Diplomarbeit

Gender Differences in Cardiovascular Regulation and Orthostatic Tolerance: A Literature Review

eingereicht von

Christina Sarah Rodler

zur Erlangung des akademischen Grades

Doktor(in) der gesamten Heilkunde

(Dr. med. univ.)

an der

Medizinischen Universität Graz

ausgeführt am

Institut für Physiologie

unter der Anleitung von

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

Graz, am 7.August 2014

Eidesstattliche Erklärung

Ich erkläre ehrenwörtlich, dass ich die vorliegende Arbeit selbstständig und ohne fremde Hilfe verfasst habe, andere als die angegebenen Quellen nicht verwendet habe und die den benutzten Quellen wörtlich oder inhaltlich entnommenen Stellen als solche kenntlich gemacht habe.

Graz, am 7.August 2014 Christina Sarah Rodler eh

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

Thank you for showing me how much fun it can be to write a review. Your motivation and mindfulness for science encouraged me to write this Diplomarbeit with interest and joy.

Meine Familie

Danke, dass ich stets auf euch zählen kann. Ein besonderes Danke richte ich an dich, kleiner Bruder, weil du mich immer wieder an die Dinge erinnerst, die ich allzu leicht zu vergessen scheine.

Tiago

You are the sort of person everyone should have one their side. You are the best friend and partner I can imagine!

I especially thank you for the help with the vector drawing software!

A minha segunda família

Pude contar sempre convosco. Vocês são a minha família e a minha segunda casa. Obrigada por tudo!

Abstract

Background: There is strong evidence for existing gender differences in cardiovascular regulation and orthostatic tolerance. Especially women are prone to orthostatic intolerance. The mechanisms underlying these differences are, however, not fully understood.

Purpose: This Diplomarbeit provides an update on current knowledge on gender differences in cardiovascular regulation and orthostatic tolerance. It identifies gaps and alludes to important aspects for future studies on the discussed area.

Methodology: A systematic literature research identified relevant articles on gender differences in cardiovascular regulation and orthostatic tolerance. Essential keywords and specific exclusion and inclusion criteria led to a final collection of 158 articles and 1 thesis, all of them being published between 1991 and 2014. The findings were grouped into four key themes: 1) Baseline gender differences affecting cardiovascular function, 2) Gender differences in cardiovascular responses, 3) Influences of sex hormones on cardiovascular regulation and 4) Differences between ethnic groups. These four key themes comprise all identified topics, containing comparisons and summaries of study results as well as suggestions for future work on gender aspects in cardiovascular regulation and orthostatic tolerance.

Discussion: Orthostatic tolerance depends on the ability to maintain blood pressure upon orthostatic stress. Premenopausal women are more susceptible to orthostatic intolerance than age-matched men. Differences in anatomy, hemodynamics and the autonomic nervous system seem to form the basis for these gender differences. Moreover, women show differences between themselves. Ovarian hormones appear to cause not only the differences between genders but also the differences between women. Estradiol promotes vasodilation and thereby attenuates vasoconstriction. Women with low orthostatic tolerance are characterized by a greater sensitivity to estradiol and a poor increase in peripheral vascular resistance. Women with high orthostatic tolerance in turn show a greater responsiveness to progesterone and a greater increase in peripheral vascular resistance. While progesterone seems to trigger the activation of the RAAS, its role in cardiovascular regulation remains poorly understood. Recently it has been shown that orthostatic tolerance is higher in black than in white premenopausal

women, whereas the underlying mechanisms remain to be identified. In summary, gender differences in orthostatic tolerance seem to be multifactorial, but the influence of female sex hormones on the autonomic nervous system appears to play a major role. Men predominantly respond to orthostatic stress by increasing peripheral resistance, whereas women tend to increase heart rate. Among women it is especially white, young women with a greater sensitivity to estradiol who are prone to orthostatic intolerance.

Zusammenfassung

Hintergrund: Vieles weist darauf hin, dass es Geschlechtsunterschiede in Kreislaufregulation und orthostatischer Toleranz gibt. Vor allem Frauen neigen zu orthostatischer Intoleranz. Dennoch sind die Mechanismen, die diesen Unterschieden zugrunde liegen, nicht gänzlich geklärt.

Ziel: Diese Diplomarbeit bietet einen aktuellen Wissensstand über Geschlechtsunterschiede in Kreislaufregulation und orthostatischer Toleranz. Sie zeigt Lücken auf und weist auf wichtige Aspekte hin, die für zukünftige Forschungsarbeiten in diesem Gebiet wichtig sind.

Methoden: Eine systematische Literaturrecherche identifizierte relevante Artikel zum Thema der Geschlechtsunterschiede in Kreislaufregulation und orthostatischer Toleranz. Die Ergebnisse wurden in Hauptthemen unterteilt, die sowohl Vergleiche als auch Zusammenfassungen der Studienergebnisse enthalten. Essentielle Schlagwörter und spezifische Ausschluss- und Einschlusskriterien führten zu einer endgültigen Sammlung von 158 Artikeln und einer Doktorarbeit, alle publiziert zwischen 1991 und 2014. Die Ergebnisse wurden in vier Hauptthemen eingeteilt: 1) Grundsätzliche Geschlechtsunterschiede, die die Kreislaufregulation beeinflussen, 2) Geschlechtsunterschiede in Kreislaufreaktionen, 3) Einflüsse von Geschlechtshormonen auf die Kreislaufregulation und 4) Unterschiede zwischen ethnischen Gruppen. Diese vier Hauptthemen umfassen alle identifizierten Themengebiete, und enthalten sowohl Vergleiche und Zusammenfassung von Studienergebnissen, als auch Vorschläge für zukünftige Forschungsarbeit in Bezug auf Geschlechtsaspekte in Kreislaufregulation und orthostatischer Toleranz.

Diskussion: Orthostatische Toleranz hängt von der Fähigkeit ab, den Bludruck während eines orthostatischen Stresses aufrecht zu erhalten. Frauen vor den Wechseljahren sind anfälliger für orthostatische Intoleranz als gleichaltrige Männer. Unterschiede in Anatomie, Hämodynamik und dem autonomen Nervensystem scheinen die Basis für diese Geschlechtsunterschiede zu bilden. Außerdem zeigen Frauen untereinander Unterschiede auf. Ovarielle Hormone sind allem Anschein nach nicht nur die Ursache für Geschlechtsunterschiede, sondern auch für Unterschiede zwischen Frauen. Östradiol fördert die Vasodilatation und schwächt dadurch die Vasokonstriktion ab. Frauen mir niedriger

orthostatischer Toleranz sind gekennzeichnet durch eine höhere Sensitivität für Östradiol und einem schwachen Anstieg des peripheren Gefäßwiderstandes. Frauen mit hoher orthostatischer Toleranz wiederum weisen eine höhere Sensitivität für Progesteron und einen höheren Anstieg des peripheren Gefäßwiderstandes auf. Während Progesteron allem Anschein nach die Aktivierung des RAAS auslöst, kann seine Rolle für die Kreislaufregulation nach wie vor nur wenig nachvollzogen werden. Unlängst wurde aufgezeigt, dass junge schwarze Frauen eine höhere orthostatische Toleranz aufweisen als junge weiße Frauen, wobei die zugrunde liegenden Mechanismen noch aufzuklären sind. Zusammengefasst sind Geschlechtsunterschiede in orthostatischer Toleranz wahrscheinlich multifaktoriell, jedoch scheint der Einfluss der weiblichen Geschlechtshormone auf das autonome Nervensystem eine größere Rolle zu spielen. Männer reagieren auf orthostatischen Stress überwiegend mit einem Anstieg des peripheren Widerstandes, während Frauen dazu tendieren, die Herzfrequenz zu erhöhen. Unter den Frauen sind es vor allem weiße, junge Frauen mit erhöhter Sensitivität für Östradiol, die anfällig für orthostatische Intoleranz sind.

Table of Contents

Glossary and Abbreviations

ACE	=	Angiotensin-Converting Enzyme
ADH	=	Antidiuretic Hormone
CBF	=	Cerebral Blood Flow
CNS	=	Central Nervous System
CO	=	Cardiac Output
CVP	=	Central Venous Pressure
EDV	=	End-Diastolic Volume
ESV	=	End-Systolic Volume
FMD	=	Flow Mediated Dilation
HDBR	=	Head Down Bed Rest
HR	=	Heart Rate
HUT	=	Head-Up Tilt
LBNP	=	Lower Body Negative Pressure
MAP	=	Mean Arterial Pressure
MCA	=	Middle Cerebral Artery
MSNA	=	Muscle Sympathetic Nerve Activity
MVP	=	Mean Venous Pressure
NO	=	Nitric Oxide
RAAS	=	Renin-Angiotensin-Aldosterone system
SA node	=	Sinuatrial Node
SV	=	Stroke Volume
SVR	=	Systemic Vascular Resistance
TPR	=	Total Peripheral Resistance
VIP	=	Volume Indifferent Point

Index of Figures

1 Introduction

Before diving into the complex area of gender differences in cardiovascular regulation and orthostatic tolerance, let us take a look at basic knowledge of the cardiovascular system and ways to observe its physiology.

1.1 The design of the Circulatory System

The circulatory system is made up of three main components. It consists of a pair of pumps (heart), a set of interconnected tubes (blood vessels) and a fluid that fills the tubes (blood). While some characteristics of the blood vessels vary from tissue to tissue and change with consecutive branching, there are general principles of vascular function that apply at all levels of the circulation. (1,2) Before describing these general principles, we will make a brief revision on the cardiovascular system's overall design.

1.1.1 Functional Parts of the Circulation

The arteries carry highly pressurized blood to the tissues. This pressure is necessary for the complete perfusion of capillaries in peripheral tissues. Such high pressure results in high wall tension and therefore, arteries' walls contain elastic and smooth muscle tissue to withstand the tensions they are exposed to. Elastic properties are predominant in the large conducting arteries and their main branches, whereas the relative amount of smooth muscle is increasing towards the smallest arteries. Larger arteries can be viewed as elastic tubes, absorbing energy during systole and releasing it during the diastole, contributing to the maintenance of a constant blood flow through the tissues during all of the cardiac cycle. Smaller arteries act as distributors, supplying the individual organs, hence characterized by a high amount of smooth muscle. The arteries' smallest branches are the arterioles which control the amount of blood that flows to the capillaries. Due to the high intrinsic tone of their muscular walls, arterioles possess the capability to close completely or to dilate severalfold. For this reason, they have an enormous impact on altering blood flow to the capillaries in response to the needs of the tissues. (1–3)

The capillaries' task is the exchange of substances between the blood and the interstitial space, such as fluid, nutrients, gases, electrolytes, hormones and metabolic end products. In order to do so, their single layer walls contain channels and intercellular clefts that allow water and other small molecular substances to

pass through. Capillary blood flow is extremely slow, further facilitating substance exchange. The blood from the capillaries is collected in the venules that gradually converge to larger veins, ultimately transporting the blood back to the heart. The venous system is a low pressure one, thus not requiring the veins to have walls as thick and strong as arteries. Nevertheless, they are muscular enough to contract and expand. By this, they can serve as a controllable reservoir of blood depending on the needs of the circulation. (1,2)

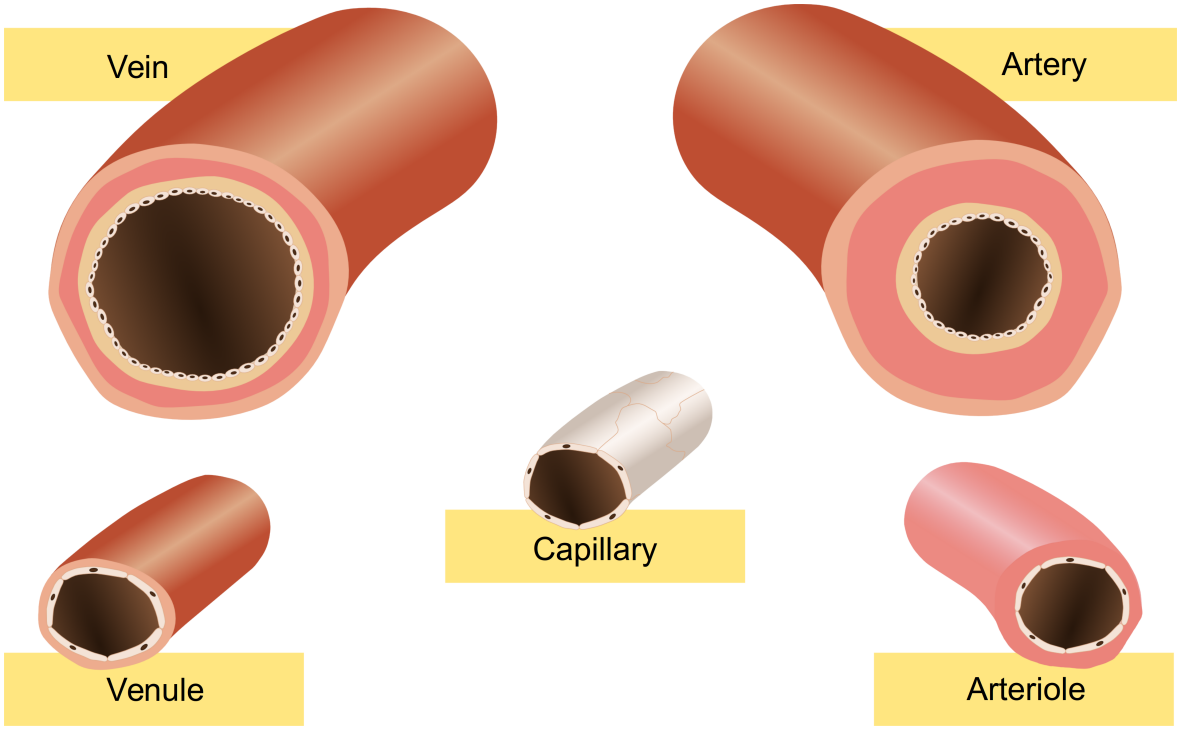

Figure 1: Blood vessels in the circulatory system

1.1.2 A short tour through the heart

The heart is an organ combining two separate valved muscular pumps. These two pumps are commonly termed right and left heart. The right heart pumps blood through the lungs, the left heart pumps it through the entire body. Both pumps work separately, but simultaneously. Each of them represents a pulsatile two-chamber pump composed of an atrium and a ventricle. The two atria act as weakly contractile primer pumps that help to move blood into the ventricles. The ventricles in turn eject the blood into the main arterial trunks, providing the powerful expulsive contraction that forces blood through the circulation. The right ventricle pushes blood into the pulmonary circulation, whereas the left ventricle

pushes it into the systemic circulation. While the blood is being pumped through the chambers of the heart there is no exchange of substances with the myocardial cells. Thus, perfusion of the heart is assured by another system, namely the coronary circulation which, contrary to the rest of the body's circulation system, perfuses the heart during the diastole. (1–3)

1.2 Cardiovascular Physiology

Now that we got a brief overview of cardiovascular anatomy, we can take a look at how its components are dynamically interconnected. The subsequent topics in this chapter provide us with information about the main physiological features of cardiovascular regulation in regards to this Diplomarbeit.

1.2.1 Interconnections between Pressure, Flow and Resistance

Blood flow in the circulation is mainly determined by blood pressure and the resistance to blood flow. The figure below (Figure 2) visualizes this determination in a scheme of a blood vessel.

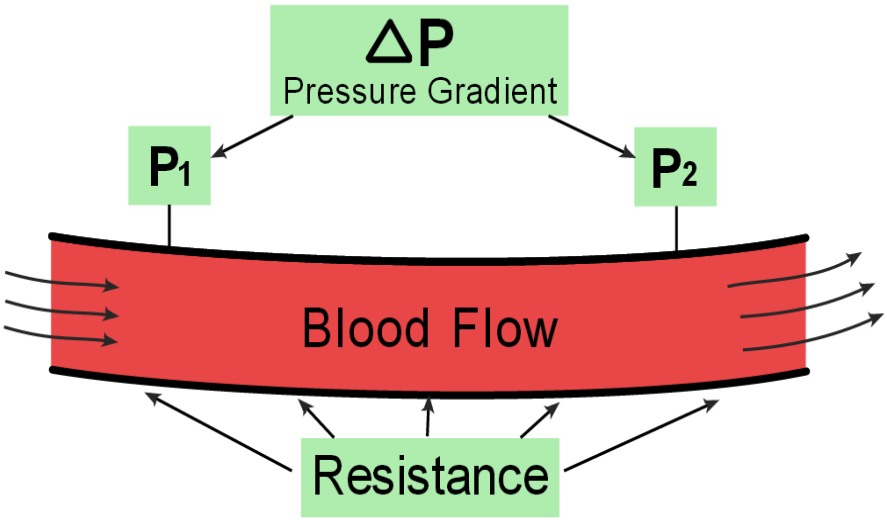

Figure 2: Relations between pressure, resistance and blood flow

Blood always flows from a region of higher pressure to a region of lower pressure. For this reason, it is important to note that it is not the absolute pressure that determines the blood flow, but the pressure difference between the two ends of a blood vessel. The resistance to blood flow is the result of friction along the inside of a blood vessel. These interconnections can be described by Ohm's law, demonstrated in the formula below (f1). (1,2)

$$Q = \frac{\Delta P}{R} \quad \text{(f1)}$$

Yet an increase in arterial pressure does not cause the proportionate increase in blood flow that we would expect from the formula. In fact, an increase in arterial pressure also leads to a decrease in vascular resistance as the vascular diameter increases due to the vessels' elasticity feature. (1)

1.2.1.1 Cardiac Output

Cardiac output is the amount of blood that is pumped by each ventricle per minute. Hence, it is the amount of blood that flows through the circulation. It is usually expressed in liters per minute. Cardiac output for the resting adult averages about 5L/min (1,2), but showing higher values in men and lower values in women. Total blood volume is in accordance with this value, thus in an average resting healthy adult, each minute total blood volume is pumped around the circuit. Cardiac output is a product of heart rate – the number of beats per minute – and stroke volume – the amount of blood ejected by each ventricle with each beat. (1,2) This equation is demonstrated in the following formula (f2).

$$CO = HR \times SV \quad \text{(f2)}$$

Cardiac output is determined almost entirely by venous return to the heart. Venous return itself is influenced by local factors in the peripheral circulation. These factors will be discussed later (1.2.2.1 Regulation of Cardiovascular Function). Cardiac output changes markedly with body size, making it necessary to include body surface area in order to compare the cardiac output of different-sized people. This is called cardiac index. (1)

Applying Ohm's law (1.2.1 Interconnections between Pressure, Flow and Resistance) to cardiac output, we can establish a connection between cardiac output and total peripheral resistance. Cardiac output represents the blood flow, arterial pressure represents the pressure difference and total peripheral resistance represents the resistance in the system. We can conclude that the longterm cardiac output level changes reciprocally with the changes in the longterm level of total peripheral resistance (f3).

$$CO = \frac{AP}{TPR} \quad \text{(f3)}$$

1.2.1.2 Heart rate

Fibers of the heart's specialized conducting system are self-exciting, meaning contraction is generated by these muscle cells themselves. The fibers of the SA node display self-excitation to the greatest extent. Thus, their discharge rate represents the heart rate, making it the heart's normal pacemaker. Due to this automaticity, rhythmical beating of the heart at the inherent autonomous discharge rate of about 100 beats/min is guaranteed in the complete absence of nervous or hormonal influences on the SA node. Nevertheless the heart rate is usually lower or higher than this as the SA node is under the permanent influence of neural and endocrine mechanisms. (1,2)

The heart is innervated by sympathetic as well as parasympathetic nerve fibers. The latter are contained in the vagus nerve. Sympathetic postganglionic fibers innervate the entire heart and release noradrenaline. Parasympathetic fibers are mainly limited to the atria and their influence is based on the release of acetylcholine. While sympathetic action leads to an acceleration in the heart rate, parasympathetic action triggers deceleration. In the resting state, the heart rate is around 70 beats/min as a result of the parasympathetic tonus. (1,2)

Adrenaline can act as a neurotransmitter as well as a hormone. It's formed in the adrenal medulla and combines with the same receptors as noradrenaline, consequently leading to an acceleration of the heart rate. (1,2)

1.2.1.3 Total Peripheral Resistance

The sum of all resistances to blood flow in all the vessels throughout the circulation defines the total peripheral resistance. We cannot measure it directly but it can be calculated from the formula we already encountered earlier (f1). We will rename the variables to have an equation that represents total peripheral resistance itself (f4).

$$TPR = \frac{MAP - MVP}{CO} \quad \text{(f4)}$$

Pressure difference in this equation is represented by the arteriovenous pressure difference. As we had already concluded earlier, the systemic vascular system is a continuous series of tubes. It starts with the aorta and ends in the right atrium. Therefore, arteriovenous pressure difference results from the pressure found in the aorta and the pressure found in the right atrium. Mean venous pressure is usually close to 0 mm Hg (2). As a result, it can be disregarded for the basic understanding. This is why we do not include the mean venous pressure in the following equation for mean arterial pressure (f5). We had mentioned earlier that the muscular walls of terminal arteries and arterioles show a high intrinsic muscle tone. Thus, it is not surprising that it is them who account for approximately 45-55% (4) of the total peripheral resistance. It is important to note that resistance in vessels is inversely proportional to the radius to the power of four. As a result, a decreased radius due to vasoconstriction will greatly increase the resistance and increased radius due to vasodilation will considerably decrease the resistance. Consequently, large changes in blood flow can occur despite high arterial pressure. We will discuss later that this effect is a result of increased or decreased sympathetic stimulation of the peripheral blood vessels. (1,2,4)

1.2.1.4 Mean Arterial Pressure

MAP is the average perfusion pressure during the cardiac cycle. The MAP in the systemic circulation enables blood flow through all the organs except the lungs (whose blood supply is guaranteed by the driving force of the mean pulmonary arterial pressure). Therefore, arterial pressure represents a crucial variable to be regulated in order to ensure the required blood flow to the organs. Alteration in the MAP is the result of a change in either cardiac output and/or total peripheral resistance. The equation relating MAP, cardiac output and the total peripheral resistance is demonstrated in the formula below (f5). (2)

$$MAP = CO \times TPR \quad \text{(f5)}$$

1.2.2 Cardiovascular Homeostasis

Homeostasis means maintenance of a state. In the case of cardiovascular homeostasis, it's about the maintenance of an adequate perfusion pressure. Therefore, the variables we discussed earlier, such as blood pressure, cardiac output and vessel resistance are adjusted to the organs' needs in order to assure

the perfusion of tissues. (4) These regulation mechanisms will be discussed below. The organs' need for an increased blood supply vary widely. Especially brain metabolism relies upon the constant supply of oxygen and glucose, which cannot be stored in the brain, making the maintenance of CBF crucial for survival of brain tissue. (4–6) Even at body rest, the brain uses between 15-20% (5,7) of the cardiac output. As there is constant changes in systemic blood pressure, cerebral circulation depends on autoregulation, assuring a relatively constant CBF as long as mean arterial blood pressures are between 50 and 150 mm Hg. (5)

1.2.2.1 Regulation of Cardiovascular Function

As the organs' needs of perfusion vary and compete, regulation is needed for the maintenance of the required arterial blood pressure. We learned earlier that arterial blood pressure is crucially depending on cardiac output and total peripheral resistance. Consequently, it is these parameters that are influenced to regulate arterial blood pressure. We will look at the several interrelated pressure controlling systems. According to when and for how long a regulating effect occurs, we can distinguish between short term and long term regulation. As a special matter of interest, we will first point out the role of the autonomic nervous system and the relevance of the main vasoactive hormones. (4)

1.2.2.1.1 The role of the Autonomic Nervous System

We learned earlier that the heart's function is regulated by the parasympathetic as well as the sympathetic nervous system. When it comes to the circulation, it is almost entirely the sympathetic nervous system that comes into play. Almost all the vessels are innervated by sympathetic nerve fibers that carry an enormous amount of vasoconstrictor nerve fibers and only a few vasodilator nerve fibers. Under normal conditions, there is continuous slow firing of vasoconstrictor nerve fibers, forming the vasomotor tone. Adrenaline as well as noradrenaline can bind to two subtypes of adrenergic receptors on arteriolar smooth muscle, namely the α- and the β2-adrenergic receptors. Activation of the α-type causes vasoconstriction and activation of the β2-type causes vasodilation. Nevertheless, in general α-adrenergic receptors greatly outnumber β2-adrenergic receptors, with the arterioles in the skeletal muscle forming an important exception. Furthermore, the autonomic nervous system offers multiple control mechanisms which will be explained in the next sections. (1,2)

1.2.2.1.2 The main vasoactive hormones

Noradrenaline and Adrenaline

Stimulation of the sympathetic nervous system causes release of noradrenaline by sympathetic nerve endings in the individual tissues. At the same time, the adrenal medullae get stimulated by sympathetic nerves to secrete both noradrenaline and adrenaline into the blood. Both act on heart and blood vessels, accelerating the heart rate and causing vasoconstriction in the peripheral circulation by binding to receptors on the vessels' smooth muscle. Noradrenaline is a more powerful vasoconstrictor than adrenaline. (1)

Angiotensin II

It is one of the most powerful vasoconstrictors and part of the renin-angiotensin-aldosterone system. It usually acts simultaneously on all the arterioles of the body, increasing total peripheral resistance. Nevertheless, after the detection of a blood pressure fall, it takes around 20 minutes before angiotensin II can get active, making it much slower than the hormones and reflexes of the sympathetic nervous system. (1) We will discuss it's role and action further in the upcoming sections (control through the kidneys 1.2.2.1.4.1).

Antidiuretic Hormone

It is also called vasopressin and is released into the blood by the posterior pituitary gland. It's two main actions are powerful vasoconstriction and retention of water in the body by increasing water absorption in the collecting ducts of the nephrons. ADH secretion is stimulated whenever their is signs of increased osmolalityty, decreased arterial pressure and/or decreased blood volume. (1) Figure 3 demonstrates the connection of ADH and blood pressure.

Atrial Natriuretic Peptide

ANP is released by atrial myocytes whenever there is an increase in atrial distension. ANP is a strong vasodilator, antagonising adrenaline and noradrenaline on vascualr smooth muscle. Furthermore, it inhibits the renin-angiotension-aldosterone system by inhibiting the release of renin. It increases the excretion of water and salt in the kidneys, consequently helping to lower the arterial blood pressure. (1,2)

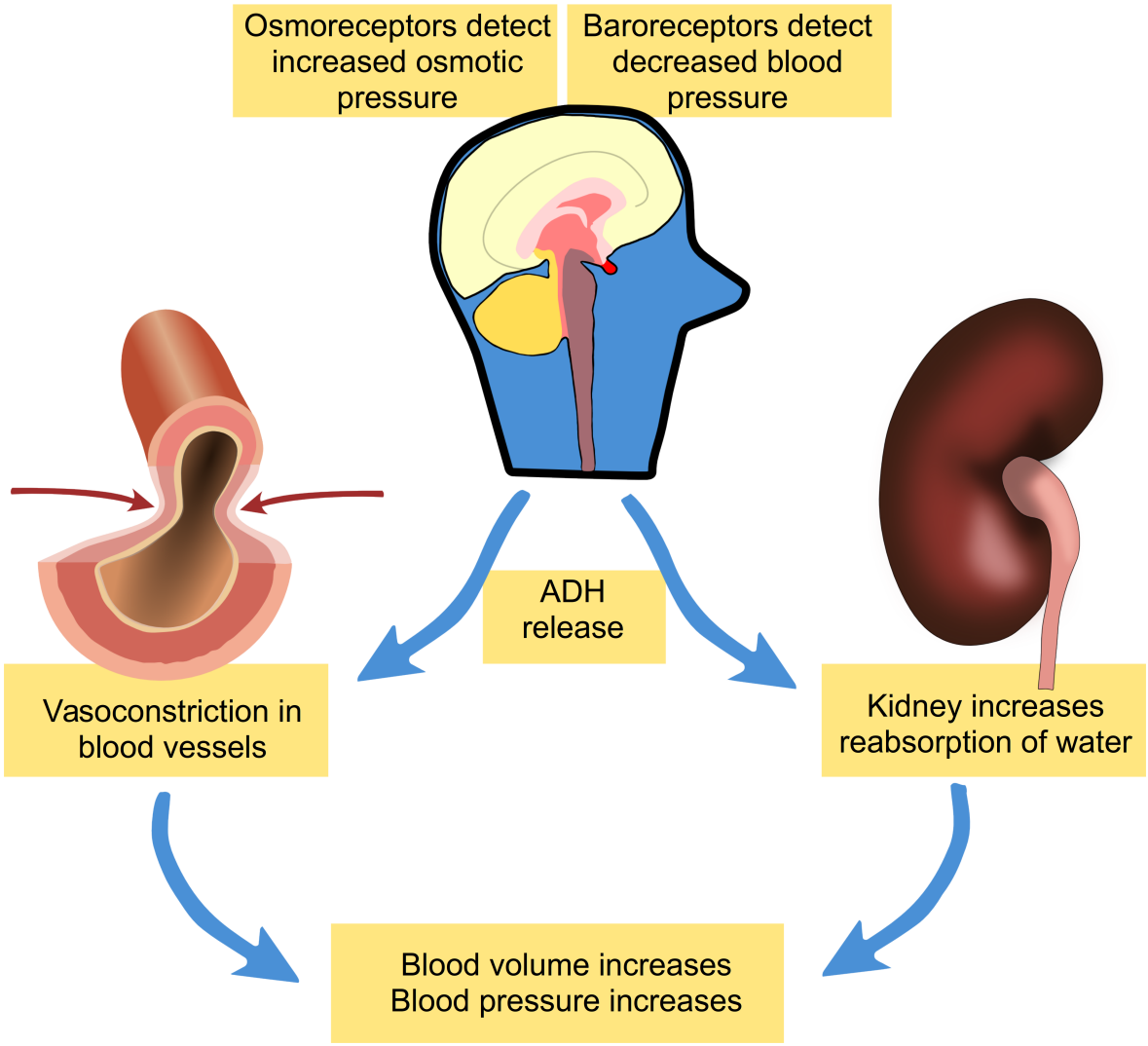

Figure 3: ADH and its influence on blood pressure

1.2.2.1.3 Short term Regulation

While local mechanisms contribute to the constant adaptation of blood flow to the required needs in the various organs and tissues, it is the autonomic nervous system that acts on a systemic level to maintain the arterial blood pressure at or near its normal operating level. Nervous control of arterial pressure is the most rapid of all mechanisms for pressure control. Responses to nervous control mechanisms occur within seconds. (1,4)

1.2.2.1.3.1 Local Control

Flow autoregulation

Whenever there is a change in blood pressure, arterioles respond with a change of resistance. The purpose is clearly to keep blood flow at the needed level. As a result, an increased blood pressure leads to vasoconstriction and a decreased blood pressure to vasodilation. This response, termed myogenic response, is mainly caused by stretch-sensitive calcium channels in the plasma-membrane. (2,4)

Active Hyperemia

Increased metabolic activity in cells near the arterioles leads to multiple local chemical changes in the extracellular fluid. In response to these changes, the arterioles' smooth muscle relaxes, resulting in vasodilation, thus increased blood flow. It makes sense that active hyperemia is most highly developed in tissues with a general high metabolic activity, such as skeletal muscle, cardiac muscle and glands. (2)

Reactive hyperemia

Reactive hyperemia occurs after a tissue has had its blood supply completely occluded. It is as a result of myogenic, metabolic and endothelial components. The myogenic response is a vasodilation to the maximum due to the stop of blood flow. The accumulation of metabolites and the lack of oxygen lead to the same reaction that we got to know in active hyperemia. At the same time endothelial cells use nitric oxide to relax the arterioles' smooth muscle, increasing vasodilation even further. (2,4)

1.2.2.1.3.2 Systemic Control

Baroreceptors

Baroreceptors are nerve endings that lie in the walls of several of the large systemic arteries. It is in the carotid sinuses and the wall of the aortic arch that baroreceptors are extremely abundant. They are stimulated when stretched and respond extraordinarily fast to sudden changes in arterial pressure. In the case of suddenly increasing blood pressure, their reflex ultimately causes vasodilation of veins and arterioles as well as a decrease in heart rate and ventricular contractility, thus decreasing total peripheral resistance as well as cardiac output. Conversely, baroreceptors respond to sudden low arterial blood pressure with a reflex that

triggers a strong sympathetic discharge throughout the body, resulting in an elevation of total peripheral resistance and cardiac output. (1,2)

Chemoreceptors

Chemoreceptors are chemosensitive cells, located in the bifurcations of the carotides and the aorta and stimulated by a lack of oxygen, an excess of carbon dioxide or a hydrogen ion excess. The transmit a signal to the vasomotor center to bring the arterial blood pressure to normal. It is especially in lower pressures that this reflex becomes important. (1)

Low-pressure receptors

Low-pressure receptors are stretch receptors that lie in the walls of the atria and the pulmonary arteries. They cannot detect systemic arterial blood pressure but they do notice increases in pressure in the low-pressure areas of the circulation caused by increase of volume. They trigger a reflex parallel to the baroreceptor reflex to make the total reflex system more potent. (1)

CNS Ischemic response

Severely decreased blood flow in the vasomotor center in the lower brain stem causes a strong excitement of the neurons in the vasomotor center itself. The result is a forceful elevation of arterial blood pressure. (1)

1.2.2.1.4 Long term Regulation

We learned that the autonomic nervous system is capable of rapid, short term control, but the most important long term regulator is the blood volume itself. It is the kidneys that play the dominant role in the control of blood volume.

1.2.2.1.4.1 Control through the kidneys

The kidneys build the fundamental basis of long-term arterial pressure control. Whenever there is an increase in extracellular fluid, blood volume, cardiac output and, consequently, arterial blood pressure rise. In response to the rising pressure, the kidneys start excreting the excess extracellular fluid and salt. These phenomena are called pressure diuresis and pressure natriuresis. As a result, arterial blood pressure returns back toward normal. Low arterial pressure in turn causes that the kidneys excrete less fluid and less salt than is ingested, building up extracellular fluid volume, blood volume and arterial blood pressure to the normal level.

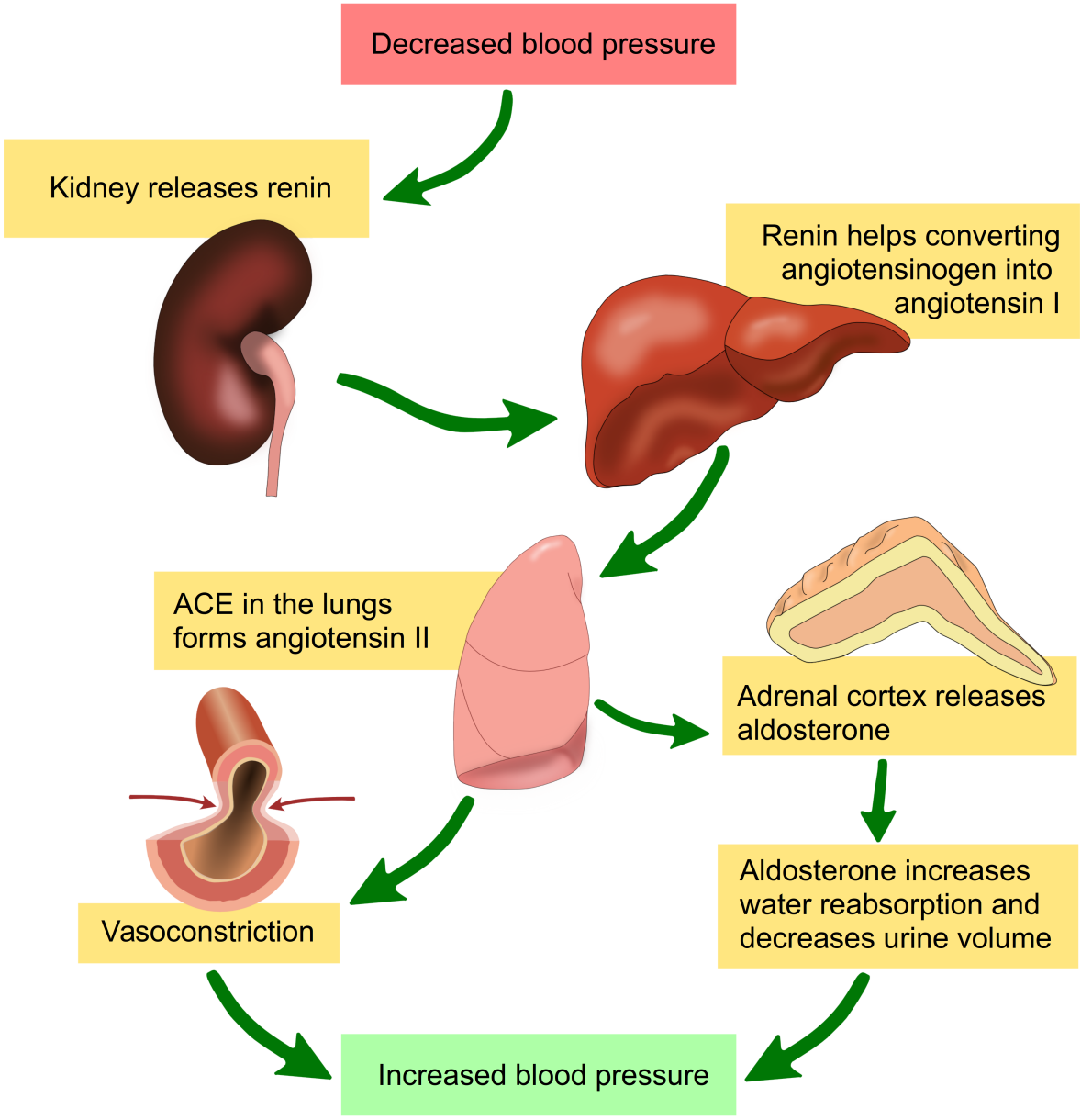

Figure 4: The RAAS and its influence on blood pressure

Aside from pressure diuresis and pressure natriuresis, the kidneys also control arterial blood pressure through the RAAS. Figure 4 illustrates the relationship of the RAAS and blood pressure. It goes like this: the afferent arterioles in the nephrons detect a fall in arterial blood pressure. As a result, the juxtaglomerular cells release the enzyme renin, which helps to convert angiotensinogen from the liver to angiotensin I in the blood which is then turned into angiotensin II in the endothelium of the lung vessels. As mentioned in a previous section, it takes around 20 minutes before angiotensin II is formed and

can get fully active. Angiotensin acts in three main ways. It causes strong vasoconstriction, acts directly on the kidneys to cause salt and water retention, and it stimulates the adrenal glands to secrete aldosterone. Aldosterone in turn leads to an increase in sodium reabsorption, causing water retention and leading to an increase of arterial blood pressure as well. (1)

1.2.2.2 Orthostasis

When a person stands up after having been lying down, blood volume in the body is redistributed. It is this change from lying to standing that we call orthostasis. On standing, due to the impact of gravity, blood that has been evenly distributed in the horizontal position, suddenly pools in the veins of the legs, causing a decrease of venous return and consequently a decrease of cardiac output (Figure 5). The pooling occurs due to the increased hydrostatic pressure in the lower body that pushes outward on the highly distensible vein walls. At the same time, gravitational force leads to an increased filtration of fluid out of the capillaries into the interstitial space in the legs. We can conclude that the price we pay for an upright posture is the fall of arterial blood pressure in the upper body, especially the head. Yet, thanks to the short term regulation mechanisms we got to know earlier, arterial blood pressure stays relatively constant whenever there is a change in body posture. (1,2,4)

The vasoconstrictive reactions of terminal arteries and arterioles lead to a rise in total peripheral resistance, resulting in a stabilization of arterial blood pressure. Heart rate increases, but cardiac output stays unaffected. (4) Therefore, in the case of orthostasis, immediate control of arterial blood pressure is mainly achieved by the reflexes that originate in the baroreceptors and the chemoreceptors. Chemoreceptors become important as soon as the arterial blood pressure falls below 80 mm Hg, as it is only then that these chemosensitive cells get stimulated by decreased oxygen as well as excess buildup of carbon dioxide and hydrogen ions. (1)

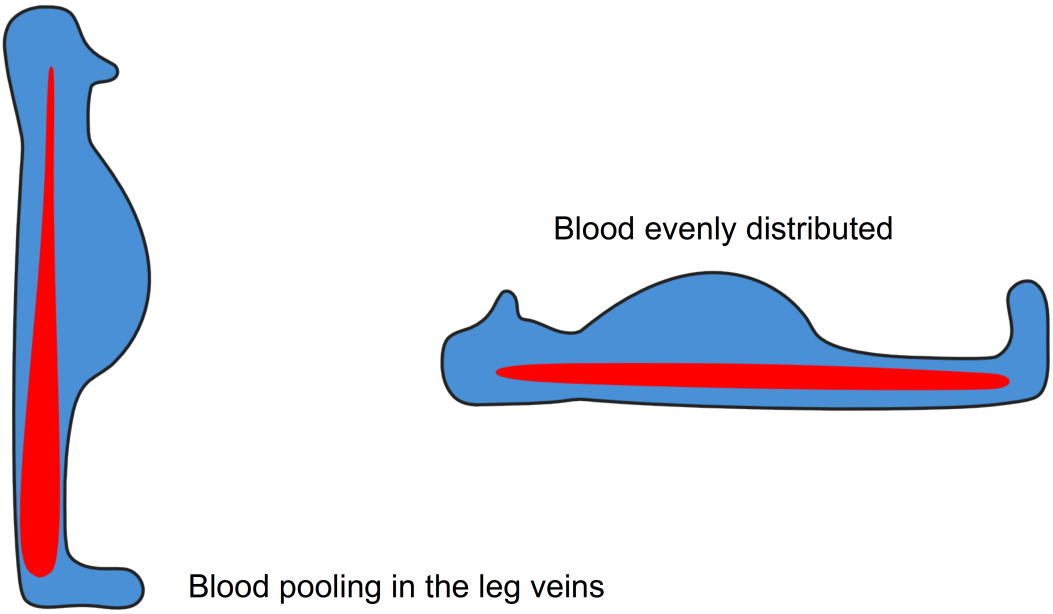

Figure 5: Redistribution of blood in Orthostasis

The blood pooling caused by an increased hydrostatic pressure in the legs during standing leads to a decrease in the effective circulating blood volume.

1.2.2.2.1 The role of the muscle pump

Besides short term regulation, the body has another way to counteract the effects of gravity, namely the skeletal muscle pump in the legs. This so called pump gets effective by contractions of the skeletal muscles in the legs (Figure 6). Already gentle contractions can offset effects of gravity by complete emptying of the leg veins. While valves in the veins already prevent reverse blood flow, the muscle contractions in the legs are responsible for shifting the blood between the venous valves upward. By this, pooled venous blood returns to the heart and capillary hydrostatic pressure decreases. (2) Consequently, venous return, stroke volume and cardiac output increase and therefore, mean arterial pressure can rise.

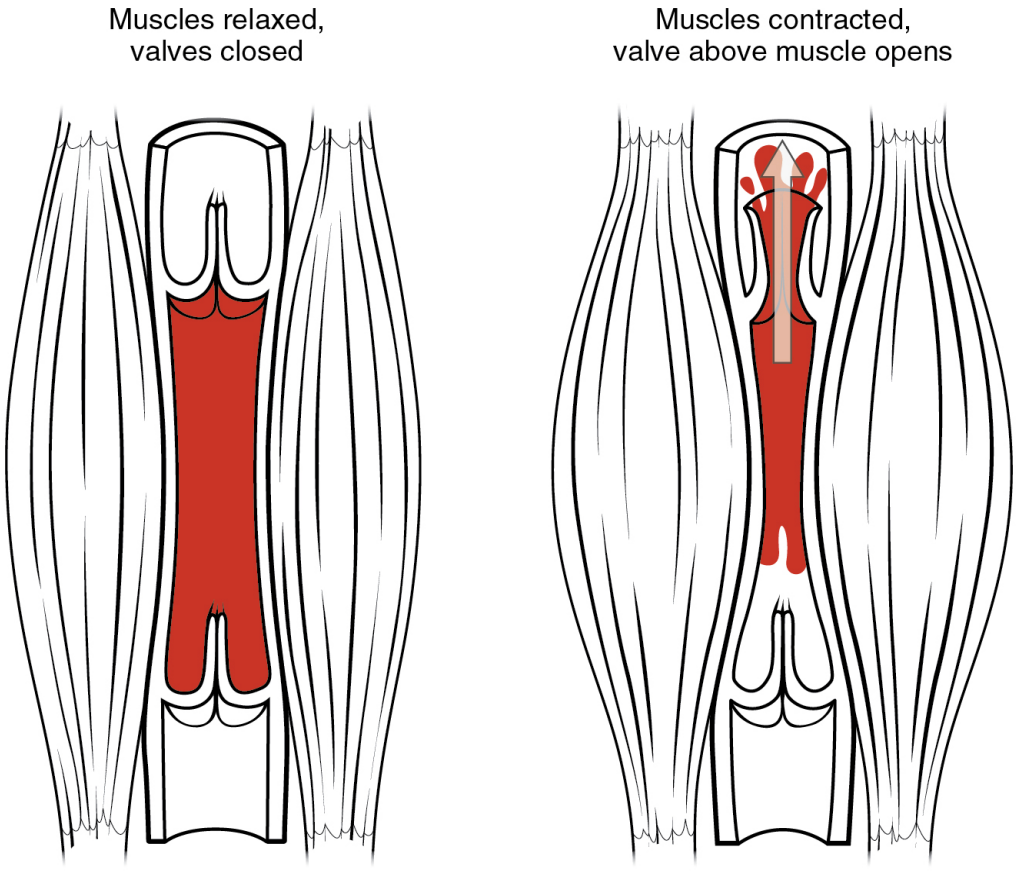

Figure 6: The skeletal muscle pump

reproduced from http://cnx.org/content/col11496/1.6/

1.2.2.2.2 Cerebral autoregulation

In a previous section we already talked about the arterioles' ability to respond to changes in hydrostatic pressure in a manner that keeps the blood flow at the needed level. This ability is termed autoregulation of blood flow. When it comes to the brain, the ability to maintain blood flow despite changes of hydrostatic pressure, is of special importance since the brain has a high metabolic demand. Hence, cerebral vasculature has an excellent ability to autoregulate cerebral blood flow. Cerebral resistance vessels are able to maintain the perfusion of the brain at constant values even with changes of arterial pressures (Figure 7) (8). They are able to change their lumen diameters whenever blood pressure changes in order to guarantee the appropriate blood flow.

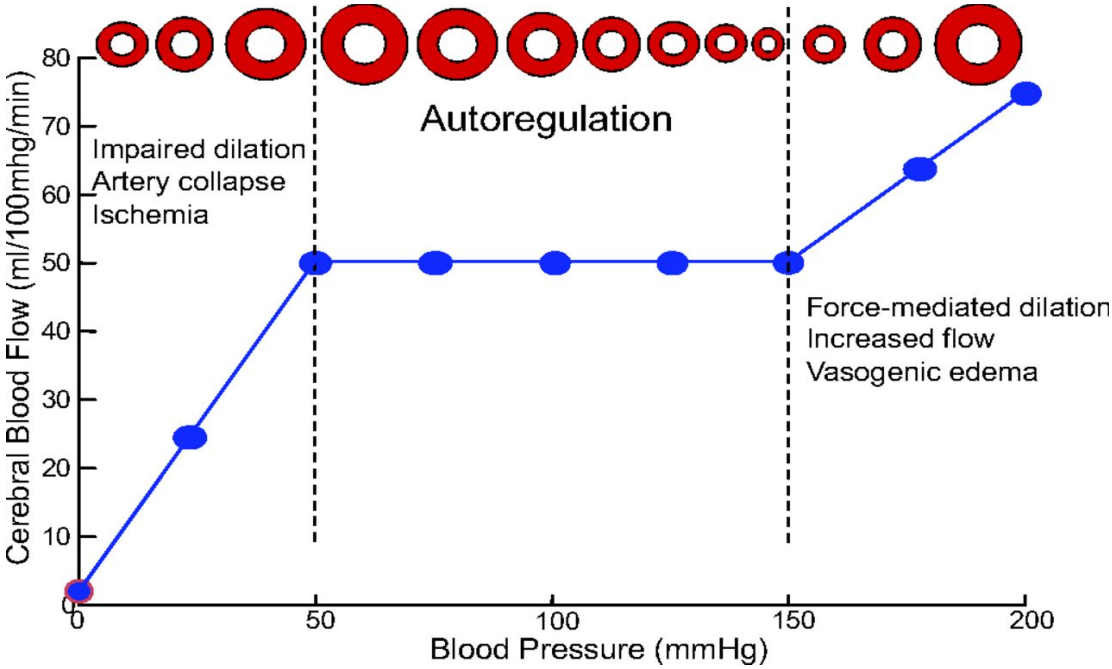

Figure 7: Limits of cerebral blood flow autoregulation

The dotted lines mark the lower and the upper limits of cerebral blood flow autoregulation.The red circles represent the different artery lumen diameters throughout blood pressure changes.

reproduced from Pires et al. (8)

1.2.2.2.3 Orthostatic intolerance

While orthostatic tolerance describes the ability to maintain blood pressure upon standing, orthostatic intolerance describes the inability to maintain arterial blood pressure upon standing (9). The hazard is the insufficient perfusion of the brain upon a change in body posture which can precipitate dizziness or even syncope (10). The brain's metabolic demands require an appropriate parenchymal perfusion. Hence, after reaching the lower limit of the brain's capability to autoregulate cerebral blood flow, the body faints. Fainting counteracts the perfusion loss. As soon as the body is in a horizontal position, venous return increases. Consequently, cardiac output increases as well, leading to a rise in mean arterial pressure, ultimately restoring an adequate cerebral blood flow.

It seems to be well established that orthostatic intolerance occurs more often in premenopausal women than in age-matched men. (11–16). The level of orthostatic tolerance can be determined by measuring suitable parameters after inducing orthostatic stress.

1.3 Inducing and Measuring Cardiovascular responses

Now that we revised the basics of Cardiovascular Physiology, we will take a look at the main methods that are used in research to induce orthostatic stress and measure responses. In the previous sections we learned that changing body posture from lying to standing already causes orthostatic stress. Nevertheless, there are better ways to induce redistribution of blood. The advantages of these models are that they make body responses better measurable and allow comparisons across individuals and groups. The methods are often used together.

1.3.1 Head-up Tilt

This method uses a table that can position persons at varying angles of upright tilt. This way, the induced postural stress is controlled and passive, disabling the action of the muscle pump in the legs. The HUT test has usually two phases. It starts with supine resting for at least 30 minutes in order to allow stabilization of the cardiovascular system. In the second phase the person is tilted upright. The chosen angles are usually between 60-90° as stress is exerted mostly at these angles. Duration of the passive tilt varies, but is usually between 20-45 minutes. Sometimes medication is administered during the passive tilt in order to potentiate orthostatic stress. During the entire test, the persons are monitorized and their blood pressure and heart rate are measured regularly. Depending on the study design, different parameters are regarded before, during and/or after the test. (17,18)

1.3.2 Lower body negative pressure

In a setting of LBNP, the person's legs are enclosed in a chamber or trousers and exposed to negative pressure. It causes blood shift from the head to the legs, hence induces venous pooling. In a supine position, levels of - 40 to - 50 mm Hg are considered to cause blood shifts very similar to those induced by the upright posture. In the initial state, cardiovascular compensation for the applied stress takes place. In the following state, cardiovascular decompensation starts,

marking the presyncopal endpoint. LBNP is usually combined with other orthostatic stress tests in order to assess cardiovascular responses. (19,20)

1.3.3 Head-down bed-rest

In microgravity, respectively weightlessness, blood pressure is equal at all levels of the body, thus showing the contrary to what is seen during orthostatic stress. After exposure to weightlessness, individuals seem to have a tendency toward lower orthostatic tolerance. HDBR is a model that simulates microgravity. Hence, it reduces the effective orthonormal gravitation influence on the human body. It induces a blood shift towards the head by keeping the head lower than the rest of the body. The person is usually placed at - 6° head-down tilt. Adaptations of the cardiovascular system can already occur after 4 hours. Nevertheless, HDBR is commonly used as a long-term model to simulate conditions of weightlessness experienced by astronauts. It is a primary research tool to examine cardiovascular alterations. Lower body negative pressure can be used as a countermeasure to HDBR by causing a fluid shift to the lower body. (21–24)

1.3.4 Water immersion

Water immersion is another model that simulates microgravity. Usually the person is immersed up to the neck in a circulating water tank, filled with thermoneutral water. During the procedure, the hydrostatic compression causes an increase of thoracic blood volume by centralizing blood from the periphery. (25,26)

2 Purpose and Objectives of the Diplomarbeit

Several studies, which will be named and discussed in this review, have shown that cardiovascular responses to stress differ according to gender and age in both animals and humans. As females are more susceptible to orthostatic intolerance, it is important to identify how cardiovascular regulation is different in males and females.

This Diplomarbeit provides an update on existing literature on gender differences in cardiovascular regulation and orthostatic tolerance. It discusses current articles that show gender differences in cardiovascular anatomy, hemodynamics and the autonomic nervous system, with particular emphasis on orthostatic intolerance.

This work also focuses on how female sex hormones and the phases of the menstrual cycle affect the cardiovascular responses and whether there are differences in orthostatic tolerance in the same female across the phases of the menstrual cycle.

As females are particularly prone to orthostatic intolerance, this work has application in the treatment and prevention of the latter.

3 Methodology

This work is a literature review on “Gender differences in cardiovascular regulation and orthostatic tolerance“. I gathered the required information by performing a systematic literature research.

3.1 Searching for Literature

I accessed databases with my student account from the Medical University of Graz. By doing so, I could not only read free full text articles but also access articles published in journals to which the Medical University of Graz subscribes to. Some relevant recent papers that I had no access to with my student account were provided by my supervisor or directly by the authors after contacting and informing them about my work on a review related to their research field.

3.1.1 Targeted Search

I used two databases, namely “PubMed“ and “Web of Science”. PubMed covers most of the published articles and learning how to perform systematic research is part of the curriculum on the Medical University of Graz. My supervisor advised me to also use the Web of Science as it provides information on how many times a paper has been cited. This was a helpful tool for the research as citing articles often offer updates and either confirm or refute findings of the original article. I actively searched for literature in the two mentioned databases from November 2013 until April 2014. Furthermore, I reviewed the reference lists of retrieved papers in order to find additional articles. I included secondary literature such as books as well.

3.1.2 Search Strategy

I wanted to get specific information on the current knowledge on gender differences in cardiovascular regulation as well as current knowledge on reasons for gender differences in orthostatic tolerance. To construct my search strategy that would help me in obtaining systematically the relevant literature, I used keywords that were identifying the essential subject. I connected the keywords with each other with the options “AND” and “OR” in order to narrow down the amount of results. The basic literature research contained the following keywords:

“cardiovascular regulation” AND “gender differences”

gender AND “orthostatic intolerance” OR “orthostatic tolerance”

“sex hormones” AND “cardiovascular regulation”

“orthostatic intolerance” AND gender OR women

“blood pressure” AND gender OR women

3.2 Selecting articles

By deciding on some inclusion and exclusion criteria I could refine the research further. In addition, I selected articles depending on whether certain topics of interest were included or not.

3.2.1 Inclusion and Exclusion criteria

I did not include articles written in another language other than English in order to avoid translation problems and misinterpretation of information. Nevertheless, I included papers from all countries as long as they were written in English. Secondary literature comprises books in English as well as German as physiology classes are held in German on the Medical university of Graz and study material is mainly in German. Furthermore, in the basic research that included the earlier mentioned keywords and phrases I only searched for articles that were published between 2008 and 2014 in order to reduce the amount of papers and mainly focus on recent information. As I also used article references, information included in my work is taken from papers whose publication years range in total from 1991 until 2014. I included articles that provided data from both human and animal studies.

3.2.2 Topics of Interest

After reading the abstracts, I was able to preselect “probably relevant” papers from the result lists. I paid special attention to abstracts that included information on either/or:

- gender, sex hormones, menstrual cycle, sex differences, oral contraceptives, menopause, race

  and one or more of the following topics:
- cardiovascular system, cardiovascular regulation
- orthostasis, orthostatic tolerance, orthostatic intolerance, orthostatic hypotension
- blood pressure, vasoconstriction, hemodynamics, venous compliance, vasoactive factors, endothelial function, brain blood flow
- autonomous nervous system, autonomic regulation, baroreflex function

- tilt table tolerance, LBNP, head-down bed rest, microgravity, orthostatic stress
- spaceflight, postspaceflight, astronauts and orthostatic intolerance

3.3 Final collection

Subsequently I saved the preselected articles to a free reference management software (Zotero) on my computer and attached them as a PDF. I read each preselected article in full text and evaluated it as either “relevant” or “not relevant” to my topic. I marked articles as relevant when the following criteria had been fulfilled:

- A topic of interest (in one of the combinations as listed above in 3.2.2) was covered and information on it provided.
- Gender aspects were respected in the study design and observations and results handled separately.
- The authors did not doubt the significance of their results.

Some articles did not look at gender differences but provided new aspects on cardiovascular regulation and/or orthostatic tolerance. These articles were included while noting that future studies should focus on possible gender differences.

I identified 158 articles as relevant and included them in the Diplomarbeit. Out of these 158 articles, 68 articles were published between 2008 and 2014, and 90 articles were published between 1991 and 2007. Moreover, I included 6 books and 1 thesis.

3.3.1 Synthesis

I printed all papers that I had marked as relevant and collected them in a folder. I identified the main aspects of each relevant paper and summarized the aspects in keywords which I then noted down on the printed version of the files. In order to group the findings in a way that would comprise every identified topic, I decided on the following 4 key themes:

1. Baseline Gender differences affecting Cardiovascular Function
2. Gender differences in Cardiovascular Responses
3. Influences of sex hormones on Cardiovascular Regulation
4. Differences between ethnic groups

3.3.2 Providing background information

The Introduction chapter (chapter 1) includes background information and is divided into the three following sections:

1. The design of the Circulatory System
2. Cardiovascular Physiology
3. Inducing and Measuring Cardiovascular Responses

I looked up information in secondary literature as well as in papers. I selected secondary literature, namely books, in English and German. I only included papers written in English. I used the following keywords and phrases to find background information for the Introduction:

“orthostatic intolerance in women”

“orthostatic tolerance in women”

“head-up tilt” AND “orthostatic tolerance”

“lower body negative pressure” AND “orthostatic tolerance”

“water immersion” AND “orthostatic tolerance”

“head-down bed rest” AND “orthostatic tolerance”

4 Review of the current literature

4.1 Differences in orthostatic tolerance

The title of this Diplomarbeit indicates that orthostatic tolerance must have something to do with gender. Indeed, we will see that there is much truth in this guess (12,16,20,27–29). While we will take a closer look at gender differences and differences within women themselves, there is other factors that are linked to orthostatic tolerance. Gender differences in cardiovascular regulation and orthostatic tolerance seem to be strongly influenced by sex hormones (30–36). Furthermore, the reviewed literature shows that cardiovascular regulation and/or orthostatic tolerance can be affected by hypovolemia (14,22,37,38), elevated environmental temperatures (39,40), gravity environment (21–23,41–45), age (27,46–49) and race (50–56).

4.2 Baseline Gender differences affecting Cardiovascular Function

Orthostatic tolerance appears to depend on the ability of maintaining cardiac preload (57). Cardiac preload itself is affected by the rate of venous return. For this reason, the distribution of blood volume plays an important role in the maintenance of cardiac output and blood pressure (57). Cardiovascular function is mainly influenced by anatomy, hemodynamics and the autonomic nervous system. Hence, the following discussion will first consider baseline gender differences in anatomy and will be followed by consideration of the impact of hemodynamics and the autonomic nervous system on orthostatic tolerance.

4.2.1 Baseline gender differences in Anatomy

4.2.1.1 Heart size

Women have a smaller left ventricular mass than men (before and after adjustment for height and body surface area) (58,59). Furthermore, hearts in women are overall smaller and less distensible, resulting in decreased cardiac filling during orthostatic challenge in comparison to men (14,60). While de Simone et al. (59) found no difference in end-diastolic dimensions of the left ventricle after adjustment for body surface area, Salton et al. (58) found that women display significantly higher end-diastolic dimensions of the left ventricle after adjustment for body surface area. Both studies found lower end-diastolic dimensions in women than in men before being adjusted for body surface area.

4.2.1.2 Additional blood pooling in women

Women have an additional blood pool in the pelvis due to arterial anastomoses between uterine and ovarian arteries and the existence of large venous plexi around the uterus, ovaries and vagina, with no equivalent in men (3,61). White and Montgomery showed that during orthostatic stress women display more pooling of blood in the pelvic region (62). Fu et. al suggest that this may be a predominant factor causing decreased cardiac filling during orthostatic stress (14,16). This suggestion is supported by Edgell et al. (63) who found compromised mechanisms of venous return during orthostatic stress in women and attribute it to splanchnic pooling. In contrast, Halliwill et al. (64) reported that the pooling of venous blood in the lower parts of the abdomen during lower body negative pressure has negligible overall hemodynamic effects. Their study suggested that orthostatic tolerance is rather affected by venous compliance in the legs. We will see later what other articles found in regard to this hypothesis.

4.2.1.3 Body height

Arvedsen et al. (65) concluded in a study that body height influences intravascular pressure gradients in individuals. The taller an individual, the larger the intravascular pressure gradient. Hence, body height plays a role as determinant of blood pressure and its regulation. As men are in average taller than women, they may differ over blood pressure and its regulation due to differences in body height. (65)

4.2.1.4 Center of gravity

Women show in general a lower longitudinal center of gravity than men by 8% to 15% as a result of a proportionately larger mass in the legs and pelvis than men of the same size. Summers et al. demonstrated in a series of computer simulation studies that a 15% lowering of the longitudinal center of gravity is enough to prevent successful compensating upon orthostatic challenge after a one month microgravity simulation. (66) However, this study only accounts for exposure to microgravity.

4.2.1.5 Volume indifferent point

By contrast, Jarvis and Pawelczyk. (57) state: “It is the location of the human volume indifferent point that predicts orthostatic tolerance. The volume indifferent point is defined as the point within the circulation where blood volume

does not change with changes in posture." Their study suggests that individuals with low orthostatic tolerance may have more inferiorly located VIPs. Yet, their results showed no sex difference in the location of the VIP when expressed as a percentage of height. (57)

4.2.2 Baseline gender differences in Hemodynamics

Women have a lower total blood volume by body weight than men (13,16). There is considerable evidence that premenopausal women have lower mean, systolic and diastolic arterial blood pressure than men of similar age. Heart rate is also lower in premenopausal women than in men of similar age. After menopause, the mentioned parameters are higher in women than in men. (42,46,67,68) Another aspect is that left ventricle end-diastolic volume and left ventricle end-systolic volume are higher in men than in women and stay significantly higher when normalized to height as well as to body surface area (58). Nonetheless, Fu et al. found no gender differences in stroke volume, cardiac output, or total peripheral resistance, when normalized to body surface area (14). It has been hypothesized that decreased orthostatic tolerance could have to do with a greater calf venous compliance in women than in men (64,69). Interestingly, it has been shown that women have less calf venous compliance than men, making it unlikely for some authors that calf venous compliance contributes to decreased orthostatic tolerance in women (15,69). By contrast, studies observing calf vasoconstrictor responsiveness (12,70–73), show greater venous blood pooling in women in comparison to men as a result of an attenuated vasoconstrictor responsiveness. Thus, less calf venous compliance together with less vasoconstrictor responsiveness may still lead to greater calf venous pooling in women in comparison to men.

4.2.3 Baseline gender differences in the Autonomic Nervous System

Evidence suggests that arterial blood pressure may be regulated differently in young men and women. The autonomic nervous system plays an important role in arterial blood pressure regulation. Mediators from adrenergic nerves help in controlling resistance vessel tone. (28,73,74) The arterial baroreflexes, in turn, influence the regulation of arterial blood pressure via a cardiovagal and a sympathetic component (75). Interestingly, it has been shown by Dutoit et al. (75)

that the sensitivities of these two components are not correlated within healthy normotensive subjects.

At rest, Custaud et al. (42) found comparable spontaneous baroreflex sensitivity between men and women, whereas during LBNP women showed a greater decrease in spontaneous baroreflex sensitivity with a greater increase in sympathetic activity. Some years later, Christou et al. (76) demonstrated that premenopausal women show lower tonic autonomic support of baseline arterial blood pressure and less effective baroreflex buffering of arterial blood pressure than healthy men of similar age, suggesting that the contribution of vasoconstrictor tone to arterial blood pressure regulation is influenced by gender (74).

Muscle sympathetic nerve activity reflects the responses of the sympathetic component of the arterial baroreflex (75). It modulates vasoconstriction in the arterioles (50). Moreover, it is considered as a good index of net whole body vasoconstrictor tone in young healthy men but not in women. The main short-term determinant of MSNA is arterial blood pressure via the sympathetic component of the arterial baroreflex. (74,77,78) An interesting aspect is that MSNA appears to have no relationship to blood pressure values at rest in neither young men nor in premenopausal women (47). Hence, both groups maintain normotension even with high MSNA. In young men, MSNA shows a positive correlation to TPR and an inverse relationship to cardiac output. Cardiac output seems to buffer the positive relationship between MSNA and TPR. It is due to these relationships that young men can balance out pressor effects of high MSNA. (47) Yet, such relationships do not exist in premenopausal women, hence vasoconstriction may not be directly related to MSNA values in young women and high MSNA seems to be balanced out in a different way (47,74). Along these lines, Kneale et al. (73) found important gender differences in sensitivity to adrenergic agonists. Broadly speaking, α-adrenergic receptors cause vasoconstriction in response to noradrenaline, whereas β2-adrenergic receptors cause vasodilation (46). A study by Kneale et al. (73) revealed that in premenopausal women the administration of noradrenaline to the brachial artery causes less vasoconstriction and the stimulation of β2-adrenergic receptors causes more forearm vasodilation than in men of similar age. Thus, greater β2 - adrenergic vasodilation in young women balances the α-adrenergic vasoconstrictor effect of noradrenaline (46,73). Similarly, Schmitt et al. (79) found a lower α-adrenergic support of arterial blood pressure in young women

compared to men of similar age. This lower support may in fact be due to elevations in β2 - adrenergic receptor sensitivity in women (73). A rather recent study by Hart et al. (46) supports this further by demonstrating that forearm vasoconstrictor responsiveness increases in young women during β-blockade, whereas no such effect can be observed in young men. Hence, the authors concluded from their data that resting arterial blood pressure in premenopausal women is markedly influenced by vascular β-adrenergic receptors. It could be due to this β2 - mediated vasodilation that MSNA is uncoupled from vasoconstriction in young women (47). As we will see later it is likely that female sex hormones are responsible for these differences (30,31,46,47,80–82).

4.3 Gender differences in Cardiovascular Responses

Gender differences in cardiovascular responses during fluid shifts may be responsible for gender differences in orthostatic tolerance. Cardiovascular responses can result from fluid shifts induced by orthostatic stress. Studies applying these methods and observing the conditions, help in revealing and understanding gender differences in cardiovascular regulation and orthostatic tolerance. As orthostatic intolerance can also occur after exposure to actual or simulated microgravity we will also take a look at gender aspects of postspaceflight induced orthostatic intolerance.

4.3.1 Responses to orthostatic stress

Orthostatic stress can be induced by simple posture changes, such as changing from lying to standing, as well as by applying lower body negative pressure or the application of external neck pressure. Head-up tilt tests are used to imitate posture change under controlled conditions, causing passive orthostasis (18). Both HUT and LBNP tolerance are found significantly reduced in women of premenopausal age (12–14,16,20,39). Some studies observed responses to orthostatic stress under hypovolemic conditions or during exposure to heat. (14,37,39,40)

4.3.1.1 Orthostatic stress and hemodynamics

When assuming an upright posture, blood pools in the lower limbs which leads to a decrease of venous return, followed by a transient fall in arterial blood pressure (83). Observations during a change of posture from supine to seated and to standing show that the human body generally reacts with an increase in heart

rate, a decrease in stroke volume index, a decrease in cardiac output index and an increase in TPR index (84,85). These adaptations serve the maintenance of arterial blood pressure and cerebral perfusion during orthostatic stress (84). Yet, there are important gender differences concerning the extent of changes. As it turns out, men predominantly respond to cardiovascular stress by increasing vascular resistance, whereas women rather tend to increase heart rate (29). When recalling the formula from the introduction, we can see that both reactions increase mean arterial pressure. Yet, one mechanism may be more effective than another during orthostatic stress. Let us find out what studies revealed.

Studies using LBNP could demonstrate that before reaching presyncope both men and women are appropriately compensating for the LBNP stress and maintaining arterial blood pressure similarly (20,86). Nevertheless, literature provides results for hemodynamic values during HUT and LBNP that partly differ. These differing findings may be due to the fact that parameters were observed at different levels of LBNP or HUT. While some authors tried to observe parameters exactly at presyncope, other authors measured them at different levels of progressing HUT and LBNP.

Several authors found that premenopausal women at presyncope show smaller stroke volume, presumably due to a decreased cardiac filling, and higher heart rates, but similar mean arterial pressure and total peripheral resistance compared with men (14,16,84). Fu et al. (14) observed the difference in stroke volume and heart rate under normovolemic as well as hypovolemic conditions. Shoemaker et al. (87) tested premenopausal women and men of similar age during progressive HUT and also found a greater increase in heart rate in women and similar total peripheral resistance. Yet, they found a smaller increase in mean arterial pressure in women. Fu et al. (14,16) explain that despite baseline mean arterial pressure being lower in premenopausal women than in men and staying lower during progressive LBNP, both genders show similar mean arterial pressure as soon as presyncope is reached. Shoemaker et al. (87) found a smaller stroke volume in women but a similar decrease of stroke volume and cardiac output during HUT in both genders. This finding is supported by Hachiya et al. (71) who found cardiac output consistently lower in women during LBNP, but a similar change from baseline in both men and women. In an interesting study by Cote et al. (88) premenopausal women were compared between each other. The study

showed higher stroke volumes in low tolerant women than in high tolerant women. This is interesting as high stroke volume would rather be expected in high tolerant women. During LBNP, stroke volume dropped faster in low tolerant women, leading to a similar final stroke volume between both low and high tolerant women. They could conclude from their data that it is the rate at which stroke volume declines that is associated to orthostatic intolerance instead of absolute stroke volume. Yet, recently Wenner et al. (30) reported that stroke volume in low tolerant women was lower at baseline and throughout LBNP when compared to high tolerant women. Kimmerly et al. (86) found greater heart rates in men than in women during low levels of LBNP. Similarly, Hachiya et al. (71) observed an earlier increase in heart rate in men during low levels of LBNP. Convertino (13) found similar heart rates but lower mean arterial pressure in women at presyncope. Nevertheless, there is evidence that heart rate is not a predictor of orthostatic tolerance (88,89). In a recent study by Nigerian physiologists (83) it has been demonstrated that water ingestion prior to orthostatic challenging causes a strong improvement of orthostatic tolerance in both young men and women, but particularly in women. They made two important observations. First, they noticed in women that pulse pressure correlated positively and heart rate negatively to orthostatic tolerance. Such a relation was not found in men. Second, they found that diastolic blood pressure (an index of vascular resistance) correlated positively with orthostatic tolerance in men but not in women. (83) This study underlines the importance of blood volume in women. Although the results of all the mentioned studies seem to be controversial, collectively, there is considerable evidence that women have stronger tachycardiac responses whereas men have stronger pressor responses to orthostatic challenge (14,16,83). Wenner et al. (30) gave new important information on this issue by demonstrating that low tolerant women upon orthostatic stress rather react with increases in heart rate, whereas high tolerant women can rely on peripheral vasoconstriction to maintain blood pressure. Hence, lower cardiac volume contributes not only to gender differences in orthostatic tolerance but also to differences within women (30).

Convertino (13) and Edgell (27) found greater elevations in thoracic impedance in women upon orthostatic stress. This finding is supported by Gotshall's suggestion (20) that women show a greater relative blood pooling in the chest than men for the same level of orthostatic stress. Furthermore, Kimmerly et

al. (86) and Edgell (27) found a significantly greater decrease in central venous pressure in women than in men during different levels of LBNP, supporting the suggestion of greater pelvic blood pooling in women during orthostatic stress (27,62).

Several studies indicate that women have less calf venous compliance then men (15,69,90). Nevertheless, Lindenberger et al. (90) only observed this gender difference in venous compliance at low transmural pressures. Furthermore, they found a larger interstitial fluid accumulation in women than in men during LBNP. Lawler et al. (91) did not find a relationship between leg muscle mass and LBNP tolerance. Hence, similarly to Meendering et al. (15) and Monahan et al. (69), they suggest that leg compliance is not a major determinant of orthostatic tolerance. Yet, already more than a decade ago, it was reported by Van Lieshout et al. (92) that during standing, tensing of the leg muscles attenuates a reduction in cerebral perfusion, stabilizes central circulatory variables and consequently, improves orthostatic tolerance. It would be interesting to investigate whether there is gender differences in the extent of improvement.

An interesting simulation study by Etter et al. (93) provided evidence that capillary filtration is an important mechanism in causing orthostatic intolerance. The simulation study showed that, during orthostatic stress, the decrease in total blood volume is controlled by the capillary filtration rate of the individual. Thus, the lower the capillary filtration rate slope, the lower the decrease in total blood volume and the higher the orthostatic tolerance. The simulation was run for male subjects only. Further investigation with women may provide further information on whether capillary filtration plays a role in gender differences in regard to orthostatic tolerance.

While the effect of fitness on orthostatic tolerance used to be viewed controversially, recently Murrell et al. tried to clarify this issue in a series of studies (94–96). Their data together with older findings indicate that orthostatic tolerance does not differ with physical fitness (13,95,96). Although it is known that orthostatic tolerance is found reduced after prolonged exercise, it is surprising that sex differences seem to get eliminated after exercise (94). Thus, after exercise women do not show a reduced orthostatic tolerance during HUT when compared to men (94).

It has been well documented that exposure to heat dramatically reduces orthostatic tolerance in both men an women (39,40,97). Passive whole body heating leads to a significant increase of heart rate and an earlier onset of the increase compared to normothermic conditions during LBNP and can be observed in both genders (40). Meendering et al. (39) demonstrated that there is no significant difference in the rate of change of cardiovascular variables between sexes.

An interesting finding has been provided by Cui et al. (98) who demonstrated that in both men and women central venous pressure rises with skin surface cooling and stays significantly greater during orthostatic stress relative to normothermia. At the same time, stroke volume was significantly more elevated during higher levels of LBNP, and arterial blood pressure was throughout all the stages of LBNP significantly greater than under normothermic conditions. These findings indicate that the induced upward shift in central venous pressure helped in preserving preload and stroke volume, hence arterial blood pressure (98). Additional studies to clarify whether there are gender differences in this area would be of interest.

4.3.1.2 Orthostatic stress and the autonomic nervous system

Orthostatic stress causes a fall in central blood volume which brings both cardiopulmonary and arterial baroreceptors into action (51). They send signals to the brain which in the following induces an increase in heart rate and an increase in peripheral resistance, by this compensating for the gravitational reduction in venous return (14). These two mechanisms are mediated by the sympathetic nervous system.

There is a growing literature that shows that premenopausal women have reduced sympathetic and enhanced parasympathetic activity in comparison to men (42,48,49,76). Reduced sympathetic activity presents itself by a lower sympathetic vascular control, whereas enhanced parasympathetic activity presents itself by a high vagal cardiac tone (49). Nevertheless, autonomic responses are not different in men and women during mild levels of orthostatic stress (86). There is no agreement yet on whether sex differences in vasoconstrictor responses upon orthostatic stress are present or not. Almost a decade ago, Fu et al. (14) concluded that men and women have generally comparable adrenergic and vasoconstrictor responses during orthostatic stress

after testing sympathetic neural responses upon HUT. Earlier to this, they had demonstrated in a previous study that responsiveness of vascular resistance during orthostatic challenge is similar in both women and men (16). By contrast, a few years later, Lott et al. (70) found attenuated vasoconstrictor responses to negative pressure in women. They concluded from their results that flow autoregulation shows intrinsic differences depending on gender. Similarly, Hachiya et al. (71) found a greater vasoconstrictor response in the calf in men during graded LBNP and also concluded that control of vascular resistance is different between men and women.

In addition, Jarvis et al. (12) argue for an attenuated vasoconstrictor response in the splanchnic circulation in premenopausal women after finding a smaller decrease of blood flow to the splanchnic region upon HUT. After pharmacologically inducing splanchnic vasoconstriction, both genders experienced an improvement in tilt table tolerance, but only in the women was this improvement significantly related to the induced splanchnic vasoconstriction (72). This finding supports the suggestion that splanchnic blood pooling attributes to lower orthostatic tolerance in women (14,16,63), the underlying cause probably being an inadequate splanchnic vasoconstriction (72).

At higher levels of LBNP and progressing HUT muscle sympathetic nerve activity is greater in men than in women (86,87). Kimmerly et al. see this elevated sympathetic response in men related to greater changes in forebrain activity (86). Forearm vascular resistance increases by the same extent during HUT in both men and women (48), but men show a strong association between plasma noradrenaline and forearm vascular resistance at rest and during hypovolemic circulatory stress, whereas women don't (37). Furthermore, women appear to respond with less plasma noradrenaline than men upon HUT (48).

In a recent study by Kim et al. (99) it was suggested that gender differences in the baroreflex control of arterial blood pressure can be seen during carotid hypertension but not during carotid hypotension. This finding is supported by Fu et al. (100) who found comparable sympathetic baroreflex control during orthostatic stress, hence carotid hypotension. Kim et al. (99) observed that blood pressure responses to carotid hypertension in young women were attributable to a larger decrease in heart rate, whereas young men predominantly responded with a decrease in vascular resistance. Thus, young women rely more on cardiac output

than on vascular resistance for the moment-to-moment control of blood pressure via the arterial baroreflex (99). These findings supports the suggestion that young women have a lower sympathetic support than young men (73,76,79). Unlike other mentioned studies (73,79), they did not see gender differences during carotid hypotension. Yet, they remark that this discrepancy may be due to the fact that they assessed beat-to-beat changes over a short period, whereas studies who found differences assessed the changes over longer steady-state period.

4.3.1.3 Orthostatic stress and endothelial function

Besides the autonomic nervous system it is the vascular endothelium that controls resistance vessel tone (73). Hence, it may be part of the pathophysiology of orthostatic intolerance.

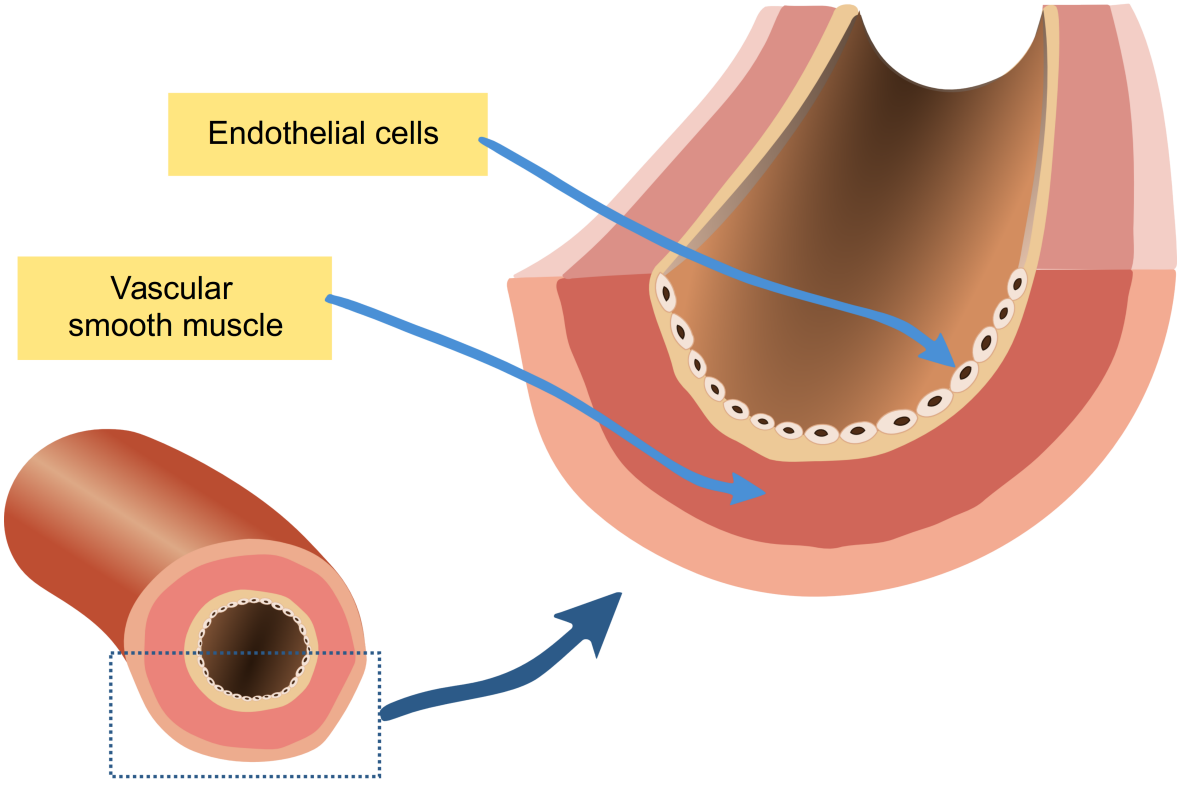

Figure 8: The blood vessel's endothelium and smooth muscle

The endothelium is only one cell layer thick and separates the blood and the vascular smooth muscle (101) (Figure 8). It produces various vasoactive factors including nitric oxide that are essential for the maintenance of endothelial function and consequently vascular homeostasis (102,103). Factors secreted by endothelial cells can induce either relaxation or contraction of the vascular smooth

muscle, leading to vasodilation or vasoconstriction (2). Increased blood flow in resistance vessels causes an increase in shear stress, which is the force exerted on the inner surface of the vessel, hence, the force exerted on endothelial cells (2). In response to an increased shear stress, endothelial cells release increased amounts of nitric oxide and prostacyclin, thereby causing vasodilation.

There is evidence that orthostatic stress increases endothelial reactivity (10,104). Guazzi et al. (104) demonstrated that the increase in endothelial reactivity is proportional to the degree of displacement. Furthermore, the authors excluded the possibility that this change in endothelial reactivity consists of changes in nitric oxide sensitivity. Therefore, they suggest that it may be due to a neural-endothelial interaction that vasculature adapts to the upright posture in an optimal manner. Goswami et al. (10) showed that a vasodilator endothelial response following orthostatic challenge can be observed in both men and women. While they found no gender differences in this response, the authors suggest that this lack of difference may be attributed to a small sample size of males. Thus, there is a need for future studies to examine this issue with a larger number of age and health matched subjects from both genders.

4.3.1.4 Orthostatic stress and brain blood flow

There is contradictory evidence whether gender differences exist in dynamic cerebral autoregulation or not. While a previous study demonstrated no gender differences in autoregulation in young children (105), another study provided evidence that young females show better autoregulation in the basilar artery (106). In a rather recent study by Deegan et al. (107) women had a significantly better autoregulation in the anterior cerebral artery during orthostatic stress in comparison to men, whereas autoregulatory responses in the middle cerebral artery were similar in both genders. Additional studies to clarify this issue would be of interest.

In order to help us recalling the main arterial blood vessels in the brain, Figure 9 illustrates the arterial circulation of the brain. Several studies have shown that women have higher systolic, diastolic and mean MCA velocity than men at rest as well as during posture change (84,105,106,108). These gender differences already exist in early childhood (105,106). Consequently, these findings indicate that women are not at greater risk for cerebral hypoperfusion during orthostatic

stress which is in interesting in consideration of the higher incidence of orthostatic intolerance in women (84).

After previous studies had suggested that cardiac output may play an important role in determining cerebral blood flow (92,97,109,110), Deegan et al. (107) investigated and refuted this possibility. They concluded from their results that cardiac output does not affect dynamic cerebral autoregulation upon sudden orthostatic stress. Thus, cerebral blood flow appears to autoregulate independent of changes in cardiac output (107).

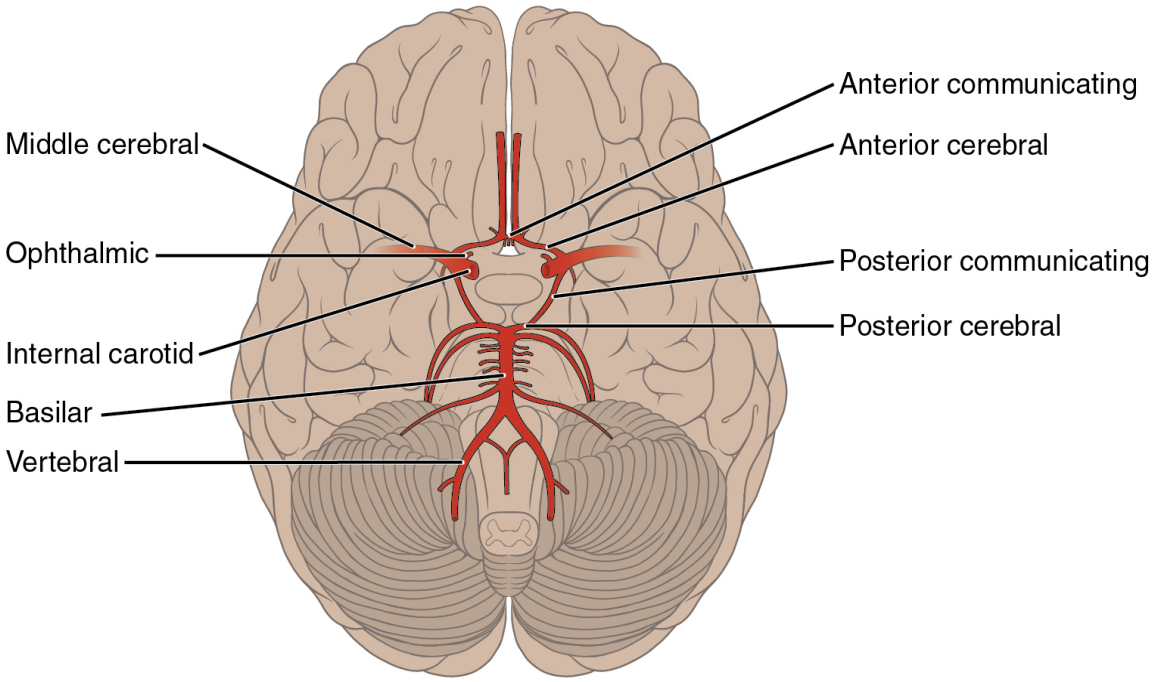

Figure 9: Arterial circulation of the brain
reproduced from: http://cnx.org/content/m46646/latest/

While it has been shown that passive heat stress reduces cerebral blood velocity (97), there is evidence that heat stress reduces cerebral blood velocity even further upon an orthostatic challenge (40). Wilson et al. (40) suggested that cerebrovascular autoregulation, maintaining cerebral perfusion during perturbations, gets impaired by heat stress. To investigate this possibility they evaluated the effect of combined heat and orthostatic stress on cerebral blood velocity and cerebral vascular resistance. Their data showed a significant decrease in cerebral blood velocity and a significant increase in cerebral vascular resistance. They concluded that changes in the cerebral vasculature during heat

stress contribute to orthostatic intolerance. In another study (97) they demonstrated that skin-surface cooling helps in preventing a drop in cerebral blood velocity during orthostatic stress. Interestingly, skin-surface cooling improves orthostatic tolerance in both normothermic and heat-stressed conditions (97). An important area for future research is determining whether there are sex differences in these observations.

4.3.2 Postspaceflight induced orthostatic intolerance

It has been well documented that after exposure to microgravity, whether simulated or actual, the susceptibility to orthostatic intolerance is significantly increased in both genders when being compared with data obtained before exposure (19,21–23,41–45,111,112). But why is postspaceflight induced orthostatic intolerance of interest for us? Well, astronauts have something in common with a specific group of people on earth: long-term bed rest patients. Both groups are predisposed to orthostatic intolerance for more or less similar reasons. While astronauts may experience orthostatic intolerance upon returning to normal gravity, long-term bed rest patients experience orthostatic intolerance upon returning to the upright posture (41). In order to understand what leads to postspaceflight induced orthostatic intolerance, data for responses to microgravity are collected on the one hand from studies that use simulated weightlessness such as HDBR and on the other hand from spaceflight studies. Although in both men and women the incidence of orthostatic intolerance is increased after exposure to microgravity, women still show a greater incidence than men (43,45,113). Therefore, several studies investigated gender differences in orthostatic intolerance and possible underlying causes of orthostatic intolerance after spaceflight (42–45,63,112,113). Furthermore, it is likely that mechanisms responsible for orthostatic intolerance after experiencing microgravity vary between short- and long-duration exposure (21). This is important as gender differences in orthostatic intolerance seem to disappear upon long-duration exposure (43).

4.3.2.1 Consequences of weightlessness

When the human body is exposed to microgravity several physical changes occur. It experiences bone demineralization, loss of muscle mass and red blood cells, fluid shifting from the lower to the upper body, cardiovascular and

sensorimotor deconditioning, and changes in the immune system (19,23). Hence, as soon as the human body re-enters earth's gravity environment, the body is challenged with time-dependent adaptation processes (111). Changes that may be important for the increased susceptibility to orthostatic intolerance after exposure to microgravity include lowered blood volume and stroke volume, lowered central venous pressure, cardiac atrophy and an attenuated baroreflex function (19). The reduction in plasma volume, thus blood volume, is the result of the fluid shifting to the upper body, leading to diuresis associated with the increase in venous return and central volume, which stimulate cardiopulmonary baroreceptors (23). In addition, the muscle loss diminishes or disables the effectiveness of the skeletal muscle pump (111) and vascular smooth muscle seems to remodel itself in response to disuse (23). Taken together, these conditions leave the body unable to adequately compensate on return to gravity and predispose it to orthostatic intolerance (41).

4.3.2.2 Cardiovascular changes after exposure to microgravity

Exposure to microgravity induces cardiovascular deconditioning in both men and women (42,63). Custaud et al. (42) observed a dramatic decrease in orthostatic tolerance in both genders following 7 days of HDBR. Interestingly, their data suggested similar cardiovascular consequences for men and women after HDBR. Furthermore, unlike several other studies (43,45,113), they did not find gender differences in orthostatic tolerance following HDBR. Edgell et al. (63) also found comparable cardiovascular changes in both genders after short periods in microgravity. Nevertheless, the authors found pelvic impedance reduced in women and higher in men after HDBR. Thus, mechanisms involved in the maintenance of venous return and cardiac output after HDBR may differ between men and women (63).

In literature, the terms finishers and non-finishers are used to describe individuals with maintained orthostatic tolerance (finishers) after exposure to microgravity and individuals who show symptoms of orthostatic intolerance (non-finishers) during a stand or tilt test. While Fritsch-Yelle et al. (113) showed that the decrease in plasma volume is similar between non-finishers and finishers, Waters et al. (45) gave more insight to this issue in a subsequent study from the same laboratory. The authors showed that there are no differences in plasma volume losses between male finishers and non-finishers, but female non-finishers do lose

significantly more plasma volume. Furthermore, female non-finishers showed to be very dependent on plasma volume to maintain standing stroke volume (45). Both studies found women to have a greater propensity toward postspaceflight orthostatic intolerance than men. Therefore, although non-finishers include both men and women, more women are non-finishers than men.

Non-finishers differ from finishers in cardiovascular responses before and after exposure to microgravity. Before exposure, non-finishers have a propensity toward higher cardiac output and lower vascular resistance (45). When it comes to cardiovascular responses during stand or tilt testing after exposure to microgravity, non-finishers show greater increases in heart rate, greater decrease in arterial blood pressure, and less of an increase in peripheral resistance than finishers (43). This is a shared feature in both male and female non-finishers. Taken together, non-finishers, men as well as women, are characterized by low peripheral vascular resistance, both before and after exposure to microgravity (45). Yet, cardiovascular changes associated with short-duration exposure are not permanent and appear to reverse spontaneously (45).

4.3.2.3 Autonomic control after exposure to microgravity

Alterations in autonomic control and baroreflex sensitivity may contribute to postspaceflight orthostatic intolerance. Waters et al. (45) concluded that finishers have hyperadrenergic responses after exposure to microgravity as well as a high vascular resistance after exposure to microgravity, which is supported by Iwasaki et al. (22). By this, finishers are able to increase resistance and maintain pressures, and therefore prevent presyncope upon stand or tilt test (45). Unlike finishers, non-finishers, male and female, are unable to increase their sympathetic response to standing after exposure, leaving them vulnerable to hypotension (45,113).

As mentioned earlier, mechanisms responsible for orthostatic intolerance after exposure to microgravity may vary between short- and long-duration exposure (21). Along these lines, Arzeno et al. (112) demonstrated in a recent study that long-duration bed rest does not affect sex differences in the autonomic control of blood pressure. In both genders they found autonomic dysfunction as a consequence of long-duration bed rest. Nevertheless, women showed a dominance of the parasympathetic system, whereas men showed a dominance of the sympathetic system, and this was preserved throughout bed rest (112). This

means that women still responded to orthostatic challenge with a larger increase in heart rate and a quicker decrease in baroreflex sensitivity with bed rest, whereas men reacted with greater increases in vascular resistance to orthostatic challenge after long-duration bed rest (112). This suggests that autonomic control contributes to sex differences in orthostatic tolerance (76,112). Future studies should investigate whether the same can be observed during and after long-duration spaceflight.

4.3.2.4 Cerebral autoregulation after exposure to microgravity

Altered cerebral hemodynamics with spaceflight could play a role in the development of orthostatic intolerance after exposure to microgravity (111). A human body in microgravity experiences chronic elevations in arterial blood pressure in the brain due to cephalic fluid shifts and it could be that cerebral autoregulation is compromised under such conditions (44,114). While short periods in microgravity appear to improve cerebral autoregulation in some individuals (115), recent studies indicate that longer periods in microgravity have a negative effect on cerebral autoregulation (44,114). Blaber et al. (44) found this reduced cerebral autoregulation associated with orthostatic intolerance. Their data showed that cerebral autoregulation was severely impaired in astronauts with orthostatic intolerance after spaceflight, whereas astronauts who did not experience orthostatic intolerance showed normal cerebral autoregulation. Furthermore, their preflight data demonstrated that cerebral autoregulation characteristics are not only different between finishers and non-finishers but also across gender. Female astronauts differed from male astronauts in cerebral blood flow velocity and cerebrovascular reactivity (for details please see (44)). Taken together, this finding suggests that although both genders experience orthostatic intolerance after exposure to microgravity, gender differences indeed seem to play a role in susceptibilty.

4.4 Influence of sex hormones on Cardiovascular Regulation

We can understand now that premenopausal women seem to regulate blood pressure differently from young men. As this difference seems to vanish after menopause, female sex hormones should be considered in regard to underlying mechanisms. Although female sex hormones are also present in men, they are found in much higher quantities in women. Their impact on the female

body is distinctive and may be responsible for gender differences concerning orthostatic tolerance. In the following sections, we will take a look at how female sex hormones influence different systems that are linked to cardiovascular regulation, and ultimately how these influences may contribute to orthostatic tolerance.

4.4.1 Female sex hormones

Female sex hormones belong to the group of steroid hormones, hence they all derive from cholesterol. Like all steroid hormones, female sex hormones have two ways of action. They can bind to intracellular receptors. By doing so, their biochemical mechanism of action is at the level of gene transcription. (2) Thus, these mechanisms have a long latency of onset (116). Besides this genomic action, there is also a non-genomic or non-transcriptional action of steroid hormones which does not require DNA binding of the receptors (116). This action is much faster than RNA and protein synthesis. Evidence suggests that target cells of steroid hormones are regulated by a complex interplay of genomic and non-genomic mechanisms (116). As we will see later, it is especially the cardiovascular system that is an important target for non-transcriptional signaling induced by estrogens.

There are two major female sex hormones: Estradiol and Progesterone. (2) Estradiol belongs to the group of estrogens. While there is actually three types of estrogens in women (Estrone (E1), Estradiol (E2) and Estriol (E3)), Estradiol is the predominant estrogen in the plasma and therefore often used synonymously with the generic term estrogen. All estrogens are produced from androgens with the help of the enzyme aromatase. They are secreted by the ovaries as well as by the placenta during pregnancy. (2) Besides the reproductive system, estrogens have important physiological role in almost every part of the body, including the nervous, immune, vascular, skeletal and endrocrine system (117). In the cardiovascular system, it has been shown that estrogen receptors are expressed in the myocardium, the endothelial cells, the smooth muscle cells, as well as in intact arteries (117).

We will see in the following section that Progesterone is secreted by the ovaries at specific times of the menstrual cycle. Besides this, it is also secreted by the adrenal glands and, during pregnancy, by the placenta. (2) Broadly speaking, progesterone has influence on several organs, including the uterus, the ovaries,

the mammary gland, the brain and the bones. In addition, progesterone receptors are also expressed in the vascular endothelium. (118)

Progesterone exerts an anti-estrogenic effect, whereas estrogen stimulates the expression of progesterone receptors. Thus, the responsiveness of progesterone depends on the presence of estrogen. (2)

4.4.2 The menstrual cycle

Premenopausal women experience the maturation of the female gamete followed by its release from the ovary as a cyclical event, termed menstrual cycle. The length of a menstrual cycle averages about 28 days with the first day of menstrual flow being designated as day 1. The menstrual cycle can be divided into phases based on events in the ovaries (ovarian cycle phases) and events in the uterus (uterine cycle phases). Figure 10 demonstrates these phases and the corresponding hormone levels.

In terms of ovarian function two phases can be described: the follicular phase and the luteal phase. These two phases are separated by ovulation. While the follicular phase is characterized by the maturing of a follicle, the luteal phase starts after the ovulation and lasts until the degradation of the corpus luteum. (2) During the early follicular phase, plasma concentration of Estradiol is low. During the second week the concentration increases rapidly due to the presence of the growing follicle that secretes more Estradiol. Then it decreases, shortly before LH peaks. In the luteal phase, Estradiol shows another increase due to the secretion by the corpus luteum. During the last days of the menstrual cycle, it rapidly decreases. Also Progesterone levels are low during the follicular phase and stay low until just before ovulation. After ovulation, the developing corpus luteum produces large amounts of progesterone. In the following, the progesterone pattern is similar to that for Estradiol. (2)

We can see now that ovarian hormones fluctuate throughout the menstrual cycle. Wenner et al. (31) concluded that many studies in the area of physiology are conducted in the early follicular phase in order to reduce variability between the sexes. Hence, it is important to keep this in mind when looking at conflicting findings regarding the influence of sex hormones.

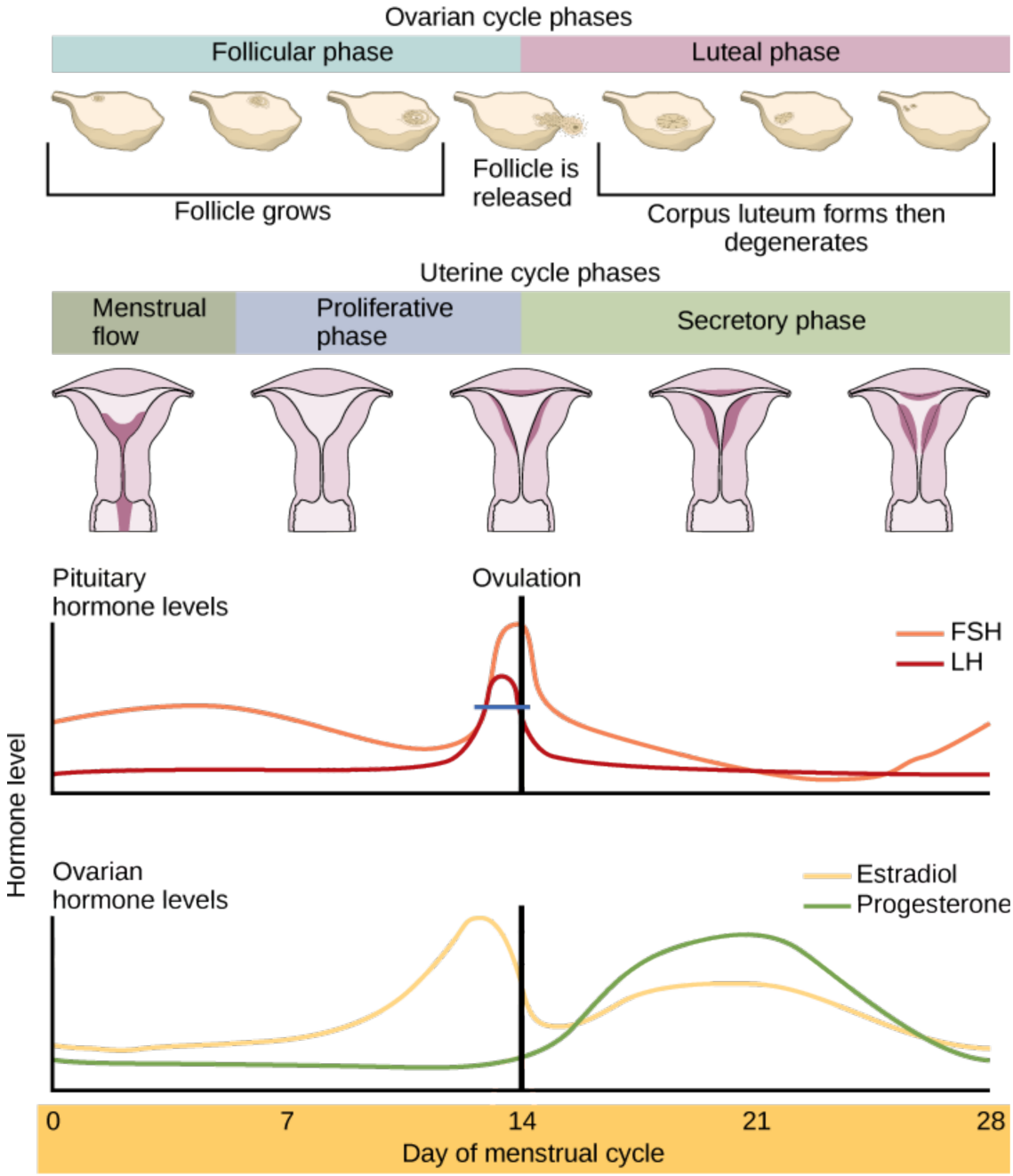

Figure 10: The menstrual cycle and hormone levels

reproduced from: https://www.boundless.com/biology/animal-reproduction-and-development/hormonal-control-of-human-reproduction/female-hormones/images/fig-ch43_04_04/

4.4.3 Sex hormones and hemodynamics

Observation by Meendering et al. (39) indicated that the menstrual cycle does not change orthostatic tolerance in premenopausal women when exposed to combined orthostatic and heat stress. This is in contrast with the findings of Chidambaram et al. (119) who demonstrated that women are unable to maintain arterial blood pressure during LBNP when being in the luteal phase, whereas they

were able to maintain it when female sex hormone levels low, like it is seen during the follicular phase. Edgell (27) found no differences in orthostatic tolerance across the menstrual cycle, yet she reported a tendency to different cardiovascular responses throughout the phases. The author suggested that different pathway to maintain venous return could still lead to similar orthostatic tolerance across the menstrual cycle. Overall, we will see that there is well established evidence that the phases of the menstrual cycle influence the vascular system in several ways (32).

There is no definite answer whether blood pressure shows variations across the menstrual cycle. While several studies (27,39,100,119–126) found no significant changes in systolic, diastolic and/or mean arterial blood pressure throughout the menstrual cycle, other studies (32,127) found significantly reduced blood pressure levels as well as an increased systemic vascular reactivity during the late follicular phase. One study (128) observed no changes in systolic blood pressure but noticed a significant decrease of diastolic blood pressure in the luteal phase in comparison to the early follicular phase. Another study (129) found slightly increased systolic and diastolic blood pressures in the luteal phase. We learned earlier that estradiol levels are highest in the late follicular phase, hence a connection between changes in blood pressure and estradiol levels are likely. In fact, Adkisson et al. (32) observed that the hemodynamic changes and vascular reactivity show a correlation with the cyclic production of estradiol during the menstrual cycle. In addition, while several studies found no significant change in heart rate (27,32,124–127), stroke volume or cardiac output across the menstrual cycle (27,127), one study found lower heart rates in the midfollicular phase (33).

As mentioned in an earlier section, women show less calf venous compliance than men, under both normovolemic and hypovolemic conditions (15,37,69). Along these lines, Meendering et al. found that calf venous compliance is not affected by fluctuating levels of neither endogenous nor exogenous estrogen and progesterone, which is in contrast with old studies from the 1960s and 1970s that have shown that changing levels of endogenous and exogenous female sex hormones influence venous distensibility (15). The authors demonstrated that women have lower calf venous compliance than men throughout the entire menstrual cycle as well as during oral contraceptive use but that the compliance does not change across the menstrual cycle. As venous compliance does not

appear to change with hormonal fluctuations, it is possible that gender differences in calf venous compliance are due to a long-term genomic effect of estradiol and/or progesterone on the structure on venous wall (15). By contrast, arterial mechanical properties appear to change during the menstrual cycle. Giannattasio et al. (129) observed that radial artery distensibility is greater around the time of ovulation than during the luteal phase. The authors suggested that this phenomenon could be explained by an estrogen-dependent reduction in vascular smooth muscle tone. This, in turn, may be due to non-genomic actions of estrogen as the phenomenon has a fast onset (34). Hence, estradiol appears to regulate vasomotor tone through both short-term and long-term effects on the vasculature (34). Interestingly, some of the rapid effects may be induced or enhanced by long-term effects of estradiol, such as increases in the expression of vasodilatory enzymes (34,130,131). We will see in the upcoming sections that estradiol can cause vasodilation by both endothelium-dependent and endothelium-independent mechanisms (132). (For details on endothelium-independent mechanisms please see (132,133).)

4.4.4 Sex hormones and the autonomic nervous system

Gender differences in orthostatic tolerance may be related to how female sex hormones influence components of the autonomic nervous system (35). In the following, we will see that many studies provide evidence for this hypothesis.

Already several years ago, it was observed in an Australian study that estradiol supplementation in perimenopausal women over the course of 8 weeks attenuates noradrenaline-induced vasoconstriction (81). Yet, the authors did not know the explanation for this phenomenon. Furthermore, low levels of estrogen as observed in the early follicular phase seem to result in an increased peripheral vasoconstriction (127). When remembering the enhanced vasodilation mediated by β2 – adrenergic receptors in premenopausal women (46,73), it appears likely that it is these receptors that are directly or indirectly influenced by estradiol and consequently cause an attenuated noradrenaline-induced vasoconstriction. Along these lines, Hirshoren et al. (125) observed a significant increase in cardiac β1 – adrenergic receptor responsiveness during the early follicular phase when ovarian hormone levels are low. Moreover, Wenner et al. (30) found that women with low orthostatic tolerance show a blunted peripheral vasoconstriction upon orthostatic stress because they are more sensitive to estradiol. In fact, we will see in the

upcoming section about the influence of female sex hormones on endothelial function that there is considerable evidence that estradiol affects the endothelium severalfold, which, in turn, also has an impact on adrenergic receptors (80,82,134). In addition, it is well established by now that the effect of sex hormones on vascular smooth muscle is mediated by endothelium-dependent as well as endothelium-independent mechanisms (134–137).

There is no agreement whether plasma catecholamine levels change throughout the menstrual cycle. On the one hand it has been reported that plasma concentrations of adrenaline (127) and noradrenaline (27,100) stay the same across the menstrual cycle. On the other hand two other studies demonstrated conflicting results, in which one found that plasma noradrenaline levels are higher (36) in the midluteal phase than in the early follicular phase and the other found levels lower (125) in the late follicular phase than in the early follicular phase. An interesting finding by Wenner et al. (35) is that hormonal responses (plasma adrenaline, plasma noradrenaline and plasma angiotensin I levels) to LBNP have been found similar in both high and low orthostatic tolerant premenopausal women. Hence, the plasma concentration of catecholamines may be of little importance in the development of orthostatic intolerance in premenopausal women. Moreover, they observed that combined estradiol with progesterone exposure only enhances cutaneous vasoconstriction in women with normal to high orthostatic tolerance but not in low tolerant women. While Freedman and Girgis (52) had already reported earlier that progesterone enhances α – adrenergic responsiveness, Wenner et al. (35) showed that progesterone induces enhanced cutaneous adrenergic responsiveness in high tolerant women. Low tolerant women in turn, stay insensitive to this progesterone mediated vasoconstriction in the skin. Thus, this lack of function may contribute to their lower orthostatic tolerance. (35) In a subsequent study, Wenner et al. (30) concluded that low tolerant premenopausal women show a greater estradiol sensitivity, whereas high tolerant premenopausal women appear to have a greater progesterone sensitivity. They found that unlike high tolerant women, low tolerant women upon orthostatic stress show an attenuated peripheral vasoconstriction that gets further reduced by exogenous estradiol administration.

More than a decade ago, Minson et al. (36) reported that sympathetic baroreflex sensitivity increases in the midluteal phase but cardiovagal baroreflex

sensitivity stays unchanged. By contrast, Hirshoren et al. (125) reported in the following that cardiovagal baroreflex sensitivity increases significantly along the luteal phase of the menstrual cycle. Some years later, Carter and Lawrence (124) demonstrated that MSNA at rest stays unchanged across the menstrual cycle, but shows a prolonged increase in the midluteal phase during recovery from mental stress. They attributed this prolonged increase to an increased sympathetic baroreflex sensitivity during the midluteal phase as it had been observed by Minson et al. (36). By contrast, Fu et al. (100) concluded from their study results that the menstrual cycle has no influences on cardiovagal baroreflex sensitivity. Yet, they found that increases in sympathetic nerve activity during orthostatic stress are lower in the early follicular than in the midluteal phase. Likewise, Middlekauff et al. (123) found no changes in cardiovagal baroreflex sensitivity across the menstrual cycle, but they observed that MSNA shows a cyclical pattern during the menstrual cycle with an increase in the midluteal and a decrease in the early follicular phase. Likewise, Carter et al. (126) found an increase in MSNA during the midluteal phase but they reported that the degree of increase was influenced by degree of surges of ovarian hormones. They observed that despite MSNA being greater in the midluteal phase, changes in MSNA were negatively correlated to changes in estradiol and tended to be positively correlated to changes in progesterone, yet this correlation to progesterone was not significant. Shortly after, Brunt et al. (138) tested the independent effects of female sex hormones in response to unloading of carotid baroreceptors and found that estrogen and progesterone have opposing influences on the baroreflex. While progesterone blunts, estradiol enhances baroreflex sensitivity. Yet, these effects can only be observed on the carotid-vasomotor baroreflex and not on the carotid-cardiovagal baroreflex. These opposing effects could explain why several studies concluded that ovarian hormones have no effect on sympathetic baroreflex sensitivity. (138) An important area for future research is determining the mechanisms behind these observed results.

4.4.5 Sex hormones and endothelial function

The vascular endothelium contains receptors for estrogen, progesterone and testosterone (34,101,139–141) and the vascular smooth muscle cells contain estrogen and androgen receptors (34,101,142). Animal-based studies revealed

several interesting aspects regarding these receptors. A study on castrated male rats indicates that testosterone and the androgen receptor are not responsible for gender differences in endothelial or vascular function (143). Ovariectomized rats, in turn, show significant changes in vascular function (143). While it has been shown that there is an increased amount of certain estrogen receptors in vascular smooth muscle cells of females (143), there is also evidence that estradiol enhances the reactivity of vascular smooth muscle (144). By now, it is well established that endothelial and vascular smooth muscle function are influenced by both endogenous and exogenous estradiol (82,101,120,122,129,132,145–148). There is evidence that progesterone can induce both vasodilation and vasoconstriction, depending on the vessel's location and on progesterone levels (31).

It is known that estradiol leads to a rapid endothelium-dependent vasodilation through an increase in basal nitric oxide release from endothelial cells (149–151). This means that estradiol seems to increase nitric oxide bioavailability (32). Nitric oxide relaxes vascular smooth muscle, thus causes vasodilation (149). We learned earlier that Adkisson et al. (32) found temporal changes in blood pressure and peripheral vascular reactivity that were perfectly corresponding with the cyclic production of estradiol during the menstrual cycle. Similarly, they observed that the mentioned changes were mirrored by the cyclic production of nitric oxide during the menstrual cycle. These findings indicate that there is a correlation of the ovarian cycle with endothelial function.

Flow mediated vasodilation is an endothelium-dependent phenomenon, mediated by nitric oxide, and can be measured during reactive hyperemia (132). It is used to assess endothelial function. There is evidence that flow mediated dilation increases simultaneously with the increase of estradiol in the follicular phase, falls right after ovulation when estradiol levels drop and rises again in the luteal phase when estradiol increases again (122). These results are supported by other authors (32,101,120) who found serum estradiol levels correlating endothelium-dependent vasodilation throughout the menstrual cycle. Figure 11 illustrates these changes in flow mediated dilation as they were observed by Hashimoto et al. (120). In contrast to all the other mentioned studies, Saxena et al. (121) investigated flow mediated dilation in the brachial artery and found no significant changes throughout the menstrual cycle. It is worth mentioning here

that the assessment of brachial artery flow mediated dilation is highly operator dependent (10), hence could explain the discrepancies.

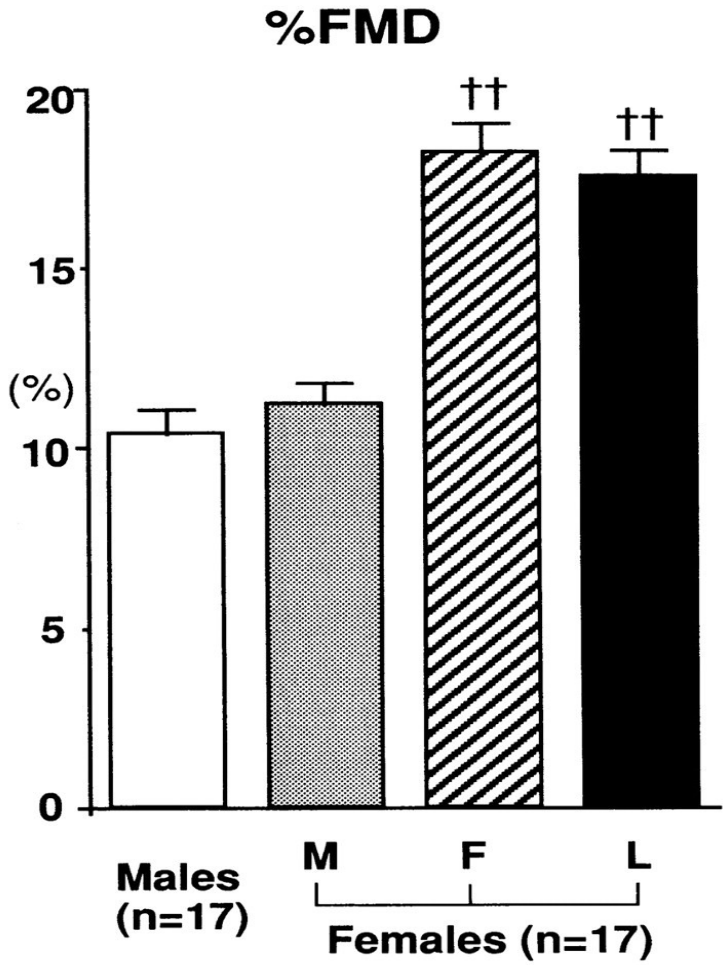

Figure 11: Effects of gender and menstrual cycle on FMD of the brachial artery.

The three bars corresponding to females show the results from the phases of the menstrual cycle: menstrual phase (M), follicular phase (F) and luteal phase (L)

†† $P<0.01$ vs males and M

(adapted from Hashimoto et el. (120))

It has been demonstrated that endothelium responds to an orthostatic challenge with an increase in flow mediated vasodilation in both men (10,104) and women (10). Surprisingly, Goswami et al. (10) did not observe gender differences in endothelial function upon orthostatic challenge between women and men. In addition, endothelial function in response to an orthostatic challenge was neither

influenced by the menstrual cycle nor by the usage of oral contraception. Their results indicate a limited role of sex hormones on endothelial function in response to an orthostatic challenge (10). Hence, results for gender differences in endothelial function at rest and during orthostatic challenge are conflicting. In order to clarify this issue, additional studies with bigger sample sizes should investigate whether sex hormones play a role in endothelial responses to orthostatic challenge or not.

4.4.6 Sex hormones and brain blood flow

Both animal- and human-based studies demonstrate that female sex hormones influence cerebral blood flow by modulating vascular smooth muscle tone (128,133,152,153). There is evidence that estradiol enhances cerebral blood flow by increasing cerebral vasodilation (133,152,153). Along these lines, it has been shown that cerebral vascular smooth muscle tone in female mice is significantly smaller than in male mice and depends on the presence of estradiol (152). Both supraphysiological and physiological levels of female sex hormones appear to influence brain blood flow (128,153). Ovarian stimulation, characterized by supraphysiological levels of female sex hormones, leads to a significant increase in cerebral blood flow (153) and the menstrual cycle causes fluctuations in cerebral blod flow that correlate with estradiol levels (128).

Estradiol affects vascular smooth muscle reactivity in cerebral arteries and arterioles by both rapid, endothelium-independent (133) and long-term, endothelium-dependent mechanism (152). Yet, it seems that the endothelium's role depends on the location and size of the vascular bed (107. The role of progesterone in modulating brain blood flow needs further investigation (153).

4.4.7 Sex hormones and the RAAS

It has been shown that reduced plasma renin activity is associated with reduced orthostatic tolerance (38). This makes sense as the activation of the RAAS causes peripheral vasoconstriction, thus would increase peripheral resistance and help in maintaining arterial blood pressure. Interestingly, it has been found that baseline levels of renin (119), plasma renin activity and aldosterone (119,125) are elevated during the midluteal phase compared to the early follicular phase, whereas their effect appears blunted at a tissue level (119). Carter et al. (126) suggested that these elevated levels of RAAS components may

contribute to their observed increase in sympathoexcitatory responses in the midluteal phases. Chidambaram et al. (119) observed that during orthostatic stress, women in the luteal phase where unable to maintain arterial blood pressure despite the elevated RAAS components. Along these lines, Cherney et al. (154) suggested that the effect of estradiol on the nitric oxide system may blunt the hemodynamic effects of RAAS activation. Moreover, it is known that nitric oxide downregulates the expression of the type 1 receptor for Angiotensin II in vascular tissue (this receptor mediates vasoconstriction) (155). Hence, high levels of estradiol in the luteal phase may trigger an NO-mediated downregulation of this receptor. This suggestion is supported by a study that showed that estradiol indeed causes a time-dependent downregulation of this receptor for Angiotensin II (156). Furthermore, exogenous estrogen administration in postmenopausal women was found to cause renin suppression (157). Progesterone in turn, appears to trigger an activation of the RAAS (158).

4.4.8 Altered hormone levels

In the following we will take a look at two situations in which levels of female sex hormones are different from those encountered throughout the menstrual cycle. Besides normally menstruating women there is premenopausal women who take oral contraceptives. The administration of exogenous female sex hormones can lead to different results for cardiovascular parameters than observations on normally menstruating women (31). One important difference to keep in mind is that exogenous hormones increase hormone exposure above that of endogenous levels that are encountered during the menstrual cycle (31). Hence, many studies investigate the influence of these altered hormonal levels and their influence on cardiovascular regulation and orthostatic tolerance. Moreover, as the levels of endogenous sex hormones are highly dynamic in premenopausal women, it is not surprising that many studies investigate the loss of function that is observed in postmenopausal women. By examining women that are not under the effect of sex hormones, the importance of sex hormones can be better assessed.

4.4.8.1 Women taking oral contraceptives

It is well known that the use of combined oral contraceptives is associated with a significant increase in systolic and diastolic blood pressure, whereas no such association exists for use of progestogen-only oral contraceptives (159).

Studies assessing endothelial function in response to the usage of oral contraceptives showed that the nitric oxide system is upregulated by oral contraceptives (154) and that estradiol increases endothelium-dependent vasodilation, whereas progestin seems to antagonize this effect (145–147).

While Minson et al. (160) observed that both cardiovagal and sympathetic baroreflex sensitivity are greater in the low hormone phases than in high hormone phases, Carter et al. (161) reported that women taking oral contraceptives have the same cardiovascular and sympathetic neural responses during low and high hormone phases of oral contraception. Yet, both studies agree that MSNA is not altered by oral contraception. It has been suggested that their conflicting results regarding sympathetic baroreflex sensitivity are a result of different technique for the assessment of sympathetic baroreflex control (123).

While some studies observed a cyclical pattern of MSNA across the menstrual cycle (123,126), MSNA seems to stay the same during both low and high hormone phases of oral contraception use. In addition, we learned earlier that some studies found augmented MSNA responses to orthostatic stress during the midluteal phase of the menstrual cycle (100,162). By contrast, women taking oral contraceptives experience similar MSNA responses to orthostatic stress in both low and high hormone phases (161).

Taking all these results together, it appears to be the fluctuations of endogenous estradiol and progesterone across the menstrual cycle that cause alterations in sympathoexcitation at rest as well as during orthostatic stress. Oral contraceptives in turn lead to rather constant hormone levels and seem to keep cardiovascular and sympathetic neural responses steady throughout both low and high hormone phases. Future studies should focus further on this issue.

4.4.8.2 Women after menopause

Although aging is associated with an increased risk of hypertension in both genders, it is women around or after menopause whose risk increases markedly (47). Thus, it seems that the dramatically reduced amount of ovarian hormones contributes to the higher risk of hypertension in postmenopausal women. Along these lines estrogen supplementation in perimenopausal women has been found to cause a significant drop in both systolic and diastolic blood pressure (81). By contrast, estrogen replacement therapy in postmenopausal women showed no effects on neither systolic nor diastolic blood pressure (163).

We had stated earlier that premenopausal women seem to have a predominance of parasympathetic control in cardiovascular regulation (42,48,49,76). In women after menopause sympathetic control appears to takes over (49). Moreover, women after menopause have very high sympathetic nerve activity in comparison to premenopausal women and young men (46). Postmenopausal women show a positive relationship of MSNA to TPR and MAP, whereas such a relationship does not exist in premenopausal women (46,74). Consequently, postmenopausal with high MSNA show high TPR and high blood pressure (47). Taken together, a high MSNA in women after menopause goes along with a high TPR, hence directly influencing arterial blood pressure and therefore most probably contributing to the increased risk of hypertension in postmenopausal women (46). Obviously, these observations suggest that it's the decrease of female sex hormones in postmenopausal women that leads to the mentioned changes.

Hunt et al. (163) reported that estrogen replacement therapy does not affect cardiovagal baroreflex function but augments sympathetic baroreflex sensitivity. This is in accordance with the results from Minson et al. (36) in premenopausal women who found that the menstrual cycle does not alter cardiovagal baroreflex function but enhances the sympathetic baroreflex sensitivity in the midliuteal phase. Interestingly, we learned in the previous section that Minson et al. (160) observed that oral contraception leads to both cardiovagal and sympathetic baroreflex sensitivity in the low hormone phases. The amount of controversial results in regard to the influence of sex hormones on the arterial baroreflexes ask for further investigations on this area.

Many years ago, Sudhir et al. (81) observed in perimenopausal women that estrogen replacement therapy blunts vasoconstrictor responses to noradrenaline. In the following, it has been shown that postmenopausal women using estrogen replacement therapy show both an augmented endothelium-dependent and endothelium-independent vasodilation in the microcirculation when being compared to postmenopausal women without replacement therapy (132). This is similar to the observed augmented vasodilation in premenopausal women in the late follicular phase (120,122,129,132). Unlike in young women, β-adrenergic receptors in postmenopausal women appear less sensitive to noradrenaline and they do not balance α-mediated vasoconstriction (46,47). Hence, an attenuated

vasoconstriction during estrogen replacement therapy appears to be the result of augmented vasodilation mediated by estradiol.

4.5 Differences between ethnic groups

We will find out in the following that cardiovascular regulation and, consequently, orthostatic tolerance in women is not only influenced by female sex hormones but also by race. Almost two decades ago Goldstein and Shapiro (53) observed that black subjects have different cardiovascular responses to orthostatic stress compared to white and Asian subjects which appeared to be due to greater sympathetic nervous system responses. Okada et al. (50) in turn, observed that elderly black subjects show an attenuated sympathetic neural reactivity but enhanced pressor responses to orthostatic stress compared to elderly whites. It also has been demonstrated that blood pressure regulation in young black subjects is different from what is known from white subjects. Young black subjects show an augmented blood pressure reactivity in comparison to age-matched white subjects (54). Investigations provided evidence that these ethnic differences in cardiovascular regulation may partly be due to variations in genes (55). One important aspect to consider though is that many studies from the past that investigated racial differences in the regulation of blood pressure did not consider gender differences, hence results from several old studies cannot tell us whether black women regulate blood pressure different from black men.

As it got more and more established that premenopausal women show a lower orthostatic tolerance than age-matched men, it also became of interest whether these differences are consistent in women from other ethnic groups. Freedman and Girgis (52) reported differences in α-adrenergic responsiveness between black and white women. While both female groups experienced an elevated vasoconstriction that was mediated by α1-adrenergic receptors during the luteal phase, only white women showed a significantly elevated α2-adrenergic vasoconstriction during the follicular phase, whereas black women showed the same response in both phases of the menstrual cycle (which was similar to the response of white women during the follicular phase). The authors did not find differences between black and white women in mean levels of estradiol or progesterone across the menstrual cycle, nor differences in levels of noradrenaline between the two female groups. Along these lines, it is interesting that one of the subtypes of the α2 – adrenergic receptor that is known for a genetic variation

common in the black population has been linked to enhanced cardiovascular stress responses (55). These are rather new findings that need further research.

The first study to investigate racial differences in orthostatic tolerance in premenopausal women was presented by Hinds and Stachenfeld (51). They observed that young black women have a significantly greater orthostatic tolerance than young white women. In addition, they noticed that black women had greater increases in plasma noradrenaline from baseline to presyncope and their concentration of plasma nordadrenaline was higher at presyncope than in white women. Furthermore, it has been reported by another study that, within both genders, black subjects have an attenuated NO-dependent vasodilation compared to their white counterparts which is probably linked to endothelial dysfunction (164). Similarly, within both genders, black subjects show a reduced β2 – adrenergic sensitivity when compared with their white counterparts (165). In a very recent study by Jarvis et al. (56) white premenopausal women during an orthostatic challenge appeared to rely predominantly on sympathetic neural activity, whereas black premenopausal women showed enhanced pressor responses and seemed to rely on the renal-adrenal system. Likewise, Okada et al. (50) found augmented pressor responses in elderly black subjects and suggested that these observations may be attributable to enhanced sympathetic vascular transduction and/or non-adrenergic vasoconstrictor mechanisms. Hence, it is possible that the underlying cause for greater orthostatic tolerance in black women has to do with fundamentally different blood pressure regulation strategies between racial groups (56) based on a combination of enhanced pressor responses (50,51,56), endothelial dysfunction (164), reduced β2 – adrenergic sensitivity (165) and enhanced renal-adrenal responses (56) in the black population. Future studies should investigate further how race affects gender differences in orthostatic tolerance and in which way black women regulate blood pressure differently from white women.

5 Conclusion

The past decades are filled with literature that shows strong evidence for existing gender differences in cardiovascular regulation and orthostatic tolerance. Yet, the reasons for these differences are not fully understood. We saw in this review that baseline gender differences such as differences in cardiovascular anatomy, hemodynamics and the autonomic nervous system may already form the basis of gender differences in cardiovascular responses. Not only do women have a smaller heart, less blood volume, an additional blood pool that attributes to splanchnic pooling during orthostatic stress, but they also show a reduced sympathetic and an enhanced parasympathetic activity in comparison to men. Along these lines, we learned that men predominantly respond to orthostatic stress by increasing vascular resistance, whereas women rather tend to increase heart rate. Both reactions increase mean arterial pressure, but the increase in vascular resistance is more effective as it helps to restore venous return. This has also been demonstrated in a study that differentiated between high and low orthostatic tolerant women. While high orthostatic tolerant women can rely on peripheral vasoconstriction in order to maintain blood pressure upon orthostatic stress, low tolerant women predominantly react with an increase in heart rate, leaving them more labile to orthostatic intolerance. A similar reaction has been shown in astronauts returning from space. Both male and female astronauts with postspaceflight induced orthostatic intolerance are characterized by greater increases in heart rate and less of an increase in peripheral vascular resistance upon standing. Although postpaceflight induced orthostatic intolerance affects both men and women, women are still more susceptible. Hence, the question remains: Why do women seem to regulate blood pressure differently from men? The answer appears to lie in the influence of female sex hormones. We learned that the described gender differences concern premenopausal women who, unlike postmenopausal women, are under the influence of ovarian hormones. Estradiol affects both endothelial and vascular function, ultimately influencing the mechanical properties of arteries and arterioles. Estradiol promotes vasodilation by increasing the availability of nitric oxide and by enhancing β2-adrenergic receptor sensitivity, thereby attenuating α-adrenergic vasoconstriction. Women after menopause lose these effects. Collectively, these influences by estradiol explain the poor increase of peripheral vascular resistance in low orthostatic

tolerant women upon orthostatic challenge. This goes along well with the finding that low orthostatic tolerant women show a greater sensitivity to estradiol, whereas high tolerant women show a greater responsiveness to progesterone. The role of progesterone in cardiovascular regulation is still poorly understood, but it has been shown that it triggers the activation of the RAAS. Thus, although studies explored several fields that may be linked to gender differences in cardiovascular regulation and orthostatic tolerance, much remains to be investigated. Only recently has it been shown that orthostatic tolerance is higher in black than in white premenopausal women, but the underlying mechanisms still remain to be identified. Hence, future studies should not only differentiate between women and men, between high and low orthostatic tolerant women, but also consider their ethnic background. Moreover, plasma concentrations of female sex hormones depend on whether women are normally menstruating or take oral contraceptives. While female sex hormones fluctuate across the menstrual cycle, oral contraceptives lead to rather constant hormone levels. Future studies should more clearly differentiate between these two groups of premenopausal women. In addition, different concentrations and combinations of exogenous female sex hormones may lead to different effects on the cardiovascular system, making it important to better differentiate between the various types of oral contraceptives as well. Such accurate differentiation should make it possible to give further insight on not only gender differences in cardiovascular regulation and orthostatic tolerance but also differences between women themselves.

6 References

1. Guyton AC. Textbook of medical physiology. 10th ed. Philadelphia: Saunders; 2000. 1064 p.

2. Widmaier EP. Vander's human physiology: the mechanisms of body function. 11th ed. Boston: McGraw-Hill Higher Education; 2008. 770 p.

3. Gray's anatomy: the anatomical basis of clinical practice. 39th ed. Edinburgh ; New York: Elsevier Churchill Livingstone; 2005. 1627 p.

4. Schmidt RF. Physiologie des Menschen: mit Pathophysiologie ; mit 77 Tabellen ; [+ IMPP-Fragen Physiologie online]. Heidelberg: Springer; 2007.

5. Stroke: pathophysiology, diagnosis, and management. 4th ed. New York: Churchill Livingstone; 2004. 1591 p.

6. Quistorff B, Secher NH, Van Lieshout JJ. Lactate fuels the human brain during exercise. FASEB J. 2008 Jun 20;22(10):3443–9.

7. Basic neurochemistry: molecular, cellular, and medical aspects. 6th ed. Philadelphia: Lippincott Williams & Wilkins; 1999. 1183 p.

8. Pires PW, Dams Ramos CM, Matin N, Dorrance AM. The effects of hypertension on the cerebral circulation. AJP Heart Circ Physiol. 2013 Jun 15;304(12):H1598–H1614.

9. Wenner MM, Haddadin AS, Taylor HS, Stachenfeld NS. Mechanisms contributing to low orthostatic tolerance in women: the influence of oestradiol. J Physiol. 2013 Feb;no–no.

10. Goswami N, Gorur P, Pilsl U, Anyaehie B, Green DA, Bondarenko AI, et al. Effect of orthostasis on endothelial function: a gender comparative study. PloS One. 2013;8(8):e71655.

11. Barnes JN. Blood pressure regulation in women – differences emerge when challenged by orthostasis. J Physiol. 2013 May 1;591(9):2239–2239.

12. Jarvis SS, Florian JP, Curren MJ, Pawelczyk JA. Sex differences in vasoconstrictor reserve during 70 deg head-up tilt. Exp Physiol. 2009 Sep 4;95(1):184–93.

13. Convertino VA. Gender differences in autonomic functions associated with blood pressure regulation. Am J Physiol. 1998 Dec;275(6 Pt 2):R1909–1920.

14. Fu Q, Witkowski S, Okazaki K, Levine BD. Effects of gender and hypovolemia on sympathetic neural responses to orthostatic stress. Am J Physiol Regul Integr Comp Physiol. 2005 Jul;289(1):R109–116.

15. Meendering JR, Torgrimson BN, Houghton BL, Halliwill JR, Minson CT. Effects of menstrual cycle and oral contraceptive use on calf venous compliance. Am J Physiol Heart Circ Physiol. 2005 Jan;288(1):H103–110.

16. 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 Jan;286(1):H449–457.

17. Naschitz JE, Rosner I. Orthostatic hypotension: framework of the syndrome. Postgrad Med J. 2007 Sep;83(983):568–74.

18. Lamarre-Cliche M, Cusson J. The fainting patient: value of the head-upright tilt-table test in adult patients with orthostatic intolerance. CMAJ Can Med Assoc J J Assoc Medicale Can. 2001 Feb 6;164(3):372–6.

19. Clément G, Pavy-Le Traon A. Centrifugation as a countermeasure during actual and simulated microgravity: a review. Eur J Appl Physiol. 2004 Jul;92(3):235–48.

20. Gotshall RW. Gender differences in tolerance to lower body negative pressure. Aviat Space Environ Med. 2000 Nov;71(11):1104–10.

21. Fischer D, Arbeille P, Shoemaker JK, O'Leary DD, Hughson RL. Altered hormonal regulation and blood flow distribution with cardiovascular deconditioning after short-duration head down bed rest. J Appl Physiol Bethesda Md 1985. 2007 Dec;103(6):2018–25.

22. Iwasaki KI, Zhang R, Zuckerman JH, Pawelczyk JA, Levine BD. Effect of head-down-tilt bed rest and hypovolemia on dynamic regulation of heart rate and blood pressure. Am J Physiol Regul Integr Comp Physiol. 2000 Dec;279(6):R2189–2199.

23. Meck JV, Dreyer SA, Warren LE. Long-duration head-down bed rest: project overview, vital signs, and fluid balance. Aviat Space Environ Med. 2009 May;80(5 Suppl):A1–8.

24. Goswami N, Loeppky JA, Hinghofer-Szalkay H. LBNP: Past Protocols and Technical Considerations for Experimental Design. Aviat Space Environ Med. 2008 May 1;79(5):459–71.

25. Regnard J, Heer M, Drummer C, Norsk P. Validity of microgravity simulation models on earth. Am J Kidney Dis Off J Natl Kidney Found. 2001 Sep;38(3):668–74.

26. Park KS, Choi JK, Park YS. Cardiovascular regulation during water immersion. Appl Hum Sci J Physiol Anthropol. 1999 Nov;18(6):233–41.

27. Edgell H. Cardiovascular responses of women to orthostatic stress, the effects of the menstrual cycle and age, and a comparison to men [Thesis]. University of Waterloo; 2010.

28. Yang H, Cooke WH, Reed KS, Carter JR. Sex differences in hemodynamic and sympathetic neural firing patterns during orthostatic challenge in humans. J Appl Physiol. 2012 May 15;112(10):1744–51.

29. Huxley VH. Sex and the cardiovascular system: the intriguing tale of how women and men regulate cardiovascular function differently. AJP Adv Physiol Educ. 2007 Mar 1;31(1):17–22.

30. Wenner MM, Haddadin AS, Taylor HS, Stachenfeld NS. Mechanisms contributing to low orthostatic tolerance in women: the influence of oestradiol. J Physiol. 2013 Feb;no–no.

31. Wenner MM, Stachenfeld NS. Blood pressure and water regulation: understanding sex hormone effects within and between men and women. J Physiol. 2012 Oct 1;590(23):5949–61.

32. Adkisson EJ, Casey DP, Beck DT, Gurovich AN, Martin JS, Braith RW. Central, peripheral and resistance arterial reactivity: fluctuates during the phases of the menstrual cycle. Exp Biol Med Maywood NJ. 2010 Jan;235(1):111–8.

33. McKinley PS, King AR, Shapiro PA, Slavov I, Fang Y, Chen IS, et al. The impact of menstrual cycle phase on cardiac autonomic regulation. Psychophysiology. 2009 Jul;46(4):904–11.

34. Mendelsohn ME, Karas RH. The protective effects of estrogen on the cardiovascular system. N Engl J Med. 1999 Jun 10;340(23):1801–11.

35. Wenner MM, Taylor HS, Stachenfeld NS. Progesterone enhances adrenergic control of skin blood flow in women with high but not low orthostatic tolerance. J Physiol. 2011 Feb 15;589(Pt 4):975–86.

36. Minson CT, Halliwill JR, Young TM, Joyner MJ. Influence of the menstrual cycle on sympathetic activity, baroreflex sensitivity, and vascular transduction in young women. Circulation. 2000 Feb 29;101(8):862–8.

37. Lindenberger M, Olsen H, Lanne T. Lower capacitance response and capillary fluid absorption in women to defend central blood volume in response to acute hypovolemic circulatory stress. AJP Heart Circ Physiol. 2008 Jun 27;295(2):H867–H873.

38. Jacob G, Robertson D, Mosqueda-Garcia R, Ertl AC, Robertson RM, Biaggioni I. Hypovolemia in syncope and orthostatic intolerance role of the renin-angiotensin system. Am J Med. 1997 Aug;103(2):128–33.

39. Meendering JR, Torgrimson BN, Houghton BL, Halliwill JR, Minson CT. Menstrual cycle and sex affect hemodynamic responses to combined orthostatic and heat stress. Am J Physiol Heart Circ Physiol. 2005 Aug;289(2):H631–642.

40. Wilson TE, Cui J, Zhang R, Crandall CG. Heat stress reduces cerebral blood velocity and markedly impairs orthostatic tolerance in humans. Am J Physiol Regul Integr Comp Physiol. 2006 Nov;291(5):R1443–1448.

41. White AR, Ryoo S, Bugaj L, Attarzadeh DO, Thiyagarajan S, Chen K, et al. Early changes in vasoreactivity after simulated microgravity are due to an

upregulation of the endothelium-dependent nitric oxide/cGMP pathway. Eur J Appl Physiol. 2010 Sep;110(2):395–404.

42. Custaud M-A, de Souza Neto EP, Abry P, Flandrin P, Millet C, Duvareille M, et al. Orthostatic tolerance and spontaneous baroreflex sensitivity in men versus women after 7 days of head-down bed rest. Auton Neurosci. 2002 Sep;100(1-2):66–76.

43. Harm DL, Jennings RT, Meck JV, Powell MR, Putcha L, Sams CP, et al. Invited review: gender issues related to spaceflight: a NASA perspective. J Appl Physiol Bethesda Md 1985. 2001 Nov;91(5):2374–83.

44. Blaber AP, Goswami N, Bondar RL, Kassam MS. Impairment of cerebral blood flow regulation in astronauts with orthostatic intolerance after flight. Stroke J Cereb Circ. 2011 Jul;42(7):1844–50.

45. Waters WW, Ziegler MG, Meck JV. Postspaceflight orthostatic hypotension occurs mostly in women and is predicted by low vascular resistance. J Appl Physiol Bethesda Md 1985. 2002 Feb;92(2):586–94.

46. Hart EC, Charkoudian N, Wallin BG, Curry TB, Eisenach J, Joyner MJ. Sex and ageing differences in resting arterial pressure regulation: the role of the β-adrenergic receptors. J Physiol. 2011 Nov 1;589(Pt 21):5285–97.

47. Hart EC, Joyner MJ, Wallin BG, Charkoudian N. Sex, ageing and resting blood pressure: gaining insights from the integrated balance of neural and haemodynamic factors. J Physiol. 2012 May 1;590(9):2069–79.

48. Barnett SR, Morin RJ, Kiely DK, Gagnon M, Azhar G, Knight EL, et al. Effects of Age and Gender on Autonomic Control of Blood Pressure Dynamics. Hypertension. 1999 May 1;33(5):1195–200.

49. Lavi S, Nevo O, Thaler I, Rosenfeld R, Dayan L, Hirshoren N, et al. Effect of aging on the cardiovascular regulatory systems in healthy women. AJP Regul Integr Comp Physiol. 2006 Sep 28;292(2):R788–R793.

50. Okada Y, Galbreath MM, Jarvis SS, Bivens TB, Vongpatanasin W, Levine BD, et al. Elderly blacks have a blunted sympathetic neural responsiveness but greater pressor response to orthostasis than elderly whites. Hypertension. 2012 Sep;60(3):842–8.

51. Hinds K, Stachenfeld NS. Greater Orthostatic Tolerance in Young Black Compared With White Women. Hypertension. 2010 Jul 1;56(1):75–81.

52. Freedman RR, Girgis R. Effects of menstrual cycle and race on peripheral vascular alpha-adrenergic responsiveness. Hypertension. 2000 Mar;35(3):795–9.

53. Goldstein IB, Shapiro D. The cardiovascular response to postural change as a function of race. Biol Psychol. 1995 Feb;39(2-3):173–86.

54. Ray CA, Monahan KD. Sympathetic vascular transduction is augmented in young normotensive blacks. J Appl Physiol Bethesda Md 1985. 2002 Feb;92(2):651–6.

55. Kurnik D, Friedman EA, Muszkat M, Sofowora GG, Xie H-G, Dupont WD, et al. Genetic variants in the alpha2C-adrenoceptor and G-protein contribute to ethnic differences in cardiovascular stress responses. Pharmacogenet Genomics. 2008 Sep;18(9):743–50.

56. Jarvis SS, Shibata S, Okada Y, Levine BD, Fu Q. Neural-humoral responses during head-up tilt in healthy young white and black women. Front Physiol. 2014 Mar 4;5.

57. Jarvis SS, Pawelczyk JA. The location of the human volume indifferent point predicts orthostatic tolerance. Eur J Appl Physiol. 2010 May;109(2):331–41.

58. Salton CJ, Chuang ML, O'Donnell CJ, Kupka MJ, Larson MG, Kissinger KV, et al. Gender differences and normal left ventricular anatomy in an adult population free of hypertension. A cardiovascular magnetic resonance study of the Framingham Heart Study Offspring cohort. J Am Coll Cardiol. 2002 Mar 20;39(6):1055–60.

59. De Simone G, Devereux RB, Roman MJ, Ganau A, Chien S, Alderman MH, et al. Gender differences in left ventricular anatomy, blood viscosity and volume regulatory hormones in normal adults. Am J Cardiol. 1991 Dec 15;68(17):1704–8.

60. Hutchinson PL, Cureton KJ, Outz H, Wilson G. Relationship of cardiac size to maximal oxygen uptake and body size in men and women. Int J Sports Med. 1991 Aug;12(4):369–73.

61. Kachlik D, Pechacek V, Musil V, Baca V. The venous system of the pelvis: new nomenclature. Phlebol Venous Forum R Soc Med. 2010 Aug;25(4):162–73.

62. White DD, Montgomery LD. Pelvic blood pooling of men and women during lower body negative pressure. Aviat Space Environ Med. 1996 Jun;67(6):555–9.

63. Edgell H, Grinberg A, Gagné N, Beavers KR, Hughson RL. Cardiovascular responses to lower body negative pressure before and after 4 h of head-down bed rest and seated control in men and women. J Appl Physiol Bethesda Md 1985. 2012 Nov;113(10):1604–12.

64. Halliwill JR, Lawler LA, Eickhoff TJ, Joyner MJ, Mulvagh SL. Reflex responses to regional venous pooling during lower body negative pressure in humans. J Appl Physiol Bethesda Md 1985. 1998 Feb;84(2):454–8.

65. Arvedsen SK, Damgaard M, Norsk P. Body height and blood pressure regulation in humans during anti-orthostatic tilting. AJP Regul Integr Comp Physiol. 2012 Apr 15;302(8):R984–R989.

66. Summers RL, Platts S, Myers JG, Coleman TG. Theoretical analysis of the mechanisms of a gender differentiation in the propensity for orthostatic intolerance after spaceflight. Theor Biol Med Model. 2010;7:8.

67. Tandri H, Daya SK, Nasir K, Bomma C, Lima JAC, Calkins H, et al. Normal reference values for the adult right ventricle by magnetic resonance imaging. Am J Cardiol. 2006 Dec 15;98(12):1660–4.

68. Reckelhoff JF. Gender Differences in the Regulation of Blood Pressure. Hypertension. 2001 May 1;37(5):1199–208.

69. Monahan KD, Ray CA. Gender affects calf venous compliance at rest and during baroreceptor unloading in humans. Am J Physiol Heart Circ Physiol. 2004 Mar;286(3):H895–901.

70. Lott MEJ, Hogeman C, Herr M, Bhagat M, Sinoway LI. Sex differences in limb vasoconstriction responses to increases in transmural pressures. AJP Heart Circ Physiol. 2008 Nov 14;296(1):H186–H194.

71. Hachiya T, Hashimoto I, Saito M, Blaber AP. Peripheral vascular responses of men and women to LBNP. Aviat Space Environ Med. 2012 Feb;83(2):118–24.

72. Jarvis SS, Florian JP, Curren MJ, Pawelczyk JA. A somatostatin analog improves tilt table tolerance by decreasing splanchnic vascular conductance. J Appl Physiol Bethesda Md 1985. 2012 May;112(9):1504–11.

73. Kneale BJ, Chowienczyk PJ, Brett SE, Coltart DJ, Ritter JM. Gender differences in sensitivity to adrenergic agonists of forearm resistance vasculature. J Am Coll Cardiol. 2000 Oct;36(4):1233–8.

74. Hart EC, Charkoudian N, Wallin BG, Curry TB, Eisenach JH, Joyner MJ. Sex differences in sympathetic neural-hemodynamic balance: implications for human blood pressure regulation. Hypertension. 2009 Mar;53(3):571–6.

75. Dutoit AP, Hart EC, Charkoudian N, Wallin BG, Curry TB, Joyner MJ. Cardiac baroreflex sensitivity is not correlated to sympathetic baroreflex sensitivity within healthy, young humans. Hypertension. 2010 Dec;56(6):1118–23.

76. Christou DD. Women Have Lower Tonic Autonomic Support of Arterial Blood Pressure and Less Effective Baroreflex Buffering Than Men. Circulation. 2005 Feb 1;111(4):494–8.

77. Charkoudian N, Joyner MJ, Sokolnicki LA, Johnson CP, Eisenach JH, Dietz NM, et al. Vascular adrenergic responsiveness is inversely related to tonic activity of sympathetic vasoconstrictor nerves in humans. J Physiol. 2006 May 1;572(3):821–7.

78. Charkoudian N, Joyner MJ, Johnson CP, Eisenach JH, Dietz NM, Wallin BG. Balance between cardiac output and sympathetic nerve activity in resting humans: role in arterial pressure regulation. J Physiol. 2005 Oct 1;568(1):315–21.

79. Schmitt JAM, Joyner MJ, Charkoudian N, Wallin BG, Hart EC. Sex differences in alpha-adrenergic support of blood pressure. Clin Auton Res Off J Clin Auton Res Soc. 2010 Aug;20(4):271–5.

80. Yono M, Yoshida M, Takahashi W, Inadome A, Seshita H, Miyamoto Y, et al. Effects of ovarian hormones on beta-adrenergic receptor-mediated relaxation in the female rabbit bladder. Urol Res. 2000 Jan;28(1):38–45.

81. Sudhir K, Elser MD, Jennings GL, Komesaroff PA. Estrogen supplementation decreases norepinephrine-induced vasoconstriction and total body norepinephrine spillover in perimenopausal women. Hypertension. 1997 Dec;30(6):1538–43.

82. Conde MV, Marín J, Fernandez-Criado C, Balfagón G. Regulation of beta-adrenoceptor-mediated relaxation of the rat aorta is modulated by endogenous ovarian hormones. Clin Sci Lond Engl 1979. 2000 Apr;98(4):381–7.

83. Olatunji LA, Aaron AO, Micheal OS, Oyeyipo IP. Water ingestion affects orthostatic challenge-induced blood pressure and heart rate responses in young healthy subjects: gender implications. Niger J Physiol Sci Off Publ Physiol Soc Niger. 2011 Jun;26(1):11–8.

84. 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 May 1;112(9):1482–93.

85. Davis SCAT, Westerhof BE, van den Bogaard B, Bogert LWJ, Truijen J, Kim Y-S, et al. Active standing reduces wave reflection in the presence of increased peripheral resistance in young and old healthy individuals. J Hypertens. 2011 Apr;29(4):682–9.

86. Kimmerly DS, Wong S, Menon R, Shoemaker JK. Forebrain neural patterns associated with sex differences in autonomic and cardiovascular function during baroreceptor unloading. AJP Regul Integr Comp Physiol. 2006 Sep 28;292(2):R715–R722.

87. Shoemaker JK, Hughson RL, Sinoway LI. Gender affects sympathetic neurovascular control during postural stress. J Gravitational Physiol J Int Soc Gravitational Physiol. 2002 Jul;9(1):P83–84.

88. Cote AT, Bredin SSD, Phillips AA, Warburton DER. Predictors of orthostatic intolerance in healthy young women. Clin Investig Med Médecine Clin Exp. 2012;35(2):E65–74.

89. Convertino VA, Cooke WH, Holcomb JB. Arterial pulse pressure and its association with reduced stroke volume during progressive central hypovolemia. J Trauma. 2006 Sep;61(3):629–34.

90. Lindenberger M, Länne T. Sex-related effects on venous compliance and capillary filtration in the lower limb. Am J Physiol Regul Integr Comp Physiol. 2007 Feb;292(2):R852–859.

91. Lawler LA, Halliwill JR, Summer JM, Joyner MJ, Mulvagh SL. Leg mass and lower body negative pressure tolerance in men and women. J Appl Physiol Bethesda Md 1985. 1998 Oct;85(4):1471–5.

92. Van Lieshout JJ, Pott F, Madsen PL, van Goudoever J, Secher NH. Muscle tensing during standing: effects on cerebral tissue oxygenation and cerebral artery blood velocity. Stroke J Cereb Circ. 2001 Jul;32(7):1546–51.

93. Etter KE, Goswami N, Sharp MK. Modelling of cardiovascular response to graded orthostatic stress: role of capillary filtration: CAPILLARY FILTRATION DURING ORTHOSTASIS. Eur J Clin Invest. 2011 Aug;41(8):807–19.

94. Murrell C, Cotter JD, George K, Shave R, Wilson L, Thomas K, et al. Influence of age on syncope following prolonged exercise: differential responses but similar orthostatic intolerance. J Physiol. 2009 Dec 15;587(Pt 24):5959–69.

95. Murrell CJ, Cotter JD, George K, Shave R, Wilson L, Thomas K, et al. Cardiorespiratory and cerebrovascular responses to head-up tilt I: influence of age and training status. Exp Gerontol. 2011 Jan;46(1):9–17.

96. Murrell CJ, Cotter JD, George K, Shave R, Wilson L, Thomas K, et al. Cardiorespiratory and cerebrovascular responses to head-up tilt II: influence of age, training status and acute exercise. Exp Gerontol. 2011 Jan;46(1):1–8.

97. Wilson TE, Cui J, Zhang R, Witkowski S, Crandall CG. Skin cooling maintains cerebral blood flow velocity and orthostatic tolerance during tilting in heated humans. J Appl Physiol Bethesda Md 1985. 2002 Jul;93(1):85–91.

98. Cui J. Effect of skin surface cooling on central venous pressure during orthostatic challenge. AJP Heart Circ Physiol. 2005 Aug 12;289(6):H2429–H2433.

99. Kim A, Deo SH, Vianna LC, Balanos GM, Hartwich D, Fisher JP, et al. Sex differences in carotid baroreflex control of arterial blood pressure in humans: relative contribution of cardiac output and total vascular conductance. Am J Physiol Heart Circ Physiol. 2011 Dec;301(6):H2454–2465.

100. Fu Q, Okazaki K, Shibata S, Shook RP, VanGunday TB, Galbreath MM, et al. Menstrual cycle effects on sympathetic neural responses to upright tilt. J Physiol. 2009 Feb 23;587(9):2019–31.

101. Sader MA, Celermajer DS. Endothelial function, vascular reactivity and gender differences in the cardiovascular system. Cardiovasc Res. 2002 Feb 15;53(3):597–604.

102. Hamburg NM, Benjamin EJ. Assessment of Endothelial Function Using Digital Pulse Amplitude Tonometry. Trends Cardiovasc Med. 2009 Jan;19(1):6–11.

103. Faizi AK, Kornmo DW, Agewall S. Evaluation of endothelial function using finger plethysmography. Clin Physiol Funct Imaging. 2009 Sep;29(5):372–5.

104. Guazzi M, Lenatti L, Tumminello G, Puppa S, Fiorentini C, Guazzi MD. The behaviour of the flow-mediated brachial artery vasodilatation during orthostatic stress in normal man. Acta Physiol Scand. 2004 Dec;182(4):353–60.

105. Tontisirin N, Muangman SL, Suz P, Pihoker C, Fisk D, Moore A, et al. Early childhood gender differences in anterior and posterior cerebral blood flow velocity and autoregulation. Pediatrics. 2007 Mar;119(3):e610–615.

106. Vavilala MS, Kincaid MS, Muangman SL, Suz P, Rozet I, Lam AM. Gender differences in cerebral blood flow velocity and autoregulation between the anterior and posterior circulations in healthy children. Pediatr Res. 2005 Sep;58(3):574–8.

107. Deegan BM, Devine ER, Geraghty MC, Jones E, Ólaighin G, Serrador JM. The relationship between cardiac output and dynamic cerebral autoregulation in humans. J Appl Physiol Bethesda Md 1985. 2010 Nov;109(5):1424–31.

108. Deegan BM, Sorond FA, Lipsitz LA, Olaighin G, Serrador JM. Gender related differences in cerebral autoregulation in older healthy subjects. Conf Proc Annu Int Conf IEEE Eng Med Biol Soc IEEE Eng Med Biol Soc Conf. 2009;2009:2859–62.

109. Joseph M, Ziadi S, Nates J, Dannenbaum M, Malkoff M. Increases in cardiac output can reverse flow deficits from vasospasm independent of blood pressure: a study using xenon computed tomographic measurement of cerebral blood flow. Neurosurgery. 2003 Nov;53(5):1044–1051; discussion 1051–1052.

110. Van Lieshout JJ, Wieling W, Karemaker JM, Secher NH. Syncope, cerebral perfusion, and oxygenation. J Appl Physiol Bethesda Md 1985. 2003 Mar;94(3):833–48.

111. Goswami N, Batzel JJ, Clément G, Stein TP, Hargens AR, Sharp MK, et al. Maximizing information from space data resources: a case for expanding integration across research disciplines. Eur J Appl Physiol. 2013 Jul;113(7):1645–54.

112. Arzeno NM, Stenger MB, Lee SMC, Ploutz-Snyder R, Platts SH. Sex differences in blood pressure control during 6 head-down tilt bed rest. AJP Heart Circ Physiol. 2013 Apr 15;304(8):H1114–H1123.

113. Fritsch-Yelle JM, Whitson PA, Bondar RL, Brown TE. Subnormal norepinephrine release relates to presyncope in astronauts after spaceflight. J Appl Physiol Bethesda Md 1985. 1996 Nov;81(5):2134–41.

114. Zuj KA, Arbeille P, Shoemaker JK, Blaber AP, Greaves DK, Xu D, et al. Impaired cerebrovascular autoregulation and reduced CO_2 reactivity after long duration spaceflight. Am J Physiol Heart Circ Physiol. 2012 Jun 15;302(12):H2592–2598.

115. Iwasaki K, Levine BD, Zhang R, Zuckerman JH, Pawelczyk JA, Diedrich A, et al. Human cerebral autoregulation before, during and after spaceflight. J Physiol. 2007 Mar 15;579(Pt 3):799–810.

116. Simoncini T, Genazzani AR. Non-genomic actions of sex steroid hormones. Eur J Endocrinol Eur Fed Endocr Soc. 2003 Mar;148(3):281–92.

117. Prossnitz ER, Barton M. The G-protein-coupled estrogen receptor GPER in health and disease. Nat Rev Endocrinol. 2011 Aug 16;7(12):715–26.

118. Graham JD, Clarke CL. Physiological action of progesterone in target tissues. Endocr Rev. 1997 Aug;18(4):502–19.

119. Chidambaram M, Duncan JA, Lai VS, Cattran DC, Floras JS, Scholey JW, et al. Variation in the renin angiotensin system throughout the normal menstrual cycle. J Am Soc Nephrol JASN. 2002 Feb;13(2):446–52.

120. Hashimoto M, Akishita M, Eto M, Ishikawa M, Kozaki K, Toba K, et al. Modulation of endothelium-dependent flow-mediated dilatation of the brachial artery by sex and menstrual cycle. Circulation. 1995 Dec 15;92(12):3431–5.

121. Saxena AR, Seely EW, Goldfine AB. Cardiovascular risk factors and menstrual cycle phase in pre-menopausal women. J Endocrinol Invest. 2012 Sep;35(8):715–9.

122. Williams MR, Westerman RA, Kingwell BA, Paige J, Blombery PA, Sudhir K, et al. Variations in endothelial function and arterial compliance during the menstrual cycle. J Clin Endocrinol Metab. 2001 Nov;86(11):5389–95.

123. Middlekauff HR, Park J, Gornbein JA. Lack of effect of ovarian cycle and oral contraceptives on baroreceptor and nonbaroreceptor control of sympathetic nerve activity in healthy women. Am J Physiol Heart Circ Physiol. 2012 Jun 15;302(12):H2560–2566.

124. Carter JR, Lawrence JE. Effects of the menstrual cycle on sympathetic neural responses to mental stress in humans. J Physiol. 2007 Dec 1;585(Pt 2):635–41.

125. Hirshoren N, Tzoran I, Makrienko I, Edoute Y, Plawner MM, Itskovitz-Eldor J, et al. Menstrual cycle effects on the neurohumoral and autonomic nervous systems regulating the cardiovascular system. J Clin Endocrinol Metab. 2002 Apr;87(4):1569–75.

126. Carter JR, Fu Q, Minson CT, Joyner MJ. Ovarian cycle and sympathoexcitation in premenopausal women. Hypertension. 2013 Feb;61(2):395–9.

127. Choi H-M, Stebbins CL, Nho H, Kim M-S, Chang M-J, Kim J-K. Effects of Ovarian Cycle on Hemodynamic Responses during Dynamic Exercise in Sedentary Women. Korean J Physiol Pharmacol Off J Korean Physiol Soc Korean Soc Pharmacol. 2013 Dec;17(6):499–503.

128. Krejza J, Mariak Z, Nowacka A, Melhem ER, Babikian VL. Influence of 17-beta-estradiol on cerebrovascular impedance during menstrual cycle in women. J Neurol Sci. 2004 Jun 15;221(1-2):61–7.

129. Giannattasio C, Failla M, Grappiolo A, Stella ML, Del Bo A, Colombo M, et al. Fluctuations of radial artery distensibility throughout the menstrual cycle. Arterioscler Thromb Vasc Biol. 1999 Aug;19(8):1925–9.

130. Weiner CP, Lizasoain I, Baylis SA, Knowles RG, Charles IG, Moncada S. Induction of calcium-dependent nitric oxide synthases by sex hormones. Proc Natl Acad Sci U S A. 1994 May 24;91(11):5212–6.

131. Binko J, Majewski H. 17 beta-Estradiol reduces vasoconstriction in endothelium-denuded rat aortas through inducible NOS. Am J Physiol. 1998 Mar;274(3 Pt 2):H853–859.

132. Arora S, Veves A, Caballaro AE, Smakowski P, LoGerfo FW. Estrogen improves endothelial function. J Vasc Surg. 1998 Jun;27(6):1141–1146; discussion 1147.

133. Patkar S, Farr TD, Cooper E, Dowell FJ, Carswell HVO. Differential vasoactive effects of oestrogen, oestrogen receptor agonists and selective oestrogen receptor modulators in rat middle cerebral artery. Neurosci Res. 2011 Sep;71(1):78–84.

134. Orshal JM, Khalil RA. Gender, sex hormones, and vascular tone. Am J Physiol Regul Integr Comp Physiol. 2004 Feb;286(2):R233–249.

135. Miller VM, Duckles SP. Vascular actions of estrogens: functional implications. Pharmacol Rev. 2008 Jun;60(2):210–41.

136. Duckles SP, Miller VM. Hormonal modulation of endothelial NO production. Pflüg Arch Eur J Physiol. 2010 May;459(6):841–51.

137. Hart EC, Charkoudian N, Miller VM. Sex, hormones and neuroeffector mechanisms. Acta Physiol Oxf Engl. 2011 Sep;203(1):155–65.

138. Brunt VE, Miner JA, Kaplan PF, Halliwill JR, Strycker LA, Minson CT. Short-term administration of progesterone and estradiol independently alter carotid-vasomotor, but not carotid-cardiac, baroreflex function in young women. AJP Heart Circ Physiol. 2013 Oct 1;305(7):H1041–H1049.

139. Rogers PA, Lederman F, Kooy J, Taylor NH, Healy DL. Endometrial vascular smooth muscle oestrogen and progesterone receptor distribution in women with and without menorrhagia. Hum Reprod Oxf Engl. 1996 Sep;11(9):2003–8.

140. McLaren J, Prentice A, Charnock-Jones DS, Millican SA, Müller KH, Sharkey AM, et al. Vascular endothelial growth factor is produced by peritoneal fluid macrophages in endometriosis and is regulated by ovarian steroids. J Clin Invest. 1996 Jul 15;98(2):482–9.

141. Venkov CD, Rankin AB, Vaughan DE. Identification of authentic estrogen receptor in cultured endothelial cells. A potential mechanism for steroid hormone regulation of endothelial function. Circulation. 1996 Aug 15;94(4):727–33.

142. Karas RH, Patterson BL, Mendelsohn ME. Human vascular smooth muscle cells contain functional estrogen receptor. Circulation. 1994 May;89(5):1943–50.

143. Ma Y, Qiao X, Falone AE, Reslan OM, Sheppard SJ, Khalil RA. Gender-specific reduction in contraction is associated with increased estrogen receptor expression in single vascular smooth muscle cells of female rat. Cell Physiol Biochem Int J Exp Cell Physiol Biochem Pharmacol. 2010;26(3):457–70.

144. Acs N, Székács B, Nádasy GL, Várbíró S, Kakucs R, Monos E. The effect of ovariectomy and oestrogen replacement on small artery biomechanics in the rat. Br J Obstet Gynaecol. 1999 Feb;106(2):148–54.

145. Meendering JR, Torgrimson BN, Miller NP, Kaplan PF, Minson CT. A combined oral contraceptive containing 30 mcg ethinyl estradiol and 3.0 mg drospirenone does not impair endothelium-dependent vasodilation. Contraception. 2010 Oct;82(4):366–72.

146. Torgrimson BN, Meendering JR, Kaplan PF, Minson CT. Endothelial function across an oral contraceptive cycle in women using levonorgestrel and ethinyl estradiol. Am J Physiol Heart Circ Physiol. 2007 Jun;292(6):H2874–2880.

147. Meendering JR, Torgrimson BN, Miller NP, Kaplan PF, Minson CT. Ethinyl estradiol-to-desogestrel ratio impacts endothelial function in young women. Contraception. 2009 Jan;79(1):41–9.

148. Chan HY, Yao X, Tsang SY, Chan FL, Lau CW, Huang Y. Different role of endothelium/nitric oxide in 17beta-estradiol- and progesterone-induced relaxation in rat arteries. Life Sci. 2001 Aug 24;69(14):1609–17.

149. Caulin-Glaser T, García-Cardeña G, Sarrel P, Sessa WC, Bender JR. 17 beta-estradiol regulation of human endothelial cell basal nitric oxide release, independent of cytosolic Ca2+ mobilization. Circ Res. 1997 Nov;81(5):885–92.

150. Russell KS, Haynes MP, Caulin-Glaser T, Rosneck J, Sessa WC, Bender JR. Estrogen stimulates heat shock protein 90 binding to endothelial nitric oxide synthase in human vascular endothelial cells. Effects on calcium sensitivity and NO release. J Biol Chem. 2000 Feb 18;275(7):5026–30.

151. Wu Q, Chambliss K, Umetani M, Mineo C, Shaul PW. Non-nuclear Estrogen Receptor Signaling in the Endothelium. J Biol Chem. 2011 Apr 29;286(17):14737–43.

152. Geary GG, Krause DN, Duckles SP. Estrogen reduces mouse cerebral artery tone through endothelial NOS- and cyclooxygenase-dependent mechanisms. Am J Physiol Heart Circ Physiol. 2000 Aug;279(2):H511–519.

153. Nevo O, Soustiel JF, Thaler I. Cerebral blood flow is increased during controlled ovarian stimulation. Am J Physiol Heart Circ Physiol. 2007 Dec;293(6):H3265–3269.

154. Cherney DZI, Scholey JW, Cattran DC, Kang AK, Zimpelmann J, Kennedy C, et al. The effect of oral contraceptives on the nitric oxide system and renal function. AJP Ren Physiol. 2007 Aug 8;293(5):F1539–F1544.

155. Ichiki T, Usui M, Kato M, Funakoshi Y, Ito K, Egashira K, et al. Downregulation of angiotensin II type 1 receptor gene transcription by nitric oxide. Hypertension. 1998 Jan;31(1 Pt 2):342–8.

156. Nickenig G, Bäumer AT, Grohè C, Kahlert S, Strehlow K, Rosenkranz S, et al. Estrogen modulates AT1 receptor gene expression in vitro and in vivo. Circulation. 1998 Jun 9;97(22):2197–201.

157. Schunkert H, Danser AH, Hense HW, Derkx FH, Kürzinger S, Riegger GA. Effects of estrogen replacement therapy on the renin-angiotensin system in postmenopausal women. Circulation. 1997 Jan 7;95(1):39–45.

158. Seely EW, Walsh BW, Gerhard MD, Williams GH. Estradiol with or without progesterone and ambulatory blood pressure in postmenopausal women. Hypertension. 1999 May;33(5):1190–4.

159. Dong W, Colhoun HM, Poulter NR. Blood pressure in women using oral contraceptives: results from the Health Survey for England 1994. J Hypertens. 1997 Oct;15(10):1063–8.

160. Minson CT, Halliwill JR, Young TM, Joyner MJ. Sympathetic activity and baroreflex sensitivity in young women taking oral contraceptives. Circulation. 2000 Sep 26;102(13):1473–6.

161. Carter JR, Klein JC, Schwartz CE. Effects of oral contraceptives on sympathetic nerve activity during orthostatic stress in young, healthy women. Am J Physiol Regul Integr Comp Physiol. 2010 Jan;298(1):R9–R14.

162. Carter JR, Lawrence JE, Klein JC. Menstrual cycle alters sympathetic neural responses to orthostatic stress in young, eumenorrheic women. Am J Physiol - Endocrinol Metab. 2009 Jul 1;297(1):E85–E91.

163. Hunt BE, Taylor JA, Hamner JW, Gagnon M, Lipsitz LA. Estrogen replacement therapy improves baroreflex regulation of vascular sympathetic outflow in postmenopausal women. Circulation. 2001 Jun 19;103(24):2909–14.

164. Mata-Greenwood E, Chen D-B. Racial differences in nitric oxide-dependent vasorelaxation. Reprod Sci Thousand Oaks Calif. 2008 Jan;15(1):9–25.

165. Lemogoum D, Van Bortel L, Van den Abeele W, Ciarka A, Degaute J-P, van de Borne P, et al. Effect of beta-adrenergic stimulation on pulse wave velocity in black and white subjects. J Hypertens. 2004 Dec;22(12):2349–53.