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HEMODYNAMIC AND AUTONOMIC PATTERNS DURING SLEEP IN ESSENTIAL HYPOTENSION

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Index

Abstract v

Abbreviations 1

CHAPTER 1 **The Cardiovascular System** 3

1.1 Heart 3

1.2 Blood Vessels 4

1.3 Circulatory Routes 5

1.4 Autonomic Cardiovascular Innervation 6

1.5 Regulation of Blood Flow 7

1.5.1 Intrinsic Regulation 8

1.5.2 Extrinsic Regulation 9

1.6 Regulation of Cardiac Output 10

1.6.1 Regulation of Heart Rate 10

1.6.2 Regulation of Stroke Volume 11

1.7 Regulation of Arterial Blood Pressure 13

1.7.1 Short-term Regulation 13

1.7.2 Long-term Regulation 15

1.8 Measurement of Cardiovascular Functions 16

1.8.1 Electrocardiography 16

1.8.1.1 *Heart Rate Variability* 18

1.8.2 Impedance Cardiography 21

1.8.3 Blood Pressure Monitoring 23

1.8.3.1 Auscultatory 23

1.8.3.2 Oscillometric 24

CHAPTER 2 **The Human Sleep** 25

2.1 Historical Perspective 25

2.2 Sleep-Wake States 27

2.2.1 Sleep Onset 27

2.2.2 NREM Sleep 28

2.2.3 REM Sleep 29

2.3 Circadian Rhythm 30

2.4 Regulation of Sleep 31

2.5 Scoring of Sleep Events 32

2.5.1 Sleep Parameters 34

2.6 Sleep and Cardiovascular Functions 35

2.6.1 Influence of Sleep and Circadian Systems on Cardiovascular Activity 35

2.6.2 Influence of Cardiovascular Activity on Sleep 40

2.6.3 Cardiovascular and Sleep Disturbances 40

2.6.4 Cardiovascular Response to Arousal from Sleep 42

CHAPTER 3 **The Essential Hypotension** 45

3.1 Classification 45

3.1.1 Orthostatic Hypotension 45

3.1.2 Secondary Hypotension 46

3.1.3 Essential Hypotension 46

3.2 Epidemiology 47

3.3 Symptoms and Associated Features 49

3.4 Cardiovascular Reactivity 51

3.5 Pathogenesis 53

3.5.1 Autonomic Dysregulation 54

3.5.2 Baroreflex Overresponsivity 55

3.5.3 Cerebral Autoregulation Deficit 56

3.5.4 Genetic Mutations 58
3.6 Treatment 58
3.7 Sleep Features 59

CHAPTER 4 **The Research** 61
Research Rationale 61
4.1 Experiment I 64
4.1.1 Introduction 64
4.1.2 Materials and Method 64
4.1.2.1 *Participants* 65
4.1.2.2 *Polysomnography* 66
4.1.2.3 *Blood Pressure Monitoring* 66
4.1.2.4 *Impedance Cardiography* 66
4.1.2.5 *Heart Rate Variability* 67
4.1.2.6 *Study Design* 67
4.1.2.7 *Data Analysis and Statistics* 67
4.1.3 Results 68
4.1.3.1 *Demographic, Screening and Polysomnographic Measures* 68
4.1.3.2 *Blood Pressure Measures* 69
4.1.3.3 *Impedance Cardiography Measures* 72
4.1.3.4 *Heart Rate Variability Measures* 74
4.1.4 Discussion 75
4.2 Experiment II 78
4.2.1 Introduction 78
4.2.2 Materials and Method 79
4.2.2.1 *Participants* 79
4.2.2.2 *Polysomnography* 79
4.2.2.3 *Blood Pressure Monitoring* 80

4.2.2.4 *Impedance Cardiography* 80
4.2.2.5 *Heart Rate Variability* 80
4.2.2.6 *Study Design* 81
4.2.2.7 *Data Analysis and Statistics* 81
4.2.3 Results 82
4.2.3.1 *Demographic and Screening Measures* 82
4.2.3.2 *Polysomnographic Measures* 83
4.2.3.3 *Cardiovascular Measures* 83
4.2.3.4 *Correlations between Screening and Sleep Measures* 87
4.2.4 Discussion 88
4.3 Experiment III 90
4.3.1 Introduction 90
4.3.2 Materials and Method 90
4.3.2.1 *Participants* 90
4.3.2.2 *Polysomnography* 90
4.3.2.3 *Study Design* 91
4.3.2.4 *Data Analysis and Statistics* 91
4.3.3 Results 93
4.3.3.1 *Demographic, Screening and Polysomnographic Measures* 93
4.3.3.2 *Arousals Measures* 93
4.3.3.3 *Heart Rate Changes* 93
4.3.4 Discussion 99

CHAPTER 5 **General Discussion** 101

References 106

Abstract

Over the past decade, a large body of knowledge has been gathered with regard to the nocturnal hemodynamic pattern, as well as the comorbidity with sleep disturbances, in several cardiovascular diseases, such as hypertension. Nevertheless, surprisingly few attention has been paid to the hypotensives states. In particular, there is paucity of studies addressing sleep in essential hypotension.

Essential hypotension represents a form of chronic low blood pressure that is not due to medical or orthostatic conditions. Unlike the other forms of hypotension and although sufferers endorse a variety of subjective distressing symptoms included sleep complaints, essential hypotension remains a poorly addressed topic. Considering in particular its pathogenesis, an autonomic dysfunction in terms of a sympathetic hypoactivation has been postulated as underlying this condition.

The present dissertation aims at providing a comprehensive picture of the hemodynamic and autonomic pattern during sleep as well as the sleep pattern in essential hypotension in comparison to normotensive state.

The aim of the *Experiment 1* was to survey the overnight profile of cardiovascular activity during a night of sleep in essential hypotensives by means of a wide range of measures derived from blood pressure monitoring, impedance cardiography and heart rate variability. In addition, in order to clarify the postulated autonomic imbalance in hypotensives, we sought to examine the nocturnal cardiac autonomic regulation by assessing the involvement of both neurovegetative divisions. Hypotensives displayed diminished cardiovascular output over the sleep period in comparison to normotensives, which was likely driven by the finding of both sympathetic hypoactivation and vagal hyperactivity in essential hypotension.

Afterwards, the focus has been turned on the sleep structure. The purpose of the *Experiment II* was twofold. Firstly, we aimed at evaluating the sleep quality and quantity in this condition in depth, by describing the sleep parameters through polysomnographic recording. Secondly, we studied the cardiovascular and autonomic patterns as a function of the sleep stage to assess whether hypotensives have a different regulation across sleep stages compared with normotensives. Comparisons over the sleep parameters failed to identify any group differences in sleep pattern, whereas lower blood pressure and myocardial contractility associated with a

decreased sympathovagal balance in hypotensives across sleep stages corroborated the nighttime cardiovascular hypoactivation and autonomic dysregulation illustrated in the *Experiment I*.

Lastly, since arousals from sleep are associated with transient elevations in cardiovascular activity, the analysis of changes in heart rate elicited by arousals from sleep was carried out in the *Experiment III* to assess the cardiovascular reactivity in essential hypotension. Hypotensive individuals exhibited a larger heart rate response over the early post arousal beats compared to normotensives, whilst groups did not differ in terms of neither the number nor the duration of arousals experienced during sleep. Given that the cardiac arousal response is primarily mediated by the parasympathetic division, this finding suggests a greater vagal withdrawal in hypotensive subjects than in normotensives, providing further support to the hypothesized parasympathetic hyperactivity in essential hypotension.

To summarize, our findings of sympathetic withdrawal matched with vagal hyperactivity underlying the nocturnal cardiovascular activity confirm and extend the hypothesis of autonomic imbalance in essential hypotension, showing that both neurovegetative divisions functions are altered in this condition. Nevertheless, since no group differences were detected with regard to the objective sleep parameters, the sleep quality and quantity appear to be preserved in this condition.

Abbreviations

AASM	American Academy of Sleep Medicine
ABPM	Ambulatorial Blood Pressure Monitoring
ANS	Autonomic Nervous System
AV	Atrio-Ventricular
BMI	Body Mass Index
BP	Blood Pressure
CBF	Cerebral Blood Flow
CO	Cardiac Output
DBP	Diastolic Blood Pressure
ECG	Electrocardiography
EDV	End-Diastolic Volume
EEG	Electroencephalography
EMG	Electromyography
EMS	Electro-mechanical Systole
EOG	Electrooculography
HF	High Frequency
HR	Heart Rate
HRV	Heart Rate Variability
IBI	Interbeat Interval
ICG	Impedance Cardiography
LF	Low Frequency
LF/HF	Low Frequency to High Frequency
LVET	Left Ventricular Ejection Time
MBP	Mean Blood Pressure
MSNA	Muscle Sympathetic Nerve Activity
NN50	Differences between Adjacent Normal-to-Normal Intervals Greater than 50 ms
NREM	Non-Rapid Eye Movement
PEP	Pre-Ejection Period
pNN50	Proportion of Differences between Adjacent Normal-to-Normal Intervals Greater than 50 ms
PNS	Parasympathetic Nervous System

PSG	Polysomnography
PSQI	Pittsburgh Sleep Quality Index
REM	Rapid Eye Movement
RMSSD	Root Mean Square of Successive Differences between Consecutive Normal-to-Normal intervals
SA	Sino-Atrial
SBP	Systolic Blood Pressure
SDANN	Standard Deviation of the Averages of Normal-to-Normal Intervals
SDNN	Standard Deviation of Normal-to-Normal Intervals
SDNNi	Standard Deviation of Normal-to-Normal Intervals Index
SE	Sleep Efficiency
SNS	Sympathetic Nervous System
SOL	Sleep Onset Latency
SV	Stroke Volume
SWS	Slow-Wave Sleep
TRT	Total Recording Time
TPR	Total Peripheral Resistance
TST	Total Sleep Time
ULF	Ultra-Low Frequency
VLF	Very-Low Frequency
WASO	Wake After Sleep Onset

CHAPTER 1

The Cardiovascular System

The cardiovascular system consists of three components [170]:

- the blood, a fluid carrying cells, hormones, respiratory gases, nutritive and wasted molecule
- the heart, which pumps blood through the blood vessels to the body tissues
- the blood vessels, which conveys the blood across the body from and to the heart

This integrate system performs several functions, as servicing the cellular metabolic supply; participating in hormones and temperature control; sheltering against the blood loss and external harmful molecules [102]. In order to perform these functions and, in the ultimate aim, to ensure the homeostasis, it co-works with other physiological systems such as the nervous, endocrine, respiratory, and urinary systems.

1.1 Heart

The heart is an inverse cone-shaped muscular organ placed in the mediastinum, inside the thoracic hollow between the lungs [170].
The cardiac muscle is enclosed in a fibrous sac, the pericardium, and consists of three layers of serous membranes: from the outermost, the epicardium, the myocardium and the endocardium.
It can be divided longitudinally into two units, the right and the left sides, which work as pumps anatomically separated but functionally coupled. The deoxygenated blood flows through the right pump and the oxygenated blood flows through the left pump.
Each side comprises in turn two chambers: the upper cavity, the atrium, receiving the blood from the veins, and the lower cavity, the ventricle, pumping the blood into the arteries. As the interatrial septum separates the atria, whereas the interventricular septum divides the ventricles, there is no mixture of the blood from the two sides.

Nevertheless, the communication between each atrium and the ventricle below is allowed by a one-way valve, termed atrio-ventricular (AV) valve. The left AV valve is named bicuspid (or mitral), while the right AV valve is called tricuspid. Other one-way valves, the semilunar valves (aortic and pulmonary), are sited at the origin of the aorta and pulmonary arteries. AV and semilunar valves open and close passively due to the difference in pressure between the cardiac chambers and the arteries. Moreover, since their shape, they ensure the unidirectionality of the blood stream through the heart, thus preventing the backflow.

All the events occurring over a heart beat compose a cardiac cycle, consisting of a repeating pattern of contraction and relaxation of the heart, associated with pressure changes. The contraction of the myocardium chambers is termed systole, while the term diastole identifies the relaxation of the heart muscle [102].

1.2 Blood Vessels

As mentioned above, the blood vessels circuit is a tubular network that allows the blood and its contents to travel from the heart to all the body's cells and back.

Blood vessels endow with some peculiar properties. The resistance is defined as the impedance the vessel opposes against the flow, resulting from the friction between the blood flowing and the intravascular walls, whilst the distensibility is the capacity of a vessel to be stretched and thus to expand accounting for the changes in blood flow. Distensibility differs from compliance as the latter refers to the total quantity of blood that can be stored in a vessel [120].

The blood vessels can be classified into three main types: arteries, veins and capillaries.

The arteries walls are thick and elastic. Due to their large radius and low resistance, the blood can flow into them rapidly. Moreover, their elastic linings allow them to expand or recoil according to the heart's contraction and relaxation.

Within each organ, arteries originate arterioles, highly muscular, small and narrow vessels playing a key role in the control of the pressure. These vessels are less elastic than arteries and the resistance they offer against the blood stream is more elevated than that which is offered by the arteries due to the arteriolar narrow lumen [311].

The arterioles branch into the capillaries, very narrow and thin vessels distributed over the body tissues that join the arterial blood to the venous blood. The elevated resistance resulting from the small radius is counterbalanced by their large number. Therefore, the total resistance in capillaries is low because of the large total cross-sectional area.

The blood moves back from the capillaries to the venules, small veins which deliver it into progressively larger veins. In spite of venules are larger and endowed with a weaker muscular coat than arterioles, the internal pressure in the venules is lower thus they can contract notably [120].

Lastly, the veins can carry a great blood volume with a relatively low increase in pressure as they are thinner and more compliant than arteries. Veins offer low resistance due to their large diameter.

1.3 Circulatory Routes

As illustrated in Figure 1.1, the pathway followed by the blood travelling across the body can be divided into two circuits: the pulmonary circuit and the systemic circuit. The route followed by the blood from the heart (right ventricle) to the lungs and back (left atrium) is called pulmonary circulation, whilst the systemic circulation consists of the pathway covered by the blood travelling from the heart (left ventricle) through the entire body excepts the lungs and back (right atrium).

The deoxygenated blood from the periphery enters the right atrium via the superior and inferior venae cavae. Via the tricuspid valve it flows into the ventricle below which squeezes it into the pulmonary trunk through the pulmonary semilunar valve. The pulmonary trunk branches into the pulmonary arteries that in turn originate the arterioles in the lungs. The gases exchange occurs in the lungs by means of the pulmonary capillaries. Afterward, the oxygenated blood is conveyed by the pulmonary venules returning via the pulmonary veins to the left atrium. By passing through the bicuspid valve, it reaches the left ventricle and through the aortic semilunar valve, the aorta. The aorta branches into several arteries which distribute the blood across all the body's tissues [102].

Over the cardiac surface, the coronary vessels flow across it ensuring the cardiac cells the necessary supply of oxygen and nutrients.

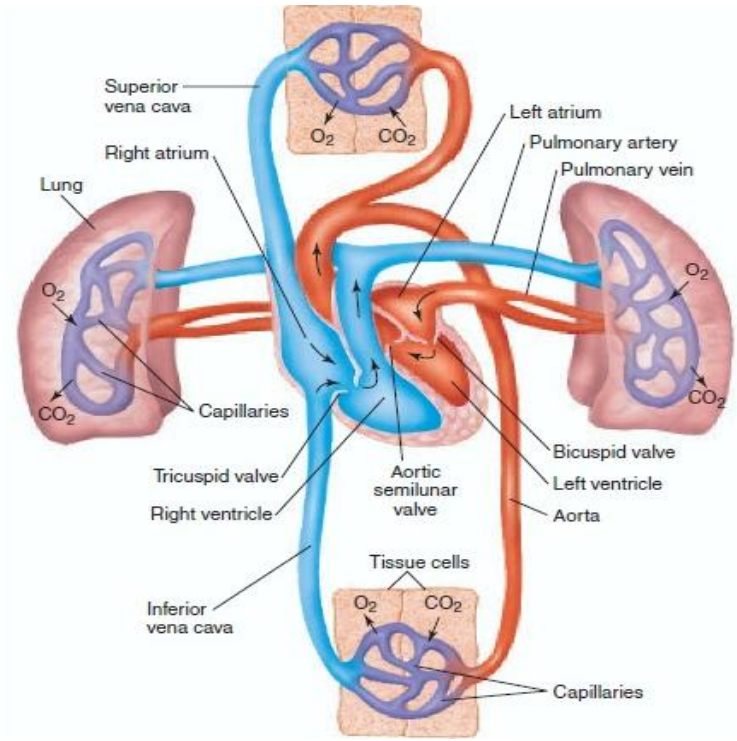

Figure 1.1 The pulmonary and systemic circulatory pathways. Deoxygenated blood is depicted in blue, oxygenated blood in red (*modified from Ref. 170).*

1.4 Autonomic Cardiovascular Innervation

The nervous influence on the heart and vasculature is primarily mediated by the autonomic nervous system (ANS), which regulates involuntary visceral functions by controlling the activity of smooth muscles, cardiac muscle and glands.

Although the ANS consists of three divisions (i.e., sympathetic, parasympathetic and enteric systems), only two of them contribute to cardiovascular functions regulation.

Parasympathetic fibers originating from the sacral segment of the spinal cord and the brainstem achieve the heart by travelling into the vagi nerves. Therefore, the parasympathetic nervous system (PNS) is also named vagal system [227]. Cardiac vagal innervation is almost exclusively limited to the atria as the projections to the ventricles are negligible. Likewise, the parasympathetic influence on the vasculature is marginal, as being restricted to few regions as the external genitalia [147].

The sympathetic nervous system (SNS) projects from the thoracic and lumbar segments of the spinal cord to both atria and ventricles. Unlike the PNS, sympathetic nerves are also largely distributed over the vascular network, particularly innervating the arterioles. The sympathetic

branch of ANS supplies also the adrenal medulla, that participates in controlling the cardiovascular functions by secreting epinephrine and norepinephrine into the blood.

The acetylcholine is the main neurotransmitter released by both SNS and PNS pre-ganglionic neurons. In the parasympathetic section, it is also the major postganglionic neurotransmitter. Differently, sympathetic postganglionic endings release primarily norepinephrine and, at a very minor degree, acetylcholine [311].

Post-ganglionic acetylcholine binds with muscarinic receptors (named M1 and M2), located mainly in the heart chambers and in the coronaries. The cholinergic sympathetic nerves are restricted to few arterioles in the skeletal muscle and coronary vessels [120].

Adrenergic receptors comprise two classes, in turn divided in two subtypes, alpha ($alpha_1$ and $alpha_2$) and beta ($beta_1$ and $beta_2$). $Beta_1$ receptors are mainly distributed across the entire myocardium hollows, while $beta_2$ are located particularly in the coronaries and arterioles in the skeletal musculature. The $alpha_1$ receptors are more abundant in the arterioles, while the $alpha_2$ are prevalent in veins. Norepinephrine released by the sympathetic endings activates mainly the $alpha_1$ and $beta_1$ receptors, while epinephrine secreted by the adrenal medulla stimulates all adrenal receptors equally [311].

Central nervous control of the autonomic cardiovascular innervations is mainly owed by the brainstem vasomotor center [120]. The vasomotor center is in turn affected by other brain regions, included the reticular substance, hypothalamus and the cerebral cortex. It integrates information from both brain regions and sensory input to modulate the sympathetic and parasympathetic responses [227].

1.5 Regulation of Blood Flow

The blood flow is the amount of blood travelling throughout a certain point in a certain time interval. The blood flow through a vessel depends on the resistance and pressure gradient. The relationship among these parameters can be described according to the Ohm's law [311]:

$$F = \Delta P/R$$

in which F is the blood flow, ΔP the difference in pressure and R the resistance.

The flow of blood across the vessels depends directly on the difference in pressure between the two ends (P_1 and P_2) of a vessel, that is the pressure gradient. The more elevated the pressure

difference, the greater the blood flow. Furthermore, the blow travels from higher pressure regions toward lower pressure regions [102].

The blood pressure (BP; mmHg) is defined as the force exerted by the blood against the blood vessels linings. The BP falls progressively with augmenting in the distance from the left ventricle, being the maximum in the aorta (100 mmHg) and the minimum in the junction of the venae cavae to the right atrium (0 mmHg).

The blood flow decreases with the increase in resistance. The resistance the vessel opposes against the flow is directly related to the viscosity of the blood and the length of the vessel, whereas it lowers with the enhancement in the radius: the larger the radius, the lower the resistance hence, keeping the other variables constant, the greater the blood flow.

Since both blood viscosity and vessel length do not vary significantly in normal physiology, the changes in the lumen of the vessel is the major mechanism by means of which the resistance is regulated.

The increase or decrease in radius via vasodilatation or vasoconstriction occur mainly in the arterioles because of their strong muscular walls that allow them to vary their diameter considerably. Vasoconstriction enhances the resistance thus reducing the blood supply to an organ, whereas vasodilatation lowers the resistance augmenting the blood flow [102].

A continuous dynamic adjustment of blood flow is pivotal in ensuring an adequate blood supply. The variation in blood flow to an organ is largely mediated by the modulation of the radius, and thus the resistance, of the arterioles. The factors participating in local blood flow control can be classified as intrinsic and extrinsic mechanisms.

1.5.1 Intrinsic Regulation

The intrinsic mechanisms involve the ability of each tissue to control the blood local flow in accordance with its own needs [311]. Local blood flow control mechanisms fall into two main categories: short-term and long-term control [120].

Short-term (or acute) mechanisms exert their action within seconds to minutes to restore blood flow very rapidly.

Acute mechanisms are elicited by changes in tissue metabolism, which lead to changes in the chemical environment. Examples of condition stimulating acute metabolic control are the active and reactive hyperemias. Active hyperemia refers to increased blood flow to a tissue due to enhanced metabolic activity (e.g., during muscle exercise). The elevation in metabolism entails lowering in oxygen concentration and nutrients and increasing in metabolites and carbon dioxide, which cause the secretion of vasodilator molecules, such as adenosine and histamine,

that promote the arteriolar dilation. The augmented local blood supply provides for the higher oxygen and nutrients consumption. Reactive hyperemia occurs in response to an interruption in blood supply lasting up to hours leading to a great blood flow within the tissue. Indeed, the lack of blood causes the tissue to release vasodilator substances resulting in a large flow when the occlusion is removed.

Short term regulation involves also the autoregulation of blood. This process occurs within an organ in response to variations in blood supply due to changes in BP and aids to maintain the blood flow almost constant in spite of those changes. When a fall in BP occurs, the consequent reduction in blood flow results in decreased resistance because of both changes in chemical environment elicitating a metabolic response and reactive relaxation of the arterioles linings caused by to fall in pressure, termed as myogenic response. The vasodilatation thus leads to the restoration of blood flow within normal values. The autoregulation is the major control mechanism of the cerebral blood flow (CBF), ensuring a constant rate of blood flow despite changes in systemic arterial pressure within physiological limits (60 to 150 mmHg) [57, 217].

Long-term mechanisms work over a period from hours to weeks and up. They act primarily by varying the degree of vascularity of a tissue, thus increasing or decreasing the size and number of vessels in order to supply for chronically high or low metabolic demands. Factors involved in the vasculature genesis include the vascular endothelial growth factor and angiogenin. Conversely, other substances cause the vessels to dissolve, as steroid hormones.

1.5.2 Extrinsic Regulation

An extrinsic control of circulation is also present, including humoral and nervous influences [311].

As the parasympathetic vascular innervation is negligible, the autonomic-mediated changes in arterioles radii are largely produced by augmenting or diminishing the sympathetic stimulation. The great majority of the sympathetic endings releases norepinephrine that binds with alpha–adrenergic receptors thus causing the vessels to constrict. However, there is also a little cholinergic sympathetic vascular innervation that drives vasodilatation in a few regions. Sympathetic excitation induces also adrenal medulla to secrete epinephrine and norepinephrine into the blood, which participate in vascular control.

Hormonal regulation includes a number of hormones affecting the vascular resistance. The major site of hormonal secretion involved in cardiovascular functions regulation is the adrenal medulla. Notwithstanding the adrenal medulla stimulates primarily the vasoconstriction in the majority of the vessels by secreting epinephrine and norepinephrine, as mentioned above, it can also perform

vasodilator effect in some tissues as the skeletal muscles and the coronary vessels, where the epinephrine binds with $beta_2$-adrenergic receptors [120]. Further hormones promoting the arterioles constriction are the angiotensin II and the antidiuretic hormone secreted by the pituitary gland. Conversely, bradykinin and the histamine act as local vasodilator agents [311].

1.6 Regulation of Cardiac Output

The amount of blood pumped by the left ventricle into the aorta per minute is named cardiac output (CO; l/min). On average, the resting CO value is about 5.5 l/min, corresponding to the total amount of blood travelling into the circulatory system.
The CO is determined by two factors: the heart rate (i.e., the number of heart beats in a minute; HR; bpm) and the stroke volume (i.e., the volume of blood ejected by the left ventricle in a heart beat; SV; ml), according to the following formula:

$$CO = HR \cdot SV$$

Hence, variations in either HR or SV lead to changes in CO. The regulation of heart pumping according to the metabolic demands is ascribed to both intrinsic mechanisms, such as the Frank-Starling law, and extrinsic mechanisms, comprising nervous and humoral control.

1.6.1 Regulation of Heart Rate

Generally, an healthy adult human heart beats about 70 times per minute, ranging from 60 to 100 times under normal conditions [102, 311].
The heart is endowed with a conduction system, consisting of specialized cardiac cells that trigger, conduct and coordinate the impulse to cardiac contraction. The sinoatrial (SA node) in the right atrium is known as the cardiac pacemaker because it exhibits a spontaneous rhythmic excitation that causes action potentials. Through the AV node, AV bundle and Purkinje fibers the stimulus spreads out to the atria and then to the ventricles causing them to depolarize hence resulting in heart beating. As the heart beating is intrinsically generated, the heart would pump at the rate set spontaneously by the SA node in the absence of extrinsic influences.
However, normally, the HR setting is notably modulated by the nervous system. Both autonomic branches innervate the conduction system with opposite effects mediated by their neurotransmitters. Indeed, the PNS leads to a slow in HR by releasing acetylcholine that decreases the rate of discharge in the SA node and the impulse conduction. On the contrary, the

norepinephrine released by the sympathetic endings stimulates the SA node and the rate of transmission in the other portions of conduction system thus increasing the HR. Since the automatic heart beating is about 100 bpm but the average resting HR is around 70 bpm, there is a vagal prevalence at rest.

The SNS cardiac control is slower than the vagal regulation due to both the slower release of norepinephrine by the sympathetic terminals and the mediation of a second messenger system to exert its effect. Thereby, the beat-to-beat cardiac setting is largely performed by the PNS [21].

Humoral modulation of HR is primarily exerted by the adrenal medulla, which accelerates the HR by releasing epinephrine.

1.6.2 Regulation of Stroke Volume

The average resting SV is about 70-80 ml per beat and its value is mainly determined by three factors: the end-diastolic volume (EDV; ml), the contractility and the total peripheral resistance (TPR; dyn·s/cm^5) [102].

The EDV, or preload, is the amount of blood in the ventricles at the end of the ventricular diastole. As the preload increases, the SV augments as well. The EDV depends on the venous return, that is the quantity of blood returning to the right atrium via the veins. A number of parameters determines the venous return, including the total blood volume, the venous pressure, the SNS modulation, the skeletal and respiratory pumps [170].

The venous return increases with the total volume of blood in the cardiovascular system, which is in turn inversely proportional to the urine and tissue-fluid volume. As it will be discussed below, the blood volume is influenced by the aldosterone and antidiuretic (vasopressin) hormones.

The return of the venous blood from the periphery to the heart depends on the venous pressure, which is markedly lower than the arterial pressure.

The venous return is aided by the skeletal muscle pump and the respiratory pump. When skeletal muscles contract thus compressing the veins, the blood is squeezed and forced to move past. The pressure difference between the thoracic and abdominal hollows occurring within the respiratory cycle facilitates the blood to return to the heart as well [170].

Lastly, the nervous system regulates the venous return via SNS. Sympathetic fibers innervate the veins causing them to constrict thus raising the venous pressure which leads in turn to increased venous return to the heart.

The contractility is the strength of ventricular contraction at any given EDV [311]. The relationship between the EDV, contractility and SV is defined by the Frank-Starling law of the

heart, which states as follows: the force of ventricular contraction is directly proportional to the preload, thereby an augmentation in EDV leads to an increase in ventricular contractility resulting in turn in heightened quantity of blood pumped into the aorta. This is owed because an elevation in EDV induces the ventricles to stretch more thereby they contract more forcefully causing a greater emptying. The Frank-Starling law accounts for the intrinsic ability of the heart to adapt to changes in venous return. Thereby, within physiologic limits, the heart pumps all the blood that returns to it [120].

The extrinsic control of the cardiac contractility is attributable to the sympathetic and adrenal medulla influences. Indeed, the SNS, via norepinephrine, and the adrenal medulla, via epinephrine, enhance the myocardial contractility stimulating the beta-adrenergic receptors [102]. As the release of norepinephrine and epinephrine also accelerate the HR, they cause the heart to contract more forcefully and quickly. On the contrary, as the parasympathetic innervation of the ventricle is little, its effect on contractility modulation is negligible [311].

Lastly, the TPR, or afterload, is the sum of all the vascular resistances within the systemic circulation [102]. Unlike the EDV and the force of contraction, the SV is inversely proportional to the TPR: the higher the TPR the lower the SV, as the TPR represents an impedance to the pumping of blood from the ventricle. Since the arterioles are the major site of resistance in the systemic circuit, changes in TPR are primarily mediated by variations in arteriolar resistance largely ascribed to adrenergic modulation [120].

To sum up, since CO is the product of HR and SV, all the intrinsic and extrinsic regulatory mechanisms modulating these latter two factors in turn affect the CO.

Indeed, as the Frank-Starling mechanism states, increased venous return causes the heart walls to stretch more, enhances the EDF and the force of contraction resulting in higher SV. Moreover, by stretching the walls of the heart chambers, the heightened volume of blood stretches also the SA node causing it to discharge more and thus increasing the HR [120].

The relationship between CO and TPR is reciprocal: the CO decreases with the increase in TPR and viceversa.

Both the neurovegetative system and adrenal medulla influence the CO. Norepinephrine and epinephrine released by the sympathetic branch and the adrenal medulla, respectively, enhance the heart pumping by elevating the HR and myocardial contractility, while the parasympathetic division modulates only the HR causing it to decelerate.

1.7 Regulation of Arterial Blood Pressure

As mentioned in the Section 1.5, the BP is the force exerted by the blood against the blood vessels walls.

Because of heart pumping is pulsatile, the arterial pressure alternates between systolic pressure level and diastolic pressure level [120]. Systolic BP (SBP) identifies the highest arterial pressure achieved during the systole (about 120 mmHg), when the blood ejected by the ventricles flows into them thus stretching the walls and raising the pressure. The lowest arterial pressure reached before the beginning of ventricular ejections is the diastolic BP (DBP, approximately 80 mmHg). The mean arterial BP (MBP) is the average arterial pressure within a cardiac cycle. As the diastole lasts twice longer than the systole, the MBP is calculated as follows:

$$MBP = 1/3\ SBP + 2/3\ DBP$$

The MBP is the product of two parameters, the CO by the TPR. Thus, the MBP heightens with the augmentation of the volume of blood pumped by the ventricle and the resistance opposed by the intravascular walls to the flow.

The variations in resistance in the arterioles through vasoconstriction or vasodilatation affect the flow in the capillaries and in turn in the arteries. Therefore, vasodilatation in the arterioles leads to fall in arterial pressure by lowering the TPR. As the arterial pressure is also determined by the CO, a decrease in the amount of blood ejected per minute diminishes the pressure as well: assuming the TPR constant, the faster the HR and the larger the SV, the higher the arterial pressure [102].

Despite the CO does not vary, the MBP in the pulmonary circuit is notably lower than the systemic MBP because of the reduced pulmonary vascular resistance.

The mechanisms underlying the arterial pressure regulation can be classified according to their action time span into two main classes: short-term and long-term control mechanisms. Short- and long-term mechanisms operated in an integrate manner to stabilize the arterial pressure [120].

1.7.1 Short-term Regulation

Short-term mechanisms exhibit a rapid action to restore quickly (within seconds to hours) an acute change in arterial pressure.

The ANS is crucial in short-term adjustment of arterial pressure, as needed during exercise and stress, by acting both on heart and vasculature simultaneously.

For instance, during muscle exercise, the skeletal musculature requires a great blood supply to account for the enhanced metabolism. The increased blood flow ensues from both local (i.e., active hyperemia) and systemic mechanisms. In order to cause the buildup of arterial pressure, the brainstem vasomotor center mediates both sympathetic excitation and parasympathetic withdrawal. Arterioles in the systemic circulation are caused to constrict, thereby an increase in TPR occurs. All the large vessels, in particular veins, are constricted as well, to enhance the return venous and in turn the preload. Due to Frank-Starling mechanism, an increase in strength of contraction occurs, further promoted by SNS stimulation to the heart that augments both contractility and accelerate HR thus rising the CO. The mentioned mechanisms aid all to elevate quickly the arterial pressure and hence the blood flow to the skeletal muscles.

Aside from acute conditions such as exercise and other types of stress, the ANS operates also all the time to retain the arterial pressure at normal levels, being involved in negative feedback reflexes underling the acute arterial pressure regulation [120].

The major mechanism responsible for the maintenance of arterial pressure is the baroreceptor reflex, which aids to minimize the fluctuations in pressure within an adequate range [102]. The baroreceptors are receptors highly sensitive to stretch, located primarily in the aortic arch and in the carotid sinuses. Their discharge rate varies according to BP. When a surge in BP occurs, the linings of these arterial regions are stretched causing the baroreceptors to increase their firing rate. Inputs from them travel to the brainstem vasomotor control center that signals to lower the arterial pressure toward normal values by sending feedback impulses via the autonomic fibers. Excitatory impulses activate the PNS whilst the SNS is inhibited, with corresponding variations in vagal and sympathetic outflows to the heart and blood vessels. Hence, drops in HR, cardiac contractility and thus CO occur. As the reduction in heart pumping is combined with peripheral vasodilatation, the arterial pressure is caused to be lowered and thereby stabilized. Conversely, when the BP declines, baroreceptors elicit an immediate reflex, resulting in augmented sympathetic discharge throughout the body which raises the arterial pressure by vasoconstriction and enhanced heart pumping. Since the baroreflex counters either surge or fall in arterial pressure, it is called a pressure buffer system [120].

The baroreceptors respond extremely rapidly to oscillations in arterial pressure. Moreover, they respond much more to fast variations in arterial pressure than to a steady pressure regardless its absolute value. Whether the baroreflex is also involved in long-term pressure regulation is still under debate. Indeed, when a change in pressure is maintained over time, it has been demonstrated that baroreceptors tend to adapt within 1 to 2 days to the new pressure level they are exposed to thus stopping to discharge. The adaptive shift of the operating range of the

baroreceptors toward the current arterial pressure has been termed resetting and led to the conclusion that the baroreflex does not participate in chronic regulation of arterial pressure. Nonetheless, this assumption has been challenged as it has been documented an influence of baroreflex on renal system, which is involved in long-term pressure control [124, 165]. Indeed, a chronic surge in pressure may lead the baroreflex to inhibit SNS stimulation of kidneys hence mediating a decrease in arterial pressure [120, 174].

Additional feedback reflexes contributing to short-term control of arterial pressure are the chemoreflex and the atrial and pulmonary artery reflexes.

Chemoreceptors respond to variations in gases concentration, acting in a similar manner than baroreceptos. As fall in arterial pressure and therefore in blood flow entails a decrease in oxygen as well as an increase in carbon dioxide, the chemincal changes activate the chemoreceptors which signal them to the vasomotor center. Thus, the stimulation of SNS leads to a surge in pressure.

Low-pressure receptors located in the atria and in the pulmonary arteries play a significant role in mitigating the variations in arterial pressure due to changes in blood volume. They discharge when blood volume rises, leading to peripheral vasodilatation, diminished sympathetic output to the kidney and heightened urine excretion [120].

When a severe fall in arterial pressure occurs resulting in reduced CBF, a central nervous system ischemic response is elicited. A sharp buildup in pressure is driven by a pronounced stimulation of the vasomotor center activity and largely mediated by a marked peripheral vasoconstriction.

Notwithstanding the majority of the nervous control of arterial pressure is mediated by the ANS, skeletal nerves and muscles play also a role in modulating arterial pressure by increasing CO and arterial pressure, as the abdominal compression reflex, or the skeletal muscle contraction during exercise.

1.7.2 Long-term Regulation

The long-term regulation of arterial pressure (from hours to months) is primarily achieved by the kidney by means of two systems: the renal-body fluid system and the renin-angiotensin-aldosterone system.

The renal-body fluid system controls the arterial pressure by balancing the intake and output of water and sodium. When the extracellular fluid is too elevated because of an excess in water or in sodium intake, it generates an increase in blood volume and thus in arterial pressure. The rise in arterial pressure stimulates the kidney to excrete the excessive extracellular fluid into the urine thus restoring blood volume and BP back toward normal [120].

Renal-body fluid system co-works with the renin-angiotensin-aldosterone system to perform the long-term control of arterial pressure. When a fall in arterial pressure occurs due to low blood volume and blood sodium, kidneys secrete into the blood stream a protein enzyme called renin. By way of the renin, the angiotensinogen, a plasma protein, is converted to angiotensin I, which is in turn converted in angiotensin II via another enzyme in the lungs. Angiotensin II stimulates vasoconstriction and renal retention of water and sodium which together aid the pressure to heighten. The vasoconstrictor effect arises almost immediately, while the increase in fluid volume takes hours and days, thus contributing to elevate pressure over longer period. The latter effect is mediated by an hormone termed aldosterone. Angiotensin II causes the adrenal glands to release aldosterone, which excites the kidneys to reabsorb water and sodium [120]. Consequently, surges in blood volume and arterial pressure are elicited.
However, additional hormones affect the blood volume levels hence participating in the long-term arterial pressure control. The antidiuretic hormone increases the blood volume as it furthers the retention of water in the kidneys. Conversely, by inhibiting both the renin and aldosterone secretion, the atrial natriuretic hormone facilitates the sodium and water excretion in the urine thus diminishing the blood volume and arterial pressure.

To summarize, short-term mechanisms exert a fast response mainly mediated by the nervous system, aiding to restore the changes in arterial pressure within seconds to minutes After few minutes from an abrupt variation in arterial pressure, mechanisms as the renin-angiotensin system are stimulated and can last for hours. Lastly, the renal–body fluid long-term mechanism requires longer to be activated and is responsible for the chronic pressure setting.

1.8 Measurement of Cardiovascular Functions

Several both invasive and non-invasive approaches have been developed to evaluate the cardiovascular system functions. Since a comprehensive overview of the methods is beyond the purpose of the present work, only the non-invasive techniques adopted in the studies described in the present dissertation will be addressed below.

1.8.1 Electrocardiography

Since the body is a good conductor of electricity, the cardiac electrical activity may be detected by electrodes placed over the body’s surface which record the changes in voltage generated by

the heart. The voltage are graphically represented by a series of deflections, the electrocardiogram (ECG) [102].

When the myocardial cells in a portion of the heart depolarize, that region originates a dipole. The dipole can be represented as a vector having direction and length determined by the position and magnitude of the dipole, respectively [234]. Magnitude of the dipole depends on the amount of myocardial mass depolarized, direction depends on the orientation of depolarized and repolarized portions of the heart. The electrical dipole originated by the depolarization signal can be detected by surface electrodes as a deflection.

Assuming the dipole in the heart, an equilateral triangle can be virtually drawn around it, termed as Einthoven's triangle. The vertexes of the fictitious triangle can be represented by the left and right arms and by the left leg. Each of these sites represents a lead, defined as a combination of two electrodes used to record the cardiac voltage. Leads can be either unipolar or bipolar. Within a bipolar lead, both electrodes (a positive and a negative terminal) are placed on active sites and the voltage detected is the difference between them. When one electrode is active and the other one is indifferent, the lead recorded is unipolar.

According to the disposition of electrodes, a number of leads can be derived.

There are three standard bipolar limbs leads: I (left arm–right arm), II (left leg–right arm), and III (left leg–left arm). By convention, the left arm in lead I is the positive pole, whereas the left leg is the positive pole in leads II and III [234]. A third electrode is placed over the right leg as ground. These leads are often approximated by electrodes placed on the chest, rather than the limbs. The proximal disposition entails two electrodes placed below the collar-bones and one along the left hip, over the fifth intercostals space [23].

Unipolar leads including the limbs are the right arm (aVR), left arm (aVL) and left leg (aVF). Precordial chest leads consist of multiple leads (V_1 to V_6) placed over the intercostal spaces.

The morphology of the signal recorded depends on the leads configuration applied.

Each phase of the cardiac cycle can be identified by a corresponding wave on the ECG recording, representing changes in potential between two cardiac portions or, in other terms, the movement of the dipole. The ECG waves are illustrated in

Figure 1.2.

The P wave represents the spread of atrial depolarization and occurs at the beginning of atrial contraction. Similarly, the electrical excitation of the ventricles is identified by the QRS complex. Lastly, the ventricular repolarization is depicted by the T wave.

It should be noted that the ECG wave corresponding to the atrial repolarization is masked by the larger QRS complex.

A set of intervals and segment can be identified on the ECG. The interval between two consecutive QRS complexes is particularly relevant. It is called RR interval (or interbeat interval, IBI; ms) and represents the time interval between two cardiac cycle that means two heart beats. Therefore, the HR can be derived from the ECG [102].

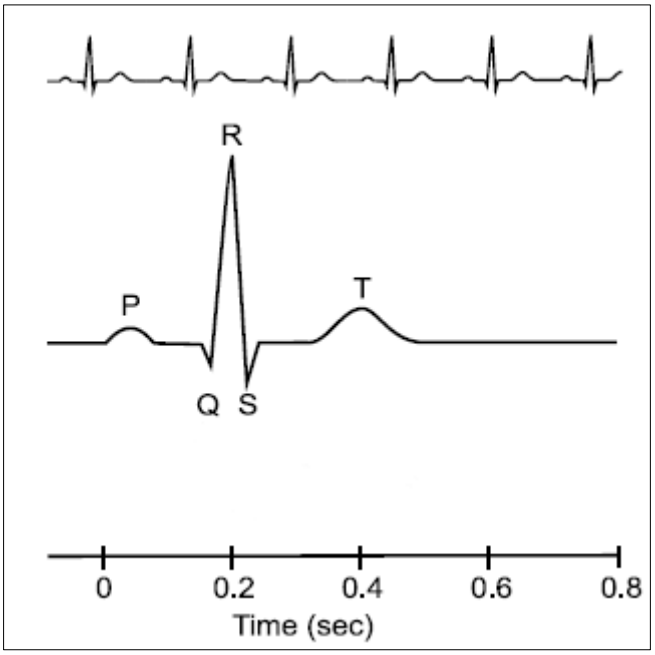

Figure 1.2. A portion of an ECG recording (upper panel). An enlarged normal cycle showing the P wave, the QRS complex and the T wave (lower panel) as a function of the time (*modified from Ref. 147)*.

1.8.1.1 Heart Rate Variability

The autonomic modulation of SA node can be derived in humans by measuring the heart rate variability (HRV). The HRV describes the temporal variation in the intervals between successive heartbeats and is thought to reflect the heart's ability to detect and adapt dynamically to contingencies [110, 229].

As mentioned in the Section 1.6.1, the SNS and PNS cardiac innervations display different temporal dynamics due to the neurotransmitters released: the vagal control has a shorter latency of action and a higher frequency capacity than did the sympathetic branch [23]. Thereby, the very short-term high-frequency (HF) fluctuations in IBIs are mediated by the vagal output [29, 91, 108]. Conversely, in spite of the low-frequency (LF) cyclic fluctuations were originally attributed to sympathetic drive [172, 191], it is currently agreed they are influenced by both autonomic branches [108, 148].

A number of approaches have been developed to quantify HRV, which have been systematized by a Task Force in 1996, leading to the publication of HRV guidelines [277].

HRV measurements fall into two main classes: time-domain and frequency-domain indices, including statistical and spectral measures, respectively. Additional methods, as the geometrical and non-linear dynamic metrics, have been proposed.

Traditionally, HRV analysis can be performed in either long-term recording, usually lasting 24-h, or short-term recording, typically lasting 5-min [277].

Time-domain measures of HRV characterize the distribution of IBIs over the recording period [149]. From the IBI series (also termed as normal-to-normal interval) derived from the ECG recording, several statistical indices can be calculated. A summary of the main time-domain indexes is listed below [277]:

- SDNN (ms): standard deviation of all normal-to-normal intervals. As it represents all sources of IBI variability across the entire selected period [281], it provides an esteem of overall HRV
- SDANN (ms): standard deviation of the averages of normal-to-normal intervals in all 5 min segments of the entire recording. It estimates long-term variation in IBIs over 24-h recordings
- SDNN index (ms): mean of the standard deviations of all normal-to-normal intervals for all 5 min segments of the entire recording
- RMSSD (ms): root mean squared of successive differences between consecutive normal-to-normal intervals
- NN50 (count): number of successive normal-to-normal intervals that differ in length by more than 50 ms
- pNN50 (%): proportion of successive normal-to-normal intervals that differ in length by more than 50 ms

As the RMSSD, NN50 and pNN50 are derived from differences in adjacent IBIs, they assess HF oscillations thus reflecting parasympathetic control of SA node [28, 95, 149].

Frequency-domain indices of HRV rely on the assumption that the neural activity underlying the autonomic modulation of heart is periodic, as sympathetic and vagal components fluctuate at different frequencies, and the signal has at least a weak stationarity (that means constant mean and variance over time) [23, 318]. The entire power spectrum can be separated into specific frequency components. Frequency-domain measures can be estimated by applying either the

non-parametric (Fast Fourier Transform) or the parametric (autoregressive modeling) approaches.

The components of interest extracted can be grouped into three frequency bands [24]:

- HF power band (0.15-0.40 Hz; ms^2): HF oscillations reflect the parasympathetic modulation of SA node synchronous with the respiratory cycle [29, 91, 108, 172, 226].
- LF power band (0.04-0.15 Hz; ms^2): LF fluctuations are thought to be affected by both sympathetic and vagal drives [3, 8, 108, 148]
- Very low-frequency (VLF) power band (0.0033-0.04 Hz; ms^2): In spite of the physiological meaning of VLF oscillations is still controversial, some evidence suggests an influence of either the renin-angiotensin system or the thermoregulation [229]
- Ultra low-frequency (ULF) power band (<0.0033 Hz; ms^2). HRV analyses performed over 24-h recording period allow also the computation of the ULF component. Similarly to VLF power, little is known about the physiological substrate underlying the ULF fluctuations, albeit the circadian rhythm has been advanced to be involved in their modulation [16, 38]

Within long-term recordings, the great majority of power (> 90%) is contained within the VLF and ULF range. However, as the likelihood that the assumption of stationarity is violated increases with the lengthening of ECG recording [24], frequency-domain measures should be preferred when analyzing short-term recordings run under stable conditions, whereas long-term recordings should be preferably processed by way of the time-domain method [277].

In addition, the total power and LF to HF (LF/HF) ratio can be computed from the spectral analysis of both short-term and long-term recordings. The latter index identifies the sympathovagal balance [318].

The power spectral density can be quantified either in absolute (ms^2) or normalized units (nu), computed as the power of each frequency component divided by the power of the total spectrum [110]. The normalized units are particularly valuable in identifying the relative value of each LF and HF band, providing a clearest esteem of the contribution of each neurovegetative branch to the total power. Moreover, normalization minimizes the effect of changes in total power on LF and HF components.

A comparison between time-domain and frequency-domain HRV measures revealed marked correlations. In particular, three clusters of indices highly correlated each other has been identified: SDNN, SDANN, total power, ULF power; VLF power, LF power, SDNN index; HF power, RMSSD, pNN50 [27].

It is widely recognized that HRV measures are powerful markers of both cardiovascular and non-cardiovascular health. A decrease in HRV has been documented in a broad spectrum of pathological conditions, including myocardial infarction, cardiac arrhythmia, diabetes, renal failure (for a review, see Ref. 229). As reviewed by Kleiger and colleagues [148], the clinical relevance of HRV is enhanced by the recognition of its predictive value for mortality risk in clinical settings. Indeed, a reduction of HRV has been consistently found to be associated with augmented mortality in a wide range of cardiovascular diseases, such as coronary artery disease and chronic heart failure (e.g., Ref. 99, 100, 203).

1.8.2 Impedance Cardiography

Impedance cardiography (ICG) technique allows the estimation of hemodynamic functions by way of a noninvasive approach.

Theoretical underpinnings underlying the ICG rely upon the relationship between voltage and resistance in an electrical circuit. In a circuit where current (*I*) is constant, the voltage (*V*) changes proportionally to the resistance (*R*), as follows:

$$V = I \cdot R$$

Through the thorax, which endows with a basal impedance (Z_0), the blood flows with a certain resistivity (*p*). As the blood is a good conductor of electrical current, the fluctuations in blood volume and velocity through the thorax occurring within a cardiac cycle generate a reciprocal change in thoracic resistance: an increase in blood flow as exhibited during systole results in decreased impedance, viceversa in diastole. In other terms, the basal thoracic impedance (Z_0) displays changes (ΔZ) over time (dZ/dt) [155].

If a constant magnitude alternating current is transmitted through the thorax, the changes occurring in thoracic impedance within each beat (ΔZ) originate a corresponding output voltage which reflects the blood volume ejected, that is the SV [262]. According to the Kubicek's formula [155], SV can be determined as follows:

$$SV = \rho \cdot (L^2/Z_0^2) \cdot (dZ/dt)_{max} \cdot LVET$$

Where *p* is the blood resistivity (ohms · cm), *L* is the distance between electrodes (cm), Z_0 the basal impedance between the recording electrodes (ohms), $(dZ/dt)_{max}$ is the maximum rate of changes (slope) in the impedance signal for a given beat (ohms per sec), LVET is the left ventricular ejection time (ms).

In order to acquire the impedance signal (Z_0) and the derivative of pulsatile impedance (*dZ/dt*), the tetrapolar band electrodes configuration can be applied. This standard electrodes disposition [262] consists of four band electrodes placed as follows: two inner voltage electrode bands placed around the base of the neck and the thorax over the xiphisternal junction, respectively, and two outer current electrodes bands positioned around the neck and the thorax at least 3 cm above the recording bands. The outer electrodes transmit a low-voltage (1-5 mA), high-frequency (20-100 kHz), alternating electrical current. Alternatively, spot electrodes array can be used [221, 228].

The ICQ requires also the simultaneous recording of ECG, preferably in lead II that maximizes the R-wave.

The generated waveforms of ECG, Z_0 and *dZ/dt*, illustrated in Figure 1.3, are aligned to derive the cardiovascular parameters.

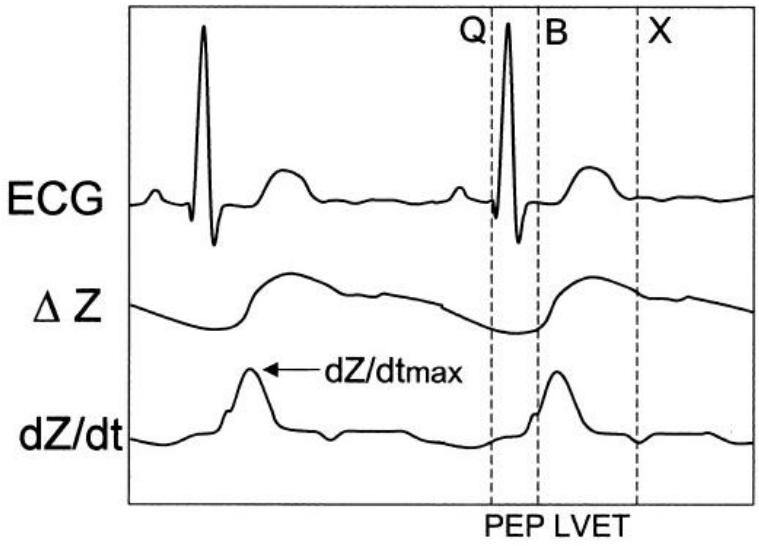

Figure 1.3. The ICG signals. From the top, the ECG, the impedance signal (Z_0) and the derivative of impedance (*dZ/dt*). The Q-, B-, X- points on the *dZ/dt* waveform are marked (*modified from Ref. 23*).

A number of markers are identified on the *dZ/dt* waveform in order to derive cardiac indices. In particular, the Q-point denotes the onset of the Q wave on the ECG, that is the onset of ventricular depolarization; the B-point on the *dZ/dt* wave occurs at the onset of the rapid slope of *dZ/dt* signal up to its peak (dZ/dt_{max}), representing the opening of the aortic valve and thus the beginning of ventricular ejection; the X-point is the minimum point on the impedance waveform and identifies the closure of the aortic valve.

By knowing the HR and SV, the CO can be derived. The ICG allows also the estimation of systolic time intervals such as the pre-ejection period (PEP; ms) and the LVET (ms). The PEP represents the time interval between the ventricular depolarization and the ventricular ejection. Given that the ventricles are innervated almost exclusively by the SNS, the PEP is inversely related to sympathetic beta-adrenergic drive. The LVET is the period of time over the ventricular ejection of blood into aorta. PEP is calculated as the interval from the onset of Q wave on the ECG and the B-point on the *dZ/dt* curve , while LVET is computed as the interval between the B- and X-points on the *dZ/dt* signal. It should be noted that the sum of both PEP and LVET gives the duration of electromechanical systole (EMS; ms) [262].

When the simultaneous recording of arterial pressure is performed, the TPR can also be computed. However, several additional indices can be derived from the ICG (for a review, see Ref. 283).

Reliability and validity of the ICG technique have been broadly established in a variety of both normal and clinical populations (for a review, see Ref. 36).

1.8.3 Blood Pressure Monitoring

The main non-invasive techniques developed to monitor the BP are the auscultatory and the oscillometric methods.

1.8.3.1 Auscultatory

The gold-standard to assess the BP is represented by the auscultatory method. This approach for measuring the BP derives its name from the fact that is based on the correlation between BP and arterial sounds [102].

The evaluation of the BP by means of the auscultatory technique requires that an inflatable rubber bladder within a cloth cuff is wrapped around the subject's upper arm and a stethoscope is placed over the brachial artery just below the cuff. They are connected to a sphygmomanometer and a squeezable bulb.

By squeezing the bulb, air is inflated into the cuff until the artery is closed so no blood flows through it. To close the artery, the cuff pressure has to be higher than the SBP. The closure of the artery is ensured by the absence of sounds as heard via the stethoscope. Thereafter, the cuff is gradually deflated to diminish the cuff pressure until the artery begins to open slightly and the blood is moving past the cuff. When the cuff pressure falls just below the SBP, the blood flow through the partially compressed artery becomes turbulent. Due to small opening and large pressure difference across the opening, it travels at very high velocity and generates vibrations,

termed as Korotkoff sounds, which occur at every systole and can be heard via the stethoscope [311]. The first Korotkoff sound produced by the blood entering the artery thus identifies the SBP, which is indicated in the manometer. As the pressure in the cuff is continued to be decreased, the sounds gain a murmuring quality (II Korotkoff sound) and then become sharper and louder (III Korotkoff sound). Afterwards, they become stifled (IV Korotkoff sound) and eventually disappear (V Korotkoff sound) [23]. The pressure at which the Korotkoff sounds disappears is the DBP, as the artery is no longer constricted and no sounds are produced because the pressure in the cuff falls to equal diastolic pressure.

1.8.3.2 Oscillometric

The oscillometric technique relies on the assumption that the peak oscillation in the blood flow occurring during the gradual deflation of the pressure cuff represents the MBP. The value is detected by an automated system which estimates indirectly the SBP and DBP values from the MBP by means of derived algorithms. Automated devices based on oscillometric measurement method are largely used for ambulatorial blood pressure monitoring (ABPM) [223].

CHAPTER 2

The Human Sleep

2.1 Historical Perspective

Interest in sleep has been existing since the dawn of history. Some of the former greatest thinkers have addressed the sleep, attempting to explain its basis and functions. However, although the human being spends about one-third of his life sleeping, the scientific study of sleep has been neglected until the last century.

Historically, sleep had been thought to be a passive state, in terms of absence of wakefulness. Whereas wakefulness was regarded as the result of continuous sensory stimulation from the environment, sleep was thought to result from the reduction in sensory input, as the reverse process.

The concept of sleep as a passive state found a scientific formulation in the theory postulated by Pavlov at the beginning of the XX century. Sleep was considered as due to an internal inhibition process, arising from specific cerebral areas, termed "*loci*", and hence spreading to cortical and subcortical structures [218].

The Pavlov's theory was later reformulated as the deafferentation theory, which attributed the sleep onset to a decline in the sensory stimulation retaining the wakefulness. The deafferentation theory, defended by Kleitman [150], relied on the experimental evidence provided by the classical works performed by Bremer on cerebral electrophysiological activity in animal preparations [40, 41]. These studies were made possible by the development of the electroencephalographic (EEG) technique [18], which allows the investigation of electrical brain activity non-invasively. A low brainstem transection, between the spinal cord and the medulla oblongata, disconnected the whole encephalon from the spinal cord, resulted in regular sleep-wake cycle. This Bremer's experimental preparation was termed *encéphale isolé*. Differently, when the transection was performed at upper level, above the lamina quadrigemina, the normal sleep-wake rhythm disappeared and a steady irreversible state of sleep occurred. As this latter preparation, called *cerveau isolé*, entailed the interruption of the large majority of sensory afferences, the findings have been interpreted as confirming the deafferentation theory of sleep.

However, the development of the EEG techniques provided the framework for the pionieristic investigation of brain activity during sleep in human beings. Berger himself [18] documented the differences in brain rhythm during sleep and wakefulness, allowing for the first time the establishment of sleep without disturbing the sleeper. Early recordings of EEG during sleep showed changes in electrical brain activity over the transition between wakefulness and sleep, in terms of increasing in amplitude and decreasing in frequency compared to wake [66]. Moreover, the observation that the EEG pattern varied across the sleep period led to the first attempt to classify the sleep phases [166]. Until that, sleep was assumed to be a unitary and homogeneous phenomenon.

Neurophysiological studies permitted to enhance the knowledge on brain circuits involved in sleep generation. Moruzzi and Magoun [198] identified a neural structure sited in the brainstem, the ascending reticular activating system, which caused EEG desynchronization and thus wakefulness when stimulated. In spite of the finding of circuits actively responsible for maintaining wakefulness, the sleep was still considered as a passive state due to functional interruption of reticular afferences.

Nevertheless, following findings challenged this hypothesis. The first convincing datum against the deafferentation theory of sleep arose from Hess' experiments [123], who demonstrated that low-frequency stimulation of medial thalamus resulted in sleepiness and a state of sleep not different from the spontaneous sleep. Further studies identified several neural structures participating in sleep onset and maintenance [20, 171, 304]. This evidence allowed the theory of sleep as passive state to be discarded and substituted by the concept of sleep as an active phenomenon.

A milestone in the sleep research history is represented by the observations conducted by Aserinsky and Kleitman on eye motility [9]. By registering the EEG and the electrooculogram (EOG) simultaneously, they observed a difference in the oculomotory activity across the sleep: while the eye movements were slow at sleep onset, rapid eye movements (REMs) occurred during consolidate sleep, combined with paradoxical cortical activation. Moreover, Aserinsky and Kleitman identified a strict association between the REMs and the occurrence of dreaming [9, 10].

A few years later, in the 1957, Dement and Kleitman carried out the first overnight recordings of EEG and EOG. By analyzing both electrophysiological patterns, two sleep stages were distinguished: the desynchronized sleep, described by EEG rhythm similar to wakefulness, with high-frequency low-amplitude waves, and by the occurrence of REMs; the synchronized sleep, characterized by low-frequency high-amplitude EEG and the lack of REMs. These sleep stages

were found to alternate cyclically over sleep and were termed, respectively, as REM and Non-REM (NREM) sleep stages. Furthermore, heterogeneous patterns were recognized within both NREM and REM stages [69].

In 1961 Berger performed the first electromyographic (EMG) recording during sleep, detecting the activity of the laryngeal muscle. A muscular relaxation was found during NREM sleep, which resulted in an abrupt fall in muscle tone in REM sleep [19].

Continuous all-night recording using this array of techniques was finally termed polysomnography (PSG) by Holland and colleagues [127]. The application of the PSG, currently regarded as the gold-standard for investigating sleep, allowed an exponential progress in sleep research. Noteworthy advances in knowledge of physiology of sleep have been gathered in the Sixties, leading to the publication of the first manual of sleep scoring [232]. The Rechtschaffen and Kales manual systematized the rules for recording and staging the sleep, according to the concurrent variations in EEG, EOG and EMG parameters. The inclusion of additional measures to the standard PSG, such as the cardio-respiratory monitoring, provided further insights in the physiology of sleep. Moreover, the introduction of PSG recording in clinical setting contributed to promote the interest toward the sleep disorders and their pathophysiology.

2.2 Sleep-Wake States

According to a behavioral definition, sleep can be described as a reversible state of perceptual disengagement from and reduced responsiveness to both internal and external environment [53].

A variety of neural cortical and subcortical circuits control the onset and the maintenance of sleep as well as the transition across different sleep stages by mutually interacting [93, 212].

2.2.1 Sleep Onset

Sleep alternates with wakefulness. The transition between sleep and wakefulness is often blurred. Indeed, both sleep onset and sleep offset are more likely to be gradual processes rather than sudden switches. In this context, aspects of both states tend to coexist over the transition, during which a period of drowsiness is often experienced. Moreover, the consistency between behavioral and physiological markers of sleep onset is only moderate.

Given these issues, the definition of sleep onset has been debated and can differ according to the criteria adopted to identify it [53].

Considering the PSG parameters, during sleep onset the EEG pattern exhibits a change from a prevalence of alpha rhythm (8-13 Hz), particularly over the occipital regions, to a low-voltage,

mixed-frequency rhythm. Slow eye-movement are displayed by the EOG, whilst the EMG shows only a mild decrease in muscle tone. However, this PSG configuration is often interrupted by arousals which contribute to complicate the identification of sleep onset.

It has to be remarked that the PSG-defined sleep onset may or not coincide with subjective perception of being asleep. Additionally, behavioral tasks documented that sensory processing persists at some extent after the onset of sleep [53, 207, 314].

Considering the neurophysiological substrate of sleep-wake states, several pathways underlie the wakefulness [256]. The arousal system consists of two major divisions. One branch originates in the brainstem cholinergic pedunculopontine and laterodorsal tegmental nuclei which project to the thalamus, cortex and spinal cord [121]. The ascending projections to the reticular nucleus of the thalamus are particularly important as this region represent the thalamic gate to the cortical areas involved in arousal maintenance [182]. The second branch of the arousal system sends fibers to the lateral hypothalamus, basal forebrain, and the cerebral cortex [135, 247, 248]. It comprises monoaminergic neurons in the locus coeruleus, dorsal and median raphe nucleus, ventral periaqueductal grey matter and tubero-mammillary nucleus. Additional afferences include hypocretinergic neurons from hypothalamus and cholinergic and GABA-ergic fibers from the basal forebrain. These nuclei, as well as the pedunculopontine and laterodorsal tegmental nuclei, discharge more in wake and REM sleep and low during NREM [107]. Both branches of the arousal system thus cooperate to achieve and sustain wakefulness.

The sleep onset is allowed by the inhibition of monoaminergic nuclei of the arousal system exerted by neurons stemming from the ventrolateral preoptic nucleus in the hypothalamus and releasing GABA and glycine [111]. Since those nuclei of the arousal system suppress the ventrolateral preoptic nucleus activity during wakefulness, this reciprocal inhibitory pathway acts as a “sleep-wake switch”, underling the transitions between these two states [109, 183, 248]. By the interruption of ascending sensory input to the cerebral cortex, the thalamic inhibition furthers the cortical synchronization.

2.2.2 NREM Sleep

Within sleep, two main states, i.e, NREM and REM phases, can be distinguished according to their peculiar physiological features.

As previously mentioned, during NREM sleep the EEG rhythm becomes synchronized by way of inactivation of the arousal system. In addition to the inhibitory effect performed by the ventrolateral preoptic nucleus, NREM-promoting pathway includes GABA-ergic neurons in the basal forebrain which suppress both cholinergic fibers of the arousal system and cortical activity

[180]. The EEG synchronization occurs prior in the prefrontal areas and thence diffuses to the entire cortex, becoming complete with the deepening of the NREM sleep. The depth of sleep is determined by the slowing in EEG activity and by the intensity of the stimulus needed to cause arousal [159].

In this context, the thalamic gate consolidates NREM sleep and inhibits arousals by heightening the threshold to responsiveness to stimuli. Functional neuroimaging has revealed reduced activity in the brainstem pons and cerebellum, in the basal forebrain and limbic cortex, especially in the anterior cingulated gyrus, the dorsolateral prefrontal and inferior parietal cortex [267]. A decrease in muscle tone occurs, as result of both activation of the brainstem GABA-ergic and glycinergic discending projection and inhibition of monoaminergic nuclei.

Autonomic activity exhibits a shift from sympathetic toward parasympathetic dominance with the deepening of NREM sleep. Metabolic rate is reduced by 5-10%, core body temperature drops. The respiratory pattern is regular but the respiratory drive is diminished. A reduction in swallowing and esophageal peristaltic activity is also observed during NREM sleep [53, 175]. During NREM sleep, the mental activity is fragmented and dreams rarely are experienced.

2.2.3 REM Sleep

Unlike the NREM sleep, the cortex is somehow active during REM sleep and reactive to sensory input, showing mixed EEG frequency.

Pontomesencephalic structures are crucial for the generation of the REM sleep and its related phenomena as the EEG desynchronization and the muscle atonia. The activation of brainstem and forebrain cholinergic nuclei, thalamus and cortex drives the EEG desynchronization [135]. A major contribution in producing the cortical arousal via thalamocortical projections appears to be owed to the pedunculopontine and laterodorsal tegmental nuclei, where a population of cholinergic neurons fires selectively in REM sleep. A significant role in modulating REM sleep is also covered by the melatonin neurons, which discharge particularly during REM [301]. Moreover, limbic regions as the amygdala, anterior cingulate gyrus, lateral hypothalamus, the orbitomedial prefrontal cortex and the parahippocampal gyrus are active as well [267]. The activation of the limbic network is likely to account for the increased frequency and complexity of dreaming observed in REM sleep. The silence in monoaminergic nuclei firing combined with the stimulation exerted by pontomedullary cholinergic and glycinergic neurons results in motor inhibition [56]. Although muscle atonia prevents dreams to be enacted, transient and occasional burst of movement can occur, particularly in the limb and facial muscles. With regard to the oculomotor activity, the REMs are generated by the pontine and midbrain cranial nerve nuclei.

An irregular autonomic activity is typically observed during REM sleep, with transient bursts of sympathetic activation in a context of reduced vagal tone [175]. Respiration is uneven and varies considerably during REM. Sexual excitation may develop. Metabolic rate increases in REM up to the extent showed in wakefulness. Arousal threshold fluctuates over the REM period.

2.3 Circadian Rhythm

Normally, environmental cues of light and darkness synchronize the physiological rhythms to the day-night cycle. Nevertheless, an endogenous circadian rhythm also exists, aiding to regulate the physiological functions regardless of external stimuli [63].

Circadian rhythms have a periodicity of around a day, ranging between 23.5 and 24.5 h in human beings [267]. Several physiological functions undergo a circadian rhythm, such as the body temperature, autonomic and autoimmune functions, the neuroendocrine secretion, and the sleep-wake cycle.

The main neuroanatomical substrate of the internal biological clock has been identified in the hypothalamic suprachiasmatic nucleus [233]. The suprachiasmatic nucleus is also named the master clock and serves as a pacemaker thus originating the circadian rhythm. It is active during the day promoting wakefulness and inhibited during night furthering the sleep. Fibers from the retinohypotalamic tract, the geniculo-hypothalamic tract and the raphe nuclei enters the sympathetic nervous system (SNS) [235]. Additional projections issue from the basal forebrain and the mammillary hypothalamus. Projections are sent from the suprachiasmatic nucleus to other areas in the hypothalamus as the ventrolateral preoptic nucleus, the thalamus and the pineal gland. By receiving afferences both from the retina and from the arousal system, it integrates environmental cues and internal input, thus aligning the intrinsic circadian rhythm with external day-night cycle [55, 134, 267].

However, despite of the suprachiasmatic nucleus is the main source of circadian rhythmicity, multiple circadian oscillators has been identified [243].

Suprachiasmatic nucleus performs a pivotal role in setting the sleep-wake cycle by controlling the circadian rhythmicity of a number of physiological processes. The secretion of melatonin hormone in the pineal gland exhibits an intrinsic circadian rhythm regulated by the suprachiasmatic nucleus. Since the release of melatonin increases during the nighttime peaking at around 3-5 am, it contributes to synchronize sleeping time with the environmental light-dark cycle. Moreover, it also acts at the levels of suprachiasmatic nucleus, further contributing to set the sleep-wake cycle [118]. Conversely, the body temperature, controlled by the anterior

hypothalamus, drops slightly in the early afternoon and falls markedly in the middle of nighttime, stimulating the sleep [267].

2.4 Regulation of Sleep

Whether an individual is awake or asleep depends on the balance of forces stimulating and inhibiting each of these two states. Two major drives have been identified as determinants of the sleep-wake rhythm [34].

The first force is an homeostatic process. Since it depends on the previous sleep and wake periods, the homeostatic process is sleep-dependent. It identifies the sleep pressure, that is the propensity to fall asleep: the longer an individual stays awake, the higher the sleep pressure. On the contrary, it decreases with the duration of sleep. Thus, sleep pressure rises during waking, declines during sleep and increases steeply with sleep deprivation.

The surge of sleep pressure is also regulated by the circadian curve. Unlike the homeostatic process, the circadian process modulates the rhythmic tendency to sleep and awaken at certain times regardless of the prior sleep. It stimulates wakefulness by progressively becoming stronger during daytime hours and dissolves rapidly after the onset of nocturnal melatonin [71, 92]. Hence, this signal opposes the buildup (during daytime) and the dissipation (during nighttime) of sleep pressure.

The homeostatic and the circadian processes interact in determining the sleep-wake timing [72]. When both sleep and circadian drives to sleep converge, the individual falls asleep.

With regard to the NREM-REM rhythmicity, circadian rhythm appears to affect more the REM sleep than the NREM sleep [64]. In contrast, NREM is primarily controlled by the homeostatic process [1]. The reciprocal distribution of NREM-REM sleep stages within each sleep cycle throughout the night is also affected by these two processes. Since the NREM dominates the beginning of the night, it is thought to reflect the homeostatic process, highest at sleep onset and diminished across the night as the sleep pressure dissipates. In contrast, as the REM sleep onset is delayed and concentrated toward the latter portion of the night coupling the dip in body temperature, it is likely to reflect the circadian drive [1].

2.5 Scoring of Sleep Events

As mentioned previously, NREM and REM sleep stages exhibit typical physiological and behavioral patterns. Both phases can be in turn divided into sub-stages. According to the Rechtschaffen and Kales scoring manual [232], NREM sleep comprises four substages (S1 to S4), characterized by a progressive increase in EEG synchronization and decrease in muscle tone. The latter two stages (S3 and S4) are usually collectively referred as slow-wave sleep (SWS). Two types of REM sleep, called tonic and phasic, are identified in REM sleep.
Recently, the standard Rechtschaffen and Kales criteria have been revised by the American Academy of Sleep Medicine (AASM), which modified partially and extended the scoring rules [131]. This resulted in a new manual for the scoring of sleep and associated events. The AASM manual renames the NREM sleep substages as N1, N2 and N3, largely corresponding to the standard stages S1, S2 and SWS, respectively. Unlike the previous system, the subdivisions of REM sleep stage are not recognized by the current AASM criteria.
Sleep staging is based on the interpretation of PSG configuration. The record is divided into consecutive segments (epochs) of equal lengths (conventionally 20 or 30 sec). According to the EEG, EOG and EMG patterns, a given sleep stage is assigned to each epoch.

- Stage W: during adult human quiet wakefulness (W), a high-frequency low-amplitude EEG activity is observed. More than 50% of the epoch displays alpha rhythm (8-13 Hz), prevalently over the occipital sites and occasionally interrupted by beta activity (>13 Hz), mainly over frontal regions. The muscle tone is high and the EOG revealed both REMs (lasting less than 500 ms) and slow eye movements (lasting more than 500 ms) as well as eye blinks
- Stage N1: it occurs most frequently in the transition from wakefulness to the other sleep stages or following arousals during sleep. In this stage, alpha waves (8-13 Hz) decrease and are replaced by a low-voltage, mixed frequency EEG pattern, including theta waves (4-7 Hz), for more than 50% of the epoch. The EOG shows slow eye movements, while the EMG activity diminishes. Toward the end of the stage, vertex sharp waves (lasting less than 500 ms) can be detected
- Stage N2: Over a theta range EEG background, characteristic EEG graphoelements as the K-complexes and the sleep spindles are showed intermittently (Figure 2.1). A K-complex is a biphasic component lasting more than 500 ms and consisting of a high-amplitude negative wave followed by a positive wave. A sleep splindle is a train of 12-14 Hz

waveform with a duration higher than 500 ms. Eye movements are not usually exhibited and the muscle tone remains lower than wakefulness

- Stage N3: The EEG displays high-amplitude low-voltage activity including delta waves (0.5-2 Hz) accounting for 20% or more of the epoch. Similarly to the N2, eye movements are absent and the EMG is low
- Stage REM: it is characterized by an EEG low-voltage mixed-frequency activity, muscle atonia and bursts of rapid eye movements. Transient myoclonic twitchings lasting less than 250 ms may be seen. Sawtooth waves, consisting of trains of sharply contoured, 2-6 Hz waves, often precede a burst of REMs on the EEG.
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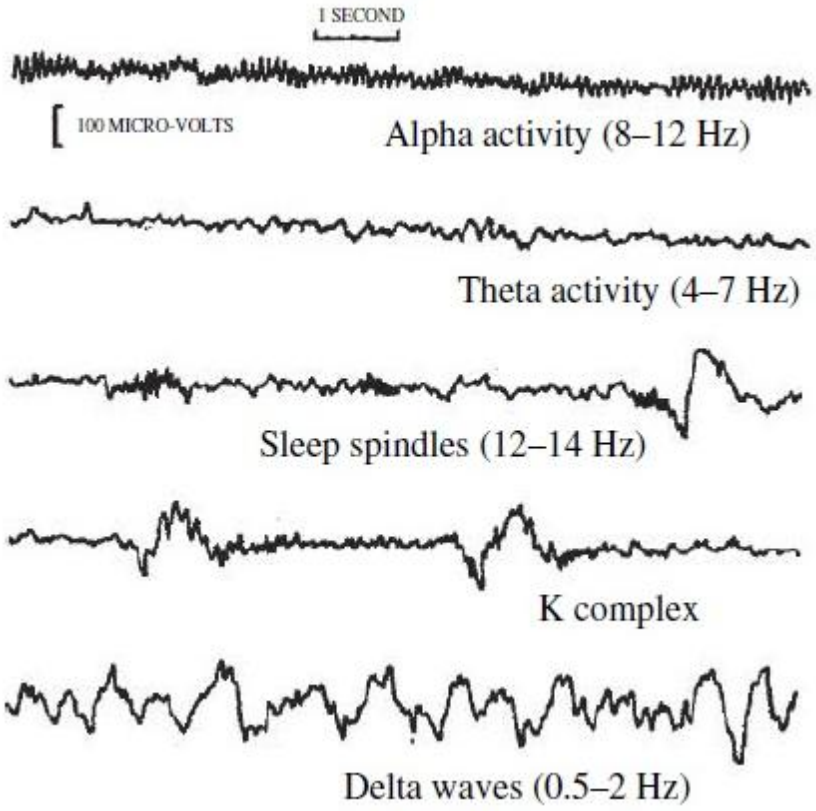

Figure 2.1. Patterns of EEG waves during sleep (*adapted from Ref. 193).*

Sleep can be occasionally interrupted by transient arousals, triggered by internal or external factors. According to the AASM rules [131], an arousal is defined as an abrupt shift in the EEG rhythm including alpha, theta and/or frequencies higher than 16 Hz. To be scored as arousal, the event has to last from 3 to 15 sec and occur after at least 10 sec of stable sleep. A concurrent heightening in EMG activity lasting at least 1 sec is required to score an arousal during REM.

Overall, NREM sleep accounts approximately for the 75–80% of sleep, distributed within each substage as follows: 2-5% in N1, 45-55% in N2 and 10-20% in N3. Hence, the residual 20-25% of sleep is made up by the REM sleep [230].

NREM and REM sleep episodes alternate cyclically throughout the night. The sleep onset is identified by the appearance of N1 sleep, followed by N2 and N3, progressively. Thereafter, a brief period of N2 sleep precedes the onset of REM, approximately 60-90 min after the sleep onset. The end of REM is signaled by an arousal from sleep or a transition back to N2 sleep.

Typically, a NREM-REM cycle lasts 90-110 min and about 4-6 cycles occur over the night [53]. Although each cycle consists of both REM and NREM stages, the ratio between them varies across the course of the night. Indeed, the early cycles consist mainly of NREM sleep, whereas the REM sleep is prevalent in the later cycles [230].

The hypnogram is a graphical representation of both the temporal arrangement of sleep stage across the night (i.e., the sleep architecture) and the amount of each stage over the entire night and within each REM-NREM cycle (i.e., the sleep structure) (Figure 2.2).

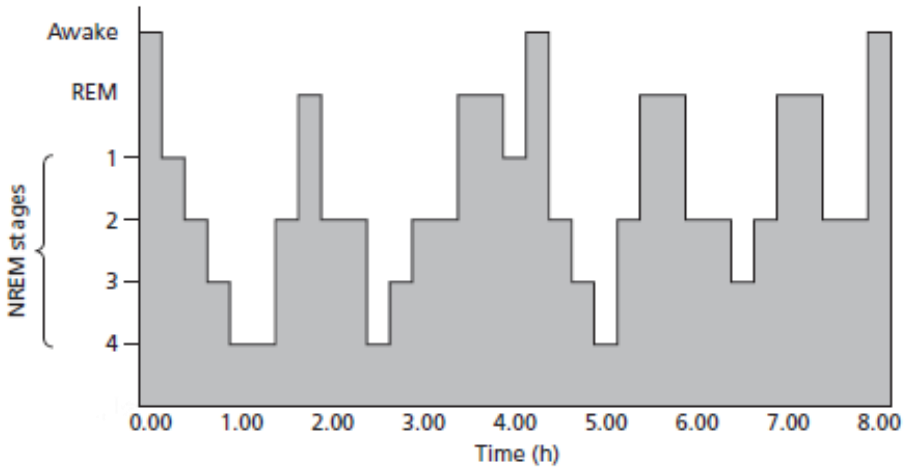

Figure 2.2. Hypnogram of a night of sleep (*adapted from Ref. 267).*

2.5.1 Sleep Parameters

The sleep scoring allows the computation of a large number of parameters which described both the sleep architecture and the sleep structure in details. A sum of the main sleep parameters is listed below [131]:

- Total recording time (TRT; min): time from the lights out to the lights on.

- Total sleep time (TST; min): time spent sleeping during the recording. It is calculated as the sum of the duration of stages N1, N2, N3 and R.
- Sleep onset latency (SOL; min): time from the lights out to the first epoch of any sleep stage.
- REM latency (min): time from the sleep onset to the first epoch of REM sleep.
- Wake after sleep onset (WASO; min): time spent awake during the recording. It is computed as the sum of W stage from the sleep onset to the lights out.
- Sleep efficiency (SE; %): proportion of time spent sleeping during the recording. It is computed as follows: (TST/TRT)·100.
- Sleep stages duration (min): time spent in each sleep stage (N1, N2, N3 and REM).
- Sleep stages proportion (%): proportion of time spent in each sleep stage (N1, N2, N3 and REM) within the TST. It is computed as follows: (Sleep stage duration/TST)·100.
- Number of arousals (count): number of arousals within the TST.
- Arousal index (ArI; %): proportion of arousals within the TST, calculated as follows: (Number of arousals/TST)·100.

2.6 Sleep and Cardiovascular Functions

Over the past decades, substantial research has been undertaken on cardiovascular functions during sleep. Similarly to most of the physiological processes, cardiovascular parameters undergo marked fluctuations over the sleep period. The variations ensue from the interaction between influences from both the sleep-wake cycle and the circadian rhythm. However, the relationship between sleep and cardiovascular system is reciprocal, as the activity level of the latter affects the sleep pattern as well.

2.6.1 Influence of Sleep and Circadian Systems on Cardiovascular Activity

It has long been known that the cardiovascular system exhibits a diurnal rhythm in terms of activation during daytime and withdrawal during nighttime.

Several studies have recorded human blood pressure (BP) over 24 h, showing a reduction in nocturnal level in comparison to diurnal value. The nadir is achieved in the middle of the night, afterward a surge occurs in the morning hours [26, 108, 177, 186, 214, 250, 265, 270, 299]. The nocturnal fall in BP is widely referred as “dipping” and its magnitude is about 10% of the diurnal value [288] (Figure 2.3).

Analyses of the circadian profile of cardiovascular parameters revealed also nocturnal decreases in heart rate (HR), stroke volume (SV) and cardiac output (CO) [108, 146, 177, 187, 214, 250, 299]. BP variability has been found to lower in the nighttime as well [177, 213]. Differently, no significant changes in total peripheral resistance (TPR) have been detected [146]. In this context, since both an enhanced baroreflex sensitivity [61, 215] and a downward shift of the baroreflex threshold [43] have been observed during sleep, the baroreflex regulatory mechanism is likely to participate in nocturnal BP lowering.

A similar rhythmicity has been disclosed with regard to the heart rate variability (HRV) measures. Overall HRV has been illustrated to decline after midnight and rise during subsequent hours [190]. Time domain HRV metrics show heightening in high frequency (HF) and diminishing in low frequency (LF) during the sleeping hours [31]. Norepinephrine and epinephrine are also reduced during nighttime [73], whereas pre-ejection period (PEP) is prolonged [45], suggesting a diminished sympathetic tone.

Taken together, these data are consistent with a circadian pattern of the sympathovagal balance: the sympathetic dominance occurring during wakefulness is gradually overcome by a vagal prevalence during night, followed by a morning rise in sympathetic outflow.

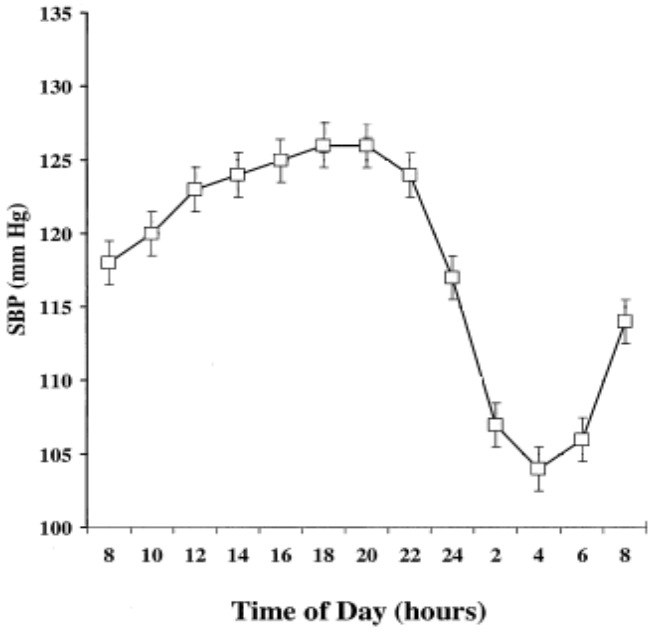

Figure 2.3. Twenty-four hours profile of systolic blood pressure (SBP) (*modified from Ref. 265*).

However, whether this pattern is due to an endogenous circadian rhythm rather than changes in posture and physical activity is unclear. Furthermore, the primary modulations exerted by the

sleep-wake cycle and the circadian rhythm on cardiovascular parameters during sleep are in turn affected by a variety of secondary influences issuing from physical exercise, posture, thermoregulation [288].

In order to evaluate the role of both sleep and circadian systems on cardiovascular functions during sleep as well as disentangle the involvement of the secondary variables, laboratory manipulations have been carried out. The application of experimental paradigms has allowed to reveal the independent contribution of both sleep-wake cycle and circadian rhythm and that these effects are not mediated by other potential confounders such as changes in posture and physical activity [47, 51, 145, 152, 292, 294] (Figure 2.4).

Studies designed at isolating the circadian influence on BP profile have provided conflicting results. By using a constant-routine protocol, no effects of circadian rhythm have been detected [145, 294], while a notably influence has been observed when participants underwent a forced desynchrony procedure [285]. The various methods employed are conceivably to account for the elusive findings [295]. On the other hand, more convincing evidence supports the effect of sleep system on BP. The larger drop occurs along the falling asleep process [52, 132, 287]. Carrington and colleagues [52] identified two components: a mild decline preceding the sleep onset and associated with preparation for sleep and a sharp fall following the sleep onset, when stable sleep is achieved. When sleep is forcedly delayed, the drop in BP is delayed as well [51].

Unlike the BP, a strong circadian influence has been documented for HR by forced desychrony and constant routine paradigms [47, 145, 285, 294, 295]. However, HR is greatly affected by the sleep process as well. Similarly to BP, the greater extent of decrease is seen at sleep onset [47, 51, 287].

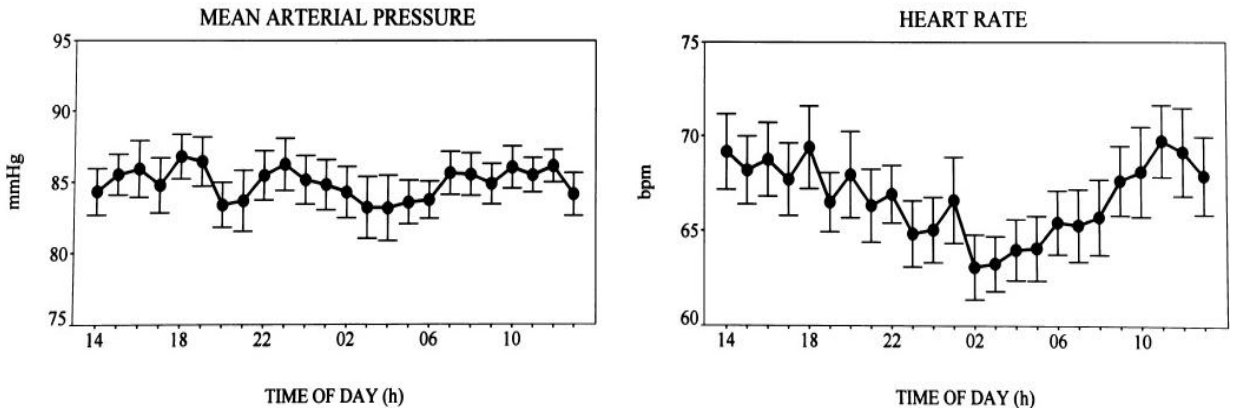

Figure 2.4. Twenty-four hours profile of mean arterial pressure (left panel) and heart rate (right panel) under constant routine protocol (*adapted from Ref. 145).*

The experimental manipulation of posture and physical exercise revealed findings of interest. Assessment of 24-h cardiovascular profile in ambulant subjects demonstrated a drop in HR and BP values during nocturnal hours in comparison to daytime similarly to that showed by recumbent subjects [108, 292].

The transition from wakefulness to sleep is characterized by a progressive shift from sympathetic toward parasympathetic control [287, 292]. Considering more closely the timing, variations in HF vagal-related HRV indices revealing an elevation in cardiac parasympathetic drive have been found to begin approximately two hours before the sleep onset and peak near to the time of sleep onset [47]. Differently, sympathetic output changes are delayed as beginning after sleep onset and continue throughout the night, as illustrated by decrease in LF to HF (LF/HF) ratio, muscle sympathetic nerve activity (MSNA), catecholamine and increase in PEP [46, 73, 271, 287].

These data are suggestive of distinct mechanisms underlying the variations in cardiovascular parameters during sleep, as the parasympathetic nervous system (PNS) appears to be more affected by circadian curve, whereas the sleep-wake cycle regulates mainly the sympathetic nervous system (SNS) [47, 145, 295]. Burgess and colleagues [46] proposed that the parasympathetic buildup is involved in the preparation to sleep, while the sympathetic decline occurring over sleep aids to maintain the individual asleep.

In addition, significant fluctuations in the autonomic control and systemic hemodynamic are also seen in association with specific sleep phases.

As discussed above, the largest drop in systemic BP occurs at sleep onset, concomitant to the transition from quiet wakefulness to light sleep (i.e., S1 NREM) but it progresses with the deepening of sleep, as further reduction have been reported in S2 [52] and slow-wave sleep (SWS) [58, 276].

Overall, cardiovascular activation declines with the NREM sleep progressing. Reduction in BP, HR and CO have been described in NREM compared to prior wakefulness becoming more pronounced as sleep deepens [43, 58, 133, 146, 187, 270, 271, 287, 292].

Changes in both autonomic divisions drive mediate the down regulation of cardiovascular functions observed in NREM. As showed in Figure 2.5, studies analyzing the HRV during sleep reported an increase in HF component combined with a decrease in LF component across NREM sleep stages [32, 287, 292, 297]. Moreover, the PEP was found to lengthen in NREM sleep [287]. On the contrary, a progressive decline in MSNA and peripheral vasodilatation is exhibited with the deepening in NREM sleep [130, 152, 153, 271, 296]. A fall in the power of LF BP variability [108, 292] has also been showed.

Taken together, the evidence suggests a heightening in vagal output [31, 213, 287, 298, 319] coupled with a sympathetic withdrawal [130, 209, 271, 275] in NREM sleep in comparison to wakefulness.

However, the autonomic branches are thought to perform a different control on cardiovascular parameters. As demonstrated by elegant pharmacological blockade study, the modulation of HR during sleep is largely owed by reciprocal changes in PNS rather than in SNS [320]. Further support from the hypothesis of HR vagal modulation arises from the concurrent cardiac deceleration and increase in HF HRV indices of cardiac vagal control. Whereas the bradycardia is mainly determined by the elevation in vagal output, the hypotension largely ensues from diminished sympathetic vascular tone in skeletal muscles [12, 268]. Given the enhancement in baroreflex sensitivity observed in NREM [61, 192], the shift from sympathetic to parasympathetic prevalence is reasonably to be ascribed to a baroreflex mechanism that hence underlies the cardiovascular hypoactivation [268, 288].

While NREM sleep is characterized by relatively stable neurovegetative activity, a markedly irregular autonomic pattern is typically observed during REM.

Superimposed on the backdrop of reduced vagal tone, abrupt transient burst of sympathetic activity are exhibited. Sympathetic surges occur mainly during phasic events in REM sleep. Indeed, transitory elevations in BP and HR are seen as concomitant to muscle twitches and REMs [58, 270, 271, 292]. Hypertensive and tachycardic periods are accompanied by surge in coronary blood flow [70].

Overall, the average value of cardiovascular parameters results to be more elevated in REM than in NREM sleep stages and may achieve levels experienced during quiet wakefulness [43, 58, 133, 146, 270, 271, 287, 288, 292, 320].

The increase in LF component of HRV and in LF/HF ratio [292, 297] associated with augmented MSNA compared to NREM [130, 271] suggest that sympathetic elevation occurring during REM sleep affects both cardiac and vascular districts. However, it has to be emphasized that the peripheral vasodilatation is not generalized during REM. The BP rise from non-REM to REM sleep is due in part to sympathetic mediated vasoconstriction in skeletal muscles, which is opposed by vasodilatation in the mesenteric and renal vascular beds [268].

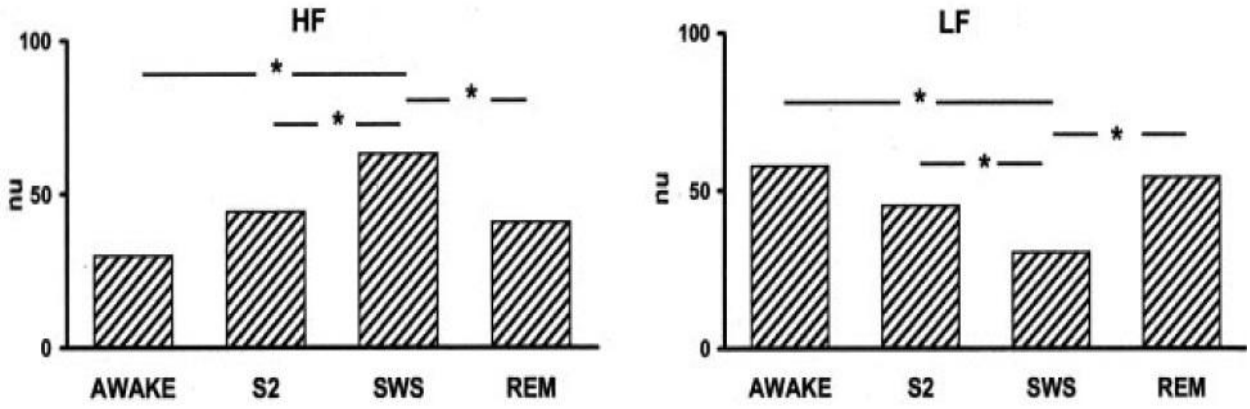

Figure 2.5. High frequency (HF, left panel) and low frequency (LF, right panel) components of heart rate variability across sleep-wake stages. *$P < 0.05$. (*modified from Ref. 133).*

2.6.2 Influence of Cardiovascular Activity on Sleep

The influence of elevated cardiovascular drive on sleep quality and quantity has been addressed in particular in insomnia (for a review, see Ref. 33). Considering only the normal sleep, research has focused on the coupling between cortical synchronization and cardiac activity during sleep, as indicated by the EEG delta rhythm and the sympathovagal balance, respectively. As multiple investigations have illustrated, a reverse relationship links these parameters, as the EEG delta activity increases with the lowering in sympathovagal balance [39, 137]. Given the evidence that the cardiac autonomic modifications have been disclosed to anticipate the EEG changes, the shift toward vagal dominance has been advanced to further the cortical synchronization [136, 137]. This hypothesis has been corroborated by the anticipatory cardiovascular response to arousal from sleep, addressed below.

2.6.3 Cardiovascular and Sleep Disturbances

Sleep disruption has been found to alter cardiovascular functions. Experimental manipulation showed that both partial and total sleep deprivations lead to augmentation in diurnal BP and HR values [106, 144, 168, 206, 280]. As further supported by HRV data, this increase is likely driven by a sympathetic hyperactivation [280, 321].

A growing body of knowledge has been gained about the acute and chronic cardiovascular consequences of sleep disorders [216]. Particularly, as recently reviewed by Bradley and Floras

[37], the significant detrimental impact of sleep breathing disorders[1] on cardiovascular health is documented by compelling evidence.

Given the reciprocal relationship between cardiovascular functions and sleep, cardiovascular diseases may result in sleep abnormalities as well. Alterations in sleep have been reported in a variety of cardiovascular conditions, included chronic heart failure [315] and post-myocardial infarction [303].

Bearing in mind the fall in BP occurring during night, a 'non-dipping BP profile' is usually defined as a nocturnal drop in BP of less than 10% than diurnal values. A non-dipping BP profile has been identified in several cardiovascular conditions especially in hypertension [244], in which an association with poor sleep quality has been also reported, as indicated by more numerous nocturnal awakenings and lower amount of SWS and REM sleep displayed by hypertensive patients [179, 219].

Moreover, an elevated nocturnal BP reflecting a reduction or frank absence of physiological dip is currently regarded as an harbinger of unfavorable outcomes [122, 208]. Indeed, as demonstrated by large prospective studies, blunted BP dip is an established sensitive predictor of both cardiovascular and non-cardiovascular mortality [17, 208, 300].

However, also an excessive nocturnal dip is considered to augment the morbidity particularly in the elderly and patients with cardiovascular disease treated with hypotensive drugs [142]. When the nocturnal hypotension is exaggerated, perfusion in some tissues may be compromised. Moreover, if the BP drops below the lower limit of autoregulation of cerebral blood flow (i.e., mean arterial pressure lower than 60 mmHg), cerebrovascular events may occur. These findings led to the hypothesis of a J-shaped curve relationship between the nocturnal dipping status and the likelihood of adverse events [141, 142].

In this context, a diurnal rhythm has been consistently reported in the occurrence of cardiovascular and cerebrovascular events (for a review, see Ref. 315). Indeed, a reduced cardiac vulnerability has been seen in the nighttime. Conversely, a high incidence of cardiac events has been documented to occur during the morning hours [199, 310]. As it has been found to coincide with the rise in BP and in overall cardiovascular activation exhibited at the end of the night, the morning surge has been advanced as accounting for this temporal association [74, 116, 140]. Another factor conceivably to be associated with the rhythmicity in cardiovascular risk is the distribution of NREM and REM periods across the night. Because of the generalized cardiovascular hypoactivation, the increased cardiac electrical stability the NREM sleep is

[1] The sleep breathing disorders include a spectrum of conditions characterized by recurrent episodes of reduction (hypopnea) or interruption (apnea) of respiration during sleep. The respiratory event is often associated with drop in blood oxygen saturation and arousal.

thought to be related with diminished cardiovascular risk in the general population [302]. In contrast with NREM, the autonomic instability characteristic of REM sleep has been linked to augmented cardiac vulnerability. The rise in HR and vasoconstriction mediated by an overall increase in SNS drive occurring in REM may provoke ventricular arrhythmias [241, 269]. Since the REM sleep amount is higher in the latter part of the night, it could be an additive factor contributing to the high cardiovascular risk observed approaching morning.

2.6.4 Cardiovascular Response to Arousal from Sleep

As mentioned above, sleep can be occasionally interrupted by transient EEG arousals. Healthy adults experience approximately 15 spontaneous arousals per hour of sleep [35].

In spite of their shortness, arousals trigger an abrupt and intense modification in cardiovascular activity, as being associated in particular with changes in HR, BP, MSNA and cerebral blood flow (CBF) velocity [30, 65, 151, 195, 204, 257, 271, 286, 287].

The cardiac response to arousal from sleep has been found to exhibit a peculiar time course. As observed by Sforza and colleagues [257], a cardiac acceleration begins approximately two beats preceding the arousal onset, peaking within four to five beats after the onset of the arousal, and it is followed by bradycardia over the seven to eight beats after that. A similar temporal dynamic has been reported by other studies aimed at assessing the HR [114, 117, 286] and BP [65, 195, 286] responses to arousal from sleep (Figure 2.6). Nonetheless, the peak and ending of BP changes are slightly delayed in respect to the variations occurring in HR [195].

Therefore, the cardiovascular response is anticipatory, as the surge begins prior the EEG-defined onset of arousal, and transient, as the values decrease down to the levels showed before the event approximately within 10 sec when sleep is restored [286].

The magnitude of cardiovascular response to arousal is largely independent by the properties of the arousal, in terms of nature, intensity and duration of arousal stimuli [286]. Whether the magnitude of response differs across sleep stage is unclear, as some evidence suggests a delayed HR recovery during SWS [257]. However, a large between-subject variability in the magnitude of the activation response has been documented [286].

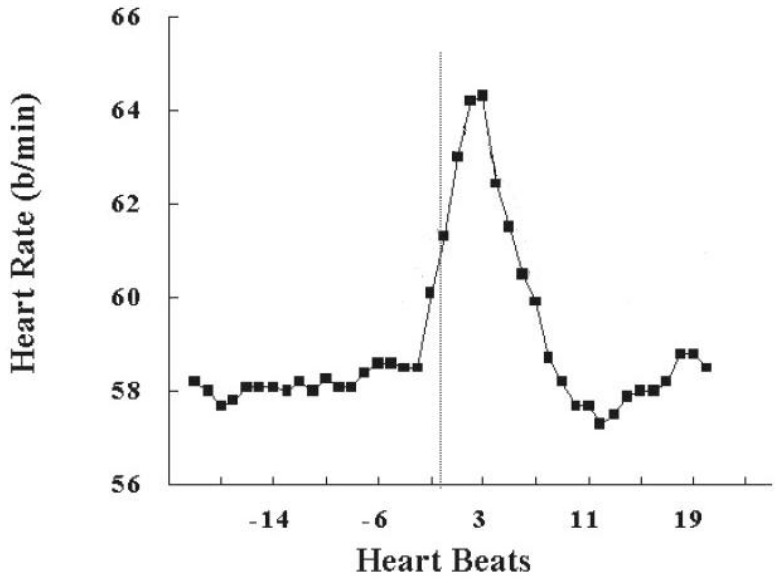

Figure 2.6. Heart rate response to arousal from sleep. The dashed line indicates the onset of the arousal (*modified from Ref. 286).*

Both branches of the autonomic system are involved in the cardiovascular arousal response setting. Also, a contribution of a baroreflex mechanism has been proposed [288].

Given the temporal delay exhibited by HR and BP responses and the evidence illustrating that SV reduces slightly and CO varies little in association with arousals [195] while sympathetic muscle activity rises [195, 271], the changes in BP arousal response are reasonably to be owed by sympathetic-mediated peripheral vasoconstriction rather than a baroreflex mechanism [266, 268].

With regard to the cardiac activation, converging evidence points toward a primarily vagal control of the HR changes to arousal. As explained in the Chapter 1, the onset of the cardiac response arising from parasympathetic stimulation is more accelerated than the onset from sympathetic stimulation because of the faster action of the vagal neurotransmitter acetylcholine. Hence, unlike the SNS, the PNS is able to react within milliseconds reducing the response latency. Further support originates from experimental blockade of autonomic nervous system (ANS) disclosing that vagal blockade abolished instantaneous HR surge [128]. Horner and coworkers [129] showed that, in spite of isolated sympathetic and parasympathetic blockade did not abolish the HR arousal response, both had an attenuating effect on HR increase. Specifically, during parasympathetic block there was a 12% HR arousal acceleration compared to 31% HR arousal increase when no blockade was applied. When sympathetic block was applied there was a 30% HR arousal rise, a magnitude similar to that which the researchers found without

blockade. Lastly, as mentioned above, the HR control during sleep is primarily performed by the PNS.

Given the massive cardiovascular surge in response to arousal from sleep, it is reasonable that the incidence of arousal from sleep is critical for cardiovascular health [260]. Recurrent arousals from sleep are experienced in a number of sleep disorders such as sleep breathing disorders and periodic limbs movement during sleep[2]. These sleep disorders are associated with increased cardiovascular morbidity as hypertension, stroke and congestive heart failure [161]. A high incidence of arousal results in frequent transient surges in cardiovascular activity and sleep fragmentation, which lead in turn to average overnight elevation in physiological parameters. As described above, the diminished cardiovascular nocturnal drop is a predictor of adverse outcomes.

[2] Periodic limb movements during sleep consist of clusters of repetitive, short lasting movements occurring over the sleep period and involving primarily the lower extremities.

CHAPTER 3

The Essential Hypotension

3.1 Classification

According to the World Health Organization [316], hypotension is defined as a condition of systolic blood pressure (SBP) below 110 mmHg in men and below 100 mmHg in women.
Three forms of hypotension are commonly distinguished, i.e. orthostatic, secondary and essential hypotension. The current work focuses on the latter form.

3.1.1 Orthostatic Hypotension

Orthostatic hypotension is referred as a sudden fall in blood pressure (BP) when assuming upright position. A clinical definition refers to a fall in SBP of at least 20 mmHg or a fall in diastolic BP (DBP) of at least 10 mmHg measured within 3 min of standing [253].
When a person lies down, the blood is equally distributed across the body regions. When we stand, about 500-1000 ml of blood moves from the upper part of the body to the lower part of the body. The pooling of the blood in the inferior extremities and splanchnic circulation results in diminished venous return to the heart that in turns lowers cardiac filling and hence the cardiac output (CO) and BP. The drop in BP triggers a baroreflex response that, by stimulating sympathetic nervous system (SNS) and inhibiting parasympathetic nervous system (PNS), causes heart rate (HR) acceleration, myocardial contractility, increase in CO, peripheral vasoconstriction and increased venous return. The compensatory reflex response restores eventually the BP.
Whenever this physiological reflex fails to compensate for the reduction in venous return, orthostatic hypotension occurs. It may be either symptomatic or asymptomatic, depending on the magnitude or duration of the phenomenon. Symptoms typically experienced include dizziness, light-headedness, nausea, headache, visual blurring, dyspnea [104].
Orthostatic hypotension is normally completely reversible and resolves spontaneously without chronic impairment after few minutes or the return to sitting or lying position. Nonetheless, if massive, it can also result in severe cerebral hypoperfusion and syncope [147].

Several physiological and pathological conditions may increase the susceptibility to orthostatic hypotension, such as aging, drugs, autonomic neuropathy, multiple system atrophy (e.g., Ref. 104, 239).

It should be emphasized that subjects suffering from orthostatic hypotension exhibit low BP usually only when standing, whereas they normally have normal BP while seated, and sometimes high BP when lying down [239].

3.1.2 Secondary Hypotension

Low BP can ensue from primary conditions, which may be either acute or chronic. Acute hypotension results from hypovolemic shock as due to hemorrhage or dehydration. The pronounced fall in blood volume and CO lowers the BP. If the blood is not restored, severe prolonged hypotension can lead to death [147].

Because arterial pressure is the product of CO and total peripheral resistance (TPR), diseases associated with a reduction in either may result in hypotension when not compensated. For instance, decreased CO can derive from decelerate HR as occurring in sinus bradycardia and atrio-ventricular (AV) nodal blockade, while lowered stroke volume (SV) is seen in heart failure and reduced venous return. Diminished vascular tone may occur in autonomic dysfunctions [147].

Additional diseases commonly associated to low BP are Addison's disease, pheochromocytoma, Wernicke's syndrome, amyloidosis, diabetes mellitus [313].

Several drugs can also cause hypotension. The excessive assumption in antihypertensives agents such as beta-blockers, calcium-channel blockers can lower the BP down to normal values. Vasodilator drugs as angiotensin-converting enzyme inhibitors and hydralazine used in heart failure may also lead to exaggerated drop in vascular tone and thereby hypotension.

3.1.3 Essential Hypotension

However, an individual may exhibit permanent low BP in spite of clinical history and physical examination rule out primary conditions underlying the hypotension.

Essential (or constitutional) hypotension is a condition of chronic low BP, with SBP lower than 110 mmHg in men and 100 mmHg in women and DBP lower than 60 mmHg [254, 307]. It occurs in absence of any identifiable pathological factors and it as associated with a constellation of symptoms, as discussed below.

An early description was made by Riesman in 1923, who named it “constitutional hypotension”. The author illustrated the features characterizing this state, such as poor circulation, physical and mental exhaustion, cold limbs [236].

It has long been debating whether a primary, chronic low BP might be considered as a distinct nosological entity, deserving of medical attention and therapeutic management.

Early evidence of ongoing controversy between who refrains from and who sustains to regard at the essential hypotension as a disease dates back to the first decades of the last century [14, 101, 105]. In this context, the opinion of Friedländer [105] is illustrative, as he claimed that hypotension is a symptom rather than a disease itself, notwithstanding he admitted there is no adequate explanation for many of the hypotensive states.

A number of reasons can account for the skepticism showed by the medical community in considering the essential hypotension as a specific disease. Firstly, the cluster of symptoms complained by hypotensives is not peculiar and can be seen in a variety of conditions, as argued by Robinson [240] and Pemberton [220]. Secondly, a low BP has been historically thought to be a marker of health and greater life expectancy, as to be regarded as the “ideal normal BP” [240].

This dispute is conceivably to justify why the essential hypotension is a such poorly addressed topic, unlike its mirror condition of essential hypertension, which has been extensively investigated and broadly established as associated with heightened risk of poor outcomes (e.g., Ref. 50, 138).

However, as addressed in details later in the current Chapter, available evidence contests these assumptions.

In addition to subjective distressing symptoms referred by hypotensives, essential hypotension has been consistently found to be associated with objective markers of electrocortical alterations [62, 85, 308] and abnormalities in both central and peripheral hemodynamics [82, 86, 273]. Furthermore, more recent investigations challenged the concept of hypotension as promoting a better survival by documenting higher morbidity and mortality occurring with low BP (e.g., Ref. 2, 167).

3.2 Epidemiology

Esteems of the epidemiology of essential hypotension vary greatly due to the arbitrary definitions of hypotension adopted.

The boundaries used to design hypotension range from SBP lower than 110 mmHg [6, 14, 220] to systolic values lower than 100 mmHg [2], either taking into account or not the limit of DBP

below 60 mmHg [220]. Statistical criteria have also been used [125, 211]. Additional variability derived by the approach used to assess BP. Moreover, the evaluation is further complicated by the fact that the majority of the investigations consists of cross-sectional rather than longitudinal studies.

Early attempts targeted at explore the epidemiology of essential hypotension date back to the Twenties. By retrospectively evaluating BP values in a group of 10.142 male subjects, Alvarez [6] and Barach [14] found a SBP below than 110 mmHg in 3.5% of the individuals.

In a large screening study carried out in a Canadian community, 17.8% of the individuals reported a prior diagnosis of low BP, a proportion comparable to hypertension diagnoses (19.8%) [259].

Pemberton [220] reviewed data from surveys of three Austrialian community investigations and identified hypotension in 1.6–2.7% of male subjects and 0.3–3.6% of female subjects, in accord with the definition of hypotension as office SBP lower than 110 mmHg for males and lower than 100 mmHg for females. When the criterion of DBP below 60 mmHg was applied, prevalence was 1.0-1.1% in men and 1.2-2.7% in women.

Employing the technique of 24-h ambulatorial BP monitoring (ABPM) in a cohort of mainly urban dwelling Irish subjects, Owens and coworker [211] found that 49% of them demonstrated hypotensive events, defined as two or more consecutive systolic or diastolic readings below the fifth percentile of BP.

In a longitudinal follow-up study, a proportion of 0.7% chronic hypotensives with office SBP lower than 100 mmHg for 8 or more years has been identified in Japan [2].

With regard to the gender, essential hypotension has a female preponderance, ranging from 13% to 1% [2, 75, 211, 259] in the female general population. Studying the low BP in German general practice, Donner-Banzhoff and coworkers [75] observed a double rate of essential hypotension in women.

Moreover, it was found to occur more frequent among the young. Consistently, Baenkler and coworkers [13] reported a high prevalence in the female population aged 20-40 years.

The epidemiology of essential hypotension entails notably socioeconomic burden.

The socioeconomic impact of essential hypotension has been quantified in a study performed by Beske and colleagues [25]. In Germany in 1978, up to 9.5 million working days have been estimated as being lost due to low BP. Additionally, from 1% to 8% of the German population were found to undergo antihypotensive therapy, leading to an estimated cost of 380 million German marks for the country.

Unlike the essential hypertension, whether chronic low BP carries either a protective effect reducing the risk for both cardiovascular and non-cardiovascular deaths in the general population, or augments the likelihood of adverse outcomes, is still under debate.

Historically, a low BP has been regarded as the optimal BP [240]. By reviewing nine large prospective studies, MacMahon and coworkers [169] observed a consistent positive monotonic relationship between BP values and risk for cardiovascular events, supporting the concept of hypotension as cardio-protective state. Moreover, people with chronic low BP have been found less likely to have a positive family history of cardiovascular disease [211]. Thereby, low BP has been associated with greater life expectancy [113, 222].

Nonetheless, growing body of literature leads to the opposite conclusion.

Low BP has been reported as being a significant predictor of increased mortality in healthy elderly [2, 181]. Moreover, several investigations demonstrated that hypotension was related to a negative prognosis in a variety of cardiovascular conditions such as coronary disease and heart failure (e.g., Ref. 160, 210).

Thereby, a relation between low BP and vulnerability to cardiovascular events has been postulated [98, 293]. Evidence supporting this hypothesis is particularly compelling with regard to DBP [96, 185, 210]. This datum is reasonable given that myocardial perfusion is mainly dependent on DBP [147].

Furthermore, additional evidence support the concept of hypotension as a source of non-cardiovascular morbidity as well.

Higher susceptibility to the development of chronic fatigue syndrome has been found by large epidemiological studies in association with low BP [167, 200, 245]. A condition of chronic hypotension has also been identified as a risk factor in pregnancy [202, 306]. Lastly, prospective investigations indicate consistently low BP as elevating vulnerability to dementia in the elderly [194, 197, 246].

3.3 Symptoms and Associated Features

The spectrum of symptoms complained by essential hypotension is heterogeneous and include tiredness, loss of appetite, dizziness, giddiness, blackouts. Hypotensives often suffer from palpitations, chest pain, headaches, breathing difficulties. Cold hands and feet, paleness and sweating are also commonly reported [220, 224, 307, 309].

As already noted in early investigations [115, 158, 238], the chief symptoms of essential hypotension is mental and physical fatigue.

By analyzing the relationship between BP and subjective symptoms, Pemberton [220] found an association between low BP and tiredness. The association was stronger for young women. This finding has been confirmed and extended by subsequent investigations. In a large cross-sectional population based survey, Wessely and colleagues [309] disclosed a negative correlation between SBP and both fatigue and dizziness, persisting after adjustment for confounders.

In addition to the chronic symptoms, more acute states can occur in precipitating conditions. Abrupt moving to upright posture may lead to a sudden fall in BP resulting in orthostatic hypotension and syncope.

Additional features observed in essential hypotension include low body temperature [2, 272] and low body mass index (BMI) [2]. Consistently with the latter aspect, the finding of low creatinine levels is suggestive of reduced muscle mass in hypotensives [2, 211]. Moreover, heightened pain sensitivity to both cold and heat pain has been detected in essential hypotension [78, 89].

In addition to somatic symptoms, hypotensive sufferers complain of cognitive and affective disturbances, as reduced concentration, lack of motivation, anxiety and depression [220, 224, 307, 309].

Several investigations designed at exploring cognitive functions documented impaired performance in essential hypotension in comparison to normotensive condition. The deficits are particularly prominent in the area of attention (Figure 3.1).

Hypotensives exhibit prolonged simple and cued reaction times suggesting that both tonic and phasic alertness are compromised [84, 85, 272]. Both selective and sustained attention are also reduced in essential hypotension [62, 84]. Poor performance in arithmetic tasks has been reported [272].

Electrophysiological studies disclosed also alterations in cortical activity related to attentional processing. Investigations on event-related potentials revealed reduced amplitude of the contingent negative variation[3] in essential hypotension [62, 85, 308]. The amplitude of this component was found to correlate with the SBP value [85, 308].

Furthermore, multiple evidence indicates declined memory in essential hypotension [62, 84, 272].

[3] The contingent negative variation is a slow event-related potential occurring during the interval between a warning signal (S1) and a second stimulus (S2) requiring a cognitive, verbal or motor response. Thus, it is thought to reflect the process of phasic alertness.

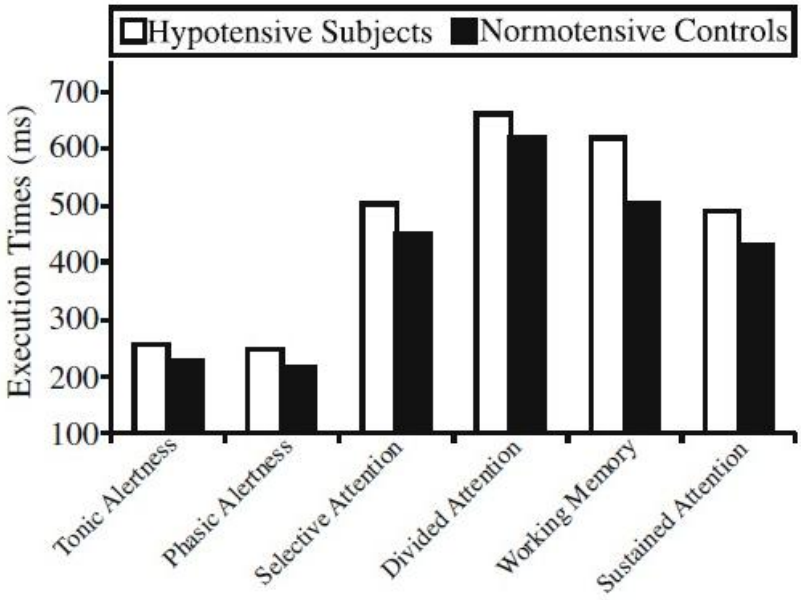

Figure 3.1. Execution times in attentional tasks in hypotensives and normotensives (*adapted from Ref. 84).*

The distressing symptoms experienced by hypotensive sufferers may lead to anxiety and depression [220, 225, 309]. In a community of elderly men, Barret-Connor and Palinkas [15] observed that low DBP was related with high depression score at questionnaires. The relationship between low BP and anxiety and depression is further supported by large cross-sectional studies as the Nord-Trøndelag Health Study [125].

Somatic, cognitive and affective disturbances experienced by hypotensives concur together to affect considerably the daily functioning in this population. Indeed, low BP was showed to be related to poor social, physical and mental well-being [242]. Hence, the compromised well-being lowers the quality of life in essential hypotension [196, 242].

3.4 Cardiovascular Reactivity

The cardiovascular reactivity can be assessed in laboratory setting through a wide range of methods (e.g., [42, 290]. According to the coping strategies involved [205], the experimental paradigms may be grouped in two main classes: active and passive tasks. Both categories include physical and mental tests and trigger different patterns of cardiovascular reactivity (e.g., Ref. 5, 143, 264).

In a passive task the subject cannot influence the results of the test. Cold pressor test and view of emotional images are physical and mental passive tasks, respectively. Typically, passive tasks evoke a cardiovascular response characterized by increase in TPR and BP and slight reduction in HR and CO. This profile reflects mainly an alpha-adrenergic activation. On the contrary, the subject is responsible for the results of an active task. Examples of physical active tasks include aerobic exercise, while mental arithmetic and speech tests are mental active tasks. Elevation in HR, CO, BP and decrease in TPR are produced by active tasks, a response primarily mediated by beta-adrenergic stimulation.

Given the different hemodynamic involvement, the cardiovascular responses elicited by active and passive have been termed as myocardial and vascular patterns, respectively [255].

The cardiovascular reactivity in essential hypotension has been primarily evaluated by way of mental arithmetic tasks, more specifically the serial subtraction test. Although it has been declined in a variety of forms, typically the serial subtraction test requires the subject to repetitively count backward starting from a given number and a given subtrahend. The test has usually a short duration (3-5 min).

By administering the mental arithmetic task to hypotensive and normotensive subjects, Duschek and Schandry [87] observed an elevation in BP in both groups compared to resting values, in accordance with literature [4, 157, 164]. Nevertheless, as illustrated in Figure 3.2, the magnitude of increase was lower in essential hypotensive participants.

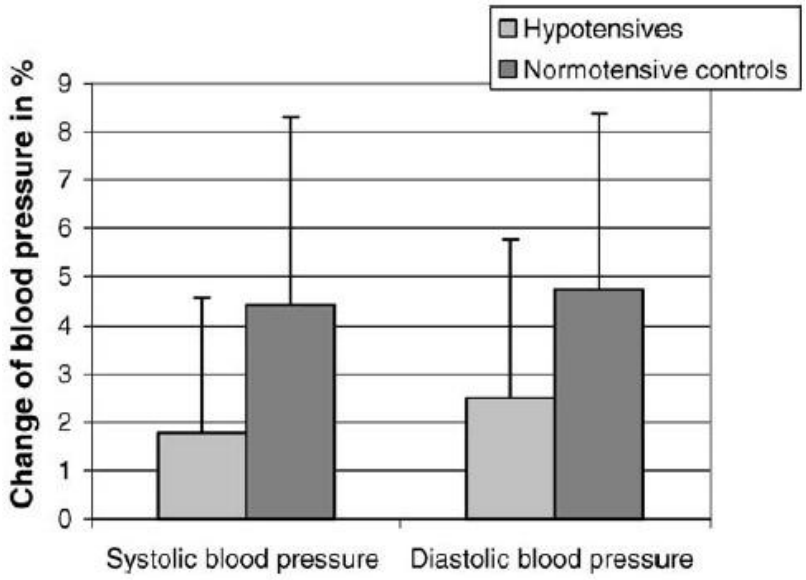

Figure 3.2. Changes of systolic and diastolic blood pressures from resting values during mental arithmetic task execution in hypotensives and normotensives (*adapted from Ref. 87).*

A more comprehensive cardiovascular assessment has been carried out by Duschek and colleagues [79]. Similarly to the prior investigation, hypotensive participants exhibited a less marked raise in both SBP and DBP in comparison to controls under stress task. The reduced augmentation in BP was largely mediated by a milder increase in CO, as no group differences were detected in respect to changes in HR, SV and TPR values.

These findings have been replicated by the same researchers in a further investigation [82], reporting a comparable enhancement in HR, SV and TPR between normotensives and hypotensives during the execution of the serial subtraction test compared to resting condition, albeit the latter subjects experienced a milder increase in CO than did controls.

Measures of central hemodynamic have found to be in accord with peripheral findings. Indeed, Stegagno and coworkers [273] measured the cerebral blood flow (CBF) velocity changes in response to a passive task such as the view of emotional images. Whilst both groups displayed a an acceleration in CBF velocity under emotional stimulation, it augmented to a lower extent in the essential hypotension group.

Taken together, these studies document a diminished cardiovascular reactivity in essential hypotension.

As reviewed by Treiber and coworkers [282], heightened levels of cardiovascular reactivity may predict the development and exacerbation of cardiovascular diseases such as carotid atherosclerosis. Hence, given the evidence linking the cardiovascular hyperreactivity to enhanced vulnerability, the findings of hyporeactivity illustrated in hypotensives is suggestive of lowered risk of adverse outcomes in this population.

3.5 Pathogenesis

Little is known about the pathogenesis of essential hypotension. Notwithstanding a number of theories has been proposed, the cause of essential hypotension is still unclear.

Various hypotheses have been advanced since early investigations. Friedländer [105] speculated an abnormal release of histamine and other vasodilators in hypotensives, while respiratory deficit and reduced oxidation were assumed by Barach [14]. In the same period, Fossier [101] proposed a narrowing of the aortic arch combined with a lengthening of the ascending aorta as cause of essential hypotension: the increased resistance to the flow offered by the narrower aortic arch, extended by the lengthening of the ascending aorta, would lower the BP down to 10-30 mmHg below the normal values.

However, these early theories have been discarded because of the scarce supporting evidence.

More recent studies aimed at addressing the psychophysiology of essential hypotension have provided data of interest about the mechanisms underlying the pathogenesis of this condition.

3.5.1 Autonomic Dysregulation

In addition to low BP, a number of investigations disclosed a diffuse hypoactivation of the cardiovascular system in essential hypotension.

In a comprehensive hemodynamic assessment, Duschek and colleagues [82] described lower HR, SV and CO in hypotensives compared to controls (Figure 3.3). The cardiovascular downregulation has been documented both at rest and under stress, as described in the Section 3.4. A diminished HR in this population has been also found in a previous report [2].

Since no difference in TPR was observed in comparison to normotensive condition [82], the essential hypotension has been proposed as being primarily attributable to cardiac rather than to vascular determinants [82]. The diminished CO might also result in reduced tissue perfusion in essential hypotension. This latter speculation has been supported by the finding of decreased capillary erythrocyte velocity in microcirculation in chronic low BP [77].

Abnormalities in autonomic balance have been hypothesized as underlying the cardiovascular downregulation displayed in essential hypotension. Particularly, a sympathetic hypoactivation has been postulated [2, 88, 103].

This assumption has been primarily justified by the evidence of reduced cardiac activity in hypotensive sufferers [2, 82].

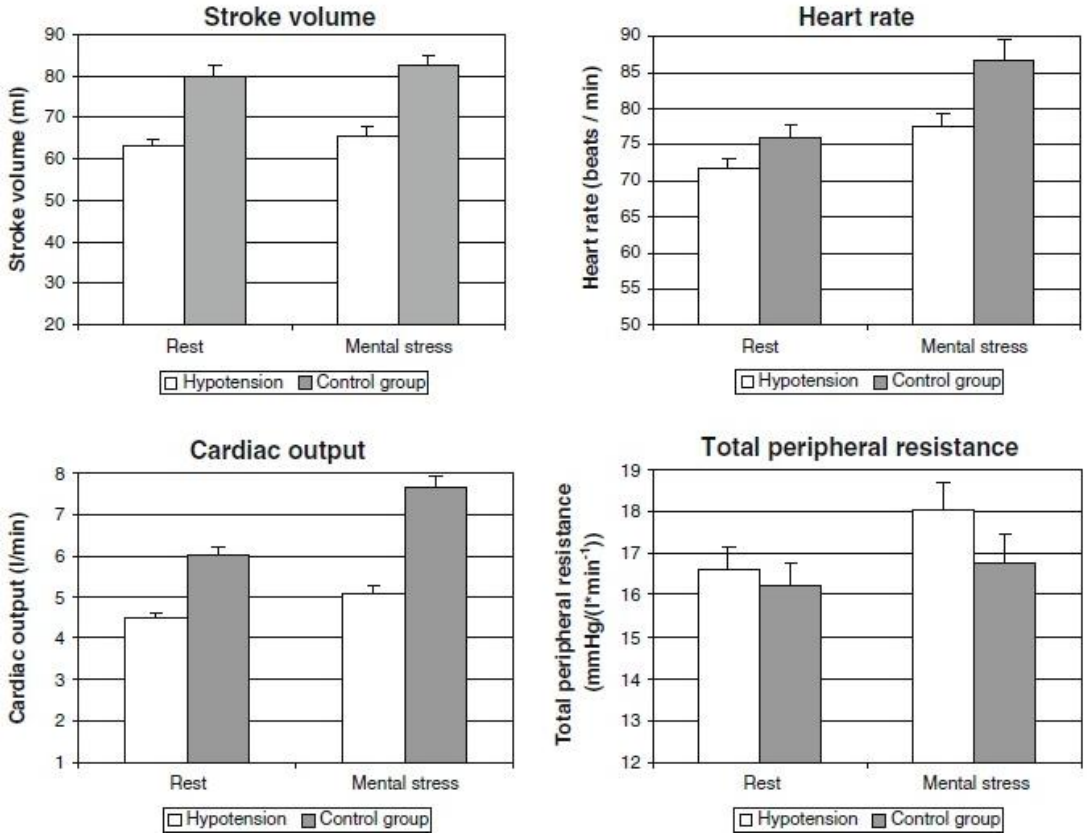

Figure 3.3. Hemodynamic parameters at rest and under mental stress in hypotensives compared to normotensives (*adapted from Ref. 82).*

By comparing the orienting response in three groups of hypotensive, normotensive and hypertensive subjects, Frederikson and coworkers [103] described a more accelerate electrodermal response habituation in the hypotensive group. As the electrodermal activity is a measure of SNS activation [67], the study gives strength to the sympathetic hypoactivation hypothesis.

Lastly, further support to the sympathetic withdrawal arises from pharmacological trials designed at assessing the effect of sympathomimetic drugs, such as the alpha-adrenergic agonist midodrine, which showed effectiveness in elevating BP and providing relief from acute symptoms [82, 83].

3.5.2 Baroreflex Overresponsivity

In the context of autonomic dysregulation theory, a role of the baroreflex has been advanced to contribute to the pathogenesis of essential hypotension [88, 308].

A baroreflex overresponsivity in chronic hypotensives has been early speculated by Weisz and coworker [308]. The authors conceptualized that an elevated baroreflex sensitivity leads to an

overcompensation of minimal transient blood pressure increases, thus stabilizing BP at a lower level. An experimental confirmation of this assumption has been provided by Duschek and colleagues [79], which detected an enhanced cardiac baroreflex sensitivity in essential hypotension both at rest and during mental stress in comparison to controls. Additional corroboration derives from pharmacological trials [83].

The hypothesis of baroreflex overresponsivity should be taken into account in the context of the involvement of baroreflex in both phasic and tonic BP regulation.

As described in Chapter 2, this mechanism is traditionally thought to participate only in short-term BP control because of the resetting. Nonetheless, recent investigations, conducted on both animal and human subjects, challenged this idea, suggesting that baroreceptors do not completely reset and may contribute to long-term BP control [120, 124, 165, 174].

Given this latter evidence, the concept of chronic low BP mediated by baroreflex mechanism is conceivable.

3.5.3 Cerebral Autoregulation Deficit

Studies employing the Transcranial Doppler Sonography disclosed aberrations in the regulation of CBF in essential hypotension.

As depicted in Figure 3.4, slower resting CBF velocity in the middle cerebral arteries of both hemispheres has been demonstrated in hypotensives compared to normotensives [86, 273]. Since these arteries supply large regions in the frontal, parietal and temporal lobes as well as subocortical areas (e.g., Ref. 7), a diffuse cerebral diminished perfusion has been thus postulated.

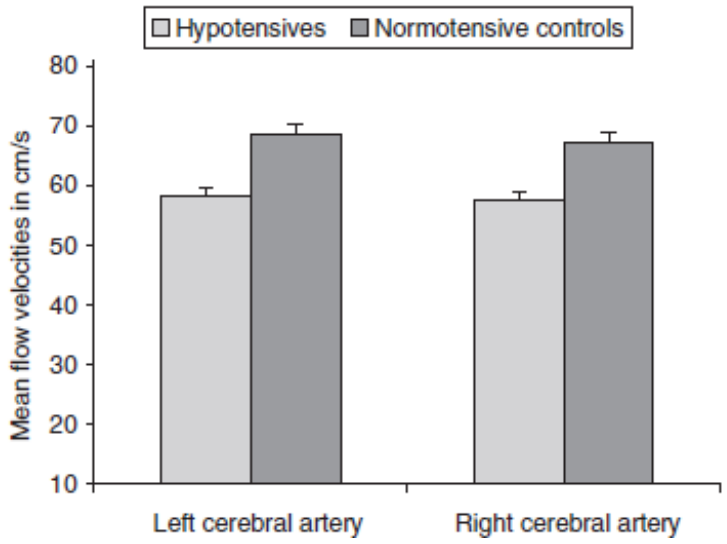

Figure 3.4. Resting blood flow velocities in the left and right middle cerebral arteries in hypotensives and normotensives (*adapted from Ref. 86).*

Bearing in mind the cerebral autoregulation mechanism, these findings are of additional interest. Indeed, this mechanism aids to maintain constant the CBF within a fairly wide range of changes in systemic BP (60 to 150 mmHg). When the systemic pressure exceeds either the upper or the lower limit, CBF increases or decreases proportionally with rising or falling in BP [57, 217].
Hence, according to the cerebral autoregulation, the CBF should not be affected in essential hypotension because of the systemic BP does not usually fallen below the inferior limit.
Differently, an impairment in this process is likely to occur in essential hypotension, as the autoregulation process is seemingly to be insufficient to compensate for the low systemic BP.
Further support to the abnormal autoregulation in essential hypotension stems from the finding that transient systemic BP oscillations were found to exert an exaggerated influence on CBF only in hypotensives [87], while a similar dependence of CBF on systemic BP was not observed in normotensives.
Moreover, a deficient adjustment of CBF to situational requirements has been recorded during task execution, in terms of blunted increase in CBF [86, 273]. Given the neurovascular coupling, in accord with the cerebral blood flow adapts dynamically depending on neural activity and brain metabolism [156, 305], the less marked augmentation in CBF in response to enhanced metabolic demand evoked by the cognitive activity is reasonably to yield to inadequate blood supply. In turns, this might account for the impaired mental functions exhibited by hypotensives, as further supported by the correlations revealed between cognitive performance and extent of CBF acceleration [86, 87].

The mechanisms proposed as underlying the essential hypotension are conceivably to interact reciprocally to cause and retain the essential hypotension and its associated features.
The baroreflex overresponsivity is likely to buffer to transient BP elevations by diminishing the sympathetic outflow and yielding to permanent low BP and, more in general, to a cardiovascular hypoactivation. In turns, the deficit in cerebral autoregulation leads to decreased CBF proportionally to the low BP.
Likewise, the physiological substrate of the cognitive impairment showed in essential hypotension can be ascribed to an interaction of the mentioned factors.
The reduced blood supply to the cerebral tissue resulting from deficient adjustment of CBF to task demands may cause reduced cortical activation and thereby poor performance. The findings of altered brain cortical activity exhibited by hypotensives is consistent with this hypothesis [62, 85, 308]. Moreover, some evidence links the baroreflex stimulation to cortical inhibition [59,

188, 231, 291]. Further strength ensues from the pharmacologic increase in both systemic BP and CBF resulting in amelioration of cognitive functions [80, 81].

3.5.4 Genetic Mutations

Genetic determinants have also been proposed, as molecular genetic studies have identified mutation in nine genes involved in BP control which provoke hypotensive forms. Notwithstanding the complexity and multiplicity of physiological processes underlying the BP regulation, all these mutations affect the renal-fluid system, as they lead to reduced salt reabsorption in the kidney thus lowering the BP [163].

3.6 Treatment

In line with the debate over the consideration of essential hypotension as a disease, antagonist opinions concerning its treatment have been advanced [68, 75, 237, 254, 259].

Therefore, there is a paucity of evidence about the management of symptoms complained by essential hypotension sufferers.

However, the therapeutic approaches fall into two classes: pharmacological and non-pharmacological therapies. It is generally agreed in the general practice that interventions, either pharmacological or non-pharmacological, targeted at elevating the BP to normotensive values should be restricted to symptomatic hypotensives rather than to all people reporting low BP [68].

Non-pharmacological strategies should be preferred to alleviate distressing symptoms and include primarily physical exercise and increased salt intake, known to be successful in raise the BP. Because elevated salt assumption can cause liquid accumulations in the legs, compressive stockings may be necessary [68].

If non-pharmacological interventions fail to elevate the BP and symptoms persist impairing considerably the daily functioning, pharmacological therapies can be prescripted [68].

As mentioned above, sympathomimetic agents, such as midodrine and etilefrine, are efficacious in raising the BP and providing relief from symptoms [80-82]. In severe cases, mineral-corticosteroids are administered [68].

A placebo-controlled double-blind trial demonstrated effectiveness of the alpha-adrenergic agent midodrine in raising the systemic BP through enhancement of peripheral vasoconstriction and heart pumping [82]. An elevation in CBF has been observed as well [81], which is likely to contribute to the improvement in cognitive performance observed after administration of midodrine [81].

Nonetheless, the midodrine has been documented to increase the baroreflex sensitivity and the vagal tone, as suggested by heart rate variability (HRV) analysis revealing increase in high-frequency (HF) power and decrease in low-frequency (LF) to HF power ratio [83]. The authors of the study hypothesized that the acute administration of midodrine triggers a counter-regulatory response targeted at restoring the BP to the low basal level through a baroreflex mechanism which augments the vagal output. Hence, given the postulated autonomic dysregulation in essential hypotension, caution is recommended in treating this condition with alpha-sympathomimetic agents, as they can exacerbate rather than reduce the autonomic imbalance.

Unfavorable effects have also been reported when administering etilefrine, a peripheral alpha- and beta-agonist. In spite of the amelioration in both BP levels and cognitive performance, a further reduction in contingent negative variation amplitude after administration of the antihypotensive drug has been showed, suggestive of diminished cortical excitability [80]. Thus, a possible adverse impact on central nervous system should be taken into account.

A surge in BP has been observed after administration of a Camphor–Crataegus berry extract combination [252]. The trial illustrated also the beneficial effects of the substance in enhancing mental functions.

3.7 Sleep Features

Daytime sleepiness and nocturnal sleep disturbances are often referred by essential hypotension sufferers [307, 309].

Nonetheless, studies aimed at addressing the sleep complaints in this population are lacking.

A large survey on BP levels and self-reported symptoms included a question regarding the sleep duration [309]. According to the average number of hours slept, three categories were defined: high sleepers (above 9 h of sleep per night), normal sleepers (7-9 h of sleep), low sleepers (below 7 h of sleep). However, regression analysis failed to found significant relationships between low BP and hours of sleep.

On the other hand, some evidence is suggestive of objective sleep abnormalities related with hypotension.

By analyzing the cumulative data of patients who attended the Stanford Sleep Disorders Clinic between 1994 and 1999, Guilleminault and coworkers [119] reported an association between low resting BP, defined as SBP below 105 mmHg and DBP below 65 mmHg, and upper airway

resistance syndrome[4]: about 20% of the patients with upper airway resistance syndrome had low BP and complain of orthostatic intolerance.

[4] The upper airway resistance syndrome is a form of sleep breathing disorder characterized by recurrent increases in resistance to airflow within the upper airway which lead to arousals and sleep fragmentation.

CHAPTER 4

The Research

Research Rationale

Over the past decades, a large body of knowledge has been gathered with regard to the nocturnal hemodynamic pattern, as well as the comorbidity with sleep disorders, in a variety of cardiovascular diseases (e.g., Ref. 303, 315). In particular, hypertensive states have been extensively investigated and the association with sleep disturbances as well as abnormal nocturnal physiological activity has been established (for a review, see Ref. 244). On the other hand, as mentioned in Chapter 3, surprisingly few attention has been paid to the sleep pattern in hypotensive conditions.

To date, there have not been any controlled study targeted at assessing quality and quantity of sleep in essential hypotension. Particularly, no polysomnographic (PSG) recordings have been carried out in this population.

The paucity of literature concerning sleep in essential hypotension appears even more surprising given the subjective complaints of sleep disturbances and diurnal sleepiness often reported by sufferers [307, 309]. Sleep disruption might contribute to generate and maintain diurnal symptoms referred by hypotensives. Support for this hypothesis arises from experimental manipulation of sleep in healthy (normotensives) subjects, illustrating that increase or decrease in sleep generate feeling of physical weakness, fatigue, poor concentration, daytime sleepiness [201].

Abnormalities in sleep may also include altered nocturnal physiological activity. As described in Chapter 2, the cardiovascular system undergoes massive fluctuations over the sleep period and within the sleep stages, due to both the influences of circadian and sleep systems (e.g., Ref. 268, 288).

To the best of our knowledge, neither the cardiovascular evolution throughout the night nor across different sleep stages have been investigated in essential hypotension yet.

Given the evidence of cardiovascular hypoactivation in this population [2, 82, 87], the examination of nocturnal physiological profile could aid to disclose whether daytime differences between hypotensives and normotensives are retained over the sleep period.

An autonomic dysregulation in terms of sympathetic withdrawal has been postulated as accounting for the reduced cardiovascular activity in hypotensive sufferers [2, 88, 103]. However, it should be remarked that this hypothesis has been advanced largely relying on indirect measures of sympathetic nervous system (SNS) outflow. Moreover, the role of parasympathetic nervous system (PNS) has not been elucidated. In this context, the evaluation of myocardial contractility may be of interest as well.

Bearing in mind that the autonomic nervous system (ANS) is known to play a key role in modulating the cardiovascular parameters during sleep (e.g., Ref. 32, 47, 287), the analysis of the nocturnal hemodynamic and neurovegetative pattern in essential hypotension may provide relevant insight into this condition.

Furthermore, since sleep is a condition relatively free of external disturbance factors that can affect physiological measurements during wakefulness (e.g., emotional status, degree of cooperation), the evaluation during sleep may reveal abnormalities in physiological functioning which measures performed in wakefulness fail to identify.

Sleep can also be employed as a paradigm to assess the cardiovascular reactivity to spontaneous phasic events.

Indeed, given the magnitude and significance of the cardiovascular oscillations occurring during arousals from sleep [195, 257, 286], the analysis of the response to arousal may provide data of interest.

As the nature of arousals from sleep has been postulated to be critical for the cardiovascular health [260], the examination of these events and their associated physiological modifications in hypotensive individuals may provide support for, or against to the assertion that hypotension is a cardio-protective state.

Moreover, taking into account that nocturnal cardiovascular measurements have been found to be better predictors for adverse outcomes than diurnal values [97, 162], a thorough investigation of the nocturnal tonic and phasic activity in essential hypotension can help to clarify the association between chronic low blood pressure (BP) and the morbidity and mortality risk, an issue still disputed.

Hence, in lights of the above mentioned considerations, the present dissertation aims at providing a comprehensive picture of the hemodynamic and autonomic pattern during sleep as well as the sleep pattern in essential hypotension. In particular, our purposes can be summarized as follows:

- To explore the sleep quality and quantity in essential hypotension by means of PSG recording, a technique allowing an objective estimation of sleep
- To assess the overnight cardiovascular profile in this population by applying a wide range of non-invasive measures
- To test the hypothesis of autonomic dysregulation underlying this condition by way of both pure sympathetic and parasympathetic indices
- To assess the cardiac reactivity in essential hypotension during sleep by analyzing the heart rate (HR) response to spontaneous arousals from sleep

Three studies have been performed in order to address these questions, as described in the next Sections.

4.1 Experiment I

4.1.1 Introduction

The descriptions of decreased HR [2, 82], stroke volume (SV) and cardiac output (CO) [82], and enhanced baroreflex sensitivity [79], combined with the effectiveness of sympathomimetic agents showed in hypotensives [80-82], have been interpreted as suggestive of a sympathetic hypoactivation in this population [2, 103]. However, it should be noted that neither cardiac nor vascular pure sympathetic indexes have been measured in the mentioned studies. An augmented parasympathetic tone could also be involved in the pathophysiology of essential hypotension. Lastly, since this evidence ensues from evaluations performed in wakefulness, whether the differences in cardiovascular parameters between hypotensives and normotensives individuals are retained during sleep is unknown.

The cardiovascular system shows a progressive downregulation from the wakefulness over the sleep period, mainly reflecting the progressive shift from sympathetic toward parasympathetic control (for a review, see Ref. 288). Abnormalities in nocturnal cardiovascular activity have been described in a variety of pathological conditions [303, 315]. In particular essential hypertension has been found to be related with blunted nocturnal dip in BP, CO and SV [274].

Given both the notably oscillations undergone by the cardiovascular system over the sleep period primarily mediated by changes in autonomic control and the lack of literature about the nocturnal profile of hemodynamic in essential hypotension, the aim of the *Experiment I* was to explore the overnight evolution of cardiovascular activity during sleep in hypotensives by means of a broad spectrum of measures. In addition, in order the clarify the postulated autonomic imbalance in essential hypotension, we sought to examine the involvement of both neurovegetative divisions in nocturnal cardiac autonomic regulation. To achieve this latter purpose, the pre-ejection period (PEP) and the high-frequency (HF) time-domain measures of heart rate variability (HRV) were estimated as noninvasive markers of cardiac sympathetic and parasympathetic drives, respectively.

We hypothesized that the nocturnal autonomic pattern in essential hypotension is characterized by both sympathetic withdrawal and heightened vagal output, leading to cardiovascular downregulation in hypotensives over the night.

4.1.2 Materials and Method

4.1.2.1 Participants

Fourteen essential hypotensives (23.43 ± 0.62 years) and 14 normotensives (22.21 ± 0.43 years) participated in this study. All subjects were recruited through advertisements placed at the University of Padova. Given the extremely low rate of essential hypotension in men [2, 13, 75], the sample was restricted to women.

By considering the high circadian and day-to-day variability in BP [54, 108, 178], the following screening procedure including multiple office BP readings was applied 1 week prior the experiment. Three sessions were carried out in the following timetables: 9-10 am, 1-2 pm, and 5-6 pm. Each participant underwent all three BP measurement sessions in a randomized order. All subjects abstained from alcohol for 24 h and from food, tobacco and beverages containing caffeine for at least 3 h prior to each BP measurement. After a resting period of 10 min, three readings were taken with 3-min interval in between. BP was measured in sitting position by using a mercury sphygmomanometer, with a standard cuff fitted to the non-dominant upper arm. Korotkoff's phases I and V were used to identify, respectively, systolic BP (SBP) and diastolic BP (DBP) values, with a deflation rate of 2 mmHg/s.

Overall, nine BP measurements were collected for each participant. In order to account for alerting reactions [258], the first reading of each session was discarded, thus the screening SBP and DBP values were derived by averaging six measurements. Subjects were classified as hypotensives if the mean SBP was lower than 100 mmHg and the mean DBP lower than 60 mmHg. Subjects reporting a mean SBP higher than 110 mmHg regardless of DBP were defined as normotensives.

A positive history of hypotensive symptoms (e.g., dizziness, faintness, fatigue) was ensured before enrolling hypotensive participants. Screening procedures also included the administration of the Pittsburgh Sleep Quality Index (PSQI; [48] to assess sleep quality. A cut-off of ≥ 5 was applied to identify sleep disturbances. Lastly, participants also filled out a questionnaire to collect medical and psychiatric anamnesis and investigate habits with regard to smoking, alcohol, caffeine and drugs consumption. In addition, data about weight and height were collected to allow calculation of body mass index (BMI, kg/m^2). Exclusion criteria for both groups were as follows: BMI ≥ 30 kg/m^2; score ≥ 5 on the PSQI; excessive tobacco, alcohol or caffeine consumption; drugs or medications affecting cardiovascular or nervous system assumption; medical or psychiatric diseases.

The experimental protocol was approved by the Ethics Committee of the University of Padova. Each participant signed an informed consent prior to commencement of the study and received 100 Euros for participation.

4.1.2.2 Polysomnography

PSG included electroencephalogram (EEG; O1-A2, O2-A1, C3-A2, C4-A1, F3-A2, F4-A1), electrooculogram (EOG; right EOG-A1, left EOG-A2), electromyogram (EMG; submentalis muscle) and electrocardiogram (ECG; precordial II lead). PSG data were recorded using a computerized system (Siesta, Compumedics, Melbourne, Australia).

Sleep was manually 30-s scored according to American Academy of Sleep Medicine (AASM) criteria [131], in order to obtain the following parameters: sleep onset latency (SOL; min), wake after sleep onset (WASO; min), sleep efficiency (SE; %), amount of rapid eye movement (REM) and non-REM (NREM) sleep (min). For the purpose of the study, sleep onset was defined as the first of 3 consecutive 30-s epochs of any sleep stage.

4.1.2.3 Blood Pressure Monitoring

BP measurements were collected during PSG by means of an automated oscillometric system (Spacelabs 90217; SpaceLabs Medical, Inc., Issaquah, WA), with a cuff of appropriate size fitted to the non-dominant upper arm. The device was set to take BP readings at 10-min intervals. The monitor was previously calibrated against a mercury sphygmomanometer to ensure accuracy.

SBP, DBP and mean BP (MBP; mmHg) were derived and all recorded measurements were manually checked for artifacts.

4.1.2.4 Impedance Cardiography

The impedance signal (Z_0) and the first derivative of pulsatile impedance (dZ/dt) were measured by Impedance Cardiograph (ICG) Minnesota model 304 B (IFM Inc., Greenwich, CT) through standard tetrapolar band electrode configuration, according to guidelines [262]. The two inner (recording) bands were placed around the base of the neck and around the thorax over the tip of the xiphoid process. The two outer (current) bands were positioned around the neck and thorax, at least 3 cm away from each of the recording electrodes. A 4-mA alternating current at 100-kHz was transmitted through the two outer electrodes and Z_0 and dZ/dt signal were recorded from the two inner electrodes and digitized at 500 Hz sampling rate. The samples were 30-s ensemble averaged by a software system (COP-WIN software Bio-Impedance Technology, Chapel Hill, NC) that summed the digitized beat-by-beat waveforms, time synchronized to the R wave of the electrocardiogram, and divided by the number of cardiac cycles, filtering respiratory and movement artifact. The positions of the B- (i.e., the onset of the left-ventricular ejection) and the X- (i.e. the closure of the aortic valve) points in the dZ/dt signal and the Q wave in the ECG were

automatically detected. Moreover, each cardiac cycle was off-line visually inspected and edited when the algorithm failed to correctly detect these points.

HR (bpm) was calculated as the number of heart beats per minute. SV (ml) was derived using the Kubicek equation [155]. CO (l/min) was computed as HR · SV. PEP (ms) was defined as the time interval between the Q wave on the ECG signal and the B-point on the *dZ/dt* signal. Total peripheral resistance (TPR; dyn·s/cm^5) was calculated as (MBP/CO)·80.

4.1.2.5 Heart Rate Variability

An automated algorithm was applied to detect the R-waves on the ECG and compute the interbeat intervals (IBIs). Isolated artifacts, missed and ectopic beats were identified and replaced with interpolated IBIs data.

According to HRV guidelines [277], overall HRV was assessed by computing the standard deviation of normal-to-normal intervals (SDNN; ms). HF variability was determined as the square root of the mean of the squared differences between consecutive normal-to-normal intervals (RMSSD; ms) and the proportion of adjacent normal-to-normal intervals that differed in length by more than 50 ms (pNN50, %). The Kubios HRV Analysis Software 2.0 (Matlab, Kuopio, Finland) was used for the HRV analyses.

4.1.2.6 Study Design

Following the screening procedure, participants were scheduled to undergo two consecutive overnight PSGs in the Psychophysiology Sleep Laboratory of the Department of General Psychology at the University of Padova. The first night allowed for adaptation and no data were analyzed. Subjects were required to refrain from smoking, drinking beverages containing alcohol or caffeine and taking naps the day before and during the day of scheduled PSGs. They were admitted to the laboratory at 10 pm and electrodes and monitoring equipment were placed. Sleep period was set from 12 pm to 8 am, time of scheduled awakening.

Cardiovascular data collection was continuous throughout the night.

4.1.2.7 Data Analysis and Statistics

The first 7 hours after sleep onset were considered for the analyses on physiological measures, selecting only stable sleep periods. Thereby, epochs of either wakefulness or sleep disturbances as arousal or body movements were discarded. Values were then averaged and analyzed in 14 30-min intervals.

All data are expressed as means ± SE. Normality of the distribution was assessed for each variable by Kolmogorov-Smirnov test.

Demographic, screening and PSG data were compared by group using unpaired *t*-tests. To assess the cardiovascular and autonomic activity as a function of time, mixed-design analyses of variance (ANOVAs) consisting of Group by Time were performed on physiological variables.

Newman-Keuls correction for multiple comparisons was applied where appropriate. Partial eta-squared effect size (η^2_p) was reported as measure of effect size. Finally, a stepwise multiple regression analysis was computed to address the relative contribution of sympathetic and parasympathetic branches of neurovegetative system in the nocturnal cardiac activity. A P value < 0.05 was considered as significant for all statistical analyses.

4.1.3 Results

4.1.3.1 Demographic, Screening and Polysomnographic Measures

Comparisons between groups on demographic, screening and PSG data are provided in Table 4.1.

Since BP values were used as the selection criteria for each group, as expected significantly lower screening SBP ($P < 0.001$), DBP ($P < 0.001$) and MBP ($P < 0.001$) were recorded in hypotensives compared to normotensives, whereas groups were comparable with regard to age, BMI and PSQI score. Likewise, hypotensive and normotensive participants did not differ with respect to any of the sleep parameters.

	Hypotensives (n = 14)	*Normotensives (n = 14)*	*t*
Demographics			
Age, yr	23.4 ± 0.6	22.2 ± 0.4	1.61
BMI, kg/m^2	21.6 ± 0.7	23 ± 0.6	-1.52
PSQI	3.5 ± 0.3	3.1 ± 0.3	0.75
Screening BP			
SBP, mmHg	88.8 ± 1.1	114.3 ± 1.2	-15.49***
DBP, mmHg	56.3 ± 1.2	68.5 ± 1.5	-6.59***
MBP, mmHg	67.1 ± 1	83.8 ± 1.3	-10.35***
PSG			
SOL, min	13 ± 2.3	17.1 ± 5.3	-0.72
WASO, min	30.2 ± 6.3	40 ± 7	-1.04
SE, %	91 ± 1.5	88.1 ± 2.2	1.11
NREM sleep amount, min	333.3 ± 7.7	333.5 ± 7.4	-0.02
REM sleep amount, min	103.5 ± 7.2	89.4 ± 6.2	1.49

Values are mean ± SE. Degree of freedom = 26.
*** $P < 0.001$
BMI, body mass index; PSQI, Pittsburgh Sleep Quality Index; BP, blood pressure; SBP, systolic BP; DBP, diastolic BP; MBP, mean BP; PSG, polysomnography; SOL, sleep onset latency; WASO, wake after sleep onset; SE, sleep efficiency; NREM, non-rapid eye movement sleep; REM, rapid eye movement sleep.

Table 4.1. Demographic, screening and polysomnographic data.

4.1.3.2 Blood Pressure Measures

Results of ANOVAs performed on all cardiovascular measures are summarized in Table 4.2.

As shown by the significant main effects of Group, ANOVAs revealed lower SBP ($P < 0.001$), DBP ($P < 0.05$) and MBP ($P < 0.01$) in hypotensives compared with normotensives during all night. The SBP also decreased in both groups from sleep onset throughout the night ($P < 0.05$). A Time effect was found also for MBP ($P < 0.05$), as well as a significant interaction Group × Time ($P < 0.01$), revealing that normotensives exhibited a marked drop in MBP from sleep onset across the night, followed by a rise approaching morning, whereas the values remained unchanged in hypotensive sufferers over time. The interaction Group × Time observed in DPB ($P < 0.05$) displayed the same profile as that of MBP. Nocturnal temporal courses of BP values by group are depicted in Figure 4.1 and Figure 4.2.

			Group		*Time*		*Group × Time*	
	Hypotensives (n = 14)	*Normotensives (n = 14)*	*F (df=1,26)*	η^2_p	*F (df=13,338)*	η^2_p	*F (df=13,338)*	η^2_p
BP								
SBP, mmHg	91 ± 1.5	104.6 ± 2.6	20.43***	0.44	1.98*	0.07	1.56	0.06
DBP, mmHg	54.9 ± 1.5	60.6 ± 2	5.35*	0.17	1.64	0.06	2.1*	0.07
MBP, mmHg	68.1 ± 1.4	75.8 ± 1.9	10.63**	0.29	1.99*	0.07	2.68**	0.09
ICG								
HR, bpm	63.8 ± 1.8	72.7 ± 2.6	7.66**	0.23	5.83***	0.18	1.06	0.04
SV, ml	92.8 ± 4.1	94.7 ± 2.4	0.16	0.01	13.45***	0.34	1.39	0.05
CO, l/min	5.9 ± 0.3	6.9 ± 0.3	5.25*	0.17	14.4***	0.36	1.59	0.06
TPR, dyn s/cm^5	969.2 ± 53	913.3 ± 38.2	0.73	0.03	8.9***	0.25	2.06*	0.07
PEP, ms	99.4 ± 3.6	86.1 ± 4.3	5.72*	0.18	5***	0.16	1.52	0.06
HRV								
SDNN, ms	92.6 ± 11	72.2 ± 10.1	1.87	0.07	3.62***	0.12	1.06	0.04
RMSSD, ms	86.2 ± 15	62.2 ± 14.5	1.32	0.05	2.08*	0.07	0.39	0.01
pNN50, %	40.8 ± 6.3	23.4 ± 4.5	5*	0.16	2.48**	0.09	0.92	0.03

Values are means ± SE. Nighttime means are averages of the first 7-hours of sleep after sleep onset.
df = degree of freedom. η^2_p = partial eta-squared
* $P < 0.05$; ** $P < 0.01$; *** $P < 0$ .001
BP, blood pressure; SBP, systolic BP; DBP, diastolic BP; MBP, mean BP; ICG, impedance cardiography; HR, heart rate; SV, stroke volume; CO, cardiac output; TPR, total peripheral resistance; PEP, pre-ejection period; HRV, heart rate variability; SDNN, standard deviation of normal-to-normal (NN) intervals; RMSSD, square root of the mean of the squared differences between consecutive NN intervals; pNN50, proportion of adjacent NN intervals that differed in length by more than 50 ms.

Table 4.2 ANOVAs results for blood pressure, impedance cardiography and heart rate variability measures.

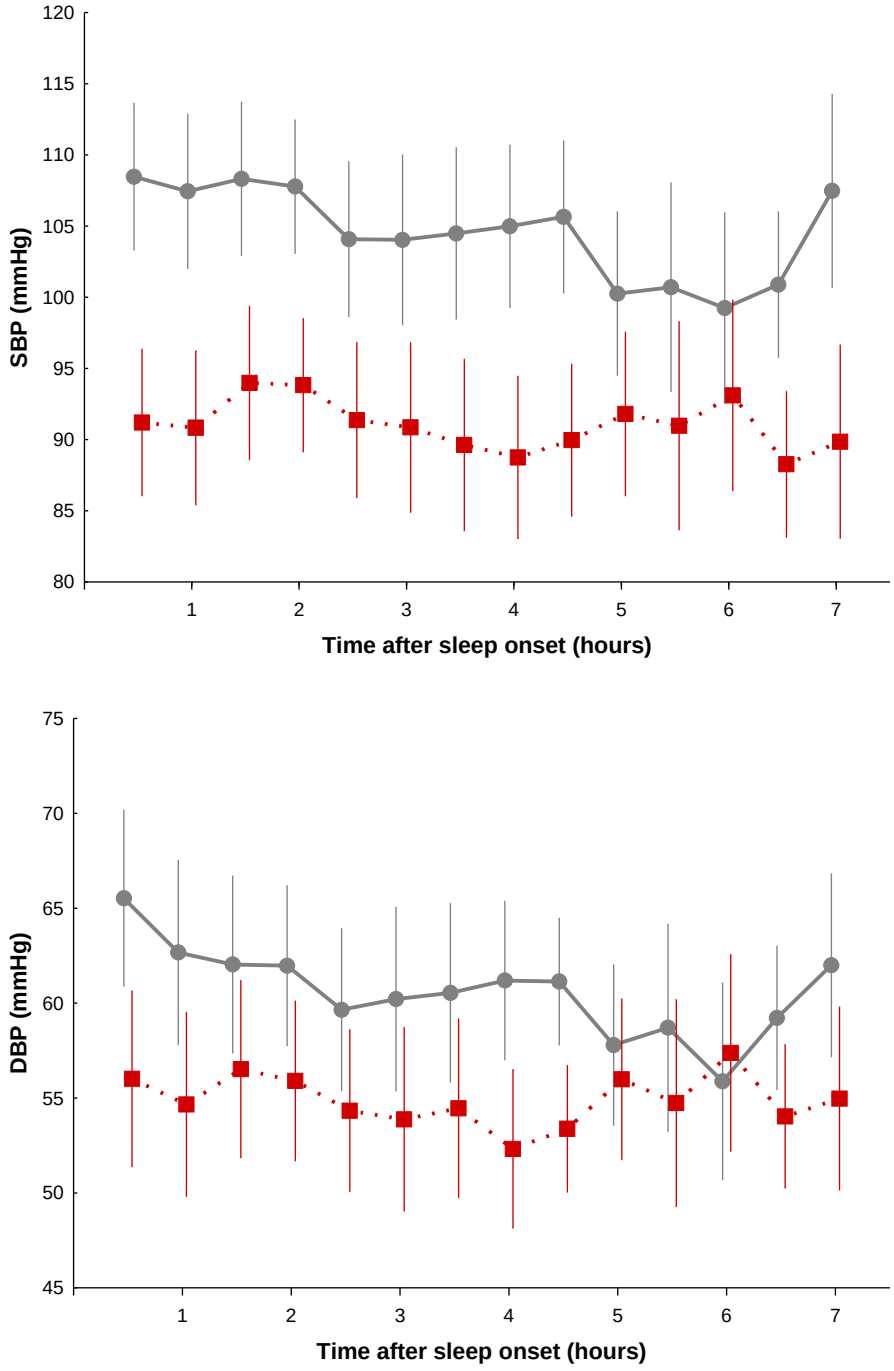

Figure 4.1 Nocturnal temporal profiles of systolic blood pressure (SBP; upper panel) and diastolic blood pressure (DBP; lower panel) in hypotensives and normotensives. Values are means ± SE. Data are 30-min averages of the first 7-hours after sleep onset. Grey lines are normotensives, red lines are hypotensives.

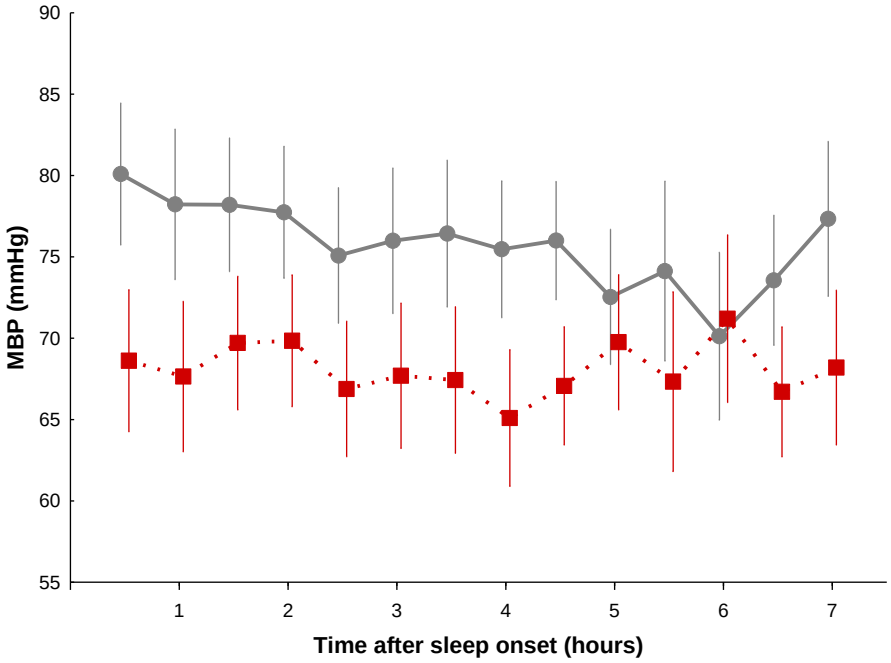

Figure 4.2 Nocturnal temporal profiles of mean blood pressure (MBP) in hypotensives and normotensives. Values are means ± SE. Data are 30-min averages of the first 7-hours after sleep onset. Grey lines are normotensives, red lines are hypotensives.

4.1.3.3 Impedance Cardiography Measures

As illustrated in Figure 4.3, hypotensives had significantly lower HR than normotensives ($P < 0.01$). Time effect also indicated a progressive reduction in HR across the night in all sample ($P < 0.001$). CO exhibited a similar pattern, as it was reduced in essential hypotension group ($P < 0.05$) and continuously decreased during sleep in both groups ($P < 0.001$). Regarding SV, a marked fall from sleep onset over time was detected in all sample ($P < 0.001$). Differently, TPR augmented during the night ($P < 0.001$), but the interaction Group × Time showed that, whereas controls reported a non significant increase, hypotensives displayed a significant progressive rise ($P < 0.05$). Lastly, PEP was found to be higher in hypotensive sufferers than in normotensives ($P < 0.05$) and to enhance throughout the night in both groups ($P < 0.001$) (Figure 4.4).

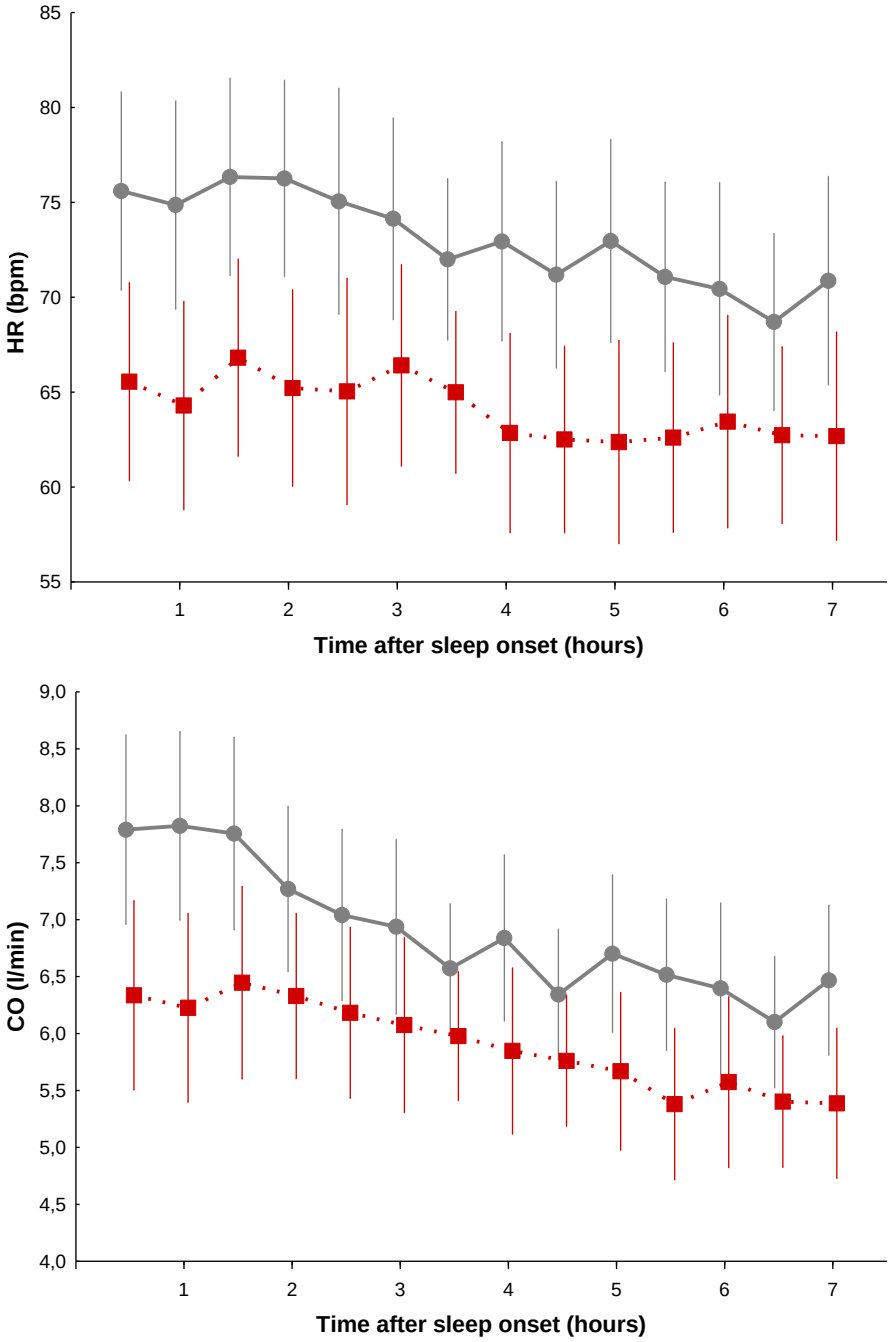

Figure 4.3 Nocturnal temporal profiles of heart rate (HR, upper panel) and cardiac output (CO lower panel) in hypotensives and normotensives. Values are means ± SE. Data are 30-min averages of the first 7-hours after sleep onset. Grey lines are normotensives, red lines are hypotensives.

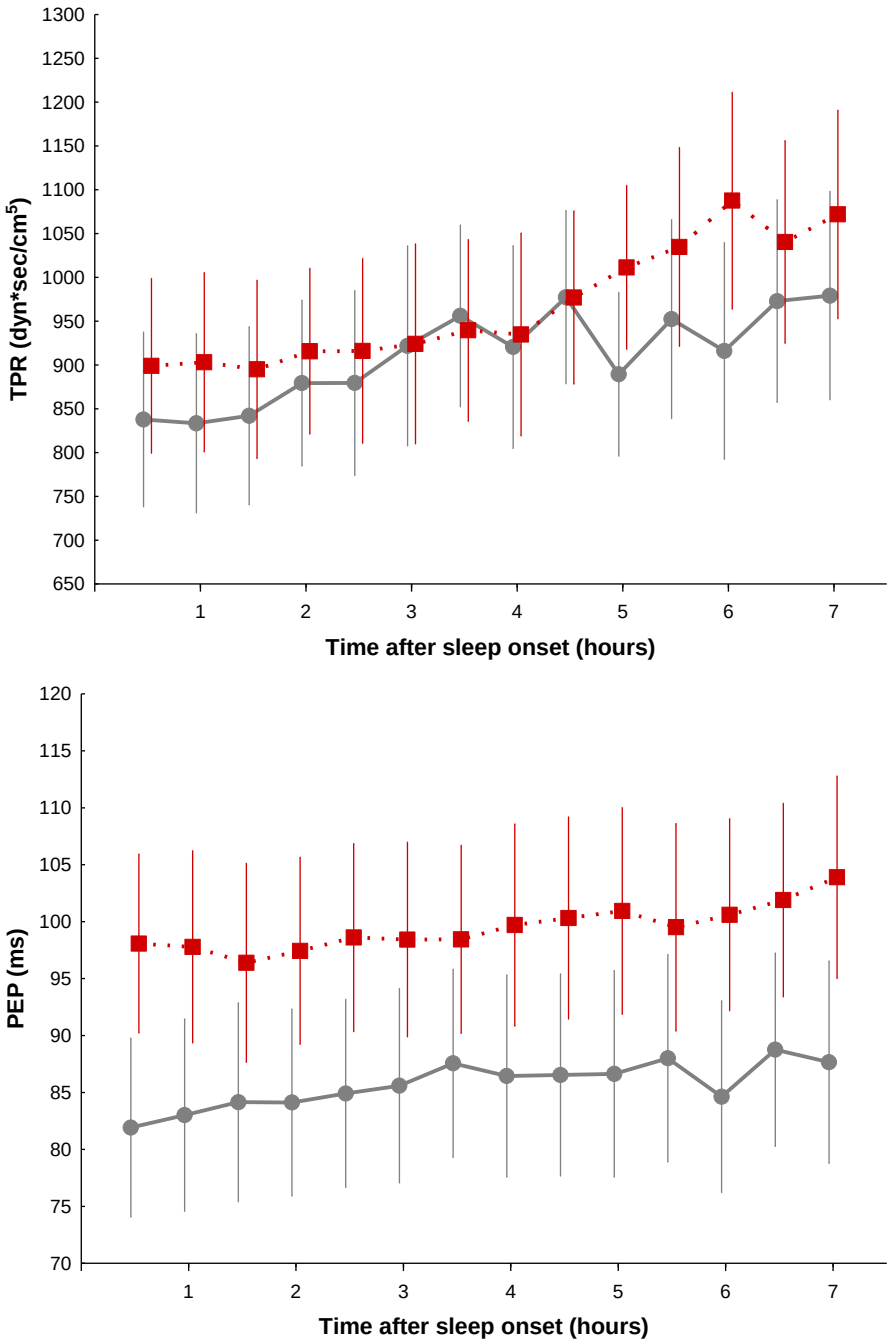

Figure 4.4 Nocturnal temporal profiles of total peripheral resistance (TPR, upper panel) and pre-ejection period (PEP, lower panel) in hypotensives and normotensives. Values are means ± SE. Data are 30-min averages of the first 7-hours after sleep onset. Grey lines are normotensives, red lines are hypotensives.

4.1.3.4 Heart Rate Variability Measures

Considering HRV measures, a significant Time main effect characterized by a gradual increase over the sleep period in both groups was observed for all variables (SDNN, $P < 0.001$; RMSSD, $P < 0.05$; pNN50, $P < 0.01$). The pNN50 was also found to be significantly more elevated in hypotensive participants in comparison with controls, as seen in Figure 4.5 ($P < 0.05$).

A stepwise multiple regression analysis was fitted to the HR values to assess the relative contribution of the sympathetic and parasympathetic system to cardiac activity during the night. Dependent variables were age, BMI, screening MBP, PEP (as index of cardiac sympathetic drive) and pNN50 (as measure of cardiac vagal tone). The model obtained for normotensives (adjusted R^2= 0.422, $F_{1,12}$ = 10.48, P < 0.01) identified the pNN50 (β = −0.683, P < 0.01) as the only significant determinant of HR in this group. Differently, in hypotensive group, both pNN50 (β = −0.542, P < 0.05) and PEP (β = −0.468, P < 0.05) resulted to be significant in a model with an adjusted R^2 = 0.622 ($F_{2,11}$ = 11.7, P < 0.01).

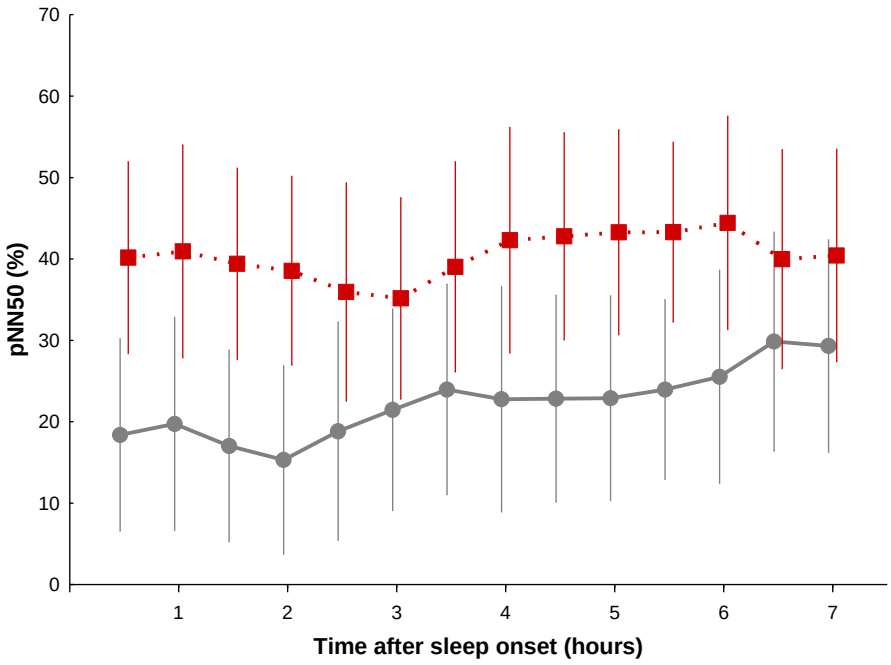

Figure 4.5 Nocturnal temporal profiles of proportion of adjacent NN intervals that differed in length by more than 50 ms (pNN50) in hypotensives and normotensives. Values are means ± SE. Data are 30-min averages of the first 7-hours after sleep onset. Grey lines are normotensives, red lines are hypotensives.

4.1.4 Discussion

The analysis of cardiovascular parameters over the sleep period disclosed markedly lower BP in hypotensive individuals than did controls. Since TPR did not differ between groups, lowered BP values were likely due to the decreased CO which resulted in turn by diminished HR. These findings are in accordance with previous studies that assessed hemodynamics in essential hypotension at rest [2, 82].

As expressed by augmented PEP values, a reduced cardiac sympathetic output was recorded in hypotensives. On the other hand, vagal-related HRV index (i.e., pNN50) also revealed

heightened cardiac vagal tone in hypotensives compared with normotensives during all night, suggesting that the parasympathetic system is also affected in essential hypotension.

Since the regression analyses disclosed that nocturnal fluctuations in HR in normotensives were mainly mediated by the parasympathetic system, in agreement with literature [320], both autonomic branches contributed to modulate the cardiac activity during sleep in hypotensives, hence supporting the speculation that the diminished cardiac activity observed in hypotensive group reasonably reflects both sympathetic and parasympathetic dysregulation.

It is also noteworthy that the different physiological pattern we observed between groups is unlikely to be ascribed to differences in sleep, since the PSG parameters were found to be comparable.

Regarding the overnight time course, all subjects exhibited the typical nocturnal cardiac autonomic regulation, with a progressive shift from sympathetic toward parasympathetic prevalence, as indicated by gradual lengthening in PEP combined with parallel augmentation in HF HRV measures, respectively [31, 46, 47, 192]. Consistently, HR and SV felt continuously from sleep onset throughout the sleep period in both groups, leading to a reduction in CO, in line with prior investigations [46, 47, 146].

Nonetheless, analysis of temporal profile also disclosed interesting differences between groups. The overall BP temporal profile in normotensives was as expected by the literature review [186, 250, 312], with a fall in BP conceivably due to a drop in CO since TPR did not change. On the contrary, hypotensives displayed a blunted reduction only in SBP whereas DBP and MBP remained unchanged during sleep. The loss of nocturnal variation in BP in essential hypotension appears to be owned by both CO and TPR changes, since as CO decreased, TPR increased throughout the night counterbalancing the fall in CO and hence maintaining BP at steady values. We can hypothesize that the parallel rise in TPR occurred as a compensatory response for the progressive drop in CO which otherwise might have resulted in an excessive and thus potentially harmful nocturnal BP fall in this population. Keeping in mind the progressive lowering in sympathetic drive along the night, the augmentation in TPR appears discrepant. However, although a consistency in discharge over targets can be assumed, the SNS drive has been also demonstrated to vary substantially in different districts [24, 173, 251]. Therefore, the reduction in SNS outflow we observed on heart might not have occurred on vasculature. In addition, beyond the direct sympathetic modulation, it should be taken into account that several factors are involved in regulating the vasculature, as reviewed in the Chapter 1. In particular, as prior reports have shown an enhanced baroreflex sensitivity in essential hypotension [79], an overresponsivity of this reflex could have contributed to BP regulation by rising the TPR to

contrast the decrease in CO [120]. This finding also challenges the hypothesis recently advanced by Duschek and coworkers [82] that the nature of essential hypotension primarily involves the cardiac activity rather than the vascular one, postulated by observing a diminished CO in absence of differences in TPR. Indeed, in spite of a lack of group differences in TPR, a contribution of vascular factors cannot be completely ruled out, since hypotensives reported an involvement of this variable in modulating the BP throughout the night.

In sum, in the present study we documented that the nocturnal autonomic pattern exhibited by essential hypotension sufferers showed both sympathetic hypoactivation and vagal hyperactivity, resulting in overnight blunted hemodynamic in hypotensive compared to normotensive individuals.

4.2 Experiment II

4.2.1 Introduction

After the exploratory analysis carried out in the *Experiment I* over the nocturnal cardiovascular profile in essential hypotension, the focus has been turned specifically on the sleep structure exhibited by this population.

Within sleep, sleep stages entail different autonomic and hemodynamic activity. NREM sleep stages show a parasympathetic prevalence which mediates a cardiovascular downregulation, while a shift toward sympathetic control occurs in REM phase, together with elevation in physiological parameters (e.g., Ref. 271, 275, 299, 319).

Several cardiovascular diseases display abnormalities in the sleep pattern. [244, 303, 315] . In particular, hypertensive sufferers exhibit increased nocturnal awakenings and low amount of slow wave sleep (SWS) and REM sleep [179, 219]. The changes in physiological activity across the sleep stages can be affected as well, in terms of lower reduction in sympathetic drive in NREM sleep in hypertensives compared to normotensives [76].

The purpose of the *Experiment II* was twofold.

Firstly, in lights of the subjective sleep complaints referred by hypotensives [307, 309] and the lack of studies surveying sleep pattern in essential hypotension, the study was targeted at evaluating the sleep quality and quantity in this condition more in depth, by describing the sleep parameters through polysomnographic recording. Although no differences in the main PSG measures between hypotensives and normotensives were observed in our previous Experiment, we aimed at clarify whether a thorough examination identified the postulated sleep alterations.

Given the notably fluctuations in physiological parameters occurring with the transition to different sleep stages, sleep can provide the framework to survey the autonomic dysfunction in essential hypotension. Thus, our second purpose was to analyze the cardiovascular and autonomic patterns as a function of the sleep stage to assess whether hypotensives have a different regulation across sleep stages compared with normotensives. The HF power band of HRV and low frequency (LF) to HF (LF/HF) ratio were employed to assess the cardiac autonomic drive, hypothesizing a reduced modulation across sleep stages in hypotensives sufferers.

Moreover, since a diminished myocardial contractility can be assumed in this population, the systolic time intervals left ventricular ejection time (LVET) and total electro-mechanical systole (EMS) were also derived.

4.2.2 Materials and Method

4.2.2.1 Participants

Fifteen hypotensives (23.6 ± 2.23 yr) and 15 normotensives (22.27 ± 1.58 yr) took part to the study. All subjects were women because of the higher prevalence of hypotension in the young female population [2, 13, 75]. The participants were recruited through advertisements posted at the faculties of the University of Padova.

In order to assign the participants to the groups, screening sessions were performed at least 1 week before the nocturnal recording. BP readings were taken in a seated position using a standard sphygmomanometer. During each screening session, after a resting period of 10 min, three consecutive BP readings, separated by 5-min rest intervals, were taken. These sessions were conducted on three different days at three different times to evaluate the reliability of the measurements independent of the circadian variations of BP. Participants with both mean SBP below 100 mmHg and DBP below 60 mmHg were assigned to the hypotensives group, while participants with a mean SBP of between 110 and 130 mmHg were enrolled as normotensives.

In addition, hypotensives had to report subjective complaints typically related to the condition of essential hypotension (e.g. fatigue, giddiness). For both groups, exclusion criteria were BMI (kg m^{-2}) $\geq$ 30, scores higher than 5 on the PSQI [48], smoking, use of psychoactive medication or drugs, medical and/or psychiatric conditions, and shift work or time-zone travels in the six months prior to the study.

All participants were asked to refrain from alcohol and caffeinated beverages for 3 h prior to the screening sessions and for 24 h prior to the experimental sessions. All participants were volunteers and informed about the purpose of the study, and they gave written informed consent. They were paid €100 for their participation. The study protocol was approved by the Ethic Committee of the Department of Psychology.

4.2.2.2 Polysomnography

Sleep recording was performed using a Siesta 802 PSG acquisition system (Compumedics, Abbotsford, Australia). It consisted of EEG (O1-A2, O2-A1, C3-A2, C4-A1, F3-A2, F4-A1), EOG (right EOG-A1, left EOG-A2), EMG (submentalis muscle), ECG (precordial II lead), thoracic and abdominal respiratory belts, oronasal thermistor and pulse oximeter.

Sleep stages (Wake, N1, N2, N3, REM) were manually scored by an experienced scorer at consecutive 30-s epochs in accord with the AASM scoring rules [131].

The following sleep parameters were computed: total recording time (TRT; min), which was fixed for both groups at 480 min, from midnight to 8 am, total sleep time (TST; min), SE (%); SOL (min), REM latency (min), WASO (min), and duration of each sleep stage (N1, N2, N3, and REM; min).

4.2.2.3 Blood Pressure Monitoring

SBP (mmHg) and DBP (mmHg) were continuously oscillometrically recorded by means of the a blood pressure monitoring device (Spacelabs 90217; SpaceLabs Medical, Inc., Issaquah, WA), every 10 min from 12 am to 8 am. The maximum cuff pressure was set at 150 mmHg to avoid possible nocturnal awakenings due to the high pressure applied on the arm.

4.2.2.4 Impedance Cardiography

LVET (ms) and EMS (ms) were 30-s ensemble averages collected by the Minnesota ICG Model 304 B (IFM Inc., Greenwich, CT, USA) with a standard tetrapolar band electrode configuration [262]. A constant sinusoidal alternating current (4 mA, 100 kHz) was transmitted through the thorax between the outer electrodes, and basal impedance (Z_0) and rate of change in the impedance waveform on a given beat (*dZ/dt*) were estimated from the inner electrodes. The position of the B-point (opening of the aortic valve and onset of left-ventricular ejection) and X-point (closing of the aortic valve and end of left ventricular ejection) in the *dZ/dt* signal and the onset of the Q-wave (onset of electromechanical systole) in the ECG signal were detected automatically by COP-WIN software (Bio-Impedance Technology, Chapel Hill, NC, USA). Finally, the exact position of these points was visually checked and manually corrected where necessary. LVET was measured as the time interval from the *dZ/dt* B-point to the *dZ/dt* X-point. EMS was considered the time interval from the onset of the ECG Q-wave to the *dZ/dt* X-point.

4.2.2.5 Heart Rate Variability

IBIs were obtained from the ECG recording. R-waves were automatically detected, visually checked, and manually adjusted where necessary. Subsequently, IBIs were computed by the Sleep Research System (SRS) Analysis Software 5.1 (Sleep Research System, School of Behavioral Science, University of Melbourne, Australia), and power spectrum analysis of HRV was performed on each 2-min artefact-free data epoch of stable sleep selected for analysis (see the Section 4.2.2.7). IBIs were first re-sampled (4 Hz) and in order to remove the slow non-stationary trend before analysis, a third-order polynomial filter was applied. The total power spectrum density (0-0.5 Hz) was subdivided into 0.02 Hz bands. An algorithm searched for the

greatest value in the frequency bands, respectively from 0.03 to 0.15 Hz for the identification of the LF component and from 0.15 to 0.40 Hz for the identification of the HF component. The absolute integrate power (arbitrary units) was quantified for both the LF and HF bands by the area between the first frequency bands on either side of the peak to fall to 50% of the peak [287]. The following measures were obtained: absolute power in the bands comprising the HF peak (HF_a), as a marker of the parasympathetic influence on the myocardium, and LF/HF_{ratio}, as an index of sympathovagal balance (absolute power in the bands comprising the LF peak, divided by HF_a). Since the HRV data were not normally distributed, a logarithmic transformation was used prior to analysis, thus the $LogHF_a$ and $LogLF/HF_{ratio}$ were obtained.
HR (bpm) was also derived from the ECG.

4.2.2.6 Study Design

Participants spent two consecutive nights of PSG recording at the Psychophysiology Sleep Laboratory, University of Padova, in a quiet, temperature-controlled and soundproof room. The first night allowed for adaptation, thus data obtained from that night were not analyzed. Subjects were admitted to the laboratory at 8 pm, and electrodes were applied. Afterward, they were allowed to engage in quiet activities, such as reading books, talking, or watching TV until 11.30 pm, when they were asked to go to bed. Sleep time was set from midnight (lights off) to 8 am (lights on). Data were continuously recorded throughout the night.

4.2.2.7 Data Analysis and Statistics

In order to obtain stable ICG and HRV measures reflecting a specific sleep stage, 2-min epochs were identified and selected throughout the PSG recording, according to specific rules [287]. The 2 min preceding the epoch and the 2-min epoch selected were required to be free of artefacts, without sleep stage transitions during the 2 min before the epoch end the epoch itself. N1 and Wake (after sleep onset) epochs were excluded from the analysis. Finally, once an epoch was identified, another epoch (falling in the same sleep stage) was not identified for further 5 min. For more details, see the Ref. [287].
A BP recording was assigned to a sleep stage if the minute preceding and following the BP reading and the 30-s epoch that correspond to the BP value were of the same sleep stage and were arousal free, otherwise the measure was discarded.
Sleep parameters, demographic variables, and nocturnal cardiovascular indexes were compared with independent *t*-tests by group. A 2 (between-group: hypotensives and normotensives) × 4 (within-sleep stage: Wake, N2, N3, and REM) analysis of covariance (ANCOVA) was applied to

the mean values of the BP, ICG, and HRV indexes, using adjusted BMI (BMI_{adj}) as a covariate. BMI was corrected in order to protect the covariate from altering the main effect of the repeated measure, calculating the mean BMI and subtracting the BMI from the mean BMI [279]. Newman-Keuls post-hoc comparisons were performed on the significant effects, and the Geisser-Greenhouse correction was applied when appropriate but non-adjusted degree of freedom are reported. Partial eta-squared effect size (η^2_p) was considered as measure of effect size.

Pearson's correlation coefficients were determined for each group to investigate the relationship between BP screening values and nocturnal BP measures. In order to explore the relation between the objective quality of sleep and physiological activation, correlations were also performed between BP screening values and SE. For all statistical analyses, the probability level was set at $P < 0.05$ for significance.

4.2.3 Results

4.2.3.1 Demographic and Screening Measures

BP screening values, BMI, age, and PSQI scores are reported in Table 4.3. Since it was used as selection criterion, the BP values were higher in hypotensives than in normotensives ($P < 0.001$ for SBP, DBP and MBP). Hypotensives displayed also lower BMI than did controls ($P < 0.001$).

	Hypotensives (n = 15)	*Normotensives (n = 15)*	*t*
Demographics			
Age, yr	23.6 ± 2.2	22.3 ± 1.6	1.89
BMI, kg/m^2	20.7 ± 2	23.03 ± 2.3	-2.97**
PSQI	3.7 ± 1.3	3.2 ± 1.2	1.02
Screening BP			
SBP, mmHg	88 ± 3.5	114.3 ± 4.5	-17.98***
DBP, mmHg	55.7 ± 3.8	68.7 ± 5.3	-7.72***

Values are mean ± SD. Degree of freedom = 28.
** $P < 0.01$; *** $P < 0.001$
BMI, body mass index; PSQI, Pittsburgh Sleep Quality Index; BP, blood pressure; SBP, systolic BP; DBP, diastolic BP.

Table 4.3 Blood pressure screening and demographic variables.

4.2.3.2 Polysomnographic Measures

No significant group differences were observed in any of the objective sleep parameters (Table 4.4).

	Hypotensives (n = 15)	*Normotensives (n = 15)*	*t*
TST, min	426 ± 42	427 ± 35	-0.02
SE, %	89 ± 9	89 ± 7	-0.02
SOL, min	14 ± 7	11 ± 11	0.63
REM latency, min	105 ± 83	95 ± 41	0.38
WASO, min	40 ± 41	42 ± 34	-0.14
N1 sleep amount, min	32 ± 10	40 ± 14	-1.78
N2 sleep amount, min	201 ± 30	193 ± 32	0.76
N3 sleep amount, min	96 ± 20	103 ± 24	-0.84
REM sleep amount, min	96 ± 29	91 ± 23	0.61

Values are mean ± SD. Degree of freedom = 28.
TST, total sleep time; SE, sleep efficiency; SOL, sleep onset latency; REM, rapid eye movement sleep; WASO, wake after sleep onset.

Table 4.4 Polysomnographic indices.

4.2.3.3 Cardiovascular Measures

Mean cardiovascular values and *t*-tests comparisons are reported in Table 4.5.

ANCOVAs showed significant Group main effects for SBP ($F_{1,27} = 24.26$; $P < 0.001$; $\eta^2_p = 0.47$) and DBP ($F_{1,27} = 9.10$; $P < 0.01$; $\eta^2_p = 0.25$), indicating lower BP across the night in hypotensives compared to normotensives.

Significant Sleep stage main effects were also observed for SBP ($F_{3,81} = 34.45$; $P < 0.001$; $\eta^2_p = 0.56$) and DBP ($F_{3,81} = 40.69$; $P < 0.001$; $\eta^2_p = 0.60$). As revealed by post-hoc comparisons, a decrease in BP values from Wake to sleep occurred in both groups.

The nocturnal BP pattern for the two groups is displayed in Figure 4.6.

	Wake			*N2*			*N3*			*REM*		
	Hypotensives	*Normotensives*	*t*	*Hypotensives*	*Normotensives*	*t*	*Hypotensives*	*Normotensives*	*t*	*Hypotensives*	*Normotensives*	*t*
BP												
SBP, mmHg	98.7 ± 10.5	117.9 ± 9.7	-5.21***	88.9 ± 6.2	103.8 ± 10.1	-4.87***	88.4 ± 6.7	104.3 ± 11.4	-4.65***	90.5 ± 7.6	106.3 ± 10.5	-4.75***
DBP, mmHg	61.6 ± 10.3	71.9 ± 9.3	-2.87***	52.3 ± 5.2	60.3 ± 6.9	-3.60***	51.9 ± 7.4	60.4 ± 9.5	-2.74**	54.3 ± 7.9	61.9 ± 7.5	-2.71**
ICG												
HR, bpm	69.2 ± 7.1	76 ± 10.8	-2.04*	62.4 ± 6.7	70.6 ± 12.3	-2.28*	64.3 ± 7.4	64.3 ± 72.9	-2.38*	67.8 ± 7.2	74 ± 12.3	-1.66
LVET, ms	324.2 ± 20.1	306.4 ± 26.1	2.08*	335.3 ± 22.3	315.3 ± 25.3	2.27*	331.6 ± 22. 9	310.8 ± 23.3	2.48*	327.3 ± 21.1	311.1 ± 25.8	1.89
EMS, ms	414.2± 23.5	392.2 ± 28.5	2.30*	429.1 ± 26.6	403.7 ± 30.1	2.45*	424.3 ± 26.2	397. 7 ± 27.6	2.71*	420.4 ± 25.2	399.1 ± 29.8	2.12*
HRV												
$LogHF_a$	2 ± 0.49	1.91 ± 1.32	0.38	2.29 ± 0.51	1.99 ± 0.59	1.45	2.19 ± 0.56	1.86 ± 0.69	1.43	1.82 ± 0.63	1.50 ± 0.70	1.07
$LogLF/HF_{ratio}$	0.18 ± 0.53	0.01 ± 0.39	1.01	-0.39 ± 0.31	-0.13 ± 0.39	-2.09*	-0.55 ± 0.35	-0.31 ± 0.38	-1.77*	0.15 ± 0.33	0.30 ± 0.39	-1.10

Values are means ± SD.
Degree of freedom = 28.
*P< 0.05, ** P < 0.01; *** P < 0.001.
BP, blood pressure; SBP, systolic BP; DBP, diastolic BP; ICG, impedance cardiography; HR, heart rate; LVET, left ventricular ejection time; EMS; electro-mechanical systole; HRV, heart rate variability; $LogHF_a$, logarithm of high frequency; $LogLF/HF_{ratio}$, logarithm of low frequency to logarithm of high frequency.

Table 4.5 Blood pressure, impedance cardiography and heart rate variability measures across sleep stages.

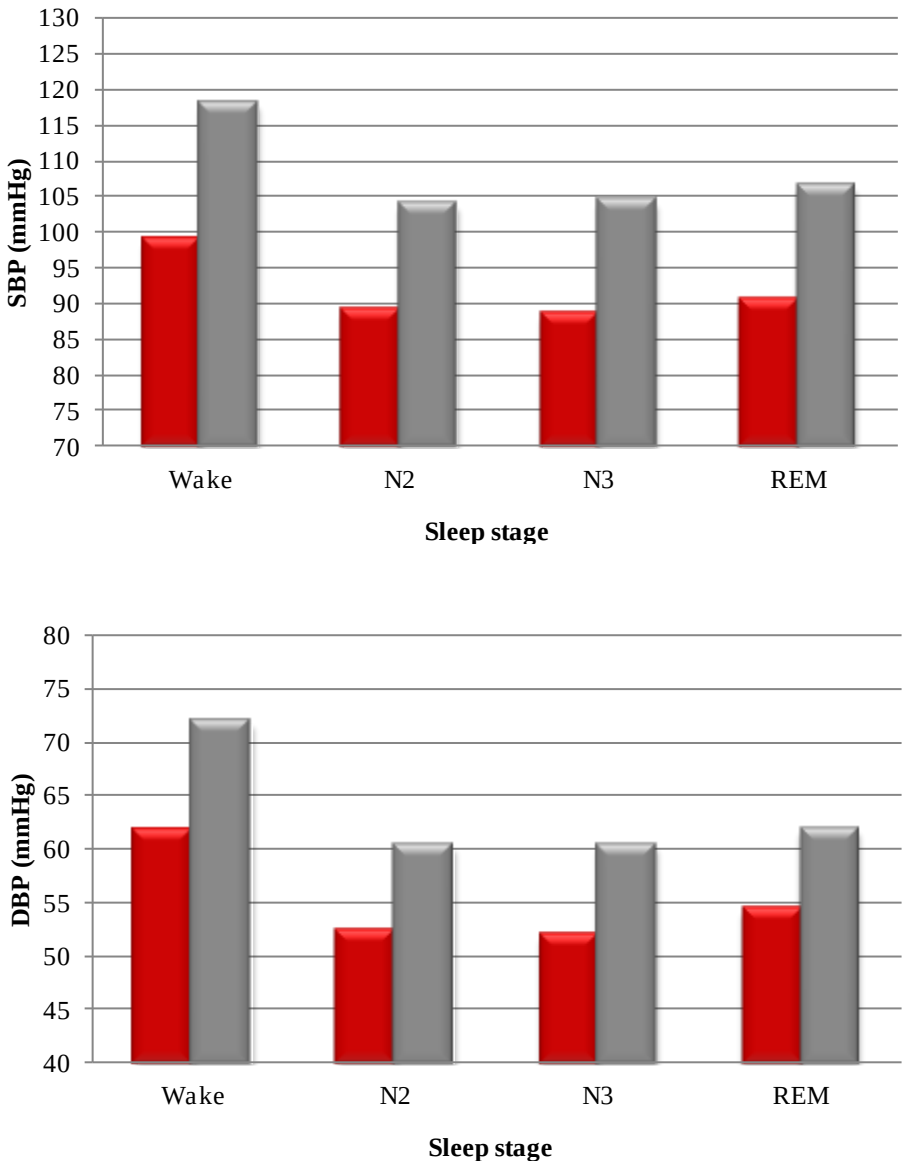

Figure 4.6 Mean systolic blood pressure (SBP, upper panel) and diastolic blood pressure (DBP, lower panel) patterns in hypotensives and normotensives across sleep stages. Hypotensives are in red, normotensives are in grey.

ANCOVAs indicated reduced HR ($F_{1,27} = 4.44$; $P < 0.05$; $\eta^2_p = 0.14$) and prolonged EMS ($F_{1,27} = 7.64$; $P < 0.01$; $\eta^2_p = 0.22$) in hypotensives compared to normotensives (Figure 4.7-Figure 4.8). A Group main effect approaching significance ($P = 0.06$) was also observed for LVET. As displayed by *t*-tests, hypotensives exhibited longer LVET in Wake, N2 and N3 stages than did controls.

A Sleep stage main effect was also found for HR ($F_{3,81} = 10.63$; $P < 0.001$; $\eta^2_p = 0.28$), LVET ($F_{3,81} = 6.62$; $P < 0.05$; $\eta^2_p = 0.20$) and EMS ($F_{3,81} = 9.08$; $P < 0.01$; $\eta^2_p = 0.25$). Post-hoc tests displayed a reduction in HR from Wake to sleep in both groups. Furthermore, HR values were higher in REM than in N2 and N3 sleep stages. LVET and EMS increased from Wake to stable

sleep in both groups. Moreover, LVET and EMS values were higher in REM than in N2 in both groups.

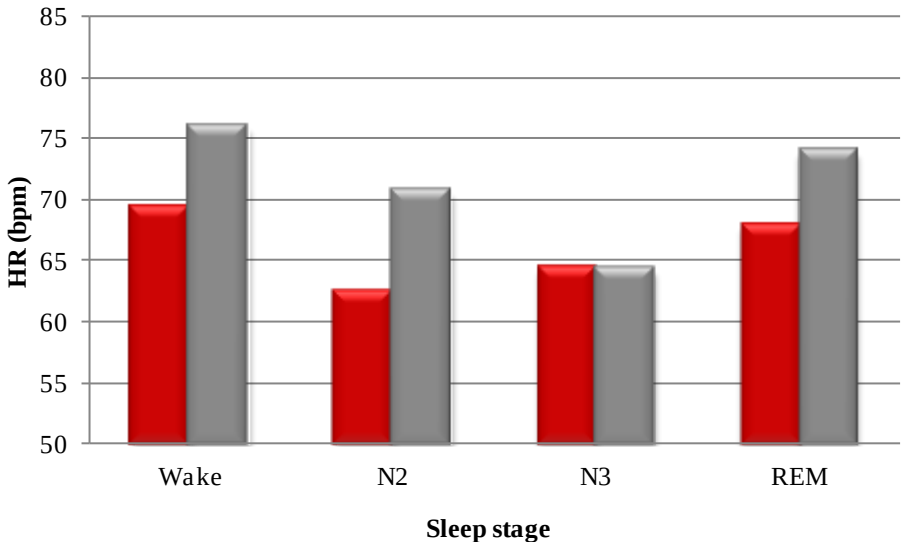

Figure 4.7 Mean heart rate (HR) patterns in hypotensives and normotensives across sleep stages. Hypotensives are in red, normotensives are in grey.

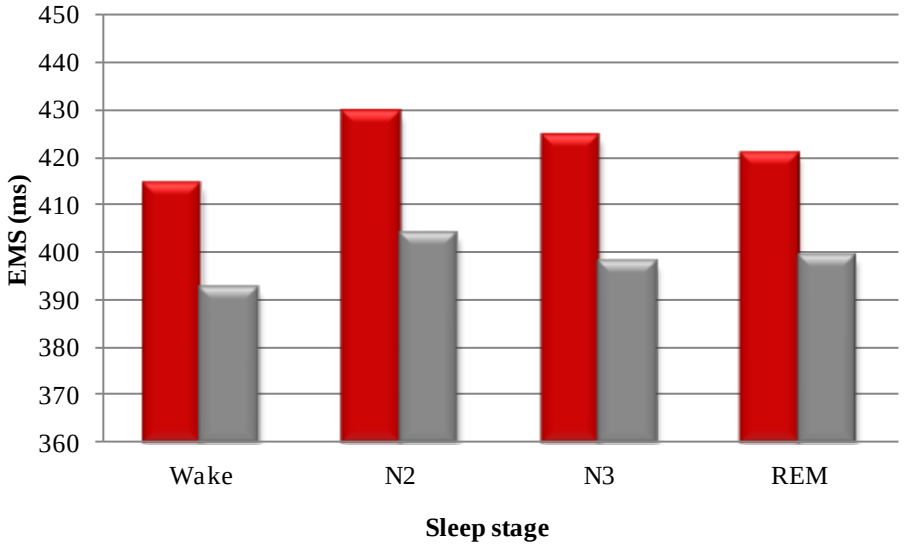

Figure 4.8 Mean electro-mechanical systole (EMS) pattern in hypotensives and normotensives across sleep stages. Hypotensives are in red, normotensives are in grey.

The ANCOVAs applied to the HRV indexes resulted in significant Sleep stage main effects for $LogHF_a$ ($F_{3,81} = 8.88$; $P < 0.01$; $\eta^2_p = 0.25$) and for $LogLF/HF_{ratio}$ ($F_{3,81} = 32.86$; $P < 0.001$; $\eta^2_p = 0.55$) (Figure 4.9). Post-hoc comparisons showed an increase in $LogHF_a$ values from Wake to N2 and from REM to N2 and to N3 and a decrease from Wake to REM in both groups. A reduction

in LogLF/HF_{ratio} values occurred from Wake to N2 and to N3, from REM to N2 and to N3, and from N2 to N3 in both groups.

Group comparisons assessed by *t*-tests showed in hypotensives significantly reduced LogLF/HF_{ratio} values, i.e. lower sympathovagal balance, in N2 and N3, whereas a trend toward significance ($P = 0.07$) was found for $LogHF_a$ within the same sleep stages (see Table 4.5).

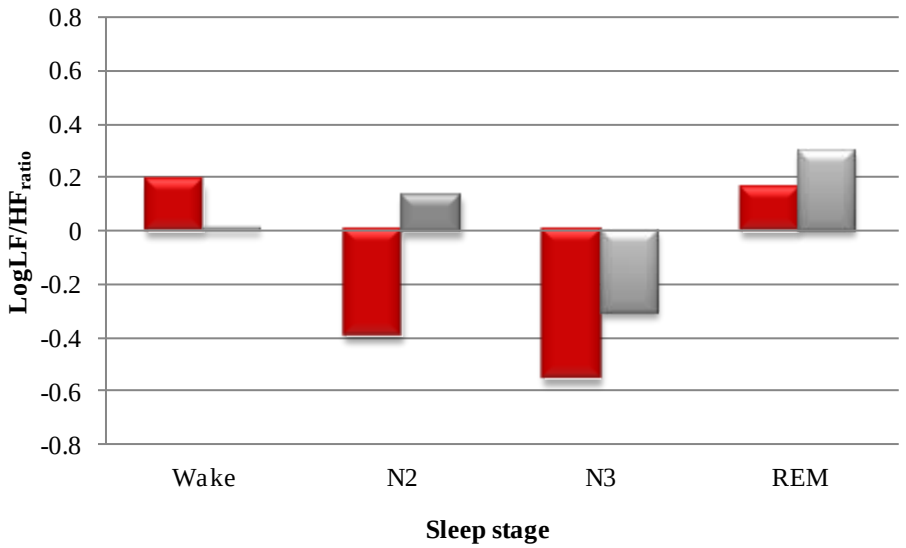

Figure 4.9 Mean logarithm of low frequency to high frequency ratio (LogLF/HF_{ratio}**)** in hypotensives and normotensives across sleep stages. Hypotensives are in red, normotensives are in grey.

4.2.3.4 Correlations between Screening and Sleep Measures

Pearson's correlations revealed strong positive relationships between BP screening values and BP nocturnal values only in the normotensive group (Table 4.6). Correlations indicated a positive relation between SE and SBP screening values in hypotensives ($r = .53$, $P < 0.05$), whereas a negative correlation was revealed in normotensives ($r = -.61$, $P < 0.01$).

		Screening values			
		Hypotensives		*Normotensives*	
Nocturnal BP recording		SBP	DBP	SBP	DBP
Wake	SBP	0.25	0.21	0.62*	0.63*
	DBP	0.14	0.40	0.62*	0.74**
N2	SBP	0.20	0.27	0.75**	0.43
	DBP	-0.01	0.57*	0.61*	0.54*
N3	SBP	0.04	0.37	0.75**	0.70**
	DBP	-0.13	0.41	0.58*	0.65**
REM	SBP	0.30	0.32	0.85***	0.48
	DBP	0.23	0.55*	0.72**	0.69**

* $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$.

Table 4.6. Pearson's correlation coefficients for screening and nocturnal systolic blood pressure (SBP) and diastolic blood pressure (DBP) values for each stage of sleep in hypotensives and normotensives.

4.2.4 Discussion

Hypotensives exhibited overall lower nocturnal BP compared to normotensives in wakefulness as well as across sleep stages. In line with our hypothesis, myocardial contractility was found to be reduced in hypotensives compared to normotensives during the whole night, as indicated by prolonged LVET and EMS. To date, no prior evidence of reduced cardiac contractility in essential hypotension has been reported.

Autonomic indices derived by HRV analysis suggest nocturnal diminished sympathovagal balance in hypotensives in comparison to normotensives, as showed by the lower $LogLF/HF_{ratio}$. These results give strength to the primary role exerted by the neurovegetative system in essential hypotension. The lower HR displayed by hypotensives sufferers compared to normotensives provides further corroboration.

Whereas a strong positive association between BP screening and nocturnal values was observed in normotensives group, no relationship was found in hypotensives. The lack of association suggests a possible impairment in BP regulation underlying the condition of essential hypotension, where diurnal and nocturnal cardiovascular measures are likely to be regulated by different processes.

Surprisingly, a drop in BP from Wake to sleep was found in both groups, which agrees with the literature on normotensive individuals [268]. Despite the extremely low diurnal BP values in hypotensives, the fall in BP at sleep onset occurs also in this population. In addition, both groups exhibited an overall reduction in myocardial contractility from Wake to stable sleep, with an

increase in correspondence to REM phases, in line with prior studies [287]. The pattern exhibited by the cardiovascular parameters across the sleep stages reflected the evolution of the neurovegetative system activity. According to the nocturnal autonomic modifications in healthy subjects [175, 284, 287], the sympathovagal balance decreased across the sleep stages with a reduction from Wake to sleep and an increase in REM in both groups. However, the lower sympathovagal recorded in hypotensives during NREM sleep stages suggests an enhanced vagal drive in deep sleep in this population.

In order to assess objective sleep in details, we employed the PSG recording. In our sample, we failed to find any group differences among sleep parameters. Hence, it is possible that the subjective complaints endorsed by essential hypotensive individuals are linked to symptoms like fatigue more than to objective sleep impairment.

Deeply investigating the relation between the condition of essential hypotension and sleep quality, an unexpected result was found with regard to the opposite correlations between objective sleep quality and BP screening values reported among hypotensives and normotensives. Whilst individuals within the normal range of BP who had elevated diurnal BP values showed reduced sleep efficiency, in hypotensive subjects higher diurnal BP reading was related to increased SE, suggesting sleep quality may be associated with an “ideal” BP level located between the upper limit of hypotension and the lower limit of normotension (i.e., SBP between 100 mmHg and 110 mmHg). In addition, the significant relation between SE and nocturnal BP measures in normotensives, showed that, within healthy conditions, a better SE is associated with a lower BP across the night.

Since we failed to find this correlation in hypotensives group, these data, combined to the absence of association between diurnal and nocturnal BP levels, converge to indicate abnormalities in the modulation of physiological variables in essential hypotension.

4.3 Experiment III

4.3.1 Introduction

Arousals from sleep are associated with abrupt and transient elevations in cardiovascular activity including HR, BP, muscle sympathetic nerve activity (MSNA) and cerebral blood flow (CBF) [30, 65, 151, 195, 204, 257, 271, 286, 287]. Concerning the HR, convincing evidence indicates that the cardiac response is primarily controlled by changes in vagal drive [128, 129].

A number of sleep disturbances such sleep breathing disorders feature recurrent arousals from sleep. Given the heightened cardiovascular risk observed in these disorders [161], it has been proposed that the high frequency of arousals and the entailed increase in physiological parameters mediate the relationship between sleep disorder and elevated cardiovascular vulnerability.

Essential hypotensives have been found to exhibit blunted cardiovascular reactivity to stress tasks in comparison to normotensives [79, 87]. As reduced cardiovascular reactivity has been documented to be associated with better survival, these findings suggest the essential hypotension can be a cardio-protective state.

The physiological response to phasic events occurring during sleep may be adopted as a paradigm to assess the cardiovascular reactivity in a condition relatively free of external disturbance factors that may confound the measurement of physiological variables in wakefulness (e.g., emotional status, degree of cooperation).

In lights of the differences disclosed in the *Experiment I* and *II* in hemodynamic and autonomic pattern over sleep between hypotensives and normotensives and given the association between the arousals experienced during sleep and the cardiovascular risk, the purpose of the *Experiment III* was to analyze the nature of the arousal from sleep in hypotensive individuals. Bearing in mind the prior mentioned reports illustrating cardiovascular hyporeactivity in this population, we expected a reduced HR response to arousal from sleep in hypotensives.

4.3.2 Materials and Method

4.3.2.1 Participants

See Section 4.2.2.1 for participants selection.

4.3.2.2 Polysomnography

See Section 4.2.2.2 for PSG equipment and sleep parameters.

From the PSG recording, arousals from sleep were manually scored according to criteria set by the American Sleep Disorders Association [11]. Specifically, an arousal was scored when a three to 15 sec change occurred in EEG frequency, including alpha, theta and/or frequencies greater than 16 Hz, except sleep spindles. EEG arousal activity lasting more than 15 seconds that is more than 50% of the standard 30 sec epoch was scored as wakefulness. It was also necessary for at least 10 sec of continuous sleep to precede the arousal and an intervening 10 sec periods for another arousal to be scored. REM arousals were scored only if accompanied by a concurrent increase in submental EMG amplitude.

The total number (count) and mean duration (sec) of arousals for the all night and across sleep stages (N1, N2, N3 and REM) were computed.

The Sleep Research System (SRS) Analysis Software 5.1 was used for HR analysis (Sleep Research System, School of Behavioral Science, University of Melbourne, Australia). SRS analysis software automatically detected R-waves before the experimenter visually checked and manually adjusted R-wave detection where necessary. For each spontaneous arousal, HR data for ten beat-to-beat intervals prior and fifteen beats-to-beats intervals post arousal were designated as -10 to -1 and 1 to 15 respectively, and exported for data analysis. This range was selected in accordance with conventions within the arousals from sleep literature (e.g., Ref. 117).

4.3.2.3 Study Design

See Section 4.2.2.6

4.3.2.4 Data Analysis and Statistics

In the preliminary analysis it was observed that HR elevations occurred at approximately three beat-to-beat intervals prior to the onset of the EEG scored spontaneous arousal (beats -3 to -1). Similar to prior studies [117], a pre arousal mean was calculated as the average HR (bpm) over beats -10 to -4. The magnitude of HR change (in percentage) was then calculated as the difference between pre arousal HR mean (beats -10 to -4) and HR at each beat-to-beat interval (beats -10 to 15) (see Figure 4.10). Mean pre- and mean post-arousal HR changes were also computed. These changes were calculated for all arousals for each participant. Mean values were calculated for each group (hypotensive and normotensive individuals) and for each sleep stage (N1, N2, N3, REM). Further whole night values were calculated by averaging group sleep stage means.

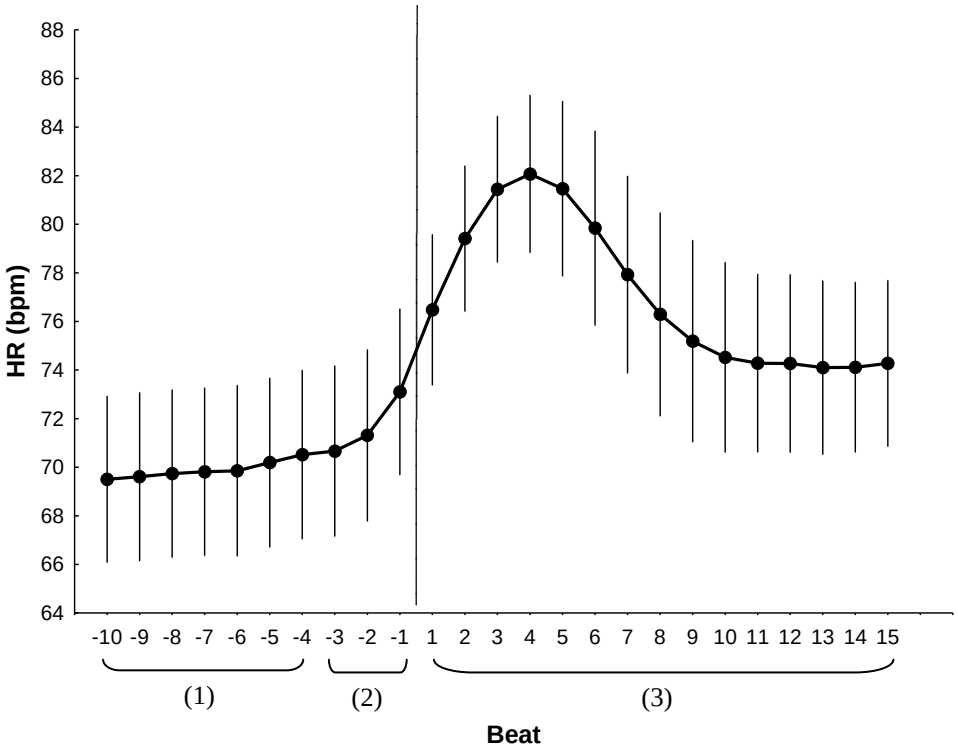

Figure 4.10 Description of the heart rate (HR) response to arousal analysis. The vertical line represents the onset of the EEG spontaneous arousal. Three intervals were defined as follows: (1) pre arousal period (beats -10 to -4), where no arousal related changes in HR occur; (2) pre arousal related HR changes (beats -3 to -1) where there is the beginning of arousal related changes in HR but prior to the EEG change; (3) post arousal HR changes (beats 1 to 15) that is HR change post EEG change indicating arousal.

Independent groups *t*-tests were applied to compare hypotensive and normotensive participants on arousal from sleep parameters and pre arousal HR mean. Several analyses were conducted to assess the magnitude of the HR response to arousal from sleep. Firstly, a Group (hypotensive and normotensive individuals) by Sleep stage (N1, N2, N3, REM) by Phase (pre-and post-arousal HR mean) mixed model ANCOVA (BMI as covariate) was carried out to determine whether the magnitude of the HR change differed across groups and stages of sleep. To compare changes between REM and NREM sleep stages a similar mixed model was performed by averaging N1, N2 and N3 stages. Newman-Keuls post-hoc tests were applied where appropriate. Lastly, separate and planned independent group *t*-tests were conducted comparing magnitude of arousal HR response at each pre-and post-arousal heart beat (beats -3 to 15) between hypotensives and normotensives, both on the whole night value and within each individual sleep stage (N1, N2, N3, REM).

Where sphericity was violated in any of the mixed model analyses, statistical significance was tested against Huynh-Feldt corrected degrees of freedom, with partial eta-squared (η^2_p) and

original degrees of freedom reported. For all tests statistical significance was defined as $P < 0.05$.

4.3.3 Results

4.3.3.1 Demographic, Screening and Polysomnographic Measures

See Section 4.2.3.1 and 4.2.3.2

4.3.3.2 Arousals Measures

Independent group *t*-tests performed on duration of arousals found no significant differences neither when sleep stages were collapsed nor within each sleep stage.

Likewise, groups did not differ with regard to the total number of arousals experienced during the all night. Normotensive individuals displayed greater number of arousals than did hypotensives in N1 sleep stage ($P < 0.01$). Number and duration of arousals from sleep comparisons are reported in Table 4.7.

	Number			*Duration*		
	Hypotensives	*Normotensives*	*t*	*Hypotensives*	*Normotensives*	*t*
N1, bpm	20.1 ± 8.4	33.3 ± 15	-1.96**	7.7 ± 1.1	7.7 ± 0.7	0.27
N2, bpm	22.3 ± 8.5	25.1 ± 10.3	-2.96	8.5 ± 1.7	8.3 ± 1.5	0.22
N3, bpm	5.9 ± 3.4	8.3 ± 6.6	-0.81	11.2 ± 4.6	9.9 ± 2.9	0.87
REM, bpm	19.3 ± 10.1	12.7 ± 7.1	-1.25	7.1 ± 1.1	7.6 ± 1.6	-0.97
All sleep stages, bpm	67.6 ± 22.2[a]	79.4 ± 20.4[a]	-1.52	8.7 ± 1.6	8.3 ± 1.2	-0.62

Values are means ± SD.
Degree of freedom = 28.
** $P < 0.01$.
[a] total count

Table 4.7 Number and duration of arousals from sleep for the whole night and across sleep stages.

4.3.3.3 Heart Rate Changes

As expected, the normotensive participants had a higher pre arousal HR mean compared to hypotensive participants the whole night ($P < 0.05$). In terms of the sleep stages, normotensive individuals compared to hypotensive individuals had significantly higher pre arousal HR in N2

($P < 0.01$) and N3 ($P < 0.05$) sleep stages, and there was a trend for normotensives to have a higher pre arousal HR mean in N1 ($P = 0.08$) (Table 4.8).

	Hypotensives (n = 15)	*Normotensives (n = 15)*	*t*
N1, bpm	69.2 ± 6.7	76.2 ± 13.3	-1.83
N2, bpm	64.2 ± 6.6	73.1 ± 10.9	-2.69**
N3, bpm	66.8 ± 7.4	74.9 ± 11	-2.33*
REM, bpm	69.3 ± 6.7	76.2 ± 13.2	-1.79
All sleep stages, bpm	67.4 ± 6.4	75.3 ± 12	-2.24*

Values are mean ± SD. Degree of freedom = 28.
* $P < 0.05$; ** $P < 0.01$

Table 4.8 Pre arousal heart rate values for the whole night and across sleep stages.

Considering the magnitude of the HR change, there was a significant Phase main effect ($F_{(1, 27)} = 134, 99$, $P < 0.001$, $\eta^2_p = 0.83$), with larger HR changes during post-arousal. The significant main effect observed for Sleep stage ($F_{(3,81)} = 15.83$, $P < 0.001$, $\eta^2_p = 0.37$) indicated greater HR changes in N3 compared to the other sleep stages. As displayed by the Sleep Stage × Phase interaction ($F_{(3,81)} = 19.21$, $P < 0.001$, $\eta^2_p = 0.42$), the pre-arousal HR responses were similar across stages, whilst a higher changes occurred during post-arousal in N3 compared to the other sleep stages and in REM compared to N2 sleep stages (Figure 4.11).

The ANCOVA performed by collapsing the NREM sleep stages revealed significant main effects of Sleep Stage ($F_{(1,27)} = 9.89$, $P < 0.01$, $\eta^2_p = 0.27$), Phase ($F_{(1,27)} = 95.3$, $P < 0.001$, $\eta^2_p = 0.78$) and significant Sleep stage × Phase interaction ($F_{(1,27)} = 25.4$, $P < 0.001$, $\eta^2_p = 0.48$): HR changes were higher in REM compared to NREM stages.

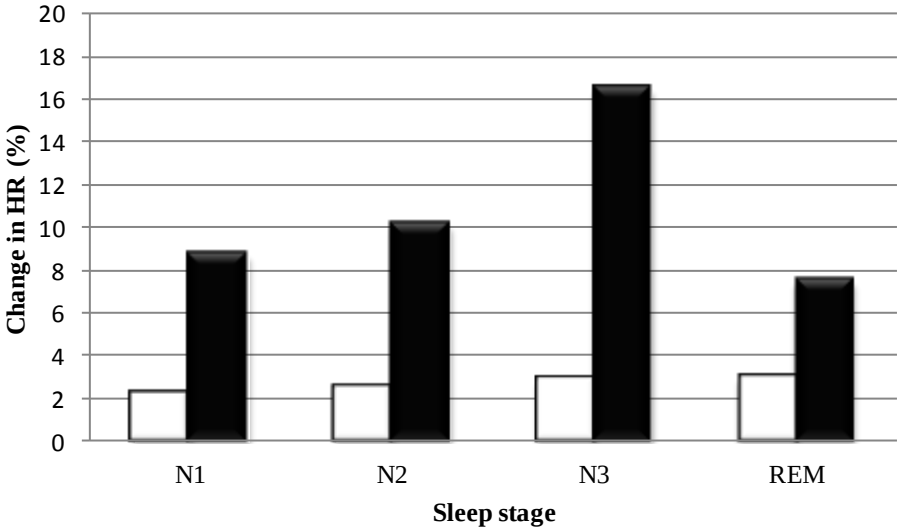

Figure 4.11 Arousal related heart rate (HR) changes across sleep stages. Pre-arousal HR changes are in white, post-arousal HR changes are in black.

Independent sample *t*-tests conducted over the beat-to-beat HR changes during the whole night revealed larger HR changes in hypotensives compared to normotensives at post-arousal beat 1 (t_{28} = 2.08, $P < 0.05$), beat 2 (t_{28} = 2.17, $P < 0.05$), beat 3 (t_{28} = 2.11, $P < 0.05$) and a trend at beat 4 ($P = 0.07$) (Figure 4.12).

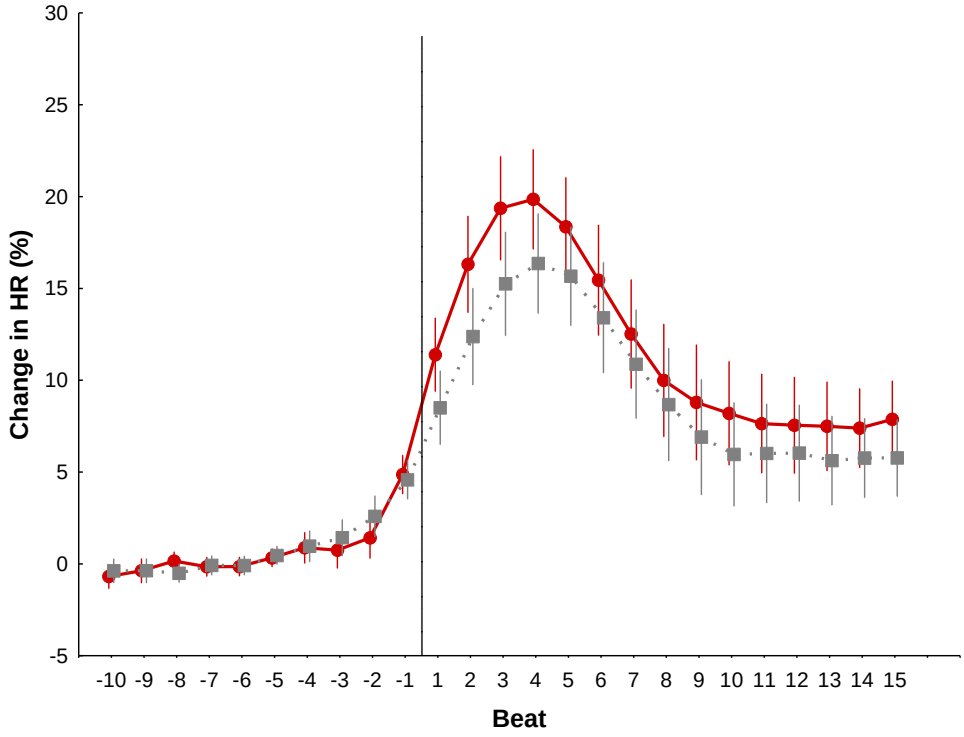

Figure 4.12 Beat-to-beat HR changes (%) comparing normotensive (grey line) and hypotensive (red line) participants over all night mean values. Values are means ± SD. The vertical line indicates the onset of EEG arousal.

Considering the sleep stages, no group differences were detected at any beat in N1 sleep stage (Figure 4.13).

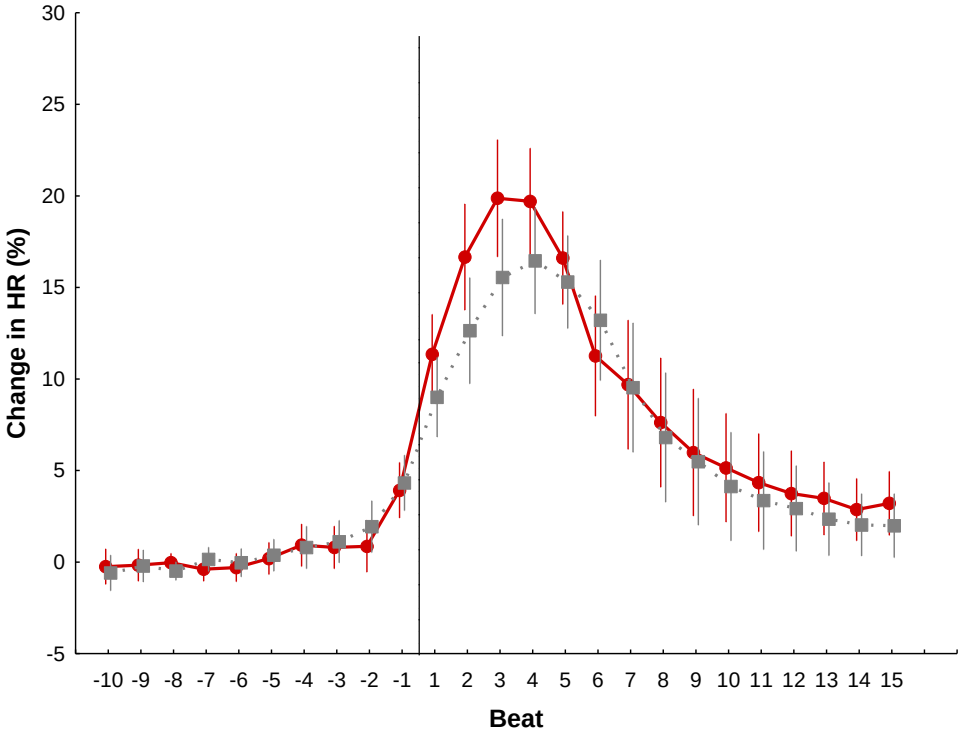

Figure 4.13 Beat-to-beat HR changes (%) comparing normotensive (grey line) and hypotensive (red line) participants in N1 sleep stage. Values are means ± SD. The vertical line indicates the onset of EEG arousal.

As illustrated in Figure 4.14, hypotensive participants exhibited larger HR response than normotensives in N2 from post-arousal beat 1 to beat 5 (beat 1, $t_{28} = 2.83$, $P < 0.01$; beat 2, $t_{28} = 2.67$, $P < 0.05$, beat 3 $t_{28} = 3.48$, $P < 0.01$; beat 4, $t_{(28)} = 3.27$, $P < 0.01$; beat 5, $t_{28} = 2.24$, $P < 0.05$).

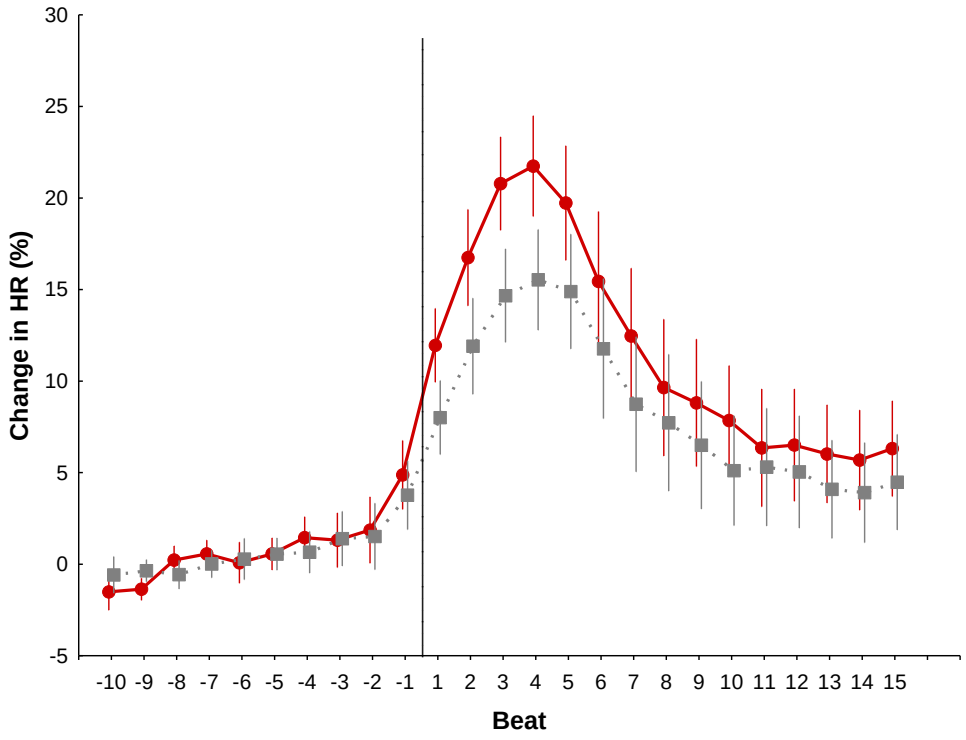

Figure 4.14 Beat-to-beat HR changes (%) comparing normotensive (grey line) and hypotensive (red line) participants in N2 sleep stage. Values are means ± SD. The vertical line indicates the onset of EEG arousal.

Hypotensive individuals also had a greater HR change in N3 from beat 1 to beat 6 (beat 1, t_{28} = 2.71, $P < 0.05$; beat 2, t_{28} = 3.3, $P < 0.01$, beat 3 t_{28} = 2.43, $P < 0.05$; beat 4, $t_{(28)}$ = 2.14, $P < 0.05$; beat 5, t_{28} = 2.33, $P < 0.05$; beat 6, t_{28} = 2.87, $P < 0.01$) and a trend toward significance at beat 7 ($P = 0.06$) (Figure 4.15).

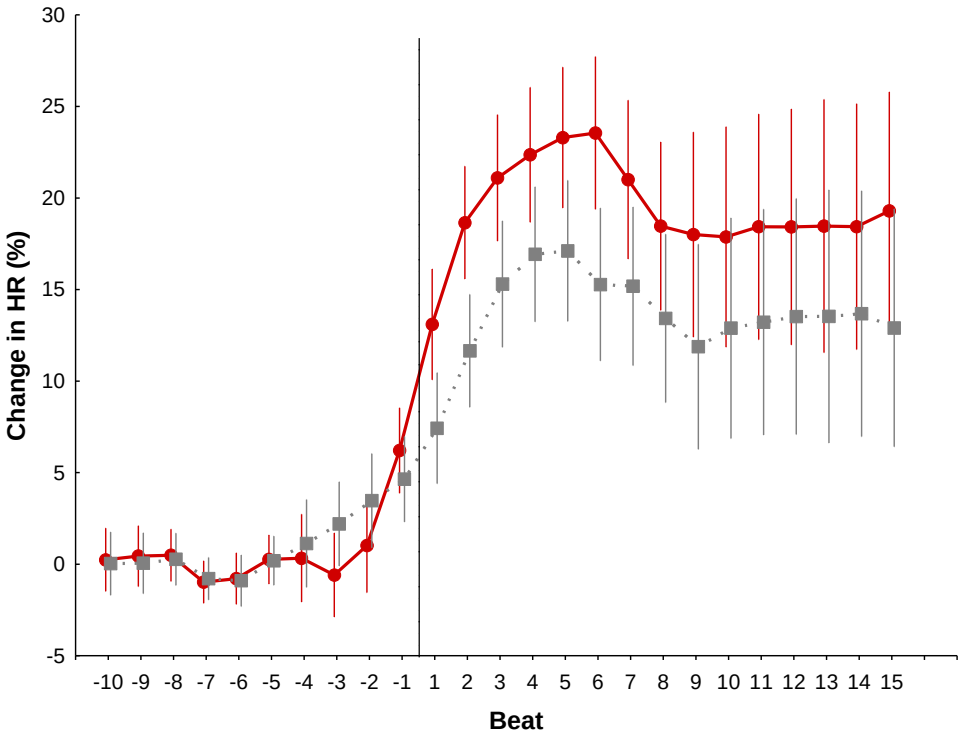

Figure 4.15 Beat-to-beat HR changes (%) comparing normotensive (grey line) and hypotensive (red line) participants in N3 sleep stage. Values are means ± SD. The vertical line indicates the onset of EEG arousal.

Lastly, no differences between hypotensive and normotensive participants were observed in the magnitude of HR arousal response in REM sleep stage, as seen in Figure 4.16.

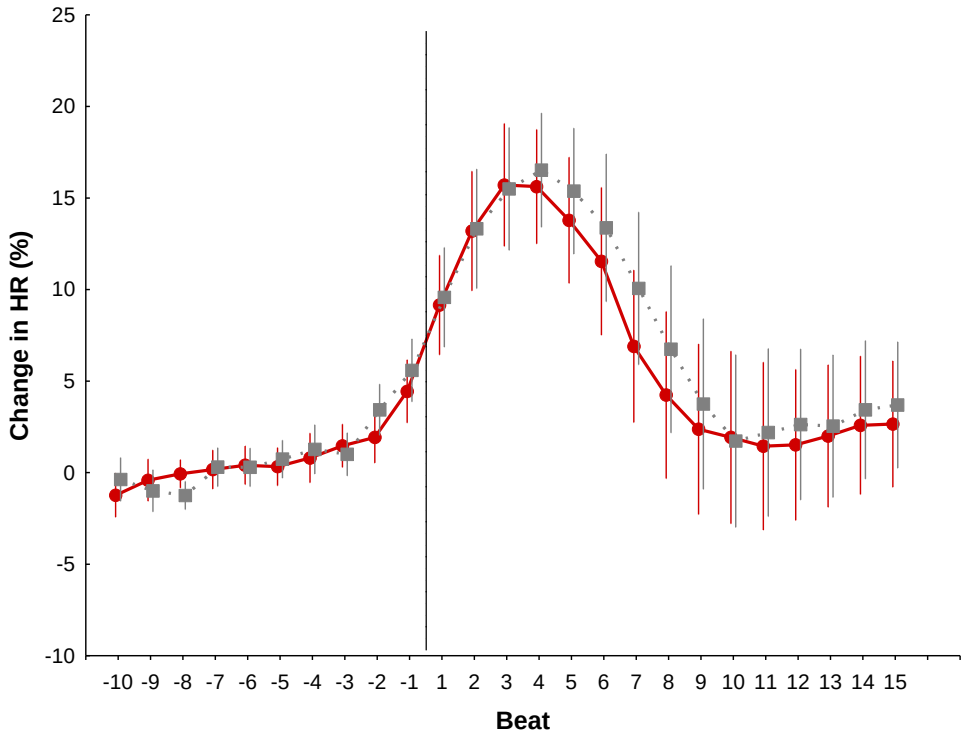

Figure 4.16 Beat-to-beat HR changes (%) comparing normotensive (grey line) and hypotensive (red line) participants in REM sleep stage. Values are means ± SD. The vertical line indicates the onset of EEG arousal.

4.3.4 Discussion

The evolution of cardiac changes was similar to prior reports [117, 257] for both groups, with a slow HR acceleration beginning prior the onset of arousal and becoming sharp after the EEG changes.

Moreover, the HR changes were found to be larger in NREM sleep compared to REM sleep regardless of group. Given the sympathetic prevalence showed in REM sleep (e.g., Ref. 270, 271, 292), this datum is in line with the assumed vagal withdrawal underlying the cardiac response to arousal from sleep [128, 129]. Indeed, the parasympathetic decline in REM is likely to result in a reduction in vagal withdrawal at arousal, thence in a less pronounced HR change in this sleep stage.

Contrary to our hypothesis, hypotensive individuals compared to normotensives exhibited a larger HR response over the early post-arousal beats during the whole night. Considering the sleep stages separately, the post-arousal HR changes were greater in hypotensives during N2 and N3 sleep stages.

The finding of enhanced HR response to arousal from sleep in essential hypotension appears to be inconsistent with prior studies reporting a diminished cardiovascular reactivity in this

population [79, 87]. A number of factors could account for this datum. The cited studies assessed the physiological response during stress task as the mental arithmetic test, which is well known to involve both autonomic branches (e.g., Ref. 4, 5, 22). Differently, as mentioned above, the HR arousal response is primarily mediated by the parasympathetic division. Hence, these findings suggest a greater vagal withdrawal in hypotensive subjects than in normotensives, providing further corroboration to the hypothesized parasympathetic hyperactivity in essential hypotension. Moreover, it should be empathized that several psychological confounders may affect the physiological response during evaluations carried out in wakefulness.

Davies and coworkers [65] suggested that longer arousal durations correlated with larger cardiovascular arousal responses. However, since no group differences were found in terms of duration of arousals, hypotensive individuals did not exhibit larger HR arousal responses because they experienced longer arousals.

Likewise, groups did not differ in regard with the total number of arousals showed. The higher frequency of arousals exhibited by normotensives in N1 sleep is reasonably to be driven by the intrinsic instability with recurrent transitions to wake typical of this sleep stage, rather than a larger amount of N1 sleep stage, since the latter did not differ between groups.

Summarizing, the analysis of the nature of arousal response in essential hypotension hypotensives revealed enhanced HR arousal changes in this group. However, since the increased cardiovascular risk associated with a greater arousal response has been linked to the frequency of arousals experienced during sleep [260], the assumed higher vulnerability would be reduced as hypotensives did not exhibit more numerous arousals than did normotensives.

CHAPTER 5

General Discussion

The aim of the present dissertation was to explore systematically the sleep pattern and the nocturnal hemodynamic and autonomic activity in essential hypotension in order to obtain a deeper insight into the pathophysiology of this condition.

As far as we know, neither the sleep structure nor the cardiovascular parameters over the sleep period have been investigated in essential hypotensives yet.

The *Experiment I* and the *Experiment II* were targeted at addressing the cardiovascular and autonomic activity during sleep in essential hypotension by applying a wide range of measures derived by the blood pressure (BP) monitoring, impedance cardiography (ICG) and heart rate variability (HRV) techniques.

Hemodynamic measurements were consistently found to be markedly lower in hypotensives compared to normotensives along the sleep period. Indeed, hypotensive sufferers exhibited constantly lower BP than normotensives, associated with decelerated heart rate (HR) and reduced cardiac output (CO) as well as diminished myocardial contractility.

The abnormally low CO may lead to insufficient tissues perfusion, thereby accounting for the decreased body temperature and cold limbs often reported by essential hypotension sufferers [2, 272, 309].

These results are line with previous investigations reporting reduced cardiovascular parameters in essential hypotension during wakefulness [2, 82], suggesting that the cardiovascular hypoactivation displayed by this population in comparison to normotensive condition is maintained also over sleep.

The cardiovascular downregulation is reasonably to reflect an autonomic imbalance. Indeed, the application of metrics broadly established as markers of sympathetic and parasympathetic influences on heart pumping (i.e., the pre-ejection period, PEP, and the high-frequency HRV indices, respectively) allowed us to identify the contribution of each neurovegetative branch on cardiac control, revealing that hypotensive sufferers exhibited enhanced vagal drive combined with reduced sympathetic tone during sleep.

It is noteworthy that, thus far, this is the first evaluation performed on both cardiac sympathetic and parasympathetic outflows in essential hypotension in comparison with normotension. In this context, it should be remembered that the hypothesis of autonomic dysfunction advanced in essential hypotension was previously largely lying on unspecific evidence [2, 88, 103].

Therefore, since we observed not only a sympathetic withdrawal but also a parasympathetic hyperactivity in hypotensive subjects, our findings confirm and extend the postulated autonomic dysfunction, yielding further information about the pathogenesis of this condition.

Further converging evidence points towards the hypothesis of abnormal cardiovascular regulation in the essential hypotension. Unlike the normotensives, whose nocturnal cardiac activity was found to be modulated primarily by the parasympathetic nervous system (PNS) in agreement with literature [320], both neurovegetative divisions were involved in the cardiac control during sleep in hypotensives. Moreover, no relationships were observed between diurnal and nocturnal BP measures in the latter individuals, differently from controls.

Additionally, the evolution of hemodynamic parameters throughout the night and across sleep stages was showed as being blunted in hypotensives thereby corroborating the advanced alterations in cardiovascular modulation.

The cardiovascular measurement was carried out in the context of polysomnographic (PSG) recording, which represents the gold-standard to assess objectively the sleep.

The thorough comparison conducted between hypotensives and normotensives over the PSG parameters within the *Experiment II* did not reveal any group differences in sleep. Hence, given the preserved sleep, the subjective complaints endorsed by hypotensives (e.g., fatigue, dizziness, cognitive impairment) are unlikely to be ascribed to abnormalities in sleep quality or quantity.

Notwithstanding, we cannot exclude that more sophisticated analysis (e.g., cyclic alternating pattern or spectral EEG investigation) may unmask subtle alterations in sleep pattern.

Furthermore, as the sleep parameters were similar between groups, the possibility that the different cardiovascular activity exhibited by hypotensives across the night was affected by differences in sleep structure is conceivably to rule out.

The PSG examination provided also the framework to explore the cardiovascular reactivity during sleep. This latter issue was addressed in the *Experiment III*, which focused on the cardiac response to arousal from sleep.

Whereas both the number and the length of arousals experienced were comparable between groups, hypotensive individuals exhibited larger HR arousal response than did normotensives.

Since the HR arousal response is mainly mediated by a decrease in cardiac parasympathetic output, the greater vagal withdrawal reported by hypotensive individuals gives further support to the preminent involvement of this autonomic branch in essential hypotension.

In lights of the available evidence describing a blunted cardiovascular reactivity in this condition in wakefulness [79, 87], the datum of enhanced HR activation may appear discrepant. However, some factors are likely to account for this lack of consistency. The majority of the studies assessing the cardiovascular response in hypotensive sufferers employed stress tasks such as the mental arithmetic task. It is broadly agreed that several variables may influence the physiological response under stress, included the extent of collaboration, subjective rating of stress, emotional arousal [317]. The effects of these confounders can be particularly significant in assessing the reactivity, hence generating misleading findings. It should also be noted that different physiological processes underlie the HR acceleration evoked by the arousal from sleep and the mental stress task. Whereas the cardiac response to arousal is primarily modulated by decreased parasympathetic output, the changes in cardiac activity elicited by the mental arithmetic tasks are owed by a reciprocal pattern of sympathetic hyperactivation and parasympathetic withdrawal (e.g., Ref. 4, 5, 22). Given the available evidence of reduced sympathetic tone in hypotensives, a smaller sympathetic activation may be predominant and thus leading to diminished cardiovascular response under stress.

However, bearing in mind that no pure cardiac autonomic indices have been estimated in hypotensives compared to normotensives in the above mentioned reports, only speculative assumptions can be drawn.

In the current study we performed an accurate sample selection, by means of multiple BP measurements. Particular attention was paid to enroll only hypotensives in which the chronic low BP was primary, thus carefully excluding secondary forms. Moreover, a positive history of symptoms related to the hypotensives condition was ensured prior the recruitment of hypotensive participants.

Nonetheless, some limitations should be acknowledged. The main limit is that the samples we tested consisted of females only. Since there is some evidence of gender differences in autonomic functions [60, 94], we cannot exclude that this might have influenced our findings. However, as the results we found in normotensives are consistent with the literature (see above), we can reasonably assume that the reliability and generalizability of our data are not reduced by the samples selection. Another weakness, related to the previous one, is the absence of control on the hormonal cycle. As PSGs were not performed during standardized phase of the ovulatory cycle, reproductive hormonal levels might have affected our findings considering their effects on

cardiovascular activity (e.g., it is known that estrogen has a vasodilator action). Nevertheless, it should be point out that no consensus has been reached on whether the autonomic and hemodynamic functions differ according to hormonal phases [112, 126, 189, 249]. Whereas HRV analysis is widely recognized as a reliable method to estimate autonomic influences on heart [24, 277], concerns may arise when considering PEP. Despite several investigations documented this measure as being inversely related to cardiac sympathetic beta-adrenergic activity [49, 261, 263], it can also be affected by variations in afterload (i.e., rise in BP may lead to augmentation in PEP [262]. The lengthening in PEP across the night might have reflected the increase in time required to overcome the more elevated external pressure owed to the heightening in BP, rather than a decrease in sympathetic nervous system (SNS) output. Nonetheless, since BP felt during sleep in normotensives and remained substantially unchanged in hypotensives, we can reasonable exclude that changes in BP contributed significantly to the augmentation in PEP values we detected in both groups. Moreover, the finding of higher PEP in hypotensives, which also exhibited lower BP, gives further strength to this interpretation.

Whether chronic low BP is associated with either diminished or augmented morbidity and mortality is still controversial [2, 113, 167, 181, 200, 211, 222, 245].

Taken together, the findings illustrated in the *Experiment I* and *II* are reasonably to support to the concept of hypotension as benign risk factor. Indeed, the pattern we detected in hypotensives during the night, characterized by decreased HR, low cardiac contractility and heightened vagal tone, in addition to reduced BP and sympathetic drive, has been widely documented by several epidemiological investigations to reflect diminished health risk [44, 90, 139, 154, 169, 173, 176, 184, 277, 278, 289]. Additional corroboration stems from investigations describing the nocturnal cardiovascular values as being more valuable prognostic markers of poor outcomes that diurnal measures [97, 162].

On the other hand, the interpretation of essential hypotension as a cardio-protective state may be challenged by the results we found in the *Experiment III*, which reported a more pronounced HR response to arousal from sleep in hypotensive subjects, suggesting higher cardiac reactivity and thus more elevated health risk.

Nevertheless, it should be empathized that the frequency of the arousals rather than the magnitude of the response has been found to be crucial in mediating the impact of the cardiovascular activation triggered by the arousals [260]. Thereby, as the number of arousals experienced was similar between hypotensives and normotensives, the burden related to the heightened magnitude of cardiac response is likely to be blunted.

However, since our results have been obtained from relatively small samples and cross-sectional studies, only speculative interpretations can be advanced. Large prospective examinations targeted at identifying the association between chronic low BP and cardiovascular risk are thus needed.

Whether both neurovegetative divisions are primarily affected, or the dysregulation occurring in one branch leads in turn to the dysfunction in the other, is still unknown. This issue requires further investigations to be clarified, as well as the role played by each autonomic system in eliciting the symptoms complained by hypotensive sufferers.

Additionally, given the evidence for altered cardiac autonomic control in hypotensives and the involvement of peripheral resistance in setting nocturnal BP, the assessment of vascular activity and particularly sympathetic alpha-adrenergic drive is recommended in order to obtain a more comprehensive insight into this condition. In this context, the recording of muscle sympathetic nerve activity (MSNA) might provide data of interest regarding to the sympathetic output over the peripheral vascular beds.

Given the previous finding of enhanced baroreflex sensitivity in essential hypotension [79] and the hypothesized involvement of this reflex in setting BP during sleep [43, 61, 215], the measurement of baroreceptors functioning during the night can aid to discern the physiological mechanism underlying the cardiovascular nocturnal modulation in this population.

Currently, the main pharmacological therapy of chronic hypotension entails the administration of sympathomimetic drugs such as midodrine. Midodrine, an alpha-adrenergic agonist, raises the BP by promoting the peripheral vasoconstriction mediated by vascular sympathetic activation. Nonetheless, this agent has been recently documented to augment baroreflex sensitivity and cardiac vagal output in hypotensives, thus exacerbating the autonomic dysregulation [83]. The development of alternative pharmacological approaches aimed at restoring the autonomic balance is therefore warranted. For instance, given our finding of enhanced vagal output in hypotensives, clinical trials designed at assessing the efficacy of cholinergic antagonists should be encouraged. Indeed, the effects of therapies targeted at lowering the vagal tone in these subjects both enhancing the BP and providing relief from subjective symptoms need to be addressed.

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