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CARDIOVASCULAR HYPERAROUSAL AND PRIMARY INSOMNIA

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To my family

To my grandparents

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LIST OF ABBREVIATIONS AND ACRONYMS

AC = Alternating Current

ACE = Angiotensin-Converting Enzyme

ADH = Antidiuretic Hormone

AIS = Athens Insomnia Scale

ANOVA = Analysis Of Variance

A-V = Atrioventricular

BDI = Beck Depression Inventory

BMI = Body Mass Index

BP = Blood Pressure

BSA = Body Surface Area

CBF = Cerebral Blood Flow

CI = Cardiac Index

CMR = Cerebral Metabolic Rate

CO = Cardiac Output

DBP = Diastolic Blood Pressure

DSM = Diagnostic and Statistical Manual of Mental Disorders (-TR = Text Revision)

ECG = Electrocardiogram

EEG = Electroencephalography

EMG = Electromyography

EOG = Electrooculography

ESS = Epworth Sleepiness Scale

HF = High Frequency

HR = Heart Rate

HRV = Heart Rate Variability

HS = Hyperarousal Scale

ICD = International Classification of Diseases

ICG = Impedance Cardiography

ICSD = International Classification of Sleep Disorders

ISI = Insomnia Severity Index

ITI = Inter Trial Interval

LF = Low Frequency

LOC = Left Outer Canthus

LVET = Left Ventricular Ejection Time

MAP = Mean Arterial Pressure

MSLT = Multiple Sleep Latency Test

n.u. = normalized units

NREM = Non Rapid Eye Movement

PEP = Pre-Ejection Period

PSA = Power Spectral Analysis

PSAS 0 Pre Sleep Arousal Scale

PSG = Polysomnography

PSQI = Pittsburgh Sleep Quality Index

RAAS = Renin-Angiotensin-Aldosterone System

REM = Rapid Eye Movement

ROC = Right Outer Canthus

RSA = Respiratory Sinus Arrhythmia

RT = Reaction Time

S-A = Sinoatrial

SBP = Systolic Blood Pressure

SD = Standard Deviation

SE = Sleep Efficiency

SEM = Slow Eye Movement

SI = Stroke Index

SOL = Sleep Onset Latency

SOP = Sleep Onset Period

SSD = Stop Signal Delay

SSRT = Stop Signal Reaction Time

SSS = Stanford Sleepiness Scale

STAI = State Trait Anxiety Inventory

STR = Systolic Time Ratio

SV = Stroke Volume

SVR = Systemic Vascular Resistance

SWS = Slow Wave Sleep

TIB = Time In Bed

TPR = Total Peripheral Resistance

TST = Total Sleep Time

ULF = Ultra Low Frequency

VLF = Very Low Frequency

WASO = Wake After Sleep Onset

PREFACE

The main purpose of this thesis is to investigate the role played by the hyperarousal, in the cardiovascular field, in both nighttime and daytime impairments, that characterize the primary insomnia population.

The first part of this thesis offers the reader an overview of the physiology of the cardiovascular system: the heart, the circulatory system, the cardiac cycle, the mechanisms to control the cardiovascular system and the cardiovascular recording techniques employed in the experiments below mentioned. A specific attention has been paid to the Impedance Cardiography, a noninvasive technique that allows to detect the electromechanical activity of the heart and in particular allows to derive the pre-ejection period a validate index considering reflecting the sympathetic activity of the neurovegetative system on the heart.

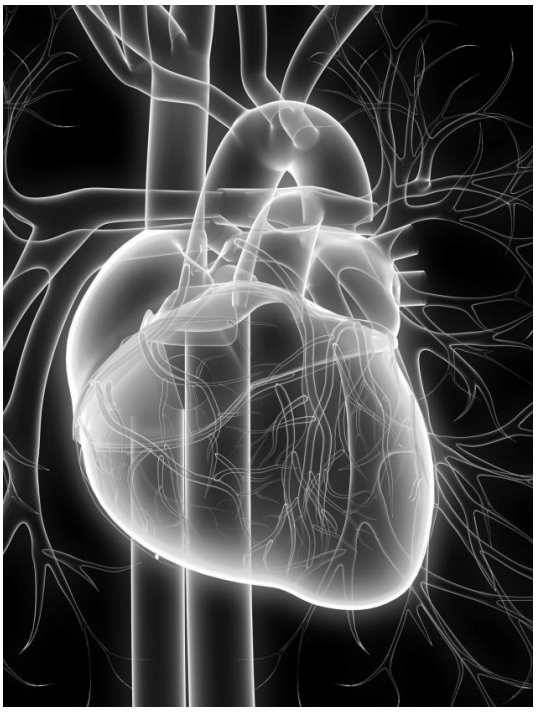
Chapter 2 describes the main features of the normal human sleep, the sleep architecture, the polysomnographic recording technique, the sleep scoring and the cardiovascular modification in normal human sleep.

Chapter 3 deepens into primary insomnia. It defines the concept of primary insomnia, the epidemiology, associations and consequences. This chapter offers an overview of the models that have been proposed for the primary insomnia, the recurrent underlying concept of hyperarousal and the main treatments in use. Furthermore, a status of the literature about daytime cognitive impairments and nighttime cardiovascular profile associated with primary insomnia, is considered in this chapter.

The last chapters describe the experiments conducted during my PhD program. Chapter 4, “Sleep Onset and Cardiovascular Activity in Primary Insomnia”, analyzes the specific “switch” between pre- and post-sleep onset. Sleep onset is considered to play a key role in the pathophysiology of primary insomnia, in that it also characterizes a specific group of primary insomniacs (sleep onset insomniacs). Chapter 5; “Cardiovascular Activity During Sleep in Primary Insomnia”, aims to investigate the nocturnal cardiovascular pattern of primary insomniacs. Moreover, in this chapter, the sleep onset is analyzed as a more extended period abandoning the idea that sleep begins at a specific moment. Finally, the last chapter “Cognitive Performance and Cardiovascular Markers of

Hyperarousal in Primary Insomnia" regards the hypothesized cognitive impairment associated with primary insomnia. Stop Signal Task, assessing motor inhibition processes, has been employed to test possible differences in cardiovascular activity and cognitive performance between insomniacs and good sleepers.

1 CARDIOVASCULAR PHYSIOLOGY



All living cells require metabolic substrates.

The cardiovascular system, one of the most important systems in the body, is constituted by the heart (a myogenic muscular organ, a pump) and the circulatory system (arrangement of blood vessels, a distribution system). The main function of the cardiovascular system is to deliver nutrients to the body tissues allowing the organism to live.[1]

The cardiovascular system plays a main role in psychophysiology research for many reasons[2]*:*

- *cardiovascular parameters, e.g. heart rate (representing the heart beat per minute) or blood pressure, are easily recorded and quantified;*
- *the cardiovascular system is composed by different subsystems under central and peripheral neurovegetative control, so it is highly sensitive to neurobehavioral processes;*
- *its complexity is reflected by a variety of disorders in which, psychological factors such as stress play a key role in the pathophysiology, suggesting a direct link with the psychosomatic medicine.*

The purpose of this chapter is to give the reader a brief overview about the physiological bases of the cardiovascular system and its regulation.

1.1 THE HEART

The heart, the central organ of the cardiovascular apparatus, is located obliquely (the apex of the heart is oriented down to the left and forward) within the middle mediastinum of the thorax, between the two lungs, anterior to the vertebral column and posterior to the sternum. It is enclosed in a fibrous sac called the pericardium lying in the pericardial cavity (a fluid-filled space), that protects the heart, anchors its surrounding structures, and prevents overfilling of the heart with blood. The heart has the shape of a cone, the volume of a human fist and its weight is about 300 g in males and 250 g in females (the adult heart is about 0.45% of body weight in males and about 0.44% in females). At rest, the cardiac rhythm of the heart, i.e. heart rate (HR), in an adult is about 72 beat per minutes.[1]

The heart is a muscular organ composed of three layers: the epicardium, the endocardium, and the myocardium. The epicardium describes the outer layer of heart tissue and it is mainly constituted by connective tissue. The endocardium is the innermost layer of heart tissue and is divided into the non valvular (visceral) and valvular endocardium, and consists of thin fibrocellular connective tissue. The myocardium (the muscular tissue of the heart), constitutes most of the mass of the heart; it is striated and it is constituted by myofibrils (containing actin and myosin filaments that slide along one another during contraction), separated by intercalated discs, gap junctions that allow an easily transit of the action potentials from a cell to another (cardiac muscle as syncytium of many heart muscle cells). Two syncytiums (atrial and ventricular syncytium) constitute respectively the walls of the two atria and ventricles allowing a delay during the passage of the electrical impulse from atria to ventricles; the atrial contraction ahead precedes the ventricular contraction (see section 1.3).[1]

The heart is anatomically divided in four cavities (chambers): two superior atria, separated by the inter-atrium septum and two inferior ventricles separated by the inter-ventricular septum. The left and right part of the heart are two separate pumps: one (right atrium and ventricle) pumps blood through the lungs (pulmonary circulation), while the other (left atrium and ventricle) pumps blood through the whole organism (peripheral circulation). The blood flows through the heart in one direction, from the atria to the ventricles, and finally to the circulation by means of four valves: atrioventricular (A-V) valves (on the right side of the heart, tricuspid and on the left side, mitral)

prevent backflow of blood during systole and semilunar valves (on the right side of the heart, pulmonary and on the left side, aortic) prevent backflow during diastole (see Figure 1.1).[1]

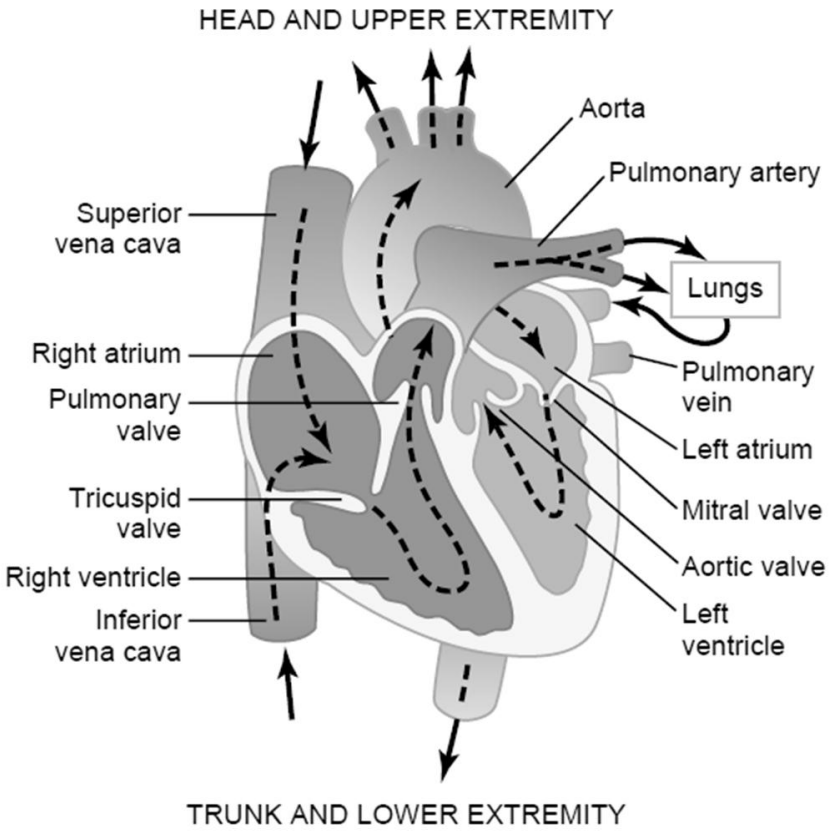


Figure 1.1 Structure of the heart and direction of blood through the heart (picture from[1]).

1.2 THE CIRCULATION

The three principal components of the circulatory system are the heart, the blood vessels, and the blood itself. Blood is composed from erythrocytes (red blood cells), leukocytes (white blood cells) and platelets (cell fragments) suspended in a liquid called plasma (the proportion of cells to plasma, i.e. hematocrit, is approximately 45% in men and 42% in women). About the 99% of blood cells are erythrocytes which contain hemoglobin (approximately 15 g/100 ml blood), a complex protein which has the ability to bind with oxygen, allowing blood to carry it; the leukocytes, cells of the immune system, defend the body against infection and foreign materials, while the thrombocytes play a key

role in blood clotting. The circulatory system, through the blood circulation, delivers nutrients to the body tissues, transports waste products away, conducts hormones from one part of the body to another and maintains homeostasis, allowing the organism to live. In an adult at rest, the amount of blood pumped in the circulation, i.e. cardiac output (CO), is about 4-6 liters per minute and it is mainly related to the cardiac rhythm of the heart and to the stroke volume (SV; amount of blood in milliliters ejected by the left ventricle on a given beat).

The circulation divided in two circuits: the pulmonary and the systemic circulation, which originate and terminate in the heart (Figure 1.2).

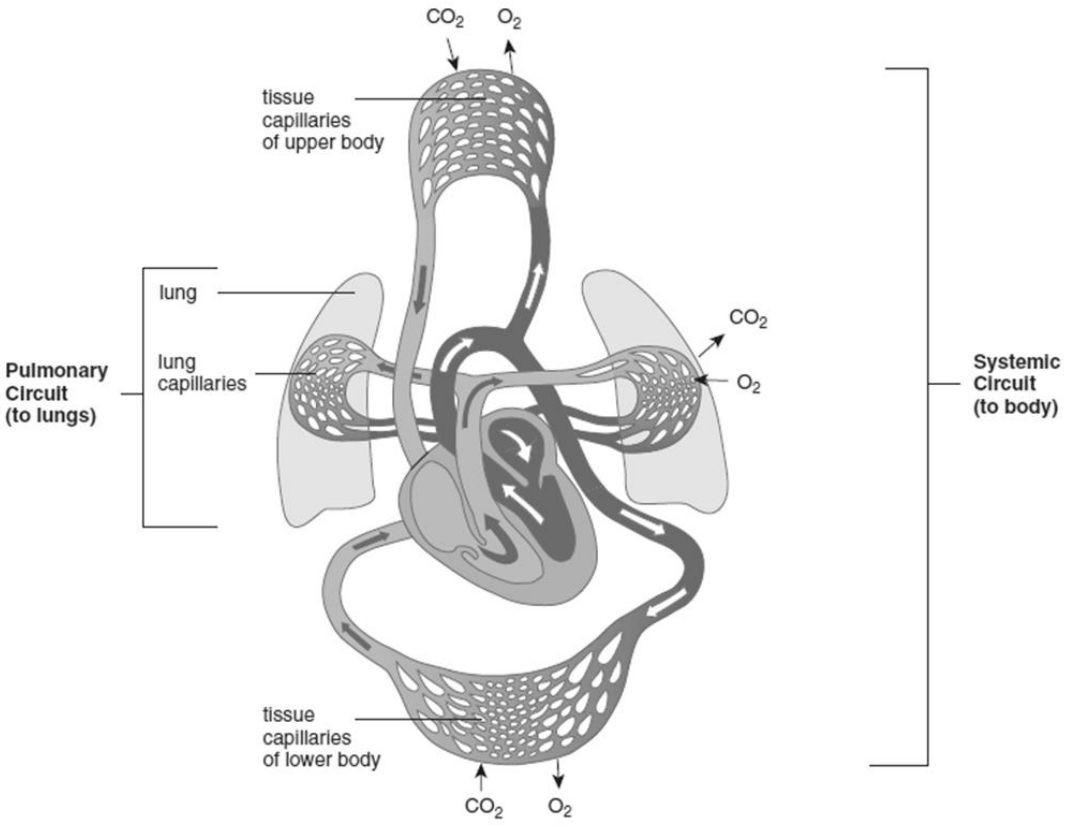


Figure 1.2 Pulmonary and systemic circulation. The right part of the heart pumps blood to the lungs while the left part pumps blood to the systemic tissue and organs. Pulmonary and systemic capillaries are responsible for gas exchange (picture from[3]).

The functional parts of the circulation may be summarized in arteries, arterioles, capillaries, venules and veins. The arteries are low-resistance tubes transporting blood under high pressure (from about 100 mmHg in the aorta to lower value of mean pressure in pulmonary arteries, about 16

mmHg).[1] The arterioles are smaller than arteries and consist in the major site of resistance to flow acting as control conduits through which blood flow into capillaries. Capillaries are the sites in which nutrients, fluid, electrolytes, hormones and other substances, are exchanged between blood and tissues. Finally, venules collect blood from capillaries and branch into larger veins, which conduct blood under low pressure (about 0 mmHg at the termination of the vena cava) from the venules back to the heart; they also provide another important function as a major reservoir for the extra blood.

The blood is not equally distributed in the body, about 84% of the total blood in the body is in the systemic circulation (64% in veins, 13% in arteries and a 7% in arterioles and capillaries), while 16% in heart and lungs.[1]

The pulmonary circulation propels blood through the lungs for exchanging oxygen and carbon dioxide; the systemic circulation provides blood to all other tissues of the body. In the pulmonary circulation, blood leaves the right ventricle via the pulmonary trunk supplying, through two pulmonary arteries, the right and left lung. In the lungs, the arteries branch in arterioles and capillaries (the smallest blood vessels which are parts of the microcirculation), in which the blood carries oxygen, then they converge in venules and veins to return into the left atrium through four pulmonary veins. In the systemic circuit, blood leaves the left ventricle via the aorta (the largest artery in the body), flows respectively into arterioles, which branch into the capillaries, which unite to form venules and then converge to form veins. The veins from the peripheral organs flow together into two large veins, the inferior vena cava which collects blood from below the heart, and the superior vena cava which collects blood from above the heart and from these veins the blood returns to the right atrium.

Three basic principles underlie all the circulatory functions:

1. the rate of blood flowing into each tissue of the body is precisely controlled in relation to the tissue need;
2. the cardiac output is controlled mainly by the sum of all the local tissue flows;
3. the arterial pressure is controlled independently of either local blood flow control or cardiac output control.

1.3 THE CARDIAC CYCLE

Cardiac cycle refers to all electromechanical events that occurs from the beginning of one heartbeat to the beginning of the next.

Each cardiac cycle is triggered by a spontaneous action potential, generated from the sinoatrial (S-A) node (depolarization of the S-A node in the right atrium); the electrical impulse is transmitted from the S-A node to the atrioventricular (A-V) node through the internodal pathways; the impulse is conducted from the atria into ventricles through the A-V bundle; finally, the left and right bundle branches of Purkinje fibers, conduct the cardiac impulse until the apexes of the ventricles (Figure 1.3). The intracellular potential rises from about -85 mV between beats to about 20 mV during each beat with an averaged action potential of about 105 mV. The electrical configuration of the conducting system allows a delay (about 0.1 sec) during the passage of the electrical impulse from atria to ventricles; so, the contraction of atria precedes the strong ventricular contraction.[2]

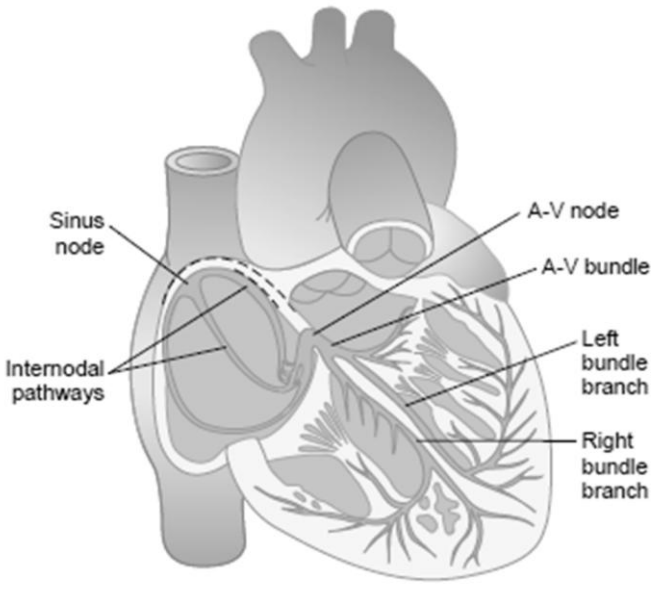


Figure 1.3 Rhythmical excitation of the heart. The electrical input is spontaneously generated by the S-A node, it is transmitted toward the A-V node trough internodal pathways and it is conducted to the atria trough the A-V bundle. The signal gets to the apexes of ventricles by means of Purkinje fibers, left and right bundle branch (picture from[4]).

The cardiac cycle is composed of two main phases: diastole, during which the heart fills with blood (period of relaxation) and systole, during which the heart acts as a pump (period of contraction). The duration of a cardiac cycle in an individual at rest is about 800 m, 500 ms during the diastole and about 300 during the systole.[2]

Blood flows continuously from the great veins into the atria; about 80% of the blood flows directly through the atria into ventricles (a process starting at the end of the systole), and increases of 20% during the atrial contraction corresponding to the P-wave on the ECG signal (during diastole the volume of each ventricle increase to about 110-120 ml, end-diastolic volume). Immediately after ventricular depolarization (beginning of the QRS complex on ECG signal; see section 1.5.1), the ventricular pressure rises abruptly causing the closure of the A-V valves and consequently (after 0.02-0.03 sec, period of isovolumic contraction, when the left ventricular pressure rises above 80 mmHg) the opening of the semilunar valves. After that, blood flows out of the ventricles (about 70% in the first third of the period of ejection). During the ventricular systole, the A-V valves are closed, the ventricular pressure increases and a large amount of blood accumulates in the atria. The high pressure in the large arteries just filled with blood, following the ventricles contraction, supports the closure of semilunar valves; ventricular pressures decrease rapidly for a period of 0.03-0.06 sec characterized by an unchanged ventricular volume, until the A-V valves open again (period of isovolumic relaxation). At the end of the systole the ventricular pressure falls again, the increases in atrial pressure push the A-V valves open and blood flows rapidly into the ventricles increasing the ventricular volume (period of rapid filling of the ventricles that lasts for about the first third of diastole). [1] Events of cardiac cycle are graphically represented in Figure 1.4.

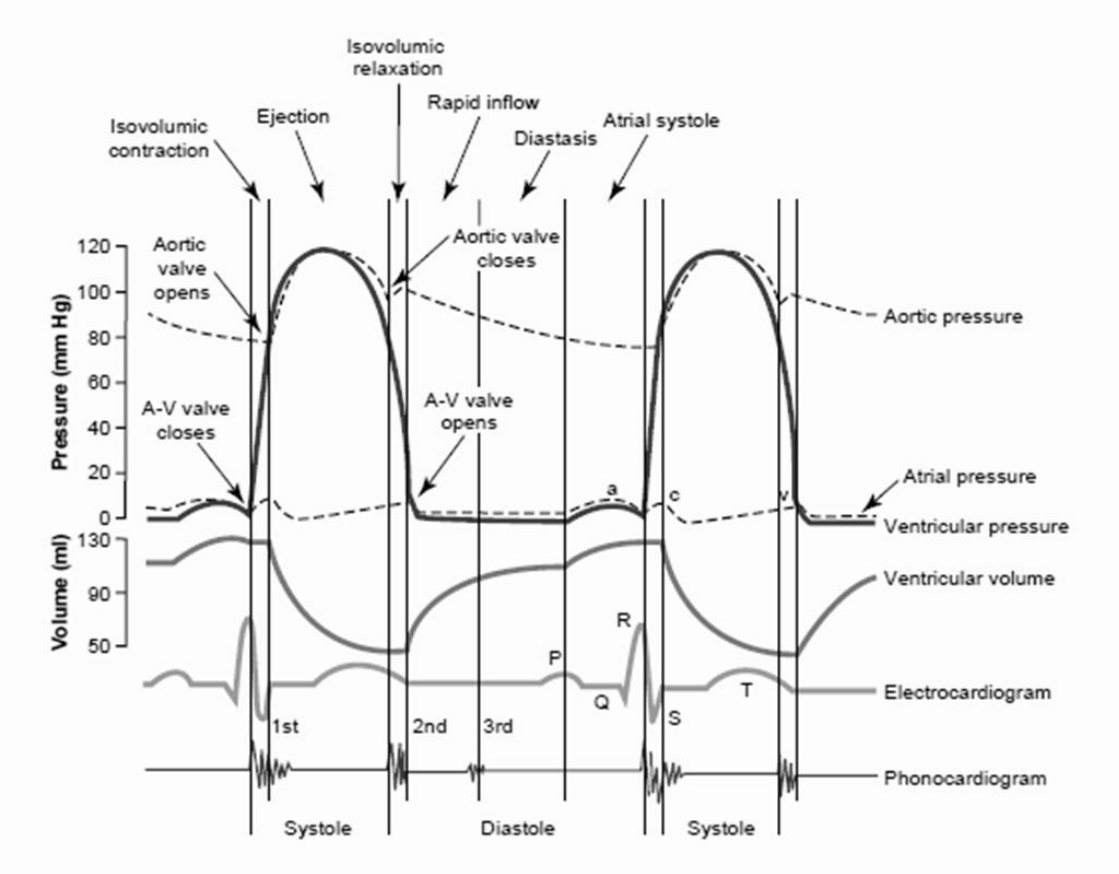


Figure 1.4 Events of the cardiac cycle. In the figure are displayed from top to bottom: changing in aortic, atrial and ventricular pressure; modification in ventricular volume; electrical events assessed by electrocardiogram and the heart sounds generated from vibrations created by closure of the heart valves and recorded by phonocardiogram. The 1st heart sound is caused by closure of the A-V valves while the 2nd heart sound is caused by closure of the semilunar valves. Sometimes it is possible to hear a 3rd heart sound due to rapid ventricular filling (picture from[1]).

1.4 MECHANISMS TO CONTROL THE CARDIOVASCULAR SYSTEM

1.4.1 CONTROL OF CARDIAC OUTPUT

Cardiac output (CO) refers to the amount of blood pumped by the left ventricle each minute, it is usually expressed in liters per minute. The cardiac output is determined by multiplying the heart rate (HR), number of heart beats each minute, and the stroke volume (SV), amount of blood pumped by the left ventricle each cardiac cycle[1]:

$$CO = HR \times SV$$

In the following sections will be provided an overview of the mechanisms involved in the control of the two determinants of the cardiac output: heart rate and stroke volume.

1.4.1.1 Control of heart rate

The autonomous discharge rate of the S-A node, in complete absence of any influences on the S-A node, is approximately 100 beats/min but under normal conditions the S-A node is under nervous or hormonal influences.[2]

The heart is controlled by sympathetic and parasympathetic (vagus) nerves of the neurovegetative system. The S-A node is innervated by parasympathetic and sympathetic postganglionic fibers: parasympathetic fibers employ acetylcholine as a primary neurotransmitter and their activity, via the muscarinic cholinergic (M) receptors, causes a decrease in heart rate; postganglionic neurons of the sympathetic system employ norepinephrine as the primary neurotransmitter and the activity in the sympathetic nerves, via the beta adrenergic ($\beta_{1\text{-}2}$) receptors, is responsible for an increase in heart rate. Under normal resting condition the activity of the parasympathetic fibers maintain what is called "vagal tone" of the heart, resulting in a resting heart rate significantly below the intrinsic firing rate of the S-A pacemaker. In a young adult human, a strong sympathetic stimulation can increase the heart rate from the normal rate of 72 beats per minute up to 180 to 200 beat per minutes, whereas a strong parasympathetic stimulation can decrease the heart rate up to 20 to 40 beat per minutes.[1]

Effects of autonomic nerves on the heart are displayed in Table 1.1.

Table 1.1 Autonomic control on the heart. Effects of sympathetic and parasympathetic stimulation on S-A node, A-V node, atrial muscle and ventricular muscle.

AREA AFFECTED	SYMPATHETIC NERVES	PARASYMPATHETIC NERVES
S-A node	Increased heart rate	Decreased heart rate
A-V node	Increased conduction rate	Decreased conduction rate
Atrial muscle	Increased contractility	Decreased contractility
Ventricular muscle	Increased contractility	Decreased contractility (negligible effect)

The sympathetic fibers are distributed mainly to the ventricles while the vagal fibers are distributed mainly to the atria (Figure 1.5), so in contrast to parasympathetic dominance over heart rate mainly in the resting state, the sympathetic system dominates the control of the strength of heart contraction, the cardiac contractility (see section 1.4.1.2).

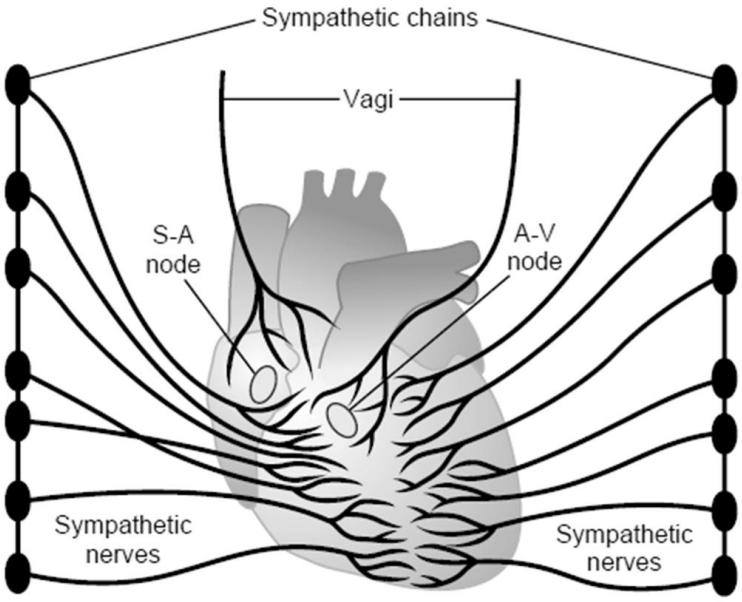


Figure 1.5 Cardiac sympathetic and parasympathetic fibers (picture from[1]).

Other less important factors are involved in modifying the heart rate as the plasma epinephrine. Epinephrine is an hormone synthesize from the adrenal medulla that increase the heart rate acting on the same beta adrenergic receptors in the S-A node where norepinephrine is released from postganglionic neurons of the sympathetic system. In addition, even the body temperature affects the heart rate: an increas in body temperature (e.g. fever) causes an increase in heart rate, while a decrease in temperature decreases it.[1]

1.4.1.2 Control of stroke volume

The mechanisms involved in the control of the stroke volume can be summarized in:

- changes in the end-diastolic volume (Frank-Starling mechanism);
- sympathetic action on ventricles;
- changes in afterload.

The end-diastolic volume is the volume of blood in the ventricles at the end of the diastole, just before contraction. The relationship between stroke volume and end-diastolic volume is known as the Frank-Starling mechanism (or Starling's law of the heart) that refers to the intrinsic ability of the

heart to control blood flow in relation to the changes in the volume of blood flowing into the heart; the greater the volume of blood entering the heart during diastole (venous return) stretching the heart muscle during filling), the greater the amount of blood ejected during systolic contraction and vice-versa. At any given heart rate, an increase in venous return causes an increase in the end-diastolic volume and thus the stroke volume.[1]

In the second mechanism, the sympathetic branch of the neurovegetative system acts via norepinephrine on the beta adrenergic (β_1) receptors increasing ventricular contractility, the strength of contraction at any given end-diastolic volume. The plasma epinephrine acts on the same receptors also increasing myocardial contractility. The action of both sympathetic nerve stimulation or plasma epinephrine do not depend from changes in end-diastolic volume.[1]

The last mechanism refers to the effect of the afterload on the stroke volume. The afterload is considered the arterial pressure against which the ventricle must contract; an increased arterial pressure tends to reduce the stroke volume, mainly in situations of heart failure.[1]

1.4.2 CONTROL OF BLOOD PRESSURE

Blood pressure (BP) is the force exerted by blood against the walls of blood vessels. During each heartbeat blood pressure varies from a maximum level during systole (SBP; systolic blood pressure), to a minimum level during diastole (DBP; diastolic blood pressure). In a healthy adult the normal values are approximately 120 mmHg for the systolic and 80 mmHg for the diastolic blood pressure.[1] Blood pressure is not homogeneously distributed across the circulatory system, it is higher in the systemic circulation compared to the pulmonary circulation and decreases as the blood is pumped away from the heart through arteries (Figure 1.6).

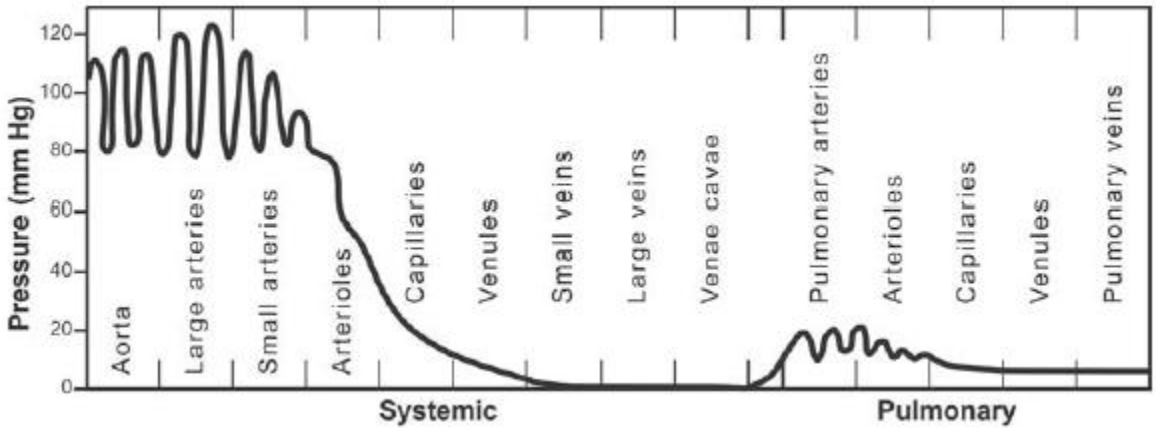


Figure 1.6 Modification in blood pressure across different types of vessels in the systemic and pulmonary circulation (picture from[2]).

The two main mechanisms to control the blood pressure are the baroreceptor feedback regulation and the renin-angiotensin-aldosterone system (RAAS).

1.4.2.1 Baroreceptor feedback regulation of arterial pressure

The baroreceptor reflex is a homeostatic mechanism providing short-term regulation of arterial pressure in a negative feedback loop: 1) a rise in arterial pressure stretches the baroreceptors (or pressure sensors) mainly localized in the carotid sinus (above the carotid bifurcation) and in the wall of the aortic arch; 2) baroreceptors transmit signals into the central nervous system. Signals from the carotid baroreceptors are transmitted through Hering's nerves to the glossopharyngeal nerves (ninth cranial nerves), and then to the tractus solitarius in the medullary area of the brain stem. Signal from the aortic baroreceptors are transmitted through the vagus nerves to the same tractus solitarius and medullary area; 3) feedback signals are sent back through the autonomic nervous system to the circulation to reduce or to increase the normal levels of arterial pressure.[1]

The baroreceptors respond extremely rapidly to changes in arterial pressure but are even more responsive to a rapidly changing pressure than to a stationary one. Baroreceptors of the carotid sinus respond to pressures ranging from about 60–180 mmHg: a decrease in blood pressure produces a decreased firing rate of the baroreceptors; conversely, an increase in blood pressure produces an increased firing rate.[1]

1.4.2.2 Renin-angiotensin-aldosterone system

The renin-angiotensin-aldosterone system (RAAS) plays an important role in blood pressure and fluid balance regulation. The most important site for renin formation is the kidney. The enzyme renin is secreted and released into circulation by specialized cells sited in the kidney, the juxtaglomerular cells. This secretion is activated in response to[5]:

1. sympathetic nervous system stimulation (acting through β_1-adrenoceptors);
2. decreased sodium delivery to the distal tubules;
3. decreased in arterial blood pressure as detected by baroreceptors.

Renin stimulates the production of angiotensin I, which is then converted in angiotensin II, via the angiotensin-converting enzyme (ACE). Angiotensin II has several functions in regulating blood volume, cardiac and vascular function, and arterial blood pressure[5]:

- it causes blood vessels constriction (Angiotensin II is a potent vasoconstrictor of arterioles), thus increasing systemic vascular resistance and blood pressure;
- it stimulates the secretion of the hormone aldosterone from the adrenal cortex. Aldosterone acts on the tubules of the kidneys to increase sodium and fluid retention, increasing the volume of fluid in the body and, therefore, increasing blood pressure;
- it stimulates the release of the antidiuretic hormone (ADH),vasopressin, from the posterior pituitary gland that acts increasing fluid retention in the kidneys and blood volume;
- it stimulates cardiac and vascular hypertrophy.

The production of angiotensine II (normally continuously synthesized under basal conditions) increases during exercise, dehydration, hypovolemia and hypertension.[5]

1.4.3 CONTROL OF THE TOTAL PERIPHERAL RESISTANCE

Arterioles are considered primary resistance vessels that, constricting or dilating their diameter, regulate arterial blood pressure and blood flow within organs. Under normal physiologic condition resistance vessels are partially constricted, a particular state of the vessel called vascular tone that it is generated by smooth muscle contraction within the wall of the blood vessel. Arterioles,

the main determinant of the systemic vascular resistance, are under local and extrinsic control mechanism that act modifying the arterioles' diameter. In general, vasoconstrictor mechanisms are responsible for maintaining the systemic vascular resistance and arterial pressure, while vasodilator mechanisms regulate the blood flow within organs.

Systemic vascular resistance (SVR), also called total peripheral resistance (TPR), is the resistance to blood flow offered by all peripheral vasculature in the systemic circulation. Mechanisms that cause vasoconstriction will increase SVR, while mechanism that cause vasodilatation will decrease SVR.

1.4.3.1 Local controls of the arterioles

The mechanisms involved in the local control of the arterioles, without involvement of nerves and hormones, can be summarized in:

- active hyperemia;
- flow autoregulation;
- reactive hyperemia;
- response to injury.

Active hyperemia refers to the phenomenon in which most organ and tissues manifest an increased blood flow (hyperemia) as a response to an increase in metabolic activity, resulting by arteriolar dilatation due to a changing in the chemical factors of the extracellular fluid (e.g. a decrease in the local concentration of oxygen when tissues become more active, which is used in the production of adenosine triphosphate).[4]

The mechanism of flow autoregulation, by contrast, is stimulated by a change in arterial pressure instead that by a changing in the metabolic activity, modifying the resistance of the vessels: when blood pressure decreases, local controls cause arteriolar vasodilatation which tends to maintain flow relatively constant; increases in arterial pressure cause the constriction of the arterioles to assure a constant blood flow. Changing in the chemical factors of the extracellular fluid (as mentioned above) and myogenic responses (direct responses of arteriolar smooth muscle to stretch caused by increased arterial pressure) are the two main factors involved in flow autoregulation.[4]

Furthermore, other two mechanisms are implicated in local control of arterioles in response to extreme situations: reactive hyperemia and response to injury; the former consists of a great transient increase in blood flow when an organ or tissue has had its blood supply completely occluded, the latter operates a vasodilatation in an injured area due to the locally release of substances that make arteriolar smooth muscle relax.[4]

1.4.3.2 Extrinsic controls of the arterioles

Most arterioles are innervated by sympathetic postganglionic nerve fibers employing norepinephrine as a primary neurotransmitter which binds to alpha adrenergic ($\alpha_{1\text{-}2}$) receptors on the vascular smooth muscle cells to cause contraction and thus vasoconstriction. The reduction in arteriolar diameter increases vascular resistance and decreases blood flow. On the other hand, with few exception, e.g. gastrointestinal circulation or genitalia erectile tissue, there is a little or less important parasympathetic involvement in the regulation of arterioles.[4]

Other mechanisms (see section 1.4.2.2) mediated by angiotensin are involved in the control of arterioles: angiotensin II acts directly, constricting resistance vessels, and indirectly, stimulating the release of vasopressin (that it also a vasoconstrictor), increasing SVR and arterial pressure.[4]

1.5 CARDIOVASCULAR RECORDING TECHNIQUES

1.5.1 ELECTROCARDIOGRAM

Electrocardiogram (ECG) is a non invasive technique for measuring the electrical activity of the heart (see section 1.3).

The normal ECG signal, as displayed in Figure 1.7, is composed by the following waves[1]:

- P wave: represents the atria depolarization. The main electrical vector is directed from S-A node to A-V node;
- QRS complex: represents the ventricles depolarization. The main electrical vector is directed from A-V node to the apex of ventricle;
- T wave: represents the electrical potentials generated during ventricles repolarization.

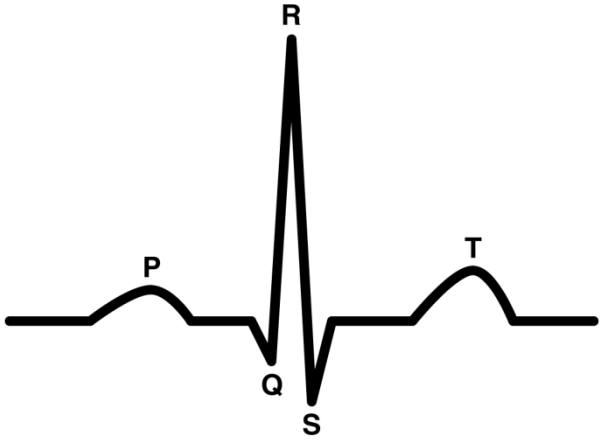


Figure 1.7 Electrocardiogram (ECG).

The beginning of atrial contraction is represented by P wave, whereas the QRS complex (ventricles depolarization) occurs at the beginning of ventricular contraction. The ventricles remain contracted until their repolarization (at the end of the T wave, 0.25-0.35 sec after depolarization). The atria repolarization (about 0.15-0.20 sec after termination of the P wave) is usually absent on electrocardiogram because is normally obscured by the QRS complex. P-Q interval is measured from the beginning of the P wave to the beginning of the QRS complex and reflects the time the electrical impulse takes to travel from the S-A node through the A-V node (about 0.16 sec). Q-T interval is measured from the beginning of the QRS complex to the end of the T wave (about 0.35 sec).

Normal voltages in the electrocardiogram mainly depend on the electrodes configuration adopted. Following the standard bipolar limb leads, the voltage of the ECG waves are[1]:

- 1.0-1.5 mV for the R wave;
- 0.1-0.3 mV for the P wave;
- 0.2-0.3 mV for the T wave.

The electric activity of the heart is recorded from the body surface using electrode leads. Conventional arrangement of electrodes for recording the standard ECG involves three bipolar leads based on Einthoven's triangle (Figure 1.8).[1]

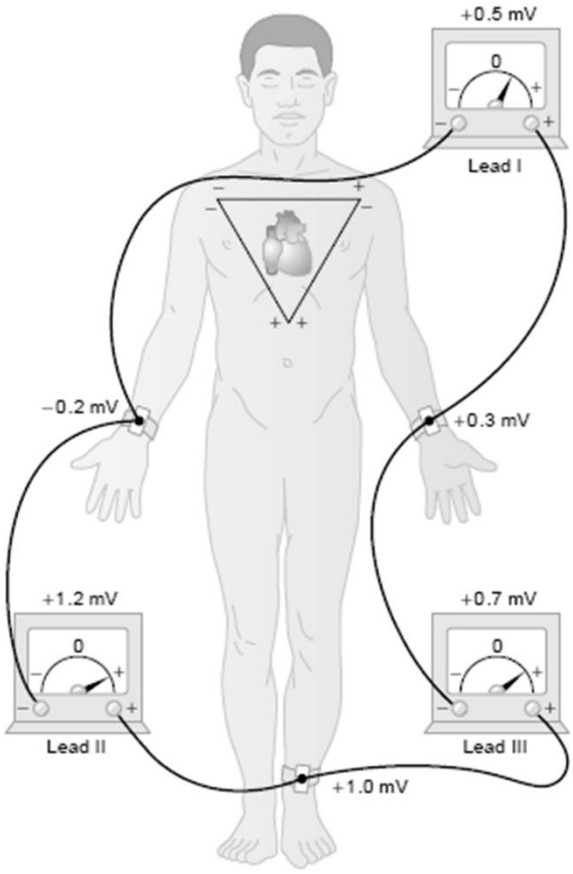


Figure 1.8 First, second and third derivation of the Einthoven configuration (picture from[1]).

1.5.1.1 Heart rate variability

Heart rate variability (HRV) is a physiological phenomenon describing the variations between consecutive heartbeats. The rhythm of the heart is continuously modulated by sympathetic and parasympathetic branches of the neurovegetative system (see section 1.4) resulting in fluctuation in heart rate. Several methods have been proposed to analyze the HRV, the most uses of which are: time-domain, frequency-domain and non-linear methods. Only the first two methods will be considered.

Time domain analysis measures the changes in heart rate over time. The simplest variable that measures the variability within the RR intervals is the standard deviation of RR intervals (SDNN), a global index of HRV reflecting the long-term components and circadian rhythms responsible for variability in the selected recording period. The square root of the mean squared successive heart period differences (RMSSD) is another time domain measures based on the variance of successive RR

interval differences. RMSSD has been applied in psychophysiology research as a measure of high frequency heart period variability and RSA (Respiratory Sinus Arrhythmia), although the RMSSD is also dependent from low frequency heart period variance.[6] Finally, pNN50 represents the percentage of differences between adjacent RR intervals that are greater than 50 ms and it is considered a measure of cardiac vagal tone modulation.[7]

Frequency domain methods describes the periodic oscillations of the RR interval series decomposing the overall heart period variance into different frequency bands, providing information on the amount of their relative intensity.[8,9] The power spectrum density (PSD) is commonly carried out employing the Fast Fourier Transformation (FFT) that decomposes the variance of a time domain representation into its frequency components. There are different peaks in the spectral density function for HRV. Two primary fluctuation of HRV are the RSA, a periodic high frequency (HF) component in a range of 0.15-0.4 Hz, and the low frequency oscillations, a low frequency (LF) component in a range of 0.04-0.15 Hz. The fluctuations below 0.04 Hz have been less investigated compared to the high and low frequency bands; they can be subdivided into very low frequency (VLF; 0.003-0.04 Hz) and ultra low frequency (ULF; 0-0.003 Hz).[8] HF band is a well accepted measure of parasympathetic nervous system activity (if the possible confounder effects of a change in respiratory rate are controlled), while LF band seems to be a mixture of sympathetic and parasympathetic influence.[8]

For a more exhaustive literature on the HRV, see.[8,9] while for a review of the interpretation of HRV measures and their implications in sleep studies, see.[10,11]

1.5.2 IMPEDANCE CARDIOGRAPHY

Impedance Cardiography (ICG) is a technique for measuring the electromechanical parameters of the heart. It is the most widely used "noninvasive technique" to assess the cardiac output by the estimation of stroke volume, derived from measurements of thoracic electrical impedance changes.[12]

The technique is based on the relationship that exists between voltage and resistance in a electrical circuit (first Ohm's law):

$$V = I \times R$$

In a circuit with constant current (I; Ampere, A), voltage (V; Volt, V) varies in direct proportion to resistance (R; Ohm, Ω).

Considering that blood (one of the body components with the lowest resistivity) is a conductor and the amount of blood varies within each cardiac cycle, each increase in thoracic blood volume following a heart-beat produces a changing in thoracic resistance.[12]

The Impedance Cardiograph System transmits a constant high-frequency alternating current (AC) through the chest (because the current is alternating, the resistivity to current depends of impedance), measure changes in thoracic impedance over changes in time in relation to the cardiac cycle, and provide an output voltage (reflecting the changes in impedance due to volumetric alterations in blood dinstribution and blood flow) considered reflecting the stroke volume.[12] The mathematical Kubicek's formula to estimate the stroke volume is the following:

$$SV = rho_b \times (L/Z_0)^2 \times LVET \times dZ/dt_{(max)}$$

SV is the stroke volume in ml, rho_b is the resistivity of blood (Ω × cm), L is the distance between the recording electrodes (cm), Z_0 is the baseline impedance between the recording electrodes (Ω), LVET is the left ventricular ejection time (sec) and $dZ/dt_{(max)}$ is the absolute value of the maximum rate of change in the impedance waveform on a given beat (Ω/sec).

Electrocardiogram (ECG) is also required for the ICG technique for two purposes:

1. for the measurements of heart rate;
2. for the identification of the onset of electromechanical systole (onset of the Q-wave in ECG signal).

Both purposes require a clear recording of the QRS complex. It is possible to assess the ECG from the impedance recording electrodes, but since does not provide a clear signal, additional ECG electrodes are often employed using typically lead II Einthoven configuration (see section 1.5.1).

1.5.2.1 Electrodes configuration

The tetrapolar band electrodes system is the electrode configuration mainly adopted in Impedance Cardiography study. Four longitudinal thin aluminium band electrodes (strips of adhesive tape, approximately 2.5 cm wide with an approximately 0.6 cm wide aluminium band inside) were

placed in tetrapolar configuration according to the configuration reported in the guidelines[12]: around the upper part of the neck (1) and the lower part of the neck (2); around the thorax at the xyphisternal joint level (3) and around the abdomen (4).

A 4 mA AC current at 100 kHz is transmitted through the thorax between the outer electrodes (source electrodes 1 and 4) and Z_0 (basal impedance; Ω), and dZ/dt (rate of change in the impedance waveform on a given beat; Ω/sec) signals are estimated from the two inner electrodes (2 and 3).[12]

The tetrapolar configuration is displayed in Figure 1.9.

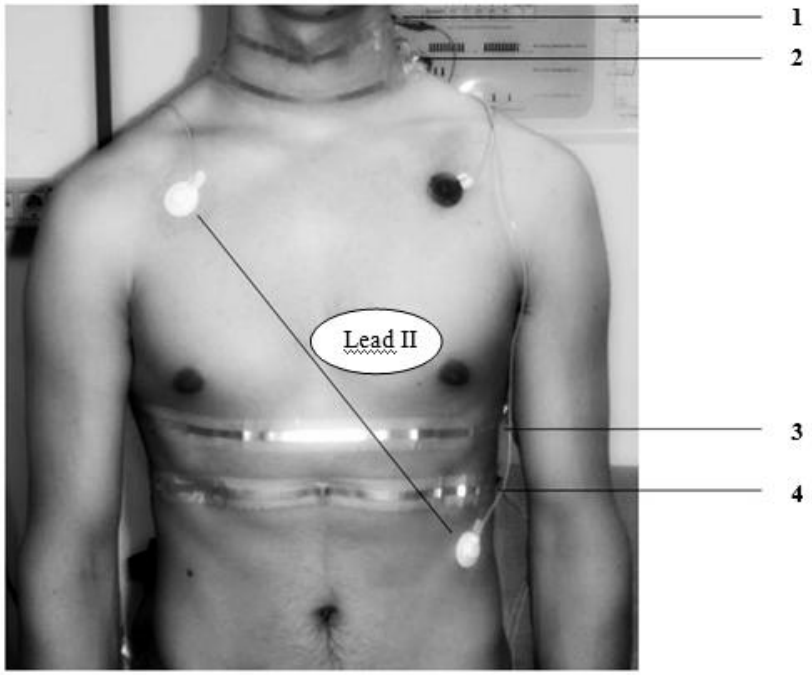


Figure 1.9 Tetrapolar band electrodes configuration. The outer electrodes (1 and 4) transmit the current while the inner electrodes (2 and 3) are used to measure voltage. ECG electrodes are displayed in lead II Einthoven configuration.

1.5.2.2 Impedance cardiogram and parameters

Waveforms (ECG, Z_0 and dZ/dt signals) normally adopted in a graphical representation for the analysis of data assessed by Impedance Cardiography are displayed in Figure 1.10.

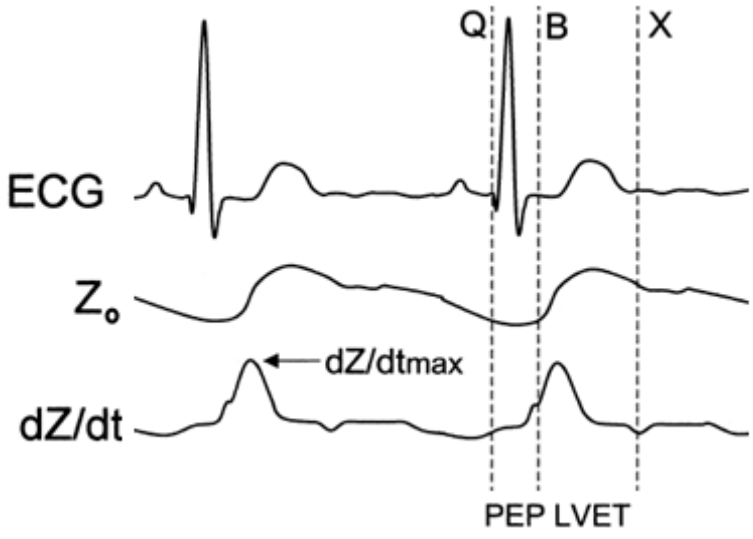


Figure 1.10 Impedance Cardiography waveforms: ECG signal, basal impedance (Z_0) and the 1st derivative of Z_0, i.e. dZ/dt signal. ECG Q-wave (Q) represents the onset of electromechanical systole; dZ/dt B-point (B) denotes the onset of the rapid upslope of dZ/dt signal and indicates the time of onset of left-ventricular ejection; dZ/dt X-point (X) denotes the lowest point in the dZ/dt signal and represents the closure of the aortic valve. PEP, pre-ejection period; LVET, left ventricular ejection time (picture modified from[2]).

Systolic time intervals, i.e. pre-ejection period (PEP) and left-ventricular ejection time (LVET), as well as volumetric measures, i.e. stroke volume (SV) and cardiac output (CO) are generally derived from the impedance signal. Two main points on dZ/dt signal, B and X, as well as Q wave onset on ECG signal (see section 1.5.1), are necessary to estimate such parameters.[12]

B-point denotes the onset of the rapid upslope of dZ/dt as it rises to its peak value ($dZ/dt_{(max)}$); it corresponds to the opening of the aortic valve (when the intraventricular pressure becomes higher than aortic pressure) and marks the time of the onset of left-ventricular ejection. In order to identify the B-point on dZ/dt signal, three methods are mainly used[12]:

1. maximum slope or maximum slope change (2nd derivative);
2. zero point crossing of the dZ/dt function (dZ/dt = 0);
3. about 55% of the time from R-wave on ECG signal to the peak $dZ/dt_{(max)}$.

X-point denotes the lowest point in the dZ/dt signal and represents the closure of the aortic valve at the end of left-ventricular ejection. X-point is usually well defined and easily recognized.

Pre-ejection period (PEP; time from the Q-point on the ECG signal to the B-point on the dZ/dt waveform) plays a main role in psychophysiology research because it is an index inversely related to the sympathetic β-adrenergic activity. PEP is the most accurate noninvasive measure reflecting the sympathetic influence of the neurovegetative system on the heart.[13] Effects of preload and afterload should be considered using PEP as an index of β-adrenergic activity to anticipate possible errors of interpretation:

- increases in preload ► decreases in PEP (increases in contractility via the heterometric autoregulation, Frank-Starling mechanism) independent of sympathetic influences;
- increases in afterload (increase in peripheral vascular resistance) ► increases in PEP.

A exhaustive set of ICG parameters is displayed in Table 1.2.

Table 1.2 ICG parameters.

Parameter	Abbrev.	Unit of measure	Definition	Derivation/Formula
Heart rate	HR	bpm	Number of heart beats each minute	R-R intervals on the ECG and derivation to beats per minutes
Stroke volume	SV	ml	Amount of blood pumped by the left ventricle each cardiac cycle	$SV = rho_b \times (L/Z_0)^2 \times LVET \times dZ/dt_{(max)}$ The terms of the equation are defined above
Cardiac output	CO	l/min	Amount of blood pumped by the left ventricle each minute	CO = SV × HR
Pre-ejection period	PEP	ms	Time interval from the beginning of electrical stimulation of the ventricles to the opening of the aortic valve (electrical systole).	Time from the Q-point on the ECG signal to the B-point on the dZ/dt waveform
Left-ventricular ejection time	LVET	ms	Time interval from the opening to the closing of the aortic valve (mechanical systole)	Time from the B-point to the X-point on the dZ/dt waveform
Systolic time ratio	STR	-	Time ratio of the electrical and mechanical systole	SRT = PEP/LVET
Cardiac index	CI	$l/min/m^2$	Cardiac output normalized for body surface area (BSA)	CI = CO/BSA
Stroke index	SI	$ml/beat/m^2$	Stroke volume normalized for body surface area (BSA)	SI = SV/BSA
Total peripheral resistance	TPR	$dyne\text{-}sec\times cm^{-5}$	Total peripheral resistance of the systemic vasculature. The determination of CO with simultaneously measurement of blood pressure (BP) permits the derivation of total peripheral resistance	TPR = MBP/CO×80 where MBP refers to mean blood pressure

2 NORMAL HUMAN SLEEP

"I am, I exist-that is certain. But for how long? For as long as I am thinking. For it could be that were I totally to cease from thinking, I should totally cease to exist".

(René Descartes)

In our life we spend our time continuously shifting from a state of wake, consciousness of the environmental events, to a state of sleep, unconsciousness, passing through states of extreme excitement, happiness, exhilaration, depression mood, fear, etc. These different states of brain activity result from different activating or inhibiting pool of neurons within the brain. Sleep is a specific state of brain activity characterized by reduced awareness and responsiveness, both to internal and external stimuli; it is distinguished from coma in which the person cannot be aroused.

Until the discover of rapid eye movements and thus the duality of sleep, sleep was universally considered as an inactive state of the brain, an intermediate state between wakefulness and death.

We pass an average of a third of our lives sleeping, sleep is indispensable for the survival of the species, nonetheless an exhaustive understanding of why we sleep is still controversial among specialists.

Several models to understand sleep and wakefulness processes have been proposed. One of these considers that the regulation of sleep-wake cycles depends from two distinct factors: a sleep-dependent homeostatic process (Process S) and a sleep-independent circadian process (Process C).[14] *The first process (S) is dependent on the previous sleeping and waking time; the propensity to sleep enhances during wake and declines during sleep. The second process (C) is independent on the previous sleeping and waking time; the propensity to sleep is driven by an endogenous factor which determines the rhythmic impulse to sleep. Therefore, the timing of sleep and waking is determined by the interaction between Process S and Process C.*

To sum up briefly, sleep is a complex state of the living organism endogenously generated and homeostatically regulated.

2.1 SLEEP ARCHITECTURE

Two different states characterize the normal human sleep: non-rapid eye movement (NREM) or synchronized sleep and rapid eye movement (REM) or desynchronized sleep. Furthermore, NREM sleep is subdivided into four sleep stages (Stage 1, Stage 2, Stage 3 and Stage 4) where Stage 3 and Stage 4 are commonly considered as slow wave sleep (SWS). Stage 1 sleep generally constitutes about 2 to 5 % of sleep, Stage 2 about 45 to 55 %, Stage 3 about 3 to 8 %, Stage 4 about 10 to 15 % and finally REM constitutes about 20 to 25 % of the night. NREM sleep is characterized by the absence of rapid eye movements and by a graduated synchronization of the EEG signal. On the contrary, REM sleep represents an active form of sleep, it is characterized by rapid eye movements and it shows a desynchronized EEG signal, similar to wake, with low amplitude and high frequencies waves.

During each night, REM and NREM cyclically alternate with each other. In the first sleep cycle, the normal young adult enters sleep through NREM sleep, usually through Stage 1 sleep that last only few minutes. This phase is a stage of transition associated with a low arousal threshold and also occurs as a transitional stage throughout the night. Following this brief phase, Stage 2 sleep occurs; it is triggered by K-complex or sleep spindle in EEG and last about 10-25 min. Stage 3 precedes Stage 4 sleep and both represent the slow wave sleep (SWS) or deep sleep characterized by high voltage and low frequency EEG signal; the arousal threshold in these stages rises to the highest level. Stage 3 sleep usually lasts only a few minutes in the first REM-NREM cycle while Stage 4 sleep generally lasts about 20-40 min and dominates the first cycle. In agreement with the standardized criteria for sleep scoring,[15] the difference between Stage 3 and 4 is the amount of the high-voltage slow wave activity ($\geq$ 75 μV, $\leq$ 2 Hz), respectively accounting for more than 20 % but less than 50 % of the EEG activity in Stage 3 sleep and more than 50 % in Stage 4 sleep. The passage from NREM to REM sleep in the first cycle is usually characterized by a presence of body movements underlying that sleep became “lighter”, brief episodes of Stage 3 sleep followed by few minutes of Stage 2 sleep. The initial REM episode is usually short (1-5 min) and it is usually followed by Stage 2 sleep, signaling the start of the next REM-NREM cycle.[16]

REM-NREM sleep cycles occur about every 90 min with a total of 4-6 cycles for night (the average length of the first REM-NREM sleep cycle is approximately 70 to 100 min while the average length of the subsequent cycles is about 90 to 120 min); NREM sleep accounts for 75-80% of sleep time; the first cycle is dominated by NREM sleep, in particular by SWS, while REM sleep dominates the last part of the night; the first REM episode usually lasts a few minutes and subsequent REMs progressively increase in duration. Brief episodes of wakefulness are dispensed latter in the night and tend to coincide with REM-NREM transitions; wakefulness within sleep usually accounts for less than 5% of the night.[16]

Usually the sleep structure is graphically represented by hypnogram, a summary of timing, duration, and sequence of every sleep stage throughout the sleep period (Figure 2.1).

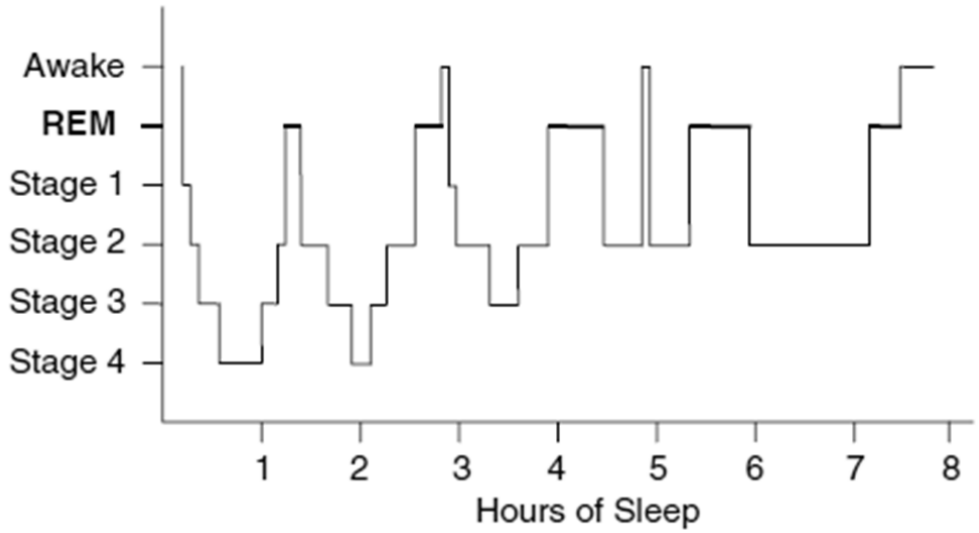


Figure 2.1 Young adult hypnogram (picture from[16]).

2.2 POLYSOMNOGRAPHY

Polysomnography (PSG) is a common technique employed in sleep studies, it consist of a comprehensive recording of the physiological changes that occur during sleep. The standard PSG monitors electroencephalographic (EEG), electrooculographic (EOG) and electromyographic (EMG)

activity. The EEG is the core measurement of polysomnography, indeed, the stages of NREM sleep, Stage 1, Stage 2 and slow wave sleep, are scored mainly using EEG signal. Additionally, EOG and EMG, respectively help to detect rapid eye movements and muscular atonia, typical features of REM sleep.

Electroencephalography is a technique that allows the recording of electrical activity in the brain's neurons, reflecting synchronous postsynaptic potentials in large groups of neurons, with a millisecond temporal resolution. It was discovered in 1924 by Hans Berger, a German psychiatrist, who performed the first electroencephalographic (EEG) recording in humans,[17] now it is one of the prime techniques for studying the human brain.

EEG generation depends of several process,[18] in particular:

1. role of post-synaptic potentials in cortical pyramidal neurons. Is hypothesized that the summation of post-synaptic potentials in cortical pyramidal neuron underlies the EEG oscillation. The synchronous activation of a large cluster of neurons and the orientation of their dendritic trunks, perpendicular to the cortical surface, allow summation and propagation of the signal to the scalp surface. Excitation at apical dendrites or inhibition of the soma provides negative potentials at the surface, while inhibition at apical dendrites or excitation of the soma provides positive potentials at the surface;
2. role of thalamo-cortical networks. Interactions between thalamic and cortical networks are considered to play a key role in specific EEG rhythms, in particular, alpha and beta oscillations (see below). Since the intrinsically rhythmical activity of thalamus is involved in EEG generation, the cortex generates the majority of scalp-recorded EEG oscillations;
3. role of local-scale and large scale synchronization. Neurons' synchronization involves a specific area of the brain, local-scale synchronization, as well as cluster of neurons of distant brain regions, large-scale synchronization (e.g. higher frequencies activity seems to originate from small neurons' population, while low frequencies activity from large cluster of neurons).

Different amplitudes and frequencies characterize EEG signal. In this connection, EEG signal can be subdivided into different bands: delta, theta, alpha, beta and gamma.[18]

Delta band reflects low-frequency activity in a range of 1-4 Hz; it is associated with sleep in healthy humans and neurological pathology. It is considered an inhibitory rhythm. Theta band reflects EEG activity in a range of 4-8 Hz and it is usually associated with sleep. Nevertheless, theta activity could be present during wakefulness: the first type of theta activity is widespread distributed on the scalp and is linked with drowsiness and impairment information processing; the second type of theta activity (frontal midline theta activity), is frontal midline distributed and is linked with focused attention, mental effort and effective stimulus processing. Alpha band reflects EEG activity in a range of 8-13 Hz with a typical amplitude of 10-45 μV (greatest amplitude over posterior, and in particular occipital, regions); it is usually associated with relaxed wakefulness. Alpha rhythm can best be seen when subjects have their eyes closed and can be suppressed by eye opening, sudden alerting and mental concentration. Beta band reflects high-frequency activity in a range of 13-30 Hz with a typical amplitude of 10-20 μV; it is associated with wake, increasing with attention and vigilance. It is mainly distributes over fronto-central regions and typically replaces alpha rhythm during cognitive activity suggesting that beta band reflect excitatory activities. Gamma band reflects high-frequency activity in a range of 36-44 Hz; it is associated with attention, arousal, object recognition and other mental processes. Gamma activity seems to be directly associated with brain activation.

EEG signal represents the differential voltage between two electrodes, an active electrode and a neutral electrode (reference electrode, it is usually placed on a low activity zone, i.e. mastoid). The wide accepted system for electrode configuration is the standardized International 10-20 system.[19] This system is based on the relationship between the location of an electrode and the underlying area of cerebral cortex. The name refers to the fact that the distances between adjacent electrodes are either 10% or 20% of the total nasion-inion or left-right mastoids distance of the skull. Each electrode site is identified with an alphabetic letter, representing the underlying area of the brain (F, frontal; C, central; P, parietal; O, occipital and T, temporal), and with a number, representing the position above that area (the odd numbers indicate the left hemisphere and the even numbers indicate the right hemisphere). This system allows EEG recording from 19 different sites across the scalp, nevertheless recent high-

resolution systems allows EEG recording up to 256 channels, thus increasing the spatial sampling of the EEG. The EEG electrodes for a nocturnal PSG are generally attached to the scalp using small gauze imbued with collodion. According to the American Academy of Sleep Medicine rules,[20] the recommended EEG derivation are F_4-M_1, C_4-M_1, O_2-M_1 (M_1, left mastoid); sampling rate, 500 Hz; low frequency filter, 0.3 Hz and high frequency filter, 35 Hz.

Electromyography (EMG) is a technique that allows the recording of electrical activity produced by skeletal muscles, by detecting the electrical potential generated by muscle cells. The EMG from muscles beneath the chin (mentalis or submentalis muscles) is used as a criterion for staging REM sleep.[20] EMG is recorded bipolarly and three electrodes should be placed to record it: one in the midline and above the inferior edge of the mandible, the last two electrodes below the inferior edge of the mandible, respectively to the right and to the left of the midline. Two electrodes are always employed for the recording, while the third electrodes is used as a back-up electrode. A sampling rate of 500 Hz and a low frequency filter of 10 Hz and a high frequency filter of 100 Hz should be adopted.[20]

Electrooculography (EOG) is a technique to record eye movement activity. EOG is based on the fact that the eye acts as a dipole with an anterior positive pole (cornea) and a posterior negative pole (retina). Assuming that the resting potential is constant, the recorded potential from electrodes placed beside the eyes is a measure for the eye position. The electrode placed nearest the cornea will register a positive potential, while the electrode nearest the retina will register a negative potential. During eye movements, the positions of the cornea and retina change compared to the fixed electrodes positions, allowing the recording of a potential change. The EOG allows the recording of REMs which is an essential sleep stage scoring criterion for staging REM sleep.[20] Furthermore, EOG is useful to assess slow eye movements (SEMs) which occur at sleep onset and/or with transitions to Stage 1 during the night. Following the American Academy of Sleep Medicine rules,[20] the recommended EEG derivation are LOC-M1 and ROC-M2 (LOC, left outer canthus; ROC, right outer canthus); sampling rate, 500 Hz; low frequency filter, 0.3 Hz and high frequency filter, 35 Hz.

2.3 SLEEP STAGING

The purpose of this section is to provide a brief summary of the main features of the sleep stages following the standardized criteria[20] for staging normal human sleep. Sleep stages (W, N1, N2, N3, R) are scored in 30-sec sequential epochs starting at the beginning of the study, a stage is subsequently assigned to each epoch.

Stage W (wakefulness). EEG is mainly characterized by alpha rhythm (8-13 Hz) that is dominant with eyes closure, attenuating with eyes opening. EOG tracing generally consist of eye blinks (conjugate vertical eye movements, 0.5-2 Hz) and rapid eye movements (conjugate, irregular, sharply peaked eye movements with an initial deflection lasting less than 500 ms). The EMG is characterized by a relatively high tonic activity that can be increased by voluntary movements (phasic activity).

Stage N1 (Stage 1 NREM sleep). EEG shows low amplitude (predominantly in a range of 4-7 Hz, i.e. theta band) and mixed frequency activity; it is characterized by the diminution of alpha waves. Especially during Stage 1, occurring at the beginning of the night, vertex sharp waves (sharply contoured waves lasting less than 500 ms, maximal over the central region) could be present and distinguishable from the background activity. SEMs (conjugate, regular, sinusoidal eye movements with an initial deflection lasting greater than 500 ms) are usually observable in the EOG. The EMG amplitude is variable and generally there is no discrete increase in EMG across the transition from wake to sleep. The EMG activity in NREM is more useful to detect and to mark arousals. Moreover, Stage 1 usually coincides with the sleep onset (the start of the first epoch scored as any stage other than stage W).

Stage N2 (Stage 2 NREM sleep). Low-voltage, mixed-frequency activity characterizes the background EEG activity. EEG markers of Stage 2 sleep are: K-complex (a well delineated negative sharp wave immediately followed by a positive component lasting greater than 500 ms) and sleep spindle (a train of distinct waves with frequency of 12-14 Hz and duration greater than 500 ms), separate from the background activity and maximal in amplitudes over the central region. The EOG usually shows no eye movement activity during Stage 2, even if SEMs may persist after the

appearance of K-complexes and sleep spindles. Since EOG channels also register EEG activity, K-complexes (high amplitude) may reflect on EOG channels. In Stage 2 the chin EMG usually shows variable amplitude, lower than in stage W.

Stage N3 (Stage 3 and 4 NREM sleep or SWS). SWS is defined by the present of high-voltage slow wave activity. In EEG tracing, slow waves have a frequency of 0.5-2 Hz and a peak to peak amplitude greater than 75 μV. Sleep spindle may persist and eye movement are not typically seen in SWS. The chin EMG usually shows variable amplitude, lower than in Stage 2, but may occasionally achieve very low levels similar to those in REM sleep.

Stage R (REM sleep). Rules to score REM sleep require: "desynchronized" EEG (usually, low amplitude and mixed frequency EEG activity), low chin EMG tone (tonic motor inhibition) and phasic burst of rapid eye movements on EOG. EEG tracing may show "sawtooth waves", trains of sharply contoured or triangular waves of 2-6 Hz with a maximal amplitude over the central regions, often preceding burst of rapid eye movements. Short irregular bursts of EMG activity usually lasting less than 250 ms superimposed on low EMG tone.

2.3.1 SLEEP ONSET

A crucial aspect of sleep is the sleep onset, this usually reflects the passage from wakefulness to NREM sleep. For many reasons, the definition of the exact moment in which an individual falls asleep, is still controversial among sleep specialists. The main parameters used in sleep scoring (EEG, EOG, EMG), as well as other physiological variables, do not show a discrete changing that could be used as a marker of the transition between wake and sleep Furthermore, there is not a clear and strong association between physiological indexes of sleep, i.e. a changing in EEG pattern, and behavioral changing that can indicate the presence of sleep.[21]

As sleep approaches, EMG may show a gradual diminution in the passage from wake to sleep, EOG shows slow eye movements and EEG normally changes from an alpha rhythm (8-13 Hz) to a mixed frequency pattern, stage 1 sleep (the occurring of slow eye movements usually precedes the changes in EEG activity). The onset of stage 1 sleep does not always coincides with perceived sleep

onset; therefore, many authors consider sleep onset coinciding with stage 2 sleep instead of stage 1 sleep.[21]

Considering sleep onset as a period rather than a specific point of time, which begin in wakefulness and continue through stage 1 and stage 2 sleep, the standardized sleep scoring system[15] seems to be inappropriate to detect the microstructure of the sleep onset period (SOP). Hori et al.[22] developed a system that precisely describes SOP. They subdivided the standard stages (wake, stage1 and stage 2) into nine stages based on EEG characteristics using 5-sec epochs. Wake is subdivided into two stages: alpha wave train and alpha wave intermittent (of more than 50% of the epoch); stage 1 is subdivided in six stages: alpha wave intermittent (of less than 50% of the epoch); EEG flattening; ripples, vertex sharp wave solitary, vertex sharp wave train or bursts, vertex sharp waves and incomplete spindles; finally stage 2 sleep corresponds to stage 9 of Hori et colleagues' system (or stage spindles).

For an exhaustive review about the process of falling asleep see.[23]

2.4 CARDIOVASCULAR MODIFICATION DURING SLEEP

Several physiologic modifications during sleep are associated with fluctuations in both autonomic branches of neurovegetative system that affects most organ systems in our body. In NREM sleep sympathetic activity does not show large changes in comparison to wakefulness, while the parasympathetic activity increases through vagus nerve dominance across sleep stages. While in NREM sleep the autonomic activity is relative stable (reflecting a prevalent parasympathetic activity associated with a quiescence of the sympathetic branch), REM sleep is characterized by a great variability in sympathetic activity that occurs in association with phasic changes in tonic parasympathetic engage.[24]

Heart rate variability (HRV) analysis is the most commonly used method to assess the autonomic influence of the neurovegetative system on the heart (see section 1.5.1.1). The employment of this technique in sleep studies suggests that cardiac parasympathetic tone increases from wake to sleep[25] and it is higher in NREM sleep compared to REM sleep.[26-29] Furthermore, vagal tone increases

within NREM sleep, from Stage 1 to Stage 4 sleep.[29] Since the methodological difficulties and an unclear meaning of the LF components of HRV, measures of central sympathetic activity have produced elusive results. Notwithstanding, studies employing the Impedance Cardiography to assess pre-ejection period, an index inversely related to the sympathetic β-adrenergic activity, found a decrease of sympathetic activity during sleep.[30,31]

The cardiovascular system is generally more stable in NREM sleep compared to REM sleep and the cardiac activity is markedly reduced in NREM sleep. HR sharply falls immediately after sleep onset without further significant changes between Stage 2 and SWS,[32] even if, under circadian influences, it continues to fall during the night.[31] BP that is less dependent from circadian control, is characterized by a sleep-related abrupt drop (5-15%) immediately following the sleep onset (pattern knows as "dipping BP profile"); BP is relatively constant over time within each stage of sleep and increases at morning wakefulness.[33]

Veerman et collegues,[34] as they were comparing cardiovascular variable during night time and daytime, found a substantial decrease in BP (9 mmHg), HR (18 bpm) and CO (29%), a small change in SV (7%), and an increase in TPR (22%). The circadian profile of these variables is shown in Figure 2.2

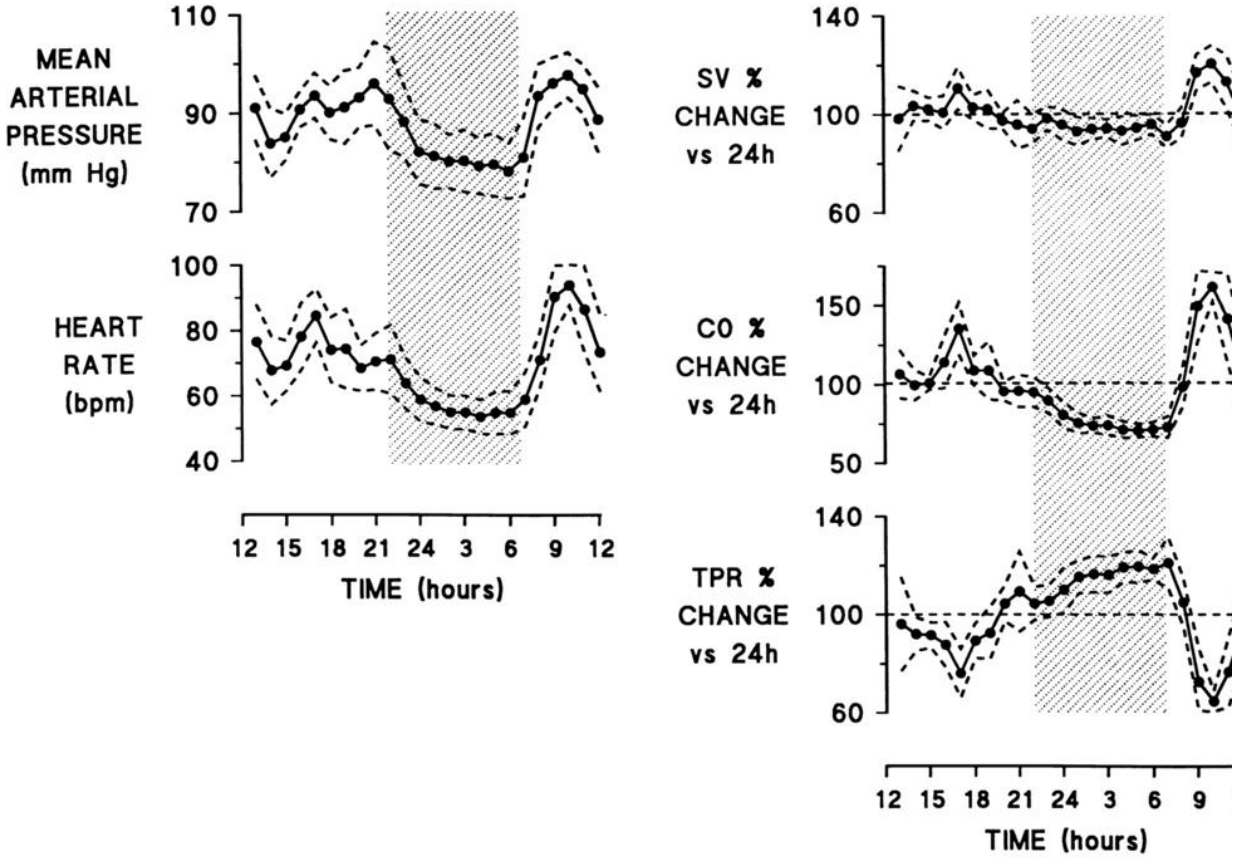


Figure 2.2 Cardiovascular modifications of hourly averages of mean arterial pressure and heart rate, and averaged percentage changes of stroke volume (SV), cardiac output (CO) and total peripheral resistance (TPR) compared with their 24-hour averages (reference level). The dotted line represents the 95% confidence intervals and the highlighted line represents the night hours where subjects stayed in bed from 10 pm to 7 am (picture modified from[34]).

Cerebral blood flow (CBF) and cerebral metabolic rate (CMR) decrease in NREM sleep (mainly in deep sleep) compared to wakefulness, while levels of CBF and CMR increase or remain unchanged in REM sleep.[35] A Transcranial Doppler Sonography study[36] showed that the mean cerebral blood flow velocity (considered reflecting the CBF) in stages 2, 3 and 4 was 15% lower than during wakefulness, while REM did not differ from the waking period.

3 PRIMARY INSOMNIA

"I am having trouble trying to sleep
I am counting sheep but running out
As time ticks by
And still I try
No rest for crosstops in my mind

On my own, here we go

My eyes feel like they are gonna bleed
Dried up and bulging out my skull
My mouth is dry
My face is numb
*F***ed up and spun out in my room*

On my own, here we go

My mind is set on overdrive
The clock is laughing in my face
A crooked spine
My senses is dulled
Passed the point of delirium

On my own, here we go […]".

("Brain Stew", Green Day)

"Perhaps, I will be able to sleep when I will be dead" (my flatmate).

3.1 CLASSIFICATION

Commonly, insomnia refers to an inadequate sleep quality or quantity experienced by a subject despite having an adequate opportunity to sleep.

Considering insomnia as a sleep disorder, the diagnostic criteria for an insomnia diagnosis are included in two mains nosologic classification: International Classification of Sleep Disorders, second edition (ICSD-2[37]) and Diagnostic and Statistical Manual of Mental Disorders, fourth edition, text revision (DSM-IV-TR[38]).

The second edition of the International Classification of Sleep Disorders[39] classifies sleep disorders into eight major categories (Table 3.1).

Table 3.1 The diagnostic classification of sleep disorders in agreement with the ICSD-2.

Insomnia	Adjustment Insomnia (Acute Insomnia)
	Psychophysiological Insomnia
	Paradoxical Insomnia
	Idiopathic Insomnia
	Insomnia Due to Mental Disorder
	Inadequate Sleep Hygiene
	Behavioral Insomnia or Childhood
	Insomnia Due to Drug or Substance
	Insomnia Due to Medical condition
	Insomnia Not Due to Substance or Know Physiological Condition. Unspecified (Nonorganic Insomnia, NOS)
	Physiological (Organic) Insomnia, Unspecified

Sleep Related Breathing Disorders	Central Sleep Apnea Syndromes ▪ Central Sleep Apnea Due to Cheyne Stokes Breathing Pattern ▪ Central Sleep Apnea Due to High-Altitude Periodic Breathing ▪ Central Sleep Apnea Due to Medical Condition Not Cheyne Stokes ▪ Central Sleep Apnea Due to Drug or Substance ▪ Central Sleep Apnea of Infancy (Formerly Primary Sleep Apnea of Newborn) Obstructive Sleep Apnea Syndromes ▪ Obstructive Sleep Apnea, Adult ▪ Obstructive Sleep Apnea, Pediatric Sleep Related hypoventilation/Hypoxemic Syndromes ▪ Sleep Related Nonobstructive Alveolar Hypoventilation, Idiopathic ▪ Congenital Central Alveolar Hypoventilation syndrome Sleep Related Hypoventilation/Hypoxemia Due to Medical Condition ▪ Sleep Related Hypoventilation/Hypoxemia Due to Pulmonary Parenchymal or Vascular Pathology ▪ Sleep Related Hypoventilation/Hypoxemia Due to Lower Airways Obstruction ▪ Sleep Related Hypoventilation/Hypoxemia Due to Neuromuscolar and Chest Wall disorders Other Sleep Related Breathing Disorder ▪ Sleep Apnea/Sleep Related Breathing Disorder, Unspecified
Hypersomnias of Central Origin Not Due to a Circadian Rhythm Sleep Disorder, Sleep Related Breathing Disorder, or Other Cause of Disturbed Nocturnal Sleep	Narcolepsy With Cataplexy Narcolepsy Without Cataplexy Narcolepsy Due to Medical Condition Narcolepsy, Unspecified Recurrent Hypersomnia Idiopathic Hypersomnia With Long Sleep Time Idiopathic Hypersomnia Without Long Sleep Time Behaviorally Induced Insufficient Sleep Syndrome Hypersomnia Due to Medical Condition Hypersomnia Due to Drug or Substance Hypersomnia Not Due to Substance or Known Physiological condition (Nonorganic Hypersomnia, NOS) Physiological (Organic) Hypersomnia, Unspecified (Organic Hypersomnia, NOS)

Circadian Rhythm Sleep Disorders	Circadian Rhythm Sleep Disorder, Delayed Sleep Phase type (Delayed Sleep Phase Disorder) Circadian Rhythm Sleep Disorder, Advanced Sleep Phase Type (Advanced Sleep Phase Disorder) Circadian Rhythm Sleep Disorder, Irregular Sleep-Wake Type (Irregular Sleep-Wake Rhythm) Circadian Rhythm Sleep Disorder, Frre Running Type (Nonentrained Type) Circadian Rhythm Sleep Disorder, Jet Lag Type (Shift Work Disorder) Circadian Rhythm Sleep Disorder Due to Medical Condition Other Circadian Rhythm Sleep Disorder (Circadian Rhythm Disorder, NOS) Other Circadian Rhythm Sleep Disorder Due to Drug or Substance
Parasomnias	Disorders of Arousal (From NREM Sleep) ▪ Confusional Arousals ▪ Sleepwalking ▪ Sleep Terrors Parasomnias Usually Associated With REM Sleep ▪ REM Sleep Behavior Disorder (Including Parasomnia Overlap Disorder and Status Dissociatus) ▪ Recurrent Isolated Sleep Paralysis ▪ Nightmare Disorder Other Parasomnias ▪ Sleep Related Dissociative Disorders ▪ Sleep Enuresis ▪ Sleep Related Groaning (Catathrenia) ▪ Exploding Head Syndrome ▪ Sleep Related Hallucinations ▪ Sleep Related Eating Disorder ▪ Parasomnia, Unspecified ▪ Parasomnia Due to Drug or Substance ▪ Parasomnia Due to Medical Condition
Sleep Related Movement Disorders	Restless Legs Syndrome Periodic Limb Movement Disorder Sleep Related Leg Cramps Sleep Related Bruxism Sleep Related Rhythmic Movement Disorder Sleep Related Movement Disorder, Unspecified Sleep Related Movement Disorder Due to Drug or Substance Sleep Related Movement Disorder Due to Medical Condition

Isolated Symptoms, Apparently Normal Variants and Unresolved Issues	Long Sleeper
	Short Sleeper
	Snoring
	Sleep Talking
	Sleep Starts (Hypnic Jerks)
	Benign Sleep Myoclonus of Infancy
	Hypnagogic Foot Tremor and Alternating Leg Muscle Activation During Sleep
	Propriospinal Myoclonus at Sleep Onset
	Excessive Fragmentary Myoclonus
Other Sleep Disorders	Other Physiological (Organic) Sleep Disorder
	Other Sleep Disorder Not Due to Substance or Known Physiological Condition
	Environmental Sleep Disorder

The concept of primary insomnia following the ICSD-2[39] includes psychophysiological insomnia, sleep state misperception, idiopathic insomnia, and some cases of inadequate sleep hygiene. The closest definition of primary insomnia is the psychophysiological insomnia, which resembles primary insomnia in particular for the concepts of arousal and conditioning factors.

On the other hand, in accord to the DSM-IV-TR,[40] sleep disorders are organized into four major sections (Table 3.2).

Table 3.2 The diagnostic classification of sleep disorders in agreement with the DSM-IV-TR.

Primary Sleep Disorders	Dyssomnias ▪ Primary Insomnia ▪ Primary Hypersomnia ▪ Narcolepsy ▪ Breathing-Related Sleep Disorder ▪ Circadian Rhythm Sleep Disorder ▪ Dyssomnia Not Otherwise Specified Parasomnias ▪ Nightmare Disorder ▪ Sleep Terror Disorder ▪ Sleepwalking Disorder ▪ Parasomnia Not Otherwise Specified

Sleep Disorder Related to Another Mental Disorder	Insomnia Related to Another Mental Disorder Hypersomnia Related to Another Mental Disorder
Other Sleep Disorders	Sleep Disorder Due to a General Medical Condition ▪ Insomnia Type ▪ Hypersomnia Type ▪ Parasomnia Type ▪ Mixed Type
Substance-Induced Sleep Disorder	Insomnia Type Hypersomnia Type Parasomnia Type Mixed Type With Onset During Intoxication With Onset During Withdrawal

The diagnostic criteria for primary insomnia from the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR[40]) are as follows:

A. the predominant complaint is difficulty initiating or maintaining sleep, or non restorative sleep, for at least 1 month;
B. the sleep disturbance (or associated daytime fatigue) causes clinically significant distress or impairment in social, occupational, or other important areas of functioning;
C. the sleep disturbance does not occur exclusively during the course of Narcolepsy, Breathing-Related Sleep Disorder, Circadian Rhythm Sleep Disorder, or a Parasomnia;
D. The disturbance does not occur exclusively du ring the course of another mental disorder (e.g. Major Depressive Disorder, Generalized Anxiety Disorder, a delirium);
E. The disturbance is not due to the direct physiological effects of a substance (e.g. a drug of abuse. a medication) or a general medical condition.

3.2 EPIDEMIOLOGY, ASSOCIATIONS, AND CONSEQUENCES OF INSOMNIA

In order to esteem the impact of insomnia on our society, different parameters must be taken into account: the criteria used to define insomnia (from symptom to disorder, from the concept of "unsatisfactory sleep" to the more recent standardized definitions of insomnia, from a night-time disorder to a daytime consequences), as well as the population studied (primary care offices, out-patient clinics, cohorts and general populations).

Epidemiological data suggest that about one-third of the general population suffers from symptoms of insomnia, 9 – 15% when daytime consequences are taken into account; 8 – 18% of the general population reports sleep dissatisfaction while about 6% of people satisfy the DSM-IV[38] criteria for a diagnosis of insomnia[41]. Morin et al.[42] interviewed a large sample (2001 subjects), reporting that 25.3% were unsatisfied with their sleep, 29.9% suffered from symptoms of insomnia and 9.5% met DSM-IV[38] and ICD-10[43] criteria for a diagnosis of insomnia. Ohayon and Reynolds,[44] in a recent cross-sectional study, interviewed 25,579 individuals over 7 different European countries. They found sleep dissatisfaction in 37% of the subjects, at least a symptom of insomnia (difficulty initiating or maintaining sleep and non-restorative sleep at least 3 nights per week) in 34.5% of the sample, symptoms with daytime consequences in 9.8% of the total sample, while at diagnostic level the 6.6% of the individuals responded to the DSM-IV criteria for an insomnia diagnosis but only the 3% of the subjects were primary insomniacs.

Most epidemiologic evidence suggests a female predisposition of insomnia[45] and symptoms of insomnia increase with aging.[41,45] Zhang and Wing[45] applied meta-analytic methods to investigate sex differences in the risk of insomnia. Analyzing 29 different studies (1,265,015 participants, female/male: 718,828/546,187), they reported a risk ratio of 1.41 for female versus male; Comparing the sex difference in the prevalence of insomnia with the age (elderly: $\geq$ 65 years; middle-age: 31-64 years; young adult: 15-30 years), they found major risk of insomnia among females with a risk ratio (female/male) increased from 1.28 in young adult to 1.73 in elderly subjects.

In addition to insomniacs' nocturnal symptoms (i.e. difficulty in falling asleep, maintaining sleep or non-restorative sleep), daytime consequences are frequently reported by insomnia sufferers, in

particular, increased daytime sleepiness, fatigue, mood disturbance, exhaustion, dysphoria and reduced quality of life; moreover, evidence of cognitive dysfunction (see section 3.6), i.e. decreased attention and memory, seems to be present within insomniacs.[46] Moreover, insomnia is associated with depression[47,48] and anxiety[47,49] and seems to be associated with an increased risk for cardiovascular diseases.[50] Nilsson and colleagues[51] and Mallon and colleagues[52] reported an association between insomnia and mortality, although depression, known to be associated with an increased risk for cardiovascular disease,[53,54] was not considered in these studies. Furthermore, hypertension, one of the most prevalent and powerful contributors to cardiovascular diseases,[55] seems to be more prevalent in insomnia patients than in good sleepers.[56-59] Other evidence suggested elevated heart rate and altered heart rate variability (HRV) in insomnia patients (see below) that are known to be risk factors for cardiovascular disease and mortality.[60,61]

Furthermore, it has been shown that insomnia is linked with absenteeism (at least twice in workers with insomnia than workers without insomnia),[62,63] accidents,[62] decreased productivity and efficiency at work and decreased job satisfaction.[62,64] The socioeconomic impact of insomnia seems to be considerable. A study conducted in the province of Quebec, Canada[65] estimated an annual direct and indirect cost per-person to the community of $5,010 for individuals with insomnia, $1,431 for those with insomnia symptoms, and $422 for good sleepers.

3.3 MODELS OF INSOMNIA

3.3.1 BEHAVIORAL PERSPECTIVE

Predisposing (biological, psychological and social), precipitating (stressful life events) and perpetuating factors (excessive time in bed, irregular timing of retiring and arising, multiple bouts of sleep, increased caffeine consumption, hypnotic and alcohol use, and daytime worries) contribute to the development of insomnia. Acute insomnia may occurs if predisposing and precipitant factors exceed a critical threshold of “sleep disruption”; insomnia becomes chronic only in the presence of concomitant perpetuating factors. After an episode of insomnia, subjects can develop maladaptive

coping strategies that may result in a conditioned arousal; this condition can perpetuate insomnia after precipitating factors have decreased.[66]

3.3.2 NEUROCOGNITIVE PERSPECTIVE

The neurocognitive perspective,[67] referring to the behavioral model, focuses specifically on a form of conditioned arousal: the cortical arousal. The authors propose that a high frequency EEG activity (beta and gamma ranges) founded in insomniacs at or around sleep onset is a main trait of chronic insomnia and may explain the differences in sensory and cognitive phenomena (e.g. discrepancies between polysomnographic measures and the subjective impressions regarding sleep quality and quantity reported by insomniacs) between insomniacs and good sleepers. Insomnia becomes chronic with the presence of perpetuating factors, there is an enhance of high frequency EEG activity (that occurs as result of classical conditioning) at or around sleep onset and/or during NREM sleep. This increased beta/gamma activity (elicited in response to the visual and/or temporal cues linked with sleepiness and sleep) seems to be related to increased sensory and information processing and to the attenuation of mesograde amnesia.

3.3.3 COGNITIVE MODEL

Cognitive model[68] considers insomnia as a consequence of cognitive processes; insomniacs tend to be worried about sleep and daytime consequences. This triggers autonomic arousal (result of sympathetic nervous system activation) and emotional distress causing an anxious state. Selective attention and monitoring are shifted internally (i.e. body sensations) and externally (i.e. the environment) for sleep-related threats developing an overestimation of the perceived deficit in sleep and daytime consequence. Counterproductive safety behaviors and erroneous belief abut sleep are also involved in this sequence of events and may lead to a real deficit in sleep and daytime functioning.

3.3.4 INTEGRATED PSYCHOBIOLOGICAL INHIBITION MODEL

The integrate psychobiological inhibition model[69] is developed as a critical review of the previously reported conceptual models about the development and persistence of insomnia. Good sleep (neurobehavioral system characterized by functional plasticity and automaticity) is viewed as a

natural state of the human organism; homeostatic and circadian process, in addition to the self-perception of good quality sleep, define the core of the model. Four interacting subsystem, sleep-stimulus control (sleep-compatible conditioning, sleep-wake sensitivity/specificity, regular sleep habits), physiological de-arousal (sleep system engagement, wake system disengagement, good sleep hygiene), cognitive de-arousal (minimal cognitive drive, accurate sleep-wake attribution), and daytime facilitation of night sleep (accurate wake-sleep attribution, effective coping skill) complete the model. In a reciprocal way, sleep homeostasis, circadian timing, and sleep quality serve to reinforce and maintain these processes. Insomnia is triggered by the acute inhibition of one or more processes associated with good sleep and may become chronic with the development of a constant inhibition in predisposed individuals.

3.3.5 PHYSIOLOGICAL MODELS OF INSOMNIA

Sleep–wake homeostatic model.[70] This model hypothesizes that primary insomnia may be the consequence of a failure in homeostatic regulation of sleep, or an attenuated increase in the sleep drive with time awake, and/or defective sensing of sleeping need.

Circadian clock model.[70] A dysfunctional circadian clock (changes in the timing of sleep-wake propensity) is considered responsible for primary insomnia.

Intrinsic sleep–wake state mechanism models.[70] Primary insomnia can result from an abnormal functioning of the systems responsible for expression of the sleep states.

Extrinsic over-ride mechanism (stress-response) model.[70] The overactivity of one of the systems considered “extrinsic” to normal sleep–wake control (e.g. stress-response system) is considered responsible for primary insomnia.

3.4 HYPERAROUSAL AND INSOMNIA

Hyperarousal is a status of hyperexcitation, a discrepancy between stimulus intensity and response amplitude. The concept of hyperarousal seems to be central in insomnia disorder.

Although the etiological mechanisms of primary insomnia are still unknown, several models suggest that a chronic condition of hyperarousal underlies the disorder. This condition is considered responsible to both night time sleep disorder and daytime complaints.

Bonnet and Arand,[71] in their theoretical review, provide evidence that primary insomnia is a primary physiological disorder of hyperarousal that can be measured and treated. They suggest that two independent systems are involved in sleep: the sleep system (involved in the sleep requirement) and the arousal system (involved in the level of physiological arousal). The relationship between the two systems is illustrated in Table 3.3.

Table 3.3 Relationship between sleep requirement (short and long) and basal arousal level (low and high) systems.

		Basal arousal level	
		Low	**High**
Sleep requirement	**Short**	*Sleepiness without objective findings*	*Insomnia*
	Long	*Idiopathic hypersomnolence*	*Sleep State of Misperception insomnia*

Situational factors (e.g. sleep, sleep deprivation, drugs, circadian time and activity) determine phasic modifications of the basal arousal level.

Evidences of influences of the arousal on sleep are suggested below:

- Increased arousal levels may produce insomnia sleep pattern and symptoms. In a study, the metabolic effect of caffeine was used to develop a physiological arousal model of chronic insomnia.[72] 12 normal young men received 400 mg of caffeine 3 times a day for 7 nights and days. The results showed an increased metabolic rate, a reduced sleep efficiency and an increased sleep latency at the multiple sleep latency test (MSLT) after caffeine assumption. At the end of the week, increased daytime fatigue and anxiety, suggested that the factors listed above could be influenced by an increased level of arousal.
- When insomniacs are totally deprived of sleep, their recovery sleep is improved[73,74] but when the influence of the phasic deprivation disappear, the sleep/wake insomnia pattern occurs again.[73] In aroused individuals, falling asleep and maintaining sleep is

more difficult; sleep would occur after sleep deprivation but as sleep was recovered, the impact of hyperarousal become predominant again.

- Role of the insomnia sleep pattern in the production of hyperarousal and other symptoms of primary insomnia (as daytime fatigue and anxiety). The EEG sleep patterns of 10 insomniacs were reproduced by experimental awakenings, over 7 nights, in a group of normal sleepers.[75] Normal sleepers reported decreased tension, vigor, lower metabolic rate and decreased body temperature during the day and decreased MSLT values. Normal sleepers estimated their wake time during the night correctly, while insomniacs overestimated it. These characteristics are not representative of insomnia and suggest that the secondary symptoms reported by insomniacs are not caused by poor sleep.
- Hyperarousal seems also to be related to the misperception of sleep parameters (i.e. the ratio of subjective to objective sleep latency). The ratio of subjective to objective sleep latency decreased under benzodiazepines administration, decreased during sleep deprivation and was directly related to the amount of sleep lost. Furthermore, the ratio of subjective to objective sleep latency increased after caffeine consumption.[71]

Additional evidence continue to suggest that insomnia is associated with inappropriate levels of arousal; according with Perlis et al.[76]:

- arousal is not a unitary construct, but can be separated into three components, i.e., somatic, cortical and cognitive;
- these systems may be measured independently; domains can be singularly or contemporaneously (with equal or different levels of involvement) activated.

A brief review of the studies that have examined psychophysiological responses in patients with insomnia and controls is provided below.

Somatic hyperarousal. Insomnia appears to be associated with decreased nocturnal production of melatonin,[77] increased norepinephrine,[78] high levels of cortisol[77,79-83] and ACTH,[82] increased body metabolic rate,[84,85] basal temperature,[86] heart rate,[86-89] phasic vasoconstrictions,[86] muscular tone[86,90,91] and electrodermal activity.[86] Heart rate variability (HRV) analysis has also shown

increased low frequency power and decreased high frequency power in insomniacs across all stages of sleep, indicating higher sympathetic and lower parasympathetic activation.[87]

Cortical hyperarousal. EEG studies have provided evidence of increased high frequency activity in both REM and NREM sleep in insomniacs,[90,92-94] thus indicating cortical hyperarousal. Across sleep onset, insomniacs show a lower increase in delta power and a lower reduction of the activity index,[95] lower delta activity[96] and reduced alpha power.[97]

Cognitive hyperarousal. Insomniacs frequently report intrusive thoughts around sleep onset.[42,98] Insomniacs also report high subjective scores of hyperactivation as shown in psychological assessments performed by questionnaire.[99,100]

3.5 TREATMENT OF INSOMNIA

3.5.1 BEHAVIOR THERAPIES

Considering the impact of cognitive and behavioral factors in the development and maintaining of insomnia, behavior therapy seems to be appropriate as a primary or adjunctive treatment of this disorder. Insomnia may assume a chronic course perpetuated by psychological and behavioral factors such as dysfunctional beliefs about sleep, anxiety, and sleep-disruptive compensatory practices. Several behavioral therapies have been developed to treat chronic insomnia and they all focus on recovering a normal sleep/wake pattern, acting on behavioral and conditioning factors. A summary of these treatment is provided below(for a review see[101]).

Relaxation Therapies. These methods focus on sleep related anxiety and bedtime arousal that disrupts sleep. These approaches use specific exercises to reduce anxiety and arousal states (e.g. progressive muscle relaxation training, autogenic training, meditation, hypnosis, biofeedback). For instance, in the progressive muscle relaxation, the patient alternately tenses and relaxes muscle groups in order to reduce muscles tension.

Stimulus Control.[102] It is a strategy that aims to establish the bedroom as a stimulus for sleep by eliminating those behaviors that are incompatible with it. The repeated association bed and bedroom with disturbed sleep pattern become conditioned cues that perpetuate insomnia. The goal of

this approach is re-associate the bed and bedroom with successful sleep effort. Insomnia patients are instructed to go to bed only when sleepy and to avoid activities that are incompatible with sleep in the bedroom (e.g. watching TV, reading, eating).

Sleep Restriction.[103] It is a behavioral intervention, based on the observation that insomnias spend excessively time in bed without sleep, that restricts the time assigned for sleep so that the time spent in bed fits with the insomniac's sleep requirement.

Paradoxical Intention. It has been developed to alleviate patient's excessive focus on sleep and anxiety over not sleeping focusing on "staying awake" as long as possible after retiring to bed.

Sleep Hygiene. Sleep hygiene therapy regards a set of recommendations about healthy sleep behaviors (e.g. refrain from consuming caffeine, alcohol and nicotine) and good sleep environmental conditions (e.g. the bedroom should be sufficiently quite, dark and comfortable).

Cognitive Therapies. These approaches are focused on dysfunctional beliefs and attitudes about sleep that are involved to the development of sleep related anxiety and to the promotion of sleep disruptive habits. They are also focused on cognitive arousal generated by sleep disruptive practices like mentally stimulating activities immediately prior to bedtime.

Cognitive-Behavioral Therapy (CBT). It is a popular muticomponent treatment approach evolved from the behavioral therapies cited above. CBT addresses a person's behavior by providing an education and establishing better sleep habits over different sessions.

3.5.2 PHARMACOLOGIC TREATMENT OF INSOMNIA

Sleep is an active process that is generated and maintained by specific cerebral structures, it is governed by different sleep neurotransmitters, hormones and peptides. The solitary tract nucleus, anterior hypothalamus–preoptic area, nonspecific thalamic nuclei, and basal forebrain are involved in the initiation of slow wave sleep, while the main neurotransmitters associated with NREM sleep are serotonin (a monoamine neurotransmitter) and gamma-aminobutyric acid (GABA). Furthermore, adenosine (a nucleoside) is considered to be involved in modulating the homeostatic slow wave sleep drive and generally promoting sleep and suppressing arousal. The pedunculopontine nuclei and the laterodorsal tegmental nuclei have major roles in the generation of REM sleep, whereas the main

neurotransmitters associated with REM sleep is acetylcholine.[101] This brief overview on neurochemistry will be useful to understand the pharmacologic action of the various hypnotic agents used in the pharmacologic treatment of insomnia.

The aims of hypnotic treatment are the alleviation of nighttime sleep disturbance, the improvement of the quality and duration of sleep and also the relief of its daytime consequences, i.e. increasing the degree of alertness during the day. Unfortunately, with many hypnotics, the dose needed to improve sleep at night, frequently causes sedation during the day. A summary of these treatment is provided below(see[101]).

Benzodiazepines (e.g. triazolam and temazepam). They act on the benzodiazepine receptor complex in the brain to facilitate GABA. In so doing they decrease sleep latency and wake after sleep onset, and thus increase total sleep time. In addition to their hypnotic properties, benzodiazepines are anxiolytics, relaxants, and anticonvulsants. Benzodiazepines can be classified into three groups according to their half-life: short (<3 hours), medium (8–24 hours), and long half-life (>24 hours). The long half-life of these medications results in daytime sleepiness and memory impairments while the short half-life may cause rebound daytime anxiety and greater withdrawal symptoms following cessation of their use.

Z-Hypnotics. These new hypnotics have less effect on sleep architecture and a more rapid onset of action compared to benzodiazepines. This selectivity translates into less dependence and tolerance, and less adverse effects, if compared with benzodiazepines. In addition, perceptual difficulties, memory problems, confusion, and rarely sleepwalking have been observed in patients using Z-hypnotics.

Melatonin (MT1/MT2) receptors agonist. This drug (Ramelteon) has a rapid onset of action and a short half-life of less than three hours. Ramelteon reduces sleep latency and increases total sleep time, but due to its short half-life, may not be effective in maintaining sleep throughout the night.

Antidepressant (e.g. trazodone, mirtazapine, amitriptyline, doxepin). A low dose of antidepressants is considered a pharmacologic treatment for insomnia in particular in patients who have comorbid depression.

3.6 COGNITIVE PERFORMANCES IN INSOMNIACS

As above mentioned, primary insomnia consists in a difficulty initiating or maintaining sleep or nonrestorative sleep, causing clinically significant distress or impairment in social, occupational, or other important areas of functioning. While in literature the subjective complaints are well illustrated, the objective evidence of daytime impairments and particularly the cognitive functioning, are poorly investigated. Studies that have investigated cognitive performances in primary insomniacs provided elusive results.

Which aspect of neurobehavioral performance are compromised in insomniacs? Research into neuropsychological functions mainly investigated impairment in attention and memory processes and paid less attention to executive functioning. Nevertheless, recent imaging studies[85,104] report, in insomnia patients, a decreased activity in the prefrontal cortex, the main area involved in executive functions, suggesting that this cognitive domain could be impaired by insomnia.

Processing speed, brain processes that subserves many other higher-order cognitive functions, in insomniac patients does not appear to differ from that of controls, as well as memory assessed by visual and verbal memory tests.[105] A recently studied aspect of memory, that suggests cognitive impairments in insomnia patients, is memory consolidation.[105] The paradigm usually adopted to test this aspect of memory is the following: participants are instructed to perform a task before the night, to spend a usual night of sleep and then to perform the task again. Evidence suggest that sleep plays a key role in memory consolidation,[106] therefore the abnormal sleep/wake pattern in insomniacs could affect the formation and consolidation of memories. Recent imaging data[107] of a reduced bilateral hippocampal volume in insomniacs, also provide a neuroanatomical indication that memory processes may be disturbed in insomnia patients.

Attention processes could be separated in three domains: focus (the selection of target information for further processing), sustain (or vigilance, i.e. the ability to maintain the focus of attention over a period of time) and shift (the ability to flexibly move the focus of attention as a response to environmental requests). In insomniacs the first one seems to be relatively maintained, while the second one seems to be compromised in primary insomniacs, but only when the tasks

involved are more complex than a simple vigilance task. Tasks requiring a shift of attention ask for a higher level of cognitive involvement because the responses are modulated by the stimulus presented. Studies comparing insomnia patients and controls on tasks of shifting attention consistency provide poor performances in insomniacs.[105]

Finally, executive functions including higher-order cognitive domains as planning, reasoning, mental flexibility and multitasking, seems to be the less investigated area, among cognitive functions, in the insomnia literature with inconclusive results.[105]

In order to understand possible cognitive impairment in this population, a more strict methodology should be used for future studies as the adoption of standardized criteria and rigorous screening methods to the recruitment of insomnia and control groups as well as controlling possible confounding variables (e.g. sleepiness, fatigue, arousal levels).

3.7 CARDIOVASCULAR SLEEP PATTERN IN INSOMNIACS

Since insomnia population can be differentiated from healthy sleepers population according to several psychological and physiological features (see section 3.4), only few studies has taken into account the former's cardiovascular activity. The purpose of this paragraph is to provide a brief overview of the studies investigating cardiovascular parameter in insomniacs.

To our knowledge, Monroe[86] has been the first to describe an elevated heart rate in poor sleepers (mean ± SD, 60.54 ± 6.97 bpm) compared to good sleepers (mean ± SD, 56.64 ± 6.68 bpm) during 7-hours night sleep, although at non significant level. Stepanski et al.,[89] assessed the physiological activity in 25 patients with chronic insomnia matched with normal sleepers; they fund significantly higher HR in insomnia group at night. Employing both subjective and objective measures of sleep quality to recruit insomniacs, Bonnet and Arand[87] confirmed an increased heart rate in all stage of sleep in 12 insomniacs compared to 12 controls. In addition, in both groups, HR was higher in wake and REM sleep in comparison to Stage 1 and Stage 2 sleep. Recent data[108] suggested a lower wake-to-sleep HR reduction in 58 subjects subjectively reported insomnia, compared to 46 healthy

controls, although between group differences in resting HR were not found. The same result has been obtained analyzing only insomnia patients with objectively determined short sleep duration.

To our knowledge, only two studies have focused on nocturnal HRV measures in insomniacs. Bonnet an Arand[87] revealed increased low frequency power and decreased high frequency power in insomniacs across all sleep stages, indicating higher sympathovagal balance. Moreover, sympathovagal balance was higher in wake compared to Stage 1 and REM sleep. In a recent paper, Jurysta et al.,[109] failed to confirm the previous data, showing group differences in high and low frequency power; they found similar HRV pattern among groups, suggesting that the insomniacs' cardiac autonomic influence was not altered across the night.

BP has been investigated by Lanfranchi at al.[110] employing 13 normotensive subjects with chronic primary insomnia and 13 good sleepers over 24-hours beat to beat BP recording. Nighttime SBP was higher in insomniacs (mean ± SD, 111 ± 15 mmHg) than in controls (mean ± SD, 102 ± 12 mmHg). In addition, insomniacs have shown a lower day to night dipping in SBP (mean ± SD, -8% ± 6%) compared to controls (mean ± SD, -15% ± 5%).

To sum up briefly, HR, SBP and sympathovagal balance seems to be elevated in insomniacs compared to healthy subjects throughout the night. Moreover, SBP failed to show a day to night dipping in insomniacs. Given the lack of literature on the insomniacs' cardiovascular modification during night, future studies seems to be necessary to provide an exhaustive nocturnal cardiovascular pattern in primary insomnia.

4 EXP. 1 SLEEP ONSET AND CARDIOVASCULAR ACTIVITY IN PRIMARY INSOMNIA

The transition from wakefulness to sleep is typically characterized by a shift from sympathetic to parasympathetic regulation. Physiological functions, depending on the neurovegetative system, decrease overall. Previous studies have shown cardiovascular and electroencephalographic hyperactivity during wakefulness and sleep in insomniacs compared with normal sleepers, but there is very little evidence of this at sleep onset.

The purpose of this study is to compare cardiovascular and autonomic responses before and after falling asleep in eight insomniacs (who met DSM-IV criteria for primary insomnia) and eight normal sleepers. Non-invasive measures of heart rate (HR), stroke volume (SV), cardiac output (CO) and pre-ejection period (PEP) were collected by Impedance Cardiography during a night of polysomnographic recording. Frequency domain measures, low-frequency (LF), high-frequency (HF) and LF/HF ratio of heart rate variability (HRV) were also estimated (LF and HF were calculated in normalized units, n.u.).

Decrements in HR and CO and increases in SV and HF n.u. were found in both groups after sleep onset compared with wakefulness. Conversely, PEP (related inversely to sympathetic β-adrenergic activity) showed increases after sleep onset in controls, but remained unchanged in insomniacs. PEP was also significantly lower in insomniacs than in normal sleepers in both conditions.

These data suggest that, whereas normal sleepers follow the expected progressive autonomic drop, constant sympathetic hyperactivation is detected in insomniacs. These results support the etiological hypothesis of physiological hyperarousal underlying primary insomnia.

4.1 INTRODUCTION

Most of the above mentioned studies (see Chapter 3) focus on nocturnal sleep or daytime wakefulness, whereas very few reports specifically investigate the sensitive transition from wakefulness to sleep, i.e., sleep onset. The definition of the exact moment of sleep onset, both in insomniacs and normal sleepers, is still controversial among sleep specialists.[23] Two main approaches, which followed sleep scoring according to the standard criteria of Rechtschaffen and Kales,[15] have been proposed: one identifies sleep onset as the first epoch of Stage 1 and the other as the first epoch of Stage 2. Among studies dealing with sleep onset in insomnia, Merica and Gaillard[95] found a lower increase in delta power and a lower reduction of the activity index (calculated as the beta/delta power ratio) in insomniacs compared with healthy subjects, across sleep onset identified as the first epoch of Stage 1. Lamarche and Ogilvie[97] analyzing a sleep onset period (SOP) ranging from lights out to the first 5 min of Stage 2, also detected reduced alpha power at the beginning of SOP. Cortical hyperactivation during SOP was also observed by Staner et al.[96] who reported that, in contrast with depressive insomniacs and healthy subjects, primary insomniacs did not show a gradual decrease in alpha and beta power but lower delta activity in the 5 min preceding sleep onset, scored as the first epoch of Stage 2. Lastly, Freedman and Sattler[91] found higher levels of frontalis EMG, chin EMG and heart rate and lower finger temperatures in insomniacs before sleep onset, whereas after it their physiological patterns were similar to those of normal sleepers.

To our knowledge, no studies have examined cardiovascular activity during the switch from wakefulness to sleep in insomniacs, but only heart rate during wakefulness and/or sleep.[91] For deeper insights into cardiovascular patterns and autonomic involvement, Impedance Cardiography was used, a non-invasive technique assessing electromechanical heart functions.[12] It is well known that physiologic activation (arousal) is modulated by the sympathetic system, whereas deactivation functions are carried out by the parasympathetic system. From a general metabolic perspective, the sympathetic system performs catabolic functions, unlike the parasympathetic system which is involved in anabolism. Therefore, traditionally, sympathetic control prevails in wakefulness and parasympathetic during sleep.[111]

The aim of the present study is to investigate the psychophysiological characteristics of sleep onset in primary insomniacs compared with good sleepers, by assessing cardiovascular measures as indexes of neurovegetative functioning. In particular, we focus on the switch from wakefulness to sleep in order to test differences among groups in the process of falling asleep. We assume that somatic hyperarousal, and in particular the hyperactivation of the cardiovascular system, is involved during the transition from wakefulness to sleep too, interfering and altering the entire sleep onset period.

4.2 METHOD

4.2.1 PARTICIPANTS

16 undergraduates participated in the study, eight suffered from primary insomnia (four males and 4 females; mean age ± SD, 23.25 ± 2.43; range 20–26 years) and eight good sleepers represented controls (3 males and 5 females; mean age ± SD, 23.25 ± 3.24; range 19–28 years). Subjects were recruited through advertisements at the Department of Psychology, University of Padova.

In order to assign them to one of the two groups, subjects were contacted for a screening session 1 week before the experiment. Participants were asked to complete a set of questionnaires: the Pittsburgh Sleep Quality Index (PSQI[112]) to assess sleep quality, the Athens Insomnia Scale (AIS[113]) and the Insomnia Severity Index (ISI[114]) to investigate insomnia disorder and severity of insomnia. In order to be included in the insomniac group, participants had to score ≥ 6 on the PSQI, ≥ 6 on the AIS and ≥ 11 on the ISI. Controls had to report questionnaire scores lower than these cut-offs. Participants were also administered a semi-structured clinical interview to collect anamnesis, and investigate their sleep history, medical and psychological state. Insomniacs were enrolled according to the DSM-IV[38] diagnostic criteria for primary insomnia.

Exclusion criteria were body mass index (BMI; kg/m^2) ≤ 30, scores higher than 95 percentile on the Beck Depression Inventory (BDI-II[115]) and on the State Trait Anxiety Inventory (STAI-Y2[116]), medical and/or psychiatric conditions, use of psychoactive drugs or medications affecting the cardiovascular system, shift work or long-range travel in the 6 months prior to the study. A week of

actigraphic monitoring and sleep logging were used to exclude circadian disorders. Subjects were asked to refrain from alcohol, caffeine or tobacco consumption the day before and the days scheduled for experiment. All participants were drug free.

All participants gave their written informed consent and received €100 for participation in the study. The study protocol was approved by the Ethics Committee of the Department of Psychology.

4.2.2 PROCEDURE

Participants were required to maintain their usual sleep schedule a week prior the test sessions; during this week they were instructed to complete a sleep log and to wear a wrist actigraph (Octagonal Basic Motionlogger, Ambulatory Monitoring, Inc., Ardsley, NY) to confirm the timing of their normal schedule. They were also instructed to fill out a set of trait questionnaires (PSQI, AIS, ISI, BDI-II, STAI-Y2, HS and ESS) to fit the inclusion/exclusion recruitment criteria. After this, participants spent two consecutive nights in the laboratory, the first night allowed for adaptation and no data were analyzed. During this night the participant followed the same steps than the experimental night to maintain the same temporal pattern. 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 nights in laboratory. They were admitted to the laboratory at 8 p.m. and electrodes were attached. Following that, they completed state questionnaires (STAI-Y1 and SSS) and then, at 9.30 p.m., performed the first task session. Before the night, participants completed a questionnaire assessing the pre-sleep activation (PSAS); they were put to bed 15 min before midnight, while the lights were turned off at midnight. Subjects were requested to go to sleep and they were left undisturbed until wake-up time at 8:00 a.m. After scheduled awakening, participants completed state questionnaires and performed a second task session, at 8.30 a.m. Finally, they were allowed to leave. The experimental design is displayed in Figure 4.1.

The experiment was conducted in a quiet, soundproof, comfortable room in the Psychophysiology Sleep Laboratory, Department of General Psychology, University of Padova.

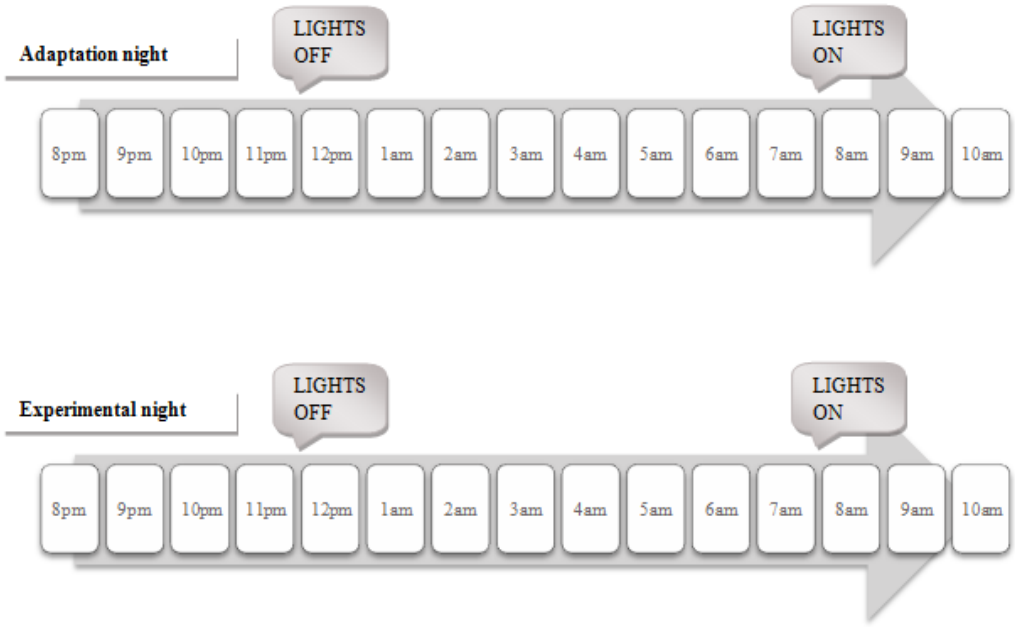


Figure 4.1 Experimental design.

4.2.3 DEPENDENT VARIABLES

4.2.3.1 Self-report measures

The Epworth Sleepiness Scale (ESS[117]), Beck Depression Inventory (BDI-II[115]), State Trait Anxiety Inventory (STAI-Y2[116]) and Hyperarousal Scale (HS[118]) were administered during the screening session in order to evaluate sleepiness, depression, anxiety and perceived cognitive arousal trait levels, respectively. In order to assess state anxiety, sleepiness, somatic and cognitive arousal, the State Trait Anxiety Inventory (STAI-Y1[116]), Stanford Sleepiness Scale (SSS[119]) and Pre-Sleep Arousal Scale (PSAS[120]) were administered on the experimental night.

4.2.3.2 Polysomnographic recordings

Polysomnographic recording included 4 EEG leads (C_3-A_2, C_4-A_1, F_3-A_2, F_4-A_1), bilateral EOG (right EOG-A_1, left EOG-A_2) and chin EMG. Data were acquired with 10-mm Ag/AgCl electrodes using a data acquisition device (BIOPAC MP100 Systems, Inc., Santa Barbara, CA). EEG signals were amplified, band-pass filtered (0.5–35 Hz) and digitized at 500 Hz. Electrodes impedance was kept below 5 kΩ.

Sleep stages (wake, Stage 1, Stage 2, SWS and REM) were scored using 30-sec epochs by an experienced scorer by visual analysis of the sleep recordings, in accord with standardized criteria.[15] The following sleep parameters were defined: total sleep time (TST; min), sleep onset latency (SOL; min), wake time after sleep onset (WASO; min), sleep efficiency (SE; %), total number of awakenings, REM latency (min) and amount of each sleep stage (Stage 1, Stage 2, SWS, REM and NREM; min).

4.2.3.3 Cardiovascular measures

The electrocardiogram (ECG) was recorded through 1 cm diameter Ag/AgCl spot electrodes in a modified Lead II Einthoven configuration. The signal was acquired on a BIOPAC MP100 acquisition system (BIOPAC Systems, Santa Barbara, CA), amplified, band-pass filtered (1 to 100 Hz) and digitalized at 500 Hz. R-waves were automatically detected by a digital trigger and IBIs computed by the software. Subsequently, the detection of R-waves was visually checked and manually adjusted. A third order polynomial filter for detrending was applied in order to remove trend components and power spectrum analysis of the HRV (using the Fast Fourier Transformation method) was conducted on each 2-min artifact free bin, to estimate spectra of very low (VLF[ms^2]; range: 0–0.04 Hz), low (LF[ms^2]; range: 0.04–0.15 Hz) and high (HF[ms^2]; range: 0.15–0.4 Hz) frequencies by Kubios HRV Analysis Software 2.0 (MATLAB, Kuopio, Finland). The followed variables were calculated: HF n.u. (HF[ms^2]/(total power[ms^2] – VLF[ms^2])), LF n.u. (LF[ms^2]/(total power[ms^2] – VLF[ms^2])) and LF/HF ratio (LF[ms^2]/HF[ms^2]), indexes of sympathovagal balance (high sympathovagal balance indicates sympathetic dominance; low sympathovagal balance indicates parasympathetic dominance). Considering that HF n.u. and LF n.u. are mathematically the same variable, only HF n.u. and LF/HF ratio have been reported in the results.

Cardiac Impedance measures were calculated by 30-s ensemble averages collected through Impedance Cardiograph Minnesota model 304 B (IFM, Greenwich, CT). Four longitudinal aluminium band electrodes were placed in tetrapolar configuration according to the configuration reported in the guidelines[12]: around the upper part of the neck (1) and the lower part of the neck (2); around the thorax at the xyphisternal joint level (3) and around the abdomen (4). A 4 mA AC current at 100 kHz was

transmitted through the thorax between the outer electrodes (1 and 4) and Z0 (basal impedance; Ω), and dZ/dt (rate of change in the impedance waveform on a given beat; Ω/s) signals were estimated from the two inner electrodes (2 and 3).

SV (blood pumped by the left ventricle with each heartbeat; ml), was obtained by applying the Kubicek equation. CO (blood pumped by the left ventricle each minute; l/min) was derived by multiplying HR (number of heartbeats per unit of time; bpm) by SV. PEP (considered to be inversely related to sympathetic *β*-adrenergic activity; ms) was calculated for each cardiac cycle as the time interval from the beginning of the electrical systole, the Q wave on the ECG signal to the opening of the aortic valve, the B point on the dZ/dt signal. LVET (refers to the duration of mechanical systole; ms) was calculated from the B point to the X point, closure of aortic valve, on the dZ/dt waveform.[12]

Each cardiac cycle was visually checked and the positions of points B and X in the dZ/dt signal and Q peak in the ECG were manually adjusted where necessary.

4.2.4 DATA ANALYSIS

Descriptive variables and scores of trait and state questionnaires were compared with independent *t*-tests by group.

Cardiovascular activity was analyzed 2.5 min before and 2.5 min after sleep onset, defined as the first epoch of Stage 1. The first artifact-free minute after lights off was considered as baseline (Figure 4.2).

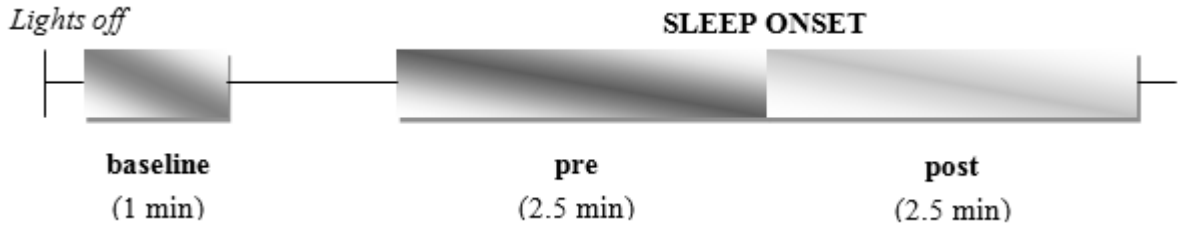


Figure 4.2 Time intervals selected for the analysis. After lights off (23:58 h), the first artifact free minute was chosen as baseline; 2.5 min before (pre) and after (post) sleep onset (first epoch of Stage 1) were selected.

A 2 (between-group: insomniacs and good sleepers) × 2 (within condition: pre- and post-sleep onset) mixed-design analysis of variance (ANOVA) was applied to the mean values of each dependent variable. Bonferroni post-hoc comparisons were employed to examine significant effects further, at a significance level of $p < 0.05$.

Cardiovascular variables were also compared in baseline and in pre- and in post-sleep onset with independent *t*-tests by group.

Lastly, in order to assess changes during the sleep onset period, a one-way repeated-measures ANOVA was conducted between baseline and sleep onset (baseline-pre and baseline-post) within each group.

4.3 RESULTS

4.3.1 DESCRIPTIVE ANALYSES

As shown in Table 4.1, there were no differences between insomniacs and good sleepers with regard to age or BMI. Insomniacs had higher PSQI, AIS and ISI scores and more elevated levels of depression, trait anxiety and perceived arousal compared with controls. There were no differences between groups with regard to sleepiness. The results of questionnaires administered before the experiment night also revealed higher PSAS scores on both scales, somatic and cognitive (Figure 4.3), in the insomnia group. No differences were found in sleepiness or state anxiety scores.

Table 4.1 Mean values and standard deviations for descriptive and subjective variables. AIS, Athens Insomnia Scale; BDI, Beck Depression Inventory; BMI, Body Mass Index; ESS, Epworth Sleepiness Scale; HS, Hyperarousal Scale; ISI, Insomnia Severity Index; PSAS, Pre-Sleep Arousal Scale; PSQI, Pittsburgh Sleep Quality Index; STAI, State Trait Anxiety Inventory. * $p < .05$; ** $p < .01$; *** $p < .001$.

	Insomniacs	**Good sleepers**	***t***
Age (year)	23.25 (2.43)	23.25 (3.24)	-0.00
BMI (Kg/m^2)	21.81 (3.60)	22.33 (2.62)	0.33
Length of insomnia (year)	4.25 (3.24)		
trait			
PSQI	9.62 (1.30)	4.62 (3.07)	-4.24***
AIS	9.62 (3.16)	2.25 (2.05)	-5.54***
ISI	13.37 (3.25)	3.00 (3.34)	-6.30***
BDI-II	11.25 (5.39)	2.62 (2.13)	-4.21***
STAI-Y2	46.87 (7.85)	34.12 (5.59)	-3.74**
HS	45.25 (3.69)	29.87 (5.72)	-6.39***
ESS	5.87 (4.22)	4.50 (2.93)	-0.76
state			
PSAS-somatic	11.37 (2.44)	8.75 (1.16)	-2.74*
PSAS-cognitive	22.00 (4.41)	14.62 (3.85)	-3.56**
STAI-Y1	50.12 (2.10)	52.25 (2.55)	1.82
SSS	2.75 (1.49)	2.12 (0.99)	-0.99

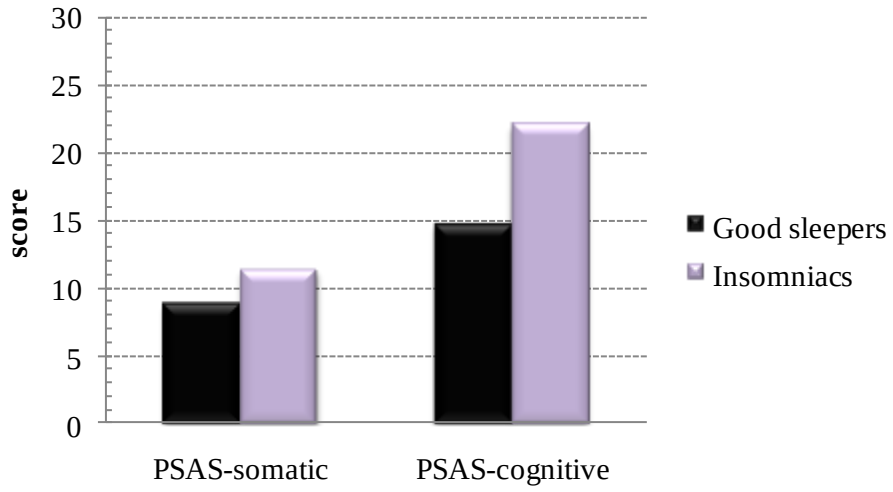


Figure 4.3 Higher mean PSAS-somatic and PSAS-cognitive scores in insomniacs, compared to controls, underlined a perceived somatic hyperactivation in primary insomnia. PSAS, Pre-Sleep Arousal Scale.

4.3.2 SLEEP PARAMETERS

As shown in Table 4.2, in subjects with insomnia, total sleep time was reduced; accordingly, because of the fixed time in bed, sleep efficiency, was also reduced. Sleep latency, WASO and total number of awakenings were higher and SWS lower in insomniacs but the group differences were not statistically significant. Furthermore, the total duration of NREM sleep was reduced in insomniacs, whereas REM, Stage 1 and Stage 2 sleep duration did not show differences among groups.

Table 4.2 Mean and standard deviations of sleep parameters in insomniacs and good sleepers across the entire night. TIB, time in bed; TST, total sleep time; WASO, wake after sleep onset; NREM, non-rapid eye movement sleep; REM, rapid eye movement; SWS, slow wave sleep . *$p < 0.05$.

	Insomniacs	**Good sleepers**	***t***
Sleep efficiency (%)	90 (4)	95 (2)	2.65*
TIB (min)	480	480	
TST (min)	433 (23)	458 (12)	2.65*
Sleep latency (min)	19 (14)	10 (6)	-1.75
WASO (min)	27 (19)	13 (8)	-2.02
REM latency (min)	92 (37)	99 (38)	0.39
Total number of awakenings	17 (11)	11 (6)	-1.55
NREM duration (min)	355 (28)	378 (11)	2.15*
REM duration (min)	79 (25)	80 (10)	0.13
Stage 1 duration (min)	51 (25)	56 (17)	0.46
Stage 2 duration (min)	216 (32)	216 (24)	0.01
SWS duration (min)	87 (47)	106 (21)	1.01

4.3.3 CARDIOVASCULAR MEASURES

4.3.3.1 Baseline

Means and standard deviations for cardiovascular variables in baseline, pre- and post-sleep onset are displayed in Table 4.3.

Independent *t*-tests showed significantly higher HR and lower PEP levels at baseline (Figure 4.4), indicating greater sympathetic activity in insomniacs compared with good sleepers. No significant differences were found for SV, CO, HF n.u. and LF/HF ratio.

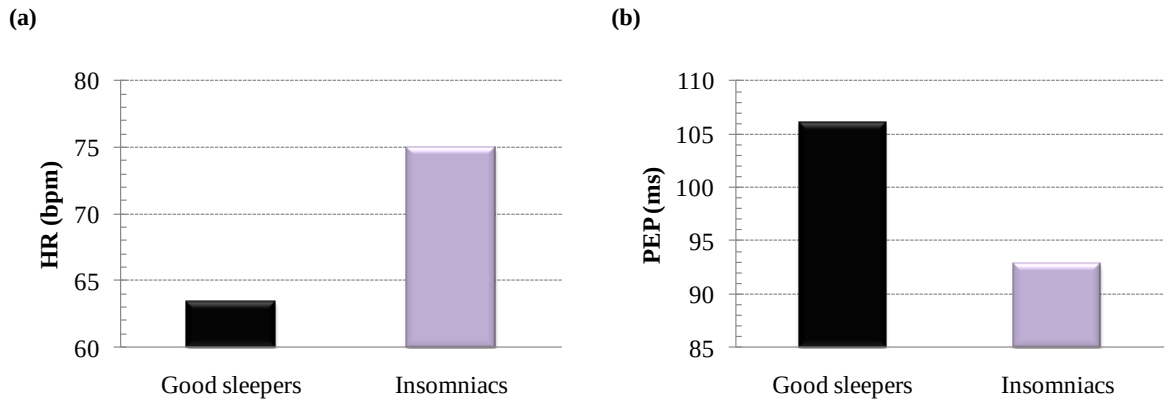


Figure 4.4 Mean HR values (a) and mean PEP values (b) in insomniacs and good sleepers during baseline condition.

Table 4.3 Mean values and standard deviations for cardiovascular variables in baseline, in pre- and post-sleep onset. HR, heart rate; PEP, pre-ejection period; LVET, left ventricular ejection time; SV, stroke volume; CO, cardiac output; HF, high frequency; LF, low frequency; n.u., normalized units. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

	BASELINE			PRE SLEEP ONSET			POST SLEEP ONSET		
	Insomniacs	**Good sleepers**	***t***	**Insomniacs**	**Good sleepers**	***t***	**Insomniacs**	**Good sleepers**	***t***
HR (bpm)	75.00 (6.91)	63.37 (12.68)	-2.28 *	70.37 (8.75)	62.32 (13.80)	-1.39	67.97 (8.56)	60.70 (13.34)	-1.30
PEP (ms)	92.75 (7.74)	106.00 (11.62)	2.68 *	95.40 (7.44)	107.55 (10.21)	2.72 *	94.90 (7.89)	109.45 (10.38)	3.15 **
LVET (ms)	296.62 (13.96)	313.50 (18.18)	2.08	302.95 (15.22)	314.90 (24.42)	1.17	307.20 (14.47	316.85 (22.80)	1.01
SV (ml)	98.99 (15.08)	120.32 (26.99)	1.95	98.72 (18.83)	109.17 (18.48)	1.12	100.23 (18.18)	110.37 (18.77)	1.10
CO (l/min)	7.41 (1.21)	7.54 (1.96)	0.16	6.82 (0.65)	6.74 (1.67)	-0.13	6.70 (0.55)	6.63 (1.61)	-0.12
HF n.u.	41.48 (24.27)	53.51 (18.68)	1.11	50.02 (13.87)	42.36 (21.40)	-0.85	57.01 (18.44)	57.24 (13.22)	0.03
LF/HF	2.53 (2.54)	1.09 (0.74)	-1.54	1.14 (0.61)	1.83 (1.13)	1.51	1.00 (0.81)	0.82 (0.39)	-0.56

4.3.3.2 Sleep onset

A table with significant and non-significant results of ANOVAs is provided (Table 4.4).

PEP was significantly lower in both pre- and post-sleep onset in insomniacs, as indicated by the group main effect. The ANOVA also showed the condition main effect, in which PEP increased during the transition from wakefulness to sleep. The significant group × condition interaction explained main effects, as highlighted by post-hoc analyses (Bonferroni test), only the increased PEP

values of good sleepers revealing reduced sympathetic activity during the transition from wakefulness to sleep; insomniacs showed no significant changes in PEP values across sleep onset (Figure 4.5).

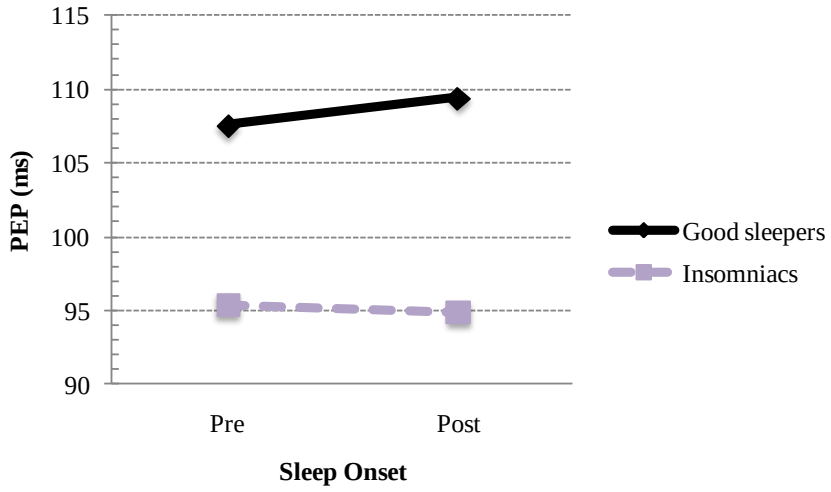


Figure 4.5 Mean PEP values during transition from pre- to post-sleep onset in insomniacs and good sleepers. PEP, pre-ejection period.

The significant condition main effect showed that HR decreased significantly from pre- to post-sleep onset in both insomniacs and controls; LVET and SV increased significantly across sleep onset in both groups and CO showed a non-significant decrease.

With regard to HRV, ANOVA showed main effect of condition for both HF n.u. and LF/HF, which respectively increased and decreased during transition suggesting a decrease in sympathovagal balance.

Table 4.4 Results of the 2 (between group: insomniacs and good sleepers) × 2 (within condition: pre- and post-sleep onset) mixed-design analysis of variance (ANOVA) applied to the mean values of each cardiovascular variable. HR, heart rate; PEP, pre-ejection period; LVET, left ventricular ejection time; SV, stroke volume; CO, cardiac output; HF, high frequency, LF, low frequency; n.u., normalized units.

	ANOVA	Current effect	*p*-value	η^2_p
HR (bpm)	Group	$F_{1,14} = 1.84$	0.20	0.12
	Condition	$F_{1,14} = 9.18$	0.00	0.27
	Group × Condition	$F_{1,14} = 0.34$	0.57	0.02
PEP (ms)	Group	$F_{1,14} = 8.66$	0.01	0.38
	Condition	$F_{1,14} = 15.24$	0.00	0.52
	Group × Condition	$F_{1,14} = 44.80$	0.00	0.76
LVET (ms)	Group	$F_{1,14} = 1.21$	0.29	0.08
	Condition	$F_{1,14} = 6.74$	0.02	0.32
	Group × Condition	$F_{1,14} = 0.93$	0.93	0.06
SV (ml)	Group	$F_{1,14} = 1.23$	0.28	0.08
	Condition	$F_{1,14} = 5.09$	0.04	0.27
	Group × Condition	$F_{1,14} = 0.06$	0.80	0.01
CO (l/min)	Group	$F_{1,14} = 0.01$	0.90	0.01
	Condition	$F_{1,14} = 4.21$	0.06	0.23
	Group × Condition	$F_{1,14} = 0.01$	0.91	0.01
HF n.u.	Group	$F_{1,14} = 0.24$	0.63	0.02
	Condition	$F_{1,14} = 7.69$	0.01	0.35
	Group × Condition	$F_{1,14} = 1.00$	0.33	0.07
LF/HF	Group	$F_{1,14} = 0.59$	0.46	0.04
	Condition	$F_{1,14} = 7.62$	0.02	0.35
	Group × Condition	$F_{1,14} = 4.34$	0.06	0.24

4.3.3.3 Comparisons between baseline and sleep onset

A table with significant and non-significant results of ANOVAs is provided (Table 4.5)

Separate one-way repeated measures ANOVA revealed that only the insomnia group increased PEP as well as LVET values in both conditions, pre- and post-sleep onset, compared with baseline. HR decreased significantly in post-sleep onset compared with baseline in insomniacs, whereas in controls CO decreased in the post condition, but only in the insomnia group. HRV analysis highlighted significantly higher HF n.u. values in post- compared with baseline, but only in the insomnia group.

Table 4.5 Results of the separate one-way repeated measures ANOVA applied to the mean values of each cardiovascular variable. HR, heart rate; PEP, pre-ejection period; LVET, left ventricular ejection time; SV, stroke volume; CO, cardiac output; HF, high frequency, LF, low frequency; n.u., normalized units.

	INSOMNIACS				GOOD SLEEPERS			
	ANOVA	**Current effect**	***p*-value**	η^2_p	**ANOVA**	**Current effect**	***p*-value**	η^2_p
HR (bpm)	Baseline-Pre	F1,7 = 3.87	0.09	0.36	Baseline-Pre	F1,7 = 0.29	0.60	0.04
	Baseline-Post	F1,7 = 7.00	0.03	0.50	Baseline-Post	F1,7 = 2.27	0.18	0.24
PEP (ms)	Baseline-Pre	F1,7 = 9.39	0.02	0.57	Baseline-Pre	F1,7 = 1.04	0.34	0.13
	Baseline-Post	F1,7 = 5.68	0.04	0.45	Baseline-Post	F1,7 = 3.87	0.09	0.36
LVET (ms)	Baseline-Pre	F1,7 = 5.62	0.04	0.45	Baseline-Pre	F1,7 = 0.16	0.70	0.02
	Baseline-Post	F1,7 = 13.21	0.00	0.65	Baseline-Post	F1,7 = 1.39	0.28	0.16
SV (ml)	Baseline-Pre	F1,7 = 0.01	0.97	0.00	Baseline-Pre	F1,7 = 2.74	0.14	0.28
	Baseline-Post	F1,7 = 0.04	0.84	0.01	Baseline-Post	F1,7 = 2.66	0.15	0.27
CO (l/min)	Baseline-Pre	F1,7 = 3.16	0.12	0.31	Baseline-Pre	F1,7 = 4.98	0.06	0.42
	Baseline-Post	F1,7 = 3.71	0.09	0.35	Baseline-Post	F1,7 = 6.82	0.03	0.50
HF n.u.	Baseline-Pre	F1,7 = 2.21	0.18	0.24	Baseline-Pre	F1,7 = 1.16	0.32	0.14
	Baseline-Post	F1,7 = 7.10	0.04	0.50	Baseline-Post	F1,7 = 0.28	0.61	0.04
LF/HF	Baseline-Pre	F1,7 = 3.69	0.10	0.34	Baseline-Pre	F1,7 = 2.15	0.19	0.23
	Baseline-Post	F1,7 = 4.76	0.06	0.40	Baseline-Post	F1,7 = 0.92	0.37	0.12

4.4 CONCLUSION

In the literature, at the present state of research, the process of falling asleep in subjects suffering from primary insomnia, together with autonomic changes and especially the cardiovascular system, is still unclear. We believe that the process of falling asleep has been poorly investigated by literature, but that it may be a key element to understanding insomnia itself.

Therefore, in the present study, we examined the time–course of cardiovascular activity during the transition from wakefulness to sleep; in particular, we considered the pattern of changes in autonomic functioning, focusing upon a short 5-min interval around sleep onset in primary insomniacs compared with good sleepers.

In insomniacs, subjective measures showed higher perceived arousal, as revealed by PSAS and HS, matching previous studies.[42,98-100] According to existing data,[121] anxiety and depression levels were also significantly greater in insomniacs than in good sleepers.

Our results are consistent with studies examining the transition from wakefulness to sleep in insomnia,[91,95-97] which found cortical and somatic hyper-activation.

Unlike other studies, which investigated cortical functioning in the sleep onset period, Freedman and Sattler[91] analyzed a broad range of physiological indexes including HR. They compared normal sleepers with subjects suffering from sleep onset primary insomnia by measuring cognitive and physiological activity before and during falling asleep. In particular, they observed higher HR from 10 min until 3 min before sleep onset in insomniacs, but failed to find differences between groups afterwards. Although different intervals were considered, these results are supported by our findings that indicate a higher initial HR (an index primarily modulated by parasympathetic activity at rest) in baseline in the insomniac group, but no differences between groups in pre- and post-sleep onset. As a matter of fact, HR showed a decrease in both groups during the transition from pre- to post-sleep onset, suggesting a parasympathetic increase. No other studies have examined cardiovascular patterns during the transition from wakefulness to sleep in insomniacs.

We used Impedance Cardiography (see section 1.5.2), a non-invasive technique of monitoring cardiac electro-mechanical functions which provides many cardiovascular indexes. Varkevisser et al.[122] used it to explore physiological changes over 24 h of total sleep deprivation in primary insomniacs compared with healthy subjects. To our knowledge, there are no other studies that have applied this technique to insomnia. Therefore, the present work is the first to use Impedance Cardiography in examining the sleep onset period in primary insomnia.

The most important result of this study is the continuous, unchanged, sympathetic hyper-activation observed in the insomniac group during sleep onset. By contrast, good sleepers showed the expected trend of increased PEP values (related inversely to sympathetic β-adrenergic activity), thus reducing sympathetic activity. This different pattern of changes between groups is an important finding, as shown by the elevated effect size level of significant interaction group × condition, even in light of the short windows applied and slow cardiovascular modifications.

HF values (that reflect a prevalence in parasympathetic control) increased significantly across the transition in both controls and insomniacs. In addition, the HF values showed an increase in post-sleep onset compared with baseline only in insomniacs: this is not due to the different sleep onset latency between groups because, even if insomniacs showed longer sleep latency, group difference was not statistically significant. Considering other sleep parameters, only sleep efficiency and NREM

duration showed significant differences. Researchers commonly report values for sleep efficiency of less than 85% in insomnia patients, whereas the present study found a mean value of 90%. This finding could bear evidence, but does not necessarily imply, that the selected subjects could actually be paradoxical insomniacs. In this study insomniacs were selected according to the DSM-IV diagnostic criteria for primary insomnia, which required as a predominant symptom, a difficulty in initiating or maintaining sleep, or non-restorative sleep, for at least 1 month. Therefore, our sample consisted of, not only sleep onset insomniacs, but also sleep maintenance insomniacs and early awakening insomniacs. This may be an explanation for the observed non-significant differences in sleep onset latency, wake after sleep onset and total number of awakenings. Moreover, relatively high sleep efficiency in insomnia group could be explained by considering that our sample was probably too small to provide a clear insomnia sleep pattern with selection criteria that were not based on the polysomnographic results. Finally, we cannot exclude that testing a sample recruited not only by DSM-IV diagnostic criteria for primary insomnia, but also considering the polysomnographic data (e.g. sleep efficiency less than 85%, sleep onset latency more than 30 min, etc.), the groups differences might have been larger.

To Summarize, insomniacs displayed continuously high sympathetic involvement matched with gradually increasing parasympathetic control. Therefore, unlike previous studies,[91,95-97] the somatic hyperarousal observed in our insomniacs, during the sleep onset period, consists of hyperactivation of both divisions of the neurovegetative system.

In the light of these results, speaking about two divisions acting only in antagonism may seem reductive. An integrated relationship between the two autonomic divisions may be more appropriate.[123] This concept suggests synergy between the two systems, rather than an antagonistic action, and leads to co-activation or co-inhibition. This "synergy perspective" may provide an interpretation for our findings.

Since primary insomnia appears to be related to chronic hyper-activation, this condition may have increasing long-term consequences, for example, the risk of developing cardiovascular diseases.[58]

Bearing the previous statements in mid and in accord to Vgontzas et al.,[82] the aim of insomnia treatment should be, not only the improvement of night-time sleep, but also the decrease of the overall level of physiological arousal.

Limitations to our study include the small sample size, which reduces its statistical power. In addition, we employed only one definition of sleep onset, i.e. the first epoch of Stage 1 sleep. It would be interesting to compare various definitions of falling asleep with the aim of assessing which is the most appropriate, from a cardiovascular perspective, in establishing the transition from wakefulness to sleep.

An interesting future prospective would also be to study cerebral haemodynamics matched with metabolic measures, to assess metabolic demands related to hyperarousal in insomnia.

5 EXP. 2 CARDIOVASCULAR ACTIVITY DURING SLEEP IN PRIMARY INSOMNIA

Previous researches has shown autonomic, neuroendocrine, neuroimmunological, elecrophysiological and neuroimaging evidence of increased levels of arousal during wakefulness and sleep in primary insomnia. However, few studies have focused on cardiovascular activity across sleep stages and there are even fewer that have studied cardiovascular activity during the process of falling asleep.

The aim of the present study is to analyze cardiovascular activity during sleep in primary insomniacs compared to good sleepers. This will be done by employing Impedance Cardiography and heart rate variability (HRV) analysis. The myocardial contractility, in insomniacs, was higher (elevated heart rate and reduced left ventricular ejection time) during wake compared to sleep. Pre-ejection period was lower in insomniacs overall the night in agreement with the hypothesized sympathetic hyperactivity underlied the disorder. In addition, HRV indexes showed an increased parasympathetic involvement (elevated high frequency) in wake, but only in insomniacs.

These findings suggest that, in insomniacs, a greater parasympathetic activation is required to fall asleep; possibly to contrast the sympathetic hyperactivation reflected in other variables. Furthermore, elevated contractility indexes suggest an association between insomnia and increased risk for cardiovascular diseases.

5.1 INTRODUCTION

Since few studies have focused on cardiovascular activity during night, our purpose was to investigate, through the night, the cardiovascular activity in primary insomniacs compared to that of good sleepers. The investigation was done with a particular attention to the autonomic indexes pre-ejection period (PEP) and measures derived from HRV analysis. We aimed to determine whether the hypothesized hyperarousal in insomniacs was constant across sleep stages and aimed to test if the hyperactivity was reflected in cardiovascular variables less directly associated with the sympathetic nervous system activity.

In order to explore group differences in the process of falling asleep, a key issue for insomnia patients, separate analyses were performed on the sleep onset period. The exact moment in which individuals fall asleep is still controversial. The classic approach, scoring sleep according to the standard criteria,[15] defines sleep onset as the first epoch of Stage 1 or the first epoch of Stage 2, implying that sleep begins at a "specific moment". Analyzing the falling asleep as a more extended process,[23] we investigated the cardiovascular modifications across quartiles (the sleep onset period subdivided in four equal time intervals), from light off to the end of the first 5 minutes of stable Stage 2, in insomniacs compare to good sleepers. Based on previous literature,[124] we hypothesized that insomniacs, compared to good sleepers, would have a constant sympathetic hyper-activation (e.g., low PEP values) matched with a larger progressive reduction of cardiovascular indexes across quartiles.

5.2 METHOD

5.2.1 PARTICIPANTS

The study involved 18 undergraduates, 9 insomniacs (4 men and 5 women; mean ± SD age: 23.00 ± 2.40; range 20-26 years) and 9 good sleepers (4 men and 5 women; mean ± SD age: 23.56 ± 3.17; range 19-28 years). The subjects were recruited through advertisements posted at the faculties of the University of Padova.

See section 4.2.1 for the participant's recruitment, the screening procedures and the insomnia diagnosis (exclusion and inclusion criteria).

All participants were informed about the purpose of the research and they gave written informed consent; they also received a 100 Euro compensation. The study protocol was approved by the Ethic Committee of the Department of Psychology.

5.2.2 PROCEDURE

As reported in the section 4.2.2.

5.2.3 DEPENDENT VARIABLES

5.2.3.1 Self-report measures

As reported in the section 4.2.3.1.

5.2.3.2 Polysomnographic recordings

As reported in the section 4.2.3.2.

5.2.3.3 Cardiovascular measures

As reported in the section 4.2.3.3.

5.2.4 DATA ANALYSES

Physiological data were analyzed as a function of sleep stages (wake, Stage 1, Stage 2, SWS, REM and NREM sleep), and also as a function of quartiles within the sleep onset period (defined as time from light-off to the end of the first 5 minutes of stable Stage 2 sleep) (Figure 5.1).

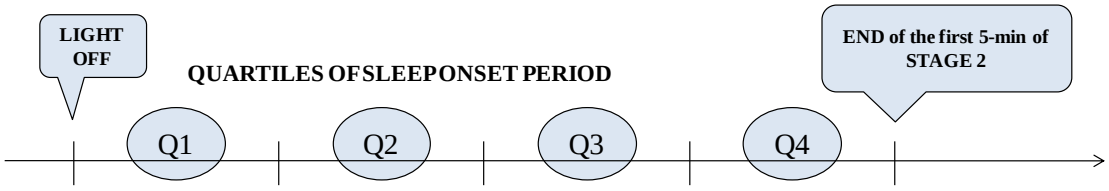


Figure 5.1 Quartiles of the sleep onset period.

Independent *t*-tests were used to evaluate differences in descriptive and subjective variables and in sleep parameters between groups. A 2 (between group: insomniacs and good sleepers) × 5

(within sleep stages: wake, Stage 1, Stage 2, SWS and REM) mixed-design ANOVA was applied to the mean values of each cardiovascular variable. Furthermore, REM-NREM differences were investigated for the cardiovascular indexes by a 2 (between group: insomniacs and good sleepers) × 2 (within sleep stages: REM, NREM) mixed-design ANOVA. In order to investigate modifications across the sleep onset period, a 2 (between group: insomniacs and good sleepers) × 4 (within quartiles: Q1, Q2, Q3, Q4) mixed-design ANOVA was applied to the mean values of each physiological variable. Bonferroni post-hoc comparisons were utilized on the significant effects and the Huynh-Feldt (H-F) correction was applied when necessary, i.e. when variables with more than two levels were involved. In these cases, uncorrected degrees of freedom, epsilon values (ε) and corrected probability levels were recorded. In addition, partial eta-squared effect size (η^2_p) and observed power have been reported as measures of effect size. Finally, independent *t*-tests were applied for each level of independent variables of the ANOVAs to investigate group differences more closely. For all statistical analyses, computed using STATISTICA 8 software (StatSoft, Inc., 2008), the probability level was set at $p < .05$ for significance.

5.3 RESULTS

5.3.1 DESCRIPTIVE ANALYSES

Insomniacs and good sleepers did not show differences in age or BMI. Scores of PSQI, AIS, and ISI were higher in insomniacs as expected. Furthermore, insomniacs reported significantly higher levels of depression, anxiety and hyperarousal, but not significant differences in somnolence, compared with good sleepers. In pre-sleep state measures, insomniacs showed higher levels of somatic and cognitive arousal, but no differences in anxiety and somnolence in comparison to controls (Table 5.1).

Table 5.1 Means and standard deviations of descriptive and subjective variables. AIS, Athens Insomnia Scale; BDI, Beck Depression Inventory; BMI, Body Mass Index; ESS, Epworth Sleepiness Scale; HS, Hyperarousal Scale; ISI, Insomnia Severity Index; PSAS, Pre-Sleep Arousal Scale; PSQI, Pittsburgh Sleep Quality Index; STAI, State Trait Anxiety Inventory. *$p < .05$, ** $p < .01$, *** $p < .001$.

	Insomniacs	**Good Sleepers**	***t***
Age (year)	23.00 (2.40)	23. 56 (3.17)	-0.42
BMI (kg/m^2)	21.83 (3.37)	22. 07 (2.58)	-0.17
Length of insomnia (yr)	4. 00 (3.12)		
trait			
PSQI	9. 67 (1.22)	4. 44 (2.90)	4. 95***
AIS	10.00 (3.16)	2. 22 (1.92)	6. 31***
ISI	13.44 (3.05)	2. 89 (3.14)	7. 24***
BDI-II	10.89 (5.16)	2. 44 (2.07)	4. 56***
STAI-Y2	45.22 (8.86)	35. 44 (6.56)	2. 66*
HS	44.56 (4.03)	30. 67 (5.85)	5. 86***
ESS	6. 11 (4.01)	5. 11 (3.30)	0. 58
state			
PSAS-somatic	11.22 (2.33)	9. 11 (1.54)	2. 27*
PSAS-cognitive	20.89 (5.30)	14. 56 (3.61)	2. 96**
STAI-Y1	50.67 (2.55)	52. 11 (2.42)	-1.23
SSS	2. 78 (1.39)	2. 33 (1.12)	0. 75

5.3.2 SLEEP PARAMETERS

As shown in Table 5.2, insomniacs, as a consequence of the same TIB, displayed a lower TST and a lower SE too. Insomniacs also had higher WASO in comparison with controls. The other sleep parameters did not show significant differences between groups.

Table 5.2 Mean and standard deviations of sleep parameters. *$p < .05$. See text for abbreviations.

	Insomniacs	Good Sleepers	*t*
SE (%)	91 (5)	96 (3)	-2.78 *
TIB (min)	480	480	
TST (min)	436 (23)	460 (12)	-2.78 *
SOL (min)	18 (14)	9 (6)	1.87
WASO (min)	26 (18)	12 (8)	2.19 *
REM latency (min)	83 (44)	97 (36)	-0.73
Total number of awakenings	18 (10)	10 (6)	1.87
NREM (min)	357 (28)	377 (11)	-1.99
REM (min)	78 (24)	83 (13)	-0.47
Stage 1 (min)	52 (23)	55 (16)	-0.30
Stage 2 (min)	223 (36)	221 (26)	0.18
SWS (min)	82 (47)	102 (23)	-1.13

5.3.3 CARDIOVASCULAR MEASURES

5.3.3.1 Sleep stages

ANOVA analyses of the sleep stage data are summarized in Table 5.3. HR showed a significant sleep stage main effect and group × sleep stage interaction. Post-hoc analyses revealed that HR decreased from wake to sleep stages in insomniacs, but not in controls (Figure 5.2).

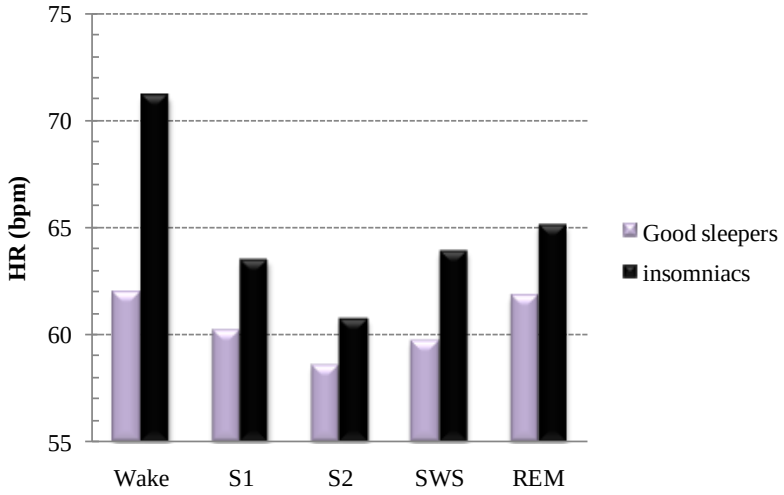


Figure 5.2 Mean of heart rate (HR) values across sleep stages in insomniacs and good sleepers. Only insomniacs show a reduction of HR from wake to sleep stages.

SV was significantly lower in insomniacs, as exhibited by a group main effect. There was also a significant sleep stage main effect in which post hoc analysis showed a higher SV in REM compared to wake and Stage 1 in both groups. Independent *t*-tests between groups revealed that good sleepers had significantly higher SV values in wake and in all the other sleep stages. A significant sleep stage main effect was found for CO that decreased from wake to sleep in both groups (Figure 5.3).

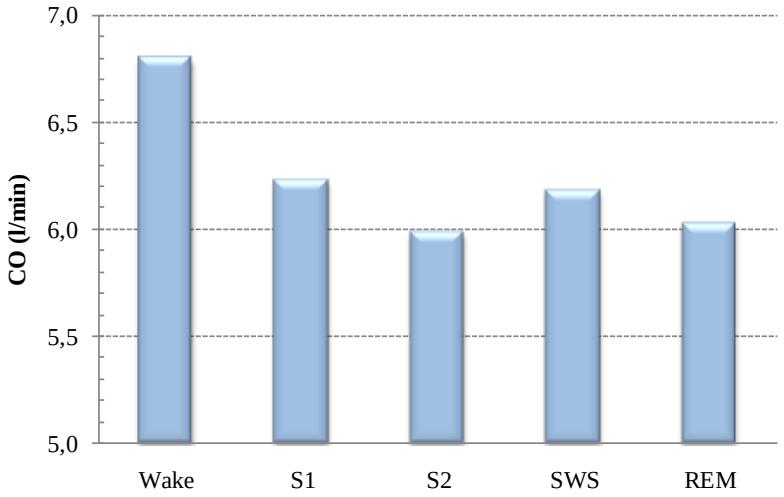


Figure 5.3 Means of cardiac output (CO) values across sleep stages.

ANOVA also indicated a significant group × sleep stage interaction as well as a main effect of sleep stage for LVET. Post-hoc analyses indicated that LVET increased from wake to sleep stages, but only in insomniacs (Figure 5.4). Independent *t*-tests between groups displayed significantly reduced LVET values in wake in insomniacs.

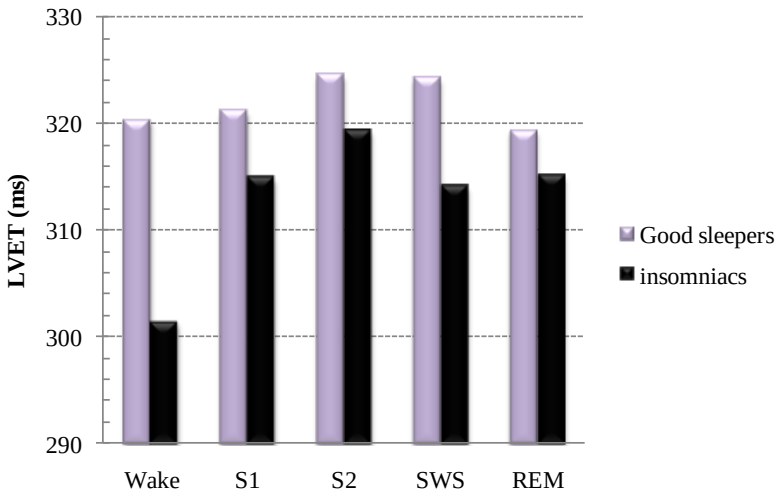


Figure 5.4 Mean of left ventricular ejection time (LVET) values across sleep stages in insomniacs and good sleepers. Only in insomniacs LVET increases from wake to sleep stages.

Lower PEP values, reflecting higher sympathetic activity, were found in insomniacs and there was a significant effect of stage. Post-hoc analyses of the significant sleep stage main effect reported lower PEP values in wake as well as in SWS with respect to Stage 1, Stage 2 and REM for both groups. Independent *t*-tests between groups underlined significantly lower PEP values in wake as well as in all sleep stages in the insomnia group in comparison to controls (Figure 5.5).

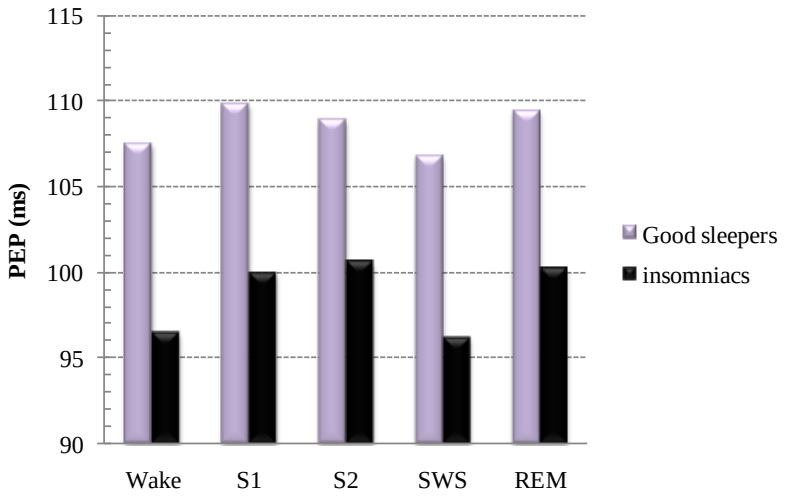


Figure 5.5 Mean of pre-ejection period (PEP) values across sleep stages in insomniacs and good sleepers.

The ANOVA indicated a significant sleep stage main effect for HF n.u. Post-hoc analyses showed higher HF n.u. in SWS in comparison to all the other sleep stages, lower HF n.u. in wake, Stage 1 and REM respect to Stage 2 and SWS. Independent *t*-tests by group reported significantly higher HF n.u. values in wake and REM in insomniacs, rather than in good sleepers (Figure 5.6). There was a significant sleep stage main effect for LF/HF ratio. Post-hoc analyses indicated lower LF/HF values in Stage 2 and SWS respect to REM, Stage 1 and wake in both groups.

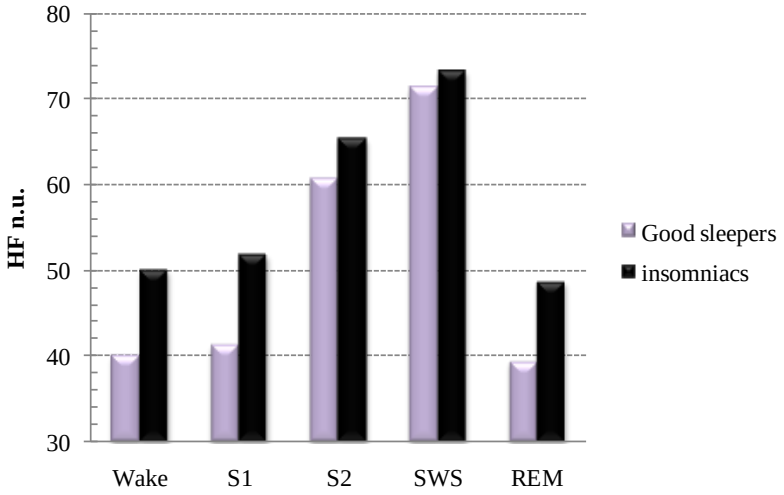


Figure 5.6 Mean of high frequency normalized unit (HF n.u.) values across sleep stages in insomniacs and good sleepers.

Table 5.3 Results of the 2 (between group: insomniacs and good sleepers) × 5 (within sleep stage: wake, Stage 1, Stage 2, SWS and REM) mixed-design ANOVAs. *$p < .05$, ** $p < .01$, *** $p < .001$. See text for abbreviations.

	GROUP			STAGE				GROUP × STAGE			
	$F_{1,16}$	η^2_p	Observed power	$F_{4,64}$	ε	η^2_p	Observed power	$F_{4,64}$	ε	η^2_p	Observed power
HR (bpm)	1.15	0.08	0.17	12.67***	0.72	0.44	0.99	3.71*	0.72	0.19	0.86
SV (ml)	7.84*	0.33	0.75	4.45**	0.76	0.22	0.92	0.12	0.76	0.01	0.07
CO (l/min)	1.74	0.10	0.24	14.96***	0.80	0.48	0.99	2.41	0.80	0.13	0.66
LVET (ms)	1.52	0.09	0.21	10.49***	0.63	0.40	0.99	5.63**	0.63	0.26	0.97
PEP (ms)	6.01*	0.28	0.64	5.88***	0.75	0.27	0.98	0.60	0.75	0.04	0.19
HF n.u.	3.25	0.17	0.40	61.38***	0.71	0.79	0.99	1.37	0.71	0.26	0.40
LF/HF	1.71	0.10	0.23	13.96***	0.51	0.47	0.99	0.62	0.51	0.04	0.19

5.3.3.2 REM-NREM differences

HR was significantly higher in REM in comparison to NREM in both groups as indicated by a sleep stage main effect. ANOVA indicated a significant sleep stage main effect for SV, reporting higher SV in NREM in both groups. Furthermore, a group main effect identified higher SV in controls compared to insomniacs. As shown by group main effect, PEP was reduced in insomniacs compared to controls over all conditions.

The ANOVA indicated a significant sleep stage main effect for HF n.u. that decreased from REM to NREM in both groups. There was a significant sleep stage main effect for LF/HF ratio highlighting lower LF/HF values in NREM with respect to REM. The ANOVA results for each variable are displayed in Table 5.4.

Table 5.4 Results of the 2 (between group: insomniacs and good sleepers) × 2 (within sleep stage: REM, NREM) mixed-design ANOVAs. *$p < .05$, ** $p < .01$, *** $p < .001$. See text for abbreviations.

	GROUP			STAGE			GROUP × STAGE		
	$F_{1,16}$	η^2_p	Observed power	$F_{1,16}$	η^2_p	Observed power	$F_{1,16}$	η^2_p	Observed power
HR (bpm)	0.65	0.04	0.12	10.24**	0.39	0.85	0.01	0.01	0.05
SV (ml)	9.68**	0.38	0.83	16.42***	0.51	0.97	0.56	0.03	0.10
CO (l/min)	2.71	0.14	0.34	1.03	0.06	0.16	0.48	0.03	0.10
LVET (ms)	0.67	0.04	0.12	3.64	0.18	0.43	1.27	0.07	0.18
PEP (ms)	5.15*	0.24	0.57	2.41	0.13	0.31	0.08	0.01	0.06
HF n.u.	2.81	0.15	0.35	206.59***	0.93	0.99	2.48	0.13	0.32
LF/HF	1.83	0.10	0.25	75.10***	0.82	0.99	3.36	0.17	0.41

5.3.3.3 Sleep onset period

Statistical analyses are presented in Table 5.5. The ANOVA indicated a significant group × quartile interaction for HR, as well as a quartile main effect (Figure 5.7). Post-hoc analyses showed that HR decreased across the sleep onset period (from Q1 to Q3 and Q4, and from Q2 to Q4) in insomniacs, but not controls. Independent *t*-tests by group reported higher HR in insomniacs in the first quartile.

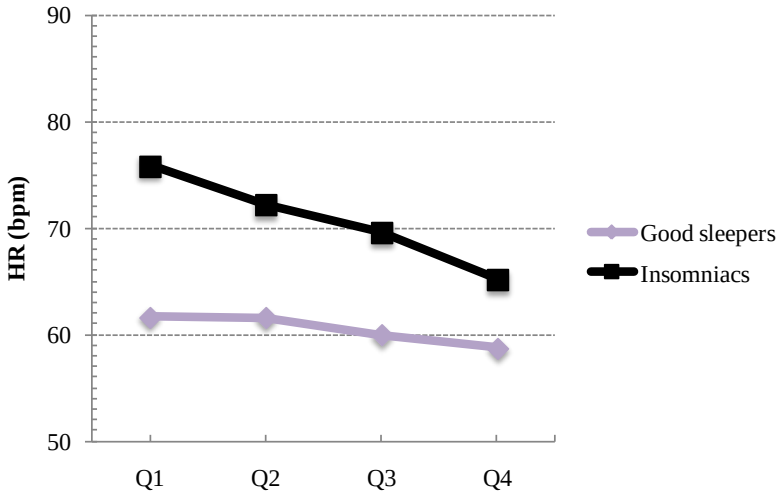


Figure 5.7 Mean and standard deviations of heart rate (HR) values across quartiles in insomniacs and good sleepers.

Independent *t*-tests by group found significantly lower SV levels in insomniacs compared to good sleepers, in Q1 and Q2. CO decreased significantly across the sleep onset period. Post-hoc analyses showed a decrease in CO from Q1 to Q2, Q3 and Q4 in both groups. Analysis of variance indicated a quartile main effect, as well as a significant group × quartile interaction in LVET. Post-hoc analyses showed that LVET increases across sleep onset period: from Q1 to Q4 and from Q2 to Q4 only in the insomnia group. Independent *t*-tests by group reported lower LVET in insomniacs compared to controls only in the first quartile.

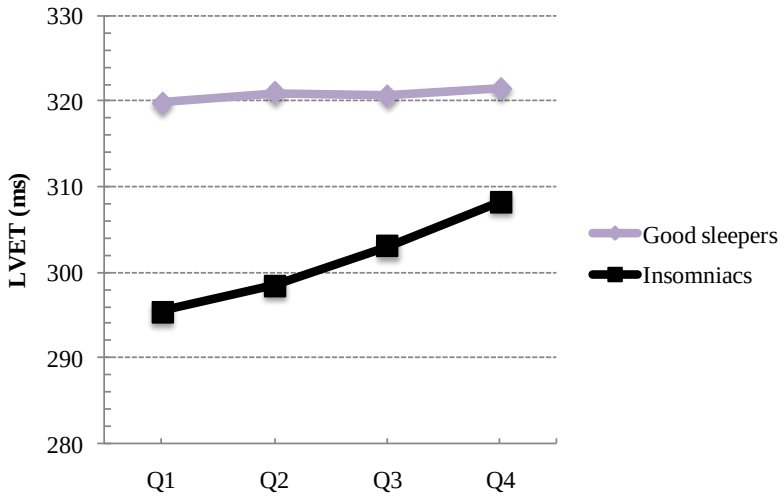


Figure 5.8 Mean and standard deviations of left ventricular ejection time (LVET) values across quartiles in insomniacs and good sleepers.

Insomniacs showed a greater sympathetic hyperactivation, i.e. lower PEP values, across sleep onset as evidenced by a group main effect. A quartile main effect was also found, with post-hoc analyses indicating an increase in PEP from Q1 to Q3 and Q4. Independent *t*-tests by group reported lower PEP in insomniacs in all quartiles. HF n.u. increased across quartiles (from Q1 to Q4), reducing the sympathovagal balance.

Table 5.5 Results of the 2 (between group: insomniacs and good sleepers) × 4 (within quartile: Q1, Q2, Q3, Q4) mixed-design ANOVAs. *$p < .05$, ** $p < .01$, *** $p < .001$. See text for abbreviations.

	GROUP			**QUARTILE**				**GROUP × QUARTILE**			
	$F_{1,16}$	**η^2_p**	**Observed power**	**$F_{3,48}$**	**ε**	**η^2_p**	**Observed power**	**$F_{3,48}$**	**ε**	**η^2_p**	**Observed power**
HR (bpm)	4.02	0.20	0.47	17.65***	0.51	0.52	0.99	5.23*	0.51	0.25	0.91
SV (ml)	4.08	0.20	0.47	1.94	0.52	0.11	0.47	1.94	0.52	0.11	0.47
CO (l/min)	0.02	0.01	0.05	8.14**	0.51	0.34	0.99	0.58	0.51	0.03	0.16
LVET (ms)	3.99	0.20	0.47	6.93**	0.65	0.30	0.97	4.59*	0.65	0.22	0.86
PEP (ms)	15.23**	0.49	0.96	7.55***	0.90	0.32	0.98	0.80	0.90	0.05	0.21
HF n.u.	0.63	0.04	0.12	2.92*	1.00	0.15	0.66	0.60	1.00	0.03	0.16
LF/HF	0.01	0.01	0.05	2.84	0.55	0.15	0.65	1.03	0.55	0.06	0.26

5.4 CONCLUSION

The aim of our study was to investigate cardiovascular activity in primary insomnia during sleep with a particular stress on autonomic activity and the process of falling asleep. Insomniacs, compared with good sleepers, showed lower PEP values and higher HR (higher sympathetic activity) and higher HF n.u. (lower sympathovagal balance) in wakefulness. The higher HR was associated with a comparable CO in insomniacs and controls, and thus lower SV in insomniacs, suggesting a sympathetic activation of the heart but not an elevated metabolism.[125] Moreover, in addition to somatic markers of hyperarousal, evidence of cognitive hyperactivity was also observed in insomniacs by PSAS measures.

Comparing wakefulness with the other sleep stages, only insomniacs showed a reduction in cardiac contractility indexes (decreases of HR associated with increases of LVET). A similar pattern was found for the sleep onset period, in which insomniacs reported a higher constant sympathetic hyper-activation with a progressive reduction in contractility indexes across quartiles.

Both groups showed a decrease in cardiovascular activity (reduction in CO), a reduction in sympathetic activity (increase in PEP values) and sympathovagal balance (decrease in LF/HF ratio and increase in HF n.u.) throughout the night as well as across quartiles of the sleep onset period. REM compared with NREM, was characterized by higher HR and LF/HF ratio and lower SV and HF n.u. in both insomniacs and controls.

In our data, according to the existing literature,[34,126] insomniacs and normal individuals, showed a decrease in cardiovascular activity during the night. Further in agreement with studies on healthy subjects[29,127-129] as well as on insomnia patients, [87,109] HRV variables showed a reduction in sympathovagal balance from wake to deep sleep, as well as through quartiles of sleep onset, in both groups. Likewise previous results,[109] REM/NREM differences indicated high heart rate and sympathovagal balance, in association with reduced stroke volume in REM compared with NREM sleep in both insomnia sufferers and healthy controls.

Insomniacs, compared with good sleepers, had lower PEP values, i.e. higher sympathetic activity, during the night as it has been reported by Varkevisser, Van Dongen and Kerkhof,[122] although

the differences were not significant in their study. Nevertheless, these results support the previous evidence of sympathetic hyperarousal found in primary insomnia (see section 3.4). Thus, sympathetic hyperactivation seems to be a main feature in this disorder. PEP was significantly lower in wakefulness compared to REM, Stage 1 and Stage 2 both in controls and insomniacs, suggesting a decrease of sympathetic involvement through the night, although PEP values were paradoxically comparable in wake and SWS. The absence of increased PEP values in SWS is inconsistent with previous findings, highlighting reduced sympathovagal balance across the night.[11]

However, it is likely that PEP values were influenced by changes in blood pressure.[34] Reductions in BP decrease PEP and as BP falls dramatically at sleep onset[128] this will likely cause a decrease in PEP at the time SWS is most abundant. Thus, the lower PEP in SWS may be secondary to a fall in BP rather than reflecting sympathetic activation.

Several studies have demonstrated an association between NREM sleep and enhanced vagal tone compared with wakefulness still, the effect of sympathetic nervous system on the heart during sleep, remains unclear.[11] Keeping in mind that PEP is the main validated index assessing sympathetic control on the heart, only a small number of studies have evaluated PEP during the night, with inconclusive results,[30,31,122,127,128] suggesting that further researches examining the autonomic variation during sleep should focus on this index.

If we consider the activation of the sympathetic nervous system in primary insomnia, the issue of falling asleep and maintaining sleep in this group of patients should be addressed. In the current study only insomniacs showed higher cardiac activity in wake and a reduction in cardiac contractility indexes (decreases of HR and increases of LVET) from wake to all the other sleep stage and across quartiles of the sleep onset period. Another difference was the amount of blood pumped during each heartbeat, which was lower in insomniacs throughout the night (lower SV values). HR was higher in insomniacs, there were no group differences in CO. Moreover, a shift towards a parasympathetic control during sleep stages was also found in insomniacs (higher HF n.u. as an index of decreased sympathovagal balance).

To our knowledge, only two other studies have focused on nocturnal HRV measures in insomniacs: Bonnet and Arand[87] found increased LF power and decreased HF power during sleep and

nighttime wakefulness in insomniacs compared with healthy controls; on the other hand, Jurysta et al.[109] failed to show any group differences in normalized units of LF and HF and LF/HF ratio. Although nocturnal HRV results in insomnia patients remain inconsistent, our data indicate paradoxically low sympathovagal balance as indicated by HF n.u. and high sympathetic activation as indicated by HR, LVET and PEP in insomniacs. We suggest this pattern should be interpreted as indicating co-activation of the two autonomic branches of the neurovegetative system,[130] likewise we suppose that converging pathways play a key role in the pathophysiology of primary insomnia.

In spite of the disagreement within the scientific community about the mathematical and physiological meaning and interpretation of the normalized frequency domain-HRV indexes, some considerations seem to be appropriate. HF n.u. and LF n.u. are mathematically the same variable and each can be considered a nonlinear transformation of the LF/HF ratio. However, although these variables are redundant, we reported both HF normalized unit and the ratio, considering them as a single dimension of information reflecting the sympathovagal balance, as proposed in Burr and colleagues.[10]

Our data have shown discrepancy in statistical outcomes of HF n.u. and LF/HF ratio (e.g. significant group differences in wakefulness for HF n.u. but not for LF/HF ratio). Considering that HF n.u. and LF n.u. reciprocally vary from 0 to 1 while the LF/HF ratio may theoretically vary from 0 to infinitive, the larger range may result in an increased variance, thus affecting the statistical outcomes.

Despite polysomnography not being indicated for the routine evaluation of primary insomnia and considering that sleep parameters failed to show large group differences, a remark about polysomnography data of our sample seems to be necessary. The mean percentage of sleep efficiency was higher, as well as the mean sleep onset latency was lower in insomniacs with respect to the limits commonly considered normal by sleep experts. When subjective estimation of sleep parameters are compared with objective polysomnography data, insomniacs are inclined to underestimate their sleep quality and when differences are large, it is believed that patients suffer from sleep state misperception; nevertheless, subjects are considered insomniacs if they report SOL > 30 min, TST < 6.5 h and SE < 85%. We cannot completely exclude that our sample falls within sleep state misperception as in our sample significant differences were found only in SE and WASO. Lack of

consistency might be due to the fact that the condition of insomnia is variable from night to night and insomniacs were enrolled according to DSM-IV[131] criteria, without polysomnographic exclusion criteria. Moreover, not significant differences observed in our sample may be a consequence of the small number of subjects.

The main limitation of the study was indeed the small sample size. This is to be attributed to the low impact of primary insomnia in the general population, the young age of the participants and the restrictive criteria used to recruit the insomnia group (insomniacs had to satisfied the DSM-IV criteria for the primary insomnia and also to report a history of insomnia for at least 1 year).

In conclusion, a reduction of cardiac contractility indexes during sleep added to a high level of sympathetic activity in both sleep onset period and sleep stages and low levels of sympathovagal balance at the beginning of the night (that suggests a high vagal tone) seem to characterize the nocturnal cardiovascular pattern of insomniacs. Our results of increased contractility indexes (known to be a stress factor for the cardiovascular system) in insomniacs support the association between insomnia and cardiovascular diseases.[50]

6 EXP. 3 COGNITIVE PERFORMANCE AND CARDIOVASCULAR MARKERS OF HYPERAROUSAL IN PRIMARY INSOMNIA

The purpose of the present study is to detect differences in cardiovascular activity and cognitive performance between insomniacs and good sleepers.

Sixteen undergraduates participated in the study, eight insomniacs enrolled in accord with DSM-IV criteria for primary insomnia, and eight good sleepers were controls. The task employed, Stop Signal Task, assesses motor inhibition processes and was administered in two sessions, before and after a night of polysomnographic recording. During task performance, cardiovascular measures such as heart rate (HR), stroke volume (SV), cardiac output (CO), pre-ejection period (PEP) and left ventricular ejection time (LVET) were continuously recorded by means of Impedance Cardiography.

Performance results showed prolonged Stop Signal Delay (SSD) in the morning in both groups and slower Stop Signal Reaction Time (SSRT) in insomniacs compared with good sleepers, while no effects were observed for performance accuracy. Analyses performed on cardiovascular parameters revealed higher HR and lower LVET values in the insomnia group as compared to healthy controls in the evening. PEP, an index inversely related to sympathetic beta-adrenergic activity, was continuously reduced in insomniacs, indicating constantly enhanced sympathetic activation.

These findings suggest a deficit of motor inhibition control in insomnia, matched with high levels of cardiovascular arousal. Overall, our results support the notion that insomnia is a hyperarousal disorder, affecting both somatic activity and cognitive performance, leading to sleep complaints as well as daytime impairment.

6.1 INTRODUCTION

Patients suffering from insomnia disorders often complain of cognitive impairment. Despite an extensive investigation into many cognitive domains such as vigilance,[132-134] selective attention,[135-141] working memory,[84,134,135,141] and memory consolidation,[142,143] executive functions have been poorly investigated in insomniacs. Fang and colleagues[144] and Vignola and colleagues[141] employed the Wisconsin Card Sorting Test, but failed in finding impaired performance among insomnia sufferers. On the other hand, Edinger and co-workers[137] found significant group differences between insomniacs and good sleepers in a switch task, which assesses attention, concentration and response inhibition. Consistently, by employing the Porteus maze test, Randazzo and coworkers[145] observed a poorer performance in insomniacs than in healthy controls.

The domain of executive functioning includes higher level cognitive processes such as planning, inhibition, reasoning and problem solving. Examining brain activity through fMRI during a fluency task, Altena and colleagues[104] reported hypoactivation of the prefrontal cortex -a key area for executive functions- in insomnia sufferers relative to controls, despite a lack of performance differences. These findings suggest a differential recruitment of cerebral resources for successful task completion.

Among executive functions, motor inhibition plays an important role in everyday life. Many situations require the interruption of an ongoing action before another, more appropriate to the context demands, can begin.

The efficiency and latency of the motor inhibition process can be assess by the Stop Signal Task (SST), a two choice reaction time task in which, occasionally and unexpectedly, a stop signal occurs requiring response inhibition.[146,147] The rationale that lies behind the Stop Signal paradigm is provided by the horse race model.[146] This model postulates a competition between two sets of mutually independent processes, one producing responses to the primary task (Go process) and the other responding to the stop signal (Stop process). If the Go process ends before the Stop process, response is given and inhibition fails. In contrast, if the Stop process finishes before the Go process, the response is suppressed. Therefore, correct response inhibition, depends on the relative end-time of

the two processes. Importantly, the Stop Signal Task allows the latency of the unobservable inhibition process to be inferred.[146,148,149]

The stop signal paradigm has been used to assess inhibitory control in a broad range of disorders, such as schizophrenia,[150,151] attention deficit and hyperactivity disorder,[152-154] obsessive-compulsive disorder,[155,156] Parkinson's disease[157] and eating disorders.[158] To our knowledge, only one study[159] has applied Stop Signal paradigm to the study of insomnia. Sagaspe and collegues[159] investigated cognitive performance by using this task in patients suffering from obstructive sleep apnea syndrome (OSAS) and insomnia, and compared the patient groups to good sleepers. They found poorer performance in the OSAS group compared to controls, but failed in finding significant differences between insomniacs and healthy controls.

Since few studies have focused on cardiovascular reactivity to the task in primary insomnia and most of them have analyzed blood pressure, heart rate and measures derived from HRV analysis, the direct sympathetic nervous system influence on the heart is still unknown. The most validated and reliable non-invasive measure of the sympathetic beta-adrenergic influence on heart is the pre-ejection period (PEP), the interval between electric and mechanical systole.[13] PEP is commonly assessed by Impedance Cardiography, a non-invasive technique which allows the recording of a wide range of cardiac parameters.

The purpose of the current study is to investigate response inhibition in insomniacs by employing the Stop Signal paradigm coupled with non-invasive cardiovascular recordings using Impedance Cardiography, thus assessing the involvement of hyperarousal in cognitive impairment in primary insomnia. Taking its cue from a previous finding of time of day effects on hyperarousal levels in insomnia sufferers[160], two-sessions were administered: one in the evening before sleeping, the other in the morning after awakening. Moreover, in order to investigate hyperactivity markers and mutual links, associations between physiological, cognitive and subjective measures were also examined.

6.2 METHOD

6.2.1 PARTICIPANTS

Eight normal sleepers (mean age = 24.75 years, S.D. = 2.71) and eight insomniacs (mean age = 22.86 years, S.D. = 2.42) participated in this study. All subjects were recruited through advertisements placed in the Faculty of Psychology of Padova University.

See section 4.2.1 for the participant's recruitment, the screening procedures and the insomnia diagnosis (exclusion and inclusion criteria).

The experimental protocol was approved by Ethic Committee of Padova University. Each subject signed informed consent and received 100 Euros for participation.

6.2.2 PROCEDURE

As reported in the section 4.2.2.

6.2.3 DEPENDENT VARIABLES

6.2.3.1 Self-report measures

As reported in the section 4.2.3.1.

6.2.3.2 Polysomnographic recording

As reported in the section 4.2.3.2.

6.2.3.3 Cognitive measures

The Stop-Signal Task consisted of a visual two-choice Reaction Time task where Go stimuli were represented by a capital letter (either O or X) displayed centrally in gray on a black screen and presented in a randomized order. Each trial began with a central fixation cross (500 ms), followed by a blank (500 ms), then the stimuli were presented for 1000 ms, in a randomized order. The Inter Trial Interval (ITI) was a blank screen of 1500 ms duration (Figure 6.1). After the onset of the Go stimulus, a 100 ms-1000 Hz tone was presented binaurally through headphones, unpredictably on 25% of trials on an equal number of times for each letter.

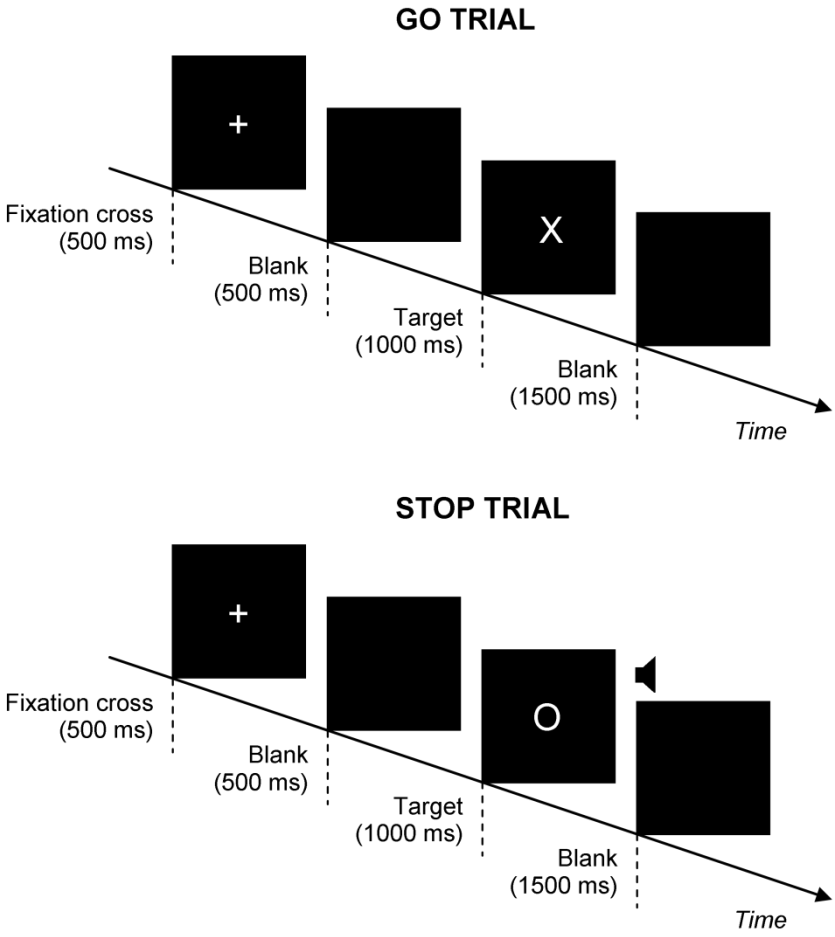


Figure 6.1 Stop Signal Task. Subjects have to respond to the target stimulus by pressing the appropriate key on the keyboard (Go trials). When a tone was emitted after the onset of the stimulus they were required to inhibit response (Stop trials).

Subjects were instructed to press a key on the keyboard in response to the onset of the target (respectively, press "V" letter to "X" stimulus and "N" to "O") as accurately and quickly as possible (Go trials). When the tone occurred, participants had to refrain from responding (Stop trials).

Stop Signal Delay (SSD; i.e., the delay between the onset of the go stimulus and the onset of the stop-signal) was initially set at 250 ms and was adjusted dynamically, depending on the response to previous Stop trials, by a tracking algorithm developed by Logan and coworkers.[149] The delay increased by 50 ms if subject withheld the response successfully, so to increase the task difficulty; on the contrary, SSD decreased by 50 ms if the inhibition failed, so to facilitate the response to the next Stop trial. The tracking procedure allowed the SSD to converge on a value at which subjects

successfully inhibited the response on 50% of stop trials. This value was used to compute the Stop Signal Reaction Time (SSRT), by subtracting the mean SSD from the mean Go RT (see Figure 6.2).

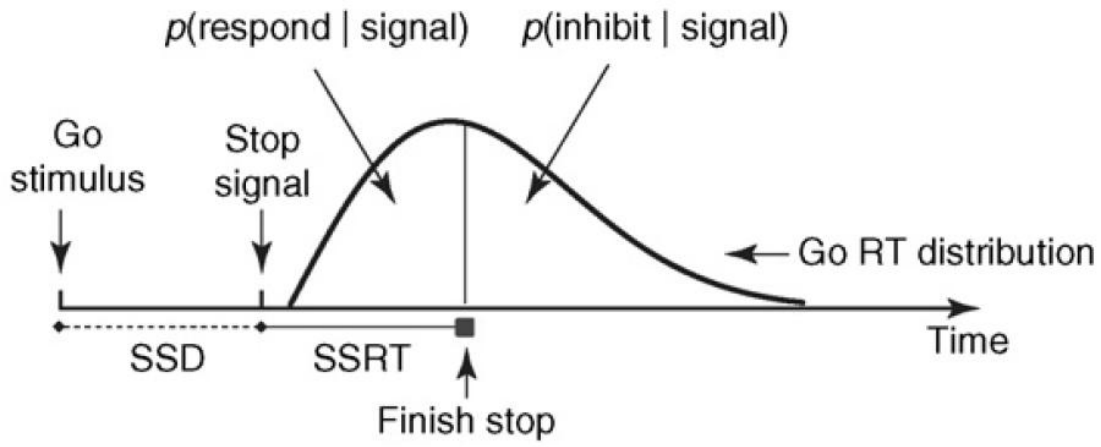


Figure 6.2 Horse race model.[146] The probability of responding on a stop-signal trial, p (respond | signal), mainly depends from the Stop Signal Delay (SSD), the Go Reaction Time (Go RT) and the Stop Signal Reaction Time (SSRT) (picture from[161]).

A task session consisted of five trial blocks, each of which was preceded by a 1 min-fixation of a cross on a blank screen as baseline. The first two blocks, each one consisting of 20 trials, were exploited as practice blocks and data obtained from them were not analyzed. The following three blocks were experimental, each one comprising 80 trials (60 Go trials and 20 Stop trials in a randomized order). There were an equal number of Xs and Os in every block and stop signals were presented on 25% of the trials, balanced over letters.

For Go trials, measures included Go accuracy (%), mean RT to Go stimuli (ms), omission error (i.e., no press; %) and discrimination choice error (i.e., press "V" when "O" and vice versa; %) rates. For Stop trials, measures included Stop accuracy (%), false alarm rates (i.e. response given; %), mean SSRT (ms) and mean SSD (ms).

The task was programmed and run with E-Prime 1.1 software (Psychology software tools, Inc., Pittsburgh, PA), and delivered to the subjects using a 17-in monitor (Intel 910GL Express Chipset) placed 60 cm in front of the subject. Testing was performed in a well enlightened, sound attenuated room.

6.2.3.4 Cardiovascular measures

As reported in the section 4.2.3.3. No HRV measures have been calculated for this analysis.

6.2.4 DATA ANALYSES

Performance data were averaged across blocks to obtain mean values for each experimental session. Absolute cardiovascular values recorded during the testing were averaged for each subject over each session. In order to assess reactivity to the task, delta values were computed by subtracting mean block values from the baseline.

Independent *t*-tests, by group, were performed on each variable in order to investigate group differences.

Mixed-design analyses of variance (ANOVAs) consisting of Group (2 levels: insomniacs vs normal sleepers) by Session (2 levels: evening vs morning) were also performed on subjective, cognitive and cardiovascular data. Newman-Keuls Post Hoc comparisons were applied on significant effects.

The Shapiro–Wilks Test on reaction times revealed a normal distribution for both groups.

Correlations were generated, for each group and session, to examine the relationship between subjective, cognitive and physiological measures.

Finally, a multiple regression analysis was performed to investigate if the depression or the insomnia ratings could better account for the insomniacs' task performance.

For all statistical analyses, probability level set at $p < .05$ was considered as significant.

6.3 RESULT

6.3.1 DESCRIPTIVE ANALYSES

Demographic data and questionnaires scores of study participants are presented in Table 6.1. Groups did not differ in age, BMI, trait anxiety and sleepiness. As expected from the inclusion criteria, insomniacs, compared to good sleepers, reported higher scores on the PSQI, ISI and AIS. Insomniacs have also shown significantly higher levels of depression and hyperarousal as measured by respectively, BDI-II and HS.

Table 6.1 Mean values and standard deviations for descriptive and subjective variables. PSQI, Pittsburgh Sleep Quality Index; AIS, Athens Insomnia Scale; ISI, Insomnia Severity Index; BDI, Beck Depression Inventory; STAI, State Trait Anxiety Inventory; HS, Hyperarousal Scale; ESS, Epworth Sleepiness Scale; SSS, Stanford Sleepiness Scale. * $p < .05$; ** $p < .01$; *** $p < .001$.

	Insomniacs	**Good sleepers**	***t***
Age (year)	22.87 (2.42)	24.75 (2.71)	1.46
BMI (Kg/m^2)	21.95 (3.58)	21.93 (3.00)	-0.01
trait			
PSQI	9.62 (1.30)	2.87 (1.25)	-10.59***
AIS	10.75 (2.38)	1.37 (0.74)	-10.65***
ISI	14.00 (2.73)	1.62 (0.74)	-12.39***
BDI-II	10.62 (5.45)	1.87 (1.46)	-4.39***
STAI-Y2	43.12 (6.66)	37.00 (6.68)	-1.83
HS	44.50 (4.31)	31.25 (5.47)	-5.38***
ESS	6.37 (4.21)	5.00 (2.83)	-0.77
state - evening			
PSAS-somatic	11.00 (2.39)	9.37 (1.60)	-1.60
PSAS-cognitive	20.25 (5.28)	13.62 (2.97)	-3.09**
STAI-Y1	51.00 (2.51)	52.00 (1.51)	0.97
SSS	2.75 (1.49)	2.12 (0.83)	-1.04
state - morning			
STAI-Y1	50.37 (1.68)	51.25 (1.91)	0.97
SSS	3.75 (1.28)	2.62 (0.92)	-2.02

Mixed-design ANOVAs performed on SSS scores indicated increased morning sleepiness in both groups, as underlined by the significant session main effect. However, analysis of STAI-Y1 scores failed to report any significant differences in anxiety (Table).

6.3.2 POLYSOMNOGRAPHIC RECORDINGS

Groups significantly differed for total sleep time (TST) and sleep efficiency (SE), which were significantly reduced in the insomniacs (Table 6.2). Insomnia sufferers have also shown a trend towards decreased REM sleep ($p = 0.058$) as well as increased wake after sleep onset ($p = 0.055$) compared to healthy controls. No other differences were observed between groups.

Table 6.2 Mean and standard deviations of sleep parameters in insomniacs and good sleepers across the entire night. TIB, time in bed; TST, total sleep time; WASO, wake after sleep onset; REM, rapid eye movement; NREM, non-rapid eye movement sleep; SWS, slow wave sleep. * $p < .05$, ** $p < .01$, *** $p < .001$.

	Insomniacs	**Good sleepers**	***t***
Sleep efficiency (%)	91 (5)	96 (2)	2.71 *
TIB (min)	480	480	
TST (min)	436 (24)	462 (12)	2.71 *
Sleep latency (min)	17 (14)	6 (5)	-1.99
WASO (min)	27 (19)	6 (5)	-1.99
REM latency (min)	82 (25)	103 (12)	1.09
Total number of awakenings	17 (11)	10 (5)	-1.80
NREM duration (min)	364 (21)	374 (7)	1.33
REM duration (min)	72 (16)	88 (14)	2.06
Stage 1 duration (min)	54 (24)	51 (13)	-0.26
Stage 2 duration (min)	226 (38)	226 (21)	-0.04
SWS duration (min)	85 (50)	98 (24)	0.70

6.3.3 RESPONSE INHIBITION

A significantly higher SSRT was found in insomniacs compared with controls, as shown by the group main effect (Figure 6.3). A significant main effect of session was also observed in SSD, which increased in the morning in both groups. No significant effects were found for accuracy, error rates and RTs, either for Go trials or for Stop trials (Table).

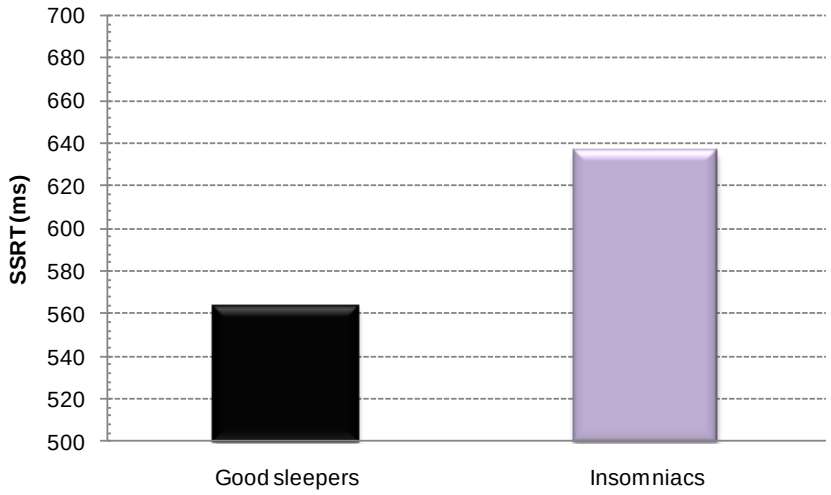


Figure 6.3 SSRT group main effect. SSRT, stop signal reaction time.

6.3.4 CARDIOVASCULAR MEASURES

Mixed-design ANOVAs, computed on the absolute values for task blocks, resulted in a significant group × session interaction for HR. Since post-hoc analyses failed to detect significant differences, independent *t*-test by group was employed to test a group difference, indicated higher HR values in insomniacs than controls in the evening session (about 12 bpm plus; $t = -2.19$, $p < .05$). Moreover, a dependent *t*-test by samples showed enhanced HR in the morning only in controls ($t = -2.82$, $p < .05$).

Insomniacs reported constantly lower PEP values, i.e. heightened sympathetic activity, as indicated by a group main effect (Figure 6.4). In addition, a significant session main effect showed, in both groups, higher PEP values in the morning.

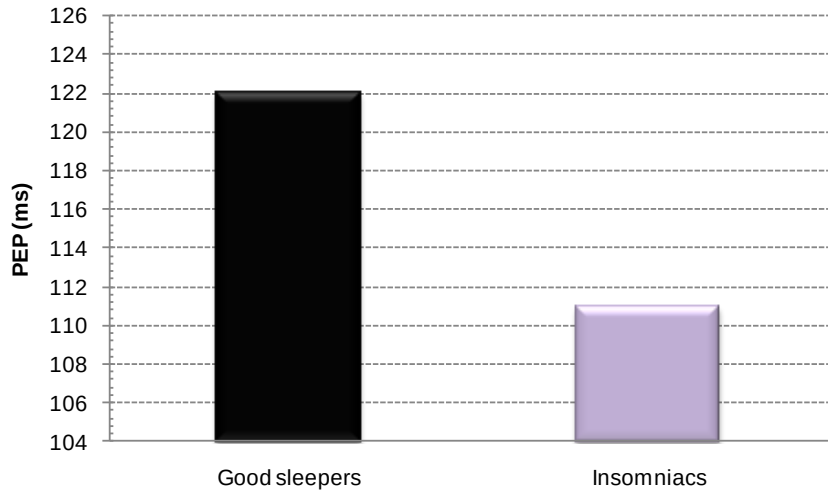


Figure 6.4 Group main effect for PEP.

As illustrated in Figure 6.5, ANOVA performed on LVET data found a significant session main effect and a group × session interaction. Post-hoc analyses revealed a reduction of LVET from evening to morning only in insomniacs.

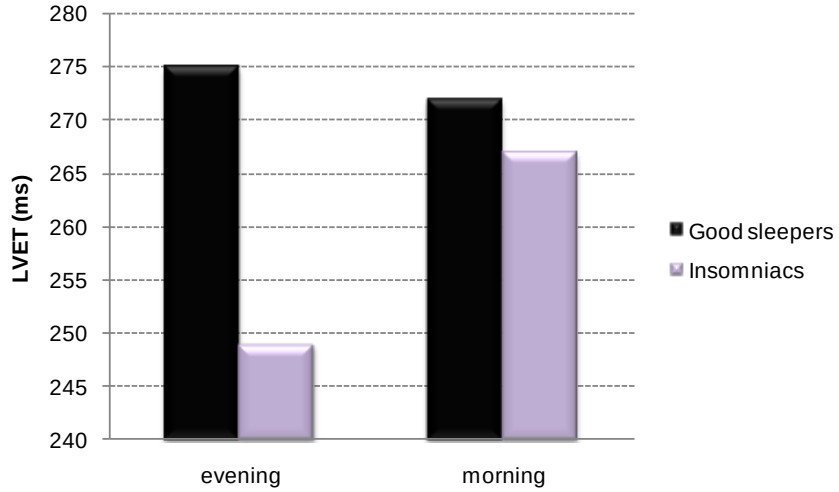


Figure 6.5 Significant group × session interaction for LVET (left ventricular ejection time).

Finally, SV values showed a decrease in the morning in both groups, whereas no differences were observed for CO. Results of comparisons are summarized in Table .

Mixed-design ANOVAs computed on delta values for each cardiovascular variable failed to find any significance, both for main and interaction effects.

Table 6.3 ANOVA 2 (between group: insomniacs and good sleepers) × 2(within session: evening and morning) results for subjective, cognitive and physiological variables. STAI, State-Trait Anxiety Inventory; SSS, Stanford Sleepiness Scale; RT, Reaction Time; SSRT, Stop Signal Reaction Time; SSD, Stop Signal Delay; HR, heart rate; PEP, pre-ejection period; LVET, left ventricular ejection time; SV, stroke volume; CO, cardiac output. * $p < .05$, ** $p < .01$, *** $p < .001$. Degree of freedom = 1, 14.

	Evening		**Morning**		**GROUP**			**SESSION**			**GROUP × SESSION**		
	Insomniacs	**Good sleepers**	**Insomniacs**	**Good sleepers**	**F**	***p***	**η^2_p**	**F**	***p***	**η^2_p**	**F**	***p***	**η^2_p**
Subjective													
STAI-Y1	51.00±2.51	52.00 ±1.51	50.38±1.69	51.25±1.91	1.32	0.270	0. 09	1.73	0.210	0.11	0.01	0.907	0.01
SSS	2.75±1.49	2.13 ±0.83	3.75±1.28	2.63±0.92	3.33	0.089	0. 19	5.25	0.038	0.27	0.58	0.458	0.04
Cognitive													
GO accuracy	0.96±0.07	0.96 ±0.08	0.92±0.09	0.97±0.03	1.51	0.240	0. 10	0.21	0.651	0.01	1.29	0.275	0.08
STOP accuracy	0.56±0.17	0.55 ±0.06	0.61±0.09	0.58±0.05	0.18	0.676	0. 01	3.48	0.083	0.20	0.31	0.588	0.02
Omissions	0.04±0.06	0.02 ±0.02	0.07±0.09	0.02±0.03	4.08	0.063	0. 23	0.74	0.404	0.05	0.49	0.696	0.03
Choice errors	0.01±0.01	0.03 ±0.06	0.01±0.01	0.01±0.01	0.68	0.422	0. 05	0.65	0.432	0.05	2.36	0.147	0.14
False alarms	0.44±0.17	0.45 ±0.06	0.39±0.09	0.42±0.05	0.18	0.676	0. 01	3.48	0.083	0.20	0.31	0.588	0.02
GO RT (ms)	629±137	556 ±70	644±130	571±85	1.88	0.192	0. 12	1.72	0.210	0.11	0.01	0.965	0.01
SSRT (ms)	222±49	185 ±23	205±33	180±26	4.84	0.045	0. 26	1.13	0.305	0.07	0.35	0.562	0.02
SSD (ms)	394±141	364 ±68	438±117	391±73	0.59	0.456	0. 04	8.71	0.011	0.38	0.51	0.486	0.03
Physiological													
HR (bpm)	84±10	72 ±12	80±11	75±12	2.30	0.152	0. 14	0.27	0.608	0.02	5.58	0.033	0.28
SV (ml)	72±15	85 ±20	70±7	77±17	1.94	0.185	0. 12	4.39	0.049	0.24	1.70	0.213	0.11
CO (l/min)	5.96±0.99	6.03 ±1.32	5.52±0.59	5.70±0.98	0.08	0.776	0. 01	2.61	0.129	0.16	0.06	0.810	0.01
PEP (ms)	108±8	119 ±9	114±8	125±7	8.47	0.011	0. 38	13.65	0.002	0.49	0.01	0.974	0.01
LVET (ms)	249±15	275 ±26	267±22	272±23	2.45	0.140	0. 15	4.85	0.045	0.26	8.90	0.010	0.39

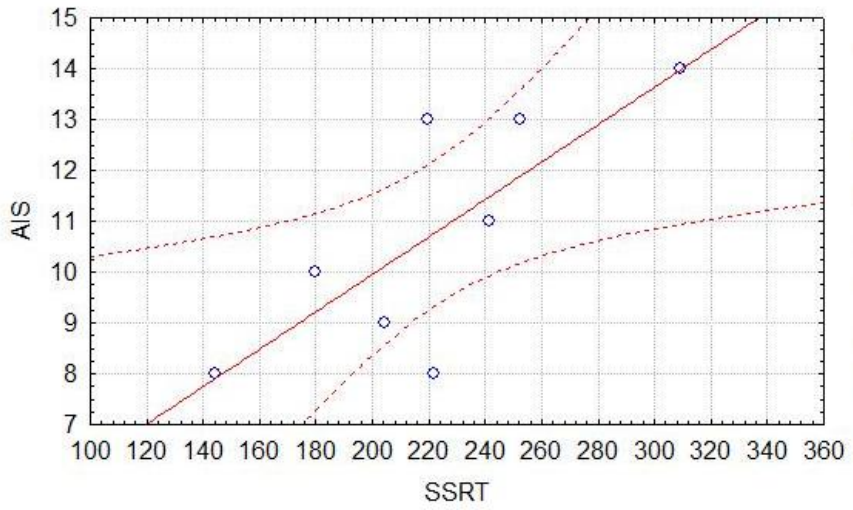
6.3.5 CORRELATIONS

6.3.5.1 Cognitive variables

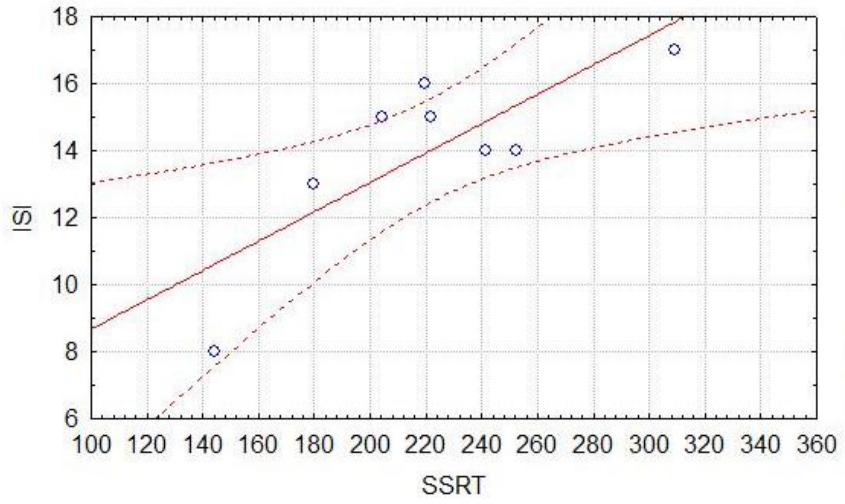
Pearson's correlation analysis, computed on cognitive variables, revealed a significant positive correlation between GO RT and STOP accuracy in both sessions and groups (insomniacs-evening: r = 0.73, $p < .05$; controls-evening: r = 0.86, $p < .01$; insomniacs-morning: r = 0.96, $p < .001$; controls-morning: r = 0.89, $p < .01$), as well as between GO RT and SSD (insomniacs-evening: r = 0.91, $p < .01$; controls-evening: r = 0.92, $p < .01$; insomniacs-morning: r = 0.97, $p < .001$; controls-morning: r = 0.96, $p < .01$).

6.3.5.2 Subjective and cognitive measures

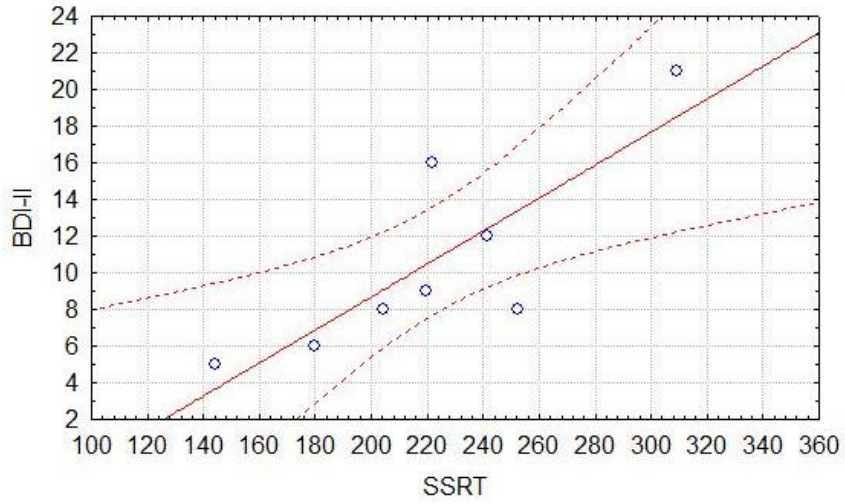
With regard to the relationship between subjective and cognitive measures, the evening session showed significant relationships between sleepiness and performance in both groups: whereas in good sleepers SSS was negatively related to GO accuracy (r = -0.91, $p < .01$) and positively to omission (r = 0.93, $p < .01$) and choice errors (r = 0.89, $p < .01$), in insomniacs SSS negatively correlated with STOP accuracy (r = -0.86, $p < .01$) and SSD (r = -0.76, $p < .05$) and positively with false alarms (r = 0.86, $p < .01$). Furthermore, SSRT was positively related to ISI (r = 0.79, $p < .05$), AIS (r = 0.76, $p < .05$) and BDI (r = 0.81, $p < .05$) scores in the insomnia group.



(a)



(b)



(c)

Figure 6.6 The graphs represent in insomnia sufferers the correlation between stop signal reaction time (SSRT) and, respectively, Athens Insomnia Scale (AIS) (a), Insomnia Severity Index (ISI) (b) and Beck Depression Inventory (BDI-II) (c) scores.

6.3.6 MULTIPLE REGRESSION ANALYSIS

In light of the previous results (see section 6.3.5), a multiple regression analysis was performed using SSRT as dependent variable and BDI-II , ISI and AIS scores as regressors.

The multiple regression model was significant (R^2 = 0.93, $F_{3,4}$ = 16.40, p = 0.010). Taken together, regressors explained a large portion of variance. However, only the effects of BDI (β = 0.54,

t = 2.94, p = 0.042) and AIS (β = 0.48, t = 2.79, p = 0.049) were statistically significant, whereas the effect of ISI as predictor was not significant (β = 0.15, t = 0.71, p = 0.515).

A stepwise removal of non significant term (i.e. ISI), left the multiple regression model significant (R^2 = 0.92, $F_{2,5}$ = 27.00, p = 0.002). The effect of the BDI (β = 0.62, t = 4.41, p = 0.007) and AIS (β = 0.54, t = 3.85, p = 0.012) as predictors was still significant, accounting for a wide portion of variance.

6.4 CONCLUSION

In order to investigate whether the hypothesized hyperarousal underlying primary insomnia affects cognitive performance, we employed SST to assess inhibition control efficiency in a group of insomniacs compared to healthy controls. Cardiovascular activity during the task, administered before and after a night of polysomnographic recording, was explored by Impedance Cardiography. The Stop Signal Reaction Time (SSRT), representing latency to Stop response, was found to be slower in insomniacs, thus indicating a reduced motor inhibition control. In both groups, the Stop Signal Delay (SSD; the delay between the onset of the go stimulus and the stop-signal) was longer in the morning than in the evening, suggesting an improvement in Stop performance.

Moreover, as previously demonstrated,[46] insomniacs did not differ from good sleeper as far as sleepiness is concerned, since it was increased in the morning in both groups. Nevertheless, it is worth noting that sleepiness seems to act differently in insomniacs and good sleepers. As matter of fact, in healthy controls high levels of sleepiness were related to poor Go trial performance, while in insomnia sufferers they were matched to poor Stop trials performance. In addition, severity of the insomnia symptoms, as assessed through self-report measures (Pittsburgh Sleep Quality Index, Athens Insomnia Scale and Insomnia Severity Index), was related to SSRT in insomniacs.

To our knowledge, only Sagaspe and co-workers[159] exploited the Stop Signal paradigm on insomnia population, finding slower SSRT in insomniacs compared to controls, but at a non significant level. Our evidence would support the fact that insomniacs' simple reaction times are relatively conserved; whereas, as proved by previous data, they provided worse performances in

complex reaction time tasks, when compared to good sleepers.[132,162] Presumably this is because tasks such as the response choice sustained attention test are cognitively more demanding than simple reaction time tasks. Therefore, these paradigms are more sensitive to subtle deficits compared to prototypical neuropsychological tests, which have failed to find cognitive impairment in insomnia and have contributed to the heterogeneity of the existing results (for a review, see[105]). Functional metabolic and neurophysiological studies demonstrate that neural systems involved in executive function are sensitive to sleep deprivation (for a review, see[163]). In addition, growing evidence supports the role of prefrontal cortex and basal ganglia in inhibition control.[164,165] It is noteworthy that some studies observed reduced activation in prefrontal cortex in insomniacs.[85,104] Overall, neuroimaging data are consistent with our finding of an inhibition deficit affecting insomniacs. Moreover, the observed deficit in motor response inhibition (i.e., slower SSRT) might be associated with difficulty in inhibiting cognitive activity, for example, in suppressing intrusive thoughts, as reported in many studies on insomniacs.[42,98,166] In addition, as the National Sleep Foundation (National Sleep Foundation, 2003) highlighted, insomnia reduces driving performance and increases risk of car accidents. Since a skill involved in driving is that of inhibition control, difficulty reported from insomnia patients might account, at least in part, for this enhanced risk.

With regard to physiological activity during the task, insomniacs exhibited more elevated cardiovascular arousal than controls, particularly in the evening session. Indeed, pre-ejection period (PEP), an index inversely related to sympathetic beta-adrenergic activity, was constantly lower in insomnia sufferers, indicating enhanced activation of the sympathetic branch of the autonomic nervous system. Moreover, in the evening session insomniacs displayed higher heart rate (HR) and reduced left ventricular ejection time (LVET) values compared to good sleepers.

Our findings are consistent with studies focused on cardiovascular activity in insomnia which found increased HR[86,87,91,167] and blood pressure,[110] both during the day and night.

Nevertheless, we did not observe group differences in task reactivity, suggesting no differences in resources mobilization between groups. This finding is partially consistent with previous work which examined cardiovascular task response in insomnia. Indeed, Stepanski and co-workers[89] observed no HR differences between insomniacs and good sleepers in a basal condition, but

observed significantly increased values in the insomnia group during a reaction time task. On the contrary, Haynes and colleagues,[88] in a study in which insomniacs had more elevated HR than controls before and after a pre-sleep mathematical task, found no differences in HR changes during performance. It is worth noting that, to our knowledge, prior to the current study, measures derived from Impedance Cardiography have not been employed to assess cardiovascular activity during task performance in insomnia patients.

Polysomnographic data showed, as expected, poorer sleep in insomniacs, demonstrated by reduced amount of sleep (total sleep time, TST) and sleep efficiency (SE). They also showed prolonged sleep latency and wake after sleep onset, although at a non significant level.

Hyperactivity in the insomnia group, established by cardiovascular indexes, could mask the expected poor performance due to altered sleep pattern. On the other hand, hyperactivity may interfere with response inhibition functions, thus inducing difficulty in stopping ongoing responses. Thus, in line with previously reported data, hyperarousal seems to be involved in night-time sleep disturbance as well as in daytime functioning (for a review, see[168]).

Nevertheless, we cannot exclude that other factors were involved in the insomniacs' performance. For example, personality traits such as perfectionism,[169,170] could play an important role in leading insomniacs to make fewer errors at the cost of speed. Furthermore, not only insomnia disorder, but also depression levels, may account for the insomniacs' poor performance, because these factors independently predicted task performance, as suggested by multiple regression analysis results.

The main limitation of the present study was the small sample size that could have reduced statistical power resulting in non-significant group differences. Since we enrolled participants according to DSM-IV criteria[131] our sample consisted of sleep onset insomniacs, maintenance insomniacs and early-awakening insomniacs and this may have increased observed variability in sleep data.

The results of cognitive deficit in insomniacs suggest that compensatory strategies are needed to contrast it. Treatment strategies addressed to reduce heightened arousal seem to be the most successful,[171] since they may have efficacy not only on night-time symptoms, but also on diurnal complaints. It might be worthwhile to evaluate if response inhibition efficiency improves after a

successful insomnia treatment. It would also be useful, in the future, it would also be useful to match cognitive performance with other physiological measures, in order to corroborate the hyperarousal hypothesis, particularly correlating central and peripheral measures.

Altogether, our results indicate that insomnia sufferers show a selective impairment in inhibition control, matched to higher sympathetic activity in both task sessions. These findings support the hypothesis that insomniacs suffer from a hyperarousal disorder affecting both somatic activity and cognitive performance, accounting not only for sleep disruption but also for diurnal complaints.

DISCUSSION

Primary insomnia is defined as a difficulty in falling asleep, maintaining sleep or non-restorative sleep, which is not due to other medical, psychiatric or sleep disorders.[40]

The current experiments provide substantial support to the concept that hyperarousal processes play a key role in the pathophysiology of primary insomnia (for a review see[168,172]). Autonomous, neuroendocrine, neuroimmunological, electrophysiological and neuroimaging studies highlighted increased levels of arousal in primary insomnia during both nighttime and daytime.[172] This condition of generalized hyperarousal interferes with the normal sleep/wake processes and causes significant distress or impairment in social, occupational, or other important areas of functioning in insomnia patients.

The first two experiments, focused on the nighttime disorder, provides evidences of an increased cardiovascular activity, that seems mainly occasioned by a great sympathetic involvement, in the first part of the night in insomniacs. This elevated objective cardiovascular activation, is matched with a perceived somatic and cognitive hyperactivation assessed by questionnaires. Furthermore, in comparing insomniacs to good sleepers, the former exhibited a large reduction of the contractility indexes during the night, but only a little reduction of the sympathetic nervous system activation; these reductions were greater across the sleep onset period. The last experiment, focused on the cognitive performance and the cardiovascular reactivity to the task, showed a selective impairment in inhibition control in insomniacs coupled to a higher sympathetic activity both during evening and morning session, suggesting that the generalized hyperactivation exhibited by insomniacs could affect the task performance.

The employment of the Impedance Cardiography technique allows, other than providing several electromechanical indexes of the myocardium, to assess the direct influence of the sympathetic branch of the neurovegetative system on the heart. Insomniacs, compared with good sleepers, had lower PEP values, i.e. higher sympathetic activity, during the night as well as during the day; this finding suggested that the sympathetic hyperactivation seems to be a main feature in this disorder.

The last, but by no means less important finding of this research regards the higher sympathovagal balance (higher HF n.u.) demonstrated by insomnia sufferers in wakefulness. This result matched with the sympathetic hyperactivation showed by insomniacs (lower PEP values), suggested that this population, probably to contrast the sympathetic hyperactivation, needs a greater parasympathetic involvement in order to fall asleep and maintain sleep.

Unfortunately, these studies, are based on very small groups of subjects, and that makes the magnitude of the reported differences, difficult to understand. Furthermore, in order to investigate the autonomic involvement of the two branches of the neurovegetative system, authors have been employed pre-ejection period (PEP) as an index of sympathetic activity and measures derived from HRV analysis as indexes of sympathovagal balance; while the PEP is a well accepted measure inversely related to the sympathetic activity,[13] the normalized units of high and low frequencies, as well as LF/HF ratio of HRV analysis, do not reflect directly the autonomic activity on the heart, so the parasympathetic involvement remains still unclear.[10]

Future investigations should use "pure" measures of parasympathetic nervous system activation, to assess the reciprocal involvement of the two branches of the neurovegetative system in the process of falling asleep and maintaining sleep in insomnia population. They should investigate if the increased levels of arousal in primary insomniacs are reflected overall cognitive, cardiovascular and electrocortical domains and in particular whether the hypothesized cardiovascular hyperactivation in insomniacs is correlated with the cognitive hyperactivation, assessed by questionnaires, as well as the hypothesized elevated high frequency EEG activity, assessed by power spectral analysis (PSA) of EEG.

In conclusion, in our view, since there are strong evidence that insomnia is related to an increased risk of cardiovascular disorders,[50] it seems necessary to provide a clear overview of the cardiovascular measures related to the cardiovascular risk in primary insomnia in order to develop specific interventions focused on reducing the hypothesized cardiovascular hyperactivation that can provide both immediate and long-term benefit.

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