Dissertation

Postural Cardiovascular Variability: A Perspective on Cerebrovascular Diseases, Sex and Seasons

Submitted by

Irhad Trozic

for the Academic Degree of

Doctor of Medical Science (Dr. scient.med)

at the

Medical University of Graz

Division of Physiology, Otto Loewi Research Centre

under the Supervision of

Assoz. -Prof. Priv.-Doz. Dr.med. Nandu Goswami, PhD.

Univ.-Prof. Dr.med.univ. Franz Fazekas

Dr. Oleksandr Bondarenko

2019

Statutory Declaration

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

Graz, January 2019

Disclosures

I here reveal that parts of the doctoral thesis have been open access published in the "Zeitschrift für Gerontologie und Geriatrie". Consequently, parts of the Doctoral thesis are similar to the published manuscript:

Postural Hemodynamic Parameters in Older Persons Have a Season-Dependency

Irhad Trozic1, Dieter Platzer2, Franz Fazekas3, Alexander I. Bondarenko4, Bianca Brix1, Andreas Rössler1, Nandu Goswami1

1. Irhad Trozic*, (irhad.trozic@medunigraz.at), Gravitational Physiology and Medicine Research Unit, Chair of Physiology, Medical University of Graz, Austria
2. Dieter Platzer*, (dieter.platzer@medunigraz.at), Gottfried Schatz Forschungszentrum, Biophysik, Medical University of Graz, Austria
3. Franz Fazekas, (franz.fazekas@medunigraz.at), Department of Neurology, Medical University of Graz, Austria
4. Alexander I. Bondarenko, (abond01@biph.kiev.ua), Bogomoletz Institute of Physiology of NAS, Kiev, Ukraine
5. Bianca Brix, (bianca.brix@medunigraz.at), Gravitational Physiology and Medicine Research Unit, Chair of Physiology, Medical University of Graz, Austria
6. Andreas Rössler, (andreas.roessler@medunigraz.at), Gravitational Physiology and Medicine Research Unit, Chair of Physiology, Medical University of Graz, Austria
7. Nandu Goswami, (nandu.goswami@medunigraz.at), Gravitational Physiology and Medicine Research Unit, Chair of Physiology, Medical University of Graz, Austria

I confirm that all co-authors have explicitly agreed to the use of their data in my thesis.

Furthermore, results of the Doctoral Thesis were earlier presented on the annual "Stroke and Neurotological disorder" conference in Istanbul, Turkey 2018 and on the "Human Physiology Workshop 2017" in Cologne.

Acknowledgements

Firstly, I must thank my supervisor Prof. Dr. Nandu Goswami for the continuous support, for his patience, and immense knowledge. His guidance helped me in all the time of research and writing of this thesis. Without his help and dedicated involvement in every step throughout the process, this thesis would have never been accomplished.

I would like to thank the rest of my thesis committee: Prof. Dr. Franz Fazekas, and Prof. Dr. Oleksandr Bondarenko, for their insightful comments and encouragement, but also for the hard question which indented me to widen my research from various perspectives. My sincere thanks go to Prof. Dr. Dieter Platzer who provided me with support during the data analysis. Without they precious support it would not be possible to finish my thesis. Also, I would like to express thanks to my Doctoral School "Translational Molecular and Cellular Biosciences" which have provided use with interesting seminars and lectures and for the immense support during my Doctoral study.

Most importantly, none of this could have happened without my family. This dissertation stands as a testament to your unconditional love and encouragement.

Table of Contents

Abbreviations and Definition

BP- Blood Pressure

Bpm- Beats per minute

CO- Cardiac Output

DBP-Diastolic blood pressure

GEE- General estimating equation

HFnu- High frequency of the heart rate variability

HR-Heart rate

HRV-Heart rate variability

HUT-Head-up tilt

LBNP-Lower body negative pressure

LFnu- Low frequency of the heart rate variability

LMM-Linear-mixed model

NaCl-Sodium chloride

NO-Nitric oxide

OH-Orthostatic hypotension

OI-Orthostatic intolerance

SBP- Systolic blood pressure

SV- Stroke Volume

TIA-Transient ischemic attack

List of Figures

List of Tables

Abstract in German

Ziele: Das Ziel dieser Studie war es zu untersuchen, wie sich Jahreszeiten (kältere Jahreszeiten und wärmere Jahreszeiten) auf hämodynamischen Mechanismen und die Herzfrequenzvariabilität während eines Sit-to-stand test bei Patienten mit einem Schlaganfall und Nicht-Schlaganfall-Teilnehmern über Geschlecht und Jahreszeiten auswirken.

Methoden: Mit einem Sit-to-stand test (5 Minuten Sitzen gefolgt von 5 Minuten Stehen) untersuchten wir die kardiovaskulären Aktivitäten bei Patienten mit einem Schlaganfall (n = 16) und Probaten ohne Schlaganfall (n = 25), Alter> 55 Jahre in zwei Jahreszeiten. Wir haben kontinuierlich über einen Task Force Monitor® den systolischen Blutdruck (SBD), den diastolischen Blutdruck (DBD), die Herzfrequenz (HF), den Schlagindex (SI) und den Herzindex (HI) sowie die Herzfrequenzvariabilität (HFV) aufgezeichnet.

Ergebnisse: Während der Ruhephase waren DBD (Delta: +15,1, SE: ± 3,75, [mmHg], p <0,05) und MBD (Delta: +14,35, SE; ± 4,18, [mmHg], p <0,05) in kälteren Monaten signifikant höher als in wärmeren Monaten und SI (Delta: -3,86, SE: ± 1,43, [ml/beat/m2], p <0,05) und HI (Delta: -0,4, SE: ± 0,11, [l/min/m2], p <0,05) waren in kälteren Monaten niedriger als in wärmeren Monaten bei Nicht-Schlaganfall-Teilnehmern. Bei Patienten mit einem Schlaganfall waren während der Ruhephase DBD (Delta: +19,92, SE: ± 8,03, [mmHg], p <0,05) und MBD (Delta: +19,29, SE: ± 8,6, [mmHg], p <0,05) in kälteren Monaten signifikant höher im Vergleich zum wärmeren Monaten und SI (Delta: -5,43, SE: ± 1,96, [ml/beat/m2], p <0,05) waren in kälteren Monaten im Vergleich zu wärmeren Monaten signifikant niedriger. Nach dem Stehen gab es in den wärmeren Monaten eine signifikante Abnahme des SBD (Delta: -16,84, SE: ± 4,38, [mmHg], p <0,05) und in den wärmeren Monaten einen Rückgang des DBD (Delta: -7,8, SE: ± 2,30, [mmHg], p <0,05)) und kälteren Monaten (Delta: -6,73, SE: ± 1,5, [mmHg], p <0,05) bei Nicht-Schlaganfall-Teilnehmern und Abnahme des MBD in wärmeren Monaten (Delta: -12,5, SE: ± 2,8, [mmHg], p <0,05) und kälteren Monaten (Delta: -8,93, SE: ± 1,8, [mmHg], p <0,05) bei Nicht-Schlaganfall-Teilnehmern und in wärmeren Monaten (Delta: -14,54, SE: ± 4,1, [mmHg], p <0,05) bei Patienten mit Schlaganfall. Nach dem Stehen zeigen hämodynamischer Parameter und Variabilität der Herzfrequenz Unterschiede zwischen Männern und Frauen. Bei weiblichen Teilnehmern ohne Schlaganfall war die hohe Frequenz (normalisiert) in wärmeren Monaten niedriger (Delta: - 20,92, SE: ± 1,63, [%],

p <0,05), die niedrige Frequenz (normalisiert) war in wärmeren Monaten höher (Delta: 20,93, SE: ± 1,63, [%], p <0,05). Bei weiblichen Patienten mit einem Schlaganfall war die hohe Frequenz (normalisiert) in kälteren Monaten niedriger (Delta: -13,72, SE: ± 1,61, [%], p <0,05), die niedrige Frequenz (normalisiert) in kälteren Monaten höher (Delta: 17,72, SE: ± 2,370, [%], p <0,05).

Schlussfolgerungen: Erstens zeigt unsere Studie, dass die zwei Gruppen in unsere Studie in vergleichbarer Weise auf orthostatische Belastungen mit einem höheren posturalen Blutdruckabfall in wärmeren Monaten ansprechen. Trotzdem zeigen Patienten ein Jahr nach einem Schlaganfall (leichter Schlaganfall) und ohne Behinderungen keine Anzeichen einer orthostatischen Hypotonie, trotz eines posturalen Blutdruckabfalls in wärmeren Monaten. Zweitens berichteten wir, dass Reaktionen der Herzfrequenzvariabilität auf orthostatische Belastungen Unterschiede zwischen Männern und Frauen zeigen. Die Ergebnisse unserer Studie deuten auf eine Saison und Geschlechtsabhängigkeit der zugrunde liegenden hämodynamischen Mechanismen während einer orthostatischen Belastung hin.

Schlüsselwörter: Schlaganfall, Geschlechtsunterschiede, Jahreszeiten, Haltungsveränderungen, orthostatische Intoleranz; Altern.

Abstract in English

Purpose: The purpose of this thesis was to study how seasons (colder seasons and warmer seasons) affects the responses of hemodynamic mechanisms and heart rate variability during a sit-to-stand test in patients with stroke and participants without a stroke across sex and seasons.

Methods: Participants performed a sit-to-stand test (5 min of sitting followed by 5 min of standing). Via a Task Force Monitor® device we examined cardiovascular responses in patients with a stroke (n= 16) and participants without a stroke (n=25), age >55 years, in two seasons. We continuously recorded via a Task Force Monitor® device beat to beat systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate (HR), stroke index (SI) and cardiac index (CI), and low frequency and high frequency of the heart rate variability (HRV).

Results: We report that during the sitting phase, DBP (delta: +15.1, SE: ±3.75, [mmHg], $p<0.05$) and MBP (delta: +14.35, SE; ±4.18, [mmHg], $p<0.05$) were significantly greater in colder months contrasted to warmer months and SI (delta: -3.86, SE: ±1.43, [ml/beat/m2], $p<0.05$) and CI (delta: -0.4, SE: ±0.11, [l/min/m2], $p<0.05$) were lower in colder months contrasted to warmer months in participants without a stroke. In patients with stroke, we report that during the sitting phase, DBP (delta: +19.92, SE: ±8.03, [mmHg], $p<0.05$) and MBP (delta: +19.29, SE: ±8.6, [mmHg], $p<0.05$) were significantly greater in colder months contrasted to warmer months and SI (delta: -5.43, SE: ±1.96, [ml/beat/m2], $p<0.05$) were significantly lower in colder months contrasted to warmer months. Furthermore, we report that after standing, there was a significant reduction in SBP in warmer months (delta: -16.84, SE: ±4.38, [mmHg], $p<0.05$) and reduction in DBP in warmer months (delta: -7.8, SE: ±2.30, [mmHg], $p<0.05$) and colder months (delta: -6.73, SE: ±1.5, [mmHg], $p<0.05$) in participants without a stroke and decrease in MBP in warmer months (delta: -12.5, SE: ±2.8, [mmHg], $p<0.05$) and colder months (delta: -8.93, SE: ±1.8, [mmHg], $p<0.05$) in participants without a stroke and in warmer months (delta: -14.54, SE: ±4.1, [mmHg], $p<0.05$) in patients with stroke. After standing hemodynamic parameters and heart rate variability responses show differences between males and females. In female participants without a stroke, high frequency (normalized) was lower in warmer months (delta: - 20.92, SE: ± 1.63, [%], $p<0.05$), low frequency (normalized) was higher in warmer months (delta: 20.93, SE: ± 1.63, [%], $p<0.05$) compared to males.

In female patients with a stroke, high frequency (normalized) was lower in colder months (delta: -13.72, SE: ± 1.61, [%], $p<0.05$), and low frequency (normalized) was higher in colder months (delta: 17.72, SE: ± 2.370, [%], $p<0.05$) compared to males.
Conclusions: First, our study shows that the two groups in our study respond comparably to orthostatic loading with greater postural blood pressure decrease in warmer months. Nonetheless, patients one-year after stroke (minor stroke) and with no disabilities demonstrated none of the signs of orthostatic hypotension despite postural blood pressure reduction in warmer months. Second, we reported that heart rate variability responses to orthostatic loading show differences between males and females. The results of our study point for a season and sex dependency of the underlying hemodynamic mechanisms during orthostatic loading.

Key terms: Stroke, sex differences, seasons, postural changes, orthostatic intolerance; ageing.

1 INTRODUCTION

1.1 THE STATE OF THE PROBLEM

Blood pressure variability is associated with development of cardiovascular disorders and mortality. Earlier studies have reported that blood pressure variability rises in older persons and patients with diseases of the nervous system (e.g. stroke, Parkinson's disease) (1, 2). In healthy and young individuals, the cardiovascular system will compensate the pooling of the blood to the lower limbs but with progressing age the baroreceptors become less sensitive to blood pressure changes resulting in inadequate reactions. Irregular reduction of blood pressure during standing is associated with postural instability, loss of consciousness and falls (3). According to various authors falls and fall-related injuries are a main problem in the older populations.

As earlier data showed third of older adults falls each year and 10-20% of falls cause serious injuries. The incidence of falls increases progressive with the advancing age of the persons. Falls can lead to loss of mobility and independence and increase overall mortality in the older population. Alongside the demographical change and the rise of the older population, many studies have expected an increase in the incidence of falls and general cost for the treatment of fall-related injuries also will rise (4). The evidence suggests that there are few factors which increase the risk for falls. First, older age is one of the main risk factors for falls. For older individuals (65- year and over) falls are common with a greater incidence compared to younger persons (5). Second, lower physical strength can increase the incidence for falls in the older population. Last, orthostatic hypotension a major contributor to an increased risk for falls. Orthostatic hypotension stands for a critical decreases of blood pressure and cerebral perfusion (6).

Several authors have defined orthostatic hypotension as a pathological decrease of systolic blood pressure and diastolic blood pressure during 3 minutes of standing. In persons with orthostatic hypotension reduced blood volume will inadequate trigger the autonomic control mechanisms because of reduced baroreceptors sensitivity and/or autonomic dysfunction. If the autonomic control mechanisms are unable to stabilise the cardiovascular system, postural blood pressure will continuously fall which in turn will affect the cerebral blood flow. Therefore, reduced cerebral blood flow will cause dizziness, loss of consciousness and syncope. Syncope is causally linked to the occurrence to falls (7).

They are many explanations why the cardiovascular system in older persons is unable to response effectively to orthostatic loading. Several studies analysed how the cardiovascular system response to orthostatic loading to get a deeper understanding of the mechanisms involved in the blood pressure regulation during standing. In the most studies, researchers continuously investigated postural blood pressure variability via beat-to-beat measurements during an orthostatic test. They are two types of orthostatic test, a passive and active test. In the first place a passive test is conduct via a tilt-table test. The tilt-table test has his advantage into clinical studies with patients who have difficulties to stand. The active tests require that the patients move from a lying/siting to a standing position without a help. The sit-to-stand test is one of the most used active orthostatic tests (8).

Earlier studies reported an interaction between orthostatic hypotension and an increased incidence of falls in older persons. Goh et al (2016) performed case-controlled study with 25 fallers and 25 non-fallers, aged 65 year and over. The subjects of the study conducted an active standing test. The investigators continuously observed blood pressure variability via a beat-to-beat monitoring device. Goh et al. (2016) reported following observation. Older fallers have larger systolic blood pressure variability during standing compared to non-fallers. Since, cerebral blood flow links to the systemic blood pressure, increased blood pressure variability can increase the incidence of postural instability in older persons. Goh et al. (2016) reasoned that baroreflex dysfunction potentially causes falls in older persons (7). A similar study came to the same conclusion. Pasma et al. (2014) performed a cross-sectional study including 207 elderly persons with a mean age of 81.9 years. The authors assessed blood pressure changes during 3 minutes of standing. They measured blood pressure variability intermitted via an automated sphygmomanometer and continues with a digital photoplethysmography. The authors report following results: i) intermittent blood pressure changes did not link to the ability to maintain standing balance, ii) continuous blood pressure variability (blood pressure decreases after 15-60 seconds after orthostatic loading) were linked to the ability to maintain standing balance, iii) orthostatic hypotension detected via continuous blood pressure measurements was linked to the ability to maintain standing balance. The authors concluded that falls likelihood increases in persons with greater postural blood pressure variability (blood pressure decreases from 15-60 seconds after orthostatic loading or standing). Pasma et al. (2014) reasoned that reduced postural blood pressure lead to a cerebral hypoperfusion. Thus reduced cerebral blood flow impaired standing balance (6).

Earlier studies have also analysed how the cardiovascular and cerebrovascular system responses to orthostatic stress in patients with cerebrovascular diseases. Kong et al. (2003) conducted a prospective study with 71 patients with ischemic and hemorrhagic stroke. The patients performed a tilt-table test up to 90 degree. Kong et al. (2003) reported following result. From the entire number of 71 patient with stroke, 37 or 52.1% patients had orthostatic hypotension. Kong et al. (2003) reasoned that orthostatic hypotension in patients with stroke is caused by baroreceptor hyposensitivity and muscle loss as a result of immobilisation (9). Phipps et al. (2012) performed a secondary analysis of medical data from outpatients with stroke. He analysed 116 patients with stroke. The authors concluded that 27% of the patients had orthostatic hypotension. Furthermore, patients with stroke compared to the overall population experience a greater incidence of orthostatic hypotension. Because of the higher incidence of orthostatic hypotension falls are a common medical problem (10).

The external factors also have an impact on the susceptibility to orthostatic hypotension. Temperature variation causes blood pressure variability with higher blood pressure in colder months and lower blood pressure in warmer months. Furthermore, earlier studies did confirm an increased incidence of postural blood pressure decreases or orthostatic hypotension in summer months (5, 11). But regarding patients with cardiovascular diseases, we have identified a lack of studies. There is for almost no studies which has analysed patient with cerebrovascular diseases on seasonal blood pressure variability and how this affects postural blood pressure regulation in warmer months. Therefore, the main aim of the study is to provide new knowledge on the mechanisms of regulation of hemodynamic parameters depending on seasons and sex and reveal seasonal and sex-dependent peculiarities of regulation of hemodynamic in the patients after stroke.

1.2 THE BLOOD PRESSURE HOMEOSTASIS

According to Chopra et al. (2011), an interplay between different physiologically system of the human body (circulatory-cardiovascular system and neuro-endocrine systems) is responsible for the control and maintenances of blood pressure stability (12). There are two mechanisms which regulate local blood flow and that are vasoconstriction and dilatation. Furthermore, blood flow and blood pressure are further determinant through changes in cardiac output. Blood pressure increases/decreases through variations in cardiac output which is equal to the changes in heart rate, stroke volume and resistance. This is the short-term blood pressure control mechanism which is in connections with the baroreceptors and the autonomic nervous system (13).

1.2.1 The autonomic nervous system

The nervous system is divided into the central and the peripheral nervous system, which has the function to control and maintain various physiological systems of the human body (14). It is known that the control of blood pressure regulation and heart function is maintained by the autonomic centres in the medulla oblongata (15). The autonomic nervous system as a part of the peripheral nervous system is responsible, without the voluntary and conscious control of the mind, to keep homeostasis of the cardiovascular, thermoregulatory and other systems. The autonomic nervous system has the function to support homeostasis, regulate heart activity, control pressure in the circulatory system and other function crucial for the functionality of the human body. The autonomic nervous system includes the cerebral cortex, amygdala, stria terminalis hypothalamus, and brainstem centres. Receptor of the afferent pathways arriving to the cranial nerves via the dorsal roots are sensitive to mechanical, chemical, and thermal stimuli. The autonomic nervous system splits into two divisions: the sympathetic division and the parasympathetic division. First, there is the sympathetic part which contributes to the heart activity, blood vessel constriction, and renin production and other autonomic function. Second, the parasympathetic system will in contrast decrease heart activity. Vasodilatation results from reduced sympathetic activity because most vessel of the circulatory system are regulated by the sympathetic activity, during rest and sleep there is a dominance of parasympathetic activity (16, 17).

1.2.2 The short-term blood pressure regulation and the baroreceptor reflexes

Autonomic mechanisms are responsible for the fast responses to an abrupt blood pressure reduction or elevation (18). The baroreceptors are an important part of the fast blood pressure control mechanisms. The baroreceptors cells are located in the main arteries especially in the aorta and carotid artery. The function of the baroreceptors is to control changes in blood pressure and to keep pressure and heart functions at an average level. As Heesch (1999). points out, when arterial pressure becomes increased baroreceptors give afferent signals to the medulla (18). The medulla oblongata is responsible to control and maintain arterial blood pressure (15). According to Chopra et al. (2011), resting arterial blood pressures, represent a resting state and a reference point for the baroreceptor activity. The baroreceptors will act in two diverse ways on the circulatory system, which depend on an elevation or decrease in arteria blood pressure. In the cases that blood pressure elevated, it reduces sympathetic activity to the heart and to the circulatory system which will bring back the arterial blood pressure to a regular level. In contrast, arterial blood pressure is maintained at an average level during a decrease of the blood flow through a discharge of the baroreceptors, this results in an intensified sympathetic activity that constrict the vessels and increases cardiac output (12, 19).

1.2.3 Baroreceptor resetting

Resetting of the baroreceptors refrains to changes in the pressure sensitivity of the baroreceptors. Chopra et al. (2011) writes that resetting of the baroreceptors can be rapid, where the receptors are under the influence of rapid changes of the blood pressure for 20 minutes or fewer or chronic resetting were the changes of the blood pressure stay over 20 minutes. In the first case the shift in pressure threshold is stable for about 30 minutes, the receptors sensitivity does not change and is reversible. In the chronic case, the changes reduced the baroreceptor sensitivity and are permanent (12).

1.2.4 Chemoreceptor reflexes

In the scientific literature described are the chemoreceptors as specialised functional units found in the aorta and arteria carotid (two bodies in the arteria carotid bifurcation and one - three in the aorta). The main function of the cells of the chemoreceptors in the aorta and arteria carotid is to regulate arterial blood pressure in the case of a reduced supply of oxygen to the tissues. They are in a close contact to the arterial blood. The respiratory centre in the medulla is responsible to response to pH changes and to regulate responses during disruptions in the balance between acid and base and an elevated level of carbon dioxide in the arterial blood. Chemoreceptors are sensitive only when the pressure falls below 80 mmHg (12, 20). The arterial pressure rises and goes back to normal as the signals from the chemoreceptors excite the vasomotor centre. The chemoreceptor reflex does not control arterial pressure so well once the arterial pressure is higher than 80 mmHg, it only prevents, in case of lower pressures, a further drop in of the arterial blood pressure (21).

1.2.5 Volume receptor or low-pressure receptors

These receptors are responsible to detect blood volume and blood pressure changes in lower pressure zones of the circulatory system, they are to find in the walls of the two heart atria and the pulmonary arteries. Stretch of these receptors stimulates autonomic responses, in a way like the baroreceptor responses. Starting stimuli by the receptors goes through the cranial nerves towards the hypothalamus where the release of anti-diuretic hormones and renin is modulated (12, 19, 22, 23).

1.2.6 Skeletal muscles

Blood vessels in the entire cardiovascular system become compressed as the skeletal muscles contract. In expectation of exercise the motoric neurons, brain stem and the vasomotor centres are excited. During exercise blood moves throughout the entire circulatory system to the heart and increases the cardiac output which can increase fivefold to sevenfold during heavy exercise. Increased cardiac output results in increased arterial pressure from 130 to 160 mmHg or 30 - 40% and blood flow increases almost twofold (24). The mechanisms by which exercises increase circulation are provided by vasodilation of the blood vessels in the muscle. According to Laughlin (1999), an increase in arterial blood pressure is equivalent to the increase in muscle activity (25). Contraction of the abdominal muscle can increase venous return and cardiac output through compression of the venous reservoirs in the abdomen. The so-called Abdominal compression reflex, which is vital for individuals with paralysed skeletal muscles during hypotensive incidents, make it possible for blood to move from the abdomen to the heart. In a case of blood volume and blood pressure changes venous reservoirs of the abdomen become compressed and blood flows from the abdomen to the heart which then increase the arterial blood pressure (13).

1.3 LONG-TERM BLOOD PRESSURE REGULATION

1.3.1 Renin-angiotensin system

Regulation of blood pressure over an extended period of time is maintained through the renin-angiotensin-aldosterone system, where elimination of renal body fluids in the kidneys has an important role. The renal elimination of fluids is crucial, when blood pressure increases, renal elimination of fluids increases too and as a result, blood volume decreases, cardiac output reduces, and the arterial blood pressure drops. Several humoral factors, hormones and sympathetic renal nerves run this system. Paul et al. (2006), state that through a formation of angiotensinogen through renin into angiotensin, renin-angiotensin-aldosterone system regulates the stability of arterial blood pressure and physiological sodium level (26).

Hromones of the renin-angiotensin-aldosterone system are:

- Synthesized renin (adrenal gland, brain, heart, vascular and visceral tissue), after being collected in the juxtaglomerular cells is released inside the renal and systemic circulation. The secretion of renin is stimulated though variations in renal baroreceptor pressure and variations in Sodium chloride (NaCl) concentration, stimulation of sympathetic nerve activity and increased angiotensinogen II activity (21, 27).
- Angiotensinogen is produced through the liver and an elevation in angiotensinogen level is related to the occurrence of hypertension (27). Angiotensin II is formed by hydrolysing inactive Angiotensin I through actions of Angiotensin-converting enzyme, localized in the endothelial, epithelial and neuroepithelial cells. Angiotensin-converting enzyme also metabolizes vasodilator peptides bradykinin and kallidin and can increase vasoconstriction and decrease vasodilation (28).
- Synthesized in the kidney Angiotensin II activity is linked to the release of aldosterone and catecholamines, raises the sympathetic activity and vasoconstriction. Occurrence of hypertension and renal damage is related to an inappropriate Angiotensin II activity. Locally produced Angiotensin (II) might contribute to tissue injury and the pathogenesis of hypertension and renal injury (27).

- The major function of aldosterone, which is released through a stimulation by angiotensin from the adrenal cortex is to induce vasoconstriction by acting on vascular smooth muscle cells (26, 27). Aldosterone a mineralocorticoid is synthesized in the cortex of the adrenal gland. Aldosterone regulate glucose metabolism and salt excretion, concentrations of electrolytes in the blood with a reabsorption of NaCl, Hydrogen carbonate ions in the kidney (12, 29).

1.3.2 The importance of hormones in blood pressure regulation

Blood pressure control depends on the activity of specific hormones. It is known that some hormones directly influence the hemodynamic control of blood pressure. For example: i) nitric oxide (NO), produced by endothelial cells reduces blood pressure and a decreased activity of NO will lead to hypertension (12); ii) endothelin and endothelin 1 (highly effective vasoconstrictor functions) are produced in the endothelium which stimulate contraction of smooth muscle cells (12, 30); iii) stimulated by thirst and decreased blood pressure Vasopressin is synthesised in the hypothalamus and then stored in the pituitary gland. The main purpose of Vasopressin is to increase water reabsorption in the kidney and to increase blood pressure (12, 29, 31); iv) adrenomedullin that can be find in the adrenal medulla and phenochromocytoma tissue is associated with occurrence of hypertension (12); v) as an endocrine organ, adipose tissue produces vasorelaxing hormones adipokines and adiponectin which can increase NO production and decreased adiponectin levels and lead to endothelial dysfunction (12); vi) produced in adipocytes Leptin role is to elevate the pressure in the blood vessels, increase the heart activity, and intensify sympathetic activity (12, 29).

1.4 AUTONOMIC BLOOD PRESSURE VARIABILITY

1.4.1 Respiratory waves

Malpas (2002) noted that the "respiratory oscillation" in blood pressure of 4-6 mmHg results from disturbed venous return and cardiac output by oscillation of the pressure in the chest cavity during breathing. The oscillation of the heart rate results from the baroreceptor activity that controls the heart activity and responds to blood pressure changes (28). Mechanisms responsible for these oscillations will be briefly discussed: i) through every respiratory cycle, signals related to breathing in the respiratory centre of the medulla spread to the vasomotor centre; ii) during the respiratory cycle pressure in the chest cavity decreases and as a result vasodilatation of blood vessels occurs, blood volume in the left side of the heart becomes smaller, and arterial blood pressure drops; iii) throughout the respiration process changes in the pressure of the vessels in the chest cavity can provoke atrial stretch. Normal respiration typically elevates the arterial pressure at the beginning of expiration and decreases it throughout the remaining part of the respiratory cycle. With deep respiration, in every respiratory cycle the blood pressure elevated and lowered by 20 mmHg (13, 32, 33).

1.4.2 Mayer waves

According to Julien (2006), reactions to cardiovascular changes and fluctuation of the sympathetic control of the vascular smooth musculature causes the so called “Mayer waves”, which are detectable as the arterial blood pressure oscillates slower than the respiration rate (frequency of 0.1 Hz). It does not relate Mayer waves to age and sex or the position of the body. The degree of the oscillation of the Mayer waves is influenced by the intensity of the cardiovascular and baroreflex changes. Mayer waves are responsible to causes the release of NO in the endothelium (34, 35). Mayer waves typically intensify during states of sympathetic activation. The baroreceptor reflex is the main cause of Mayer waves. As blood pressure increases and triggers the baroreceptors, the sympathetic nervous system becomes inhibited and within a few seconds the pressure drops. Then, lowered pressure decreases the baroreceptor stimulation and reactivates the vasomotor centre. After that, the pressure increases again. The response is delayed for a few seconds after which the pressure starts another cycle which repeats the oscillation continually. Chemoreceptor reflex oscillation produces the Mayer waves, too. It typically oscillates when the baroreceptor reflex oscillates and is responsible for vasomotor waves at arterial pressures between 40- and 80-mmHg (13).

1.5 SEX DIFFERENCES IN BLOOD PRESSURE REGULATION

Sex differences in cardiovascular physiology result from anatomical, neuronal and hormonal differences between the sexes. Women have anatomically a smaller heart, less blood volume and lower blood pressure compared to men. In women the parasympathetic nervous system control of the heart prevails while in men the sympathetic nervous system control of the blood pressure regulation is predominant (36, 37). The incidence of cardiovascular diseases is higher in men compared to women at the same age. Reckelhoff et al. (2001) proposed that sex-specific characteristics in the regulation of the cardiovascular system and the protection against cardiovascular diseases in women can be explained by the activity of the sex hormones oestrogen, progesterone (38). Oestrogen is a potent vasodilator-agent and prevents vasoconstriction of cerebral arteries caused by beat-amyloid peptides (39). Furthermore, the renin-angiotensin system which handles the blood pressure regulation over a period, is differently activated in men and women.

According to Kolar and Ostadal (2013), women are protected against angiotensin II mediated hypertension because of the depressor effects of oestrogen (40). Also, sex hormones in women are responsible for the different responses to sodium intake (38). In postmenopausal women the activity of renin is enhanced (41). It is reported that blood pressure increases in women following the menopause and after the menopause it become similar and over the 60-year of age the incidence become higher compared to men because of the reduction in sex hormones. Merz et al. (2016) said that young women have a better vascular function compared to men but through the menopausal induced vascular changes women in the later decades experience a higher incidence of vascular dysfunction and stiffening than premenopausal women. These changes are responsible for the higher incidence of hypertension in postmenopausal women (42).

1.6 BLOOD PRESSURE REGULATION AND AGEING

Aging is characterised by physiological changes that affect vascular functions. According to earlier authors changes in arterial stiffness are associated with age-induced increase in arterial blood pressure. In elderly over 50 years of age, increased vascular resistance causes an increase in diastolic blood pressure. As Pinto (2007) shows, "decreased baroreceptor sensitivity, increased responsiveness to sympathetic nervous system stimuli, altered renal and sodium metabolism and an altered renin-aldosterone relationship" are factors that cause an increase in blood pressure in the elderly population (43). According to Fisher, ageing is associated with delayed maximum cardiovascular responses to acute carotid baroreceptor loading. Gordan et al. (2015) also suggest that slow cardiovascular responses to carotid hypertension in older individuals is a consequence of age-related reductions in resting cardiac parasympathetic tone (16).

O'Mahony et al. (2000) claim that decreased baroreceptor stretches cause "reduced reflex changes in heart rate and sympathetic vascular tone for each variation in systolic blood pressure". Also, because of ageing being related to increased central brainstem baroreflex gain, increased arterial stiffness causes the decline in baroreceptor sensitivity (44). Ageing and atherosclerosis change baroreceptors function. With the development of an atherosclerotic plaque, the vascular wall stiffens, and this causes a decreased deformation of the receptors in response to pressure changes. Thus, efferent signalling is reduced while sympathetic outflow is increased. Furthermore, changes in the heart rate because of altered baroreceptor functions are also associated with progressing age.

According to Kougias et al. (2010) ageing causes a decline in the heart rate control which depends on the baroreceptors, but regular exercise can reverse it. Moreover, research has shown that hypertension and aging in humans alters the baroreceptor reflex control of heart activity in response to vasoactive agents (19). It is reported by Edgell et al. (2012) that women after menopause have a reduced control of the heart, decreased baroreceptor sensitivity, increase sympathetic activity and decreased parasympathetic activity (45). Parker et al. (2010) reported that muscle sympathetic activity increases in aging more in women compared to men. Also, older women have a higher incidence of hypertension (because of reduced baroreflex sensitivity), excite carotid artery stiffens, and blood pressure increases (46).

1.7 ORTHOSTASIS

1.7.1 Overview

As defined by Chopra et al. (2011), orthostasis represent a movement from a postural horizontal position to a vertical position of the human body. This movement shifts blood volume and causes the activation of the circulation controlling mechanisms (12). The upright position of the body causes a movement of the blood to the lower body. As blood moves to the lower limbs, baroreceptors will detect changes in blood pressure, and this will activate autonomic centres in the brain. Through modulation of the heart rate and vascular peripheral resistance autonomic centres will react to compensate these changes and to keep a normal blood pressure. Skeletal muscles in the lower limbs are a crucial factor against blood pressure changes. Through the activity of the sympathetic nervous system, neuropeptides and the hormone of the adrenal medulla norepinephrine blood pressure is stabilized by modulating vascular stiffens, heart rate and by controlling endocrine and renal activity (30).

1.7.2 Orthostatic intolerance

The lack of ability to sustain the standing position because of cognitive, visual and pain symptoms is called orthostatic intolerance (OI) (30). The most common types of OI are:

- orthostatic hypotension,
- postural tachycardia syndrome and
- vasovagal syncope.

1.7.3 Orthostatic hypotension

According to Gupta et al. (2007), postural blood pressure decreases during three minutes of standing that cause characteristic symptoms of faintness and syncope is called orthostatic hypotension. Orthostatic hypotension is a condition by which the systolic/diastolic blood pressure falls by 20/10 mmHg during at least 3 minutes of standing or during 60° of head-up tilt (HUT). In elderly people the following symptoms are more common: disturbed speech, visual changes, falls, confusion, and impaired cognition (47). This condition is mostly associated with syncope, falls, fall-related injuries and mortality. The prevalence of orthostatic hypotension increases with age, 20% (>65 years) or 30% (>75 years) in community dwelling individuals resident at home. In elderly patients resident in nursing homes, orthostatic hypotension occurs oftener. The main causes of orthostatic hypotension are: a) pathological causes (adrenal failure, dehydration, myocardial ischemia); b) age-related causes that affect the cardiovascular and autonomic control mechanisms for blood pressure regulation (47).

According to Takahashi et al. (2015) analysing 212 men and 303 women, from 35 to 75 years of age during postural changes, vascular stiffness is potentially a key factor which contributes to the increased occurrence of orthostatic hypotension in the elderly population. Furthermore, Takahashi et al. (2015) concluded that orthostatic hypotension can be an indicator of individual susceptibility for developing cardiovascular diseases (48). According to Gupta et al. (2007) the treatment of orthostatic hypotension involves nonpharmacological intervention (reduction of antihypertensive medication during summer), and pharmacological interventions (fludrocortisone) (47).

1.7.4 Postural tachycardia syndrome

According to Sheldon et al. (2015), the term postural tachycardia syndrome refers to a disorder characterised by an increase of the heart rate by 30 to 40 beats per minute (greater in the morning than in the evening), without the presence of orthostatic hypotension. Furthermore, postural tachycardia syndrome is associated with the occurrence of faintness or pre-syncope in some persons. The cause of postural tachycardia syndrome is a failure of the autonomic nervous system (reduction of the parasympathetic control of the heart) which in a healthy individual slows down the heart activity. Symptoms of postural tachycardia syndrome are light-headedness, palpitations, tremor, generalized weakness, blurred vision, exercise intolerance, and fatigue. The prevalence of postural tachycardia syndrome is 0.2%, between 15 and 25 years, and more frequent in women (49).

1.7.5 Vasovagal syncope

Previously it has been noted that syncope is as a condition, caused by a deficiency of cerebral perfusion (50% loss of blood volume and oxygen) that is characterized by a prompt loss of awareness. The incidence of syncope during the lifetime is 40% and half presenting during adolescence. Causes for syncope are hypotension and transient ischemic attack (TIA) (30). Sheldon et al. (2015) note that syncope occurs during the transition to an upright position of the body or with stress (emotional). Vasovagal syncope is common in older persons after the 60-year of age (women 42%, men 32%). The first occurrence of syncope is reported to be at around the 14-years of age (49). According to Edvardsson et al. (2014) syncope is more frequent in patients over 65-year of age with no differences between men and women. Nevertheless, Edvardsson et al. (2014) stated that, in their study with five hundred seventy patients (306 women and 264 men), women experienced more often a trauma by syncope than men (41% vs 30%) (50).

1.8 SEX-SPECIFIC DIFFERENCES IN ORTHOSTATIC (IN)TOLERANCE

Sex-based differences in orthostatic tolerance and blood pressure regulation are well reported (51). Previously, authors have noted that premenopausal women have lower orthostatic tolerance and experience more orthostatic hypotension and syncope than men of the same age but after menopause these differences disappear, and women will have the same incidence of orthostatic hypotension and syncope as in men. The main sex-based differences at rest are that in women parasympathetic activity is enhanced, they have a smaller heart that is less distensible, reduced blood volume, pressure and stroke volume compared to men. Contrary, predominance of the sympathetic nervous system control is evident in men (36, 37).

Previously, it was reported that during orthostatic stress, women responded primarily with a reduced stroke volume and elevated heart rate. Contrary, men responded to orthostatic stress with increased peripheral vascular resistance (51). In a study by Fu et al. (2004), with 13 men and 10 women, during a Lower body negative pressure (LBNP) test, is reported that LBNP tolerance was reduced in women and that the reason behind this lies in a reduced stroke volume and cardiac filling (52). Some authors reported that hormones are key factors responsible for sex differences in orthostatic tolerance. Wenner et al. (2013) studied women with lower orthostatic tolerance and with higher orthostatic tolerance during a LBNP tests. In this study, lower orthostatic tolerance in women resulted from higher oestradiol sensitivity and lower progesterone sensitivity (51). Other authors have note that responsible for the orthostatic sex-based differences are to find in different responses of the autonomic mechanisms. In a study by Reulecke et al. (2016) with 12 men and 12 women, is reported that during a head-up tilt (HUT), sympathetic activity was enhanced, and parasympathetic activity decreased against an orthostatic stress in men but not in women, but all other hemodynamic variables show none sex differences during an orthostatic challenge (36). It is reported that after menopause women respond differently to orthostatic stress compared to younger women. Edgell et al. (2012) reported that younger women respond to orthostatic stress with greater decreases in stroke volume and greater elevation in heart rate compared to postmenopausal women and men. Also, according to Edgel et al. (2012), after menopause venous return is better maintained in women (45).

1.9 ORTHOSTATIC (IN)TOLERANCE AND THE RELATION TO FALLS IN OLDER PERSONS

Orthostatic intolerance is the main cause of falls and falls-leaded injuries in older people. Well known is that the incidence of orthostatic intolerance and falls are increasing with progressing age and the most vulnerable groups are older adults (8). Orthostatic intolerance refers to conditions that occur during standing and are reversed by lying down. The most mentioned causes of orthostatic intolerance and syncope are conditions in which the blood pressure recovery to orthostasis is delayed. According to Finucane et al. (2017), in older individuals blood pressure stabilization shows impairments after standing because stabilizations of blood pressure takes over 30 seconds compared to younger ones (53). In the most cases orthostatic intolerance and syncope is caused by orthostatic hypotension (54, 55). As previously stated, orthostatic hypotension is a condition by which the systolic/diastolic blood pressure falls by 20/10 mmHg during at least 3 minutes of standing or during 60° of HUT. But it was proposed that only systolic blood pressure should be considered because in 95% of people with orthostatic hypotension systolic blood pressure was reduced (56). Another condition like orthostatic hypotension is "delayed blood pressure recovery" (53). Both conditions, orthostatic hypotension and "delayed recovery of orthostatic blood pressure", are associated with orthostatic intolerance, syncope and falls (57). The main causes of orthostatic hypotension are to find in an impaired circulatory system because of a reduced blood volume or decreased vasoconstriction because of an impairment of the autonomic control mechanisms (57). Takahashi et al. (2015) proposed that arterial stiffness is another main cause of orthostatic hypotension (48).

According to Pasma et al. (2014), reduction in blood pressure during standing and orthostatic hypotension are linked to a reduced ability of older people to standing balance which in turn can cause falls (6). Finucane et al. (2017) previously reports that orthostatic hypotension and related conditions are related to falls and falls-related injuries. (53). Also, impaired orthostatic blood pressure responses and related hypotensive disorders are important clinically which shows an individual's predisposition for syncope and unexplained falls. In the last decades we witness the increasing number in older persons over 65 years of age. Aging is characterising by physiological changes that worsen the autonomic control mechanisms that are needed to support normal cerebral blood flow and

postural stability during standing. Postural instability and falls are the primary cause of injuries, that will have required hospitalisation or rehabilitation care, in older persons (3, 58). Pasma et al. (2014) stated that patients that experience blood pressure reduction during standing will have reduced standing stability (6). Goh et al. (2016), conducted a study with 25 fallers and 25 non-fallers. The author reported that falls in older individuals are linked to an impaired baroreflex response, and that older fallers have a larger increase in a fluctuation in systolic blood pressure during standing compared to non-fallers. Furthermore, this changes in blood pressure are linked to posture instability in these individuals (7).

1.10 SEASONAL VARIABILITY AND ORTHOSTATIC (IN)TOLERANCE

Earlier studies have reported that the autonomic nervous system is influenced by the exposure temperature. Also, it is well known that blood pressure is higher in winter months than in summer (blood pressure decreases with increasing temperature) (59-62). According to various authors the proposed causes are: 1) the activation of the sympathetic nervous system by catecholamines (secretion increases by cold temperatures), 2) influences on vascular functions (cold alters endothelial function, NO increases with elevated temperature) (60-62). According to Fares (2013), there are influences of vitamin D, and hormones (Vasopressin, norepinephrine, epinephrine, angiotensin II, aldosterone and catecholamine) on seasonal blood pressure variability. Vitamin D increases during summer and decreases in autumn and winter. Evidences suggest that hormones are important for the understanding of seasonal variation in blood pressure. The following hormones were shown to be involved in seasonal variability: 1) excretion of catecholamines and sodium is significantly higher in winter than in summer (31, 61); 2) plasma vasopressin reduces on cold air exposure; 3) plasma aldosterone, norepinephrine, plasma epinephrine significantly increases from summer to winter (31); 4) endothelin-1 with low values in January and peak values in July (31, 63). Authors have reported an age- dependent difference in seasonal blood pressure. Brennan et al. (1982) reported in his study with 17 000 men and women with mild hypertension, a higher blood pressure in winter than in summer, and greater values in older persons than in younger persons (64, 65). Radak et al. (2016) and Weiss et at. (2006) have reported that orthostatic blood pressure drop was greater in the morning in summer than in winter, and orthostatic hypotension is higher in summer (64%) than in winter. Some risk factors that are predisposing to stroke and TIA are greater in winter than in summer (60, 62). Weiss et. al. (2006) concluded that the seasonal variation in orthostatic blood pressure is caused by 1) hypovolemia due to excess sweating; 2) salt and fluid loss; and 2) peripheral vasodilatation in response to high ambient temperature (62).

1.11 STROKE

1.11.1 Overview

According to Chen et al. (2016), Cardiovascular diseases, including stroke, are a major healthcare issue, and between 2010-2030 will cause a total direct medical cost from 273 to 818 billion dollars in the USA. Among well-known risk factors for stroke are hypertension and diabetes (uncontrolled diabetes) (66, 67). Hypertension and elevated blood pressure (especially systolic blood pressure) in persons over the 65-year of age, is a significant pre-condition that can increase the risk for cerebrovascular diseases (68). High blood pressure after acute stroke is common. Approximately 75% post-stroke patients have high blood pressure and in 40% cases the high blood pressure stay high after the first week (69). Panayiotou et al. (1999) reported that changes in blood pressure during postural changes occur one or three weeks after stroke (70). Gibson et al. (2013) divided stroke into ischemic events (85%) and cerebral haemorrhages. The main cause of ischemic stroke is a deficiency of optimal blood flow to the brain because of thrombotic or embolic occlusion of cerebral vessels (71). The primary clinical features of stroke are abrupt onset focal neurologic deficit (except focal haemorrhage). According to Gibson et al. (2013), "symptoms of ischemic stroke are: aphasia, dis-coordination, dysarthria, diplopia, facial weakness, hemiparesis, visual disturbance, and vertigo, light-headedness, mental status change, headache, and other neurological or non-neurological symptoms". Women present more non-specific (pain or altered mental status) and diffuse symptoms (disorientation, generalized weakness, fatigue and mental status change). Contrary, in men there is a dominance of focal neurological signs (sensory defects, ataxia, and diplopia) (71).

Chen et al. (2016), noted that daily life routine has a major impact on the occurrence of stroke. Persons with diabetes, hypertension and lack of daily activity have a higher risk for developing stroke (67). Stroke is a common pathological condition among elderly people after the 55-year of age, and more common among men (72). According to Gibson et al. (2013) there is a sex difference in the relation to stroke. Women before the onset of the menopause have a lower incidence of stroke because of the protective effect of female sex hormones. The prognosis after ischemic stroke is poorer in women compared to men. Women after the onset of stroke have an increased risk to become depressed, experience more disability and the rate of mortality is greater compared to men (71). The mortality

rate after 30 days of stroke is 28% (ischemic stroke 19%), and after 1-year the survival rate is 77%. The prognosis and outcome differ from person to person and is influenced by the difficulty and complication of the post-stroke condition and on the pre-stroke health status of patients. To maintain a normal blood circulation and tissue functions should be the therapy goal in acute stage of the diseases (73). Bansal et al. (2013) note that after acute cerebral ischemia, supply of oxygen to the tissue is deficient and because of this it is important to sustain a normal supply of oxygen to the damaged tissue through administration of oxygen supplements. Also, antihypertensive agents should be considered, because 24-48 hours after the onset of stroke the blood pressure increases. Hypoglycaemia in post-stroke survivors is associated with poor outcome and can cause focal neurological signs that mimic stroke and can lead to brain injury, the normalization of serum glucose is important. Also increased body temperature is associated with poor outcome and maintain normothermia can improve the outcome of patients (74, 75).

1.11.2 Orthostatic intolerance in post-stroke patients

After stroke occurs, patients often have reductions in blood pressure upon standing. This reduction can lead to serious blood flow reduction to the brain. Condition like orthostatic hypotension and falls occur because of reduced cerebral blood flow. Reported is by Kong et al. (2003) and Robinson et al. (1995) that in acute post-stroke patients orthostatic hypotension is common compared to healthy older individuals. Post-stroke survivors have a predisposition to orthostatic hypotension because of higher resting blood pressure, autonomic dysfunction (sympathetic hyperfunction and parasympathetic hypofunction), and impairment baroreflex responses. Sudden falls are causal linked to orthostatic hypotension. In post-stroke patients sudden falls are common compared to healthy older individuals. The incidence of falls in post-stroke patient is highest when patients returns home. Patient more often falls indoor and during changes from a sitting to a standing position. Falls increases risks for further injuries and hospitalizations. Reported is that orthostatic hypotension has potential predecessor and marker role for stroke. Clinical emphasizes the importance of detecting such changes in post-stroke patients but also in healthy individuals (9, 76).

2 AIMS AND OBJECTIVES

The **main aim** of the study is to **provide new knowledge on the mechanisms of regulation of hemodynamic parameters depending on seasons and sex and reveal seasonal and sex-dependent peculiarities of regulation of hemodynamic in after-stroke patients to optimize care/treatment protocols of after-stroke patients.** To this aim we analysed:

- baseline hemodynamic parameters and heart rate variability differences between non-stroke participants and stroke patients and males and females across two seasons;
- postural hemodynamic parameter and heart rate variability changes in non-stroke participants and stroke patients across two seasons;
- postural hemodynamic and heart rate variability changes in males and females in the non-stroke and stroke group across two seasons;
- differences in postural blood pressure changes across two seasons.

We have hypothesized that *baseline hemodynamic parameters and heart rate variability will show significant differences in patients with stroke and participants without stroke across sex and seasons,* and *hemodynamic and heart rate responses to orthostatic stress induced by a sit-to-stand test will show significant differences between patients with stroke and participants without stroke across sex and seasons*.

3 METHODOLOGY

3.1 LITERATURE SEARCH

We identify relevant publication by searching through Google Scholar, PubMed and Web of Science. Our search terms include (blood pressure variability AND sex AND age AND stroke AND seasons). The search was filtered only for the period of 2003 to 2017. Also, we performed a manual search for relevant articles of bibliographies libraries. We limited searches to studies on humans and in English language. Included were original research, randomised and non-randomised controlled trials, systemic reviews that examined the effects of sex, age, posture and seasons on the cardiovascular system and the autonomic system, among healthy subjects and stroke patients. Searches were conducted through 2016-2018. We first checked abstracts for completeness and accuracy. We specified standards by which we researched abstracts and full-papers for our literature review. We extracted and interpret data relating to: study evidence, observation period, study design, sample size, outcome, study population, and result of the study (77).

3.2 SIT-TO-STAND PROTOCOL

In this section we will describe some aspects of the methodical procedure. In the neurology department of Graz, we performed a prospective study on 41 subjects (Stroke: n=16, Control: n=25). The mean age of stroke patients was 65.81 ± 1.85, and healthy controls 63.72 ± 1.39-year-old. Men are more present in the stroke group 11 (69%). For the purpose to eliminate confounding variables the participants were at the same age, with no difference in height and weight (**Table 1.**) (78).

Table 1. Population characteristics of the studied groups (78).

Populations characteristics	Stoke (n=16)	Non-stroke (n=25)	Sig.
Males (%)	11 (69)	11 (44)	
Age (yrs)	65.81 ± 1.85	63.72 ± 1.39	p=0.371
Height (cm)	173.5 ± 2.22	170.48 ± 1.8	p=0.298
Weight (kg)	83.5 ± 4.09	78.44 ± 3.24	P=0.340
Anti-diabetic medication			
Biguanide	2 (12.5%)	-	N.f.
Antihypertensive medication			
ACE-inhibitor	6 (37.5%)	1 (4%)	N.f.
β1-selective beta blockers	2 (12.5%)	2 (8%)	N.f.
Angiotensin II receptor antagonists	1 (6.25%)	2 (8%)	N.f.
Thiazide	2 (12.5%)	-	N.f.
Calcium channel blockers	2 (12.5%)	-	N.f.

In this study included are stroke patients (one-year survivors), with mild to moderate ischemic stroke. As a control group were included age-matched healthy persons without a history of stroke or any other pathological condition. Participants were excluded if they had coexisting neurological illnesses (epilepsy, dementia, Parkinson's disease), and intracranial vessel stenosis. Also, participants were told to abstain 24 hours before the measurements from consuming coffee and/or nicotine (78).

Table 2. Characteristics of the patients with a stroke (78).

Stroke characteristics	
Stroke aetiology	
Large vessel disease	17%
Cardio-embolic source	42%
Cryptogenic stroke	42%
Initial NIHSS (at hospitalization)	
Non-stroke symptoms (score: 0)	33%
Minor stroke (score: 1-4)	67%
Baseline NIHSS (at examination)	
Non-stroke symptoms (score: 0)	58%
Minor stroke (score: 1-4)	42%
Disability (Modified Rankin Scale)	
No symptoms after stroke (score: 0)	67%
No significant disability after stroke (score: 1)	33%

Table 3. Vascular risk factors in the patients with stroke and participants without stroke (78).

Vascular risk factors	Stoke (n=16)	Non-stroke (n=25)
Atrial fibrillation	1 (6.25%)	-
Peripheral arterial disease	2 (12.5%)	-
Coronary heart disease	2 (12.5%)	-
Nicotine abuse	2 (12.5%)	1 (4%)
Obesity	1 (6.25%)	-
Arterial hypertension	10 (62.5%)	2 (8%)
Dyslipidemia	8 (50%)	2 (8%)
Diabetes mellitus	2 (12.5%)	-

The experimental protocol started after participant arrived between 9:00AM to 11:00AM in our laboratory. We asked the participants to remove they clothe and seat down on a chair. We placed electrodes on specific parts of the body and then started the recording the hemodynamic parameters. We used a finger plethysmograph and an upper arm sphygmomanometer to measure the hemodynamic responses. After the participant sat down, we placed the finger-plethysmograph cuff on the middle finger on the right arm at the heart level and the upper arm sphygmomanometer on the left arm. A Task Force Monitor ® (TFM, CNSystems, Graz, Austria) recorded the hemodynamic and heart rate variability parameters (78). The subjects remained motionless for 5 min in a sitting position. After the first 5 min of sitting, we asked the participants to stand up. Upon completion of the 5 min of standing, we helped the participants to the seated position. The responses were recorded again for 5 min. All reasonable precautions such as help during standing and medical personnel availability were in place in case of collapse or syncope. We repeated the protocol in two different seasons, winter (November-April) and summer (May-October). The Ethics Committee of the Medical University of Graz approved the study. We obtained informed consent from all participating subjects in this study. Basic neurological assessment was provided for the participating subjects (clinical neurological examination; extra- and intracranial duplex sonography) and all subjects received medical clearance to participate prior to performing a single sit-to-stand test (78).

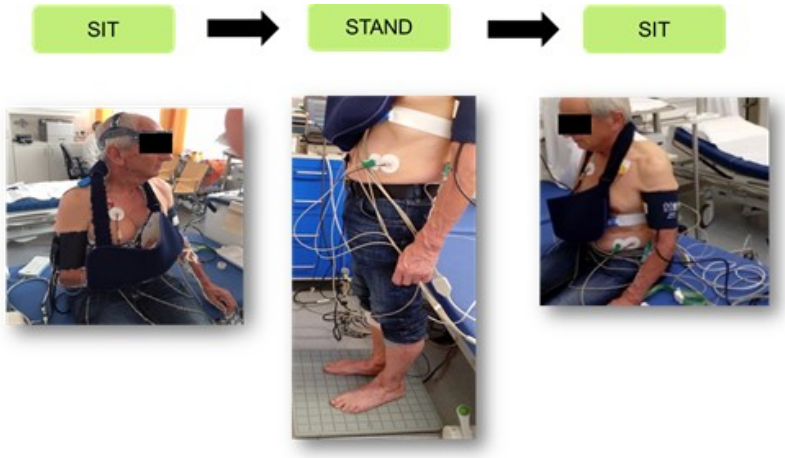

Figure 1. In the figure above seen is a patient with a stroke. The patients performed a sit-to-stand manoeuvre. We have placed the electrodes on the patient. After the electrodes were placed, we continuously recorded hemodynamic responses during 5 minutes of sitting and 5 minutes of standing (79).

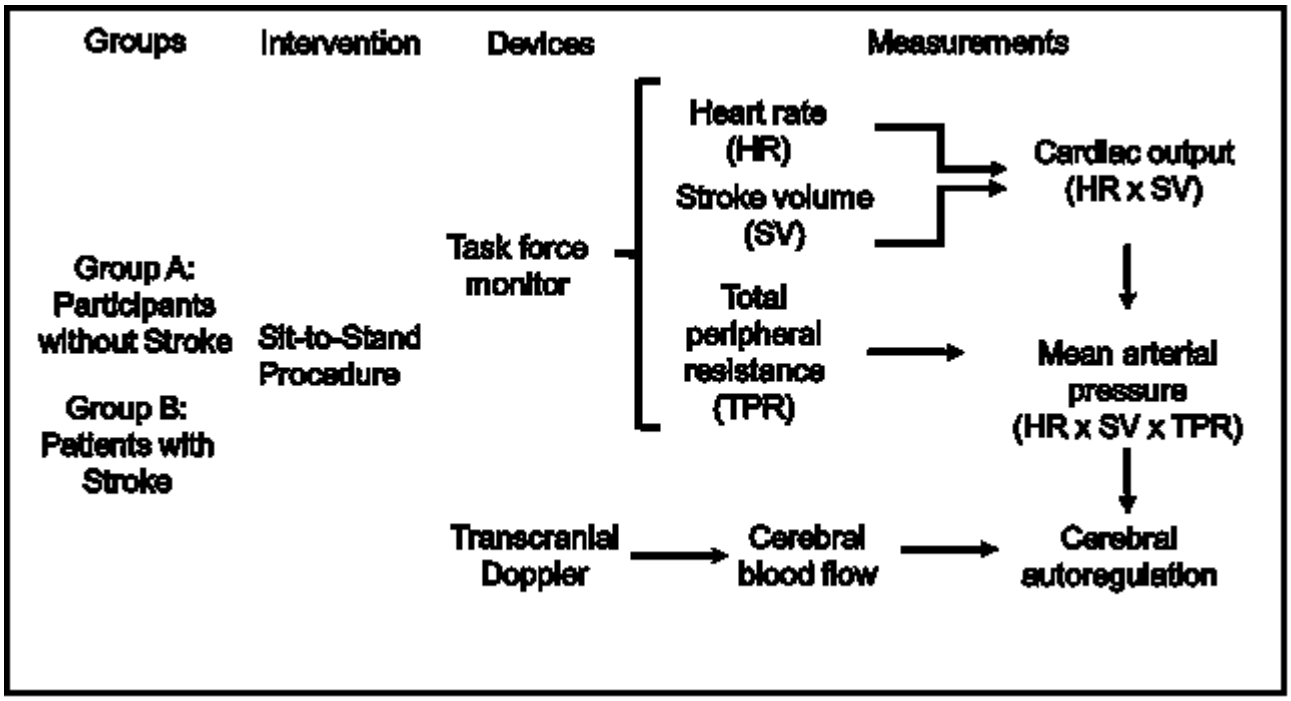

Figure 2. In the figure above, we see there were two groups which have performed a sit-to -stand test. Following hemodynamic and heart rate variability parameters were monitored via a Task Force Monitor ® device: arterial blood pressure (systolic and diastolic blood pressure), heart rate (bipolar 3-lead ECG), stroke volume (SV) and stroke index (SI), is the amount of blood which is ejected into the aorta via each heartbeat by the left ventricle; cardiac output (CO) is the circulating blood in a minute, and the cardiac index (CI) is the cardiac output indexed by the body surface area; power spectral analysis of the heart rate; sympathetic tone characterised by the low frequency (LF: 0.04-0.15 Hz); vagal tone characterised by the high frequency (HF 0.15-0.4 Hz); power components of the RR–interval (RRI), describe the time interval between two R-peaks in the ECG (78).

Statistical methods

We investigated the data using MATLAB (2016b) and IBM SPSS (23) software. Six epochs were chosen from distinct phases (sitting, standing) of the procedure (Figure 3). The data are presented as mean ± SE. The data sample was first checked for a normal distribution and outliers. We analysed the time course of the intervention with a Linear-mixed model (LMM). The LMM is designed for data with continuous variables in which the residuals are normally distributed but are not independent or have constant variances (longitudinal or repeated measures studies) (80). Furthermore, multiple-comparison test with Bonferroni correction was used to analyse the differences between epoch 1 and epoch 2-6. The following was analysed by the General estimating equation (GEE): i) differences at rest between patients with stroke and participants without stroke and between males and females, ii) seasonal differences at rest in patients with stroke and participants without stroke and male and females, iii) differences between patients with stroke and participants without stroke and males and females during the orthostatic loading (sit-to-stand test). The GEE is a robust model for longitudinal data with a small sample size and provides the population- average estimates of the population. GEE has been applied into a clinical trial and biomedical studies (81). In both model we specified subjects as a random factor and time course, sex and seasons as a fixed factor (78).

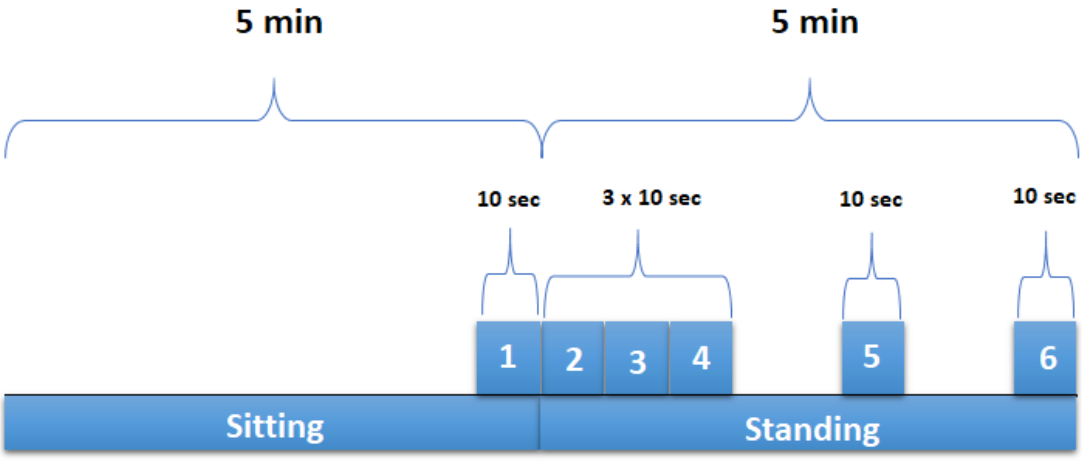

Figure 3. In the figure above, we see the sit-to-stand protocol with the specific time points of 10 seconds (Epochs): 1. Epoch 1=290-300 sec; 2. Epoch 2= 0-10 sec; 3. Epoch 3=10-20 sec; 4. Epoch 4=20-30 sec; 5. Epoch 5=180-190 sec; 6. Epoch 6=290-300 sec of standing. The epochs were analysed with an LMM and GEE statistical method (78).

4 RESULTS

A total number of 41 subjects (patients with a stroke: n=16, participants without a stroke: n=25) were between 2014 and 2015 assessed at the Department of Neurology in Graz. The demographic characteristics are presented in the (**Table 1.**). The mean age of the patients with stroke was 65.81 ± 1.85-year-old, and participants without a stroke 63.72 ± 1.39-year-old (69% men). We have not found any significant differences in age, height, or weight between the two groups (78).

4.1 HEMODYNAMIC AND HEART RATE VARIABILITY PARAMETERS AT REST

4.1.1 Hemodynamic and heart rate variability parameters at rest in patients with a stroke and participants without a stroke across seasons

We report that during the sitting phase, in participants without a stroke, systolic blood pressure stayed constant in both seasons with no significant variations (warmer months: 126.43 ± 6.31 vs colder months: 126.86 ± 3.9, [mmHg], Fig. 4.a), diastolic blood pressure was significantly greater in colder months contrasted to the warmer months (warmer months: 69.73 ± 3.20 vs colder months: 84.84 ± 2.01, [mmHg], $p < 0.05$, Fig. 4.b), mean blood pressure was significantly greater in colder months contrasted to the warmer months (warmer months: 88.96 ± 3.64 vs colder months: 103.31 ± 4.18, [mmHg], $p<0.05$, Fig. 4.c). Moreover, stroke index was significantly lower in colder months contrasted to the warmer months (warmer months: 32.64 ± 1.15 vs colder months: 28.78 ± 1.43, [ml/beats/m2], $p<0.05$, Fig. 4.d) and cardiac index was significantly lower in colder months contrasted to the warmer months (warmer months: 2.53 ± 0.09 vs colder months: 2.14 ± 0.1, [l/min/m2], $p<0.05$, Fig. 4.e). The heart rate, high frequency (normalized) and low frequency (normalized) of the heart rate variability stayed constant in both seasons with no significant alterations (78).

In patients with stroke, we report that during the sitting phase, systolic blood pressure stayed constant in both seasons with no significant variations (warmer months: 119.79 ± 8.77 vs colder months: 133.89 ± 6.05, [mmHg], Fig. 4.a), diastolic blood pressure was significantly greater in colder months contrasted to warmer months (warmer months: 70.70 ± 6.38 vs colder months: 90.62 ± 4.52, [mmHg], $p<0.05$, Fig. 4.b) and mean blood pressure was significantly greater in colder months contrasted to warmer months (warmer months: 88.50 ± 6.49 vs colder months: 107.80 ± 5.08, [mmHg], $p<0.05$, Fig. 4.c). The stroke index was significantly lower in colder months contrasted to warmer months (warmer months: 32.25 ± 1.28 vs colder months: 26.82 ± 1.55, [ml/beats/m2], $p<0.05$, Fig. 4.d). The cardiac index, heart rate, high frequency (normalized) and low frequency (normalized) of the heart rate variability stayed constant in both seasons with no significant alterations (78).

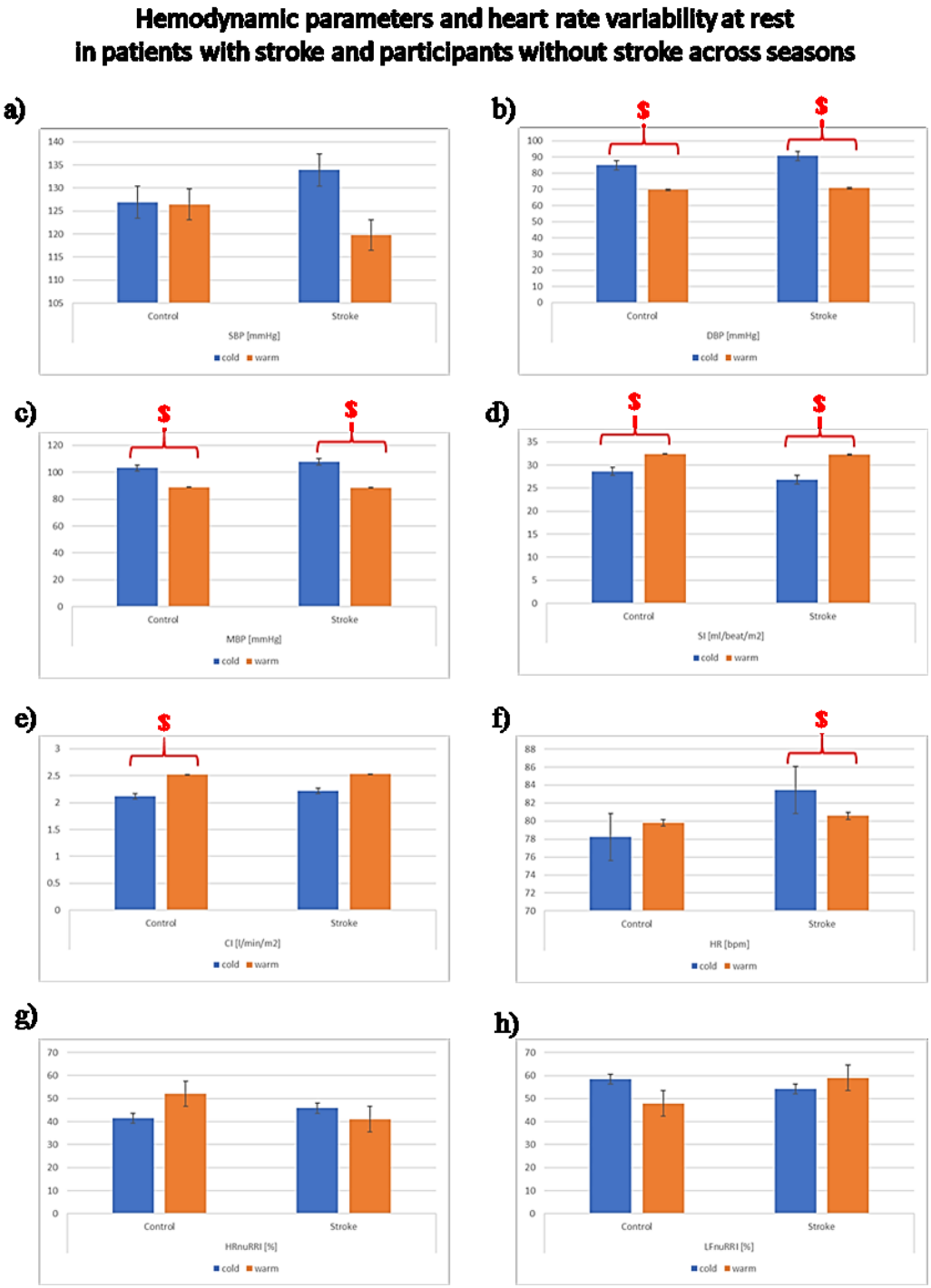

Figure 4. In the figure above, we see hemodynamic parameters and heart rate variability responses at rest in patients with stroke and participants without stroke. $= represent significant differences between the colder season and warmer season. Values are mean ±SE.

4.1.2 Hemodynamic and heart rate variability parameters at rest in males and females across seasons

We reported that during the sitting phase, in males without stroke, cardiac index was significantly lower in colder months contrasted to warmer months (colder months: 2.13 ± 0.16 vs warmer months: 2.52 ± 0.09, [l/min/m2], $p<0.05$, Fig. 5.e). In females without stroke, diastolic blood pressure was significantly greater in colder months contrasted to warmer months (colder months: 86.41 ± 2.5 vs warmer months: 69.34 ± 3.22, [mmHg], $p<0.05$, Fig. 5.b) and mean blood pressure was significantly greater in colder months contrasted to warmer months (colder months: 106.86 ± 2.89 vs warmer months: 90.30 ± 4.22, [mmHg], $p<0.05$, Fig. 5.c).

We report that during the sitting phase, in males with stroke, diastolic blood pressure was significantly greater in colder months contrasted to warmer months (colder months: 92.12 ± 5.90 vs warmer months: 63.73 ± 2.8, [mmHg], $p<0.05$, Fig. 5.b), mean blood pressure was significantly greater in colder months contrasted to warmer months (colder months: 109.12 ± 6.6 vs warmer months: 80.42 ± 0.99, [mmHg], $p<0.05$, Fig. 5.c), heart rate was significantly greater in colder months contrasted to warmer months (colder months: 86.74 ± 5.37 vs warmer months: 68.29 ± 2.07, [bpm], $p<0.05$, Fig. 5.f). In females with stroke, stroke index was significantly lower in colder months contrasted to warmer months (colder months: 24.1 ± 2.1 vs warmer months: 30.81 ± 1.16, [ml/beats/m2], $p<0.05$, Fig. 5.d) and cardiac index was significantly lower in colder months contrasted to warmer months (colder months: 1.78 ± 0.21 vs warmer months: 2.67 ± 0.29, $p<0.05$, [l/min/m2], Fig. 5.e).

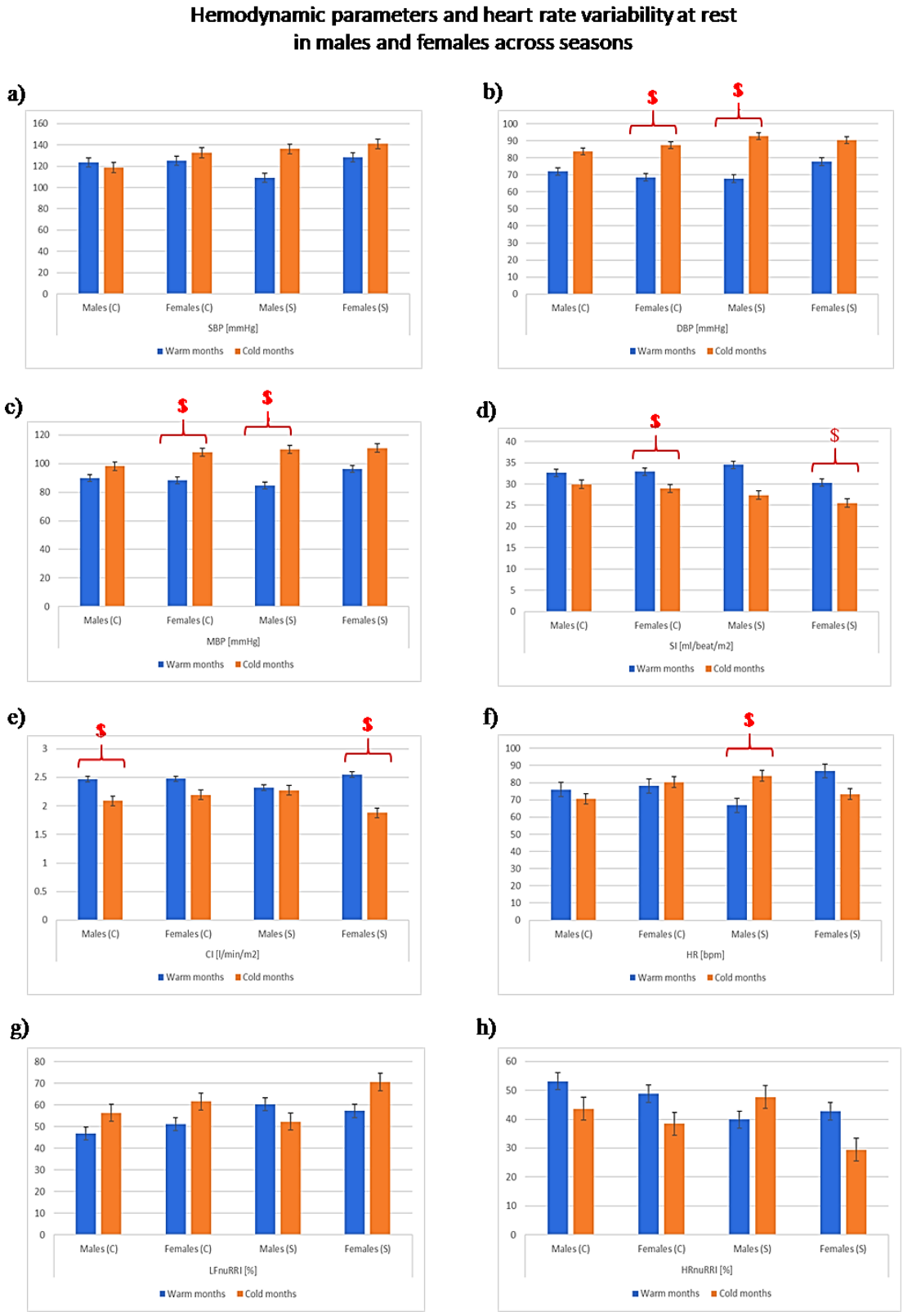

Figure 5. In the figure above, we see hemodynamic parameters and heart rate variability responses at rest in males and females. $= represent significant differences between the colder season and warmer season. Values are mean ±SE.

4.2 POSTURAL HEMODYNAMIC AND HEART RATE VARIABILITY PARAMETERS RESPONSES IN TWO SEASONS

4.2.1 Postural hemodynamic and heart rate variability parameters responses in patients with a stroke and participants without a stroke

Reported are hemodynamic and heart rate variability responses to orthostatic loading (standing) contrasted to the sitting phase. In participants without a stroke, in warmer months, systolic blood pressure reduced significantly during 20 seconds of standing (Epoch 1: 126.43 ± 7.29 vs Epoch 3: 109.59 ± 7.29, [mmHg], $p<0.05$, Fig. 6.a), In colder months diastolic blood pressure reduced significantly after the first 10 seconds of standing (Epoch 1: 84.84 ± 1.98 vs Epoch 2: 79.15 ± 1.98, [mmHg], $p<0.05$, Fig. 6.c), and reduced significantly after 20 seconds of standing (Epoch 1: 84.84 ± 1.98 vs Epoch 3: 78.11 ± 1.98, [mmHg], $p<0.05$, Fig. 6.c) but afterwards stabilized. In warmer months diastolic blood pressure reduced significantly after the 20 seconds of standing (Epoch 1: 69.73 ± 3.80 vs Epoch 3: 61.94 ± 3.80, [mmHg], $p<0.05$, Fig. 6.c) and afterwards stabilized. In colder months mean blood pressure reduced significantly after the 10 seconds of standing (Epoch 1: 103.31 ± 2.45 vs Epoch 2: 98.13 ± 2.45, [mmHg], $p<0.05$, Fig. 6.e), and again after the 20 seconds of standing (Epoch 1: 103.31 ± 2.45 vs Epoch 3: 94.38 ± 2.45, [mmHg], $p<0.05$, Fig. 3.e) and afterwards stabilized. In the warmer months mean blood pressure reduced significantly after the 20 seconds of standing (Epoch 1: 88.96 ± 4.58 vs Epoch 3: 76.49 ± 4.58, [mmHg], $p<0.05$, Fig. 6.e) and afterwards stabilized. In colder months cardiac index raised significantly after 20 seconds of standing (Epoch 1: 2.12 ± 0.12 vs Epoch 3: 2.52 ± 0.12, [l/min/m2], $p<0.05$, Fig, 7.a). The stroke index, heart rate, low frequency (normalized) and high frequency (normalized) of the heart rate variability stayed constant to the end of the sit-to-stand protocol in both seasons (78).

We report that in patients with stroke, in warmer months only, mean blood pressure reduced significantly during 20 seconds of standing contrasted to the sitting phase (Epoch 1: 88.50 ± 6.39 vs Epoch 3: 73.95 ± 6.39, [mmHg], $p<0.05$, Fig. 6.f). The systolic blood pressure and diastolic blood pressure stayed steady to the end of the sit-to-stand protocol in both seasons. Also, cardiac index, stroke index, heart rate, low frequency (normalized) and high frequency (normalized) of the heart rate variability stayed steady to the end of the sit-to-stand protocol in both seasons (78).

Table 4. Time course of hemodynamic parameters and heart rate variability responses in colder months in patients with stroke and participants without stroke (78)

Parameters	Groups	Epochs					
		Epoch1	Epoch2	Epoch3	Epoch4	Epoch5	Epoch6
SBP [mmHg]	Control	126.9 (4.0)	123.3 (3.98)	118.77 (3.98)*	125.5 (3.97)	129.6(4.02)	128.1 (4.02)
	Stroke	133.9 (5.73)	138.4 (5.73)	124.56 (5.73)	135.53 (5.73)	138.9 (5.73)	135.87 (5.73)
DBP [mmHg]	Control	84.84 (1.98)	79.15 (1.98)*	78.11 (1.98)*	82.8 (1.98)	87.77 (2.02)	85.29 (2.02)
	Stroke	90.62 (4.29)	89.55 (4.29)	83.7 (4.29)	90.6 (4.29)	90.32 (4.29)	90.34 (4.29)
MBP [mmHg]	Control	103.31 (2.45)	98.13 (2.45)	94.4 (2.45)*	100.71 (2.45)	105.95 (2.49)	103.8 (2.49)
	Stroke	107.80 (4.71)	108.86 (4.71)	98.82 (4.71)	107.81 (4.71)	109.26 (4.71)	107.84 (4.71)
SI [ml/beat/m2]	Control	28.64 (1.61)	30.87 (1.61)	30.03 (1.61)	29.12 (1.61)	27.14 (1.61)	27.13 (1.60)
	Stroke	26.82 (2.15)	28.34 (2.19)	28.27 (2.19)	26.57 (2.30)	26.98 (2.19)	27.01 (2.19)
CI [l/min/m2]	Control	2.12 (0.12)	2.5 (0.12)	2.52 (0.12)*	2.24 (0.12)	2.13 (0.12)	2.13 (0.12)
	Stroke	2.22 (0.21)	2.43 (0.22)	2.77 (0.22	2.30 (0.23)	2.28 (0.22)	2.19 (0.22)
HR [bpm]	Control	78.20 (3.38)	83.57 (3.38)	81.4 (3.38)	80.09 (3.38)	80.87 (3.42)	78.98 (3.38)
	Stroke	83.43 (4.47)	86.26 (4.64)	97.84 (4.64)	87.72 (5.04)	85.71 (4.64)	82.27 (4.64)
LFnuRRI [%]	Control	58.48 (4.70)	58.70 (4.83)	58.4 (4.75)	61.86 (4.75)	63.60 (4.75)	62.19 (4.70)
	Stroke	54.17 (5.95)	58.55 (6.18)	58.12 (6.33)	58.4 (6.33)	56.66 (6.06)	63.41 (6.06)
HRnuRRI [%]	Control	41.51 (4.70)	41.3 (4.83)	41.6 (4.75)	38.13 (4.75)	36.4 (4.75)	37.8 (4.70)
	Stroke	45.82 (5.95)	41.45 (6.18)	41.87 (6.33)	41.6 (6.33)	43.33 (6.06)	36.6 (6.06)

*= p<0.05 significant time interaction between baseline and 2-6 epoch in colder months (red). Values are mean and (±SE)

Table 5. Time course of hemodynamic parameters and heart rate variability responses in warmer months in patients with stroke and participants without stroke (78)

Parameters	Groups	Epochs					
		Epoch1	Epoch2	Epoch3	Epoch4	Epoch5	Epoch6
SBP [mmHg]	Control	126.44 (7.29)	130.94 (7.29)	109.6 (7.29)*	128.51 (7.29)	130.14 (7.36)	124.37 (7.36)
	Stroke	119.8 (8.60)	120.43 (8.60)	101.74 (8.60)	113.60 (8.60)	122.66 (8.60)	121.11 (8.60)
DBP [mmHg]	Control	69.73 (3.80)	70.58 (3.80)	61.94 (3.80)*	71.76 (3.80)	72.81 (3.84)	70.92 (3.84)
	Stroke	70.70 (6.42)	69.11 (6.42)	60.31 (6.42)	68.12 (6.42)	74.12 (6.42)	73.23 (6.42)
MBP [mmHg]	Control	88.96 (4.58)	90.84 (4.58)	76.5 (4.58)*	88.99 (4.58)	91.31 (4.63)	88.37 (4.63)
	Stroke	88.5 (6.39)	87.45 (6.39)	73.95 (6.39)*	83.5 (6.39)	91.15 (6.39)	90.66 (6.39)
SI [ml/beat/m2]	Control	32.40 (1.14)	32.96 (1.16)	32.13 (1.16)	31.53 (1.16)	29.47 (1.14)	29.48 (1.14)
	Stroke	32.25 (1.52)	33.33 (1.52)	31.97 (1.52)	31.94 (1.52)	30.58 (1.52)	29.6 (1.52)
CI [l/min/m2]	Control	2.52 (0.13)	2.75 (0.13)	2.55 (0.13)	2.58 (0.13)	2.31 (0.13)	2.3 (0.13)
	Stroke	2.53 (0.18)	3.01 (0.18)	2.51 (0.18)	2.41 (0.18)	2.33 (0.18)	2.24 (0.18)
HR [bpm]	Control	79.81 (3.90)	84.43 (4.03)	81.64 (4.03)	82.1 (4.03)	78.33 (3.92)	78.46 (3.92)
	Stroke	80.58 (5.23)	88.37 (5.23)	79.42 (5.23)	76.09 (5.23)	76.9 (5.23)	76.46 (5.23)
LFnuRRI [%]	Control	47.92 (6.54)	51.4 (6.95)	51.7 (6.68)	55.15 (6.68)	57.23 (6.57)	60.65 (6.57)
	Stroke	58.97 (10.13)	56.29 (10.35)	60.23 (10.35)	61.45 (10.13)	61.31 (10.13)	60.29 (10.13)
HRnuRRI [%]	Control	52.07 (6.54)	48.59 (6.95)	48.29 (6.68)	44.84 (6.68)	42.76 (6.57)	39.34 (6.57)
	Stroke	41.02 (10.13)	43.7 (10.35)	39.76 (10.35)	38.54 (10.13)	38.68 (10.13)	39.7 (10.13)

*= p<0.05 significant time interaction between baseline and 2-6 epoch in warmer months (red). Values are mean and (±SE)

4.2.2 Postural hemodynamic and heart rate variability parameters responses in males and females

We report that in males without a stroke, in warmer months, systolic blood pressure reduces significantly during the 20 seconds of standing related to the sitting phase (Epoch 1: 123.60 ± 9.50 vs Epoch 3: 104.85 ± 9.50, [mmHg], $p<0.05$, Fig. 6.a). The mean blood pressure, in colder months, reduces significantly during the 30 seconds of standing (Epoch 1: 98.10 ± 3.30 vs Epoch 3: 87.95 ± 3.30, [mmHg], $p<0.05$, Fig. 6e). The mean blood pressure, in warmer months, reduces significantly during the 30 seconds of standing (Epoch 1: 89.74 ± 6.67 vs Epoch 3: 74.95 ± 6.67, [mmHg], $p<0.05$, Fig. 6.e). In females without a stroke, in colder months, the stroke index reduces significantly during the last 5 minutes of standing (Epoch 1: 28.89 ± 1.25 vs Epoch 6: 25.87 ± 1.253, [ml/beats/m2], $p<0.05$, Fig. 7.a).

We report that in females with stroke, in colder months, heart rate raises significantly during the 10 seconds and 30 seconds of standing (Epoch 1: 73.32 ± 8.20 vs Epoch 2: 84.25 ± 8.20 vs Epoch 4: 83.98 ± 8.20, [bpm], $p<0.05$, Fig. 7.f) and afterwards stabilized.

4.2.3 Sex differences in postural hemodynamic and heart rate variability parameters responses

We report that in males and females without a stroke high frequency (normalized) of the heart rate variability at 10 seconds of standing shows significant sex-specific differences in warmer months (males: 51.48 ± 8.82 vs females: 30.56 ± 1.63, [%], $p<0.05$, Fig. 8.a). In males and females without a stroke low frequency (normalized) of the heart rate variability at 10 seconds of standing show significant sex-specific differences between males and females in warmer months (males: 48.51 ± 8.82 vs females: 69.43 ± 1.63, [%], $p<0.05$, Fig. 8.c).

We report that in males and females with a stroke high frequency (normalized) of the heart rate variability show significant sex-specific differences in colder months at 10 seconds (males: 42.52 vs females: 28.80, $p<0.05$, [%], Fig. 8.b) and 20 seconds of standing (males: 40.06 ± 4.10 vs females: 27.16 ± 1.61, [%], $p<0.05$, Fig. 8.b). In males and females with a stroke in colder months low frequency (normalized) of the heart rate variability at 10 seconds of standing show significant sex-specific differences (males: 57.47 ± 6.80 vs females: 75.19 ± 2.37, [%], $p<0.05$, Fig. 8.d) and at 20 seconds of standing show sex-specific differences (males: 59.93 ± 4.10 vs females: 72.83 ± 1.61, [%], $p<0.05$, Fig. 8.d).

Table 6. Time course of hemodynamic parameters and heart rate variability responses in colder months in males and females

Parameters	Groups	Epochs					
		Epoch1	Epoch2	Epoch3	Epoch4	Epoch5	Epoch6
SBP [mmHg]	Males (C)	118.902 (5.920)	117.800 (5.920)	109.804 (5.920)	120.441 (5.920)	125.790 (6.004)	124.065 (6.004)
	Females (C)	132.733 (5.420)	126.461 (5.420)	123.107 (5.420)	128.032 (5.420)	133.686 (5.497)	133.817 (5.493)
	Males (S)	136.151 (8.008)	138.639 (8.008)	126.873 (8.008)	138.479 (8.008)	142.550 (8.008)	138.438 (8.008)
	Females (S)	140.944 (13.597)	146.711 (13.597)	130.679 (13.597)	137.183 (13.597)	144.338 (13.597)	143.202 (13.597)
DBP [mmHg]	Males (C)	83.571 (2.741)	79.599 (2.741)	75.040 (2.741)	82.926 (2.741)	89.259 (2.846)	87.531 (2.846)
	Females (C)	87.419 (3.328)	79.576 (3.328)	80.362 (3.328)	83.766 (3.328)	89.615 (3.375)	88.469 (3.372)
	Males (S)	92.722 (5.493)	89.830 (5.493)	86.318 (5.493)	92.450 (5.493)	96.472 (5.493)	93.585 (5.493)
	Females (S)	90.443 (8.035)	94.177 (8.035)	84.891 (8.035)	91.557 (8.035)	85.198 (8.035)	89.335 (8.035)
MBP [mmHg]	Males (C)	98.107 (3.305)	95.892 (3.305)	87.959 (3.305)*	97.963 (3.305)	104.442 (3.402)	102.624 (3.402)
	Females (C)	107.789 (3.734)	100.035 (3.734)	98.314 (3.734)	102.994 (3.734)	109.142 (3.795)	108.426 (3.793)
	Males (S)	109.846 (6.321)	108.934 (6.321)	101.123 (6.321)	109.972 (6.321)	114.178 (6.321)	110.560 (6.321)
	Females (S)	110.782 (9.621)	115.397 (9.621)	102.459 (9.621)	109.454 (9.621)	108.796 (9.621)	110.595 (9.621)
SI [ml/beat/m2]	Males (C)	29.926 (3.283)	33.230 (3.283)	32.158 (3.283)	30.848 (3.283)	26.371 (3.283)	27.087 (3.362)
	Females (C)	28.898 (1.259)	29.670 (1.259)	28.301 (1.259)	27.634 (1.259)	27.080 (1.259)	25.871 (1.253)*
	Males (S)	27.390 (2.276)	28.657 (2.352)	28.483 (2.352)	27.231 (2.522)	27.145 (2.352)	27.033 (2.352)
	Females (S)	25.512 (2.986)	27.287 (2.986)	26.837 (2.986)	25.048 (2.986)	25.399 (2.986)	26.040(2.986)
CI [l/min/m2]	Males (C)	2.087 (0.228)	2.691 (0.228)	2.746 (0.228)	2.378 (0.228)	2.073 (0.228)	2.181 (0.228)
	Females (C)	2.194 (0.130)	2.360 (0.130)	2.326 (0.130)	2.175 (0.130)	2.218 (0.130)	2.090 (0.130)
	Males (S)	2.274 (0.219)	2.447 (0.228)	2.830 (0.228)	2.314 (0.247)	2.318 (0.228)	2.244 (0.228)
	Females (S)	1.878 (0.313)	2.255 (0.313)	2.240 (0.313)	2.100 (0.313)	2.081 (0.313)	2.037 (0.313)
HR [bpm]	Males (C)	70.572 (3.755)	81.103 (3.755)	84.604 (3.755)	78.274 (3.755)	79.261 (3.755)	80.643 (3.755)
	Females (C)	80.304 (4.365)	83.162 (4.365)	79.327 (4.365)	80.214 (4.365)	82.662 (4.400)	80.687 (4.365)
	Males (S)	83.925 (4.804)	84.998 (5.015)	98.922 (5.015)	85.851 (5.500)	85.990 (5.015)	83.617 (5.015)
	Females (S)	73.320 (8.202)	84.256 (8.202)*	83.340 (8.202)**	83.984 (8.202)*	82.149 (8.202)	78.508 (8.202)
LFnuRRI [%]	Males (C)	56.364 (6.302)	55.551 (6.781)	56.712 (6.302)	59.361 (6.302)	60.800 (6.302)	57.665 (6.302)
	Females (C)	61.554 (5.883)	61.121 (5.974)	63.642 (5.923)	66.202 (5.923)	68.868 (5.923)	65.895 (5.883)
	Males (S)	52.323 (7.209)	55.588 (7.464)	54.849 (7.598)	59.684 (7.598)	63.441 (7.331)	68.166 (7.331)
	Females (S)	70.563 (7.949)	73.433 (7.949)	71.076 (7.949)	67.160 (7.949)	51.115 (7.949)	61.084 (7.949)
HRnuRRI [%]	Males (C)	43.636 (6.302)	44.449 (6.781)	43.288 (6.302)	40.639 (6.302)	39.200 (6.302)	42.335 (6.302)
	Females (C)	38.446 (5.883)	38.879 (5.974)	36.358 (5.923)	33.798 (5.923)	31.132 (5.923)	34.105 (5.883)
	Males (S)	47.677 (7.209)	44.412 (7.464)	45.151 (7.598)	40.316 (7.598)	36.559 (7.331)	31.834 (7.331)
	Females (S)	29.437 (7.949)	26.567 (7.949)	28.924 (7.949)	32.840 (7.949)	48.885 (7.949)	38.916 (7.949)

***= p<0.05 significant time interaction between epoch 1 and epoch 2-6 in colder months (red). Values are mean and (±SE)**

Table 7. Time course of hemodynamic parameters and heart rate variability responses in warmer months in males and females

Parameters	Groups	Epochs					
		Epoch1	Epoch2	Epoch3	Epoch4	Epoch5	Epoch6
SBP [mmHg]	Males (C)	123.602 (9.507)	126.761 (9.507)	104.854 (9.507)*	121.450 (9.507)	120.352 (9.507)	119.292 (9.507)
	Females (C)	125.268 (12.015)	128.648 (12.015)	112.006 (12.015)	130.305 (12.015)	133.490 (12.255)	126.361 (12.255)
	Males (S)	109.243 (10.230)	107.243 (10.230)	92.0 (10.230)	97.769 (10.230)	113.871 (10.230)	116.081 (10.230)
	Females (S)	128.561 (11.080)	130.822 (11.080)	112.796 (11.080)	125.618 (11.080)	131.098 (11.080)	128.592 (11.080)
DBP [mmHg]	Males (C)	71.963 (5.974)	72.036 (5.974)	61.330 (5.974)	70.776 (5.974)	70.826 (5.974)	70.123 (5.974)
	Females (C)	68.576 (4.247)	69.994 (4.247)	63.972 (4.247)	72.998 (4.247)	76.724 (4.331)	75.608 (4.331)
	Males (S)	67.761 (5.378)	63.118 (5.378)	56.435 (5.378)	61.942 (5.378)	71.105 (5.378)	72.681 (5.378)
	Females (S)	77.772 (10.153)	77.929 (10.153)	69.586 (10.153)	78.212 (10.153)	81.440 (10.153)	80.685 (10.153)
MBP [mmHg]	Males (C)	89.745 (6.671)	90.387 (6.671)	74.957 (6.671)*	86.610 (6.671)	87.286 (6.671)	86.369 (6.671)
	Females (C)	88.332 (5.751)	90.707 (5.751)	79.283 (5.751)	91.108 (5.751)	95.450 (5.847)	92.814 (5.847)
	Males (S)	84.648 (5.079)	80.726 (5.079)	69.506 (5.079)	75.769 (5.079)	87.916 (5.079)	90.310 (5.079)
	Females (S)	96.123 (10.073)	96.494 (10.073)	83.728 (10.073)	94.098 (10.073)	98.445 (10.073)	97.881 (10.073)
SI [ml/beat/m2]	Males (C)	32.633 (1.388)	33.505 (1.485)	31.603 (1.485)	31.706 (1.485)	29.250 (1.396)	29.416 (1.396)
	Females (C)	32.917 (2.370)	34.900 (2.370)	33.112 (2.370)	32.451 (2.370)	28.897 (2.370)	28.526 (2.370)
	Males (S)	34.514 (2.622)	37.403 (2.622)	36.458 (2.622)	36.318 (2.622)	31.989 (2.622)	31.386 (2.622)
	Females (S)	30.323 (2.165)	31.754 (2.165)	34.537 (2.165)	32.388 (2.165)	30.164 (2.165)	29.630 (2.165)
CI [l/min/m2]	Males (C)	2.465 (0.114)	2.773 (0.121)	2.616 (0.121)	2.653 (0.121)	2.316 (0.115)	2.300 (0.115)
	Females (C)	2.474 (0.277)	2.783 (0.277)	2.689 (0.277)	2.498 (0.277)	2.353 (0.277)	2.299 (0.277)
	Males (S)	2.318 (0.316)	2.786 (0.316)	2.722 (0.316)	2.568 (0.316)	2.349 (0.316)	2.238 (0.316)
	Females (S)	2.552 (0.228)	3.079 (0.228)	2.811 (0.228)	2.548 (0.228)	2.346 (0.228)	2.340 (0.228)
HR [bpm]	Males (C)	75.980 (4.070)	84.976 (4.229)	81.752 (4.229)	83.979 (4.229)	78.415 (4.095)	77.825 (4.095)
	Females (C)	78.113 (6.856)	80.214 (6.856)	80.745 (6.856)	76.855 (6.856)	80.284 (6.856)	79.905 (6.856)
	Males (S)	66.835 (4.711)	73.986 (4.711)	74.223 (4.711)	70.243 (4.711)	73.422 (4.711)	70.948 (4.711)
	Females (S)	86.824 (7.343)	94.463 (7.343)	84.199 (7.343)	80.909 (7.343)	79.387 (7.343)	80.840 (7.343)
LFnuRRI [%]	Males (C)	46.858 (8.127)	43.858 (8.127)	43.447 (8.494)	48.194 (8.494)	53.474 (8.212)	57.573 (8.212)
	Females (C)	51.143 (10.882)	58.126 (10.993)	59.713 (10.882)	60.847 (10.882)	59.308 (10.882)	63.501 (10.882)
	Males (S)	60.198 (21.427)	60.138 (21.427)	61.271 (21.427)	60.674 (21.427)	63.100 (21.427)	63.075 (21.427)
	Females (S)	57.210 (10.541)	50.744 (11.196)	56.773 (11.196)	60.336 (10.541)	61.154 (10.541)	62.951 (10.541)
HRnuRRI [%]	Males (C)	46.858 (8.127)	43.849 (8.778)	43.447 (8.494)	48.194 (8.494)	53.474 (8.212)	57.573 (8.212)
	Females (C)	51.143 (10.882)	58.126 (10.993)	59.713 (10.882)	60.847 (10.882)	59.308 (10.882)	63.501 (10.882)
	Males (S)	60.198 (21.427)	60.138 (21.427)	61.271 (21.427)	60.674 (21.427)	63.100 (21.427)	63.075 (21.427)
	Females (S)	57.210 (10.541)	50.744 (11.196)	56.773 (11.196)	60.336 (10.541)	61.154 (10.541)	62.951 (10.541)

***= p<0.05 significant time interaction between epoch 1 and epoch 2-6 in warmer months (red). Values are mean and (±SE)**

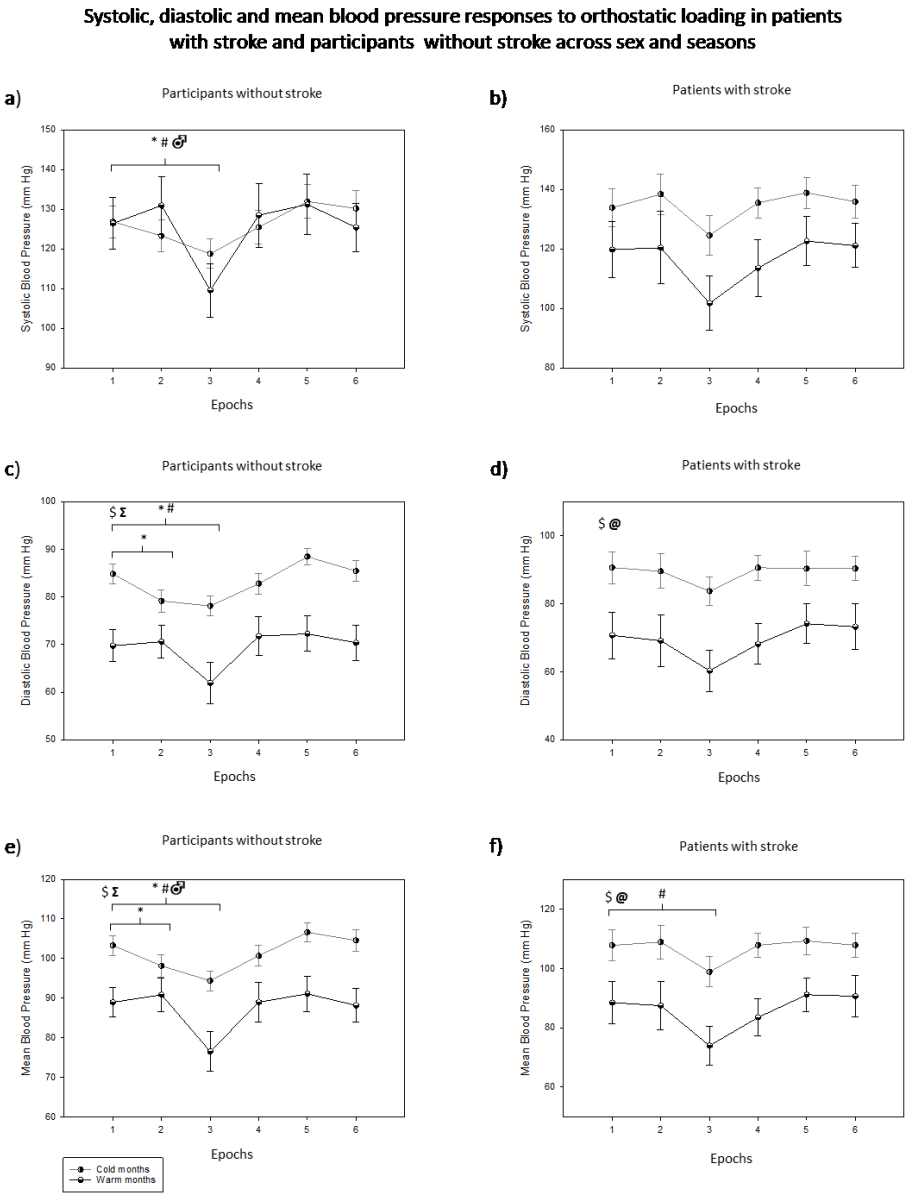

Figure 6. Line-plot with error-bars for Systolic blood pressure, diastolic blood pressure and mean blood pressure in patients with stroke and participants without a stroke across sex and seasons. $=significant seasonal differences at rest in patients with stroke and participants without stroke; @= significant seasonal differences at rest in males with and without stroke; Σ= significant seasonal differences at rest in females with and without stroke; *= significant time interaction between baseline and 2-6 epoch in cold seasons, #= significant time interaction between baseline and 2-6 epoch in warm seasons. ♀= significant time interaction between epoch 1 and epoch 2-6 in females; ♂= significant time interaction between epoch 1 and epoch 2-6 in males; Δ= significant sex differences in postural hemodynamic parameters and heart rate variability responses. $p< 0.05$ significance. Values are mean and ± SE (78).

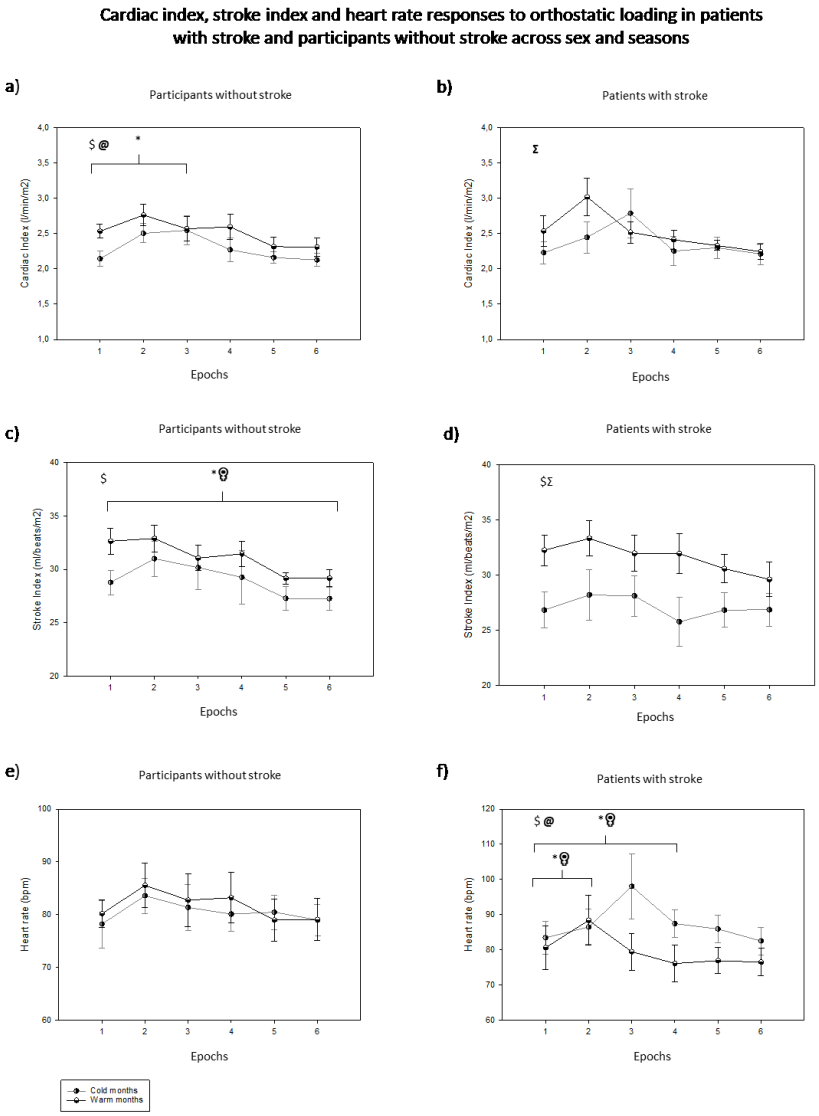

Figure 7. Line-plot with error-bars for cardiac index, stroke index and heart rate in patients with stroke and participants without a stroke across sex and seasons. $=significant seasonal differences at rest in patients with stroke and participants without stroke; @= significant seasonal differences at rest in males with and without stroke; Σ= significant seasonal differences at rest in females with and without stroke; *= significant time interaction between epoch 1 and 2-6 epoch in cold seasons, #= significant time interaction between epoch 1 and 2-6 epoch in warm seasons. ♀= significant time interaction between epoch 1 and epoch 2-6 in females; ♂= significant time interaction between epoch 1 and epoch 2-6 in males; Δ= significant sex differences in postural hemodynamic parameters and heart rate variability responses. $p< 0.05$ significance. Values are mean and ± SE (78).

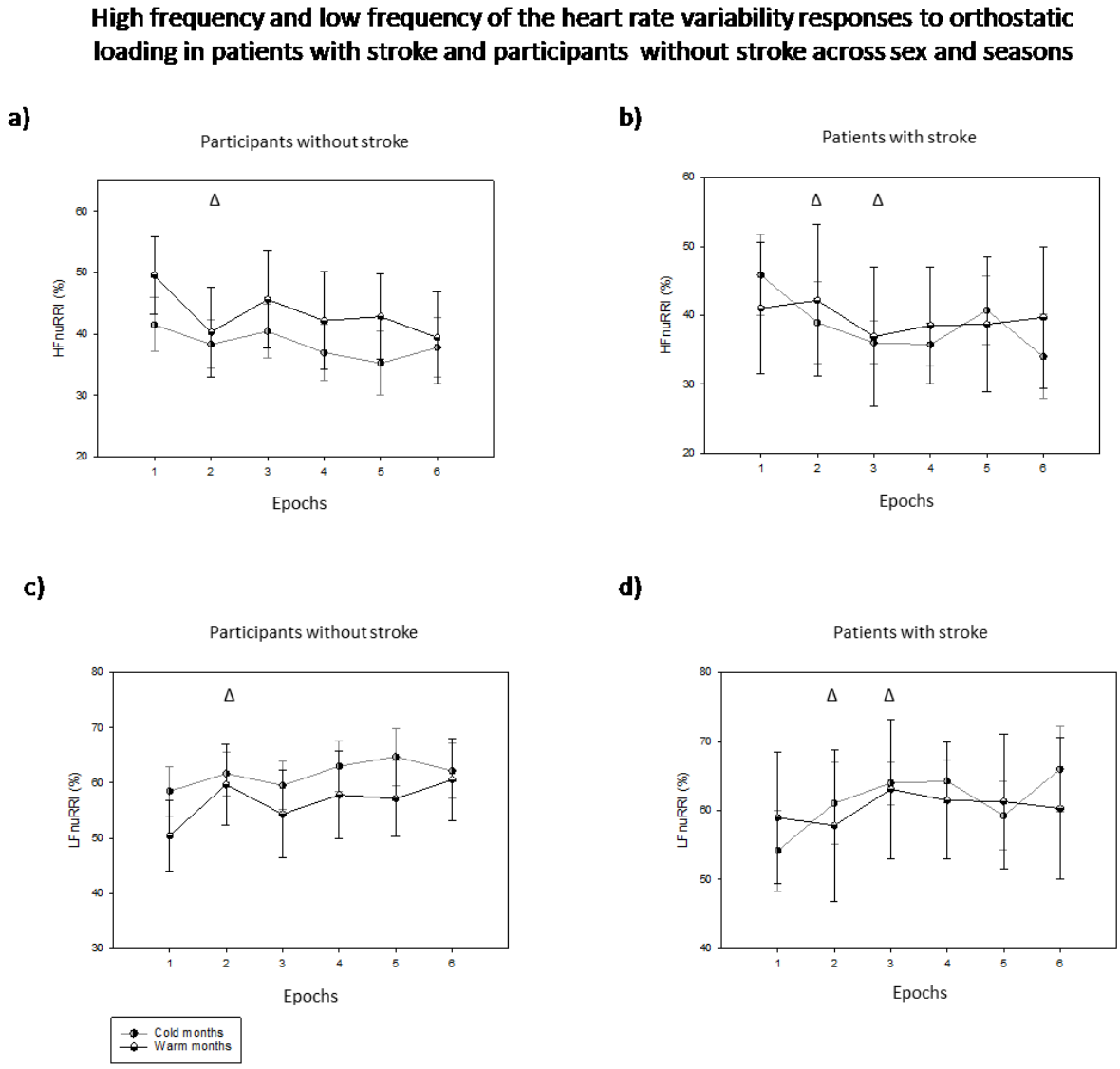

Figure 8. Line-plot with error-bars for high frequency and low frequency of the heart rate variability in patients with stroke and participants without a stroke across sex and seasons. Δ= significant sex differences in postural hemodynamic parameters and heart rate variability responses. $p< 0.05$ significance. Values are mean and ± SE (78).

5 DISCUSSION

The aim of this study was to analyse seasonal variations in postural blood pressure changes and differences in postural blood pressure change between patients with a stroke and participants without a stroke across sex and seasons. The main findings of our study are: 1) we saw seasonal hemodynamic parameters and heart rate variability differences at rest: a) baseline diastolic blood pressure and mean blood pressure were greater and stroke index was lower in both groups in colder months; b) cardiac index was lower only in non-stroke participants in colder months; 2) we reported following sex differences in baseline hemodynamic parameters and heart rate variability: a) in females without a stroke, resting diastolic and mean blood pressure were greater in colder months contrasted to warmer months, b) in males without a stroke, only cardiac index was lower in colder months contrasted to warmer months, c) in females with a stroke, cardiac index and stoke index was lower in colder months contrasted to warmer months, d) In males with a stroke, baseline diastolic, mean blood pressure and baseline heart rate was greater in colder months contrasted to warmer months 3) standing up (from 10 to 30 seconds) resulted in: a) reductions in systolic blood pressure in warmer months in participants without a stroke; b) reductions in diastolic blood pressure, mean blood pressure in warmer and colder months in participants without a stroke; c) reductions in mean blood pressure in warmer months in patients with stroke; d) rises in cardiac index in colder months in participants without a stroke only; 4) we observed responses to standing (from 10 to 30 seconds) in males and females: a) in males without a stroke, systolic blood pressure showed reductions in warmer months, mean blood pressure reductions in both seasons, b) in females without a stroke, during the last 5 minutes of standing, stroke index showed reductions in colder months, c) in females with stroke, during 10 to 30 seconds of standing, heart rate rises were seen in colder months, 5) heart rate variability responses to orthostatic loading show differences between males and females, 6) no significant differences at baseline for hemodynamic parameters and heart rate variability were detected between stroke patients and non-stroke participants in both seasons; 7) no significant differences for hemodynamic parameters and heart rate variability during the sit-to-stand test were seen between the stroke patients and non-stroke participants in both seasons.

5.1 BLOOD PRESSURE VARIABILITY

Our results could not confirm the hypothesis that hemodynamic parameters and heart rate variability show differences between patients with stroke and participants without a stroke. We report that at rest blood pressure, stroke index, cardiac index, heart rate and heart rate variability do not show significant differences between patients with stroke and participants without a stroke. Healthy individuals maintain blood pressure homeostasis through specific autonomic reflexes (baroreflex, and renal fluid regulation). But with progressing age these autonomic reflexes become less effective causing chronic elevation of blood pressure or hypertension (82, 83). High blood pressure or hypotension represent an important risk factor for some of the common cardiovascular and cerebrovascular diseases. The risk for cerebrovascular diseases and stroke increases in the older population with hypertension (84). Hypertension is a changeable risk factor, and physicians recommend to lower high blood pressure below 140 mmHg which reduce the risk for stroke (85). The intake of antihypertensive medication is a crucial tool to reduce high blood pressure but do not fully end the risk for stroke (86, 87).

According to earlier reported studies at admission patients with a stroke have elevated blood pressure, which during the first ten days decreases without antihypertensive therapy. The aetiology of elevated blood pressure is multifactorial, altered sympathetic and parasympathetic activity, raised catecholamine in the circulation and raised natriuretic peptide in the brain. Qureshi et al. (2007) argue that the elevated blood pressure is a protective mechanism which improve the blood flow to the brain in stroke patients but if in the acute stage remain uncontrolled can worsen the long-term prognosis (88). Carlsson et al. (1992) report that the blood pressure elevated in two third (69%) of the patients with a stroke (89). Kohok et al. (2017) reported in a retrospective cohort study with 265 patients that blood pressure stays elevated in patients with high blood pressure during one year at discharge (90). Also, reported is that patients with stroke have an increased heart rate, stroke volume and cardiac output during 24 hours at admission, but it stabilizes quickly. As reported previously by Treib et al. (1996), cardiac output and stroke volume changes seen in acute stroke patients lead to elevations of blood pressure (91, 92).

Patients with stroke have alterations of vascular functions (increased vascular stiffens and endothelial dysfunction) which negatively influence the long-term prognosis after

stroke. Xu et al. 2017 point out that in elderly individuals and patients with stroke the renin-angiotensin system is intensified. Also, some hormones of the renin-angiotensin system, especially enhancement of Angiotensin II activity alter vascular function via inflammatory effects. These inflammatory factors via arterial stiffens and endothelia dysfunction cause alteration of cerebral blood flow regulation in patients with a stroke (93). We have hypothesized that hemodynamic responses will show differences between patients with stroke and participants without stroke. However, our result could not show any alterations of cardiovascular functions in patients one-year after stroke occurred. Thus, patients with stroke during our study did receive an antihypertensive therapy which could have influenced the results. Our finding supports the earlier mentioned stabilization of blood pressure and other hemodynamic parameters after the acute phase of stroke.

5.2 SEX AND BLOOD PRESSURE VARIABILITY

We rejected our hypothesis that at rest hemodynamic parameters and heart rate variability show differences between males and females. Our results do not support this hypothesis, as we saw none sex-differences on hemodynamic parameters and heart rate variability at rest. In our study men and women without stroke had similar baseline blood pressure, cardiac index, stroke index, heart rate and lower frequency and a higher frequency of the heart rate variability. Furthermore, our results show that sex of the participants had no-significant impact on these parameters in patients with stroke.

Sex differences in cardiovascular physiology are because of anatomical, neuronal and hormonal differences. The differences in cardiovascular and blood pressure regulation become noticeable after the puberty, thus afterwards blood pressure become higher in men. The evidences are not jet clear if the androgens promote high blood pressure and cardiovascular diseases. Some authors point out that both testosterone and oestradiol promote protection against inflammation processes. But through the interaction with the immunes system (T cells) and the renin-angiotensin system (angiotensin II) men are more prone to inflammatory processes. The renin-angiotensin system differently regulated blood pressure in men and women. In men testosterone production decline over the life spam. Evidence suggest that lower testosterone level have a negative effect on the cardiovascular system, promoting endothelium dysfunctions, arterial stiffening (93). Hormonal factors protect women against pathological cardiovascular changes. Premenopausal women tend to have a lower incidence of cardiovascular diseases and hypertension than men (39, 94). The incidence of hypertension changes in women over time after the menopause it become similar and over the 60-year of age the incidence become higher compared to men. Postmenopausal women are more affected by vascular changes because of hormonal decline. A loss of oestrogen causes higher plasma renin activity, increased oxidative stress, sympathetic activation, reduce autonomic activity, reduced baroreceptor sensitivity and arteria stiffness which are responsive for the higher incidence of hypertension in postmenopausal women (41). Because women in our study were postmenopausal, we realise that the physiological changes which occur after the menopause would explain the similar blood pressure, hemodynamic parameters and heart rate variability responses at rest in both sexes. Moreover, women after the menopause and age-matched men have a similar incidence of atherosclerosis, carotid intima-media

thickening and coronary artery calcification. For instance, the incidence of obstructed coronary disease is lower in women prior the menopause but after the menopause increases up to 79% (42).

Stroke is the third leading cause of mortality worldwide in women. In younger and middle-aged adult there is a higher incidence of stroke in men but in the older population (over 80) women are more affected by stroke (95, 96). Evidence suggest that hormonal, but also physiological factor play a significant role in the higher incidence of stroke in males. Testosterone is known to has a negative effect on the infarcted brain, increasing the size of the infarct. The male brain, and especially neurons of the male brain are known to produce more neurotoxicity. Also, the genes of the males are known to promote hypertension. Hypotension is the main risk factor for stroke. With the influence of the sex hormone it become clear why men are more prone to stroke. But after the menopause women are more affected. Female sex hormones play a significant role in the handling of injuries after stroke. Stroke induced injuries can be reversed with admission of oestrogen and progesterone and oestradiol. These hormones protect the brain after the ischemic infarct against inflammatory processes, tissues injuries and damage. But after the menopause, hormonal change causes a higher testosterone level in females. Hormonal changes are key factor which are responsible for the higher incidence of hypertension and stroke in postmenopausal females (97).

The difference between males and females is also clear regarding the outcome and prognosis after stroke. Women are more likely to suffer long-term difficulties after stroke (97). The most common causes of stroke in women are atrial fibrillation and diabetes (95, 96). When women experience their first stroke, they are much older than men (98). Earlier studies have noted that age, physical abilities prior the stroke and post-stroke morbidities are factors which can worsen the prognosis after stroke. The recovery after stroke depend on physical abilities prior the stroke which is minor in women than in men. Because of the minor physical abilities prior the stroke most women have difficulties to perform independently activities of daily living six months after stroke (95, 96, 99). Unfortunately, we have none data about physical abilities or health status before and after stroke but regarding hemodynamic parameters one-year after stroke; we saw none significant differences between males and females which is supported by earlier studies. Nonetheless, a limitation of the results is the structure of the groups, with a larger number of male participants enrolled in the stroke group due to the fact that the incidence of stroke

is higher in men compared to women. Thus, we see that in our study most patients with stroke were males, which earlier studies supported (100).

5.3 SEASONS AND BLOOD PRESSURE VARIABILITY

We confirmed our hypothesis that at rest hemodynamic parameters and heart rate variability show differences between warmer months and colder months. Our result shows significant seasonal difference at rest of hemodynamic parameters in patients with stroke and participants without a stroke. We report that at rest diastolic blood pressure and mean blood pressure were higher in colder months compared to warmer months in both groups. At rest the heart rate was similar in both seasons, but stroke index was lower in colder months in both groups and cardiac index was lower in colder months only in participants without a stroke. We report that in females without a stroke at rest diastolic blood pressure and mean blood pressure were higher in colder months compared to warmer months. In males without a stroke at rest cardiac index was lower in colder months compared to warmer months. At rest in females after a stroke cardiac index and stoke index were lower in colder months compared to warmer months. In post-stroke males at rest the diastolic blood pressure, the mean blood pressure and the heart rate were higher in colder months compared to warmer months.

It is known that the cardiovascular system behaves different in winter and summer in both sexes. The main reason for seasonal differences in cardiovascular regulation are higher sympathetic activity, increased hormone activity in winter and increased peripheral vasodilation in summer (31). Earlier studies have reported about the effects of seasons on the cardiovascular system in healthy participants. Sega et al. (1998) and Brennan et al. (1982) reported that blood pressure was lower in summer and higher in winter. Heart rate was similar over the four seasons (23, 66). Radak and Tanaskovic (2016), explained the seasonal differences in blood pressure by higher sympathetic tone, an elevated level of catecholamines in colder months and the effect of heat on blood pressure regulation (vasodilatation), reduced peripheral resistance, dehydration in summer, and by an increased sympathetic tone in winter (21, 59, 64). Iwahori et al. (2018) and Kunutsor et al. (2010) reported that seasonal variation of blood pressure, higher systolic and diastolic blood pressure values in winter and lower in summer, have been associated with seasonal variation of cardiovascular diseases with a higher incidence of hypertension, stroke and myocardial infarction in winter than in summer. Furthermore, the authors conclude that reduction in blood pressure, during the months in which the blood pressure is higher, will reduce the incidence of mortality of stroke and coronary

heart diseases (101, 102). But, some authors noted that the intake of antihypertensive medications can lead to orthostatic hypotension in summer (103).

We saw that in our study the systolic blood pressure stayed unaffected. We assume that the constant systolic blood pressure and decreased diastolic and mean blood pressures in the warmer months might be due to the constant interior temperature in the laboratory and the cooler Austrian climate. Since, systolic blood pressure changeability is more common in countries with warmer climate and less in countries with a colder climate (5). In the case of elevated diastolic blood pressure and less frequent with elevated systolic blood pressure physicians will prescribe antihypertensive medication (96). However, our results confirm the influence of physiological responses caused by seasonal temperature changes on blood pressure and other hemodynamic parameters.

5.4 POSTURAL BLOOD PRESSURE VARIABILITY

We have theorised that hemodynamic and heart rate responses to orthostatic stress induced by a sit-to-stand test will show significant differences between non-stroke participants and stroke patients across seasons. Our result shows that orthostatic loading started by a sit-to-stand test results in cardiovascular adjustments to compensate the blood pooling to the lower body. We report that in non-stroke participants systolic blood pressure decreased in warmer months (a -16.83 mmHg) but not in colder months, diastolic blood pressure decreased in warmer months (a -7.83 mmHg) and colder months (a -6.74 mmHg), mean blood pressure decreased in warmer months (a -12.5 mmHg) and colder months (a -8.91 mmHg), cardiac index increased, during 20 seconds of standing, in colder months. In stroke patients mean blood pressure, during 10-20 seconds of standing, decreased in warmer months (a -14.55 mmHg). It is known that when humans stand up, blood moves from the upper body to the lower limbs. Baroreceptors in the large arteries (aorta and the carotid artery) will respond to the reduction in blood volume and blood pressure and send impulses to the central nervous system. Autonomic responses mediated by the central nervous system will increase heart rate and peripheral resistance to stabilise blood pressure (13). Some authors have earlier mentioned that the decreases in blood pressure during standing is more pronounced in warmer seasons, because of the effects of a higher environment temperature which induces an increased sweating, salt and fluid loss, hypovolemia and peripheral vasodilatation (62). The sympathetic nervous system will act to keep blood pressure by increasing heart rate and cardiac contractility and reducing blood in non-cutaneous areas. This will prevent a collapse of the systemic blood pressure and cerebral perfusion (104). Sometimes the autonomic reflexes cannot responses efficiently to the blood pressure reductions. Blood pressure will further fall and causes a decrease in cerebral blood flow.

Orthostatic hypotension is a widespread problem in the elderly population. Evidence suggests that the incidence of orthostatic hypotension increase with the age which has also an impact on the mortality rate. Fedorowski et al. (2011) conducted a screening procedure to assess cardiovascular diseases among middle age adults (mean age: 45 years). Overall analysed were 32.068 participants during a sit-to-stand test. The authors concluded that participants with orthostatic hypotension were more likely to be older and with hypertension. The main finding of the authors was that thus with orthostatic

hypotension had a higher mortally rate (due injuries and neurological diseases) compared to participants without orthostatic hypotension (105).

Older persons are more affected by higher incidence of orthostasis hypotension because of physiological changes during progressing age. Autonomic dysfunction, baroreceptor hyposensitivity which causes hypertension are also involved in the ethology of orthostatic hypotension (106). Hiitola et al. (2009) performed a cross-sectional study. The investigators analysed home-dwelling participants (n=653), mean age 81 during a sit-to-stand test. Hiitola et al. (2009) reported following results. Participants with a resting systolic blood pressure above 160 mmHg are at a 20% higher risk to have systolic orthostatic hypotension than those with lower blood pressure (106). Authors also reported an interaction regardless the number of used medications. Participants with a higher number of regular used medications had a higher incidence of orthostatic hypotension. But antihypertensive medication did not influence the incidence of orthostatic hypotension (105, 106).

Persons with a higher incidence of orthostatic hypotension have also an increased incidence of falls and related injuries. Shaw et al. (2015) conducted a cross-sectional study, on 59 elderly subjects (long-term dwelling). The subjects performed a passive orthostatic test. The authors measured cerebral blood perfusion and systolic blood pressure via a beat-to-beat method. The authors reported following results. Elderly subjects diagnosed with a susceptibility to falls had a reduced postural systolic blood pressure. The systolic blood pressure reduction during standing was higher compared to non-fallers. Also, reduction of the cerebral perfusion during the orthostatic test was higher than in the control group. The authors conclude that orthostatic regulation mechanisms in fallers show alteration compared to non-fallers (107).

According to an earlier study, patients with stroke have a higher incidence of orthostatic hypotension and falls compared to persons of the same age. Phipps et al. (2012) performed a secondary analysis of medical data from outpatients with stroke. He analysed 116 patients with stroke. The authors concluded that patients with stroke compared to the overall population experience a greater incidence of orthostatic hypotension. Because of the higher incidence of orthostatic hypotension falls are a common medical problem (10). We saw none differences between patients with stroke and elderly healthy persons. We guess that this results from the similar health conditions in both groups. The both groups had similar blood pressure at rest and similar health status (no disabilities and immobilization). Previously mentioned studies reported that higher

blood pressure at rest and disabilities and immobilizations showed a higher probability for orthostatic hypotension. This could explain why we did not saw cases of orthostatic hypotension and differences between the groups

5.5 SEX AND POSTURAL BLOOD PRESSURE VARIABILITY

Our results confirmed the hypothesis that hemodynamic parameters and heart rate variability responses to orthostatic stress induced by a sit-to-stand test will show significant sex differences across seasons. In our study orthostatic loading (sit-to-stand test) results in hemodynamic responses in both sexes. We reported that in non-stroke males, during 20 seconds of standing, systolic blood pressure decreased in warmer months (-18.75 mmHg), mean blood pressure, during 30 seconds of standing decreased in warmer months (-14.8 mmHg) and colder months (-10.15 mmHg). In females without a stroke, during the last 5 minutes of standing, stroke index decreased in colder months (-3.0), heart rate, during 10-30 seconds of standing increased in colder months (+10.6 bpm).

In the literature reported is that there are sex differences in postural blood pressure variability which is a normal physiological phenomenon. During standing to compensate the blood pressure changes, males response with increases in peripheral vascular resistance while females response with increases in stroke volume and heart rate. Women have lower orthostatic tolerance than men of the same age. Because of lower orthostatic tolerance, younger women experience more syncope. In the later years post-menopausal women experience less orthostatic hypotension compared to younger women (45). Our results shown sex differences in hemodynamic responses to orthostatic loading (sit-to-stand test). Females without a stroke had a lower high frequency (normalized) and a higher low frequency (normalized) values of the heart rate variability during 10 seconds of standing in warmer months compared to males without a stroke. Also, females with a stroke had significant higher mean blood pressure during 30 seconds of standing in warmer months compared to males with a stroke. Low frequency (normalized) of the heart rate variability during 10-20 seconds of standing were higher in females with a stroke in colder months compare to males with stroke.

Our study is in contrast to two earlier published study by Barantke et al. (2008) on 362 subjects (206 women, and 156 men) age from 10 to 88 years, reported that during standing: i) the heart rate was higher in women compared to man; ii) and the systolic and diastolic blood pressure shows no significant sex differences, iii) lower frequency of heart rate variability was higher in men, iv) and high frequency was higher in women (108). Also, reported is by Sarafian et al. (2017), analysing 23 healthy young adults (10 women and 13 men) during a graded incremental tilting test, that there were no sex differences in

heart rate and blood pressure. The lower frequency of the heart rate variability during tilting were lower in women compared to men (109). We see that there are differences in the results between these two studies and our study; we assume that this is particularly a consequence of the differences in the age profile of the included participants. In the first study we see that included are women of all ages without any age differentiation and in the second study included are only younger women.

5.6 SEASONAL POSTURAL BLOOD PRESSURE VARIABILITY

We confirm our hypothesise that hemodynamic responses to orthostatic stress will show significant seasonal difference in patients with stroke and participants without stroke. We saw a greater blood pressure decreases in patients with stroke and participants without stroke, in warmer months compared to colder months. However, we cannot report any case of orthostatic hypotension or syncope in this study because of the less effective orthostatic loading protocol (sit-to-stand test) or the health status in both groups. Our patients had a minor stroke at hospitalization and overall no disability after stroke. Some authors have earlier reported that orthostatic intolerance is common in patients with pre-stroke morbid condition, a severe stroke, post-stroke disability and prolonged immobilisation (9, 10, 95, 110). We realise that our patients had tendencies to orthostatic hypotension, because of the older age, autonomic dysfunction and/or stroke, but our patients were healthy and cardiovascular and autonomic mechanisms where able to response effectively to orthostatic stress (sit-to-stand test). We assume that in patients with severe stroke and disability and immobilisation changes between seasons were much more dramatically and orthostatic hypotension and syncope would occur.

Several researchers have earlier reported an influence of seasonal temperature variations on blood pressure reduction caused by upright standing. Radak and Tanaskovic (2016) and Wiess et al. (2006) noted that blood pressure drop upon standing was higher in summer than in winter, and that the incidence of orthostatic hypotension is higher in summer (64%) than in winter (60, 62). Additionally, Wiess et al. (2006) reported faster heart rate upon standing in winter, which they explained with increased sympathetic activity (62). In persons with pathological conditions (aging, autonomic dysfunctions, cerebrovascular diseases) or which use blood pressure lowering medication responses to standing will not be adequate which in turn reduced cerebral blood flow and result in a lose of consciousness and syncope (111). It has been reported that in patients after a stroke because of endothelial dysfunctions, autonomic dysfunction and impairment of the baroreflex responses blood pressure regulation during standing is impaired. Patients after a stroke have a higher incidence of orthostatic hypotension and falls compared to healthy older persons. Furthermore, Korpelainen et al. (1994) reported in his study during a tilt table test with 40 patients with acute stroke, that responses of the heart rate to tilting stimuli is suppressed and this remains up to 6 months after the first measurement

(parasympathetic hypofunction) (110). Kong et al. (2003) performed a tilt table study with 71 patients (74.6% infarcts and 25.4% haemorrhages) during 4-months rehabilitations program. They reported that orthostatic hypotension was common in 52.1% patents because of older age, muscle weakness and prolonged immobilisation or bed rest (9). We could not find any study related to seasonal variability of postural blood pressure on patients with stroke which make our study unique.

Nevertheless, in our study we could not observe any significant differences in hemodynamic parameters and heart rate responses to orthostatic loading (sit-to-stand test) between patients with stroke and participants without a stroke. We assume that because our patients with stroke had minor stroke at hospitalization, not at all post-stroke disabilities and immobilization we saw none differences between the two groups. Still a main limitation of the study is the small sample size and the composition of the two groups (more males than females in the stroke groups). Nevertheless, studies which examine hemodynamic responses to orthostatic loading in patients with stroke across seasons are rare, this study can be a good basis for further studies with a larger sample size. Our results underline the importance to a further study with much more patients, with severe stroke and post-stroke disabilities. Furthermore, patients with severe stroke should be checked for changes in postural blood pressure variability since these changes are linked to the prevalence of falls due orthostatic hypotension (62).

5.7 CONCLUSION

In this thesis we examined hemodynamic responses to orthostatic loading and differences in hemodynamic responses to orthostatic loading between patients with a stroke and participants without a stroke and between males and females. At first, our observation shows that resting blood pressure values in patients with a stroke and in participants without a stroke depend on season, being higher in colder months. Second, standing up leads to a significant decrease in systolic blood pressure in warmer months, a significant decrease in diastolic blood pressure in both seasons in non-stroke participants and a significant decrease in mean blood pressure in warmer months in both groups. Our study shows that patients with stroke and older participants without stroke respond comparably to orthostatic loading with greater blood pressure decrease in warmer months. Since our patients were one-year after stroke, with a lesser stroke at hospitalization and with no additional disability or immobilization reported is no case of orthostatic hypotension even with blood pressure reduction in warmer months. At last, heart rate variability responses to orthostatic loading show differences between males and females. Females had a lower high frequency (normalized) and a higher low frequency (normalized) values of the heart rate variability during standing. To our knowledge this is the first study that examined the seasonal postural hemodynamic responses during an orthostatic loading (sit-to-stand test) in patients with a stroke. The results of our study point for a season and sex dependency of the underlying mechanisms that needs to be considered within the rehabilitation procedures of patients with stroke.

6 BIBLIOGRAPHY

1. Wu C, Shlipak MG, Stawski RS, Peralta CA, Psaty BM, Harris TB, et al. Visit-to-Visit Blood Pressure Variability and Mortality and Cardiovascular Outcomes Among Older Adults: The Health, Aging, and Body Composition Study. Am J Hypertens. 2017;30(2):151-8.
2. Wang JQ, Shi XB, Ma CS, Zheng H, Xiao J, Bian H, et al. Visit-to-visit blood pressure variability is a risk factor for all-cause mortality and cardiovascular disease: a systematic review and meta-analysis. J Hypertens. 2017;35(1):10-7.
3. Goswami N, Blaber AP, Hinghofer-Szalkay H, Montani JP. Orthostatic Intolerance in Older Persons: Etiology and Countermeasures. Front Physiol. 2017;8.
4. Hoffman GJ, Hays RD, Shapiro MF, Wallace SP, Ettner SL. The Costs of Fall-Related Injuries among Older Adults: Annual Per-Faller, Service Component, and Patient Out-of-Pocket Costs. Health Serv Res. 2017;52(5):1794-816.
5. Bird ML, Pittaway JK, Cuisick I, Rattray M, Ahuja KDK. Age-Related Changes in Physical Fall Risk Factors: Results from a 3 Year Follow-up of Community Dwelling Older Adults in Tasmania, Australia. Int J Environ Res Public Health. 2013;10(11):5989-97.
6. Pasma JH, Bijlsma AY, Klip JM, Stijntjes M, Blauw GJ, Muller M, et al. Blood Pressure Associates with Standing Balance in Elderly Outpatients. PLoS One. 2014;9(9).
7. Goh CH, Ng SC, Kamaruzzaman SB, Chin AV, Poi PJH, Chee KH, et al. Evaluation of Two New Indices of Blood Pressure Variability Using Postural Change in Older Fallers. Medicine. 2016;95(19).
8. Shaw BH, Claydon VE. The relationship between orthostatic hypotension and falling in older adults. Clin Auton Res. 2014;24(1):3-13.
9. Kong KH, Chuo AM. Incidence and outcome of orthostatic hypotension in stroke patients undergoing rehabilitation. Arch Phys Med Rehabil. 2003;84(4):559-62.
10. Phipps MS, Schmid AA, Kapoor JR, Peixoto AJ, Williams LS, Bravata DM. Orthostatic hypotension among outpatients with ischemic stroke. J Neurol Sci. 2012;314(1-2):62-5.
11. Barnett AG, Sans S, Salomaa V, Kuulasmaa K, Dobson AJ, Project WM. The effect of temperature on systolic blood pressure. Blood Press Monit. 2007;12(3):195-203.

12. Chopra S, Baby C, Jacob JJ. Neuro-endocrine regulation of blood pressure. Indian J Endocrinol Metab. 2011;15 Suppl 4:S281-8.
13. Arthur C. Guyton JEH. Textbook of Medical Physiology. Elsevier. 2006.
14. How does the nervous system work? : IQWiG (Institute for Quality and Efficiency in Health Care); 2009.
15. Ludwig PE DS. Neuroanatomy, Central Nervous System (CNS) [Updated 2017 Jun 16]. In: StatPearls [Internet]. . Treasure Island (FL): StatPearls Publishing. 2018.
16. Gordan R, Gwathmey JK, Xie LH. Autonomic and endocrine control of cardiovascular function. World J Cardiol. 2015;7(4):204-14.
17. McCorry LK. Physiology of the autonomic nervous system. Am J Pharm Educ. 2007;71(4).
18. Heesch CM. Reflexes that control cardiovascular function. Adv Physiol Educ. 1999;22(1):S234-S43.
19. Kougias P, Weakley SM, Yao QZ, Lin PH, Chen CY. Arterial baroreceptors in the management of systemic hypertension. Med Sci Monit. 2010;16(1):RA1-RA8.
20. Kalmar AF, Van Aken J, Caemaert J, Mortier EP, Struys MM. Value of Cushing reflex as warning sign for brain ischaemia during neuroendoscopy. Br J Anaesth. 2005;94(6):791-9.
21. Atlas SA. The renin-angiotensin aldosterone system: Pathophysiological role and pharmacologic inhibition. J Manag Care Pharm. 2007;13(8):S9-S20.
22. Zoller RP, Mark AL, Abboud FM, Schmid PG, Heistad DD. The role of low pressure baroreceptors in reflex vasoconstrictor responses in man. J Clin Invest. 1972;51(11):2967-72.
23. Goetz KL, Bond GC, Bloxham DD. Atrial receptors and renal-function. Physiol Rev. 1975;55(2):157-205.
24. OpenStax College. Anatomy and Physiology. Rice University 2013.
25. Laughlin MH. Cardiovascular response to exercise. Adv Physiol Educ. 1999;22(1):S244-S59.
26. Paul M, Mehr AP, Kreutz R. Physiology of local renin-angiotensin systems. Physiol Rev. 2006;86(3):747-803.
27. Kobori H, Nangaku M, Navar LG, Nishiyama A. The intrarenal renin-angiotensin system: From physiology to the pathobiology of hypertension and kidney disease. Pharmacol Rev. 2007;59(3):251-87.

28. Malpas SC. Neural influences on cardiovascular variability: possibilities and pitfalls. Am J Physiol-Hrt Circulat Physiol. 2002;282(1):H6-H20.
29. J. BP. Lehninger: principles of biochemistry (4th edn) D. L. Nelson and M. C. Cox, W. H. Freeman & Co., New York, 1119 pp (plus 17 pp glossary), ISBN 0-7167-4339-6 (2004). Cell Biochem Funct. 2005;23(4):293-4.
30. Stewart JM. Common Syndromes of Orthostatic Intolerance. Pediatrics. 2013;131(5):968-80.
31. Hiramatsu K, Yamada T, Katakura M. Acute effects of cold on blood-pressure, renin-angiotensin-aldosterone system, catecholamines and adrenal-steroids in man. Clin Exp Pharmacol Physiol. 1984;11(2):171-9.
32. Erlanger J, Festerling EG. Respiratory waves of blood pressure, with an investigation of a method for making continuous blood pressure records in man. J Exp Med. 1912;15(4):370-U12.
33. Perel A. The physiological basis of arterial pressure variation during positive-pressure ventilation. Réanimation. 2005;14(3):162-71.
34. Julien C. The enigma of Mayer waves: Facts and models. Cardiovasc Res. 2006;70(1):12-21.
35. Morris KF, Nuding SC, Segers LS, Baekey DM, Shannon R, Lindsey BG, et al. Respiratory and Mayer wave-related discharge patterns of raphe and pontine neurons change with vagotomy. J Appl Physiol. 2010;109(1):189-202.
36. Reulecke S, Charleston-Villalobos S, Voss A, Gonzalez-Camarena R, Gonzalez-Hermosillo J, Gaitan-Gonzalez MJ, et al. Men and women should be separately investigated in studies of orthostatic challenge due to different gender-related dynamics of autonomic response. Physiol Meas. 2016;37(3):314-32.
37. Prabhavathi K, Selvi KT, Poornima KN, Sarvanan A. Role of biological sex in normal cardiac function and in its disease outcome - a review. Journal of clinical and diagnostic research : JCDR. 2014;8(8):BE01-BE4.
38. Reckelhoff JF. Gender differences in the regulation of blood pressure. Hypertension. 2001;37(5):1199-208.
39. Cannoletta M, Cagnacci A. Modification of blood pressure in postmenopausal women: role of hormone replacement therapy. International journal of women's health. 2014;6:745-57.
40. Kolar F, Ostadal B. Sex differences in cardiovascular function. Acta Physiologica. 2013;207(4):584-7.

41. Lima R, Wofford M, Reckelhoff JF. Hypertension in Postmenopausal Women. Curr Hypertens Rep. 2012;14(3):254-60.
42. Merz AA, Cheng SS. Sex differences in cardiovascular ageing. Heart. 2016;102(11):825-31.
43. Pinto E. Blood pressure and ageing. Postgrad Med J. 2007;83(976):109-14.
44. O'Mahony D, Bennett C, Green A, Sinclair AJ. Reduced baroreflex sensitivity in elderly humans is not due to efferent autonomic dysfunction. Clin Sci (Lond). 2000;98(1):103-10.
45. Edgell H, Robertson AD, Hughson RL. Hemodynamics and brain blood flow during posture change in younger women and postmenopausal women compared with age-matched men. J Appl Physiol. 2012;112(9):1482-93.
46. Parker BA, Kalasky MJ, Proctor DN. Evidence for sex differences in cardiovascular aging and adaptive responses to physical activity. Eur J Appl Physiol. 2010;110(2):235-46.
47. Gupta V, Lipsitz LA. Orthostatic hypotension in the elderly: Diagnosis and treatment. Am J Med. 2007;120(10):841-7.
48. Takahashi M, Miyai N, Nagano S, Utsumi M, Oka M, Yamamoto M, et al. Orthostatic Blood Pressure Changes and Subclinical Markers of Atherosclerosis. Am J Hypertens. 2015;28(9):1134-40.
49. Sheldon RS, Grubb BP, Olshansky B, Shen WK, Calkins H, Brignole M, et al. 2015 Heart Rhythm Society Expert Consensus Statement on the Diagnosis and Treatment of Postural Tachycardia Syndrome, Inappropriate Sinus Tachycardia, and Vasovagal Syncope. Heart Rhythm. 2015;12(6):E41-E63.
50. Edvardsson N, Garutti C, Rieger G, Linker NJ, Investigators PS. Unexplained Syncope: Implications of Age and Gender on Patient Characteristics and Evaluation, the Diagnostic Yield of an Implantable Loop Recorder, and the Subsequent Treatment. Clin Cardiol. 2014;37(10):618-25.
51. Wenner MM, Haddadin AS, Taylor HS, Stachenfeld NS. Mechanisms contributing to low orthostatic tolerance in women: the influence of oestradiol. Journal of Physiology-London. 2013;591(9):2345-55.
52. Fu Q, Arbab-Zadeh A, Perhonen MA, Zhang R, Zuckerman JH, Levine BD. Hemodynamics of orthostatic intolerance: implications for gender differences. Am J Physiol Heart Circ Physiol. 2004;286(1):H449-57.

53. Finucane C, O'Connell MDL, Donoghue O, Richardson K, Savva GM, Kenny RA. Impaired Orthostatic Blood Pressure Recovery Is Associated with Unexplained and Injurious Falls. J Am Geriatr Soc. 2017;65(3):474-82.
54. Lee H, Kim HA. Orthostatic hypertension: An underestimated cause of orthostatic intolerance. Clin Neurophysiol. 2016;127(4):2102-7.
55. van Wijnen VK, Ten Hove D, Gans ROB, Nieuwland W, van Roon AM, Ter Maaten JC, et al. Orthostatic blood pressure recovery patterns in suspected syncope in the emergency department. Emerg Med J. 2018;35(4):226-30.
56. Fedorowski A, Hamrefors V, Sutton R, van Dijk JG, Freeman R, Lenders JWM, et al. Do we need to evaluate diastolic blood pressure in patients with suspected orthostatic hypotension? Clin Auton Res. 2017;27(3):167-73.
57. van Wijnen VK, Finucane C, Harms MPM, Nolan H, Freeman RL, Westerhof BE, et al. Noninvasive beat-to-beat finger arterial pressure monitoring during orthostasis: a comprehensive review of normal and abnormal responses at different ages. J Intern Med. 2017;282(6):468-83.
58. Burns ER, Stevens JA, Lee R. The direct costs of fatal and non-fatal falls among older adults - United States. Journal of Safety Research. 2016;58:99-103.
59. Sega R, Cesana G, Bombelli M, Grassi G, Stella ML, Zanchetti A, et al. Seasonal variations in home and ambulatory blood pressure in the PAMELA population. J Hypertens. 1998;16(11):1585-92.
60. Radak D, Tanaskovic S. "Summer Dizziness" as a Neglected Phenomenon of Antihypertensive Drug Overuse in Patients With Carotid Disease: A Hypothesis. Angiology. 2016;67(9):797-8.
61. Fares A. Winter Hypertension: Potential mechanisms. International Journal of Health Sciences. 2013;7(2):210-9.
62. Weiss A, Beloosesky Y, Grinblat J, Grossman E. Seasonal changes in orthostatic hypotension among elderly admitted patients. Aging Clin Exp Res. 2006;18(1):20-4.
63. Koplove HM. Principles of biochemistry - Lehninger,al. Chemical Engineering. 1984;91(23):145-6.
64. Brennan PJ, Greenberg G, Miall WE, Thompson SG. Seasonal variation in arterial blood pressure. Br Med J (Clin Res Ed). 1982;285(6346):919-23.
65. Shaffer F, McCraty R, Zerr CL. A healthy heart is not a metronome: an integrative review of the heart's anatomy and heart rate variability. Front Psychol. 2014;5:1040.

66. Joseph Loscalzo ASF, Dennis L. Kasper, Dan L. Longo, Eugene Braunwals, Stephen L. Hauser, J. Larry Jameson. Harrison's Cardiovascular medicine. The McGraw-Hill Companies. 2010.
67. Chen R, Ovbiagele B, Feng W. Diabetes and Stroke: Epidemiology, Pathophysiology, Pharmaceuticals and Outcomes. Am J Med Sci. 2016;351(4):380-6.
68. Hörnsten C, Weidung B, Littbrand H, Carlberg B, Nordström P, Lövheim H, et al. High blood pressure as a risk factor for incident stroke among very old people: a population-based cohort study. J Hypertens. 2016;34(10):2059-65.
69. Willmot M, Leonardi-Bee J, Bath PMW. High blood pressure in acute stroke and subsequent outcome - A systematic review. Hypertension. 2004;43(1):18-24.
70. Panayiotou B, Reid J, Fotherby M, Crome P. Orthostatic haemodynamic responses in acute stroke. Postgrad Med J. 1999;75(882):213-8.
71. Gibson CL. Cerebral ischemic stroke: is gender important? J Cereb Blood Flow Metab. 2013;33(9):1355-61.
72. Michael Brainin W-DHaHS. Textbook of stroke medicine. Cambridge University Press. 2010.
73. Adams HP, del Zoppo G, Alberts MJ, Bhatt DL, Brass L, Furlan A, et al. Guidelines for the early management of adults with ischemic stroke - A guideline from the American Heart Association/American Stroke Association Stroke Council, Clinical Cardiology Council, Cardiovascular Radiology and Intervention Council, and the atherosclerotic peripheral vascular disease and quality of care outcomes in research interdisciplinary working groups. Stroke. 2007;38(5):1655-711.
74. Bansal S, Sangha KS, Khatri P. Drug Treatment of Acute Ischemic Stroke. Am J Cardiovasc Drugs. 2013;13(1):57-69.
75. Steiner T, Al-Shahi Salman R, Beer R, Christensen H, Cordonnier C, Csiba L, et al. European Stroke Organisation (ESO) guidelines for the management of spontaneous intracerebral hemorrhage. Int J Stroke. 2014;9(7):840-55.
76. Robinson TG, Potter JF. Postprandial and orthostatic cardiovascular changes after acute stroke. Stroke. 1995;26(10):1811-6.
77. Pautasso M. Ten Simple Rules for Writing a Literature Review. PLoS Comput Biol. 2013;9(7).
78. Trozic I, Platzer D, Fazekas F, Bondarenko AI, Brix B, Rössler A, et al. Postural hemodynamic parameters in older persons have a season-dependency. Z Gerontol Geriatr. 2019.

79. Tang A, Eng JJ, Krassioukov A. Application of the Sit-Up Test for orthostatic hypotension in individuals with stroke. Autonomic Neuroscience-Basic & Clinical. 2012;168(1-2):82-7.
80. Brady T West KBW, Andrzej T Galecki. Linear mixed models: a practical guide using statistical software. 2014/7/17.
81. Wang M. Generalized Estimating Equations in Longitudinal Data Analysis: A Review and Recent Developments. Advances in Statistics. 2014.
82. Buford TW. Hypertension and aging. Ageing Research Reviews. 2016;26:96-111.
83. Bolívar JJ. Essential hypertension: an approach to its etiology and neurogenic pathophysiology. Int J Hypertens. 2013;2013:547809-.
84. Hornsten C, Weidung B, Littbrand H, Carlberg B, Nordstrom P, Lovheim H, et al. High blood pressure as a risk factor for incident stroke among very old people: a population-based cohort study. J Hypertens. 2016;34(10):2059-65.
85. Gaciong Z, Sinski M, Lewandowski J. Blood Pressure Control and Primary Prevention of Stroke: Summary of the Recent Clinical Trial Data and Meta-Analyses. Curr Hypertens Rep. 2013;15(6):559-74.
86. Appleton JP, Sprigg N, Bath PM. Blood pressure management in acute stroke. Stroke and vascular neurology. 2016;1(2):72-82.
87. Howard G, Banach M, Cushman M, Goff DC, Howard VJ, Lackland DT, et al. Is Blood Pressure Control for Stroke Prevention the Correct Goal? The Lost Opportunity of Preventing Hypertension. Stroke. 2015;46(6):1595-+.
88. Qureshi AI, Ezzeddine MA, Nasar A, Suri MFK, Kirmani JF, Hussein HM, et al. Prevalence of elevated blood pressure in 563,704 adult patients with stroke presenting to the ED in the United States. Am J Emerg Med. 2007;25(1):32-8.
89. Carlsson A, Britton M. Blood-pressure after stroke - a one-year follow-up-study. Stroke. 1993;24(2):195-9.
90. Kohok DD, Sico JJ, Baye F, Myers L, Coffing J, Kamalesh M, et al. Post-stroke hypertension control and receipt of health care services among veterans. J Clin Hypertens. 2018;20(2):382-7.
91. Treib J, Haass A, Krammer I, Stoll M, Grauer MT, Schimrigk K. Cardiac output in patients with acute stroke. J Neurol. 1996;243(8):575-8.
92. Fuhrer H, Reinhard M, Niesen WD. Paradigm Change? Cardiac Output Better Associates with Cerebral Perfusion than Blood Pressure in Ischemic Stroke. Front Neurol. 2017;8.

93. Xu XL, Wang B, Ren CH, Hu JN, Greenberg DA, Chen TX, et al. Recent Progress in Vascular Aging: Mechanisms and Its Role in Age-related Diseases. Aging Dis. 2017;8(4):486-505.
94. Kienitz T, Quinkler M. Testosterone and blood pressure regulation. Kidney Blood Press Res. 2008;31(2):71-9.
95. Lai S-M, Duncan PW, Dew P, Keighley J. Sex differences in stroke recovery. Prev Chronic Dis. 2005;2(3):A13-A.
96. Bell CL, LaCroix A, Masaki K, Hade EM, Manini T, Mysiw WJ, et al. Prestroke factors associated with poststroke mortality and recovery in older women in the Women's Health Initiative. J Am Geriatr Soc. 2013;61(8):1324-30.
97. Wilson ME. Stroke: understanding the differences between males and females. Pflugers Archiv-European Journal of Physiology. 2013;465(5):595-600.
98. Yao X-Y, Lin Y, Geng J-L, Sun Y-M, Chen Y, Shi G-W, et al. Age- and gender-specific prevalence of risk factors in patients with first-ever ischemic stroke in china. Stroke research and treatment. 2012;2012:136398-.
99. Caso V, Paciaroni M, Agnelli G, Corea F, Ageno W, Alberti A, et al. Gender Differences in Patients with Acute Ischemic Stroke. Womens Health. 2010;6(1):51-7.
100. Appelros P, Stegmayr B, Terent A. Sex Differences in Stroke Epidemiology A Systematic Review. Stroke. 2009;40(4):1082-90.
101. Iwahori T, Miura K, Obayashi K, Ohkubo T, Nakajima H, Shiga T, et al. Seasonal variation in home blood pressure: findings from nationwide web-based monitoring in Japan. BMJ open. 2018;8(1):e017351-e.
102. Kunutsor SK, Powles JW. The effect of ambient temperature on blood pressure in a rural West African adult population: a cross-sectional study. Cardiovasc J Afr. 2010;21(1):17-20.
103. Huang JJ, Sharda N, Bin Riaz I, Alpert JS. Summer Syncope Syndrome. Am J Med. 2014;127(8):787-90.
104. Schlader ZJ, Wilson TE, Crandall CG. Mechanisms of orthostatic intolerance during heat stress. Autonomic Neuroscience-Basic & Clinical. 2016;196:37-46.
105. Fedorowski A, Hedblad B, Melander O. Early postural blood pressure response and cause-specific mortality among middle-aged adults. Eur J Epidemiol. 2011;26(7):537-46.

106. Hiitola P, Enlund H, Kettunen R, Sulkava R, Hartikainen S. Postural changes in blood pressure and the prevalence of orthostatic hypotension among home-dwelling elderly aged 75 years or older. J Hum Hypertens. 2009;23(1):33-9.
107. Shaw BH, Loughin TM, Robinovitch SN, Claydon VE. Cardiovascular responses to orthostasis and their association with falls in older adults. BMC Geriatr. 2015;15.
108. Barantke M, Krauss T, Ortak J, Lieb W, Reppel M, Burgdorf C, et al. Effects of Gender and Aging on Differential Autonomic Responses to Orthostatic Maneuvers. J Cardiovasc Electrophysiol. 2008;19(12):1296-303.
109. Sarafian D, Miles-Chan JL. The Influence of Gender and Anthropometry on Haemodynamic Status at Rest and in Response to Graded Incremental Head-UpTiltin Young, HealthyAdults. Front Physiol. 2017;7.
110. Korpelainen JT, Sotaniemi KA, Suominen K, Tolonen U, Myllyla VV. Cardiovascular autonomic reflexes in brain infarction. Stroke. 1994;25(4):787-92.
111. Sinha P, Taneja DK, Singh NP, Saha R. Seasonal variation in prevalence of hypertension: Implications for interpretation. Indian J Public Health. 2010;54(1):7-10.