.35 (95% CI: 1.17-24.4, *p* value of 0.03). (251)

4.4.7 Genotype Positive Phenotype Negative Hypertrophic Cardiomyopathy

Genotype Positive Phenotype Negative Hypertrophic Cardiomyopathy finds reference to carriers of a mutation relevant to Hypertrophic Cardiomyopathy, yet with no presentation of a phenotypic expression (260).

Repeatedly, akin to the prevalence of gene mutations generally encountered in Hypertrophic Cardiomyopathy, genotype positive phenotype negative individuals preponderantly demonstrate mutations in the genes MYH7 and MYBPC3 (264, 265, 261).

Of note, even though multiple mutations find consideration to imply an increased severity of morphologic manifestation (55, 64, 29), reports of genotype positive phenotype negative persons carrying multiple mutations (261, 266), are existent, providing evidence for a subjacent complexity of unfolding genetic, epigenetic and environmental processes and their interaction implicated in the formation of the disease's eventual phenotypic manifestation. As these factors nevertheless, partially hold the appearance of an insufficient single responsibility, involvement of additional constituents seem tenable.

The vast majority of genotype positive phenotype negative individuals are reported to demonstrate no symptoms (265, 267), no application of cardiac medication (265), or to be encountered within NYHA functional class I (265, 268), demonstrating the condition's subjacency in affected persons.

Overall, electrocardiographically detected abnormal Q-waves in genotype positive phenotype negative persons are encountered in the proportion of 18.4-67.0%. (264, 270, 98)

Of note, while genotype positive phenotype negative individuals echocardiographically demonstrated no significant difference with regard to the Global Longitudinal Strain rate, the specific segmental examination of the left ventricle revealed detectable distinctions, even in absence of a macromorphologic manifestation. (272) Aforementioned is inter alia exemplified by the region of the basal septum, with genotype positive phenotype negative individuals in comparison to control study participants exhibiting a decrease in strain rate (16.8% ± 3.1% compared to 19.0% ± 4.0%, respectively, *p* value of 0.02). (272)

Additionally, in comparison to control subjects, genotype positive phenotype negative persons were determined with a decrease in global early diastolic mitral annular velocity, with 14.2 ± 0.3 cm/s and 12.3 ± 0.3 cm/s (*p* value of <0.0001), respectively. (265) Aforementioned constitutes a difference of 13%. (265)

Of interest, even though genotype positive phenotype negative individuals demonstrate no macromorphologic evident left ventricular hypertrophy, structural abnormalities are existent. These include myocardial crypts, with one of the entities encountered in the amount of 32.9-81.3%. (262, 275, 276, 280) Further altered structures constitute the increased longitudes of the anterior mitral valve leaflets, determined with 18 ± 3 mm in control subjects and 21 ± 3 mm in genotype positive phenotype negative individuals (*p* value of <0.01), respectively. (267) Additionally, global trabecular complexity of the left ventricle, determined in utilization of Fractal Analysis, in genotype positive phenotype negative individuals compared to control subjects was found increased, with a fractal dimension of 1.176 ± 0.06 and 1.149 ± 0.03 (*p* value of 0.012), respectively. (266) The cognizant exploration of aforementioned structural abnormalities combined may lead to an increased detection of otherwise not recognized individuals subject to Hypertrophic Cardiomyopathy.

Furthermore, genotype positive individuals without a left ventricular hypertrophic manifestation, present, in comparison to control subjects, an increase in serum carboxyl terminal propeptide, with 82.16 ± 3.03 µg per liter and 107.73 ± 4.65 µg per liter (*p* value of <0.001), respectively. (282) Aforementioned represents a difference of 31%. (282) As aforementioned value is quantifiable, its potential of representing an objective indicator of incipient processes related to Hypertrophic Cardiomyopathy or the disease per se, is existent and may be implemented in the instrumentarium of diagnostic proceedings.

Cardiac Phosphocreatine to Adenosine Triphosphate ratio in genotype positive individuals with a maximal left ventricular hypertrophy of <13 mm in comparison to control subjects was determined to present a diminution (1.57 ± 0.60 and 2.44 ± 0.30, *p* value of <0.001) (287) Furthermore, detection of a suboptimal management with regard to the Ca^{2+} concentration in myocytes proceeding from $\alpha MHC^{403/+}$ mice, is existent. (286) Either of antecedent affirmations demonstrate alterations in persons representing mutation carriers, yet with an absence in hypertrophy to encompass not only morphologic aspects, but is yet encountered as well at the subcellular level and may represent evidence for further possible investigation at this scale.

4.5 Therapeutic Intervention

Within context of Hypertrophic Cardiomyopathy, general measures include inter alia the nonparticipation in effortful physical activity (288), the reduction in corporal weight (17), as well as in case of LVOTO, the avoidance of dehydration (17, 288) and consumption of alcohol in an excessive conduct (17). Aside of aforementioned means to be easily accessible, they are as well applicable by every individual afflicted by the ailment.

Additionally to general measures being implementable, in patients subject to Hypertrophic Cardiomyopathy exhibiting as well the presence of a LVOTO, the pharmacological intervention constitutes the primary approach. (292) Hereof, in principal, the agents of β-Adrenoceptor Blockers are to be considered, according to both, the ACCF/AHA collaboration as well as ESC, as the initial pharmacological measure. (288, 17) In general, β-Receptor Antagonists induce a negative chronotropic and inotropic effect as well as cause an attenuation of an expected increase in cardiac frequency concomitant with the circumstances of exertional physical activity or stress. (341) Generally, the beneficial effects in reference to Hypertrophic Cardiomyopathy are regarded to proceed partially from the impediment of eventualities mediated by catecholamines. (290, 293) The latter include the increase in cardiac frequency, the ventricle's contractility, and rigidity. (293) The results of the collective effects of β-Adrenoceptor Blocking Agents constitute the improvement of the ventricle's relaxation as well as the elevation of the time lapse of diastolic filling. (293) As a consequence, improvement of the left ventricular pressure at end distole and perfusion is effectuated. (293)

Verapamil is included as a secondary option subsequent to β-Adrenoceptor Blocking Agents, in case of their ineffectiveness, unwanted secondary effects, or contraindications. (288, 17) In general, Verapamil holds a reduction in inotropy and chronotropy as well as effectuates a diminution in cardiac afterload. (341) Furthermore, Diltiazem finds consideration as being

applicable as an alternative to Verapamil (288) or within context of pharmacological intolerance or contraindication of β-Adrenoceptor Blockers or Verapamil intake (17). The agent exerts negative inotropic effects (342), even though the negative inotropy manifests to a lesser extent as in comparison to Verapamil (342), as well as holds a negative chronotropic effects (290). Beneficial effects of Verapamil and Diltiazem in context of Hypertrophic Cardiomyopathy are considered to be found in part in their negative inotropic and chronotropic characteristics as well as partially in their improvement of diastolic properties of the myocardium. (290, 293)

In case of an ameliorative nonsuccess within context of the sole administration of β-Adrenoceptor Blockers or Verapamil, Disopyramide is regarded as applicable in addition to aforementioned agents. (17, 288) Disopyramide holds the property of an ample negative inotropy. (300) As such, according to Sherrid et al. (343) the agent reduces the left ventricular ejection acceleration and in turn effectuates a diminution of the hemodynamic force exherted on the protruding mitral valve leaflet. (343) Furthermore, the mitral-septal contact experiences a delay. (343) As a result, the final pressure gradient presents decreased. (343)

In principal, within context of Heart Failure exhibiting a left ventricular EF of ≥50% and an absence in LVOTO, administration of β-Adrenoceptor Blocking Agents, Verapamil, Diltiazem, as well as Loop Diuretics is advocated. (17) Conversely, a left ventricular EF of <50% and a symptomatically manifest Heart Failure directs to the application of Diuretics, β-Adrenoceptor Blocking Agents, Angiotensin Converting Enzyme Inhibitors, Angiotensin Receptor Blockers as well as Mineralocortiocoid Receptor Antagonists, (17) with the ESC denoting the administration to be eventuated consonantly to its guidelines of Heart Failure (302) in the year of 2012. (17) The administration of β-Adrenoceptor Blocking Agents in individuals presenting Heart Failure with a preserved EF concomitant with AF may be effectuated with the intention of controlling the ventricular rate. (302) In general, application of β-Adrenoceptor Blocking Agents in persons subject to Heart Failure with a reduced EF results in an extensive improvement of the EF. (302) Furthermore, the agents hold an anti-ischemic property, possibly reduce the risk of SCD, and effectuate a diminution in overall mortality. (302) The recommendation of Diuretics is based on their amelioration of dyspnea and edema in individuals presenting signs and symptoms of congestion. (302) The aforementioned is effectuated inattentive of existent EF. (302) The utilization of Angiotensin Converting Enzyme Inhibitors in patients subject to Heart Failure with a reduced EF is found in their moderate effect of left ventricular remodelling. (302) In addition, Angiotensin Converting Enzyme Inhibitors were identified to hold with regard to aforementioned individuals a reduction in mortality and morbidity. (344)

Angina Pectoris resembling pain, in case of an ascertained exclusion of LVOTO (within resting conditions or provocation) or obstructive Coronary Artery Disease, finds recommendation of a β-Adrenoceptor Blocking Agents or Calcium Antagonists application. (17) The administration of oral Nitrates in aforementioned circumstances might be attentively eventuated. (17) Furthermore, according to Ammirati et al., the agent Ranolazine holds the potential of effectuating an amelioration of Angina Pectoris. (292) In general, the application of β-Adrenoceptor Blocking Agents and Calcium Antagonsists within aforementioned circumstances is based on the improvement of distolic function and the reduction of oxygen demand in the myocardium. (17) Generally, Nitrates induce a dilatation of the coronary arteries and effectuate an improvement in subendocardial oxygenation (345).

In general, according to the ESC, the diminution of LVOTO by means of invasive procedures is advocated within context of a gradient of ≥50 mm Hg, a NYHA functional class of III to IV, and/or repeated occurrences of Syncope within physical activity. (17) The pharmacological approach must have been eventuated prior. (17) As hemodynamic impedance increases continuously beginning with the gradient of ≥50 mm Hg, placement of the threshold at aforementioned value presents appropriate. Furthermore, the severity of clinical manifestations encountered in patients demonstrating NYHA functional class III or IV surpasses the consideration of a contraindication of invasive procedures as therapeutic measures.

The aforementioned includes the procedure of Ventricular Septal Myectomy (17), with a median accomplished reduction in LVOTO gradient of 77% (308) and a sustained improvement of symptoms in 70-80% of cases (17). The pooled rate of all-cause mortality within context of Ventricular Septal Myectomy is noted with 1.1% per person year. (309) Of note, performing of the procedure at centers regarded to conduct Ventricular Septal Myectomy at an increased number is associated with a rate of deceases within the 30 postoperative days of 0.46%. (312)

Another available procedure constitutes Alcohol Septal Ablation accomplishing a reduction of the LVOTO gradient from initial overall 67 ± 36 mm Hg to 16 ± 21 mm Hg (315) and within resting conditions from 70 ± 38 mm Hg to 35 mm Hg (316). The pooled rate of all-cause mortality in individuals undergoing Alcohol Septal Ablation is noted with 1.5% per person year. (309)

While both interventions represent appreciable medical measures in reference to the reduction of the LVOTO gradient, aforementioned entity finds a slightly greater diminution in context of Ventricular Septal Myectomy. Additionally, in comparison to Alcohol Septal Ablation, the former procedure is associated with an overall more decreased rate of all-cause mortality (1.1%

compared to 1.5%). In contrast, nevertheless, on basis of their undertaken operational complexity, the intervention of Alcohol Septal Ablation appears to constitute the more minimal therapeutic measure.

In general, according to the ESC, entire elucidation of Cardiac Pacing in patients subject to Hypertrophic Cardiomyopathy to hold an absolute beneficial effect, is not existent. (17) This medical approach, may find consideration in individuals presenting inter alia a LVOTO of ≥50 mm Hg at resting conditions or in context of physical provocation. (17)

Aforementioned cogitation might find substantiation as, according to Kappenberger et al., DDD Pacing resulted in a reduction of LVOT gradient, examined subsequent to one year of pacing from initial present 59 ± 36 mm Hg to 30 ± 25 mm Hg (*p* value of <0.001). (17, 323, 325) As a consequence, application of DDD pacing as well as pacing in general in patients subject to Hypertrophic Cardiomyopathy with LVOTO might implicate beneficial effects.

Of note, pacing location in affected individuals constitutes an issue of relevance. Reduction in LVOT gradient was noted to hold a variance contingent upon region of pacing. (323, 326) Lead placement at the right ventricular apex is to be favored over high septum pacing, with the former presenting a gradient reduction from a mean of 96 ± 33 mm Hg to 38 ± 24 mm Hg. (326)

Akin to DDD Pacing, according to Berruezo et al., Biventricular Pacing was found to present as well a diminution of the LVOT gradient, specifically mentioned within resting conditions as from initial 74 ± 23 mm Hg to 40 ± 26 mm Hg at the time period of three months (*p* value of <0.05) and 28 ± 17 mm Hg at one year (*p* value of <0.05). (323, 327) As such, beneficial effects in affected patients are encountered as well in consequence of Biventricular Pacing.

As a result, Cardiac Pacing in patients with Hypertrophic Cardiomyopathy presenting a LVOT gradient might find the prospective occupancy of representing an eminent treatment option.

Of interest, Berruezo et al. denote within context of pacing as well a decline in left ventricular mass from initial 356 ± 110 g to 315 ± 70 g at the time period of three months (*p* value of 0.13) and 284 ± 42 g determined at one year (*p* value of <0.05). (327) Aforementioned constitutes an auxiliary occurrence in patients subject to the condition, approaching the substantial causality of Hypertrophic Cardiomyopathy.

In principal comparable to the variance in LVOT gradient reduction encountered in reference to pacing location (326), the setting of pacing as well demonstrated to exert influence on the gradient (328). The mode of Biventricular Pacing was found to present most beneficial in 66.7%

of individuals and a left ventricular preexcitation of 40 ms to be encountered as most favorable in 66.7% of patients. (328)

Lenarczyk et al. reported Cardiac Resynchronization Therapy Defibrillators to had attained a decrement in the peak LVOT gradient from 84 to 33 mm Hg (p value of <0.05) while the mean LVOT gradient was denoted with a diminution from 38 to 13 mm Hg (p value of <0.05). (328) As such restoration of the ordinary pattern of the heart beat presents beneficial in the reduction of LVOT gradient.

Advocacy of orthotopic Cardiac Transplantation is according to the ESC existent within the circumstance of affirmative eligibility of affected persons, left ventricular EF of <50% as well as a NYHA functional class of III-IV (17) This applies in case of nonsuccess of an antecedently eventuated pharmacological approach or therapy-resistant Ventricular Arrhythmia. (17) A preserved EF of ≥50% may find consideration with the aforementioned NYHA functional classes being elicited by diastolic dysfunction and circumstance of ineffectiveness of a pharmacological therapy. (17) According to the ACCF/AHA collaboration, possibility of conducting the surgical procedure is present in case of advanced Heart Failure, non-existence of an obstruction and an EF of ≤50%. (288) The aforementioned is to be considered within context of a nonsuccess of an antecedent pharmacological approach. (288) On occasion the surgical intervention in the situational condition of a preserved EF is to be considered. (288)

Maron et al. denote the overall cardiac transplant survival rates subsequent to the procedure of Cardiac Transplantation at the time periods of 1, 5, and 10 years with 85%, 75%, and 61%, respectively. (329) The rates for aforementioned time periods in the collective receiving Cardiac Transplantation in consequence of diseases other than Hypertrophic Cardiomyopathy were encountered with 82%, 70%, and 49%, respectively. (329) As the rates in reference to individuals undergoing the surgical procedure as a result of Hypertrophic Cardiomyopathy displayed no significant difference in comparison to the ones encountered in the overall collective of persons with the performance of Cardiac Transplantation in consequence of other conditions (Logrank Test p value of 0.05), apprehension of equalized outcome with regard to either collectives is justified.

According to Maron et al., in comparison to individuals receiving Cardiac Transplantation as a result of Hypertrophic Cardiomyopathy, persons undergoing the procedure in consequence of Ischemic Heart Disease were determined to demonstrate less favorable 1, 5, and 10 years survival rates, with 82%, 69%, and 48% (Logrank Test p value of 0.02), respectively. (329) Akin to the authorship of Maron et al. (329) Kato et al. (330) identified patients receiving

Cardiac Transplantation with Hypertrophic Cardiomyopathy as causality to exhibit compared to individuals undergoing the surgical intervention in consequence of Ischemic Heart Disease more favorable 1 and 5 years survival rates, with 90.1% as to 85% and 83.9% as to 67.1% (*p* value of 0.0359), respectively (330). In consequence of the antecedently mentioned, the collective of patients receiving Cardiac Transplantation as a result of the condition of Hypertrophic Cardiomyopathy might as well demonstrate different survival rates in comparison to other certain subdivisions of diseases.

4.6 Conclusion

The ailment of Hypertrophic Cardiomyopathy, even though hitherto to have been accorded yet extensive investigation, nevertheless still serves as a partially enigmatic entity amidst conditions. Its relevance, as encountered in different parts of the world, including the United States of America (26), the United Kingdom (28), France (29), Germany (30), Brazil (31), the Republic of South Africa (32), China (33), and Japan (34), as well as clinical identification being established in collectively 122 countries of the world (35), is of global scale. The etiologic basis of the disease in the extent of up to 60% of persons within their adolescence or adulthood constitutes mutations encountered in genes encoding for cardiac sarcomeric proteins (17). Hundreds of gene mutations effectuating the disease have been identified (38). As such, placement of Hypertrophic Cardiomyopathy to constitute a condition of cardiac sarcomeric proteins with genetic subjacency appears partially to present justifiable. In general, the preponderance of encountered mutations found detection pertaining to the sarcomeric genes of MYH7 and MYBPC3 (39), collectively in one publication identified in as much as up to 82.3% of cases (29). A distinct subdivision of conditions encountered within the spectrum of Hypertrophic Cardiomyopathy, is constituted by Hypertrophic Cardiomyopathy Phenocopies. (3) While manifesting cardiac hypertrophy, yet holding a different pathogenesis, these diseases are regarded as to phenotypically mimic Hypertrophic Cardiomyopathy (3) and are, even though not with certainty affirmable, estimated to amount to 5-10% of all clinically diagnosed Hypertrophic Cardiomyopathy occurrences (3).

The relevance of genetic aspects within Hypertrophic Cardiomyopathy finds substantiation as - even though not unequivocally evident (46) - a Genotype-Phenotype Correlation in the ailment is discussed, an incomplete and age associated Penetrance has been demonstrated (18, 46), and determinants such as Complex Genotypes (55, 64) and Modifier Genes (65, 66) exert influence on the condition. Furthermore, Epigenetics as well as environmental factors have been taken into consideration of influencing the ailment of Hypertrophic Cardiomyopathy. (46)

Macroscopically, Hypertrophic Cardiomyopathy demonstrates cardiac hypertrophy to be regarded as to affect in principal the left ventricle. (79) Nevertheless, involvement of the right ventricle, presenting as a biventricular condition (80), or the isolated occurrence of right ventricular hypertrophy (81), is existent.

The preponderance of persons with Hypertrophic Cardiomyopathy present asymptomatic. (17) The possibility of a symptomatic manifestation eventuating at an early age or after decades of a person's life time, is existent. (94)

An abnormal ECG is demonstrated by the extent of 91.8-96.9% (95–98) of individuals with Hypertrophic Cardiomyopathy. Furthermore, Two-Dimensional Echocardiography is regarded as the most accessible investigative method in reference to diagnosing the condition. (25) Of note, within aforementioned assessing method, the parameter of EF to a frequent extent presents normal or even supernormal. (3, 99) In comparison to a common assessment via Two-Dimensional Echocardiography, Cardiac MRI represents a superior diagnostic modality. (17)

Although once thought to constitute a pathognomonic abnormality of obstructive Hypertrophic Cardiomyopathy (107), echocardiographic detection of SAM of the mitral valve complex has been as well reported within circumstances other than Hypertrophic Cardiomyopathy (108–110). The entity of LVOTO is considered to be effectuated at least by means of the hypertrophy located at the septal base and the occurrence of SAM of the mitral valve. (5) In 56.3% of individuals with obstructive Hypertrophic Cardiomyopathy coaptation of the mitral valve leaflets in mid-systole is absent in consequence of SAM of the anterior mitral cusp, resulting in a regurgitant jet at the mitral valve detected via Transesophageal Echocardiography. (119)

The entity of AF is regarded as a sequela in patients subject to Hypertrophic Cardiomyopathy (123), demonstrating a prevalence of 22.5% (95% CI: 20.1-24.8%) and an incidence of 3.1% (95% CI: 2.6-3.5%), with both inlcuding paroxysmal as well as permanent AF (124). In concurrence of the proportion of 57.8% to present paroxysmal AF, persistent AF is encountered in 42.2% of persons (125).

Although once considered to be preponderantly present in individuals with LVOTO (129), the proportion of 44% of individuals subject to Hypertrophic Cardiomyopathy complicated by Infective Endocarditis was found in absence of LVOTO (130). Individuals with Infective Endocarditis demonstrate a concentric or asymmetric septal phenotypic expression in 38% and 29% of cases, respectively. (130)

Heart Failure constitutes aside of SCD one of the causalities of premature decease in individuals demonstrating the condition of Hypertrophic Cardiomyopathy. (134) The amount of 3.5% of persons are found in End Stage Hypertrophic Cardiomyopathy determined exclusively by the factor of an EF of <50%. (135) An end-stage form of Hypertrophic Cardiomyopathy demonstrated by an EF of <50% as well as hypokinesia and the dilation of the left ventricular cavity is encountered in 4.9% of individuals. (136)

The rate of SCD in individuals presenting Hypertorphic Cardiomyopathy per year amounts to 1%. (140) The extent in LVWT correlates directly with the risk for SCD, with 0/1000 person-years (95% CI: 0-14.4/1000 person-years) with regard to a wall thickness of ≤15 mm and 18.2/1000 person-years (95% CI: 7.3-37.6/1000 person-years) for a wall thickness of ≥30 mm. (146)

The condition of Hypertrophic Cardiomyopathy is encountered with a variability in morphologic expression, holding different patterns of hypertrophy (76). Its hypertrophic manifestation presents with substantial interindividual variation in reference to its extent as well as distribution. (151) Possibility of a subdivision of Hypertrophic Cardiomyopathy into an asymmetric, concentric, apical, and midventricular form as well as a mass-like manifestation, right ventricular involvement and genotype positive phenotype negative conjuncture, is existent. (76)

The morphologic form of Asymmetric Septal Hypertrophy is defined by the thickness of the interventricular septum of ≥15 mm (77, 76, 157) or a septum to left ventricular posterior wall ratio of >1.5 (77, 76). According to William et al. the ratio is delineated with >1.3 in normotensive persons and >1.5 for individuals presenting Hypertension. (157) It represents the most encountered form, with a range of 44.7-90% (158–160, 79). Mutations in the genes MYBPC3, MYH7, and MYL2, encoding for sarcomeric thick filament proteins, were determined to effectuate in the proportion of 94% of cases an asymmetric phenotypic expression of Hypertrophic Cardiomyopathy. (118) Further subdivision of the variant according to the morphologic form of the interventricular septum into the Asymmetric Sigmoid Form, Reverse Septal Contour, and Neutral Septal Form, has been denoted. (162)

Concentric Hypertrophic Cardiomyopathy finds description of demonstrating diffuse left ventricular hypertrophy (76, 149), with each ventricular segment delineated to present a comparable involvement of hypertrophy in concurrence with a reduction of intraventricular dimension (76). The extent of 11.3% of persons with mutation in the genes TNNT2, TNNI3, TPM1, and ACTC, encoding for thin filament proteins, were encountered with a concentric

phenotypic expression of Hypertrophic Cardiomyopathy, while 41% of individuals presenting a mutation in the gene TNNI3 were identified with either an apical or concentric hypertrophic manifestation. (118) An essential task represents the differentiation of Concentric Hypertrophic Cardiomyopathy and ailments with the possibility of presenting with a concentric left ventricular manifestation, including Athlete's Heart (172), Hypertension (76, 77), Aortic Stenosis (77), or Infiltrative and Deposition Diseases, such as Amyloidosis (77), Anderson-Fabry Disease (77), or Cardiac Sarcoidosis (77).

The variant of Apical Hypertrophic Cardiomyopathy has been denoted holding the characteristics of left ventricular hypertrophy demonstrating primary restriction to the region of the cardiac apex with a maximal wall thickness of ≥15 mm. (82) Apical Hypertrophic Cardiomyopathy apparently presents with an inhomogeneous dispensation in reference to geographical region (209, 210), with individuals being affected by Hypertrophic Cardiomyopathy exhibiting the variant in the proportions of 37.7% (211) within the Republic of Korea, 15% (212) of the Japanese population, and as few as 1.9-3% (213, 212) within the United States of America. The preponderance of individuals subject to Apical Hypertrophic Cardiomyopathy were encountered with mutations in the genes MYBPC3 and MYH7, with either one presenting a proportion of 33% of cases. (215) One publication notes the extent of persons afflicted by the variant to exhibit mutations in the gene encoding for β-Myosin Heavy Chain with 43%. (171)

Midventricular Hypertrophic Cardiomyopathy finds description of presenting with a region of stricture at the level of mid-cavity in consequence of a hypertrophied septum in apposition with the left ventricular wall including the possible involvement of at least the anterior papillary muscle. (226) The pressure of ≥30 mm Hg constitutes a defining entity. (227, 228) The mutation of Met149Val, while being encountered within Apical Hypertrophic Cardiomyopathy and other phenotypic expressions of Hypertrophic Cardiomyopathy, was denoted to as well result in the midventricular variant of the disease. (171) Even though denotation of the entity is existent within the context of the apical morphologic form of Hypertrophic Cardiomyopathy (220), apprehension of Left Ventricular Apical Aneurysm to represent a distinct constituent of midventricular hypertrophy has been voiced (228).

Mass-Like Hypertrophic Cardiomyopathy exhibits an extensive thickening as a focus within the left ventricle. (76) Its differentiation from neoplasms (77) constitutes a substantial circumstance. Within context of MRI, radio frequency saturation enables a labeling of myocardial tissue by alteration of its magnetization prior to the process of imaging. (239) In

regard of distinguishing neoplastic tissue from Hypertrophic Cardiomyopathy, aforementioned technique should assist. Nevertheless, it is voiced, that the procedure of tagging finds necessity of further testing. (238, 241, 242) The distinction between neoplasia and small contractile areas of persisting myocardium encountered within context of infiltrative conditions requires elevated assessing caution. (238)

With regard to Right Ventricular Involvement, while its definition denoted to yet necessitate the eventuation of standardization (244), the European Association of Cardiovascular Imaging and Saudi Heart Association consider a right ventricular wall thickness of <5 mm to constitute an ordinary extent (103). A similar notion to the latter affirmation is shared by other societies. (251) The extent of 90.9% of individuals demonstrating a RVWT of ≥10 mm were identified to represent carriers of one or more mutations in sarcomeric genes holding an association to the ailment of Hypertrophic Cardiomyopathy. (249) In aforementioned persons, the majority of mutations were encountered concerning the gene TTN, with a proportion of 81.8% of individuals, while mutations in the genes MYH7 and MYBPC3 were present in 54.5% and 36.4% of cases, respectively. (249) Right ventricular hypertrophy presents both, a biventricular involvement (80) as well as a manifestation isolated to the right ventricle (81).

Genotype Positive Phenotype Negative Hypertrophic Cardiomyopathy delineates the situational condition of individuals representing carriers of a mutation in a gene with relevance to Hypertrophic Cardiomyopathy, yet in absence of a phenotypic expression (260). The preponderance of mutations in genotype positive phenotype negative individuals are encountered in the genes of MYH7 and MYBPC3 (264, 265, 261) with varying prevalence contingent upon authorship, with 52.6% and 36.8% (264), 50% and 36.8% (265), or 18.6% and 62.5% (261) of cases, respectively. Even though consideration of presence of multiple mutations to implicate an increase in severity of the morphologic expression is existent (55, 64, 29), cases of genotype positive phenotype negative persons being subject to multiple mutations have been reported (261, 266). While denoted to demonstrate no phenotypic expression (260), possibility structural abnormalities in genotype positive phenotype negative individuals to be present, including Myocardial Crypts (262, 275, 276, 280) as well as increased longitudes of the anterior mitral valve leaflets (267), frequency in accessory muscle bundles (209), and left ventricular trabecular complexity (266), is existent. Affected persons, furthermore demonstrate an increase in serum carboxy terminal propeptide (282) and an expansion in extracellular volume (283). Additionally, genotype positive individuals demonstrating a maximal left ventricular hypertrophy of <13 mm were encountered with a diminution of the cardiac Phosphocreatine to Adenosine ratio. (287)

With regard to the ailment of Hypertrophic Cardiomyopathy measures of therapeutic intention have been initiated. The approach conveying a general character inter alia include means such as the nonparticipation in effortful physical activity (288), a reduction in corporal weight (17), as well as within context of LVOTO, the avoidance of dehydration (17, 288) and consumption of alcohol in an excessive conduct (17). A subsequent measure in persons presenting LVOTO constitutes the induction of the pharmacological intervention, considered additionally to general measures to represent the primary approach (292). In this regard, in principal, β-Adrenoceptor Blocking Agents find consideration as the initial pharmacological mean to be utilized. (288, 17) In case of their ineffectiveness, unwanted secondary effects, or contraindications, the application of Verapamil, a Class IV Antiarrhythmic Agent, is to be effectuated. (288, 17) Diltiazem is to be apprehended as an alternative to Verapamil (288) or may find application within context of a pharmacological intolerance or contraindication in reference to the utilization of β-Adrenoceptor Blockers or Verapamil (17). Within the situational condition of an ameliorative nonsuccess of a sole application of β-Adrenoceptor Blocking Agents or Verapamil, the Class Ia Antiarrhythmic Agent Disopyramide (17, 294) is considered administrable in addition to aforementioned agents (17, 288).

In patients subjects to Hypertrophic Cardiomyopathy in absence of LVOTO, pharmacological treatment orientates by the presence of Heart Failure. Within context of patients demonstrating Heart Failure with a left ventricular EF of ≥50% as well as no LVOTO, the application of β-Adrenoceptor Blocking Agents, Verapamil, Diltiazem, and Loop Diuretics find utilization in reference to attaining a diminution of the diastolic pressures of the left ventricle and an enhancement of its filling. (17) Individuals exhibiting a left ventricular EF of <50% as well as the symptomatic manifestation of Heart Failure may according to the ESC be subject to a pharmacologic intervention in utilization of Diuretics, β-Adrenoceptor Blockers, Angiotensin Converting Enzyme Inhibitors, Angiotensin Receptor Blocking Agents as well as Mineralocorticoid Receptor Antagonists. (17)

Presence of a pressure gradient elicited by LVOTO may as well be diminished by the surgical procedure of Ventricular Septal Myectomy or the intervention of Alcohol Septal Ablation. In comparison to the latter approach, Ventricular Septal Myectomy presents a slightly more favorable pooled rate of all-cause mortality, with 1.5% and 1.1%, respectively (309). Furthermore, according to Barry J. Maron, effectuating of Ventricular Septal Myectomy at five Hypertrophic Cardiomyopathy dedicated centers in North America encompassing an elevated number of patients, was reported in the amount of 3.695 of individuals with 17 cases of deceases within the 30 postoperative days, constituting 0.46%. (312)

While according to the ESC, entire elucidation of Cardiac Pacing in Hypertrophic Cardiomyopathy affected individuals to hold an absolute beneficial effect, is not existent (17), nevertheless DDD Pacing was encountered with a decrement in LVOT gradient (324, 17, 323, 325). The decrease in LVOT gradient presents with a variance contingent upon location of pacing. (323, 326) Akin to DDD Pacing, report of Biventricular Pacing to effectuate a diminution of LVOT gradient, is existent. (327) Furthermore, the restoring of the ordinary pattern of the heart beat within utilization of Cardiac Resynchronization Therapy Defibrillators was demonstrated to hold a decrement in peak as well as mean LVOT gradient (328).

With regard to a subdivision of individuals subject to Hypertrophic Cardiomyopathy encountered with affirmative eligibility, the option of Cardiac Transplantation presents as available. The surgical procedure was determined to demonstrate statistically no significant difference in overall cardiac transplant survival rates for the time periods of 1, 5, and 10 years between patients receiving Cardiac Transplantation in consequence of Hypertrophic Cardiomyopathy and the overall collective of individuals undergoing the intervention not as a result of the ailment (with Ischemic, Dilated, or Restrictive Cardiomyopathy as causality). (329) Nevertheless, equalized outcome might not be existent in the comparison with individual subdivisions of diseases.

The ailment of Hypertrophic Cardiomyopathy has been subject of a considerable extent of persons directing their attention to. As much information as has been gathered up until present time, entire elucidation of this in part question raising condition has not been attained.

5 References

1. Willius FA, Dry TJ. A History of the Heart and the Circulation. W. B. Saunders Company; 1948.

2. Braunwald E. The Simon Dack Lecture. Cardiology: The Past, the Present, and the Future. J Am Coll Cardiol 2003 Dec 17; 42(12):2031–41.

3. Fuster V, Harrington RA, Narula J, Eapen ZJ, editors. Hurst's the Heart. 14th Edition. New York: McGraw-Hill Education; 2017.

4. Treier DJ, Elwell WA. Evangelical Dictionary of Theology. 3rd Edition. Grand Rapids: Baker Academic; 2017.

5. Liew AC, Vassiliou VS, Cooper R, Raphael CE. Hypertrophic Cardiomyopathy-Past, Present and Future. J Clin Med 2017 Dec 12; 6(12).

6. Vulpian A. Contribution a L'Étude des Rétrécissments de L'Orifice Ventriculo-Aortique. Archives de Physiologie Normale et Pathologique 1868:456–7.

7. Liouville H. Rétrécissement Cardiaque Sous-Aortique. Gazette Médicale de Paris 1869:161–3.

8. Hallopeau M. Rétrécissement Ventriculo-Aortique. Gazette Médicale de Paris 1869:683–4.

9. Brock R. Functional Obstruction of the Left Ventricle (Acquired Aortic Subvalvar Stenosis). Guy's Hosp Rep 1957; 106(4):221–38.

10. Teare D. Asymmetrical Hypertrophy of the Heart in Young Adults. Br Heart J 1958 Jan; 20(1):1–8.

11. Braunwald E, Aygen MM. Idiopathic Myocardial Hypertrophy without Congestive Heart Failure or Obstruction to Blood Flow. Clinical Hemodynamic and Angiographic Studies in Fourteen Patients. Am J Med 1963 Jul; 35:7–19.

12. Morrow AG, Lambrew CT, Braunwald E. Idiopathic Hypertrophic Subaortic Stenosis. II. Operative Treatment and the Results of Pre- and Postoperative Hemodynamic Evaluations. Circulation 1964 Nov; Suppl 4:120-151.

13. Moreyra E, Klein JJ, Shimada H, Segal BL. Idiopathic Hypertrophic Subaortic Stenosis Diagnosed by Reflected Ultrasound. Am J Cardiol 1969 Jan; 23(1):32–7.

14. Jarcho JA, McKenna W, Pare JAP, Solomon SD, Holcombe RF, Dickie S et al. Mapping a Gene for Familial Hypertrophic Cardiomyopathy to Chromosome 14q1. N Engl J Med 1989 Nov 16; 321(20):1372–8.

15. Tanigawa G, Jarcho JA, Kass S, Solomon SD, Vosberg H-P, Seidman JG et al. A Molecular Basis for Familial Hypertrophic Cardiomyopathy: An α/ß Cardiac Myosin Heavy Chain Hybrid Gene. Cell 1990 Sep 7; 62(5):991–8.

16. Geisterfer-Lowrance AAT, Kass S, Tanigawa G, Vosberg H-P, McKenna W, Seidman CE et al. A Molecular Basis for Familial Hypertrophic Cardiomyopathy: A ß Cardiac Myosin Heavy Chain Gene Missense Mutation. Cell 1990 Sep 7; 62(5):999–1006.

17. Elliott PM, Anastasakis A, Borger MA, Borggrefe M, Cecchi F, Charron P et al. 2014 ESC Guidelines on Diagnosis and Management of Hypertrophic Cardiomyopathy: The Task Force for the Diagnosis and Management of Hypertrophic Cardiomyopathy of the European Society of Cardiology (ESC). Eur Heart J 2014 Oct 14; 35(39):2733–79.

18. Harrison TR, editor. Harrison's Principles of Internal Medicine. 20th Edition. New York: McGraw-Hill; 1962.

19. Maron BJ, Maron MS. A Discussion of Contemporary Nomenclature, Diagnosis, Imaging, and Management of Patients with Hypertrophic Cardiomyopathy. Am J Cardiol 2016 Dec 16; 118(12):1897–907.

20. Maron BJ, Epstein SE. Hypertrophic Cardiomyopathy: A Discussion of Nomenclature. Am J Cardiol 1979 Jun; 43(6):1242–4.

21. Braunwald E, Morrow AG, Cornell WP, Aygen MM, Hilbish TF. Idiopathic Hypertrophic Subaortic Stenosis: Clinical, Hemodynamic and Angiographic Manifestations. Am J Med 1960 Dec 1; 29(6):924–45.

22. Parker DP, Kaplan MA, Connolly JE. Coexistent Aortic Valvular and Functional Hypertrophic Subaortic Stenosis. Clinical Physiologic and Angiographic Aspects. Am J Cardiol 1969 Sep; 24(3):307–17.

23. Wallooppillai NJ, Atukorale DP, Jayasinghe MdS, Kulathungam S. Familial Hypertrophic Cardiomyopathy in Ceylon. Br Heart J 1973 Feb; 35(2):181–8.

24. Morrow AG, Braunwald E. Functional Aortic Stenosis; A Malformation Characterized by Resistance to Left Ventricular Outflow without Anatomic Obstruction. Circulation 1959 Aug; 20(2):181–9.

25. Maron BJ. Hypertrophic Cardiomyopathy: A Systematic Review. JAMA 2002 Mar 13; 287(10):1308–20.

26. Maron BJ, Gardin JM, Flack JM, Gidding SS, Kurosaki TT, Bild DE. Prevalence of Hypertrophic Cardiomyopathy in a General Population of Young Adults. Echocardiographic Analysis of 4111 Subjects in the CARDIA Study. Coronary Artery Risk Development in (Young) Adults. Circulation 1995 Aug 15; 92(4):785–9.

27. Semsarian C, Ingles J, Maron MS, Maron BJ. New Perspectives on the Prevalence of Hypertrophic Cardiomyopathy. J Am Coll Cardiol 2015 Mar 31; 65(12):1249–54.

28. Elliott PM, Gimeno Blanes JR, Mahon NG, Poloniecki JD, McKenna WJ. Relation Between Severity of Left-Ventricular Hypertrophy and Prognosis in Patients with Hypertrophic Cardiomyopathy. Lancet 2001 Feb 10; 357(9254):420–4.

29. Richard P, Charron P, Carrier L, Ledeuil C, Cheav T, Pichereau C et al. Hypertrophic Cardiomyopathy: Distribution of Disease Genes, Spectrum of Mutations, and Implications for a Molecular Diagnosis Strategy. Circulation 2003 May 6; 107(17):2227–32.

30. Maron BJ, Schiffers A, Klues HG. Comparison of Phenotypic Expression of Hypertrophic Cardiomyopathy in Patients From the Unites States and Germany. Am J Cardiol 1999 Feb 15; 83(4):626–7.

31. Piva e Mattos B, Scolari FL, Torres MAR, Simon L, Centeno de Freitas V, Giugliani R et al. Prevalence and Phenotypic Expression of Mutations in the MYH7, MYBPC3 and TNNT2 Genes in Families with Hypertrophic Cardiomyopathy in the South of Brazil: A Cross-Sectional Study. Arq Bras Cardiol 2016 Sep; 107(3):257–65.

32. Ntusi NA, Shaboodien G, Badri M, Gumedze F, Mayosi BM. Clinical Features, Spectrum of Causal Genetic Mutations and Outcome of Hypertrophic Cardiomyopathy in South Africans. Cardiovasc J Afr 2016 May/Jun; 27(3):152–8.

33. Zou Y, Song L, Wang Z, Ma A, Liu T, Gu H et al. Prevalence of Idiopathic Hypertrophic Cardiomyopathy in China: A Population-Based Echocardiographic Analysis of 8080 Adults. Am J Med 2004 Jan 1; 116(1):14–8.

34. Hada Y, Sakamoto T, Amano K, Yamaguchi T, Takenaka K, Takahashi H et al. Prevalence of Hypertrophic Cardiomyopathy in a Population of Adult Japanese Workers as Detected by Echocardiographic Screening. Am J Cardiol 1987 Jan 1; 59(1):183–4.

35. Maron BJ, Rowin EJ, Maron MS. Global Burden of Hypertrophic Cardiomyopathy. JACC Heart Fail 2018 May; 6(5):376–8.

36. Olivotto I, Maron MS, Adabag AS, Casey SA, Vargiu D, Link MS et al. Gender-Related Differences in the Clinical Presentation and Outcome of Hypertrophic Cardiomyopathy. J Am Coll Cardiol 2005 Aug 2; 46(3):480–7.

37. Maron BJ, Carney KP, Lever HM, Lewis JF, Barac I, Casey SA et al. Relationship of Race to Sudden Cardiac Death in Competitive Athletes with Hypertrophic Cardiomyopathy. J Am Coll Cardiol 2003 Mar 19; 41(6):974–80.

38. Marian AJ. Hypertrophic Cardiomyopathy: From Genetics to Treatment. Eur J Clin Investig 2010 Apr; 40(4):360–9.

39. Akhtar M, Elliott P. The Genetics of Hypertrophic Cardiomyopathy. Glob Cardiol Sci Pract 2018 Aug 12; 2018(3):36.

40. Charron P, Arad M, Arbustini E, Basso C, Bilinska Z, Elliott P et al. Genetic Counselling and Testing in Cardiomyopathies: A Position Statement of the European Society of Cardiology Working Group on Myocardial and Pericardial Diseases. Eur Heart J 2010 Nov; 31(22):2715–26.

41. Maron BJ, Ommen SR, Semsarian C, Spirito P, Olivotto I, Maron MS. Hypertrophic Cardiomyopathy: Present and Future, with Translation into Contemporary Cardiovascular Medicine. J Am Coll Cardiol 2014 Jul 8; 64(1):83–99.

42. Lopes LR, Elliott PM. A Straightforward Guide to the Sarcomeric Basis of Cardiomyopathies. Heart 2014 Dec; 100(24):1916–23.

43. Maron MS. Clinical Utility of Cardiovascular Magnetic Resonance in Hypertrophic Cardiomyopathy. J Cardiovasc Magn Reson 2012 Feb 1:14:13.

44. Marian AJ, Braunwald E. Hypertrophic Cardiomyopathy: Genetics, Pathogenesis, Clinical Manifestations, Diagnosis, and Therapy. Circ Res 2017 Sep 15; 121(7):749–70.

45. Maron BJ, Maron MS, Semsarian C. Genetics of Hypertrophic Cardiomyopathy After 20 Years: Clinical Perspectives. J Am Coll Cardiol 2012 Aug 21; 60(8):705–15.

46. Ho CY, Charron P, Richard P, Girolami F, Van Spaendonck-Zwarts KY, Pinto Y. Genetic Advances in Sarcomeric Cardiomyopathies: State of the Art. Cardiovasc Res 2015 Apr 1; 105(4):397–408.

47. Sabater-Molina M, Pérez-Sánchez I, Hernández Del Rincón JP, Gimeno JR. Genetics of Hypertrophic Cardiomyopathy: A Review of Current State. Clin Genet 2018 Jan; 93(1):3–14.

48. Colan SD, Lipshultz SE, Lowe AM, Sleeper LA, Messere J, Cox GF et al. Epidemiology and Cause-Specific Outcome of Hypertrophic Cardiomyopathy in Children: Findings From the Pediatric Cardiomyopathy Registry. Circulation 2007 Feb 13; 115(6):773–81.

49. Bernstein HS, Bishop DF, Astrin KH, Kornreich R, Eng CM, Sakuraba H et al. Fabry Disease: Six Gene Rearrangements and an Exonic Point Mutation in the Alpha-Galactosidase Gene. J Clin Invest 1989 Apr; 83(4):1390–9.

50. Linhart A, Elliott PM. The Heart in Anderson-Fabry Disease and Other Lysosomal Storage Disorders. Heart 2007 Apr; 93(4):528–35.

51. Elliott P, Baker R, Pasquale F, Quarta G, Ebrahim H, Mehta AB et al. Prevalence of Anderson-Fabry Disease in Patients with Hypertrophic Cardiomyopathy: The European Anderson-Fabry Disease Survey. Heart 2011 Dec; 97(23):1957–60.

52. Watkins H, McKenna WJ, Thierfelder L, Suk HJ, Anan R, O'Donoghue A et al. Mutations in the Genes for Cardiac Troponin T and Alpha-Tropomyosin in Hypertrophic Cardiomyopathy. N Engl J Med 1995 Apr 20; 332(16):1058–64.

53. Watkins H, Rosenzweig A, Hwang D-S, Levi T, McKenna W, Seidman CE et al. Characteristics and Prognostic Implications of Myosin Missense Mutations in Familial Hypertrophic Cardiomyopathy. N Engl J Med 1992 Apr 23; 326(17):1108–14.

54. Charron P, Dubourg O, Desnos M, Bennaceur M, Carrier L, Camproux A-C et al. Clinical Features and Prognostic Implications of Familial Hypertrophic Cardiomyopathy Related to the Cardiac Myosin-Binding Protein C Gene. Circulation 1998 Jun 9; 97(22):2230–6.

55. Van Driest SL, Vasile VC, Ommen SR, Will ML, Tajik AJ, Gersh BJ et al. Myosin Binding Protein C Mutations and Compound Heterozygosity in Hypertrophic Cardiomyopathy. J Am Coll Cardiol 2004 Nov 2; 44(9):1903–10.

56. Girolami F, Ho CY, Semsarian C, Baldi M, Will ML, Baldini K et al. Clinical Features and Outcome of Hypertrophic Cardiomyopathy Associated with Triple Sarcomere Protein Gene Mutations. J Am Coll Cardiol 2010 Apr 6; 55(14):1444–53.

57. Fujita T, Fujino N, Anan R, Tei C, Kubo T, Doi Y et al. Sarcomere Gene Mutations are Associated with Increased Cardiovascular Events in Left Ventricular Hypertrophy: Results from Multicenter Registration in Japan. JACC Heart Fail 2013 Dec; 1(6):459–66.

58. Charron P, Carrier L, Dubourg O, Tesson F, Desnos M, Richard P et al. Penetrance of Familial Hypertrophic Cardiomyopathy. Genet Counsel 1997; 8(2):107–14.

59. Jensen MK, Havndrup O, Christiansen M, Andersen PS, Diness B, Axelsson A et al. Penetrance of Hypertrophic Cardiomyopathy in Children and Adolescents: A 12-Year Follow-Up Study of Clinical Screening and Predictive Genetic Testing. Circulation 2013 Jan 1; 127(1):48–54.

60. Vermeer AMC, Clur S-AB, Blom NA, Wilde AAM, Christiaans I. Penetrance of Hypertrophic Cardiomyopathy in Children who are Mutation Positive. J Pediatr 2017 Sep; 188:91–5.

61. Niimura H, Bachinski LL, Sangwatanaroj S, Watkins H, Chudley AE, McKenna W et al. Mutations in the Gene for Cardiac Myosin-Binding Protein C and Late-Onset Familial Hypertrophic Cardiomyopathy. N Engl J Med 1998 Apr 30; 338(18):1248–57.

62. Maron BJ, Niimura H, Casey SA, Soper MK, Wright GB, Seidman JG et al. Development of Left Ventricular Hypertrophy in Adults with Hypertrophic Cardiomyopathy Caused by Cardiac Myosin-Binding Protein C Gene Mutations. J Am Coll Cardiol 2001 Aug; 38(2):315–21.

63. Van Rijsingen IAW, Hermans-Van Ast JF, Arens YHJM, Schalla SM, Die-Smulders CEM de, Van Den Wijngaard A et al. Hypertrophic Cardiomyopathy Family with Double-Heterozygous Mutations; Does Disease Severity Suggest Double-Heterzygosity? Neth Heart J 2009 Dec; 17(12):458–63.

64. Ingles J, Doolan A, Chiu C, Seidman J, Seidman C, Semsarian C. Compound and Double Mutations in Patients with Hypertrophic Cardiomyopathy: Implications for Genetic Testing and Counselling. J Med Genet 2005 Oct; 42(10):e59.

65. Tesson F, Dufour C, Moolman JC, Carrier L, Al-Mahdawi S, Chojnowska L et al. The Influence of the Angiotensin I Converting Enzyme Genotype in Familial Hypertrophic Cardiomyopathy Varies with the Disease Gene Mutation. J Mol Cell Cardiol 1997 Feb; 29(2):831–8.

66. Perkins MJ, Van Driest SL, Ellsworth EG, Will ML, Gersh BJ, Ommen SR et al. Gene-Specific Modifying Effects of Pro-LVH Polymorphisms Involving the Renin-Angiotensin-Aldosterone System Among 389 Unrelated Patients with Hypertrophic Cardiomyopathy. Eur Heart J 2005 Nov; 26(22):2457–62.

67. Brugada R, Kelsey W, Lechin M, Zhao G, Yu Q-T, Zoghbi W et al. Role of Candidate Modifier Genes on the Phenotypic Expression of Hypertrophy in Patients with Hypertrophic Cardiomyopathy 1997 Dec; 45(9):542–51.

68. Patel R, Lim DS, Reddy D, Nagueh SF, Lutucuta S, Sole MJ et al. Variants of Trophic Factors and Expression of Cardiac Hypertrophy in Patients with Hypertrophic Cardiomyopathy. J Mol Cell Cardiol 2000 Dec; 32(12):2369–77.

69. Maron BJ, Spirito P, Wesley Y, Arce J. Development and Progression of Left Ventricular Hypertrophy in Children with Hypertrophic Cardiomyopathy. N Engl J Med 1986 Sep 4; 315(10):610–4.

70. Alberti C, Chevenne D, Mercat I, Josserand E, Armoogum-Boizeau P, Tichet J et al. Serum Concentrations of Insulin-Like Growth Factor (IGF)-1 and IGF Binding Protein-3 (IGFBP-3), IGF-1/IGFBP-3 Ratio, and Markers of Bone Turnover: Reference Values for French Children and Adolescents and Z-Score Comparability with other References. Clin Chem 2011 Oct; 57(10):1424–35.

71. Marian AJ. Pathogenesis of Diverse Clinical and Pathological Phenotypes in Hypertrophic Cardiomyopathy. Lancet 2000 Jan 1; 355(9197):58–60.

72. Egger G, Liang G, Aparicio A, Jones PA. Epigenetics in Human Disease and Prospects for Epigenetic Therapy. Nature 2004 May 27; 429(6990):457–63.

73. Ucar A, Gupta SK, Fiedler J, Erikci E, Kardasinski M, Batkai S et al. The miRNA-212/132 Family Regulates Both Cardiac Hypertrophy and Cardiomyocyte Autophagy. Nat Commun 2012; 3:1078.

74. Olivotto I, Maron BJ, Tomberli B, Appelbaum E, Salton C, Haas TS et al. Obesity and Its Association to Phenotype and Clinical Course in Hypertrophic Cardiomyopathy. J Am Coll Cardiol 2013 Jul 30; 62(5):449–57.

75. Turkbey EB, McClelland RL, Kronmal RA, Burke GL, Bild DE, Tracy RP et al. The Impact of Obesity on the Left Ventricle: The Multi-Ethnic Study of Atherosclerosis (MESA). JACC Cardiovasc Imaging 2010 Mar; 3(3):266–74.

76. Baxi AJ, Restrepo CS, Vargas D, Marmol-Velez A, Ocazionez D, Murillo H. Hypertrophic Cardiomyopathy from A to Z: Genetics, Pathophysiology, Imaging, and Management. Radiographics 2016 Mar-Apr; 36(2):335–54.

77. Chun EJ, Choi SI, Jin KN, Kwag HJ, Kim YJ, Choi BW et al. Hypertrophic Cardiomyopathy: Assessment with MR Imaging and Multidetector CT. Radiographics 2010 Sep; 30(5):1309–28.

78. Prisant MD. Hypertensive Heart Disease. J Clin Hypertens 2005 Apr; 7(4):231–8.

79. Wigle ED, Sasson Z, Henderson MA, Ruddy TD, Fulop J, Rakowski H et al. Hypertrophic Cardiomyopathy. The Importance of the Site and the Extent of Hypertrophy. A Review. Prog Cardiovasc Dis 1985 Jul-Aug; 28(1):1–83.

80. Maron BJ, McIntosh CL, Klues HG, Cannon RO, III, Roberts WC. Morphologic Basis for Obstruction to Right Ventricular Outflow in Hypertrophic Cardiomyopathy. Am J Cardiol 1993 May 1; 71(12):1089–94.

81. Mittal SR. Isolated Right Ventricular Hypertrophic Obstructive Cardiomyopathy. J Assoc Physicians India 2010 Apr; 58:243–4.

82. Yan L, Wang Z, Xu Z, Li Y, Tao Y, Fan C. Two Hundred Eight Patients with Apical Hypertrophic Cardiomyopathy in China: Clinical Feature, Prognosis, and Comparison of Pure and Mixed Forms. Clin Cardiol 2012 Feb; 35(2):101–6.

83. Falicov RE, Resnekov L. Mid Ventricular Obstruction in Hypertrophic Obstructive Cardiomyopathy. New Diagnostic and Therapeutic Challenge. Br Heart J 1977 Jul; 39(7):701–5.

84. Davies MJ, Pomerance A, Teare RD. Pathological Features of Hypertrophic Obstructive Cardiomyopathy. J Clin Pathol 1974 Jul; 27(7):529–35.

85. Klues HG, Maron BJ, Dollar AL, Roberts WC. Diversity of Structural Mitral Valve Alterations in Hypertrophic Cardiomyopathy. Circulation 1992 May; 85(5):1651–60.

86. Hughes SE. The Pathology of Hypertrophic Cardiomyopathy. Histopathology 2004 May; 44(5):412–27.

87. Klues HG, Roberts WC, Maron BJ. Anomalous Insertion of Papillary Muscle Directly Into Anterior Mitral Leaflet in Hypertrophic Cardiomyopathy. Significance in Producing Left Ventricular Outflow Obstruction. Circulation 1991 Sep; 84(3):1188–97.

88. Unverferth DV, Baker PB, Pearce LI, Lautman J, Roberts WC. Regional Myocyte Hypertrophy and Increased Interstitial Myocardial Fibrosis in Hypertrophic Cardiomyopathy. Am J Cardiol 1987 Apr 15; 59(9):932–6.

89. Davies MJ, McKenna WJ. Hypertrophic Cardiomyopathy - Pathology and Pathogenesis. Histopathology 1995 Jun; 26(6):493–500.

90. Maron BJ, Roberts WC. Quantitative Analysis of Cardiac Muscle Cell Disorganization in the Ventricular Septum of Patients with Hypertrophic Cardiomyopathy. Circulation 1979 Apr; 59(4):689–706.

91. Maron BJ, Anan TJ, Roberts WC. Quantitative Analysis of the Distribution of Cardiac Muscle Cell Disorganization in the Left Ventricular Wall of Patients with Hypertrophic Cardiomyopathy. Circulation 1981 Apr; 63(4):882–94.

92. Maron BJ, Wolfson JK, Epstein SE, Roberts WC. Intramural ("Small Vessel") Coronary Artery Disease in Hypertrophic Cardiomyopathy. J Am Coll Cardiol 1986 Sep; 8(3):545–57.

93. Herzkrankheiten: Pathophysiologie, Diagnostik, Therapie. 5. Vollständig Überarbeitete und Aktualisierte Auflage. Berlin: Springer; 2004.

94. Hensley N, Dietrich J, Nyhan D, Mitter N, Yee M-S, Brady M. Hypertrophic Cardiomyopathy: A Review. Anesth Analg 2015 Mar; 120(3):554–69.

95. Savage DD, Seides S, Clark, C. E., Henry WL, Maron BJ, Robinson FC et al. Electrocardiographic Findings in Patients with Obstructive and Nonobstructive Hypertrophic Cardiomyopathy. Circulation 1978 Sep; 58(3 Pt 1):402–8.

96. McLeod CJ, Ackerman MJ, Nishimura RA, Tajik AJ, Gersh BJ, Ommen SR. Outcome of Patients with Hypertrophic Cardiomyopathy and a Normal Electrocardiogram. J Am Coll Cardiol 2009 Jul 14; 54(3):229–33.

97. Calore C, Melacini P, Pelliccia A, Cianfrocca C, Schiavon M, Di Paolo FM et al. Prevalence and Clinical Meaning of Isolated Increase of QRS Voltages in Hypertrophic Cardiomyopathy versus Athlete's Heart: Relevance to Athletic Screening. Int J Cardiol 2013; 168(4):4494–7.

98. Ryan MP, Cleland JGF, French JA, Joshi J, Choudhury L, Chojnowska L et al. The Standard Electrocardiogram as a Screening Test for Hypertrophic Cardiomyopathy. Am J Cardiol 1995 Oct 1; 76(10):689–94.

99. Cardim N, Galderisi M, Edvardsen T, Plein S, Popescu BA, D'Andrea A et al. Role of Multimodality Cardiac Imaging in the Management of Patients with Hypertrophic Cardiomyopathy: An Expert Consensus of the European Association of Cardiovascular Imaging Endorsed by the Saudi Heart Association. Eur Heart J 2015 Mar; 16(3):280a-280hh.

100. Loncaric F, Bijnens B, Sitges M. Added Value of Cardiac Deformation Imaging in Differential Diagnosis of Left Ventricular Hypertrophy. Glob Cardiol Sci Pract 2018 Aug 12; 2018(3):21.

101. Nistri S, Olivotto I, Betocchi S, Losi MA, Valsecchi G, Pinamonti B et al. Prognostic Significance of Left Atrial Size in Patients with Hypertrophic Cardiomyopathy (from the Italian Registry for Hypertrophic Cardiomyopathy). Am J Cardiol 2006 Oct 1; 98(7):960–5.

102. Brenes JC, Doltra A, Prat S. Cardiac Magnetic Resonance Imaging in the Evaluation of Patients with Hypertrophic Cardiomyopathy. Glob Cardiol Sci Pract 2018 Aug 12; 2018(3):22.

103. Rickers C, Wilke NM, Jerosch-Herold M, Casey SA, Panse P, Panse N et al. Utility of Cardiac Magnetic Resonance Imaging in the Diagnosis of Hypertrophic Cardiomyopathy. Circulation 2005 Aug 9; 112(6):855–61.

104. Chan RH, Maron BJ, Olivotto I, Pencina MJ, Assenza GE, Haas T et al. Prognostic Value of Quantitative Contrast-Enhanced Cardiovascular Magnetic Resonance for the Evaluation of Sudden Death Risk in Patients with Hypertrophic Cardiomyopathy. Circulation 2014 Aug 5; 130(6):484–95.

105. Veselka J, Anavekar NS, Charron P. Hypertrophic Obstructive Cardiomyopathy. Lancet 2017 Mar 25; 389(10075):1253–67.

106. Shah PM, Gramiak R, Kramer DH. Ultrasound Localization of Left Ventricular Outflow Obstruction in Hypertrophic Obstructive Cardiomyopathy. Circulation 1969 Jul; 40(1):3–11.

107. Boughner DR, Schuld RL, Persaud JA. Hypertrophic Obstructive Cardiomyopathy. Assessment by Echocardiographic and Doppler Ultrasound Techniques. Br Heart J 1975 Sep; 37(9):917–23.

108. Bulkley BH, Fortuin NJ. Systolic Anterior Motion of the Mitral Valve without Asymmetric Septal Hypertrophy. Chest 1976 May; 69(5):694–6.

109. Levisman JA. Systolic Anterior Motion of the Mitral Valve due to Hypovolemia and Anemia. Chest 1976 Nov; 70(5):687–8.

110. Luckner G, Margreiter J, Jochberger S, Mayr V, Luger T, Voelckel W et al. Systolic Anterior Motion of the Mitral Valve with Left Ventricular Outflow Tract Obstruction: Three Cases of Acute Perioperative Hypotension in Noncardiac Surgery. Anesth Analg 2005 Jun; 100(6):1594–8.

111. Sherrid MV, Balaram S, Kim B, Axel L, Swistel DG. The Mitral Valve in Obstructive Hypertrophic Cardiomyopathy: A Test in Context. J Am Coll Cardiol 2016 Apr 19; 67(15):1846–58.

112. Wigle DE, Rakowski H, Kimball BP, Williams WG. Hypertrophic Cardiomyopathy. Clinical Spectrum and Treatment. Circulation 1995 Oct 1; 92(7):1680–92.

113. Spirito P, Maron BJ. Patterns of Systolic Anterior Motion of the Mitral Valve in Hypertrophic Cardiomyopathy: Assessment by Two-Dimensional Echocardiography. Am J Cardiol 1984 Nov 1; 54(8):1039–46.

114. Maron MS, Olivotto I, Betocchi S, Casey SA, Lesser JR, Losi MA et al. Effect of Left Ventricular Outflow Tract Obstruction on Clinical Outcome in Hypertrophic Cardiomyopathy. N Engl J Med 2003 Jan 23; 348(4):295–303.

115. Elliott PM, Gimeno JR, Tomé MT, Shah J, Ward D, Thaman R et al. Left Ventricular Outflow Tract Obstruction and Sudden Death Risk in Patients with Hypertrophic Cardiomyopathy. Eur Heart J 2006 Aug; 27(16):1933–41.

116. Maron MS, Olivotto I, Zenovich AG, Link MS, Pandian NG, Kuvin JT et al. Hypertrophic Cardiomyopathy is Predominantly a Disease of Left Ventricular Outflow Tract Obstruction. Circulation 2006 Nov 21; 114(21):2232–9.

117. Ciró E, Maron BJ, Bonow RO, Cannon RO, Epstein SE. Relation Between Marked Changes in Left Ventricular Outflow Tract Gradient and Disease Progression in Hypertrophic Cardiomyopathy. Am J Cardiol 1984 Apr 1; 53(8):1103–9.

118. Coppini R, Ho CY, Ashley E, Day S, Ferrantini C, Girolami F et al. Clinical Phenotype and Outcome of Hypertrophic Cardiomyopathy Associated with Thin-Filament Gene Mutations. J Am Coll Cardiol 2014 Dec 23; 64(24):2589–600.

119. Grigg LE, Wigle ED, Williams WG, Daniel LB, Rakowski H. Transesophageal Doppler Echocardiography in Obstructive Hypertrophic Cardiomyopathy: Clarification of Pathophysiology and Importance in Intraoperative Decision Making. J Am Coll Cardiol 1992 Jul; 20(1):42–52.

120. Song B-R, Ren Y, Zhang H-J. Surgical Treatment for Hypertrophic Obstructive Cardiomyopathy with Concomitant Mitral Valve Abnormalities: A Cohort of 26 Cases. Heart Surg Forum 2018 Nov 7; 21(6):E443-E447.

121. Maron BJ, Spirito P. Implications of Left Ventricular Remodeling in Hypertrophic Cardiomyopathy. Am J Cardiol 1998 Jun 1; 81(11):1339–44.

122. Maron BJ, Spirito P, Green KJ, Wesley YE, Bonow RO, Arce J. Noninvasive Assessment of Left Ventricular Diastolic Function by Pulsed Doppler Echocardiography in Patients with Hypertrophic Cardiomyopathy 1987 Oct; 10(4):733–42.

123. Siontis KC, Geske JB, Ong K, Nishimura RA, Ommen SR, Gersh BJ. Atrial Fibrillation in Hypertrophic Cardiomyopathy: Prevalence, Clinical Correlations, and Mortality in a Large High-Risk Population. J Am Heart Assoc 2014 Jun 25; 3(3):e001002.

124. Guttmann OP, Rahman MS, O'Mahony C, Anastasakis A, Elliott PM. Atrial Fibrillation and Thromboembolism in Patients with Hypertrophic Cardiomyopathy: Systematic Review. Heart 2014 Mar; 100(6):465–72.

125. Guttmann OP, Pavlou M, O'Mahony C, Monserrat L, Anastasakis A, Rapezzi C et al. Predictors of Atrial Fibrillation in Hypertrophic Cardiomyopathy. Heart 2017; 103(9):672–8.

126. Cecchi F, Olivotto I, Montereggi A, Santoro G, Dolara A, Maron BJ. Hypertrophic Cardiomyopathy in Tuscany: Clinical Course and Outcome in an Unselected Regional Population. J Am Coll Cardiol 1995 Nov 15; 26(6):1529–36.

127. Olivotto I, Cecchi F, Casey SA, Dolara A, Traverse JH, Maron BJ. Impact of Atrial Fibrillation on the Clinical Course of Hypertrophic Cardiomyopathy. Circulation 2001 Nov 20; 104(21):2517–24.

128. Lee S-E, Park J-K, Uhm J-S, Kim JY, Pak H-N, Lee M-H et al. Impact of Atrial Fibrillation on the Clinical Course of Apical Hypertrophic Cardiomyopathy. Heart 2017 Oct; 103(19):1496–501.

129. Spirito P, Rapezzi C, Bellone P, Betocchi S, Autore C, Conte MR et al. Infective Endocarditis in Hypertrophic Cardiomyopathy: Prevalence, Incidence, and Indications for Antibiotic Prophylaxis. Circulation 1999 Apr 27; 99(16):2132–7.

130. Dominguez F, Ramos A, Bouza E, Muñoz P, Valerio MC, Fariñas MC et al. Infective Endocarditis in Hypertrophic Cardiomyopathy: A Multicenter, Prospective, Cohort Study. Medicine (Baltimore) 2016 Jun; 95(26):e4008.

131. Sims JR, Anavekar NS, Bhatia S, O'Horo JC, Geske JB, Chandrasekaran K et al. Clinical, Radiographic, and Microbiologic Features of Infective Endocarditis in Patients with Hypertrophic Cardiomyopathy. Am J Cardiol 2018 Feb 15; 121(4):480–4.

132. Wilson W, Taubert KA, Gewitz M, Lockhart PB, Baddour LM, Levison M et al. Prevention of Infective Endocarditis: Guidelines from the American Heart Association: A Guideline from the American Heart Association Rheumatic Fever, Endocarditis, and Kawasaki Disease Committee, Council on Cardiovascular Disease in the Young, and the Council on Clinical Cardiology, Council on Cardiovascular Surgery and Anesthesia, and the Quality of Care and Outcomes Research Interdisciplinary Working Group. Circulation 2007 Oct 9; 116(15):1736–54.

133. Habib G, Hoen B, Tornos P, Thuny F, Prendergast B, Vilacosta I et al. Guidelines on the Prevention, Diagnosis, and Treatment of Infective Endocarditis (New Version 2009): The Task Force on the Prevention, Diagnosis, and Treatment of Infective Endocarditis of the European Society of Cardiology (ESC). Endorsed by the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) and the International Society of Chemotherapy (ISC) for Infection and Cancer. Eur Heart J 2009 Oct; 30(19):2369–413.

134. Hecht GM, Klues HG, Roberts WC, Maron BJ. Coexistence of Sudden Cardiac Death and End-Stage Heart Failure in Familial Hypertrophic Cardiomyopathy. J Am Coll Cardiol 1993 Aug; 22(2):489–97.

135. Harris KM, Spirito P, Maron MS, Zenovich AG, Formisano F, Lesser JR et al. Prevalence, Clinical Profile, and Significance of Left Ventricular Remodeling in the End-Stage Phase of Hypertrophic Cardiomyopathy. Circulation 2006 Jul 18; 114(3):216–25.

136. Biagini E, Coccolo F, Ferlito M, Perugini E, Rocchi G, Bacchi-Reggiani L et al. Dilated-Hypokinetic Evolution of Hypertrophic Cardiomyopathy: Prevalence, Incidence, Risk Factors, and Prognostic Implications in Pediatric and Adult Patients. J Am Coll Cardiol 2005 Oct 18; 46(8):1543–50.

137. Melacini P, Basso C, Angelini A, Calore C, Bobbo F, Tokajuk B et al. Clinicopathological Profiles of Progressive Heart Failure in Hypertrophic Cardiomyopathy. Eur Heart J 2010 Sep; 31(17):2111–23.

138. Maron BJ, Epstein SE, Roberts WC. Hypertrophic Cardiomyopathy and Transmural Myocardial Infarction without Significant Atherosclerosis of the Extramural Coronary Arteries. Am J Cardiol 1979 Jun; 43(6):1086–102.

139. Maki S, Ikeda H, Muro A, Yoshida N, Shibata A, Koga Y et al. Predictors of Sudden Cardiac Death in Hypertrophic Cardiomyopathy. Am J Cardiol 1998 Sep 15; 82(6):774–8.

140. Elliott PM, Gimeno JR, Thaman R, Shah J, Ward D, Dickie S et al. Historical Trends in Reported Survival Rates in Patients with Hypertrophic Cardiomyopathy. Heart 2006 Jun; 92(6):785–91.

141. O'Mahony C, Elliott P, McKenna W. Sudden Cardiac Death in Hypertrophic Cardiomyopathy. Circ Arrhythm Electrophysiol 2013 Apr; 6(2):443–51.

142. Saumarez RC, Camm AJ, Panagos A, Gill JS, Stewart JT, Belder MA de et al. Ventricular Fibrillation in Hypertrophic Cardiomyopathy is Associated with Increased Fractionation of Paced Right Ventricular Electrograms. Circulation 1992 Aug; 86(2):467–74.

143. Baudenbacher F, Schober T, Pinto JR, Sidorov VY, Hilliard F, Solaro RJ et al. Myofilament Ca2+ Sensitization Causes Susceptibility to Cardiac Arrhythmia in Mice. J Clin Invest 2008 Dec; 118(12):3893–903.

144. Maron BJ, Lipson LC, Roberts WC, Savage DD, Epstein SE. "Malignant" Hypertrophic Cardiomyopathy: Identification of a Subgroup of Families with Unusually Frequent Premature Death. Am J Cardiol 1978 Jun; 41(7):1133–40.

145. D'Andrea A, Caso P, Severino S, Cuomo S, Capozzi G, Calabrò P et al. Prognostic Value of Intra-Left Ventricular Electromechanical Asynchrony in Patients with Hypertrophic Cardiomyopathy. Eur Heart J 2006 Jun; 27(11):1311–8.

146. Spirito P, Bellone P, Harris KM, Bernabò P, Bruzzi P, Maron BJ. Magnitude of Left Ventricular Hypertrophy and Risk of Sudden Death in Hypertrophic Cardiomyopathy. N Engl J Med 2000 Jun 15; 342(24):1778–85.

147. Elliott PM, Poloniecki J, Dickie S, Sharma S, Monserrat L, Varnava A et al. Sudden Death in Hypertrophic Cardiomyopathy: Identification of High Risk Patients. J Am Coll Cardiol 2000 Dec; 36(7):2212–8.

148. Monserrat L, Elliott PM, Gimeno JR, Sharma S, Penas-Lado M, McKenna WJ. Non-Sustained Ventricular Tachycardia in Hypertrophic Cardiomyopathy. J Am Coll Cardiol 2003 Sep 3; 42(5):873–9.

149. Klues HG, Schiffers A, Maron BJ. Phenotypic Spectrum and Patterns of Left Ventricular Hypertrophy in Hypertrophic Cardiomyopathy: Morphologic Observations and Significance as Assessed by Two-Dimensional Echocardiography in 600 Patients. J Am Coll Cardiol 1995 Dec; 26(7):1699–708.

150. Davies MJ. The Cardiomyopathies: An Overview. Heart 2000 Apr; 83(4):469–74.

151. Wang L, Seidman JG, Seidman CE. Narrative Review: Harnessing Molecular Genetics for the Diagnosis and Management of Hypertrophic Cardiomyopathy. Ann Intern Med 2010 Apr; 152(8):513–20.

152. Tower-Rader A, Desai MY. Phenotype-Genotype Correlation in Hypertrophic Cardiomyopathy: Less Signal, More Noise? Circ Cardiovasc Imaging 2017 Feb; 10(2).

153. Epstein SE, Henry WL, Clark CE, Roberts WC, Maron BJ, Ferrans VJ et al. Asymmetric Septal Hypertrophy. Ann Intern Med 1974; 81(5):650–80.

154. Schmincke A. Ueber Linkseitige Muskulöse Conusstenosen. Deutsche Medizinische Wochenschrift 1907; 50:2082–3.

155. Davies LG. A Familial Heart Disease. Br Heart J 1952 Apr; 14(2):206–12.

156. Emanuel R, Marcomichelakis J, Withers R, O'Brien K. Asymmetric Septal Hypertrophy and Hypertrophic Cardiomyopathy. Heart 1983 Apr; 49(4):309–16.

157. Williams LK, Frenneaux MP, Steeds RP. Echocardiography in Hypertrophic Cardiomyopathy Diagnosis, Prognosis, and Role in Management. Eur J Echocardiogr 2009 Dec; 10(8):iii9-14.

158. Helmy SM, Maauof GF, Shaaban AA, ElMaghraby AM, Anilkumar S, Shawky AHH et al. Hypertrophic Cardiomyopathy: Prevalence, Hypertrophy Patterns, and Their Clinical and ECG Findings in a Hospital at Qatar. Heart Views 2011 Oct; 12(4):143–9.

159. Yang HS, Song J-K, Song J-M, Kang D-H, Lee CW, Hong M-K et al. Comparison of the Clinical Features of Apical Hypertrophic Cardiomyopathy versus Asymmetric Septal Hypertrophy in Korea. Korean J Intern Med 2005 Jun; 20(2):111–5.

160. Shapiro LM, McKenna WJ. Distribution of Left Ventricular Hypertrophy in Hypertrophic Cardiomyopathy: A Two-Dimensional Echocardiographic Study. J Am Coll Cardiol 1983 Sep; 2(3):437–44.

161. Park K-M, Im SI, Kim EK, Lee S-C, Park S-J, Kim JS et al. Atrial Fibrillation in Hypertrophic Cardiomyopathy: Is the Extent of Septal Hypertrophy Important? PLOS ONE 2016 Jun 3; 11(6):e0156410.

162. Binder J, Ommen SR, Gersh BJ, Van Driest SL, Tajik AJ, Nishimura RA et al. Echocardiography-Guided Genetic Testing in Hypertrophic Cardiomyopathy: Septal Morphological Features Predict the Presence of Myofilament Mutations. Mayo Clin Proc 2006 Apr; 81(4):459–67.

163. Lewis JF, Maron BJ. Clinical and Morphologic Expression of Hypertrophic Cardiomyopathy in Patients ≥65 Years of Age. Am J Cardiol 1994 Jun 1; 73(15):1105–11.

164. Dalldorf FG, Willis PW, IV. Angled Aorta ("Sigmoid Septum") as a Cause of Hypertrophic Subaortic Stenosis. Hum Pathol 1985 May; 16(5):457–62.

165. Waller BF. The Old-Age Heart: Normal Aging Changes Which Can Produce or Mimic Cardiac Disease. Clin Cardiol 1988 Aug; 11(8):513–7.

166. Bos JM, Theis JL, Tajik AJ, Gersh BJ, Ommen SR, Ackerman MJ. Relationship Between Sex, Shape, and Substrate in Hypertrophic Cardiomyopathy. Am Heart J 2008 Jun; 155(6):1128–34.

167. Rossen RM, Goodman DJ, Ingham RE, Popp RL. Echocardiographic Criteria in the Diagnosis of Idiopathic Hypertrophic Subaortic Stenosis. Circulation 1974 Oct; 50(4):747–51.

168. Maron BJ, Gottdiener JS, Epstein SE. Patterns and Significance of Distribution of Left Ventricular Hypertrophy in Hypertrophic Cardiomyopathy. A Wide Angle, Two Dimensional Echocardiographic Study of 125 Patients. Am J Cardiol 1981 Sep; 48(3):418–28.

169. Litovsky SH, Rose AG. Clinicopathologic Heterogeneity in Hypertrophic Cardiomyopathy with Regard to Age, Asymmetric Septal Hypertrophy, and Concentric Hypertrophiy Beyond the Pediatric Age Group. Arch Pathol Lab Med 1998 May; 122(5):434–41.

170. Lai Z-Y, Shih C-M, Chang N-C, Wang T-C. Clinical and Morphologic Features of Hypertrophic Cardiomyopathy in Elderly Patients 85 Years or Older. Japanese Heart Journal 1999 Mar; 40(2):155–64.

171. Arad M, Penas-Lado M, Monserrat L, Maron BJ, Sherrid M, Ho CY et al. Gene Mutations in Apical Hypertrophic Cardiomyopathy. Circulation 2005 Nov 1; 112(18):2805–11.

172. To ACY, Dhillon A, Desai MY. Cardiac Magnetic Resonance in Hypertrophic Cardiomyopathy. JACC Cardiovasc Imaging 2011 Oct; 4(10):1123–37.

173. Maron BJ. Distinguishing Hypertrophic Cardiomyopathy From Athlete's Heart: A Clinical Problem of Increasing Magnitude and Significance. Heart 2005 Nov; 91(11):1380–2.

174. Maron BJ. Sudden Death in Young Athletes. N Engl J Med 2003 Sep 11; 349(11):1064–75.

175. Pelliccia A, Maron BJ, Spataro A, Proschan MA, Spirito P. The Upper Limit of Physiologic Cardiac Hypertrophy in Highly Trained Elite Athletes. N Engl J Med 1991 Jan 31; 324(5):295–301.

176. Maron BJ, Pelliccia A, Spirito P. Cardiac Disease in Young Trained Athletes. Insights into Methods for Distinguishing Athlete's Heart From Structural Heart Disease, with Particular Emphasis on Hypertrophic Cardiomyopathy. Circulation 1995 Mar 1; 91(5):1596–601.

177. Nakamura T, Sugihara H, Kinoshita N, Yoneyama S, Azuma A, Nakagawa M. Can Serum Carnitine Levels Distinguish Hypertrophic Cardiomyopathy From Hypertensive Hearts? Hypertension 2000 Aug; 36(2):215–9.

178. Dunn FG, Chandraratina P, deCarvalho JGR, Basta LL, Frohlich ED. Pathophysiologic Asessment of Hypertensive Heart Disease with Echocardiography. Am J Cardiol 1977 May 26; 39(6):789–95.

179. Toshima H, Koga Y, Nagata H, Toyomasu K, Itaya K-I, Matoba T. Comparable Effects of Oral Diltiazem and Verapamil in the Treatment of Hypertrophic Cardiomyopathy. Double-Blind Crossover Study. Japanese Heart Journal 1986 Sep; 27(5):701–15.

180. Criley MJ, Blaufuss AH, Abbasi AS. Letter: Nonobstructive IHSS. Circulation 1975 Nov; 52(5):963–4.

181. Doi YL, Deanfield JE, McKenna WJ, Dargie HJ, Oakley CM, Goodwin JF. Echocardiographic Differentiation of Hypertensive Heart Disease and Hypertrophic Cardiomyopathy. Br Heart J 1980 Oct; 44(4):395–400.

182. Puntmann VO, Jahnke C, Gebker R, Schnackenburg B, Fox KF, Fleck E et al. Usefulness of Magnetic Resonance Imaging to Distinguish Hypertensive and Hypertrophic Cardiomyopathy. Am J Cardiol 2010 Oct 1; 106(7):1016–22.

183. Cerqueira MD, Weissman NJ, Dilsizian V, Jacobs AK, Kaul S, Laskey WK et al. Standardized Myocardial Segmentation and Nomenclature for Tomographic Imaging of the Heart. A Statement for Healthcare Professionals From the Cardiac Imaging Commitee of the Council on Clinical Cardiology of the American Heart Association. Circulation 2002 Jan 29; 105(4):539–42.

184. Rudolph A, Abdel-Aty H, Bohl S, Boyé P, Zagrosek A, Dietz R et al. Noninvasive Detection of Fibrosis Applying Contrast-Enhanced Cardiac Magnetic Resonance in Different Forms of Left Ventricular Hypertrophy Relation to Remodeling. J Am Coll Cardiol 2009 Jan 20; 53(3):284–91.

185. Kato TS, Noda A, Izawa H, Yamada A, Obata K, Nagata K et al. Discrimination of Nonobstructive Hypertrophic Cardiomyopathy From Hypertensive Left Ventricular Hypertrophy on the Basis of Strain Rate Imaging by Tissue Doppler Ultrasonography. Circulation 2004 Dec 21; 110(25):3808–14.

186. Ruiz-Guerrero L, Barriales-Villa R. Storage Diseases with Hypertrophic Cardiomyopathy Phenotype. Glob Cardiol Sci Pract 2018 Aug 12; 2018(3):28.

187. Hansen MW, Merchant N. MRI of Hypertrophic Cardiomyopathy: Part 2, Differential Diagnosis, Risk Stratification, and Posttreatment MRI Appearances. AJR Am J Roentgenol 2007 Dec; 189(6):1344–52.

188. Prasad K, Atherton J, Smith GC, McKenna WJ, Frenneaux MP, Nihoyannopoulos P. Echocardiographic Pitfalls in the Diagnosis of Hypertrophic Cardiomyopathy. Heart 1999 Nov; 82 Suppl 3:III8-III15.

189. Maceira AM, Joshi J, Prasad SK, Moon JC, Perugini E, Harding I et al. Cardiovascular Magnetic Resonance in Cardiac Amyloidosis. Circulation 2005 Jan 18; 111(2):186–93.

190. Fattori R, Rocchi G, Celletti F, Bertaccini P, Rapezzi C, Gavelli G. Contribution of Magentic Resonance Imaging in the Differential Diagnosis of Cardiac Amyloidosis and Symmetric Hypertrophic Cardiomyopathy. Am Heart J 1998 Nov; 136(5):824–30.

191. Gillmore JD, Maurer MS, Falk RH, Merlini G, Damy T, Dispenzieri A et al. Nonbiopsy Diagnosis of Cardiac Transthyretin Amyloidosis. Circulation 2016 Jun 14; 133(24):2404–12.

192. Nakao S, Takenaka T, Maeda M, Kodama C, Tanaka A, Tahara M et al. An Atypical Variant of Fabry's Disease in Men with Left Ventricular Hypertrophy. N Engl J Med 1995 Aug 3; 333(5):288–93.

193. Linhart A, Paleček T, Bultas J, Ferguson JJ, Hrudová J, Karetová D et al. New Insights in Cardiac Structural Changes in Patients with Fabry's Disease. Am Heart J 2000 Jun; 139(6):1101–8.

194. Rapezzi C, Arbustini E, Caforio ALP, Charron P, Gimeno-Blanes J, Heliö T et al. Diagnostic Work-Up in Cardiomyopathies: Bridging the Gap Between Clinical Phenotypes and Final Diagnosis. A Position Statement from the ESC Working Group on Myocardial and Pericardial Diseases. Eur Heart J 2013 May; 34(19):1448–58.

195. Moon JCC, Sachdev B, Elkington AG, McKenna WJ, Mehta A, Pennell DJ et al. Gadolinium Enhanced Cardiovascular Magnetic Resonance in Anderson-Fabry Disease.

Evidence for a Disease Specific Abnormality of the Myocardial Interstitum. Eur Heart J 2003 Dec; 24(23):2151–5.

196. Bussinguer M, Danielian A, Sharma OP. Cardiac Sarcoidosis: Diagnosis and Management. Curr Treat Options Cardiovasc Med 2012 Dec; 14(6):652–64.

197. Smedema J-P, Snoep G, Van Kroonenburgh MPG, Van Geuns R-J, Cheriex EC, Gorgels APM et al. The Additional Value of Gadolinium-Enhanced MRI to Standard Assessment for Cardiac Involvement in Patients with Pulmonary Sarcoidosis. Chest 2005 Sep; 128(3):1629–37.

198. Patel MR, Cawley PJ, Heitner JF, Klem I, Parker MA, Jaroudi WA et al. Detection of Myocardial Damage in Patients with Sarcoidosis. Circulation 2009 Nov 17; 120(20):1969–77.

199. Silverman KJ, Hutchins GM, Bulkley BH. Cardiac Sarcoid: A Clinicopathologic Study of 84 Unselected Patients with Systemic Sarcoidosis. Circulation 1978 Dec; 58(6):1204–11.

200. Simonen P, Lehtonen J, Kandolin R, Schildt J, Marjasuo S, Miettinen H et al. F-18-Fluorodeoxyglucose Positron Emission Tomography-Guided Sampling of Mediastinal Lymph Nodes in the Diagnosis of Cardiac Sarcoidosis. Am J Cardiol 2015 Nov 15; 116(10):1581–5.

201. Uemura A, Morimoto S-I, Hiramitsu S, Kato Y, Ito, T., Hishida, H. Histologic Diagnostic Rate of Cardiac Sarcoidosis: Evaluation of Endomyocardial Biopsies. Am Heart J 1999 Aug; 138(2 Part 1):299–302.

202. Kurmann R, Mankad SV, Mankad R. Echocardiography in Sarcoidosis. Curr Cardiol Rep 2018 Sep 26; 20(11):118.

203. Burstow DJ, Tajik J, Bailey KR, DeRemee RA, Taliercio CP. Two-Dimensional Echocardiographic Findings in Systemic Sarcoidosis. Am J Cardiol 1989 Feb 15; 63(7):478–82.

204. Roberts WC, McAllister HA, JR, Ferrans VJ. Sarcoidosis of the Heart. A Clinicopathologic Study of 35 Necropsy Patients (Group I) and Review of 78 Previously Described Necropsy Patients (Group II). Am J Med 1977 Jul; 63(1):86–108.

205. Lewin RF, Mor R, Spitzer S, Arditti A, Hellman C, Agmon J. Echocardiographic Evaluation of Patients with Systemic Sarcoidosis. Am Heart J 1985 Jul; 110(1 Part 1):116–22.

206. Kusano KF, Satomi K. Diagnosis and Treatment of Cardiac Sarcoidosis. Heart 2016 Feb; 102(3):184–90.

207. Sakamoto T, Tei C, Murayama M, Ichiyasu H, Hada Y, Hayashi T et al. Giant T Wave Inversion as a Manifestation of Asymmetrical Apical Hypertrophy (AAH) of the Left Ventricle. Echocardiographic and Ultrasono-Cardiotomographic Study. Japanese Heart Journal 1976 Sep; 17(5):611–29.

208. Yamaguchi H, Ishimura T, Nishiyama S, Nagasaki F, Nakanishi S, Takatsu F et al. Hypertrophic Nonobstructive Cardiomyopathy with Giant Negative T Waves (Apical Hypertrophy): Ventriculographic and Echocardiographic Features in 30 Patients. Am J Cardiol 1979 Sep; 44(3):401–12.

209. Gruner C, Chan RH, Crean A, Rakowski H, Rowin EJ, Care M et al. Significance of Left Ventricular Apical-Basal Muscle Bundle Identified by Cardiovascular Magnetic Resonance Imaging in Patients with Hypertrophic Cardiomyopathy. Eur Heart J 2014 Oct 14; 35(39):2706–13.

210. Paluszkiewicz J, Krasinska B, Milting H, Gummert J, Pyda M. Apical Hypertrophic Cardiomyopathy: Diagnosis, Medical and Surgical Treatment. Kardiochir Torakochirurgia Pol 2018 Dec; 15(4):246–53.

211. Moon J, Shim CY, Ha J-W, Cho IJ, Kang MK, Yang W-I et al. Clinical and Echocardiographic Predictors of Outcomes in Patients with Apical Hypertrophic Cardiomyopathy. Am J Cardiol 2011 Dec 1; 108(11):1614–9.

212. Kitaoka H, Doi Y, Casey SA, Hitomi N, Furuno T, Maron BJ. Comparison of Prevalence of Apical Hypertrophic Cardiomyopathy in Japan and the United States. Am J Cardiol 2003 Nov 15; 92(10):1183–6.

213. Olson TM, Doan TP, Kishimoto NY, Whitby FG, Ackerman MJ, Fananapazir L. Inherited and De Novo Mutations in the Cardiac Actin Gene Cause Hypertrophic Cardiomyopathy. J Mol Cell Cardiol 2000 Sep; 32(9):1687–94.

214. Rodgers-Fischl P, Kolodziej AR, Sorrell VL, Rugg SS. Apical Hypertrophic Cardiomyopathy in an African American: A Case Presentation and Literature Review 2016 Mar 2; 4(2):1056.

215. Towe EC, Bos JM, Ommen SR, Gersh BJ, Ackerman MJ. Genotype-Phenotype Correlations in Apical Variant Hypertrophic Cardiomyopathy. Congenit Heart Dis 2015 May-Jun; 10(3):E139-45.

216. Monserrat L, Hermida-Prieto M, Fernandez X, Rodríguez I, Dumont C, Cazón L et al. Mutation in the Alpha-Cardiac Actin Gene Associated with Apical Hypertrophic

Cardiomyopathy, Left Ventricular Non-Compaction, and Septal Defects. Eur Heart J 2007 Aug; 28(16):1953–61.

217. Choi E-Y, Rim S-J, Ha J-W, Kim Y-J, Lee S-C, Kang D-H et al. Phenotypic Spectrum and Clinical Characteristics of Apical Hypertrophic Cardiomyopathy: Multicenter Echo-Doppler Study. Cardiology 2008; 110(1):53–61.

218. Klarich KW, Attenhofer J, Christine H, Binder J, Connolly HM, Scott CG et al. Risk of Death in Long-Term Follow-Up of Patients with Apical Hypertrophic Cardiomyopathy. Am J Cardiol 2013 Jun 15; 111(12):1784–91.

219. Sakamoto T, Amano K, Hada Y, Tei C, Takenaka K, Hasegawa I et al. Asymmetric Apical Hypertrophy: Ten Years Experience. Postgrad Med J 1986 Jun; 62(728):567–70.

220. Jan MF, Todaro MC, Oreto L, Tajik AJ. Apical Hypertrophic Cardiomyopathy: Present Status. Int J Cardiol 2016 Nov 1; 222:745–59.

221. Chang S-A, Kim H-K, Kim D-H, Kim J-C, Kim Y-J, Kim H-C et al. Left Ventricular Twist Mechanics in Patients with Apical Hypertrophic Cardiomyopathy: Assessment with 2D Speckle Tracking Echocardiography. Heart 2010 Jan; 96(1):49–55.

222. Kasirye Y, Manne JR, Epperla N, Bapani S, Garcia-Montilla R. Apical Hypertrophic Cardiomyopathy Presenting as Recurrent Unexplained Syncope. Clin Med Res 2012 Feb; 10(1):26–31.

223. Eriksson MJ, Sonnenberg B, Woo A, Rakowski P, Parker TG, Wigle ED et al. Long-Term Outcome in Patients with Apical Hypertrophic Cardiomyopathy. J Am Coll Cardiol 2002 Feb 20; 39(4):638–45.

224. Yamada M, Teraoka K, Kawade M, Hirano M, Yamashina A. Frequency and Distribution of Late Gadolinium Enhancement in Magnetic Resonance Imaging of Patients with Apical Hypertrophic Cardiomyopathy and Patients with Asymmetrical Hypertrophic Cardiomyopathy: A Comparative Study. Int J Cardiovasc Imaging 2009 Apr; 25 Suppl 1:131–8.

225. Pelliccia F, Pasceri V, Limongelli G, Autore C, Basso C, Corrado D et al. Long-Term Outcome of Nonobstructive versus Obstructive Hypertrophic Cardiomyopathy: A Systematic Review and Meta-Analysis. Int J Cardiol 2017 Sep 15; 243:379–84.

226. Falicov RE, Resnekov L, Bharati S, Lev M. Mid-Ventricular Obstruction: A Variant of Obstructive Cardiomyopathy. Am J Cardiol 1976 Mar 4; 37(3):432–7.

227. Minami Y, Kajimoto K, Terajima Y, Yashiro B, Okayama D, Haruki S et al. Clinical Implications of Midventricular Obstruction in Patients with Hypertrophic Cardiomyopathy. J Am Coll Cardiol 2011 Jun 7; 57(23):2346–55.

228. Efthimiadis GK, Pagourelias ED, Parcharidou D, Gossios T, Kamperidis V, Theofilogiannakos EK et al. Clinical Characteristics and Natural History of Hypertrophic Cardiomyopathy with Midventricular Obstruction. Circ J 2013; 77(9):2366–74.

229. Yan L-R, Zhao S-H, Wang H-Y, Duan F-J, Wang Z-M, Yang Y-J et al. Clinical Characteristics and Prognosis of 60 Patients with Midventricular Obstructive Hypertrophic Cardiomyopathy. J Cardiovasc Med 2015 Nov; 16(11):751–60.

230. Fighali S, Krajcer Z, Edelman S, Leachman RD. Progression of Hypertrophic Cardiomyopathy into a Hypokinetic Left Ventricle: Higher Incidence in Patients with Midventricular Obstruction. J Am Coll Cardiol 1987 Feb; 9(2):288–94.

231. Maron MS, Finley JJ, Bos JM, Hauser TH, Manning WJ, Haas TS et al. Prevalence, Clinical Significance, and Natural History of Left Ventricular Apical Aneurysms in Hypertrophic Cardiomyopathy. Circulation 2008 Oct 7; 118(15):1541–9.

232. Elsheshtawy MO, Mahmoud AN, Abdelghany M, Suen IH, Sadiq A, Shani J. Left Ventricular Aneurysms in Hypertrophic Cardiomyopathy with Midventricular Obstruction: A Systematic Review of Literature. Pacing Clin Electrophysiol 2018 Jul; 41(7):854–65.

233. Lazaros G, Kouvousis N, Kotsanis A, Matsakas E. Apical Hypertrophic Cardiomyopathy with Midventricular Obstruction and Apical Aneurysm. Int J Cardiol 2007 Jan 8; 114(2):E45-7.

234. Sato Y, Matsumoto N, Yoda S, Kunimasa T, Matsuo S, Komatsu S et al. Mid-Ventricular Obstructive Hypertrophic Cardiomyopathy with Apical Aneurysm: Report of 2 Cases. Int J Cardiol 2008 Oct 13; 129(3):e88-90.

235. Zenovich AG, Lesser JR, Hanna CA, Maron BJ. Identical Twins with Hypertrophic Cardiomyopathy and Apical Aneurysm. Am J Cardiol 2006 Apr 1; 97(7):1109.

236. Efthimiadis GK, Pliakos C, Pagourelias ED, Parcharidou DG, Spanos G, Paraskevaidis S et al. Hypertrophic Cardiomyopathy with Midventricular Obstruction and Apical Aneurysm Formation in a Single Family: Case Report. Cardiovasc Ultrasoun 2009 Jun 16; 7(26).

237. Nakamura T, Matsubara K, Furukawa K, Azuma A, Sugihara H, Katsume H et al. Diastolic Paradoxic Jet Flow in Patients with Hypertrophic Cardiomyopathy: Evidence of Concealed Apical Asynergy with Cavity Obliteration. J Am Coll Cardiol 1992 Mar 1; 19(3):516–24.

238. Hansen MW, Merchant N. MRI of Hypertrophic Cardiomyopathy: Part I, MRI Appearances. AJR Am J Roentgenol 2007 Dec; 189(6):1335–43.

239. Zerhouni EA, Parish DM, Rogers WJ, Yang A, Shapiro EP. Human Heart: Tagging with MR Imaging--A Method for Noninvasive Assessment of Myocardial Motion. Radiology 1988 Oct; 169(1):59–63.

240. Bouton S, Yang A, McCrindle BW, Kidd L, McVeigh ER, Zerhouni EA. Differentiation of Tumor From Viable Myocardium Using Cardiac Tagging with MR Imaging. J Comput Assist Tomogr 1991 Jul-Aug; 15(4):676–8.

241. Bergey PD, Axel L. Focal Hypertrophic Cardiomyopathy Simulating a Mass: MR Tagging for Correct Diagnosis. AJR Am J Roentgenol 2000 Jan; 174(1):242–4.

242. Çoban G, Yıldırım MA, Dönmez FY, Tarhan NÇ, Erdoğan İ, Coşkun M. Magnetic Resonance Tagging for Diagnosis of Focal Hypertrophic Cardiomyopathy in a Child. Pediatr Int 2015 Jun; 57(3):465–8.

243. Severino S, Caso P, Cicala S, Galderisi M, Simone L de, D'Andrea A et al. Involvement of Right Ventricle in Left Ventricular Hypertrophic Cardiomyopathy: Analysis by Pulsed Doppler Tissue Imaging. Eur J Echocardiogr 2000 Dec; 1(4):281–8.

244. Keramida K, Lazaros G, Nihoyannopoulos P. Right Ventricular Involvement in Hypertrophic Cardiomyopathy: Patterns and Implications. Hellenic J Cardiol 2018 Nov 30.

245. Rudski LG, Lai WW, Afilalo J, Hua L, Handschumacher MD, Chandrasekaran K et al. Guidelines for the Echocardiographic Assessment of the Right Heart in Adults: A Report From the American Society of Echocardiography Endorsed by the European Association of Echocardiography, a Registered Branch of the European Society of Cardiology, and the Canadian Society of Echocardiography. J Am Soc Echocardiogr 2010 Jul; 23(7):685-713; Quiz 786-8.

246. Foale R, Nihoyannopoulos P, McKenna W, Kleinebenne A, Nadazdin A, Rowland E et al. Echocardiographic Measurement of the Normal Adult Right Ventricle. Heart 1986 Jul; 56(1):33–44.

247. Maron MS, Hauser TH, Dubrow E, Horst TA, Kissinger KV, Udelson JE et al. Right Ventricular Involvement in Hypertrophic Cardiomyopathy. Am J Cardiol 2007 Oct 15; 100(8):1293–8.

248. McKenna WJ, Kleinebenne A, Nihoyannopoulos P, Foale R. Echocardiographic Measurement of Right Ventricular Wall Thickness in Hypertrophic Cardiomyopathy: Relation to Clinical and Prognostic Features. J Am Coll Cardiol 1988 Feb; 11(2):351–8.

249. Guo X, Fan C, Tian L, Liu Y, Wang H, Zhao S et al. The Clinical Features, Outcomes and Genetic Characteristics of Hypertrophic Cardiomyopathy Patients with Severe Right Ventricular Hypertrophy. PLOS ONE 2017 Mar 21; 12(3):e0174118.

250. Amano Y, Kitamura M, Takano H, Yanagisawa F, Tachi M, Suzuki Y et al. Cardiac MR Imaging of Hypertrophic Cardiomyopathy Techniques Findings and Clinical Relevance. Magn Reson Med Sci 2018 Apr 10; 17(2):120–31.

251. Nagata Y, Konno T, Fujino N, Hodatsu A, Nomura A, Hayashi K et al. Right Ventricular Hypertrophy is Associated with Cardiovascular Events in Hypertrophic Cardiomyopathy: Evidence From Study with Magnetic Resonance Imaging. Can J Cardiol 2015 Jun; 31(6):702–8.

252. Roşca M, Călin A, Beladan CC, Enache R, Mateescu AD, Gurzun M-M et al. Right Ventricular Remodeling, Its Correlates, and Its Clinical Impact in Hypertrophic Cardiomyopathy. J Am Soc Echocardiogr 2015 Nov; 28(11):1329–38.

253. Mozaffarian D, Caldwell JH. Right Ventricular Involvement in Hypertrophic Cardiomyopathy: A Case Report and Literature Review. Clin Cardiol 2001 Jan; 24(1):2–8.

254. Frustaci A, Chimenti C, Natale L. Right Ventricular Aneurysm Associated with Advanced Hypertrophic Cardiomyopathy. Chest 1998 Feb; 113(2):552–4.

255. Frank S, Braunwald E. Idiopathic Hypertrophic Subaortic Stenosis. Clinical Analysis of 126 Patients with Emphasis on the Natural History. Circulation 1968 May; 37(5):759–88.

256. Shimizu M, Kawai H, Yokota Y, Yokoyama M. Echocardiographic Assessment of Right Ventricular Obstruction in Hypertrophic Cardiomyopathy. Circ J 2003 Oct; 67(10):855–60.

257. Efthimiadis GK, Parharidis GE, Karvounis HI, Gemitzis KD, Styliadis IH, Louridas GE. Doppler Echocardiographic Evaluation of Right Ventricular Diastolic Function in Hypertrophic Cardiomyopathy. Eur J Echocardiogr 2002 Jun; 3(2):143–8.

258. Suzuki J-I, Chang J-M, Caputo GR, Higgins CB. Evaluation of Right Ventricular Early Diastolic Filling by Cine Nuclear Magnetic Resonance Imaging in Patients with Hypertrophic Cardiomyopathy. J Am Coll Cardiol 1991 Jul; 18(1):120–6.

259. McKenna WJ, Stewart JT, Nihoyannopoulos P, McGinty F, Davies MJ. Hypertrophic Cardiomyopathy without Hypertrophy: Two Families with Myocardial Disarray in the Absence of Increased Myocardial Mass. Heart 1990 May; 63(5):287–90.

260. Sylvester J, Seidenberg P, Silvis M. The Dilemma of Genotype Positive-Phenotype Negative Hypertrophic Cardiomyopathy. Am J Sports Med 2014 Mar-Apr; 13(2):94–9.

261. Gray B, Ingles J, Semsarian C. Natural History of Genotype Positive-Phenotype Negative Patients with Hypertrophic Cardiomyopathy. Int J Cardiol 2011 Oct 20; 152(2):258–9.

262. Captur G, Lopes LR, Mohun TJ, Patel V, Li C, Bassett P et al. Prediction of Sarcomere Mutations in Subclinical Hypertrophic Cardiomyopathy. Circ Cardiovasc Imaging 2014 Nov; 7(6):863–71.

263. Dimitrow PP, Cheng TO. Hypertrophic Cardiomyopathy: Genotype-Positive, Phenotype-"Almost" Negative. Diagnostic Role of Exercise in Provocation of Left Ventricular Outflow Tract Gradient. Int J Cardiol 2014 Dec 20; 177(3):736–7.

264. Lakdawala NK, Thune JJ, Maron BJ, Cirino AL, Havndrup O, Bundgaard H et al. Electrocardiographic Features of Sarcomere Mutation Carriers with and without Clinically Overt Hypertrophic Cardiomyopathy. Am J Cardiol 2011 Dec 1; 108(11):1606–13.

265. Ho CY, Carlsen C, Thune JJ, Havndrup O, Bundgaard H, Farrohi F et al. Echocardiographic Strain Imaging to Assess Early and Late Consequences of Sarcomere Mutations in Hypertrophic Cardiomyopathy. Circ Cardiovasc Genet 2009 Aug; 2(4):314–21.

266. Captur G, Lopes LR, Patel V, Li C, Bassett P, Syrris P et al. Abnormal Cardiac Formation in Hypertrophic Cardiomyopathy: Fractal Analysis of Trabeculae and Preclinical Gene Expression. Circ Cardiovasc Genet 2014 Jun; 7(3):241–8.

267. Maron MS, Olivotto I, Harrigan C, Appelbaum E, Gibson CM, Lesser JR et al. Mitral Valve Abnormalities Identified by Cardiovascular Magnetic Resonance Represent a Primary Phenotypic Expression of Hypertrophic Cardiomyopathy. Circulation 2011 Jul 5; 124(1):40–7.

268. Ho JE, Shi L, Day SM, Colan SD, Russell MW, Towbin JA et al. Biomarkers of Cardiovascular Stress and Fibrosis in Preclinical Hypertrophic Cardiomyopathy. Open Heart 2017 Nov 1; 4(2):e000615.

269. Maron BJ, Yeates L, Semsarian C. Clinical Challenges of Genotype Positive (+)-Phenotype Negative (-) Family Members in Hypertrophic Cardiomyopathy. Am J Cardiol 2011 Feb 15; 107(4):604–8.

270. Konno T, Shimizu M, Ino H, Yamaguchi M, Terai H, Uchiyama K et al. Diagnostic Value of Abnormal Q Waves for Identification of Preclinical Carriers of Hypertrophic Cardiomyopathy Based on a Molecular Genetic Diagnosis. Eur Heart J 2004 Feb; 25(3):246–51.

271. Charron P, Dubourg O, Desnos M, Bouhour J-B, Isnard R, Hagege A et al. Diagnostic Value of Electrocardiography and Echocardiography for Familial Hypertrophic Cardiomyopathy in Genotyped Children. Eur Heart J 1998 Sep; 19(9):1377–82.

272. De S, Borowski AG, Wang H, Nye L, Xin B, Thomas JD et al. Subclinical Echocardiographic Abnormalities in Phenotype-Negative Carriers of Myosin-Binding Protein C3 Gene Mutation for Hypertrophic Cardiomyopathy. Am Heart J 2011 Aug; 162(2):262-267.e3.

273. Ho CY, Sweitzer NK, McDonough B, Maron BJ, Casey SA, Seidman JG et al. Assessment of Diastolic Function with Doppler Tissue Imaging to Predict Genotype in Preclinical Hypertrophic Cardiomyopathy. Circulation 2002 Jun 25; 105(25):2992–7.

274. Child N, Muhr T, Sammut E, Dabir D, Ucar EA, Bueser T et al. Prevalence of Myocardial Crypts in a Large Retrospective Cohort Study by Cardiovascular Magentic Resonance. J Cardiovasc Magn Reson 2014 Sep 16.

275. Maron MS, Rowin EJ, Lin D, Appelbaum E, Chan RH, Gibson CM et al. Prevalence and Clinical Profile of Myocardial Crypts in Hypertrophic Cardiomyopathy. Circ Cardiovasc Imaging 2012 Jul; 5(4):441–7.

276. Brouwer WP, Germans T, Head MC, Van Der Velden J, Heymans MW, Christiaans I et al. Multiple Myocardial Crypts on Modified Long-Axis View are a Specific Finding in Pre-Hypertrophic HCM Mutation Carriers. Eur Heart J Cardiovasc Imaging 2012; 13(4):292–7.

277. Johansson B, Maceira AM, Babu-Narayan SV, Moon JC, Pennell DJ, Kilner PJ. Clefts Can Be Seen in the Basal Inferior Wall of the Left Ventricle and the Interventricular Septum in Healthy Volunteers as well as Patients by Cardiovascular Magnetic Resonance. J Am Coll Cardiol 2007 Sep 25; 50(13):1294–5.

278. Urbano-Moral JA, Gutierrez-Garcia-Moreno L, Rodriguez-Palomares JF, Matabuena-Gomez-Limon J, Niella N, Maldonado G et al. Structural Abnormalities in Hypertrophic

Cardiomyopathy Beyond Left Ventricular Hypertrophy by Multimodality Imaging Evaluation. Echocardiography 2019 Jul; 36(7):1241–52.

279. Arow Z, Nassar M, Monakier D, Assali A, Vaknin-Assa H, Kornowski R et al. Prevalence and Morphology of Myocardial Crypts in Normal and Hypertrophied Myocardium by Computed Tomography. Int J Cardiovasc Imaging 2019 Jul; 35(7):1347–55.

280. Germans T, Wilde AAM, Dijkmans PA, Chai W, Kamp O, Pinto YM et al. Structural Abnormalities of the Inferoseptal Left Ventricular Wall Detected by Cardiac Magnetic Resonance Imaging in Carriers of Hypertrophic Cardiomyopathy Mutations. J Am Coll Cardiol 2006 Dec 19; 48(12):2518–23.

281. González A, López B, Ravassa S, Beaumont J, Arias T, Hermida N et al. Biochemical Markers of Myocardial Remodelling in Hypertensive Heart Disease. Cardiovasc Res 2009 Feb 15; 81(3):509–18.

282. Ho CY, López B, Coelho-Filho OR, Lakdawala NK, Cirino AL, Jarolim P et al. Myocardial Fibrosis as an Early Manifestation of Hypertrophic Cardiomyopathy 2010 Aug 5; 363(6):552–63.

283. Ho CY, Abbasi SA, Neilan TG, Shah RV, Chen Y, Heydari B et al. T1 Measurements Identify Extracellular Volume Expansion in Hypertrophic Cardiomyopathy Sarcomere Mutation Carriers with and without Left Ventricular Hypertrophy. Circ Cardiovasc Imaging 2013 May 1; 6(3):415–22.

284. Rowin EJ, Maron MS, Lesser JR, Maron BJ. CMR with Late Gadolinium Enhancement in Genotype Positive-Phenotype Negative Hypertrophic Cardiomyopathy. JACC Cardiovasc Imaging 2012 Jan; 5(1):119–22.

285. Geisterfer-Lowrance AAT, Christe M, Conner DA, Ingwall JS, Schoen FJ, Seidman CE et al. A Mouse Model of Familial Hypertorphic Cardiomyopathy. Science 1996 May 3; 272(5262):731–4.

286. Fatkin D, McConnell BK, Mudd JO, Semsarian C, Moskowitz IG, Schoen FJ et al. An Abnormal Ca(2+) Response in Mutant Sarcomere Protein-Mediated Familial Hypertrophic Cardiomyopathy. J Clin Invest 2000 Dec; 106(11):1351–9.

287. Crilley JG, Boehm EA, Blair E, Rajagopalan B, Blamire AM, Styles P et al. Hypertrophic Cardiomyopathy due to Sarcomeric Gene Mutations is Characterized by Impaired Energy Metabolism Irrespective of the Degree of Hypertrophy. J Am Coll Cardiol 2003 May 21; 41(10):1776–82.

288. Gersh BJ, Maron BJ, Bonow RO, Dearani JA, Fifer MA, Link MS et al. 2011 ACCF/AHA Guideline for the Diagnosis and Treatment of Hypertrophic Cardiomyopathy: A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation 2011 Dec 13; 124(24):e783-831.

289. Sorajja P, Ommen SR, Nishimura RA, Gersh BJ, Berger PB, Tajik AJ. Adverse Prognosis of Patients with Hypertrophic Cardiomyopathy who have Epicardial Coronary Artery Disease. Circulation 2003 Nov 11; 108(19):2342–8.

290. Spoladore R, Maron MS, D'Amato R, Camici PG, Olivotto I. Pharmacological Treatment Options for Hypertrophic Cardiomyopathy: High Time for Evidence. Eur Heart J 2012 Jul; 33(14):1724–33.

291. Olivotto I, Tomberli B, Spoladore R, Mugelli A, Cecchi F, Camici PG. Hypertrophic Cardiomyopathy: The Need for Randomized Trials. Glob Cardiol Sci Pract 2013 Nov 1; 2013(3):243–8.

292. Ammirati E, Contri R, Coppini R, Cecchi F, Frigerio M, Olivotto I. Pharmacological Treatment of Hypertrophic Cardiomyopathy: Current Practice and Novel Perspectives. Eur J Heart Fail 2016 Sep; 18(9):1106–18.

293. Marian AJ. Contemporary Treatment of Hypertrophic Cardiomyopathy. Tex Heart Inst J 2009; 36(3):194–204.

294. Chaudhry GM, Haffajee CI. Antiarrhythmic Agents and Proarrhythmia. Crit Care Med 2000 Oct; 28(10 Suppl):N158-N164.

295. Rosing DR, Kent KM, Borer JS, Seides SF, Maron BJ, Epstein SE. Verapamil Therapy: A New Approach to the Pharmacologic Treatment of Hypertrophic Carrdiomyopathy. I. Hemodynamic Effects. Circulation 1979 Dec; 60(6):1201–7.

296. Rosing DR, Kent KM, Maron BJ, Epstein SE. Verapamil Therapy: A New Approach to the Pharmacologic Treatment of Hypertrophic Cardiomyopathy. II. Effects on Exercise Capacity and Symptomatic Status. Circulation 1979 Dec; 60(6):1208–13.

297. Betocchi S, Piscione F, Losi M-A, Pace L, Boccalatte M, Perrone-Filardi P et al. Effects of Diltiazem on Left Ventricular Systolic and Diastolic Function in Hypertrophic Cardiomyopathy. Am J Cardiol 1996 Aug 15; 78(4):451–7.

298. Verlinden NJ, Coons JC. Disopyramide for Hypertrophic Cardiomyopathy: A Pragmatic Reappraisal of an Old Drug. Pharmacotherapy 2015 Dec; 35(12):1164–72.

299. Morady F, Scheinman MM, Desai J. Disopyramide. Ann Intern Med 1982 Mar; 96(3):337–43.

300. Sherrid MV, Barac I, McKenna WJ, Elliott PM, Dickie S, Chojnowska L et al. Multicenter Study of the Efficacy and Safety of Disopyramide in Obstructive Hypertrophic Cardiomyopathy. J Am Coll Cardiol 2005 Apr 19; 45(8):1251–8.

301. Pollick C. Muscular Subaortic Stenosis: Hemodynamic and Clinical Improvement After Disopyramide. N Engl J Med 1982 Oct 14; 307(16):997–9.

302. McMurray JJV, Adamopoulos S, Anker SD, Auricchio A, Böhm M, Dickstein K et al. ESC Guidelines for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in Collaboration with the Heart Failure Association (HFA) of the ESC. Eur Heart J 2012 Jul; 33(14):1787–847.

303. Rousseau MF, Pouleur H, Cocco G, Wolff AA. Comparative Efficacy of Ranolazine Versus Atenolol for Chronic Angina Pectoris. Am J Cardiol 2005 Feb 1; 95(3):311–6.

304. Chaitman BR, Skettino SL, Parker JO, Hanley P, Meluzin J, Kuch J et al. Anti-Ischemic Effects and Long-Term Survival During Ranolazine Monotherapy in Patients with Chronic Severe Angina. J Am Coll Cardiol 2004 Apr 21; 43(8):1375–82.

305. Morrow AG, Brockenbrough EC. Surgical Treatment of Idiopathic Hypertrophic Subaortic Stenosis: Technic and Hemodynamic Results of Subaortic Ventriculomyotomy. Ann Surg 1961 Aug; 154:181–9.

306. Messmer BJ. Extended Myectomy for Hypertrophic Obstructive Cardiomyopathy. Ann Thorac Surg 1994 Aug; 58(2):575–7.

307. Minakata K, Dearani JA, Nishimura RA, Maron BJ, Danielson GK. Extended Septal Myectomy for Hypertrophic Obstructive Cardiomyopathy with Anomalous Mitral Papillary Muscles or Chordae. J Thorac Cardiovasc Surg 2004 Feb; 127(2):481–9.

308. Liebregts M, Vriesendorp PA, Mahmoodi BK, Schinkel AFL, Michels M, Ten Berg JM. A Systematic Review and Meta-Analysis of Long-Term Outcomes After Septal Reduction Therapy in Patients with Hypertrophic Cardiomyopathy. JACC Heart Fail 2015 Nov; 3(11):896–905.

309. Osman M, Kheiri B, Osman K, Barbarawi M, Alhamoud H, Alqahtani F et al. Alcohol Septal Ablation vs Myectomy for Symptomatic Hypertrophic Obstructive Cardiomyopathy: Systematic Review and Meta-Analysis. Clin Cardiol 2019 Jan; 42(1):190–7.

310. Fitzgerald P, Kusumoto F. The Effects of Septal Myectomy and Alcohol Septal Ablation for Hypertrophic Cardiomyopathy on the Cardiac Conduction System. J Interv Card Electrophysiol 2018 Aug; 52(3):403–8.

311. Ommen SR, Maron BJ, Olivotto I, Maron MS, Cecchi F, Betocchi S et al. Long-Term Effects of Surgical Septal Myectomy on Survival in Patients with Obstructive Hypertrophic Cardiomyopathy. J Am Coll Cardiol 2005 Aug 2; 46(3):470–6.

312. Maron BJ, Dearani JA, Ommen SR, Maron MS, Schaff HV, Nishimura RA et al. Low Operative Mortality Achieved with Surgical Septal Myectomy: Role of Dedicated Hypertrophic Cardiomyopathy Centers in the Management of Dynamic Subaortic Obstruction. J Am Coll Cardiol 2015 Sep 15; 66(11):1307–8.

313. Mateo JJS, Gimeno JR. Alcohol Septal Ablation in Hypertrophic Cardiomyopathy. Glob Cardiol Sci Pract 2018 Aug 12; 2018(3):30.

314. Sigwart U. Non-Surgical Myocardial Reduction for Hypertrophic Obstructive Cardiomyopathy. Lancet 1995 Jul 22; 346(8969):211–4.

315. Veselka J, Jensen MK, Liebregts M, Januska J, Krejci J, Bartel T et al. Long-term Clinical Outcome After Alcohol Septal Ablation for Obstructive Hypertrophic Cardiomyopathy: Results from the Euro-ASA Registry. Eur Heart J 2016 May 14; 37(19):1517–23.

316. Nagueh SF, Groves BM, Schwartz L, Smith KM, Wang A, Bach RG et al. Alcohol Septal Ablation for the Treatment of Hypertrophic Obstructive Cardiomyopathy. A Multicenter North American Registry. J Am Coll Cardiol 2011 Nov 22; 58(22):2322–8.

317. Liebregts M, Vriesendorp PA, Ten Berg JM. Alcohol Septal Ablation for Obstructive Hypertrophic Cardiomyopathy: A Word of Endorsement. J Am Coll Cardiol 2017 Jul 25; 70(4):481–8.

318. Batzner A, Pfeiffer B, Neugebauer A, Aicha D, Blank C, Seggewiss H. Survival After Alcohol Septal Ablation in Patients with Hypertrophic Obstructive Cardiomyopathy. J Am Coll Cardiol 2018 Dec 18; 72(24):3087–94.

319. Liebregts M, Vriesendorp PA, Steggerda RC, Schinkel AFL, Balt JC, Ten Cate FJ et al. Effect of Alcohol Dosage on Long-Term Outcomes After Alcohol Septal Ablation in Patients with Hypertrophic Cardiomyopathy. Catheter Cardiovasc Interv 2016 Nov 15; 88(6):945–52.

320. Seggewiss H, Gleichmann U, Faber L, Fassbender D, Schmidt HK, Strick S. Percutaneous Transluminal Septal Myocardial Ablation in Hypertrophic Obstructive Cardiomyopathy: Acute Results and 3-Month Follow-Up in 25 Patients. J Am Coll Cardiol 1998 Feb; 31(2):252–8.

321. Spirito P, Rossi J, Maron BJ. Alcohol Septal Ablation: In Which Patients and Why? Ann Cardiothorac Surg 2017 Jul; 6(4):369–75.

322. Van Der Lee C, Scholzel B, Ten Berg JM, Geleijnse ML, Idzerda HH, Van Domburg RT et al. Usefulness of Clinical, Echocardiographic, and Procedural Characteristics to Predict Outcome After Percutaneous Transluminal Septal Myocardial Ablation. Am J Cardiol 2008 May 1; 101(9):1315–20.

323. Daubert C, Gadler F, Mabo P, Linde C. Pacing for Hypertrophic Obstructive Cardiomyopathy: An Update and Future Directions. Europace 2018 Jun 1; 20(6):908–20.

324. Nishimura RA, Trusty JM, Hayes DL, Ilstrup DM, Larson DR, Hayes SN et al. Dual-Chamber Pacing for Hypertrophic Cardiomyopathy: A Randomized, Double-Blind, Crossover Trial. J Am Coll Cardiol 1997 Feb; 29(2):435–41.

325. Kappenberger L, Linde C, Daubert C, McKenna W, Meisel E, Sadoul N et al. Pacing in Hypertrophic Obstructive Cardiomyopathy. A Randomized Crossover Study. PIC Study Group. Eur Heart J 1997 Aug; 18(8):1249–56.

326. Gadler F, Linde C, Juhlin-Dannfeldt A, Ribeiro A, Rydén L. Influence of Right Ventricular Pacing Site on Left Ventricular Outflow Tract Obstruction in Patients with Hypertrophic Obstructive Cardiomyopathy. J Am Coll Cardiol 1996 Apr; 27(5):1219–24.

327. Berruezo A, Vatasescu R, Mont L, Sitges M, Perez D, Papiashvili G et al. Biventricular Pacing in Hypertrophic Obstructive Cardiomyopathy: A Pilot Study. Heart Rhythm 2011 Feb; 8(2):221–7.

328. Lenarczyk R, Woźniak A, Kowalski O, Sokal A, Pruszkowska-Skrzep P, Sredniawa B et al. Effect of Cardiac Resynchronization on Gradient Reduction in Patients with Obstructive Hypertrophic Cardiomyopathy: Preliminary Study. Pacing Clin Electrophysiol 2011 Nov; 34(11):1544–52.

329. Maron MS, Kalsmith BM, Udelson JE, Li W, DeNofrio D. Survival After Cardiac Transplantation in Patients with Hypertrophic Cardiomyopathy. Circ Heart Fail 2010 Sep; 3(5):574–9.

330. Kato TS, Takayama H, Yoshizawa S, Marboe C, Schulze PC, Farr M et al. Cardiac Transplantation in Patients with Hypertrophic Cardiomyopathy. Am J Cardiol 2012 Aug 15; 110(4):568–74.

331. Biagini E, Spirito P, Leone O, Picchio FM, Coccolo F, Ragni L et al. Heart Transplantation in Hypertrophic Cardiomyopathy. Am J Cardiol 2008 Feb 1; 101(3):387–92.

332. European Union. Regulation (EC) N°141/2000 of the European Parliament and of the Council of 16 December 1999 on orphan medicinal products. 2000. [cited 6th of January, 2020]. Available from: URL: http://eurlex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L2000:018:0005:EN:PDF.

333. The Senate and House of Representatives of the United States of America in Congress Assembled. Public Law 107-280, 107th Congress 2002 [cited 2020 Feb 25]. Available from: URL: https://history.nih.gov/research/downloads/PL107-280.pdf.

334. U.S. Census Bureau. Global Population Profile 2002: International Population Reports 2004 [cited 2020 Feb 25]. Available from: URL: https://www.census.gov/content/dam/Census/library/publications/2004/demo/wp-02.pdf.

335. Yarmohammadi H, Varr BC, Puwanant S, Lieber E, Williams SJ, Klostermann T et al. Role of CHADS2 Score in Evaluation of Thromboembolic Risk and Mortality in Patients with Atrial Fibrillation Undergoing Direct Current Cardioversion (From the ACUTE Trial Substudy). Am J Cardiol 2012 Jul 15; 110(2):222–6.

336. Rivard L, Khairy P. Mechanisms, Clinical Significance, and Prevention of Cognitive Impairment in Patients with Atrial Fibrillation. Can J Cardiol 2017 Dec; 33(12):1556–64.

337. Ott A, Breteler MMB, De Bruyne MC, Van Harskamp F, Grobbee DE, Hofman A. Atrial Fibrillation and Dementia in a Population-Based Study: The Rotterdam Study. Stroke 1997 Feb; 28(2):316–21.

338. Dublin S, Anderson ML, Haneuse SJ, Heckbert SR, Crane PK, Breitner JCS et al. Atrial Fibrillation and Risk of Dementia: A Prospective Cohort Study. J Am Geriatr Soc 2011 Aug; 59(8):1369–75.

339. Di Nisio M, Prisciandaro M, Rutjes AWS, Russi I, Maiorini L, Porreca E. Dementia in Patients with Atrial Fibrillation and the Value of the Hachinski Ischemic Score. Geriatr Gerontol Int 2015 Jun; 15(6):770–7.

340. Noureldin RA, Liu S, Nacif MS, Judge DP, Halushka MK, Abraham TP et al. The Diagnosis of Hypertrophic Cardiomyopathy by Cardiovascular Magnetic Resonance. J Cardiovasc Magn Reson 2012 Feb 20.

341. Brunton LL, Hilal-Dandan R, Knollmann BC, editors. Goodman & Gilman's The Pharmacological Basis of Therapeutics. 13th Edition. New York, Chicago, San Francisco: McGraw Hill Education; 2018.

342. Arrigo M, Bettex D, Rudiger A. Management of Atrial Fibrillation in Critically Ill Patients. Crit Care Res Pract 2014; 2014:840615.

343. Sherrid MV, Pearle G, Gunsburg DZ. Mechanism of Benefit of Negative Inotropes in Obstructive Hypertrophic Cardiomyopathy. Circulation 1998 Jan; 97(1):41–7.

344. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS et al. 2016 ESC Guidelines for the Diagnosis and Treatment of Acute and ChronicHeart Failure: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure of the European Society of Cardiology (ESC) Developed with the Special Contribution of the Heart Failure Association (HFA) of the ESC. Eur Heart J 2016; 37(27):2129–200.

345. Noronha B, Duncan E, Byrne J. A. Optimal Medical Management of Angina. Curr Cardiol Rep 2003 Jul; 5(4):259–65.