Diploma Thesis

Longitudinal Left Ventricular Strain Analysis in Conditions of Chronic Heart Failure – Insights of the RoC-HF Study

submitted by

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Statutory Declaration

I hereby declare that this thesis is my own original work and that I have fully acknowledged by name all of those individuals and organizations that have contributed to the research for this thesis. The acknowledgement has been made in the text to all other material used. Throughout this thesis and in all related publications I followed the “Guidelines of the Medical University of Graz on Good Scientific Practice”.

Graz, March 18th, 2021 Nora Schwegel eh.

Acknowledgement

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Another thank you is dedicated to my family for their limitless support and encouragement.

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Abbreviations and Definitions

ACCF	*American College of Cardiology Foundation*
AF	*atrial fibrillation*
AHA	*American Heart Association*
ASE	*American Society of Echocardiography*
AVC	*aortic valve closure*
BMI	*body mass index*
BNP	*brain natriuretic peptide*
CABG	*coronary artery bypass graft*
CHF	*chronic heart failure*
CMP	*cardiomyopathy*
CMR	*cardiac magnetic resonance*
EACVI	*European Association of Cardiovascular Imaging*
ECG	*electrocardiography*
ED	*end-diastole*
EDV	*end-diastolic volume*
EF	*ejection fraction*
eGFR	*estimated glomerular filtration rate*
ES	*end-systole*
ESC	*European Society of Cardiology*
ESV	*end-systolic volume*
GCS	*global circumferential strain*
gl.	*according to current guidelines*
GLS	*global longitudinal strain*
GRS	*global radial strain*
HCM	*hypertrophic cardiomyopathy*
HF	*heart failure*

HFmrEF	*heart failure with mid-range ejection fraction*
HFpEF	*heart failure with preserved ejection fraction*
HFrEF	*heart failure with reduced ejection fraction*
ICM	*ischemic cardiomyopathy*
ISCV	*IntelliSpace Cardiovascular*
KDIGO	*Kidney Disease Improving Global Outcomes*
LS	*longitudinal strain*
LVEF	*left ventricular ejection fraction*
LVOT-SV	*left ventricular outflow tract stroke volume*
NP	*natriuretic peptides*
NT-proBNP	*N-terminal pro brain natriuretic peptide*
NYHA	*New York Heart Association*
PLAX	*parasternal long axis view*
PSAX	*parasternal short axis view*
PTCA	*percutaneous transluminal coronary angioplasty*
RoC-HF	*Role of Comorbidities in Chronic Heart Failure*
seg.	*calculated with well trackable segments*
SR	*strain rate*
STE	*speckle-tracking echocardiography*
SV	*stroke volume*
TDI	*tissue doppler imaging*
TTE	*transthoracic echocardiography*
2D-CPA	*2-dimensional cardiac performance analysis*
2DE	*2-dimensional echocardiography*
3DE	*3-dimensional echocardiography*

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Zusammenfassung

Hintergrund und Ziel: Die chronische Herzinsuffizienz stellt wegen ihrer hohen Prävalenz, Krankheitslast und Mortalität eines der weltweit führenden Probleme des Gesundheitswesens mit entsprechenden finanziellen Belastungen dar. Die Echokardiographie ist der Goldstandard in der Diagnostik und im Management der Herzinsuffizienz. Die Einführung myokardialer Deformationsbildgebung in die klinische Routine könnte die Diagnostik und das Management von Herzinsuffizienz erleichtern. Da es nur wenige Daten zur Interpretation solcher *globalen longitudinalen Strain (GLS)* Werten bei Herzinsuffizienzpatient*innen gibt, soll mit dieser Arbeit die Evidenz erweitert werden.

Material und Methoden: Es wurden 177 Patient*innen mit klinisch stabiler, kompensierter chronischer Herzinsuffizienz untersucht. Neben Anamnese und körperlicher Untersuchung wurden verschiedene GLS-Parameter in digital archivierten zweidimensionalen transthorakalen echokardiographischen Untersuchungen typischer apikaler Kammerblicke ausgewertet. Zusätzlich wurde die linksventrikuläre Ejektionsfraktion (LVEF) anhand der biplanen Methode nach Simpson gemäß aktueller Richtlinien (n = 164) sowie anhand einer triplanen Methode ausgewertet. Venöse Blutproben wurden laborchemisch aufgearbeitet und die Parameter NT-proBNP und Nierenfunktion in die Analyse dieser Arbeit aufgenommen.

Resultate: Alle GLS-Werte zeigten eine signifikante und starke Korrelation untereinander. Sie wiesen auch eine signifikante Korrelation zu beinahe allen inkludierten echokardiographischen Parametern auf, welche miteinander ebenfalls stark korrelierten. Im Vergleich zur LVEF zeigten alle GLS-Parameter eine stärkere Korrelation zu Plasmakonzentrationen von NT-proBNP, besonders unter Einbeziehung der Einflussfaktoren Alter, BMI, eGFR und Vorhofflimmern. Außerdem zeigte sich, dass GLS der LVEF in Bezug auf Reproduzierbarkeit, Durchführbarkeit und Anwendung überlegen ist.

Conclusio: GLS ist ein robuster und gut reproduzierbarer Parameter. Die zusätzliche Anwendung von GLS-Parametern in der Routineechokardiographie könnte die Diagnostik der Herzinsuffizienz erleichtern und zur Verbesserung des Therapiemanagements bei chronischer Herzinsuffizienz beitragen.

Abstract

Background and Aim: Chronic heart failure is a major issue in public health, with an increasing prevalence. It is the leading cause of hospitalization worldwide, associated with increased morbidity and mortality, and imposes a fundamental financial burden to health care. Echocardiography is the gold standard for the diagnosis and management of heart failure, and with the admission of myocardial deformation imaging into clinical routine, additional imaging data could facilitate diagnostics and management of heart failure patients. As only limited data on global longitudinal strain (GLS) evaluation in heart failure is available, this thesis aims to give closer insights.

Material and Methods: A total of 177 clinically stable and compensated patients with chronic heart failure underwent a comprehensive examination including anamnesis and physical examination. Different GLS parameters were evaluated via post-processing of digitally archived two-dimensional transthoracic echocardiography cine loops of the typical apical chamber views. The left ventricular ejection fraction (LVEF) was measured according to current guidelines using Simpson's biplane method (n = 164). Moreover, triplane LVEF was assessed. Venous blood sampling was obtained and NT-proBNP and kidney function was further investigated.

Results: There was a significant and strong correlation amongst all strain evaluation methods observed. Furthermore, strain showed significant correlation to almost all included common echocardiographic parameters, including both biplane and triplane LVEF, which also had a strong correlation amongst themselves. In comparison to LVEF, all strain parameters showed stronger correlation to NT-proBNP plasma concentration, especially under consideration of age, BMI, eGFR, and atrial fibrillation history as confounding parameters. Furthermore, strain revealed to be superior to LVEF regarding reproducibility, feasibility, and applicability.

Conclusion: Strain showed to be a robust and reproducible parameter regardless of echocardiographic training. In addition to routine echocardiography, strain could facilitate the diagnosis of heart failure and improve therapy management of chronic heart failure.

1 Introduction

1.1 Chronic Heart Failure

According to the current guidelines of the European Society of Cardiology (ESC) on diagnostic and treatment of chronic heart failure (CHF), *"heart failure (HF) is a clinical syndrome characterized by typical symptoms (e.g. breathlessness, ankle swelling and fatigue) that may be accompanied by signs (e.g. elevated jugular venous pressure, pulmonary crackles and peripheral oedema) caused by a structural and/or functional cardiac abnormality, resulting in a reduced cardiac output and/or elevated intracardiac pressures at rest or during stress"* [1].

1.1.1 Scope of the Problem

CHF is a major issue in clinical and public health with an increasing prevalence. Currently, it is estimated that more than 37,7 million persons worldwide suffer from CHF [2]. This situation is more dramatic in the older population with a prevalence of 5-9% at the age of ≥65 years [3], and a 60-90-day mortality after diagnosis of about 10% and a hospitalization rate of about 30% [4]. This makes CHF one of the leading causes of morbidity and mortality and the leading cause of hospitalization [5]. Therefore, its impact on the healthcare system is extremely high. In 2012, total costs for CHF were estimated with about US$ 30.7 billion in the united states alone, about 1.1% of the total US health care spending. Those costs are estimated to expand to US$ 69.8 billion by 2030 [2].

Depending on definitions, the overall prevalence of HF is about 1-2% in developed countries [1], rapidly rising with age. The risk for HF varies by age, sex, ethnicity and history of myocardial infarction and other comorbidities. For instance, the lifetime risk at age 45 for HF for men is 27,4% whilst for women it is 23,8% [6, 7].

Overall HF and heart failure with reduced ejection fraction (HFrEF) are more prevalent in men than in women, while women more often appear to have heart failure with preserved ejection fraction (HFpEF) [3,6].

CHF is a chronic phase emerging from a variety of cardiac diseases, therefore there are many different underlying etiologies with partly overlapping categories, as listed in table 1.

Many patients have several different pathologies simultaneously and their identification is a significant part of the diagnostic survey, as they may require specific therapeutic intervention [1].

1.1.2 Classification by Ejection Fraction

The classification of heart failure is commonly done by measuring the left ventricular ejection fraction (LVEF). Normal values are defined as a LVEF of equal to or larger than 50%.

Unfortunately, patients with CHF present with a wide range of LVEF. Overall, an LVEF of smaller than 50% is considered to be reduced whilst an LVEF > 50 % is considered to be preserved. Patients affected from CHF with an LVEF of > 50 % are defined as heart failure with preserved ejection fraction (HFpEF). The guidelines from the ESC published in the year 2016 for the first time introduced the term mid-range reduced leading to a classification of heart failure with mid-range ejection fraction (HFmrEF) for an LVEF of 40 to 50% while an LVEF of smaller than 40% is defined as reduced leading to the classification of heart failure with reduced ejection fraction (HFrEF) [1]. This differentiation is important because of different underlying etiologies, patient demographics, comorbidities, prognosis, diagnosis and therapy response [8-10]. Lastly, no HF specific treatment could convincingly demonstrate a reduction of morbidity and mortality in patients with an LVEF of greater than 40%.

The historical term ‘diastolic HF’ [11] refers to diastolic dysfunction (impaired left ventricular filling) being generally accepted as likeliest cause of HFpEF. However, patients with HFpEF also show subtle systolic dysfunction whereas most patients with HFrEF (historically classified as ‘systolic HF’) have impaired diastolic function. Therefore, a classification by systolic/diastolic dysfunction is not recommended anymore [1].

Myocardial Conditions	
Ischemic	Myocardial scar Coronary artery disease Coronary artery dissection Coronary artery embolism Endothelial dysfunction
Primary CMP *(familial)*	Dilated CMP Hypertrophic CMP Restrictive CMP Arrhythmogenic right ventricular CMP Left ventricular non-compaction
Secondary CMP *(acquired)*	Inflammatory CMP Endocrine/metabolic acquired CMP Peripartum CMP CMP due to infiltration Takotsubo-CMP
Loading Conditions	
Hypertension	
Valvular heart disease	rheumatic degenerative
Septum defects	
Pericardial disease	Constrictive pericarditis Pericardial effusion
Endocardial disease	Hypereosinophilic syndromes Endomyocardial fibrosis Endocardial fibroelastosis
Volume overload	Renal failure Iatrogenic
High output states	Arteriovenous fistula Sepsis Anemia Thyrotoxicosis Paget's disease
Congenital Heart Disease	
Arrhythmias	
Tachyarrhythmia	Atrial Ventricular
Bradyarrhythmia	Sinus node dysfunction Atrioventricular block

Table 1: Overview of different etiologies of heart failure. CMP = cardiomyopathy.

1.1.3 Classification by Symptom Severity

The New York Heart Association (NYHA) functional classification is a model to grade the severity of symptoms and exercise capacity, whereas the American College of Cardiology Foundation/American Heart Association (ACCF/AHA) classification describes stages of HF based on development and progression [12,13], as shown in tables 2 and 3.

Of note, symptom severity correlates only poorly with LVEF. However, there is a significant relation to hospitalization and mortality [14-16].

1.1.4 Diagnostic Tools and Diagnosis

Signs and Symptoms

The diagnosis of HF is often described as "*a clinical diagnosis based on a careful history and physical examination" [12]*, referring to the clinical assessment of more or less typical and specific symptoms and signs. However, those are often non-specific and therefore cannot be used to differentiate safely between HF and other diseases[1].

Detailed medical history in combination with symptoms and signs related to HF can give a good lead to the likelihood of the presence of HF. They are important in monitoring disease progression and response to therapy but by themselves are an

NYHA class	
I	No limitations of physical activity; ordinary activity does not cause any symptoms
II	Slight limitation in ordinary physical activities (fatigue, palpitations, dyspnea); no symptoms at rest
III	Marked limitation, less than ordinary physical activities cause symptoms; no symptoms at rest
IV	Inability to perform any physical activity without discomfort; symptoms present even at rest

Table 2: NYHA functional classification of heart failure

insufficient diagnostic tool, as shown by different studies [1,17,18].

Natriuretic Peptides

The natriuretic peptides (NP), especially brain natriuretic peptide (BNP) and N-terminal proBNP (NT-proBNP), are the gold standard biomarkers in the diagnosis of HF. Due to myocardial wall stretching and distension, and neurohormonal activation, cardiomyocytes synthesize proBNP, which during secretion splits into the physiologically active BNP and the inactive NT-proBNP [19]. The biological functions of NP include various mechanisms like vasodilation, natriuresis, and improve myocardial relaxation. Plasma concentration of NP correlates with age, sex, and BMI [20] and is also affected by renal failure and atrial fibrillation [21]. Elevated levels are directly correlating to prognosis, NYHA score, and intra-ventricular pressure, and inversely to cardiac output [19].

NT-proBNP has a longer half-life than BNP (70 vs. 20 minutes) because of the different clearance mechanisms and is therefore commonly used in clinical evaluations [22]. With a negative predictive value of 0.98 at a cut-point of 125 pg/mL, the measurement of NT-proBNP is a valid test for ruling-out HF. Moreover, the prognosis and therapeutical management can depend on NP levels [1,12,23].

ACCF/AHA stage	
A	High risk for HF, no structural heart disease or symptoms
B	Structural heart disease, no signs or symptoms of HF
C	Structural heart disease, prior or current symptoms
D	Refractory HF, requiring interventions

Table 3: ACCF/AHA classification of heart failure stages. HF = heart failure

Electrocardiography

Abnormal ECG findings can increase the probability of a present HF but have a poor specificity (56% [24]). The routine ECG use in diagnosis is recommended to rule-out HF, since it is highly unlikely in patients with a normal ECG [1,25](sensitivity 89% [24]).

Echocardiography

Providing information on ventricular function, chamber volumes, wall thickness and valve function [26], it is the most valuable diagnostic tool in patients with suspected HF and crucial to establishing the diagnosis as well as to determine an appropriate therapy [27].

Of several existing imaging modalities, transthoracic echocardiography (TTE) is the diagnostic gold standard mainly because it is an accurate, easily available, safe, and inexpensive method to assess both systolic and diastolic function [1,12,26].

The evaluation of left ventricular systolic function is usually done by the assessment of the LVEF. For measurements of LVEF in 2-dimensional echocardiography (2DE), the biplane Simpson's rule is recommended [26]. Recently other parameters besides LVEF, e.g. strain and strain rate, find their way into regular clinical use.

1.2 Deformation Imaging

1.2.1 The Concept of Strain Evaluation

Strain describes the deformation of the myocardium during the cardiac cycle. This deformation is determined by myofiber architecture. Interconnected fiber layers cause a complex left ventricular deformation throughout the wall [28,29]. This usually is described with three orthogonal components oriented along the left ventricular axes, as shown in figure 1. Since the heart is a 3-dimensional structure, there are in fact six strains. In addition to the above mentioned longitudinal, radial, and circumferential strain there are three directions of shear strain that result from the

three layers moving over each other in shearing motion during myocardial contraction [30,31]. It should be mentioned that those latter parameters are hardly used in clinical context and the by far most important parameter is the longitudinal strain [28].

Layer-specific Analysis

Given the opportunity to distinguish different layers within the ventricular wall in echocardiography (commonly subdivided in endocardial, myocardial and (sub)epicardial layer), layer specific measurements are possible by selecting the wanted part. Though it should be mentioned that their clinical usability is limited [28] due to mechanical layer interdependence [32] and limited resolution of the generated cines. Software vendors utilize by default either layer specific or mid-/fullwall strain, resulting in relevant inter-vendor differences in strain measurements [32,33].

Segmental Analysis

Segmental analysis provides individual values for each anatomical unit of the left ventricular myocardium, the so-called segments. Their number depends on the chosen model and varies between a 16-, 17-, and 18-segment model.

Those models aim to reflect the coronary perfusion territories, resulting in comparable myocardial mass and therefore allowing comparison between different imaging modalities [30]. They also create a graphic evaluation of local values, the bull's eye.

Global Analysis

Global strain, especially global longitudinal (GLS) and global circumferential strain (GCS), are used as unitless parameters to describe left ventricular global function.

It is calculated using the entire myocardial line lengths deformation or alternatively, by averaging the values of numerous points within the myocardial line or averaging the segmental values.

The global longitudinal strain can be calculated as an averaged full wall strain or as an endocardial, midline or epicardial strain [30].

1.2.2 Basic Parameters

Velocity, displacement, strain, and strain rate (SR) are the required measurements

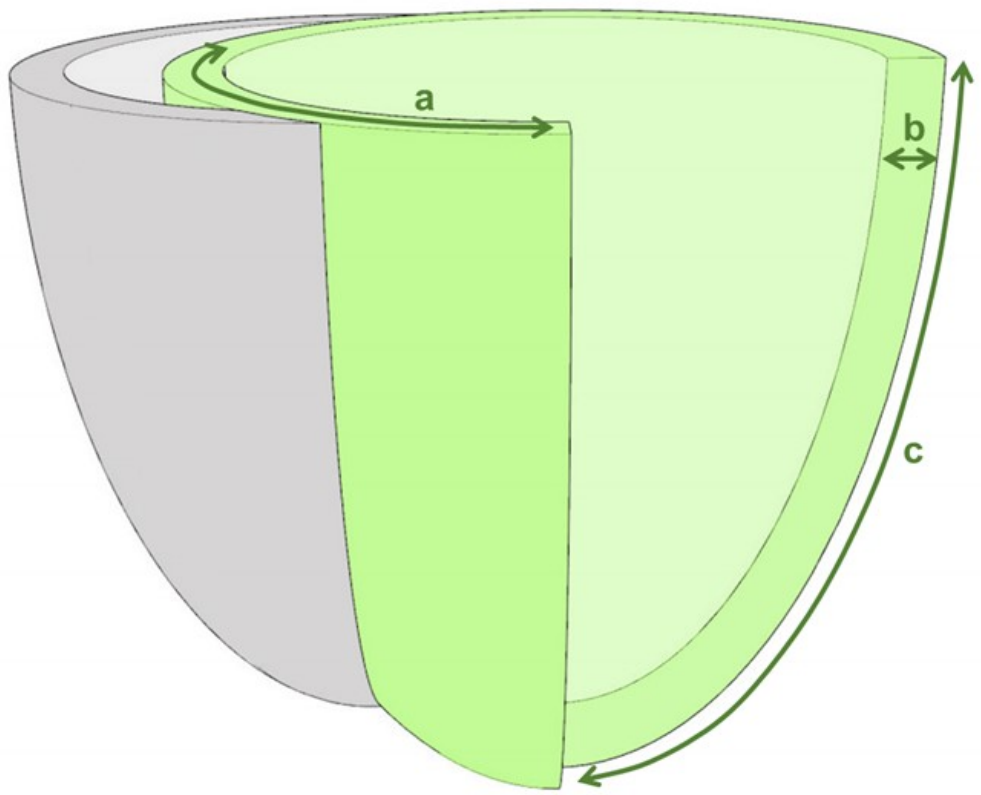

Figure 1: Schematic overview of the orientation of the three directions of strain.
Highlighted in green: Left ventricle.
a: Circumferential strain: Change of the radius in the short axis; perpendicular to longitudinal and radial axis.
b: Radial strain: Thickening and inward movement; perpendicular to longitudinal axis and epicardium.
c: Longitudinal strain: Systolic shortening from base to apex.
Modified from Voigt and Cvijic, 2- and 3-Dimensional Myocardial Strain in Health and Diseases, JACC Cardiovascular Imaging, 2019.

for the characterization of myocardial function, mechanics, and deformation.

Displacement is the distance a certain object, i.e. speckle or cardiac feature, moves between two frames, measured in centimeters (cm) or millimeters (mm). Velocity describes how fast a certain object changes its location, measured in centimeter per second (cm/s) or millimeter per second (mm/s).

Strain is a parameter for the deformation of an object compared to its original shape. Given that a hypothetical one-dimensional line may only deform in length, there are two common ways to describe this deformation – the Lagrangian and the Natural strain [30,34].

SR describes the change of strain per time.

Lagrangian Strain

The Lagrangian strain shows the fractional change in length of the object in comparison to its original length. Comparing the measured length at a given point (L_t) to a predefined reference length (L_0), usually end-diastolic length [29, 30].

$$S_L(t) = \frac{L(t) - L_0}{L_0}$$

The derivative of this strain is the Lagrangian SR, which is basically the deformation or strain per time unit.

$$SR_L(t) = \frac{ds_L}{dt} = \frac{1}{dt}\frac{dL}{dt}$$

Natural Strain

In Lagrangian strain L_0 is a constant, whereas in Natural strain the reference length changes during the object's deformation process.

As the temporal derivative of Natural strain, the Natural SR does not depend on reference times and describes the instantaneous rate of deformation [29,30].

$$SR_N = \frac{ds_N(t)}{dt} = \frac{1}{L(t)}\frac{dL}{dt}$$

Strain is dimensionless, results are expressed in percentage or fraction – while shortening results in negative values and lengthening in positive ones. SR is reported as s^{-1}.

In small deformations, Lagrangian and Natural strain values are nearly equal. During large deformations (for instance ventricular filling or ejection) they differ significantly [30]. They are nonlinearly related and can therefore be converted into each other.

1.2.3 Techniques

Echocardiography: Tissue Doppler Imaging

By measuring regional myocardial velocities, tissue Doppler imaging (TDI) can offer a one-dimensional assessment of Natural strain [28,35]. Spatial velocity differences between neighboring regions in the myocardium imply either lengthening or compression of interposed tissue [36].

Thus TDI-based data of wall movement is dependent on velocities, their point of measurement and the angle between the direction of the myocardial movement and the ultrasound. Underestimating tissue movement that is not parallel to the scan lines is therefore a fundamental limitation of TDI based strain [26,37].

Echocardiography: Speckle-tracking

The myocardial tissue has inhomogeneous acoustic properties. The resulting interference pattern forms speckles (bright and dark pixels) in the myocardium.

These unique dots do not represent myocardial structures but move together with the tissue [28].

Speckles within a defined region are tracked by software and followed frame to frame during one cardiac cycle. Analyzing their spatial movement allows the calculation of strain and SR [38]. Unlike TDI-based strain assessment, speckle-tracking echocardiography (STE) uses the Lagrangian strain [35]. Also, STE provides strain independent of the angle of insonation and translational movement [31,39].

STE can be applied to processed 2-dimensional and 3-dimensional echocardiographic image datasets [28].

Cardiac Magnetic Resonance and Myocardial Tagging

To cardiac magnetic resonance (CMR) images, in analogy to speckle-tracking in echocardiography, feature-tracking based software can be applied, allowing the quantification of longitudinal, circumferential, and radial strain [40].

The currently used spatial modulation of magnetization technique, like STE, tracks a small patch of pixels aka tags moving with the myocardium through a sequence of standard clinical steady-state free precession cine images [41].

1.2.4 Image Acquisition

Strain analysis is currently done offline, as a post-processing method in digitally saved, ECG triggered 2-dimensional cine loops. The images used for STE strain analysis are acquired from the minimum dataset of a standard TTE [42].

Electrocardiographic gating of the used cine loops is essential for the correct timing of events during the cardiac cycle and is therefore highly important for a correct strain analysis. There should be at least three cardiac cycles recorded, with minimal heart rate variability to ensure valid tracking [31], making it difficult amongst patients without sinus rhythm, especially amongst patients with atrial fibrillation [43].

For any given heart rate there is an optimal frame rate. Literature recommends frame rates ranging from 40fps to 80fps for normal heart rates in adults [34], depending on the used tracking technique and software. With increasing heart rate, mechanical events become shorter; therefore, the frame rate should be increased proportionally [30,31].

1.2.5 Resulting Parameters

Strain and Strain-rate Curves

Strain and SR curves, as pictured in figure 2, offer a variety of values at clinically relevant timings. Both curves provide a time to peak (ms), peak-systolic strain (%) and a peak value (%), for averaged global and segmental values.

Bull's-eye Plot

Bull's-eye plots provide segmental values of time to peak, peak-systolic strain and peak value in a color coded visual-plot, as shown in figure 3. Conventionally, but software dependent, they come in a color spectrum from red (representing normal values) to light pink (reduced strain) or even blue (highly reduced values), providing an easy way of visualizing regional dyssynchrony and/or dysfunction.

Normal Values

Currently, the most commonly measured parameter in both, clinical examination and research, is the left ventricular global longitudinal strain (GLS), as it occurs to be the most robust and reproducible value.

Different studies attempted to define expectable ranges for GLS, GCS and GRS.

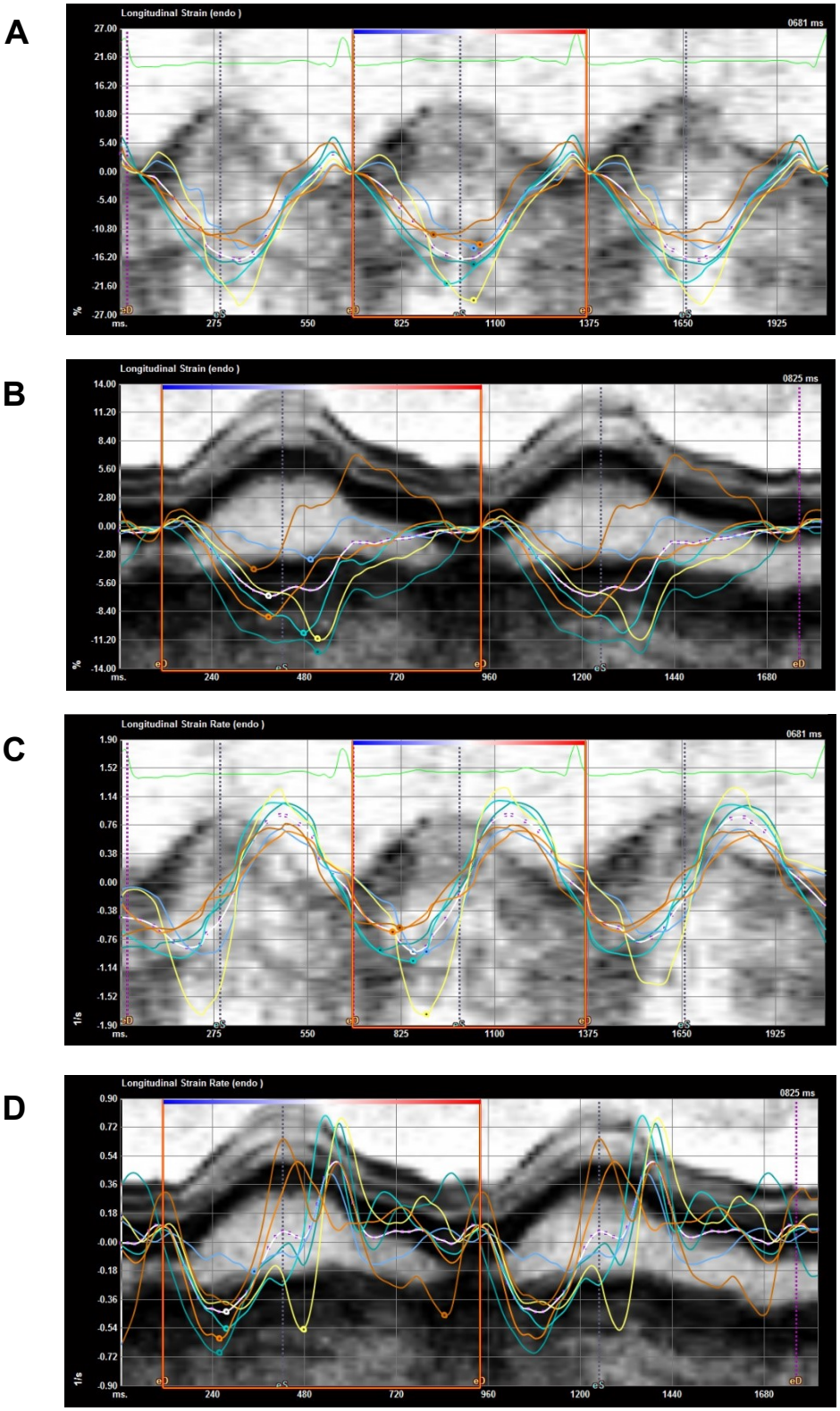

Figure 2: Examples of endomyocardial strain- and strain-rate curves. Different segments in apical two chamber view measured with 2D-CPA using the software TomTec.
A: Longitudinal Strain [%] curves in a healthy adult with peak values around - 19 %
B: Longitudinal Strain [%] curves in a patient with HFrEF with peak values around - 9 %
C: Longitudinal Strain-rate [s^{-1}] curves in a healthy adult
D: Longitudinal Strain-rate [s^{-1}] curves in a patient with HFrEF

However, the ranges for GCS and GRS deviate too much to establish universal values [26,28,31,44,45].

The average GLS in studies of normal range is -19,7% [45], with a limit of normal set at -18%. Values between -18% and -16% should be interpreted as borderline, values above -16% as pathological [46].

Gender, BMI, and frame rate are not considered as significant sources of variation [31], whereas high blood pressure is associated with higher strain values [45] and with higher age strain decreases [26]. There is also a moderate, yet statistically significant bias among different vendors [32,47].

1.2.6 Factors influencing Strain

Strain only values myocardial deformation, neglecting any circumstances under which the myofibers have to shorten. It therefore is not only dependent on myocardial contractility but is also influenced by factors that determine overall cardiac performance.

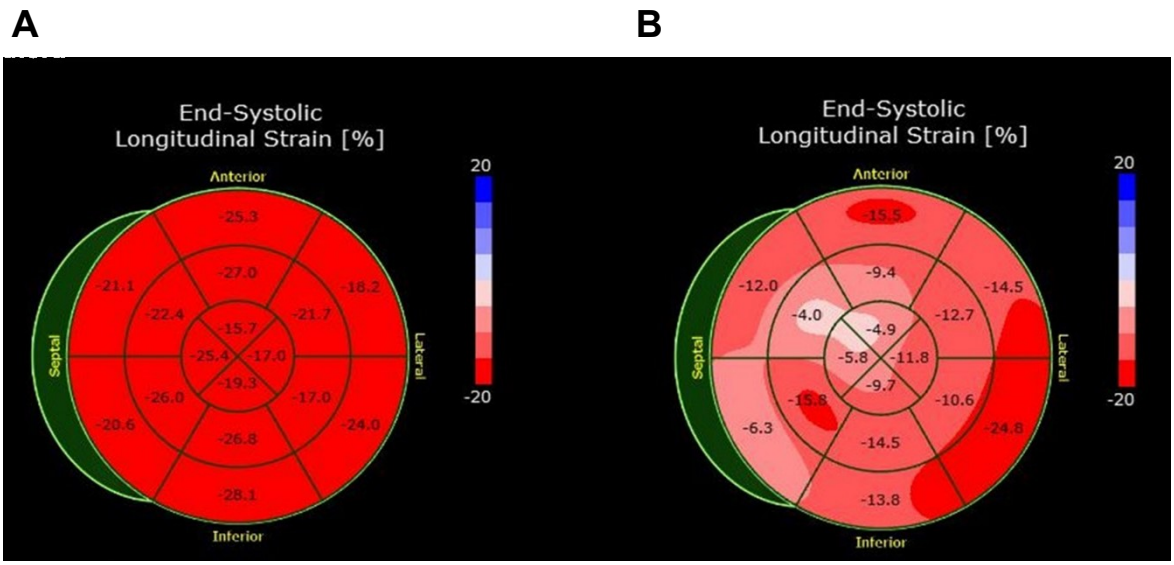

Figure 3: Example of a Bull's-eye plot. End-Systolic Longitudinal Strain [%] measured with Auto-Strain using the software TomTec.
A: Bull's-eye plot in a 26-year-old healthy adult, GLS = -22.0%
B: Bull's-eye plot in a 35-year-old patient with HFrEF, GLS = -11.5%

Studies have shown a significant dependence of strain to loading conditions and heart rate, whereas SR appears to be more independent [28,48-50].

With preserved contractility, strain increases with increasing preload, confirming the Frank-Starling concept that pre-stretching myocardial fibers leads to augmented contraction [28]. The relation to afterload and heart rate on the other hand, is inversely proportional, meaning a decrease in strain values with increasing afterload or heart rate due to decrease of stroke volume [48].

Biphasic behavior appears in patients with chronic preload increase, where strain remains or normalizes due to remodeling and decreases progressively as the ventricle begins to fail. For instance, patients with chronic mitral regurgitation show GLS values of <-18.1%, which in principle is within the normal GLS range, but in this case indicates left ventricular dysfunction and poor prognosis [26,51].

Geometric factors of the ventricle determine how chamber pressure translates into wall stress and how fiber stress leads to volume change, as depicted in LaPlace's law or similar models [52,53].

In patients with volume overload caused by regurgitation, deformation increases in early stage of disease. Thus, higher strain values reflect the overload itself, not enhanced contractility. Later on, due to adapting to increasing stroke volume and adaptive remodeling, long-lasting overload results in progressive chamber enlargement, increasing wall stress and contractile dysfunction with reducing strain values.

On the other hand, in patients with pressure overload, wall thickness increases and chamber size decreases, compensating the excess wall stress due to elevated chamber pressure [28]. In this setting EF remains within a normal range for a long time, whereas strain is already significantly reduced [54].

To detect initial left ventricular dysfunction, strain could be normalized to loading conditions and wall thickness [55-57] but clinical proof and data on the feasibility of these concepts are missing [28].

Besides hemodynamic and geometric factors, other tissue characteristics may influence the shortening of the myofibers, e.g. fibrosis and different depositions are associated with decreased contractility.

Reduced longitudinal strain is often an early sign for irreversible myocyte damage as the subendocardial fibers are frequently the first ones to be affected [28]. With transmural extension of the damage other strain values are also impaired [58].

Impaired regional systolic shortening in combination with newly occurring post-systolic shortening after aortic valve closure (AVC) may reveal acute ischemia [59]. Post-systolic shortening, as sign of delayed relaxation, is a sensitive but unspecific marker for regional dysfunction, also found in other pathologies with regional scar formation, like chronic ischemic scar, localized HCM or Fabry disease [60-62]. However, combined with normal systolic function, slight post-systolic shortening is also a frequent finding in healthy hearts and should therefore not to be overestimated [60].

Globally reduced myocardial contractility results only in decreased GLS values and, later, in reduced LVEF. Regional patterns of strain are normal except for reduced peak values.

Inhomogeneous regional strain values may also be due to conduction delays, resulting in inhomogeneous activation and dyssynchrony in contraction patterns [28,63].

1.2.7 Strain in Heart Failure

Diagnosis of HF, especially in early stages, can be challenging. While echocardiography per se has already been a crucial factor for making a firm diagnosis of HF for a long time, STE parameters – in particular 2D-STE GLS – have recently been reported to be sensitive markers for the detection of subtle left ventricular myocardial abnormalities. GLS has even been reported to be superior to conventional measurements like LVEF in predicting the outcome of various cardiac conditions and events [64-68].

Identification of different HF phenotypes relies on evaluation of left ventricular function. Since symptomatic HF often comes with normal LVEF values (HFpEF), myocardial strain, offering incremental functional information, becomes more valid.

Both longitudinal and circumferential strain are related to LVEF [54], as strain and LVEF decrease with progressing HF. But strain reacts early to even minor changes in cardiac function, making it a precursor to later changes in LVEF [28,69]. Decreased left ventricular GLS can also reveal the presence of covert systolic dysfunction in HFpEF, despite fully preserved LVEF [70].

The main advantage of strain is its sensitivity to subtle changes in myocardial performance. This allows the detection of subclinical dysfunction, which may help to prevent progression through early treatment [46,66].

1.3 Gaps in Evidence

Although there are many studies about the importance and interpretation of strain in different conditions, there is only little given data about strain evaluation in patients with chronic heart failure. The normal ranges for strain mentioned in previous chapters are based on the average population, and further data about the interpretation of different strain values in patients with chronic heart failure is missing.

1.4 Aim of the Thesis

Given the omnipresence of chronic heart failure and the difficulties in diagnostics and therapy management in patients with heart failure, the main aim of this thesis is to give closer insights into the evaluation and interpretation of different strain parameters in patients with clinically stable and compensated chronic heart failure.

Another aim of this thesis is to further investigate the relation between different strain parameters and common echocardiographic parameters, especially LVEF, and the laboratory parameter NT-proBNP.

2. Methods

The used data was obtained from the RoC-HF (Role of Comorbidities in Chronic Heart Failure) study performed at the department of cardiology at the Medical University of Graz.

2.1 Study Overview and Study Population

The RoC-HF study is a prospective, cross-sectional, single-centered, epidemiological cohort study. The permission to perform the study was granted by the Ethics committee of the Medical University of Graz (28-467ex15/16). Patients were recruited directly at the department of cardiology. All patients gave written informed consent to use the obtained data for scientific purposes. In total, 160 male and 45 female subjects with stable chronic heart failure with reduced ejection fraction were examined following the study protocol of the RoC-HF study. However, for the main analysis of this diploma thesis, that depends on the availability of transthoracic echocardiography, 28 datasets could not be analyzed. Data from 22 subjects were not stored in the digital archive IntelliSpace Cardiovascular (ISCV; Philips, Eindhoven, Netherlands) and 6 studies had to be excluded due to bad image quality. In the end, datasets of 177 subjects (139 male and 38 female) could be analyzed.

Inclusion criteria were age ≥18 years, present symptoms NYHA II-IV, a left ventricular ejection fraction under 50% at the first visit, ongoing treatment according to current ESC HF Guidelines [1], and a previous diagnosis of heart failure with reduced ejection fraction <40% requiring optimization of heart failure therapy. Major exclusion criteria were unplanned hospitalization within one month prior to the first study visit, changes in the ongoing heart failure treatment within one month prior to the first visit, coronary or peripheral revascularization procedures, valvular procedures or any major surgical procedure, acute coronary syndrome, stroke, or transient ischemic attack within three months prior to the baseline visit. Furthermore, patients with acute illness, life expectancy to less than one year due to any disease

except HFrEF, primary significant valve disease (moderate to severe), or prior organ transplantation were excluded.

2.2 Transthoracic Echocardiography

Transthoracic echocardiography was performed on each patient during their first visit by experienced cardiologists using a Vivid 7 or Vivid E9 (GE Healthcare, Chalfont St Giles, UK) with an image rate set at least at 70 frames per second. To define and track end-diastole and end-systole, ECG was applied simultaneously.

The protocol for transthoracic echocardiography includes 2D, 3D, and doppler image acquisition. At least three cardiac cycles in sinus rhythm or five cardiac cycles in atrial fibrillation were recorded of the following transthoracic angulations: parasternal long axis view (PLAX), parasternal short axis view (PSAX; at the level of the heart valves, at the level of the mitral valve, at the level of the papillary muscles, and at the level of the apex), apical two chamber view, apical three chamber view, apical four chamber view, apical five chamber view, and the subcostal view. ECG recording was performed in every study. Loops and images were then transferred to the digital archive ISCV.

2.3. Assessment of Strain

In this study all image data was analyzed offline, using the post-processing program TomTec (TOMTEC Imaging Systems, Munich, Germany) in digitally saved, ECG triggered 2D TTE cine loops of the typical apical chamber views.

Strain was determined through two different analyzing methods using post-processing speckle-tracking software on typical apical chamber views. For this purpose, echocardiographic images were acquired with the above-mentioned GE devices, stored in EchoPAC (GE Healthcare, Chalfont St Giles, UK) and exported into ISCV. For further assessment, the DICOM files were then imported into TomTec and analyzed.

2.3.1 AutoStrain

AutoStrain (TOMTEC Imaging Systems, Munich, Germany) is an automated measurement tool for the assessment of left ventricular longitudinal strain along the endocardium. After manually assigning the correct apical long axis view, the application automatically generates endomyocardial border contours, allowing to edit those contours manually with re-tracking if needed. After approval by the investigator, AutoStrain analysis provides (1) a color-coded visualization of dynamic longitudinal strain results on the basis of selected loops; (2) a segmental visualization of both end-systolic strain and time-to-peak strain, portrayed in two 16-segment bull's-eye plots; (3) and a parameter list derived from triplane GLS analysis.

2.3.2 2D-CPA Global Longitudinal Strain

2D Cardiac Performance Analysis (TOMTEC Imaging Systems, Munich, Germany) is a speckle-tracking based software tool, enabling vendor-independent offline

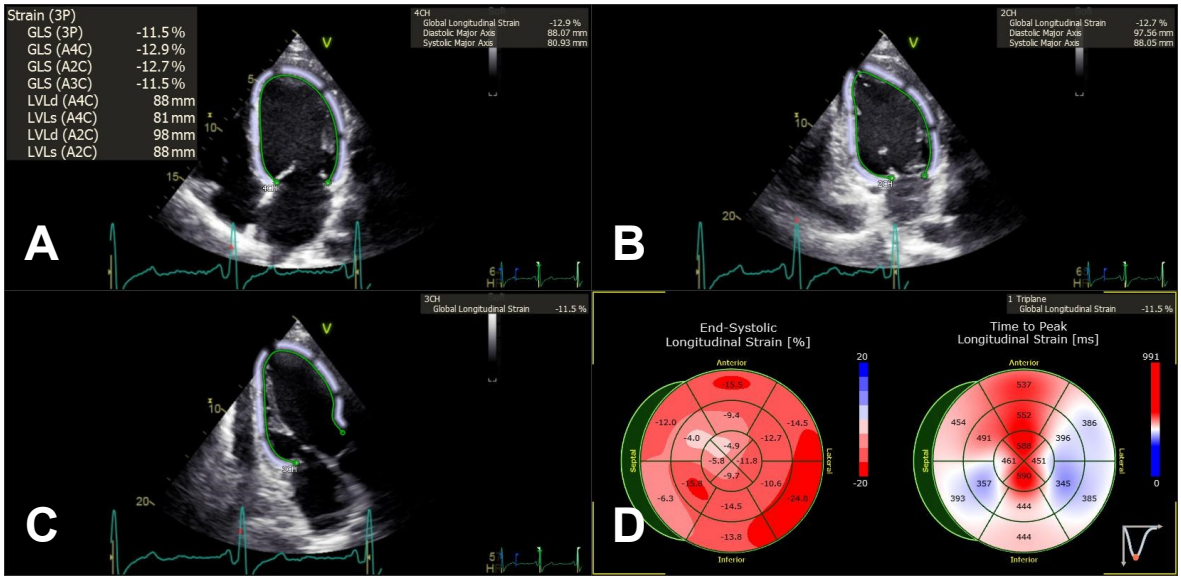

Figure 4: Example of an AutoStrain measurement using the software TomTec. Pictured was a patient with heart failure with reduced ejection fraction with a GLS of -11.5%.
A: Apical four chamber view
B: Apical two chamber view
C: Apical three chamber view
D: Bull's eye plots for end-systolic [%] and time-to-peak Longitudinal Strain [ms]

analysis of cardiac deformation. The preselected images were loaded in 2D CPA and allocated to the corresponding views in the program. If multiple cardiac cycles have been acquired, one cardiac cycle was predefined, and within end-systole (ES) and end-diastole (ED) were defined via M-Mode. After placing three reference points (anterior annulus, posterior annulus, apex) at the endocardium in ES, the software generates endomyocardial and epicardial border contours, allowing manual editing for correct tracing. When adjusted correctly, tracking was initiated and the proposed contour in ED was adjusted.

The analysis results in a color-coded visualization of layer-specific global and segmental strain values, displayed in-loop and as strain and strain-rate curves for each image. Furthermore, average endo- and myocardial triplane GLS values are provided, and peak-systolic-strain, end-systolic-strain and time-to-peak are visualized in 16-segment bull's-eye plots.

Both, AutoStrain and 2D CPA GLS, were calculated with the entire contour length using the following (simplified) formula:

$$GLS = \frac{L_S - L_D}{L_D}$$

2.3.3 2D-CPA Average Longitudinal Strain

The Peak Global Average Longitudinal Strain is the peak value of an average strain curve of all segments (arithmetic mean). It was calculated with segmental peak strain values acquired through 2D CPA.

The assessment with 2D CPA for Global Longitudinal Strain and Average Longitudinal Strain was performed twice. Using the same images for both analyzing cycles, each one was performed on a different cardiac cycle if more than one was acquired and assessable.

2.4. Left Ventricular Ejection Fraction and Stroke Volumes

The biplane LVEF was evaluated through TTE according to current ESC guidelines [26], using the Simpson method. In addition to the biplane LVEF, a triplane LVEF was assessed through the 2-dimensional Cardiac Performance Analysis, calculating end-systolic and end-diastolic volumes in standard apical chamber views by endomyocardial contouring.

Left ventricular stroke volumes (SV) were calculated with biplane and triplane volumes:

$$SV = EDV - ESV$$

Left ventricular outflow tract stroke volume (LVOT-SV) was calculated with following formula:

$$LVOT - SV = \left(\frac{LVOT}{20}\right)^2 * \pi * VTI_{LVOT}$$

2.5 Blood Sampling and Assessment of Laboratory Parameters

Venous blood samples were taken of each patient and were processed directly after

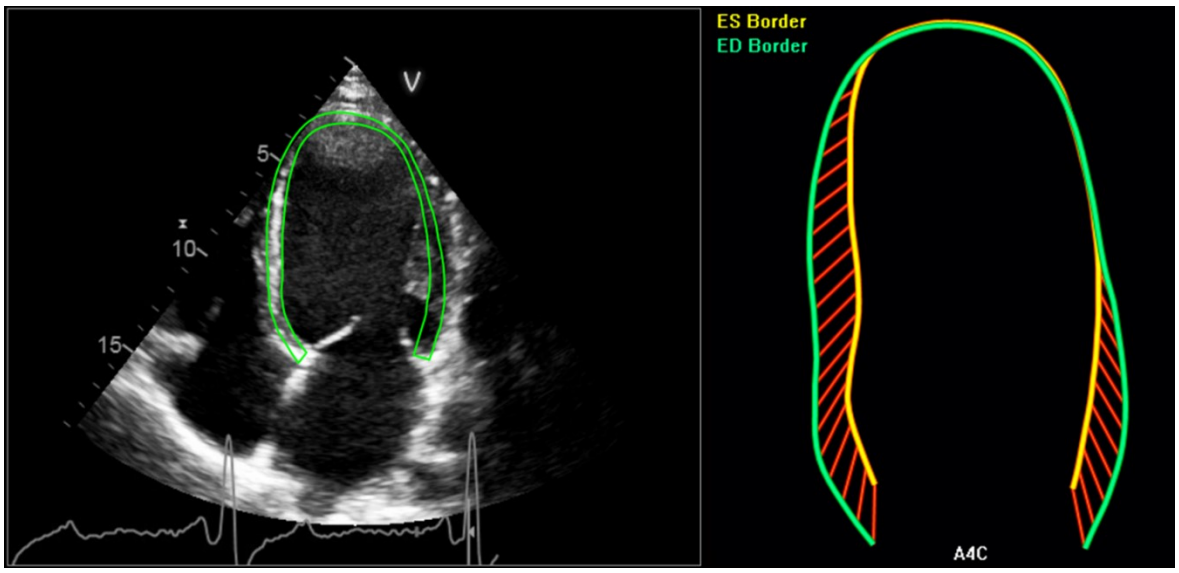

Figure 5: Example of endomyocardial contouring. Apical four chamber view in 2D-CPA, using the software TomTec.

collection for the purpose of immediate and most accurate determination of the parameters at the Clinical Institute of Medical and Chemical Laboratory Diagnostics and at the Laboratory platform of Division of Endocrinology.

In this work, the N-terminal pro Brain Natriuretic Peptide (NT-proBNP) and estimated Glomerular Filtration Rate (eGFR; calculated according to current guidelines [71] with CKD-EPI) were further evaluated. Both laboratory parameters were determined from the blood plasma of a Lithium-Heparin probe.

2.6 Data Analysis and Statistics

Data was exported, merged by a recorded macro and cleaned in Excel (Microsoft Office 365, Microsoft Corporation, Redmond, US) and then imported to IBM SPSS statistics 26 (IBM Corporation, Armonk/New York, US) for further statistical analysis. Results were considered statistically significant with (two-sided) p-values <0.05.

All data was tested for normal distribution and variance homogeneity. For normal distribution, graphic evaluation and the Shapiro-Wilk-test was used. For group-comparison, unpaired t-test was used for normally distributed parameters and Man-Whitney-U-test was used for parameters that did not fulfill the criteria of normal distribution. For group-comparison, unpaired t-test, and ANOVA with Tukey-HSD multiple comparison post hoc test were used.

Correlation analysis for normal distributed parameters was done with Pearson's Product-Moment Correlation and Spearman's Rank-Order Correlation was used for non-normally distributed data. In order to perform a Linear Regression Analysis, NT-proBNP and age were transformed through natural logarithm to create linearity.

The following parameters were deemed to be normally distributed: AutoStrain, endomyocardial GLS, endomyocardial average-LS, stroke volume (SV), and eGFR.

End-diastolic volume (EDV), end-systolic volume (ESV), left ventricular outflow tract stroke volume (LVOT-SV), LVEF, NT-proBNP, body mass index (BMI), and age did not meet the criteria of normal distribution.

3. Results

For greater clarity, the following paragraphs picture a summary of this work's results. Full correlation analyses are to be found in the appendix.

3.1 Subjects

A total number of 177 patients was included in this work. The gender distribution was 78.5% (n = 139) for males and 21.5% (n = 38) for females.

The mean age in the study population was 64.5 ± 10.3 years (males 64.3 ± 10.5 years, females 65.4 ± 9.9 years). The oldest and the youngest participant, both from the male subgroup, were 83.7 and 27.4 years old.

The mean BMI was 28.7 ± 5.0 kg/m^2, with no significant difference within the gender groups (males 28.7 ± 4.6 kg/m^2, females 28.6 ± 6.1 kg/m^2). According to the accepted definitions, 22.0% (n = 39) were classified normal weight with a BMI of 18.5-24.9 kg/m^2; 40.1% (n = 71) were classified overweight with a BMI of 25.0-29.9 kg/m^2; 34.5% (n = 61) as obese with a BMI of 30.0-39.9 kg/m^2; and 2.8% (n = 5) met the criteria of severe obesity, with a BMI over 40 kg/m^2. One patient was underweight, with a BMI of 15.9 kg/m2 [72].

NT-proBNP was elevated (≥ 125 pg/mL) [1] in 92.7% (n = 164) of the study population, with a median of 907 (IQR 328 – 2217) pg/mL. The gender groups showed no significant difference (males 907 (IQR 335 – 2194) pg/mL, females 904 (IQR 232 – 2352) pg/mL).

Overall, the kidney function was impaired with an estimated mean GFR (n = 171) of 65 ± 23 mL/min. After normalization of the values for female subjects, the eGFR significant was higher in males (67 ± 24 mL/min, females 58 ± 17 mL/min, p = 0.03). According to the KDIGO-classification [71], 17.5% (n = 31) of the subjects showed normal or high eGFR with values ≥ 90 mL/min, 39.5% (n = 70) had mildly decreased renal function with eGFR 60-89 mL/min, 20.3% (n = 36) had mildly to moderately decreased values with eGFR 45-59 mL/min, 13.0% (n = 23) had moderately to severely reduced eGFR 30-44 mL/min, 5.1% (n = 9) had severely decreased

function with eGFR 15-29 mL/min and two patients (1.1%) had kidney failure with an eGFR < 15 mL/min.

Atrial fibrillation was present in 41.8% (n = 74) of the study population, more common in the male subgroup (86.2%, n = 62) than in the female (45.6%, n = 12).

3.2 Left Ventricular Volumes

Biplane EDV, ESV, and SV were evaluated in 164 subjects (128 male, 36 female). The mean biplane EDV was 155 ± 61 mL (male 164 ± 62 mL, female 121 ± 44 mL), the mean biplane ESV was 102 ± 50 mL (male 110 ± 52 mL, female 76 ± 33 mL), the mean biplane SV was 53 ± 16 mL (male 55 ± 16 mL, female 45 ± 15 mL).

Triplane EDV, ESV, and SV was available in 177 patients (139 male, 38 female) with overall comparable measurements: mean triplane EDV was 157 ± 61 mL (male 165 ± 61 mL, female 125 ± 47 mL), mean triplane ESV was 106 ± 52 mL (male 113 ± 54 mL, female 82 ± 39 mL), and mean triplane SV was 50 ± 15 mL (male 53 ± 15 mL, female 43 ± 13 mL).

Calculated mean LVOT-SV was available in 165 subjects (130 male, 35 female) and showed significantly higher values with a mean of 59 ± 20 mL (male 61 ± 19 mL, female 55 ± 24 mL).

NT-proBNP correlated significantly with biplane and triplane EDV, and biplane and triplane ESV. Neither biplane nor triplane SV showed significant correlation to NT-proBNP, but LVOT-SV showed a weak yet significant negative correlation.

The volumes also showed significant positive correlation among themselves.

3.3 Left Ventricular Ejection Fraction

The biplane LVEF was assessed in 164 patients (128 male, 36 female). The mean biplane EF was 35.8 ± 8.2%, slightly lower in the males with 35.1 ± 8.3% compared to the females with 38.4 ± 7.4%.

	total	% borderline*	% pathological*	N
Age *[mean, years]*	64.5 ± 10.3			177
BMI *[mean, kg/m²]*	28.7 ± 5.0	40.1	37.3	177
NT-proBNP *[median, pg/mL]*	907 (328 – 2217)	22.6	70.1	177
GFR *[mean, mL/min]*	65 ± 23	40.9	41.1	171
Biplane EDV *[mean, mL]*	155 ± 61	♂ 16.4 ♀ 16.7	♂ 38.3 ♀ 41.7	164
Triplane EDV *[mean, mL]*	157 ± 61	♂ 15.8 ♀ 15.8	♂ 37.4 ♀ 50.0	177
Biplane ESV *[mean, mL]*	102 ± 50	♂ 13.3 ♀ 27.8	♂ 70.3 ♀ 66.7	164
Triplane ESV *[mean, mL]*	106 ± 52	♂ 13.6 ♀ 15.8	♂ 74.0 ♀ 76.3	177
Biplane SV *[mean, mL]*	53 ± 16			164
Triplane SV *[mean, mL]*	50 ± 15			177
LVOT-SV *[mean, mL]*	59 ± 20			165
Biplane LVEF *[mean, %]*	35.8 ± 8.2	31.7	66.5	164
Triplane LVEF *[mean, %]*	34.2 ± 8.8	25.4	72.3	177
AutoStrain *[mean, %]*	-12.2 ± 3.8	13.7	82.7	139
GLS *[mean, %]*	-12.1 ± 3.6	10.7	85.9	177
GLS gl. *[mean, %]*	-12.1 ± 3.7	11.6	85.2	155
Average LS *[mean, %]*	-13.7 ± 3.6	17.5	72.3	177
Average LS seg. *[mean, %]*	-13.8 ± 3.7	16.9	70.6	177
Average LS gl. *[mean, %]*	-13.8 ± 3.7%	19.4	69.0	155

*Table 4: Overview. N max = 177. *borderline: BMI 25-30 kg/m2; NT-proBNP 125-300 pg/mL in SR, 125-600 pg/ml in AF; eGFR 60-90 mL/min; EDV male 151-174 mL, female 107-120 mL; ESV male 62-73 mL, female 43-55 mL; LVEF 40-49%; strain -16 to -18%; *pathological: BMI > 30 kg/m2; NT-proBNP > 300 pg/mL in SR, > 600 pg/mL in AF; GFR < 60 mL/min; EDV male >175 mL, female > 121 mL; ESV male > 74 mL, female > 56 mL; LVEF < 40%; strain > -16%*

66.5% (n = 109) of these patients had a biplane LVEF < 40%, whereas 31.7% (n = 52) had values 40-49%, and 1.7% (n = 3) had LVEF > 50%.

The triplane LVEF was available in all patients (n = 177), with a mean of 34.2 ± 8.8% (male 33.8 ± 8.8%, female 35.8 ± 8.6%)

Through triplane evaluation, 72.3% (n = 128) of the patients had an LVEF < 40%, 25.4% (n = 45) had values 40-49%, and 2.3% (n = 4) had LVEF > 50%.

Both, biplane and triplane LVEF, showed significant negative correlation with NT-proBNP, and there was a significant positive correlation to LVOT-SV. However, only triplane LVEF correlated weakly positive with triplane SV. Regarding biplane and triplane LVEF, there was no significant correlation with biplane SV, BMI, GFR, or age. As expected, biplane and triplane LVEF showed a strong significant positive correlation.

In multivariate linear regression analysis, biplane ($\beta = -0.586$, $p < 0.001$, $R^2_k = 0.218$) as well as triplane LVEF ($\beta = -0.597$, $p < 0.001$, $R^2_k = 0.216$) showed a significant negative association to ln(NT-proBNP) under the consideration of ln(age), BMI, GFR, and AF history as confounders [1,20].

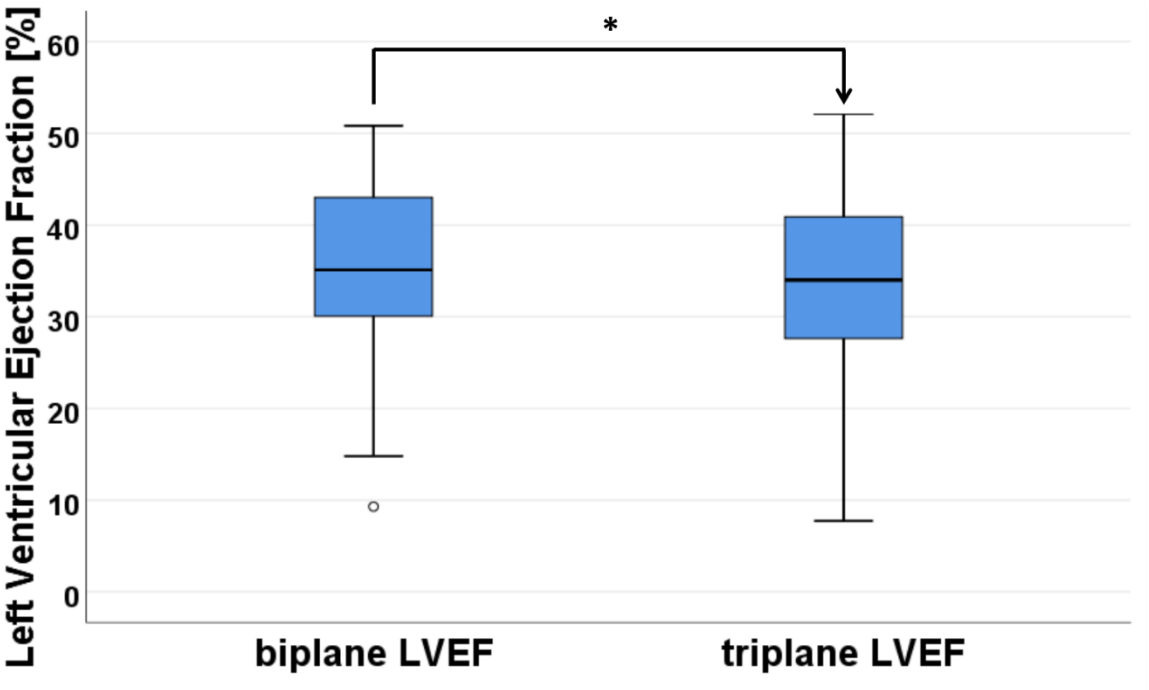

Figure 6: Boxplot displaying significant correlation (*) between biplane and triplane left ventricular ejection fraction.

3.4 Longitudinal Strain

Three different measurements of longitudinal strain were performed, as described in the previous chapter: AutoStrain (n = 139), global longitudinal strain and average longitudinal strain. Furthermore, average longitudinal strain was subdivided into average longitudinal strain including all patients and available segments (average LS; n = 177), average longitudinal strain including only good segments (average LS seg.; n = 177) and average longitudinal strain according to current guidelines [26] (average LS gl.; n = 155), excluding studies with suboptimal regional tracking in more than two segments in a single view. Global longitudinal strain was subdivided into GLS including all patients (GLS; n = 177) and GLS according to current guidelines (GLS gl.; n = 155), as described above. Figure 7 shows an overview of the different strain measurements.

3.4.1 AutoStrain

AutoStrain was available in 139 patients. The mean value was -12.2 ± 3.7%, with

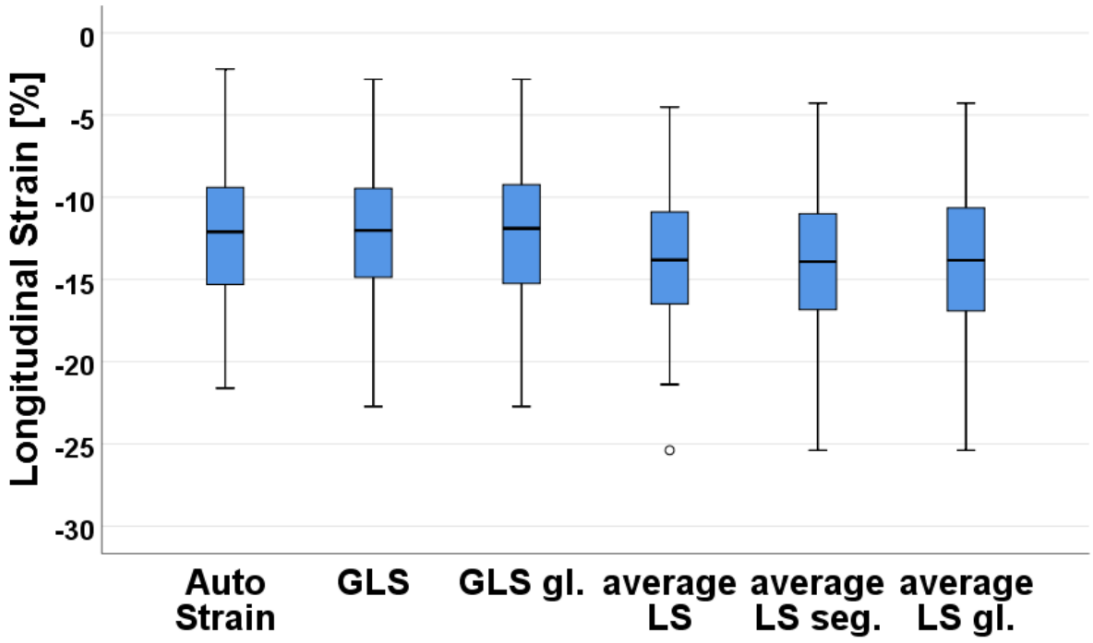

Figure 7: Boxplot displaying different strain measurement methods. GLS = Global Longitudinal Strain; gl. = adjusted to current guidelines; LS = Longitudinal Strain; seg. = calculated with well tracked segments

no significant differences between gender groups (male -12.2 ± 3.8%, female -12.2± 3.6%).

82.7% of the available patients had pathological strain values in AutoStrain, with values less negative than -16%, 13.7% had borderline strain values, with -16 to -18%, and 3.6% had normal values (< -18%).

AutoStrain correlated strongly with all other strain parameters. Furthermore, there were significant positive correlations with NT-proBNP, biplane and triplane EDV, and biplane and triplane ESV. Negative correlations were found with biplane and triplane LVEF, and LVOT-SV. There was no significant correlation to biplane or triplane SV, BMI, GFR or age.

Regression analysis for AutoStrain and ln(NT-proBNP) under the consideration of ln(age), BMI, GFR, and AF history, showed a significant linear relationship between these parameters ($\beta = 0.636$, $p < 0.001$, $R^2_k = 0.271$).

3.4.2 Global Longitudinal Strain

The mean GLS (n = 177) was -12.1 ± 3.7%. There was no significant difference between gender subgroups (male -12.0 ± 3.6%, female -12.5 ± 3.6%). Determined through GLS, 85.9% of the patients had pathological strain values, while only 10.7% were classified borderline and 3.4% normal.

GLS adjusted to current guidelines (n = 155) had a mean value of -12.1 ± 3.7%, also with no significant difference between genders (male -12.0 ± 3.7%, female -12.2 ± 3.7%). With this analysis, 85.2% of the included patients showed pathological values, 11.6% had borderline and 3.2% had normal strain values.

Correlation analysis between strain measurements showed a strong correlation to all other methods.

GLS and GLS gl. strongly negatively correlated with biplane and triplane LVEF, and LVOT-SV, and significantly positively with NT-proBNP, biplane and triplane EDV, and biplane and triplane ESV. There was no significant correlation to biplane or triplane SV, BMI, GFR or age.

Regression analysis showed a significant linear relationship between both, GLS and GLS gl., and ln(NT-proBNP) under consideration of ln(age), BMI, GFR , and AF history (GLS $\beta = 0.616$, $R^2_k = 0.278$; GLS gl. $\beta = 0.622$, $R^2_k = 0.277$; $p < 0.001$ for each).

	GLS pathological (≥ -16%) 152 patients		**GLS borderline (-18 to -16%)** 19 patients		**GLS normal (≤ -18%)** 6 patients	
	Total	**N**	**Total**	**N**	**Total**	**N**
Biplane EDV *[mean, mL]*	160 ± 63	140	128 ± 35	19	108 ± 18	5
Biplane ESV *[mean, mL]*	108 ± 52	140	70 ± 21	19	57 ± 9	5
Biplane SV *[mean, mL]*	52 ± 17	140	58 ± 15	19	51 ± 9	5
Biplane LVEF *[mean, %]*	34.2 ± 7.7	140	45 ± 3.2	19	47.4 ± 2.3	5
Triplane EDV *[mean, mL]*	161 ± 63	152	134 ± 33	19	112 ± 24	6
Triplane ESV *[mean, mL]*	112 ± 54	152	76 ± 21	19	58 ± 10	6
Triplane SV *[mean, mL]*	49 ± 15	152	58 ± 14	19	54 ± 14	6
Triplane LVEF *[mean, %]*	32.5 ± 8.1	152	43.4 ± 4.5	19	47.9 ± 3.3	6
LVOT-SV *[mean, mL]*	58 ± 19	142	72 ± 24	17	68 ± 31	6
BMI *[mean, kg/m²]*	28.8 ± 5.1	152	28.0 ± 3.9	19	27.8 ± 4.8	6
GFR *[mean, mL/min]*	65 ± 23	148	67 ± 22	19	65 ± 20	4
NT-proBNP *[median, pg/mL]*	1070 (427 – 2463)	152	298 (158 – 1240)	19	231 (179 – 649)	6
Age *[mean, years]*	64.4 ± 10.6	152	65.1 ± 9.6	19	65.4 ± 6.1	6

Table 5: Overview of values of different biomarkers in pathological, borderline, and normal strain values.

3.4.3 Average Longitudinal Strain

The average longitudinal strain (n = 177) was -13.7 ± 3.6%. There were no significant differences between the male and the female subgroup (male -13.5 ± 3.5%, female -14.2 ± 3.7%).

According to average LS, 72.3% had pathological strain values, whereas 17.5% had borderline and 10.2% had normal values.

Average LS seg., calculated only through segments with good tracking (n = 177), was -13.8 ± 3.7%, also without significant differences between genders (male -13.7 ± 3.6%, female -14.4 ± 3.8%).

It revealed 70.6% of the study population with pathological, 16.9% with borderline, and 12.4% with normal values.

Average LS gl., calculated according to current guidelines (n = 155), had a mean of -13.8 ± 3.7%, once again without significant difference between genders (male -13.6 ± 3.7%, female -14.2 ± 3.8%).

Average LS gl. showed pathological strain values in 69.0%, borderline values in 19.4% and normal values in 11.6% of the included subjects.

	Reduced EF*		**Mid-range EF***		**Preserved EF***	
	N	Mean ± SD	N	Mean ± SD	N	Mean ± SD
AutoStrain	95	-10.5 ± 3.0%	41	-15.8 ± 2.4%	3	-17.5 ± 2.0%
GLS	109	-10.3 ± 2.7%	52	-15.5 ± 2.7%	3	-16.5 ± 1.8%
GLS gl.	103	-10.3 ± 2.7%	48	-15.7 ± 2.5%	3	-16.5 ± 1.8%
Average LS	109	-11.9 ± 2.7%	52	-17.1 ± 2.5%	3	-18.5 ± 2.1%
Average LS seg.	109	-12.0 ± 2.8%	52	-17.3 ± 2.6%	3	-18.8 ± 1.9%
Average LS gl.	103	-12.0 ± 2.8%	48	-17.4 ± 2.4%	3	-18.8 ± 1.8%

*Table 6: Overview of different strain values. *reduced EF: < 40%; mid-range EF: 40 – 49%; preserved EF: ≥ 50%*

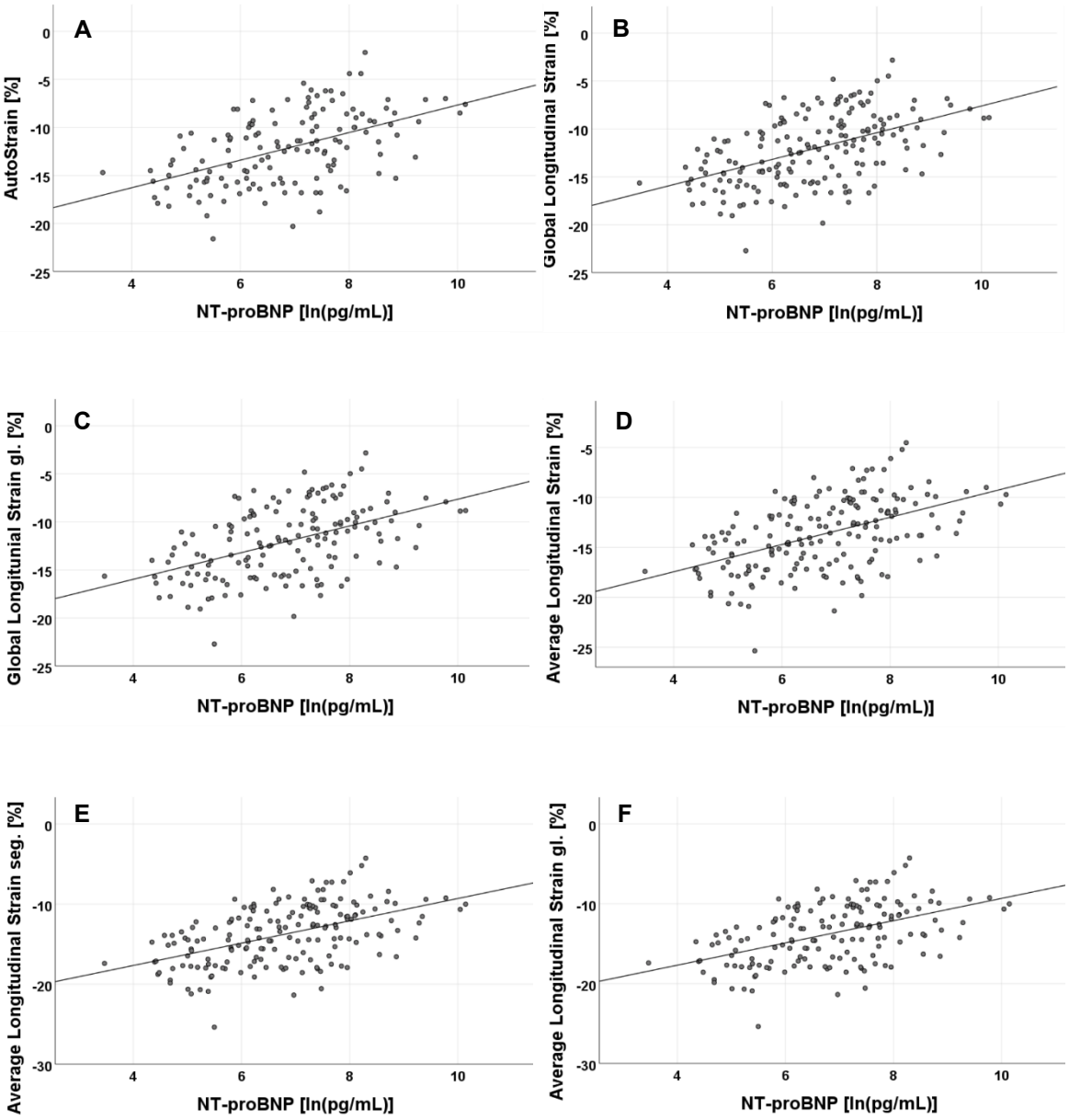

Figure 8: Scatterplot displaying significant correlations and linear regression between different strain measurements and NT-proBNP.
A: AutoStrain and NT-proBNP, r = 0.505
B: Global Longitudinal Strain and NT-proBNP, r = 0.510
C: Global Longitudinal Strain according to current guidelines and NT-proBNP, r = 0.491
D: Average Longitudinal Strain and NT-proBNP, r = 0.512
E: Average Longitudinal Strain (well tracked segments) and NT-proBNP, r = 0.511
F: Average Longitudinal Strain according to current guidelines and NT-proBNP, r = 0.491

Not surprisingly, all average LS parameters showed significantly positive correlation to other strain measurement methods. There was also a significantly positive correlation with NT-proBNP, biplane and triplane EDV, biplane and triplane ESV, and significantly negative correlation to biplane and triplane LVEF, and LVOT-SV. There were no significant correlations to biplane or triplane SV, BMI, GFR or age.

Regression analysis showed significant linear relationships between all three average LS parameters and ln(NT-proBNP) under consideration of the above mentioned confounders (average LS $\beta = 0.620$, $R^2_k = 0.322$; average LS seg. $\beta = 0.614$, $R^2_k = 0.293$; average LS gl. $\beta = 0.626$, $R^2_k = 0.292$; $p < 0.001$ for each).

3.4.4 Strain in Reduced, Mid-range, and Preserved Ejection Fraction

Overall, strain values were significantly higher (less negative) in reduced LVEF in comparison to mid-range LVEF ($p < 0.001$). In view of the small number of cases in HFpEF (biplane n = 3; triplane n = 4), no further statistical analysis was done for this subgroup. Table 6 shows an overview of the different strain measurements in reduced, mid-range, and preserved biplane EF.

4. Discussion

This study observed relations between different strain parameters and common echocardiography measurements in patients with chronic heart failure. LVEF and NT-proBNP represent the most used and important parameters to diagnose and determine the severity of heart failure. The results of this thesis demonstrated that (1) all strain evaluation methods significantly correlated with each other, (2) strain had significant correlation to biplane and triplane assessed LVEF, NT-proBNP, and left ventricular volumes, (3) both assessment methods of LVEF correlated with each other, and with NT-proBNP, and (4) no significant correlation between strain, age, gender, and BMI was observed.

4.1 Traditional Biomarkers in Heart Failure

Natriuretic peptides are the gold-standard biomarkers in determining the diagnosis of heart failure. All major societies, including the European Society of Cardiology, the Heart Failure Association of the ESC, the American Heart Association, the Heart Failure Society of America, and the American College of Cardiology [1,73] recommend the use of NP as one of the initial diagnostic tests, especially in non-acute setting, in their clinical practice guidelines.

They suggest NP plasma concentrations to be used as exclusion markers for suspected HF, as they have an excellent negative predictive value (0.94 – 0.98) with an upper limit for BNP of 35 pg/mL and for NT-proBNP for 125 pg/mL in a non-acute setting. These limits are applicable similarly to HFrEF and HFpEF, although, on average, NP values are lower in HFpEF than in HFrEF [1].

On the other side, patients with HF have considerably higher concentrations, and NP levels do correlate with symptom severity. The International Collaborative of NT-proBNP (ICON) study [74] compared NT-proBNP concentrations in 1256 acutely dyspneic patients, revealing significantly higher plasma concentrations in patients with decompensated HF compared to those without HF (median NT-proBNP concentrations: 4639 vs. 108 pg/mL, $p < 0.001$). In patients with stable CHF NT-proBNP levels are usually lower than in patients with decompensated HF, and

patients with HFrEF show higher NT-proBNP plasma concentrations in comparison to patients with HFmrEF and HFpEF. Pan et. al [75] found a median NT-proBNP of 1065 pg/mL in patients with HFrEF, in patients with HFmrEF NT-proBNP was 607 pg/mL, and in patients with HFpEF NT-proBNP was only slightly elevated with a median of 410 pg/mL found. Similar results were found in this study, though it should be said that our subjects had higher NT-proBNP plasma concentrations, with an overall median of 907 pg/mL and 1279 pg/mL in patients with an LVEF ≤ 40%. However, in the observed cohort of this thesis more patients had AF, mean BMI was higher, and eGFR was more impaired in comparison to subjects observed by Pan et. al, which explains the higher values.

However, the positive predictive value (0.44 – 0.57 [1]) of NP alone is not specific enough to be considered as diagnostic markers since factors like AF and impaired kidney function affect values. However, plasma concentrations exceeding defined cut-off limits are a strong indication for further examination, in particular cardiac imaging [76].

Beyond NT-proBNP, cardiac imaging provides crucial information to establish the diagnosis and to determine risk stratification and appropriate treatment in HF. Indeed, LVEF is the current gold standard for the evaluation of left ventricular systolic function. In clinical practice, the most used evaluation method is the biplane Simpson's LVEF in 2D-echocardiography. In recent years, with technical progress in 3D-echocardiography, triplane LVEF found its way into regular use, as 3-dimensional echocardiography (3DE) does not make geometric presumptions and is therefore less sensitive to errors and foreshortening and provides more adequate values [77].

Bras et. al [78] found a strong correlation between Simpson's biplane and 3DE LVEF (r = 0.813) in patients with a history of myocardial infarction. In this thesis, a similar correlation was found by correlating biplane LVEF to triplane LVEF, with the main difference in measuring triplane LVEF through 2DE. In contrast to 3D triplane LVEF, in 2DE not all measurements are performed during the same cardiac cycle – with the exception of using a multiplane-capable transducer. In return, 2DE offers improved image quality and applicability compared to 3DE. One might expect little

differences between 2D acquired triplane LVEF and 2D biplane EF. The results of this thesis support this suggestion and since there is no previously published data available so far, this thesis generates first evidence in this field.

The main disadvantage of the use of LVEF to estimate global function is its lack in validity to diagnose diastolic dysfunction and subtle systolic dysfunction. LVEF is normal in more than 50% of patients with heart failure (HFpEF), with increasing prevalence [79]. Thus, a normal LVEF doesn't imply a normal left ventricular function, as it is a characteristic of change in ventricular volume and not a measure of contractility. Therefore, the diagnosis of HFpEF remains challenging. Elevated NP plasma concentrations support the diagnosis, but normal levels do not definitively exclude a diagnosis of HFpEF, especially in obese patients [20].

4.1.1 Diagnostic Implications

HF treatment is indicated in all patients with left ventricular dysfunction, systolic or diastolic. However, pharmacological therapy heavily depends on LVEF. Current guideline recommendations on HF medication [1] are subdivided into treatment of HFrEF and treatment for HFpEF, which currently includes patients with HFmrEF. So far, only the treatment of HFrEF could convincingly demonstrate a reduction of morbidity and mortality, unlike treatment in HFmrEF and HFpEF [8,10]. In short, therapy for CHF should be intensified according to guidelines if the LVEF is measured lower than 35 % [1]. NPs may provide additional information and an approach to treatment-guidance. The PROTECT-study [80] showed an improvement in cardiovascular event rates in patients with HFrEF under NT-proBNP-guided therapy, but other studies like the TIME-CHF [81] and the STARBRITE-trial [82] showed no improvement in outcomes or hospitalization rates. However, the latter trials applied slightly different inclusion criteria for LVEF (≤ 45 % vs. ≤ 35 %). Because of this unclear evidence for improvement due to NP-guided therapy, there are currently no specific guideline recommendations and heart failure treatment is strictly guided by LVEF and heart failure symptoms.

4.2 Strain Imaging in Heart Failure

Deformation imaging, especially longitudinal strain, is already known as a reliable and reproducible parameter for the evaluation of left ventricular dysfunction [1,26,28,83]. However, there only is little published data to strain evaluation in heart failure patients, and this thesis findings give further insights into strain values in those patients.

GLS seems to be the most robust parameter and allows the detection of subtle alterations in myocardial mechanics, even despite the absence of left ventricular dilatation and with preserved LVEF. Kraigher-Krainer et. al [54] investigated strain values in 219 HFpEF patients from the PARAMOUNT study compared with a control group (n = 50) and an age- and gender-matched group of patients with hypertensive heart disease without HF (n = 44). Although LVEF did not differ significantly between patients with HFpEF and the normal controls, they found clearly reduced strain values in subjects with HFpEF compared to normal controls and patients with hypertensive heart disease without HF.

Their results may explain the findings of this thesis, as more subjects showed pathological strain values (69.0-85.9%) than pathological LVEF (66.5-72.3%).

Strain showed to be very effective in differentiating between etiologies of myocardial dysfunction. It shows typical patterns in sarcoidosis [84], amyloidosis, hypertrophy in athlete's heart, ischemic CMP, and other causes of myocardial hypertrophy [85]. This may contribute to diagnostics, as increased left ventricular mass is a common nonspecific finding particularly in patients with HFpEF. In this thesis, longitudinal strain also showed stronger correlation to NT-proBNP plasma concentrations in comparison to both biplane and triplane LVEF, especially after adjusting for age, BMI, eGFR, and AF history. Some previously published studies support these findings [86,87], and this relation becomes more important in patients with preserved systolic function, as the correlation between LVEF and NT-proBNP decreases with increasing LVEF, as pictured by De Vecchis et. al [88].

Furthermore, a number of studies revealed strain with a greater prognostic value than LVEF, especially in patients with an LVEF above 45%, in which the reliability of LVEF as an outcome marker is pretty low [89].

Park et. al [90] suggest GLS to be considered as the standard measurement in patients with acute HF, as reduced strain showed significantly higher mortality, whereas LVEF seemed not to be associated with mortality. Sengeløv et. al [91] revealed strain as the sole echocardiographic parameter, that remained an independent predictor of mortality after adjustment for age, sex, BMI, blood lipids, heart rate, mean arterial pressure, ICM, PTCA, CABG, and noninsulin-dependent diabetes mellitus in patients with HFrEF.

Kalam et. al [68] published a large systematic review including 5721 subjects with HF, myocardial infarction, valvular disease, and various cardiac diseases directly compared longitudinal strain against LVEF in predicting major adverse cardiac event. The study revealed strain to have superior prognostic value to LVEF and being associated with better risk stratification.

These data imply that strain imaging should have an impact on strategies of HF prevention and therapeutic guidance given its availability in routine diagnostics.

4.3 Strain Evaluations

This thesis included three different methods for the assessment of left ventricular strain leading to five different strain parameters, as described in the corresponding chapters. All parameters had significant correlations with each other, although average LS seemed to be overall slightly lower (more negative) compared to AutoStrain and GLS. This may be caused by methodological differences, as average LS is calculated as the mean of all analyzed segments so that regional deformation abnormalities, particularly of apical segments, are attenuated when compared to GLS. Moreover, average LS includes only time to peak values, therefore possibly underestimating global impairment. Average segmental strain values also tend to have a higher (inter-vendor-) variability (up to 4.5%), as demonstrated by the European Association of Cardiovascular Imaging and American Society of Echocardiography (EACVI-ASE) Strain Standardization Task Force [92].

Amzulescu et. al [93] compared global and regional strain values in 2DSTE and 2DCMRtag in 136 patients. They found a good agreement between GLS and 2DCMRtag strain, but in comparison GLS provided systematically lower (more negative) values. (- 15 ± 5% vs. - 10 ± 4%) On regional level, average LS values increased from base to apex. This segmental nonuniformity was also found in Bogaert et. al [94] and clarifies the tendency of average LS to overestimate apical deformation. Though the EACVI and ASE originally declared averaged segmental LS as a mathematically equivalent to GLS [30], in recently published data the EACVI-ASE Strain Standardization Task Force [92] recommend GLS for global evaluation in clinical setting and a cautious usage of segmental values, which is supported by this thesis' findings.

Regarding reproducibility and feasibility, GLS seems to be even superior to LVEF, regardless of echocardiographic training. Karlsen et. al [95] demonstrated the superior reproducibility of strain in 47 patients with acute coronary syndrome, who underwent examination by both an experienced physician and a trainee. Both examiners performed evaluation of Simpson's LVEF and GLS. The intra-class correlation coefficient (ICC) for GLS was clearly higher than for LVEF (0.89 vs 0.63). Although the difference between Simpson's LVEF measurements in this thesis was less significant (ICC 0.85), measurements of left ventricular SV showed more discrepant results (ICC 0.75), whereas repeated GLS measurements produced very similar results (ICC 0.99). This is of particular importance since measurement errors of the LVEF may lead to wrong therapy decisions regarding heart failure medication.

4.4 Limitations and Strengths

A major limitation in this thesis was working with a post-processing software. Therefore, if single views were not available or image quality was too low, patients had to be excluded (n = 6). Due to technical problems, retrieval of echocardiography studies failed in 22 patients. Next, for a valid strain assessment through 2D-CPA, TOMTEC recommends a framerate of at least 20 frames/heart cycle, with a maximum of 60 frames/cycle. As this recommended framerate was not available in every patient, 39 datasets were evaluated with suboptimal rates. In the assessment

of AutoStrain time points within the heart cycle are automatically predefined, as the software sets ES and ED, and there is no possibility to manually adapt those. Therefore, with incorrect tracing, patients had to be excluded. Furthermore, 42% of the patients had atrial fibrillation at the time point of the echocardiography. Though the assessment of strain is possible in AF, sinus rhythm would be preferable due to more comparable heart cycles and hemodynamics.

The strength of this thesis is the validation of the reproducibility of included parameters. All patients had performed echocardiography for image acquisition and analysis by an experienced physician, and further analyses for this thesis were done after a relatively short period of training. Though measured left ventricular volumes deviated, both evaluations for biplane LVEF correlated significantly with each other and with triplane LVEF. Two measurement cycles were done for strain, and the results showed a strong correlation. Furthermore, bias was kept small by blinding to underlaying pathologies and performing 2D-CPA blinded to resulting triplane LVEF.

4.5 Conclusion

As rapid technological progress in echocardiography adds a wealth of information to the assessment of left ventricular function, speckle-tracking based deformation imaging can certainly improve diagnostics in patients with expected heart failure. Global longitudinal strain is proved to be a reproducible and feasible deformation parameter and has recently found its way into routine clinical practice. However, sufficient data on the interpretation of strain values in patients with chronic heart failure is still missing.

The findings of this thesis not only revealed strain to be a valid, reproducible, and applicable parameter regardless of echocardiographic training, but also showed that strain could provide important additional data in the diagnosis of HF, and could also ameliorate HF therapy, as it could enable therapeutical intervention in early stages of HF, prior to a stage of decreasing LVEF.

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		NT-proBNP	Biplane EDV	Triplane EDV	Biplane ESV	Triplane ESV	Biplane SV	Triplane SV	LVOT-SV
NT-proBNP	*Coefficient*	-	,317**	,343**	,393**	,412**	,031	-,003	-,208**
	Sig.	-	,000	,000	,000	,000	,698	,967	,007
	N	-	164	177	164	177	164	177	165
Biplane EDV	*Coefficient*	,317**	-	,956**	,967**	,930**	,760**	,617**	-,023
	Sig.	,000	-	,000	,000	,000	,000	,000	,779
	N	164	-	164	164	164	164	164	155
Triplane EDV	*Coefficient*	,343**	,956**	-	,940**	,966**	,690**	,661**	-,041
	Sig.	,000	,000	-	,000	,000	,000	,000	,603
	N	177	164	-	164	177	164	177	165
Biplane ESV	*Coefficient*	,393**	,967**	,940**	-	,967**	,594**	,465**	-,120
	Sig.	,000	,000	,000	-	,000	,000	,000	,136
	N	164	164	164	-	164	164	164	155
Triplane ESV	*Coefficient*	,412**	,930**	,966**	,967**	-	,549**	,469**	-,134
	Sig.	,000	,000	,000	,000	-	,000	,000	,087
	N	177	164	177	164	-	164	177	165
Biplane SV	*Coefficient*	,031	,760**	,690**	,594**	,549**	-	,853**	,228**
	Sig.	,698	,000	,000	,000	,000	-	,000	,004
	N	164	164	164	164	164	-	164	155
Triplane SV	*Coefficient*	-,003	,617**	,661**	,465**	,469**	,853**	-	,214**
	Sig.	,967	,000	,000	,000	,000	,000	-	,006
	N	177	164	177	164	177	164	-	165
LVOT-SV	*Coefficient*	-,208**	-,023	-,041	-,120	-,134	,228**	,214**	-
	Sig.	,007	,779	,603	,136	,087	,004	,006	-
	N	165	155	165	155	165	155	165	-

Appendix table 1: *Overview of correlations between Left Ventricular Volumes. Spearman-Rho correlation.*
*** correlation significant (two-sided) on the level of 0.01*

		Biplane LVEF	Triplane LVEF
NT-proBNP	*Coefficient*	-,402**	-,432**
	Sig.	,000	,000
	N	164	177
Biplane EDV	*Coefficient*	-,539**	-,570**
	Sig.	,000	,000
	N	164	164
Triplane EDV	*Coefficient*	-,567**	-,586**
	Sig.	,000	,000
	N	164	177
Biplane ESV	*Coefficient*	-,721**	-,726**
	Sig.	,000	,000
	N	164	164
Triplane ESV	*Coefficient*	-,726**	-,763**
	Sig.	,000	,000
	N	164	177
Biplane SV	*Coefficient*	,075	-,012
	Sig.	,338	,881
	N	164	164
Triplane SV	*Coefficient*	,116	,156*
	Sig.	,140	,038
	N	164	177
LVOT-SV	*Coefficient*	,331**	,306**
	Sig.	,000	,000
	N	155	165
Biplane LVEF	*Coefficient*	-	,914**
	Sig.	-	,000
	N	-	164
Triplane LVEF	*Coefficient*	,914**	-
	Sig.	,000	-
	N	164	-
BMI	*Coefficient*	-,002	-,016
	Sig.	,982	,830
	N	164	177
eGFR	*Coefficient*	-,050	,025
	Sig.	,529	,741
	N	158	171
Age	*Coefficient*	,017	-,008
	Sig.	,833	,919
	N	164	177

Appendix table 2: *Overview of correlations between biplane and triplane LVEF and different parameters. Spearman-Rho correlation.*
*** correlation significant (two-sided) on the level of 0.01*
** correlation significant (two-sided) on the level of 0.05*

		AutoStrain	GLS	GLS gl.	Average LS	Average LS seg.	Average LS gl.
AutoStrain	*Coefficient*	-	,981**	,981**	,959**	,958**	,958**
	Sig.	-	,000	,000	,000	,000	,000
	N	-	139	139	139	139	139
GLS	*Coefficient*	,981**	-	1,000**	,968**	,966**	,972**
	Sig.	,000	-	,000	,000	,000	,000
	N	139	-	155	177	177	155
GLS gl.	*Coefficient*	,981**	1,000**	-	,972**	,972**	,972**
	Sig.	,000	,000	-	,000	,000	,000
	N	139	155	-	155	155	155
Average LS	*Coefficient*	,959**	,968**	,972**	-	,995**	,998**
	Sig.	,000	,000	,000	-	,000	,000
	N	139	177	155	-	177	155
Average LS seg.	*Coefficient*	,958**	,966**	,972**	,995**	-	1,000**
	Sig.	,000	,000	,000	,000	-	,000
	N	139	177	155	177	-	155
Average LS gl.	*Coefficient*	,958**	,972**	,972**	,998**	1,000**	-
	Sig.	,000	,000	,000	,000	,000	-
	N	139	155	155	155	155	-

Appendix table 3: *Correlations between different strain measurements. Pearson correlation.*
*** correlation significant (two-sided) on the level of 0.01*

		AutoStrain	GLS	GLS gl.	Average LS	Average LS seg.	Average LS gl.
NT-proBNP	*Coefficient*[1]	,505**	,510**	,491**	,512**	,511**	,491**
	Sig.	,000	,000	,000	,000	,000	,000
	N	139	177	155	177	177	155
Biplane EDV	*Coefficient*[1]	,508**	,493**	,522**	,523**	,537**	,545**
	Sig.	,000	,000	,000	,000	,000	,000
	N	139	164	154	164	164	154
Triplane EDV	*Coefficient*[1]	,530**	,497**	,540**	,536**	,546**	,574**
	Sig.	,000	,000	,000	,000	,000	,000
	N	139	177	155	177	177	155
Biplane ESV	*Coefficient*[1]	,652**	,632**	,657**	,664**	,673**	,681**
	Sig.	,000	,000	,000	,000	,000	,000
	N	139	164	154	164	164	154
Triplane ESV	*Coefficient*[1]	,677**	,643**	,676**	,678**	,688**	,709**
	Sig.	,000	,000	,000	,000	,000	,000
	N	139	177	155	177	177	155
Biplane SV	*Coefficient*[2]	-,046	-,029	-,023	-,018	-,003	-,014
	Sig.	,589	,715	,777	,824	,972	,862
	N	139	164	154	164	164	154
Triplane SV	*Coefficient*[2]	-,127	-,124	-,106	-,102	-,093	-,085
	Sig.	,137	,099	,189	,177	,220	,295
	N	139	177	155	177	177	155
LVOT-SV	*Coefficient*[1]	-,310**	-,304**	-,322**	-,326**	-,326**	-,346**
	Sig.	,000	,000	,000	,000	,000	,000
	N	130	165	146	165	165	146
Biplane LVEF	*Coefficient*[1]	-,826**	-,797**	-,816**	-,819**	-,815**	-,836**
	Sig.	,000	,000	,000	,000	,000	,000
	N	139	164	154	164	164	154
Triplane LVEF	*Coefficient*[1]	-,815**	-,823**	-,841**	-,833**	-,838**	-,860**
	Sig.	,000	,000	,000	,000	,000	,000
	N	139	177	155	177	177	155
BMI	*Coefficient*[1]	,024	,027	,058	,035	,025	,056
	Sig.	,779	,725	,470	,647	,738	,492
	N	139	177	155	177	177	155
eGFR	*Coefficient*[2]	-,118	-,134	-,103	-,104	-,108	-,075
	Sig.	,178	,080	,213	,175	,161	,365
	N	133	171	149	171	171	149
Age	*Coefficient*[1]	,000	,018	-,021	-,019	-,014	-,048
	Sig.	1,000	,808	,791	,807	,854	,555
	N	139	177	155	177	177	155

Appendix table 4: *Correlations between strain measurements and different parameters.*
*** correlation significant (two-sided) on the level of 0.01*
[1] Spearman-Rho correlation
[2] Pearson correlation