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Assessment of autonomic nervous system function in patients with vasovagal syncope

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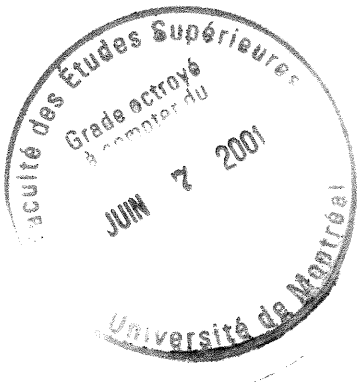

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Ce mémoire intitulé:

Assessment of autonomic nervous system function
in patients with vasovagal syncope

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ABSTRACT

Vasovagal syncope is the most common form of neurally mediated syncope. It can compromise quality of life and lead to serious morbidity and alteration of normal living. The vasovagal response which is characterized by development of hypotension with or without bradycardia presents a profound failure of circulatory control mechanisms that normally maintain the arterial pressure.

In spite of numerous investigations there are still many unanswered questions regarding the pathophysiology of neurocardiogenic syncope. Head-up tilt (HUT) table testing, by providing a controlled orthostatic stress, has become a widely accepted diagnostic tool to assess an individual's susceptibility to neurally mediated syncope.

Since alterations in the autonomic nervous system are thought to play a major role in the pathogenesis of vasovagal syncope, we used spectral analysis of HRV, a non-invasive measure of cardiac autonomic regulation, to evaluate autonomic function in 40 syncopal patients before and during the tilt test.

Frequency domain measurements of the high (HF) and low (LF) frequency bands and the ratio LF/HF were derived from Holter recordings, computed by Fast Fourier analysis for 256 second intervals at rest, immediately after tilt and before the end of the test (BET) which for patients with positive response to tilt (PT) was considered as the time the test was terminated because of significant symptoms (syncope or pre syncope).

Twenty patients exhibited a positive response to tilt testing which was predominant cardioinhibitory (CI) in 8 patients, vasodepressive (VD) in 2 patients and mixed (Mix) in 10 patients. Twenty patients showed a negative response to tilt (NT). The mean HF values at rest and at tilt were higher in the PT group compared

to the NT group. Both groups showed a decrease in the HF band ($p<0.05$) and an increase in the LF/HF ratio ($p<0.05$) after tilt and BET. In both groups LF increased with tilt but decreased significantly in the PT group before syncope.

The three subgroups of PT patients showed two different patterns of changes in autonomic activity. Both the CI and the Mix groups showed higher values of HF bands at rest compared to the VD group and NT as well. Tilting to 70° caused a significant decrease in HF and a significant increase in LF/HF ratio in the CI and the Mix groups but in the VD group the pattern of changes was not the same. It was only the VD group that showed a decrease in the LF/HF ratio before syncope compare to the base line (rest) values.

Conclusions. Our results suggest that first, patients with vasovagal syncope show a higher parasympathetic tone at rest and during tilt compared to NT patients. Second, at least two main types of autonomic behavior exist in tilt induced syncope which could imply different pathophysiological mechanisms involved. This study also suggests that accentuation of sympathetic activity does not necessarily precede tilt induced vasovagal syncope. Therefore, the hypothesis that sympathetically mediated activation of cardiac mechanoreceptors by an increase in cardiac contractility may not be universally applicable to all presentations of vasovagal syncope.

RÉSUMÉ

La syncope vasovagale ou neurocardiogénique est la cause la plus fréquente de perte de connaissance. Elle peut compromettre la qualité de la vie, causer des accidents et empêcher une vie normale. La syncope vasovagale se manifeste par une brusque hypotension et de la bradycardie marquée et correspond à une panne des mécanismes de régulation de la tension artérielle normale. Malgré de nombreuses études, plusieurs questions demeurent sans réponse concernant la pathophysiologie de la syncope neurocardiogénique.

La table basculante (HUT) ou test d'inclinaison, en fournissant un effort orthostatique commandé, est un outil diagnostique accepté pour évaluer la susceptibilité d'un individu à la syncope neurocardiogénique.

Dans le présent travail, nous avons utilisé l'analyse spectrale de la variabilité de fréquence cardiaque, avant et pendant le test d'inclinaison, pour évaluer la fonction du système nerveux autonome chez 40 patients qui ont eu une syncope récente. La puissance spectrale des oscillations à haute fréquence (HF) et à basse fréquence (LF) et le rapport LF/HF ont été dérivés des enregistrements de Holter. La transformée rapide de Fourier a été utilisée pour analyser des intervalles de 256 secondes au repos, juste après l'inclinaison et avant de terminer l'essai (BET) pour les patients présentant une réponse negative (NT) et au moment de la syncope pour des patients présentant une réponse positive à l'inclinaison (PT).

Vingt patients ont démontré une réponse positive au test d'inclinaison qui était cardioinhibiteur prédominant (CI) chez 8 patients, une réponse mixte (Mix) chez 10 patients et vasodépressive (VD) chez 2 patients. Vingt patients ont démontré une réponse négative à l'inclinaison (NT). Les deux groupes ont démontré une diminution de la puissance spectrale des oscillations de haute fréquence ($p<0.05$) et une augmentation du rapport LF/HF ($p<0.05$) après inclinaison et BET. La puissance spectrale des oscillations de basse fréquence dans les deux groupes a augmenté avec

l'inclinaison mais a diminué de manière significative dans le groupe de PT avant le moment de la syncope.

Les trois sous-groupes de patients de PT ont démontré deux configurations différentes des bandes spectrales. Les groupes de CI et de Mix ont présenté des valeurs de puissance spectrale plus élevées pour les oscillations de hautes fréquences au repos comparé à VD.

Une inclinaison à 70° a causé une diminution significative de la puissance spectrale des oscillations de haute fréquence et une augmentation significative du rapport LF/HF pour les groupes CI et Mix mais pas pour le groupe de VD. Seulement le groupe VD a démontré une diminution du rapport LF/HF avant de la syncope comparativement au repos.

Conclusions. Nos résultats suggèrent que les patients ayant une syncope vasovagale démontrent un tonus parasympathique plus élevé au repos et pendant l'inclinaison comparativement aux patients avec une réponse négative au test d'inclinaison. L'observation de 2 types de réponse à l'inclinaison suggère la possibilité qu'il y ait plus d'un mécanisme physiopathologique pour expliquer la syncope vasovagale. La présente étude suggère de plus que l'accentuation de l'activité sympathique comme facteur déclencheur pour augmenter la contractilité cardiaque ne précède pas nécessairement la syncope vasovagale induite par l'inclinaison.

KEY WORDS:

Vasovagal Syncope

Autonomic Nervous System

Head Up Tilt Table Test

Heart Rate Variability

Spectral Analysis

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LIST OF ABREVIATIONS

AV node : Atrioventricular node

BET : Before end of test

BPM : beat per minute

CI : Patients with predominant cardioinhibitory reaction during syncope

HF : High frequency

HR : Heart rate

HRV : Heart rate variability

HUT : Head up tilt

Hz : Hertz

LBNP :Lower body negative pressure

LF : Low frequency

min : minute

Mix : Patients with mixed reaction during syncope

ms : millisecond

NMS : Neurally mediated syncope

NT : Patients with negative HUT test

NTS :Nucleus tractus solitarius

Nu :Normalized unit

PT : Patients with positive HUT test

SA node :sinoatrial node

ULF : Ultra low frequency

VD : Patients with pure vasodilatory reaction during syncope

VLF : Very low frequency

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To

My Parents,

Saeedeh, Parnian and Kaveh

CHAPTER I

INTRODUCTION

"Fainting spells are among the most common problems clinicians are faced with."

Syncope is defined as a transient loss of consciousness with concurrent loss of postural tone followed by spontaneous recovery. Syncope is one of the oldest recorded medical problems. Hippocrates is said to have recorded the first description of syncope, and it is from the Greek that we drive this medical term for fainting. [1] It is usually described by the patients or bystanders as " fainting" or "passing out".

Syncope accounts for about 3% of emergency room visits and up to 6% of hospital admissions[2]. It is common in healthy young adults (reported by 12% to 48%), and a frequent symptom in the elderly; a 6% incidence and 23% previous lifetime episodes were found in a long-term care institution[3]. Presyncope or near-syncope which may occur even more frequently implies a state in which the patient senses that syncope is imminent, but complete loss of consciousness does not occur.

Syncope and presyncope are commonly classified as being of either cardiovascular or non-cardiovascular origins. The former category (cardiovascular mechanisms) includes mechanisms resulting from structural cardiac and/or vascular diseases as well as a diverse group of neurally mediated reflex (cardioneurogenic) syncopal syndromes. The non-cardiovascular category encompasses organic central nervous system diseases, metabolic/endocrine disturbances, and psychiatric disorders. Among all types of syncope, the most common (approximately 60%) [4] is vasovagal syncope. Morbidity from syncope ranges from lacerations and contusions to subdural hematomas, limb fractures, and organ damage from automobile accidents and falls.[5,6]

Annual mortality due to all cardiac causes of syncope is 20-30%, whereas mortality for noncardiac causes is 5-10%[7]. Among cardiac causes, vasovagal syncope has usually a relatively benign prognosis. A more frequent concern is the potential for physical injury, particularly in elderly patients or in individuals exposed to harm as a result of their occupation (e.g., drivers, construction workers).

1.1 Nomenclature

- *"Neurally mediated syncope,"* *"neurocardiogenic syncope,"* and *"neurally mediated syncopal syndromes"* are essentially equivalent terms encompassing a range of clinical conditions, in which the triggering of a neural reflex results in a usually self-limited period of complete or near complete loss of both consciousness and postural tone (e.g., vasovagal syncope).

- "*Vasovagal syncope*" is the term used to characterize the most common form of the "neurally mediated syncope"(NMS).

The terms "vasodepressor (VD) and "cardioinhibitory (CI)" refer to the principal circulatory phenomena responsible for systemic hypotension in vasovagal syncope. In terms of clinical recognition, these phenomena have been defined by the Vasovagal International Study (VASIS) group, although a true internationally accepted set of definitions has yet to be agreed upon by the principal cardiological societies. When bradycardia is the predominant cause of the drop in blood pressure, the event is considered to be CI. Conversely, if vascular dilatation is the principal disturbance, then the episode is said to be the result of the VD mechanism. Most often, however, both physiological disturbances are present in a so-called mixed form[8]. Nevertheless, it is now apparent that for the most part, both VD and CI phenomena contribute in all instances of NMS.

1.2 General Objective

This study concerns the assessment of the influence of the autonomic nervous system (ANS) on the cardiovascular system in patients with vasovagal syncope. Heart rate variability (HRV) was chosen as a non-invasive marker of ANS activity. Spectral analysis of HRV based on the Fast Fourier transform has been used in order to document modifications of autonomic function. We investigated the role of the ANS in vasovagal syncope via inter- and intra-group comparisons of two groups of syncopal patients before and during the HUT. We also compared different hemodynamic responses to the HUT test in patients with positive response to tilt in order to determine whether there are different pathophysiological mechanisms involved in vasovagal syncope.

1.3 Hypotheses

1. After the initiating events of syncope, a complex hemodynamic response develops which results in marked hypotension, variable bradycardia, and loss of consciousness. Several theories have been advanced to account for these hemodynamic events. Among these theories the ventricular mechanoreceptor theory has gained wide acceptance. It seemed to explain some clinical pathophysiological observations and provide a rational basis for the combination of isoproterenol and HUT testing in diagnosis of NMS. Some clinical experimental observations, however, are not explained by this theory, and they challenge the concept of activation of ventricular mechanoreceptors as responsible for the universal development of NMS. We examined whether this theory explains the rational basis for occurrence of the syncope in our patients.

2. Spectral analysis of heart rate is a promising method with adequate theoretical justification for evaluation of ANS activity. Moreover, its application in health and disease has shown that it reliably identifies ANS impairment in certain diseases[23]. It could also allow alterations to be characterized and hopefully quantified. We hypothesized that the underlying predisposing factor in vasovagal syncope is a shift in the balance of ANS activity toward enhanced sympathetic stimulation shortly before the onset of vasovagal syncope and pronounced withdrawal of parasympathetic activity during the 5 minutes preceding vasovagal syncope.
3. Patients with a positive HUT test show different hemodynamic and chronotropic responses during syncope. Positive tilt test patients can be classified into three subgroups: predominant CI, pure vasodilatory and mixed. These responses are believed to have common pathophysiological mechanisms. We hypothesized that the autonomic nervous system behavior is different in patients with CI and VD reactions.

1.4 Rationale

It might be obvious that the appropriate management of a patient with vasovagal syncope depends on the better understanding of the physiology of the central and the peripheral mechanisms that are involved. Findings from the studies on pathophysiological mechanisms in vasovagal syncope could have clinical implications and may help to tailor drug therapy more effectively.

If a variable role of ANS in syncopal patients is shown more specific treatment for the different response types could be provided.

CHAPTER II

REVIEW OF THE LITERATURE

2.1 Control Mechanisms of Heart Rate

2.1.1 Anatomical and Physiological Basis

The principal control of heart rate (HR) is relegated to the ANS. Changes in HR usually involve a reciprocal action of the two divisions of the ANS, parasympathetic and sympathetic nerves.

Under resting conditions, vagal tone prevails and variation in heart period is largely dependent on vagal modulation. However, under certain conditions heart rate may change by selective action of just one division of the ANS, rather than by reciprocal changes in both divisions. There are also numerous reflexes that influence HR; among them, arterial baroreceptors and their reflex effects are the most important.[9]

2.1.2. Parasympathetic Pathways

"The presence of parasympathetic efferent post ganglionic neurons on the heart has been appreciated for a long time" There are varied opinion concerning the location of parasympathetic efferent preganglionic neurons which project axons to cardiac parasympathetic postganglionic neurons. A consensus of opinion is developing that they are located for the most part in the nucleus ambigous of the medulla in most mammalian species[10]. The precise location varies from species to species.[11] Efferent vagal fibers pass inferiorly through the neck as the cervical vagus

nerves. They then pass through the mediastinum to synapse with postganglionic cells on the epicardial surface or within the walls of the heart itself. They innervate the sinoatrial (SA) node, the atrioventricular (AV) conducting pathways, and the atrial muscle.

Most of the cardiac ganglion cells are located near the SA and AV conduction tissue. The right and left vagi are distributed differentially to the various cardiac structures. The right vagus nerve affects the SA node predominantly. Stimulation slows SA nodal firing or may even stop it for several seconds. The left vagus nerve mainly inhibits AV conduction tissue, to produce various degrees of AV block[11]. However the distribution of the efferent vagal fibers overlap, such that left vagal stimulation also depresses the SA node and right vagal stimulation affects AV conduction.

Parasympathetic efferent postganglionic neurons, when activated, either chemically or electrically, suppress atrial rate and force[12], AV nodal conduction[13], and ventricular contractile force[14]. The parasympathetic influence on HR is mediated via release of acetylcholine by the vagus nerve and response of the muscarinic receptors. The effect of any vagal impulse on the SA and AV nodes is brief because it is rich in acetylcholinesterase that rapidly hydrolyzes acetylcholine. Furthermore, the released acetylcholine activates special K^+ channels, which don't need a second messenger system to operate. Therefore, effects of vagal activity on SA and AV nodal function have a very short latency (about 50 to 100 ms)[11]. The combination of the rapid decay and brief latency of the response provides the potential of beat by beat control of SA and AV nodal function.[11]

Parasympathetic influences exceed sympathetic effects probably through two independent mechanisms: (1) a cholinergically induced reduction of norepinephrine released in response to sympathetic activity and (2) a cholinergic attenuation of the response to an adrenergic stimulus.[15]

2.1.3. Sympathetic Pathways

Sympathetic preganglionic neurons in the spinal cord that are involved in cardiac regulation project axons via right and left cranial thoracic spinal cord nerves to sympathetic efferent postganglionic neurons in all intrathoracic ganglia[10]. The cardiac sympathetic fibers originating in the intermediolateral columns of the upper five or six thoracic and lower one or two cervical segments of the spinal cord, emerge from the spinal column from the white communicating branches and enter the paravertebral chains of ganglia. Although sympathetic efferent postganglionic neurons have long been considered to be located primarily in paravertebral ganglia (stellate and cranial thoracic sympathetic chain ganglia), recent anatomical and functional evidence indicates that such neurons are also located in middle and superior cervical ganglia, mediastinal ganglia and intrinsic cardiac ganglia[16]. The preganglionic and postganglionic neurons synapse mainly in the stellate or middle cervical ganglia, depending on the species[11].

Sympathetic and parasympathetic fibers then join to form a complex plexus of mixed efferent nerves to the heart. The postganglionic cardiac sympathetic fibers approach the base of the heart along the adventitial surface of the great vessels. On reaching the base of the heart, these fibers are distributed to the various chambers as an extensive epicardial plexus. Then they penetrate the myocardium.

The adrenergic receptors in the nodal regions and in the myocardium are predominantly of the beta type. As with the vagus nerves, the left and right sympathetic fibers are distributed differentially. In the dog, the fibers on the left side have more pronounced effects on myocardial contractility than do fibers on the right side, whereas the fibers on the left side have much less effect on HR than do the fibers on the right side. The sympathetic influence on HR and contractility is mediated by release of norepinephrine. In contrast to the abrupt termination of the response after vagal stimulation, effects of the sympathetic activity decay very gradually after cessation of stimulation.[11] Postganglionic efferent sympathetic nerves, when activated, shorten sinus cycle length and atrioventricular conduction

time, producing tachycardia. Sympathetic stimulation of the myocardium increase contractility and reduces refractoriness of ventricular and atrial myocardium. Likewise, efferent sympathetic nerve fibers innervate the peripheral vascular beds[10]. Thus, the regulation of myocardial conduction and contractility and of peripheral vascular tone depends on the overall balance of activation of the sympathetic and parasympathetic limbs[17].

2.1.4. Reflex Control of Cardiovascular System

It is well documented that several groups of peripheral receptors contribute to the reflex control of circulation. These include the arterial baroreceptors and chemoreceptors, receptors within the heart as well as the airways and lungs[18]. The primary site of interaction of these afferents within the central nervous system is at the level of the nucleus tractus solitarius (NTS), which its functional role is significant in the control of HR and peripheral vascular resistance[19]. Neurophysiological studies have shown that specific areas of the NTS receive innervation from the arterial baroreceptors and that these same regions of the nucleus receive a variable innervation from other vagal afferents and the arterial chemoreceptors. Since the NTS receives a patterned input from afferents arising from receptors which reflexly affects both the cardiovascular and respiratory system and since it also receive input from many regions of the central nervous system, it is a potential site of integration[20].

2.1.5. Baroreceptor Reflex

Neural mechanisms responsible for the control of blood pressure are modulated by arterial and cardiopulmonary baroreceptors that regulate arterial pressure and vascular tone in humans[21]. The arterial baroreceptors, which increase their rate of discharge in response to stretch, are located in the aortic arch and carotid sinus.

Increased baroreceptor activity results in reflex cardiac slowing and peripheral vasodilation. The sensory fibers (both myelinated and nonmyelinated) from the

carotid sinus nerve traverse the glossopharyngeal nerve to the brain stem, and the sensory fibers from the aortic arch traverse the aortic depressor and vagal nerves[19]. Discharges from these receptors result in excitation of resting (tonic) parasympathetic output to the SA node and tonic inhibition of sympathetic output to the heart and peripheral circulation. Decrease in baroreceptor impulses has the opposite effects[19].

2.1.6. Ventricular Receptor Reflexes

Sensory receptors near the endocardial surfaces of the ventricular walls initiate reflex effects similar to those elicited by the arterial baroreceptors. Excitation of these endocardial receptors diminishes HR and peripheral resistance. Ventricular receptors are excited by a variety of mechanical and chemical stimuli, but their physiologic functions are not clear. These receptors are suspected to be involved in the initiation of vasovagal syncope[11].

2.2. *Heart Rate and Heart Rate Variability*

Heart rate variability has been widely used in the last decade as a research tool to evaluate the ANS in patients with cardiovascular diseases. It has been used to study cardiovascular physiology and pharmacology, and to predict risk of death or arrhythmic events in patients with coronary heart disease. The clinical relevance of HRV was first demonstrated in 1965 when Hon and Lee noted that fetal distress was preceded by alterations in inter-beat intervals before any appreciable change occurred in HR itself[22,23].

In normal adults the average HR at rest is approximately 70 beats per minute. During emotional excitement or muscular activity it may accelerate to rates considerably above 100. In the intact individual, HR, at any instant in time, represents the resultant of many influences on the vagal and sympathetic centers. At rest, both autonomic divisions are thought to be tonically active with the vagal effect dominant. Changes in HR usually involve a reciprocal action of the two divisions of the ANS[17]. Thus, an increased HR usually is produced by diminution of parasympathetic activity and concomitant increase in sympathetic activity; deceleration is usually achieved by the opposite mechanisms. Some reflexes however may increase HR through a decrease in vagal tone, an increase in sympathetic activity, or both[17]. Others exert the opposite effects.

In the intact person or animal, several reflexes are likely to operate simultaneously and, for at least some of these, the interactions may be quite complex. Receptors exist in almost all parts of the body which, when subjected to intense or noxious stimuli may activate cardiovascular reflexes. There is also a cyclical variation in HR associated with respiration. It accelerates during inspiration and slows during expiration. The magnitude of the oscillation is variable, but usually it can be exaggerated by slow deep breathing[24]. The mechanism linking the variability of HR to respiration is complex and involves both central and reflex interactions[25]. It is not necessary for breathing to actually occur, since it has been

shown[26]. that sinus arrhythmia may persist in paralyzed animals after stopping the ventilatory pump. Thus, the mechanism seems to be due partly to a central effect.

The physiological importance of HR lies in its contribution to cardiac output:

Cardiac output = Stroke volume × Heart rate

Maintenance of a steady state HR and blood pressure is governed by a complex interplay of biophysical and neurohumoral mechanisms. It is now recognized that autonomic regulatory signals from centers in the midbrain control beat to beat variations of HR and BP. It has been shown that efferent sympathetic and vagal activities directed to the sinus node are characterized by discharges largely synchronous with each cardiac cycle that can be modulated by central (vasomotor and respiratory centers) and peripheral (oscillation in arterial pressure and respiratory movements) oscillators[27].

Reverend Stephen Hales provided the oldest well documented report of beat to beat variability in conjunction with arterial blood pressure recordings in 1733. It is only in the last decades that the use of the beat to beat variations of cardiovascular parameters to quantify the changes in sympathetic and vagal activities controlling the cardiovascular system has become possible. In 1981, Askelrod et al. were the first to propose the general hypothesis that the power spectrum analysis of HR fluctuations might be used as a quantitative measure of beat to beat cardiovascular control.[28] Since then, access to powerful computer resources has resulted in a revolutionary change in perspective, allowing a focus on the time and frequency domain structures of the beat to beat variations in cardiovascular parameters.

Mathematical analysis of HR variability shows that HR is influenced by different frequency components derived from activity of different parts of the ANS. Although the influence of the ANS on HRV was recognized early in this century, only recently have several studies made it clear that parasympathetic and sympathetic nervous activities influence HRV at different parts of the frequency spectrum.

Power spectral measures of the RR time series can delineate cyclic fluctuations in the RR intervals in terms of their frequency and power. Some standard frequencies have been estimated for use in cardiac physiological or epidemiological studies.

High frequency (HF) power (0.05-0.4 Hz) that is synchronous with respiration estimates cyclical fluctuations with a nominal period of 2.5 to 6.7 seconds. To estimate HF power centered on 0.25 Hz, data should be collected for about 10 to 15 times the period of the fluctuations being estimated-that is, about 1 minute (4-second period × 15)[32]. Low frequency (LF) power (0.04-0.15 Hz) corresponds to heart period and arterial pressure fluctuations and is known as vasomotor waves. To estimate LF power centered on 0.10 Hz, data should be collected for about 2.5 minutes (10-second period × 15). Below LF power (< 0.04 Hz), RR interval power spectra are log-linear and inversely related to the log of frequency, that is, the lower the frequency, the greater the power (so called l/f relationship)[29,30].

Efferent vagal activity is a major contributor to the HF component[23]. The interpretation of LF is more controversial. Some researchers consider it a marker of sympathetic modulation while others claim that it includes both sympathetic and parasympathetic influences[30]. Houle et al concluded that changes in the LF power appear to be dependent on the method used to augment sympathetic activity as well as the method of analysis[31]

The physiological interpretation of even lower frequency components of HRV, frequencies (below 0.05 Hz) the very low frequency (VLF) and ultra low frequency (ULF) components, needs further elucidation. Some investigators attribute the very low frequency oscillations to thermoregulatory mechanisms or to changes in the renin-angiotensin system[32].

The sum of these various components of RR variability is total power. Since the absolute power of a given spectral component gives no information about its relative contribution to the total power, some form of normalization appears essential in order to permit an appreciation of the distribution of power across the frequency axis[32]. The representation of LF and HF components of the power spectrum in normalized units demonstrates the controlled and balanced behavior of the two branches of the ANS. Moreover, the normalization tends to minimize the effect of changes in total power on the values of LF and HF components[30]. In the absence of a computation of normalized units, the LF/HF ratio can also provide information on the state of the sympathovagal balance[32,33].

2.3. Measurement of Heart Rate Variability

Analysis of the beat to beat oscillation in the R-R interval is generally performed by two mathematical methods, frequency and time domain measures. Frequency domain measures of HRV are more commonly used for mechanistic studies because they resolve parasympathetic and sympathetic influences better than do time domain measures. A number of studies have indicated spectral analysis of HRV provides a robust method for measuring vagal modulation of R-R intervals. Under special circumstances, spectral analysis of HRV can provide insight into the activity of the sympathetic nervous system as well[30].

The simplest method to use is time domain analysis but there is more experience and theoretical knowledge on physiological interpretation of the frequency domain measures compared with the time domain measures derived from stationary short-term recordings. On the contrary, many time and frequency domain variables measured over the entire 24-hour period are strongly correlated with each other[24]. These 2 analytical techniques are complementary in that they are different mathematical analyses of the same phenomenon. Therefore this could explain why certain time and frequency domain variables are strongly correlated. In Figure 2.1, the prerequisite steps in order to obtain data for HRV analysis are presented.

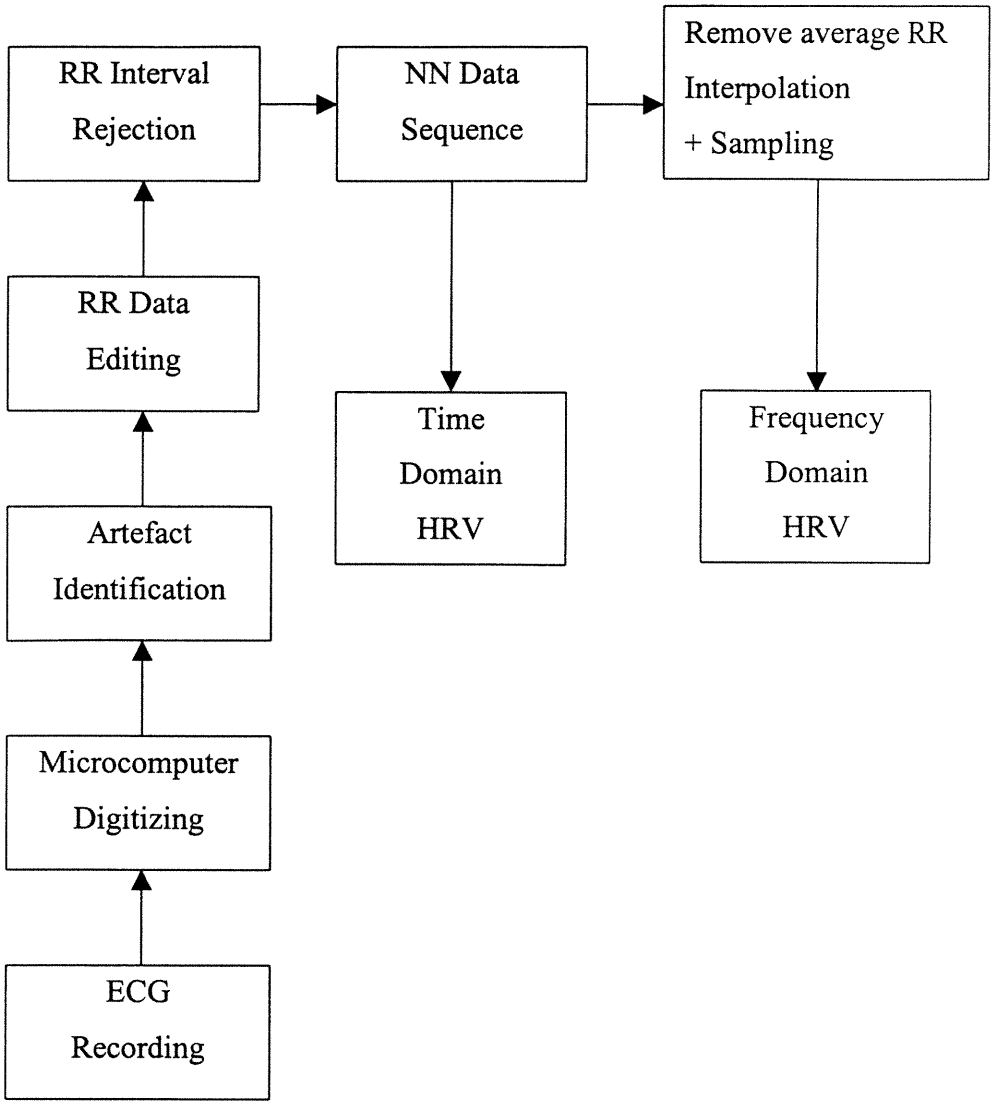


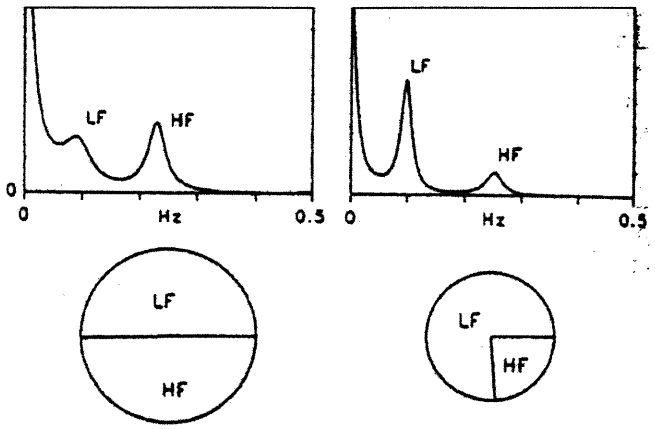
Figure. 2. 1. Steps used when recording and processing the ECG signal in order to prepare data for HRV analysis. Modified from reference[23].

2.3.1. Spectral or Frequency Domain Analysis

Cyclical changes in heart rate and hemodynamic parameters such as arterial blood pressure have been known since the eighteenth century[34]. Spectral analysis of HRV, a non-invasive measure of cardiac autonomic regulation, is an important technique of both theoretical and practical bioengineering and allows the assessment of neurocardiac function non-invasively. It evaluates and quantifies periodicity. The main observation is that specific frequency peaks appear in the power spectrum, which are related to underlying biological processes (Figure 2.2), and changes in these peaks can be interpreted as characteristic responses to various regulatory influences on the cardiovascular system[22]. Spectral analysis is most commonly accomplished by Fast Fourier transformation to separate R-R intervals into characteristic high, low, very low, and ultra low frequency bands. The respiration–linked HF variations manifested as sinus arrhythmia on the ECG, and as second order waves in the blood pressure, have been considered as a marker of parasympathetic responsiveness. LF fluctuations slower than the respiration rate have been considered to be predominantly influenced by sympathetic system tone. The HF component is clearly related to respiratory activity, and the LF component to the blood pressure control system.

The heart rate signal must meet a number of conditions that are prerequisites for meaningful power spectrum analysis: ideally the signal should be random, stationary, and sufficiently long. Preprocessing the data by proper detrending and filtering is mandatory to meet these criteria[35].

Frequency bandwidths for HF and LF have been defined according to recommendations by the Joint Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology[30] It is well established that the HF band is associated with vagal tone as it corresponds to respiratory sinus arrhythmia. The LF band reflects mainly sympathetic outflow, although several investigators maintain that the LF band is influenced by both vagal and sympathetic activity. The origins and mechanisms of the VLF (0.005-0.04 Hz) and ULF (less than 0.005 Hz) oscillations remain unclear.



At Rest During Tilt

Figure 2. 2. Spectral Analysis of RR interval variability in a healthy subject at rest and during 90° head-up tilt.

At rest, two major components of similar power are detectable at low and high frequencies. During tilt, the LF component becomes dominant.[30] Vertical axis shows: PSD [$ms^2 \times 10^3/Hz$].

PSD: power spectral density

2.3.2. Non-Spectral or Time Domain Analysis

Non-spectral parameters involve computing indexes that are not directly related to specific cycle lengths. In these methods, either the HR at any point in time or the intervals between successive normal complexes are determined. This method offers a simple means of identifying patients with decreased HRV. Time domain parameters that can be analyzed include mean R-R interval; SDANN, standard deviation of the averaged normal sinus R-R intervals calculated for all 5-minute segments of the entire recording; SDNN, standard deviation of all normal sinus R-R intervals; SDNN index, mean of the standard deviations of all normal R-R intervals for all 5-minute segments of the entire recording; pNN50, the percentage of the adjacent R-R intervals that differed by more than 50 ms; and rMSSD, the root mean square of the differences between adjacent R-R intervals.

Another time domain measure of HRV is the triangular index, a geometric measure obtained by dividing the total number of all R-R intervals measured on a discrete scale with bins of 7.8 ms. The height of the histogram equals the total number of intervals found in the modal bin[23].

2.4 Physiologic Response to Orthostatic Stress

It has become well established that in the normal subject, upright posture (active standing or passive head-up tilting) cause an abrupt redistribution of blood to the distensible veins below the heart with diminished venous return and cardiac output.

Normally, around 25% of the circulating blood volume is in the thorax while in the supine position. Immediately after the assumption of upright posture, gravity produces a downward displacement of roughly 500 ml of blood to the abdomen and lower extremities[1]. Approximately 50% of this amount is redistributed within seconds after standing, and almost one quarter of total blood volume may be involved in this process.

As a consequence, venous return to the heart decreases and cardiac filling pressures and stroke volume may decrease by 40%. Short –term circulatory adaptation to the upright position has been dissected into an initial response (first 30 seconds) with characteristic and marked changes in blood pressure and HR, and a phase of stabilization (after 1-2 min upright). [1,36] The initial fall in thoracic blood volume in addition to the decrease in blood pressure at the level of the carotid sinus because of the decrease in hydrostatic pressure in the vessels above the heart, initiates a rapid autonomic reflex (i.e., baroreflex) that increases sympathetic outflow.

Neural mechanisms responsible for the control of blood pressure are modulated by arterial and cardiopulmonary baroreceptors that regulate arterial pressure and vascular tone in humans. Aortic and carotid sinus arterial baroreceptor discharge is directly related to stretching caused by arterial pressure. The reduction in blood pressure produced by downward displacement of blood is sensed by arterial baroreceptors, which are scattered throughout the vasculature but located principally in the aortic arch and carotid sinus[37]. These receptors send afferent signals to the

medulla, where they communicate with the nucleus ambigous and dorsal motor nucleus of the vagus nerve (governing parasympathetic activity) and the ventromedial and ventrolateral medulla (governing sympathetic activity)[38]. The mean firing rate of these receptors is related directly to the level of arterial pressure. Hence, when arterial pressure increases, the firing of these receptors increases, resulting in sympathetic withdrawal and parasympathetic mediated bradycardia. Conversely, when arterial pressure falls, the firing of these receptors decreases, resulting in sympathetic excitation and withdrawal of parasympathetic activity leading to tachycardia [21]

Cardiopulmonary receptors function as a part of this baroreceptor activity by virtue of the presence of mechanoreceptors (C-fibers), consisting of unmyelinated fibers found in the atria, ventricles (particularly in the inferoposterior aspect of the left ventricle), and the pulmonary vasculature[39]. These receptors discharge during systole and their firing rate is related directly to the force of myocardial contraction as well as wall stretch as determined by the level of cardiac filling pressures[40]. Although C-fibers seem to respond to either stretch or pressure, stretch activation appears to be more important. Like arterial baroreceptors, cardiopulmonary receptors send afferent signals (via the vagal nerves) to the dorsal vagal nucleus of the brainstem that inhibit sympathetic efferent activity. When cardiac firing is reduced the discharge of these receptors falls and their inhibitory influence on sympathetic efferent activity declines, resulting in increased sympathetic drive[41]. This mechanism could explain resultant tachycardia and vasoconstriction in an apparent effort to maintain normal blood pressure. Yet this very increase in sympathetic tone may both sensitize and facilitate activation of the cardiac mechanoreceptors.

Therefore, the normal response to upright posture is an increase in HR (reflex tachycardia), more forceful contraction of left ventricle and vasoconstriction. Figure 2.3, summarizes the neurohumoral responses to orthostatic stress.

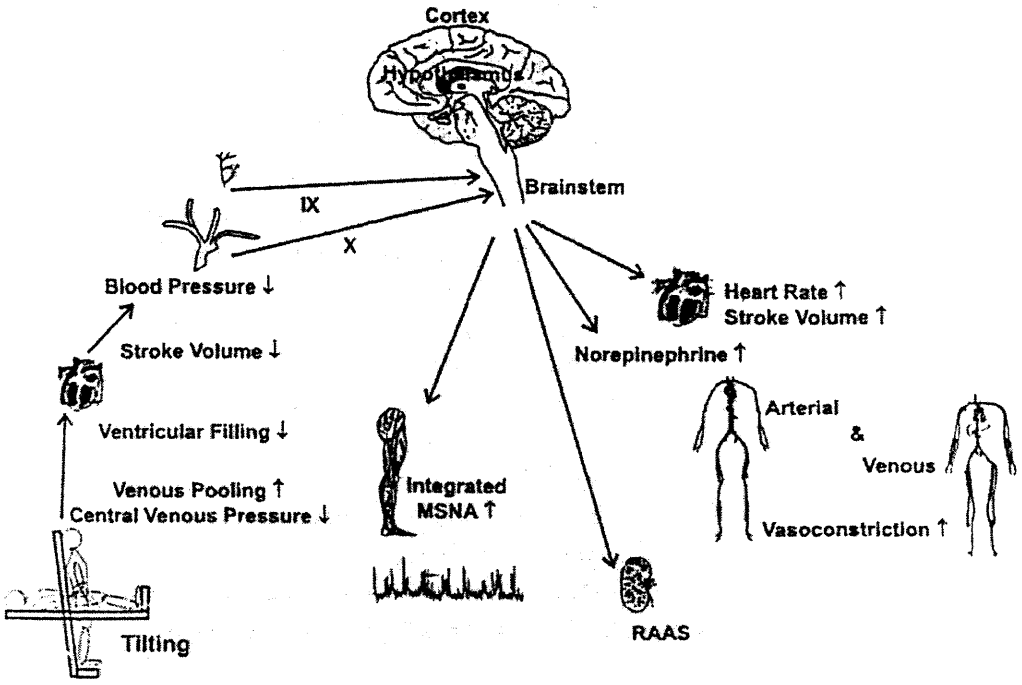


Figure 2. 3. Neurohumoral responses to orthostatic stress. Some of the changes set in motion by passive upright tilt are shown[42].

IX indicates the glossopharyngeal nerve; X, vagal nerve;
and RAAS, renin angiotensin system.

2.5 Pathophysiology of Neurally Mediated Syncope

Although the pathophysiology of NMS and especially of the vasovagal faint is not completely understood, Benditt[8,] has considered four basic elements to address current concepts. The leading causes of neurally mediated syncopal syndromes could underlie each of these pathways.

I. The afferent limb
II. Central nervous system processing
III. The efferent limb
IV. Feedback loops

2.5.1. The Afferent Limb

The afferent neural signals, initiator of neurally mediated syncopal events, originate from either the central nervous system directly or from peripheral receptors (cardiac and/or cardiopulmonary mechanoreceptors, carotid baroreceptors, cardiac chemoreceptors and cardiopulmonary receptors) that respond to mechanical or chemical stimuli, pain, or possibly even temperature change. These impulses are mainly transmitted to the NTS in the medulla, which is anatomically closely related to the dorsal and ambigous nuclei of the vagus nerve.

2.5.2. Central Nervous System Processing

Vagus and glossopharyngeal nerves carry the principal cardiovascular baroreceptor and chemoreceptor nerve traffic to NTS in the medulla. The NTS also receives afferent impulses from other cranial nerves, the hypothalamus, the spinal cord, and brainstem, and it may be influenced by circulating neurohumoral factors

because it is close to the area postrema in which the blood-brain barrier is believed to be weak. Signals from the NTS address the vagal preganglionic nuclei in the medulla, sympathetic preganglionic nuclei in the spinal cord, and other brainstem nuclei and higher central nervous system centers[38]. The central nervous system processing of the individual afferent neural impulses is different. These differences manifest as a range of hemodynamic and arrhythmic responses and could result from certain central neurotransmitter release. Experimental studies suggest increased levels of centrally released vasoactive agents such as serotonin[43] and nitric oxide[44] similarly, pancreatic polypeptide, vasopresin,[44] endogenous opoid peptides and endothelin[45] have been proposed to play a role in the pathogenesis of NMS. The interaction of peripheral and central factors may influence the manner in which a syncopal event becomes manifest. For example, in hypersensitive carotid sinus syndrome, bradycardia is usually the preceding event to the VD response. Conversely, hypotension due to vasodilation is typically, but not always, evident prior to marked bradycardia in NMS that is posturally induced. The reason for such differences is unknown. Finally, it should be acknowledged that certain cerebral sites (particularly the insular cortex) might be the source of apparent neurally mediated syncopal syndromes[8].

2.5.3. The Efferent Limb

Central nervous sytem processing and efferent signals result in both bradycardia and vasodilation, which are characteristic features of the neurally mediated faint. The bradycardia is primarily due to enhanced (or possibly unbalanced) efferent parasympathetic tone and is mediated by efferent signals transmitted via the vagus nerve[8]. Vasodilation, on the contrary, is considered to be primarily the result of diminished sympathetic vasoconstrictor tone[46]. Interaction between the mediators of the sympathetic and parasympathetic nervous system at the nerve endings and the magnitude of sympathetic or parasympathetic activation are important aspects of the control of vascular tone and the severity of vasodilation.

Intrinsic responsiveness of cardiac and vascular smooth muscle cells to neurohumoral mediators is another important factor that could affect both afferent and efferent neural reflex responses.

The role of other noncatecholamine neurohumoral substances, specifically, certain vasoactive peptides (e.g., vasoactive intestinal peptide, calcitonin gene-related peptide), and purinergic agonists (e.g., adenosine) released from perivascular nerves, should be considered as possible peripheral contributors to reflex vasodilation[38,47,48,49,50] in NMS.

2.5.4. Feedback Loops

Normal arterial baroreceptor activity is critical for maintaining cardiovascular homeostasis in normal subjects. However, for uncertain reasons, the usual protective actions of the carotid and aortic baroreceptors are insufficient to fully reverse the vasodepression and/or bradycardia in syncopal patients[8]. The hypothesis that in syncopal patients, compared with normal subjects, these baroreflex activities are reduced has been supported by several studies[51,52,53,54]. On the other hand, there are some experiments suggesting greater baroreceptor activity in the syncope-prone patients[55,56] which raises the possibility that the normal activity of the baroreceptor reflex is being overridden by some other factors.

2.6. Vasovagal Syncope

True syncope consists of the transient loss of both consciousness and postural tone with rapid spontaneous recovery. Among all causes of syncope, the neurally mediated syncopal syndromes are believed to be the most common. NMS syndromes encompass a number of conditions that present with distinct clinical scenarios but are believed to have many pathophysiological similarities. The triggers for these forms of syncope may arise within the central nervous system itself (e.g., syncope associated with fear or anxiety) or from any of a number of peripheral receptors, which respond to various stimuli (e.g., mechanical, chemical, pain). The most widely recognized of these trigger sites is the carotid sinus baroreceptor, which is at least in part responsible for hypersensitive carotid sinus syncope.

In typical vasovagal syncope, the location and nature of the trigger sites are less certain and remain controversial. Although exaggerated activation of the sympathetic drive to the heart has been shown as a possible trigger mechanism of syncope in humans (as previously mentioned), this sympathetic activity to the heart and vessels is different from one patient to another[57].

Initially there is a normal response to upright position, which leads to peripheral vasoconstriction and increased myocardial inotropy and chronotropy. However, in patients with vasovagal syncope, inappropriate vasodilation and/or bradycardia result from reflex mechanisms producing hypotension and syncope (Figure 2.4). Bradycardia, varying from minor slowing to temporary heart block or sinus arrest, is vagally mediated and administration of atropine or cardiac pacing can reverse the negative chronotropic effects. Lewis was the first who observed that in-spite of reversing bradycardia with atropine, hypotension and loss of consciousness could still occur[58]. Therefore, bradycardia is seldom the only mechanism of syncope. Apparently a combination of parasympathetic enhancement and withdrawal of sympathetic activity is responsible, as has been shown by numerous human and animal studies[59].

Using the HUT test, Furlan et al.[60] identified two different patterns of the autonomic drive to the heart preceding syncope. One manifests as a progressive increase in the markers of cardiac sympathetic modulation up to the onset of syncope and the second, as a sympathetic inhibition with an impending vagal predominance.

Patients with a positive response to the HUT table test show different responses which allow classification of the vasovagal episodes as VD (reduction in systolic blood pressure < 80 mmHg with less than 10% decrease in HR), CI (reduction in HR to less than 40 bpm or asystole less than3 sec) or mixed (reduction in both arterial pressure and HR but not to less than 40 bpm).[61]

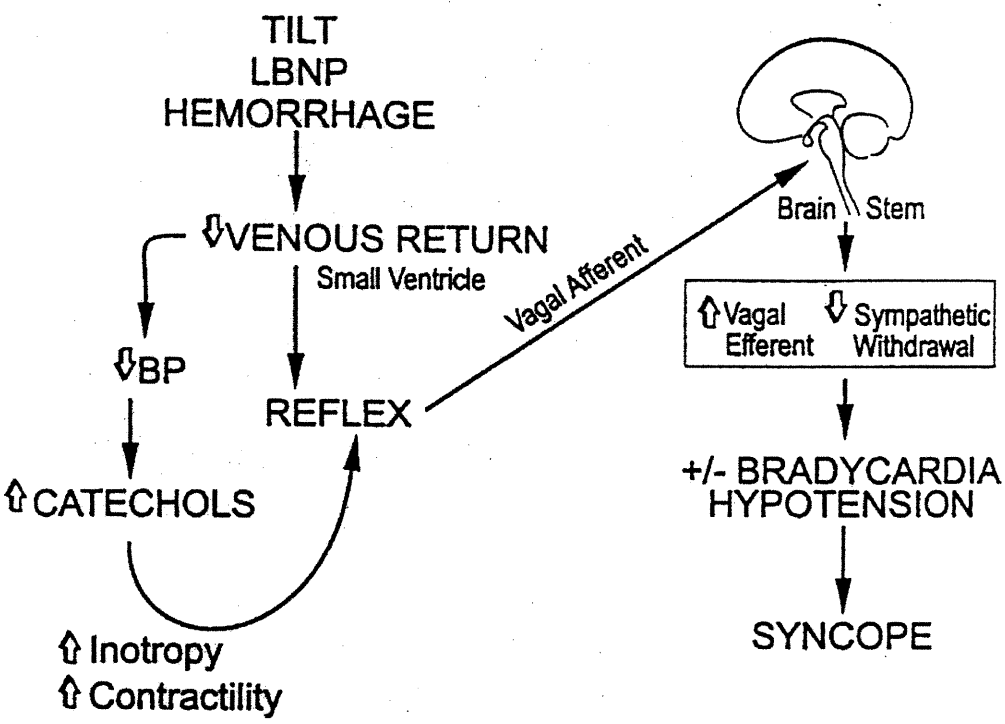


Figure. 2. 4. Hemodynamic and autonomic changes provoked by physiologic stimuli that lead to vasovagal syncope.[45]

LBNP = lower body negative pressure.

2.7. Head-up Tilt Table Test

Starting in 1945, investigators began to study the physiological and pathological effects of orthostatic stress in human[62]with later a focus on the body's response to the stresses of aviation and the microgravity environment of space travel. During this period, the head up tilt (HUT) table test came into use in order to provide a controlled setting in which the body's responses to changes in position could be carefully observed and recorded[3].

It was not until 1986, that Kenny et al.[63] used HUT testing to provoke vasovagal syncope by providing a passive continuous orthostatic stress. Today, the HUT test (Figure 2.5) has become a widely accepted diagnostic tool to assess an individual's susceptibility to NMS[64,65] in the absence of a "gold-standard" diagnostic test for vasovagal syncope. When initial history, physical examination, and appropriate neurological and cardiovascular investigations have failed to determine a cause of recurrent syncope the HUT test, if properly used, can be used to confirm one's clinical suspicions and to establish a diagnosis[64].

By providing a controlled orthostatic stress, it can uncover an individual's predisposition to neurally mediated hypotension and bradycardia. The ability to provoke hypotensive syncopal episodes using the HUT table test in a controlled laboratory setting, has provided the opportunity to make detailed observations of the physiological changes that take place during these events and has also allowed for a much greater understanding of these disorders and for evaluating the efficacy of therapy. The use of tilt guided medical therapy in neurocardiogenic syncope is however controversial as spontaneous remission occurs in the majority of patients.

Two principal methods of performing HUT table testing have been developed. The first uses prolonged HUT alone, without provocative pharmacological agents, to produce dependent venous pooling and thereby provoke the aforementioned reflexes in susceptible individuals. The second, based on the previous observations that

catecholamine levels rise significantly prior to the onset of syncope, uses a concomitant isoproterenol infusion during HUT testing as a way of increasing the sensitivity of the test[64]. Some other pharmacological provocative agents that have been used are: nitrates (because of venodilatory properties)[66], the endogenous nucleoside adenosine[67] (enhances sympathetic nervous activity and promotes vasodilatation), and endrophonium[68] and clomipramine[69] with less widespread adoption.

2.7.1 Sensitivity and specificity of the HUT test

It is impossible to exactly duplicate the clinical and environmental circumstances that may result in syncope in every patient. However, the ability of the HUT test to differentiate symptomatic patients from asymptomatic control subjects with a level of precision considered acceptable for other clinically used testing procedures has been well established[70, 71]. Calculation of the exact sensitivity and specificity of the HUT test is difficult, particularly in view of the variable methodologies used by different researchers. The literature would suggest that HUT testing used without pharmacological provocation at angles between 60°and 80° shows a specificity of up to 90%[64]. Natale et al.[72] reported that HUT testing at 60°, 70° and 80° demonstrated specificities of 92%, 92%, and 80% in the presence of concomitant low dose isoproterenol provocation. Determination of the exact sensitivity of HUT is largely dependent on the physiological mechanisms that result in NMS.[64] A sensitivity range of 32% to 85% at tilt angles between 60° and 70° has been reported in several studies.[65,73]

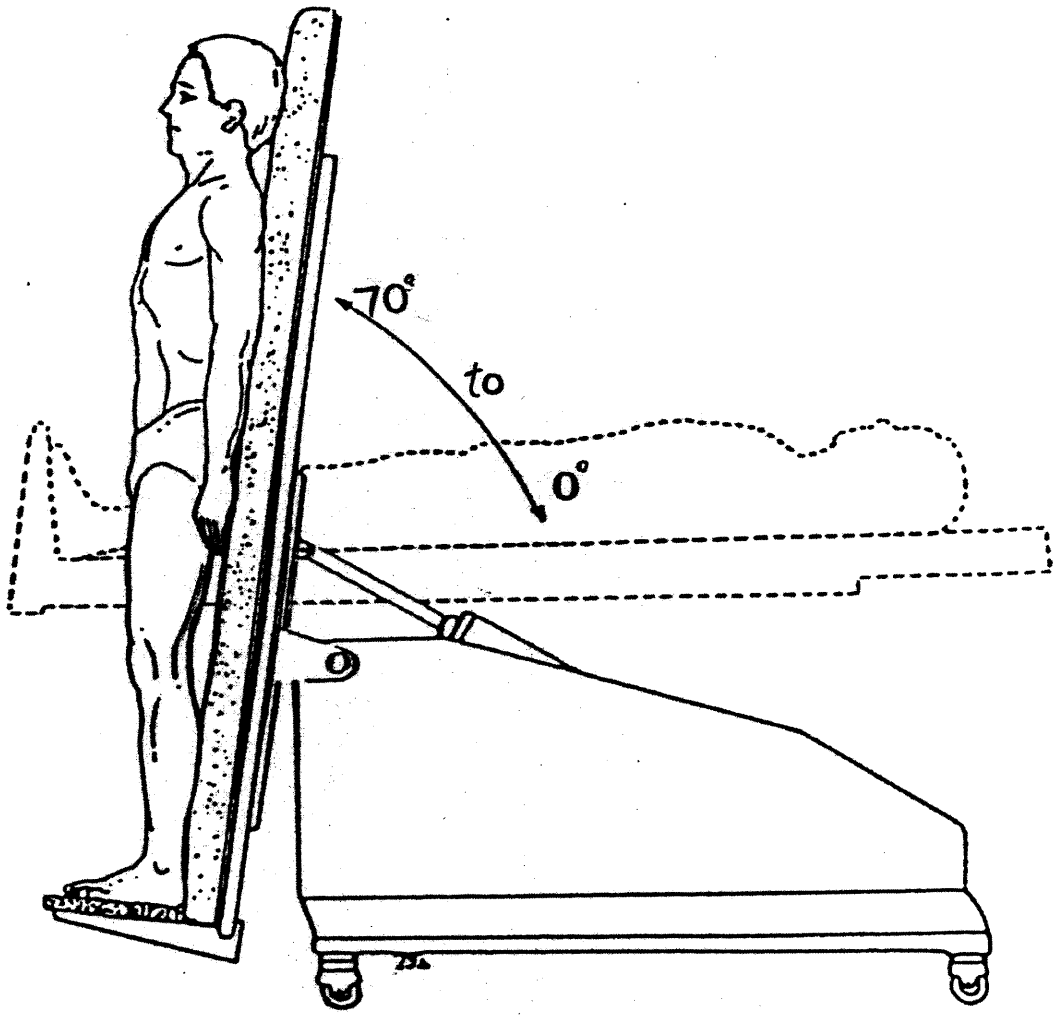


Figure2. 5. A schematic representation of HUT table test.[3]

CHAPTER III

METHODOLOGY OF INVESTIGATION

The present study investigated cardiovascular autonomic regulation in patients with NMS. To this purpose, we continuously recorded HR and blood pressure during the HUT test and applied a spectral analysis of RR interval to the analyzed data in order to document modification of ANS activity. We also used HRV analysis to compare bradycardic and hypotensive response to HUT test in a group of patients with positive non-pharmacological HUT test.

First we compared syncopal patients, with a positive response to the HUT test to the patients with a negative response. Secondly, we made an intra group comparison of findings from patients with vasovagal syncope. Each of the experimental sessions took place in the Clinical Research Unit of Hôpital du Sacré-Coeur de Montréal. The methods and procedures of this study will be delineated within the ensuing sections: (3.1) Patients selection and preparation; (3.2) Experimental task and protocol; (3.3) Data acquisition and analysis; and (3.4) Statistical analysis.

3.1. Patient Selection and Preparation

The study population consisted of 40 subjects divided into 2 main groups and 3 subgroups as explained below. These patients were selected from a set of 67 who had unexplained syncope and were referred to the Clinical Research Center of Hôpital du Sacré-Coeur de Montréal between December 1999 and October 2000 for HUT test. The main criteria used for selection of the study group are as follows:

1. Not having any illnesses such as heart failure, diabetes mellitus and neuropathy.
2. Having non-pharmacological HUT test.
3. Having intact Holter recording during the test, i.e., properly recorded signals.

The etiology of reported syncope in these 67 patients could not be established prior to HUT testing despite thorough clinical examination and 24-hour Holter recording.

According to the HUT test results, positive or negative, they were divided into two main groups of 20 tilt-negative and 20 tilt-positive patients. In the second part of the study we classified the positive non-pharmacological HUT test patients into 3 subgroups of Mixed, CI and VD reactions according to the hemodynamic and chronotropic responses observed during syncope.

Patients were not taking any medications with effects on ANS for at least 3 days prior to HUT testing. Subjects had also been advised not to eat before tilt testing since midnight and to refrain from moderate, heavy or sustained exercise for a period of 12 hours prior to testing.

3.2 Experimental Task and Protocol

3.2.1 Head up Tilt Table Test

Tilt testing was performed in the morning either between 8:30-10:00 or 10:00 to 12:00 in a quiet dimly lit room and at a comfortable room temperature (20-22°C). During the tilt maneuver, subjects were adequately secured to the table by belts around the hips and below the knees as a safety precaution. All patients were given 100 mL of Normal Saline solution 0.9% through a peripheral intravenous cannula for each hour beginning 15 minutes before the test.

The tilt test was performed on an electrically driven tilt table capable of rotating from 0° to 90° from a horizontal line. First, the subjects remained in the supine position at 0° for 10 minutes. The table was then positioned at an angle of 70° (with foot support). Patients remained in the upright position for 40 minutes. The test was interrupted when syncope or pre-syncope with hypotension occurred at which time the subject was immediately returned to the supine position.

The test was considered negative if the patient remained asymptomatic for 40 minutes and positive, if syncope occurred or if a drop in blood pressure to less than 70 mm Hg with pre syncopal symptoms was observed. Patients with a positive HUT test, with isoproterenol infusion were not included in the analysis of this study.

Patients with a positive tilt test were divided into three groups according to the proposed classification for tilt induced vasovagal syncope by Sutton et al.[60]

We considered patients to have VD syncope when; "their heart rate increased initially but decreased afterward by no less than 10% from the maximum peak with hypotension during syncope", and CI syncope when "the HR decreased to <40 bpm during syncope for more than 10 seconds or when asystole was observed for more

than 3 seconds, occurring concomitantly with hypotension" and finally, mixed when; "hypotension occurred prior to or concomitantly with bradycardia, and (a) HR increased before symptoms occurred, and decreased afterward, although it remained higher than 40 bpm, (b) HR was lower than 40 bpm for <10 seconds, or (c) asystole occurred for <3 seconds."[74]

3.2.2. Electrocardiography and Holter Monitoring

Prior to testing, ten adhesive electrocardiogram (ECG) electrodes were positioned: six on the anterior chest and one on each limb. Continuous single lead ECG monitoring was performed but when needed a 12-lead ECG or a 3-lead rhythm strip could be obtained.

Continuous 3-lead digital rhythm recording during the entire duration of the HUT test and, in the case of presyncope or syncope, also during the recovery phase (approximately 10 minutes after syncope), were obtained using a Holter system (Space Lab Burdick) with a sampling rate of 500 sample/second/channel and 16 bit per sample.

3.3 Data Acquisition and Analysis

A continuous ECG was recorded during the entire test by Holter (Space Lab Burdick) recorded on a digital disc (Altair-Disc^{TM} recorder) , with an electronic mark. The 6600 series Altair-Disc^{TM} recorder is designed to record two or three channels of ECG data from ambulatory patients for up to 24 hours. The resulting recording data can then be analyzed by a Burdick Altair PC Holter system to produce a comprehensive report of arrhythmic (and/or ischemic) episodes. Recorded data was transferred to a computer and after visualization and verification (for any rhythm disorder) beat to beat analysis was performed by a special program. Afterward,

for spectral analysis. As showed in Figure 2.1, transformed and analyzed data were subjected to the power spectral analysis program.

A Fast Fourier Transform function algorithm was applied to the R-R tachogram to obtain the power frequency spectrum. For Spectral analysis Hanning window was chosen and data were all detrended. Frequency bandwidths were selected according to recommendations of the Joint Task Force of the European society of Cardiology and the North American Society of Pacing and Electrophysiology (NASPE)[30]. The magnitude of either the HF or LF spectral power component presented in normalized units (Nu) to represent the relative value of each power component in proportion to the total power minus the VLF component. An index of sympathovagal balance was estimated by the ratio of LF to HF spectral power components (LF/HF).

First, we compared the spectral indexes of HRV for 256 seconds intervals at certain specified event times, in patient groups with positive and negative HUT test. Analyzing time started at times defined as below:

In patients with negative HUT test,

1. Five minutes after beginning of the recording in supine position (Rest).
2. Immediately after tilt to the upright position (Tilt).
3. Ten minutes before the end of the test (10'BET)
4. Five minutes before the end of the test (5'BET)

In patients with positive HUT test,

1. Five minutes after beginning of the recording in supine position (Rest).
2. Immediately after tilt to the upright position (Tilt).
3. Five minutes before syncope in the upright position (5'BS).

In order to make the results comparable between the two groups of positive and negative patients, an interval was chosen to correspond to "before the end of the test" (BET) which was considered the last 5 minutes of the test for patients with negative HUT and 5 minutes before the syncope for the patients with positive HUT

(Figures 3.1 and 3.2). For the 3 sub-groups of positive patients (Mixed, CI and VD reaction) we compared the same indexes for the same three 256 seconds intervals described above.

3.4 Statistical Analysis.

Group mean and standard error of the mean (SEM) as well as standard deviation (SD) were calculated from each individual's power spectral indices for all specific time intervals during the test. A one-way analysis of variance (ANOVA) was used to compare the HR and HRV components (HF, LF, VLF bands and LF/HF) at rest position to either 3 (with negative tilt) or 7 (with positive tilt) specific time intervals for intra-group comparison. For evaluation of frequency band changes at different positions we also used a paired *t*-test for intra-group comparison. Normality was tested, using the Kolmogorov-Smirnov test.

Group differences in the magnitude of response to tilt were assessed using unpaired student *t*-test where data were normally distributed.

A two sided P-value <0.05 was the criterion of significance in all tests.

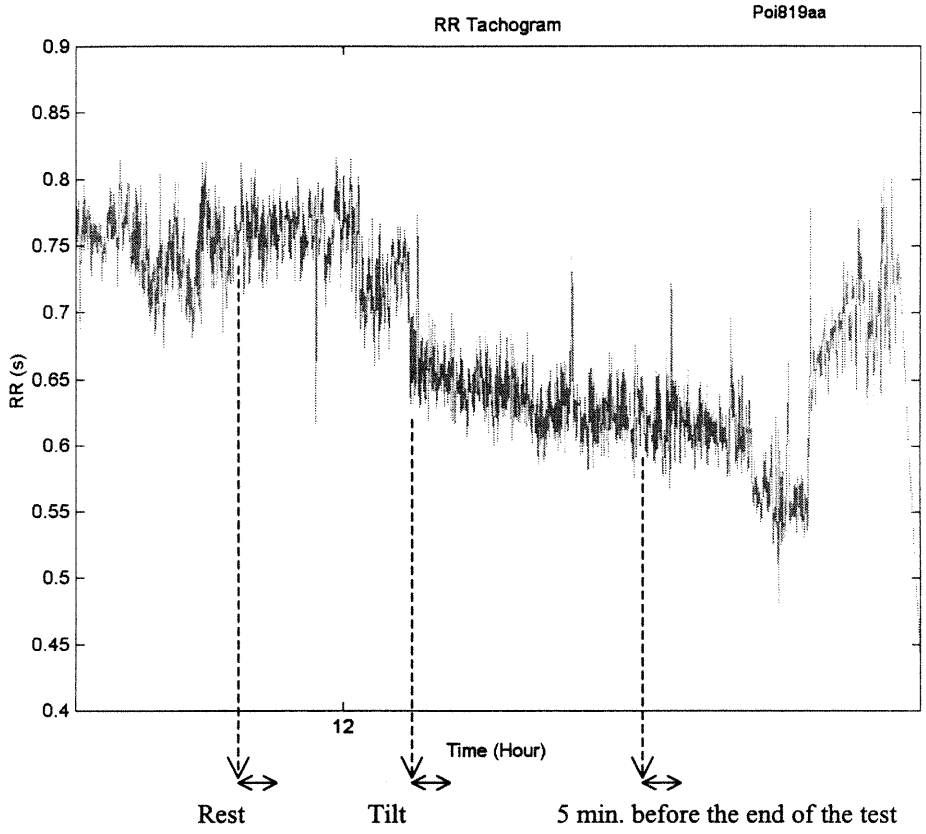


Figure 3.1. A tachogram of a patient with negative HUT test.

Time points that considered for the analysis at Rest, Tilt and 5 minutes before the end of the test has been shown.

Horizontal markers show 256-second interval which has been analyzed by spectral analysis.

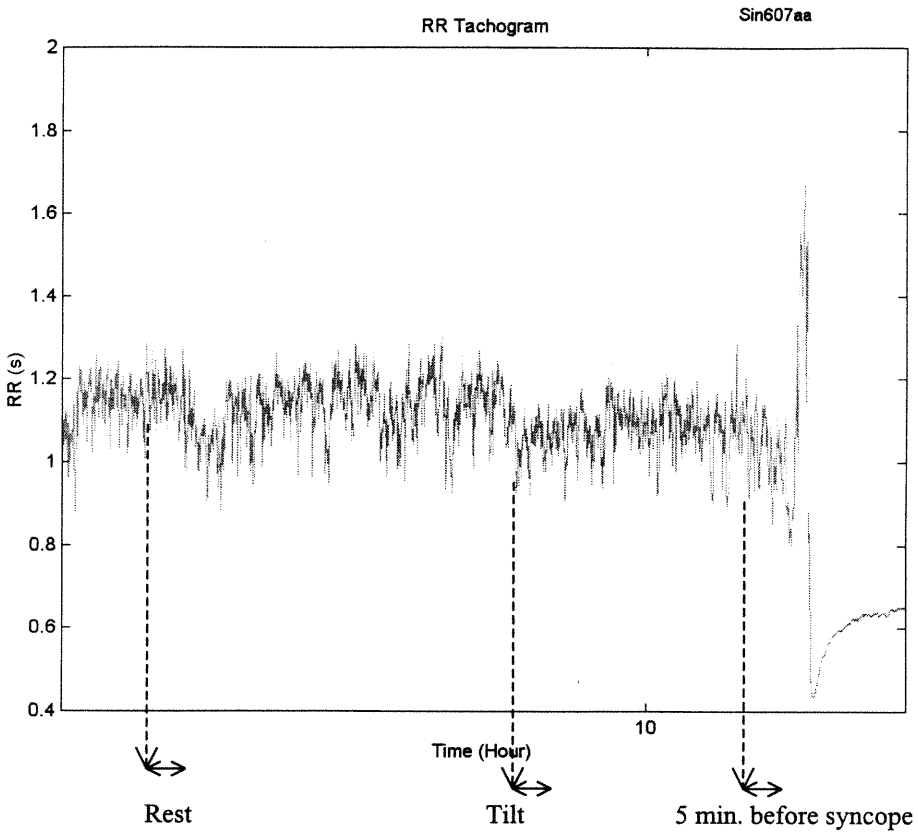


Figure 3.2. A tachogram of a patient with positive HUT test.

Time points that considered for the analysis at Rest, Tilt and 5 minutes before the end of the test has been shown.

Horizontal markers show 256-second interval which has been analyzed by spectral analysis.

CHAPTER IV

RESULTS

The purpose of present study was to assess the ANS behavior during HUT testing in patients with syncope and also to investigate the different responses to HUT testing in patients with vasovagal syncope.

This chapter is divided into the following sections: (4.1) Participant characteristics, (4.2) Heart rate responses to tilt (4.3) Intra-group Comparison of HRV indices, (4.4) Inter-group comparison of HRV indices.

In each section the results will be shown under two subdivisions, Study group A and Study group B. Study group A contains syncopal patients with positive and negative HUT test result. Study groups B contains patients with vasovagal syncope (positive HUT test) who are classified into mixed, CI and VD subgroups.

4.1 Participant Characteristics

Patients have selected according to the previously mentioned criteria, were included as study participants. All patients had a history of at least 1 episode of syncope within the last 6 months. There was no evidence of structural heart disease by history, physical examination and non-invasive cardiovascular evaluation (ECG and 24-hour Holter monitoring) in any participant. The participants included 22 women and 18 men with a mean age of 43 ± 16* (range 21 to 81 years).

Participants were divided into two groups according to their HUT test result. Twenty patients with positive HUT (12 women and 8 men) aged 39 ± 14* years old (rang 21 to 73) were included in the study as well as 20 patients with negative HUT (10 women and 10 men) aged 48 ± 18* years old (rang 23 to 81).

The twenty patients with positive HUT were those diagnosed with vasovagal syncope in whom symptoms were provoked at HUT without using any pharmacological agent. The twenty patients with negative HUT were those who remained undiagnosed despite the use of isoproterenol during tilt.

The first study (A), compares the above 2 groups according to their positive or negative response to HUT. In the second study (B), patients with positive HUT, were classified into 3 subgroups depending on their hemodynamic response during the vasovagal reaction (Sutton's classification)[60]. Distribution of age and sex in each group is shown in tables 4.1 and 4.2.

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*Values indicated are Mean ± SD

4.2. Heart Rate Responses to Tilt

Study A Baseline HR, which is considered to be the HR at rest and supine position, was similar in both groups, 69 ±13 (mean ± SD) in the positive test group versus 73 ± 14 in the negative test group, $p<0.05$. Tilting to 70° caused an initial significant increase ($p<0.04$) of HR in patients with a positive HUT test but not in the negative HUT group. Syncopal patients with a positive test also had a statistically significant increase in HR 5 minutes before syncope as did the negative test patients at 10 and 5 minutes before the end of the test. There was no significant differences in any specified events between two groups. (Table 4.3 and Figure 4.1)

Study B The effects of HUT on HR in patients with a positive response are shown in tables 4.4 and 4.5.

Mean resting HR in the Mix group was higher as compared to the CI group 73 ± 14 versus 62 ± 9 respectively. However, this difference between two subgroups was not statistically significant. Tilting had a very significant effect on increasing the HR in both the CI ($p = 0.02$) and the Mix group ($p = 0.002$), using the paired t-test for comparison.

In the VD group with only 2 patients (which is not enough to be considered as an individual group for statistical analysis), there was no increase in HR with tilt. Further, in all subgroups, there was an increase in HR (compared to rest) shortly before syncope.

Table4. 1. Distribution of age and gender in syncopal patients.

Groups	**Positive HUT**	**Negative HUT**
N	20	20
Sex		
F	12	10
M	8	10
Age (years) †	39 ± 14	48 ± 18

Table 4. 2. Distribution of age and gender in patients with Positive HUT

Groups	**Cardioinhibitory**	**Mixed**	**Vasodepressor**
N	8	10	2
Sex			
F	5	5	2
M	3	5	0
Age (years) †	34 ± 11	39 ± 11	61 ± 17

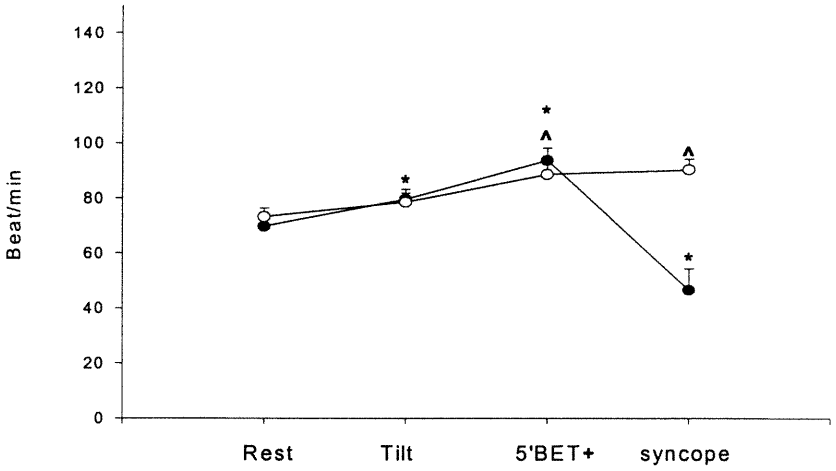
N: Number of patients in each group, F: female, M: Male, † Mean ± SD

Table 4.3. Heart Rate changes in patients with positive and negative HUT.

	Positive	Negative
Rest	69 ± 13	73 ± 14
(Max, Min)	(98, 50)	(99, 50)
Tilt	78 ± 15*	79 ± 14
(Max, Min)	(110, 53)	(98, 53)
5 min BET‡	93 ± 20**	90 ± 17**
(Max, Min)	(136, 56)	(113, 56)

Values are Mean ± Standard deviation

‡ 5 min. BET: The end of the test for patients with vasovagal syncope is considered the syncopal time and for patients with negative HUT test is the end of upright position. *P< 0.05, **P< 0.0001, Compare to Rest position



+ 5'BET: has been considered 5 min. before the end of the test for patients with negative HUT test and 5 min. before the vasovagal syncope in patients with vasovagal syncope.

—●— Patients with vasovagal syncope, n=20, * $p<0.05$, compare to Rest

—○— Patients with negative HUT test, n=20, ^ $p<0.05$, compare to Rest

Figure 4. 1. A comparison of HR changes in HUT positive and negative patients

Table 4. 4. Heart rate changes during HUT test in all patients with vasovagal syncope (positive HUT test).

A comparison of the subgroups with predominant cardioinhibitory and mixed response to tilt.

	HR	Rest	Tilt	5'BS	Syncope	1'AS	2'AS	3'AS
ALL	Mean ± SD	69 ± 12	78 ± 15*[1]	93± 20 *[2]	49± 34 *[3]	68 ± 32	71± 27.00	72± 26
	Max, Min	(98, 50)	(110, 53)	(136, 56)	(99, 0)	(152, 0)	(146, 40)	(143, 43)
CI	Mean ± SD	62 ± 9	71 ± 15*[4]	84 ± 17*[5]	15 ± 20*[6]	64 ± 49	78 ± 40	78 ± 38
	Max, Min	(75, 50)	(101, 53)	(113, 57)	(43, 0)	(152, 0)	(146, 40)	(143, 43)
Mix	Mean ± SD	73 ± 14	84 ± 14*[7]	99 ± 22*[8]	68 ± 16	70 ± 16	66 ± 15	68 ± 14
	Max, Min	(98, 55)	(110, 63)	(136, 67)	(98, 44)	(103, 41)	(94, 40)	(98, 45)

All: Patients with vasovagal syncope, $N_{Pos} = 20$, *[1]P = 0.04, *[2] P = <0.0001, *[3]P = 0.0002

CI: Predominant Cardioinhibitory Reaction to HUT, $N_{CI} = 8$, Mix: Mixed reaction to HUT, $N_{Mix} = 9$

* Significantly different from rest, *[4] P = 0.0228, *[5]P = 0.0018, *[6] P = 0.0015, *[7]P = 0.0024, *[8]P =0.0012

5'BS: 5 minutes before Syncope. 1', 2', 3' AS: 1,2,3 minutes after syncope.

Table 4. 5. Heart rate changes during HUT test in Patients with Pure vasodilatory (VD) response

	Rest	Tilt	5'BS	Syncope	1'AS	2'AS	3'AS
P1	77	77	107	99	77	63	61
P2	81	79	85	89	70	73	73

P: Patient, SD: Standard Deviation

4.3 *Intra-group Comparison of HRV Indices*

Study A In both groups of patients with negative and positive tilt tests, the mean values of HF spectral power decreased significantly after tilt and five minutes before the end of the test which for patients with positive HUT is considered to be 5 minutes before syncope. This finding applied to the mean values and the individual results from all members of both groups except for two patients with positive HUT who showed minimal increase in HF when tilted. Tilting also caused a significant increase in LF/HF ratio in both groups, whereas the LF bands showed a minimal increase in both groups and less changes in patients with positive HUT.

In patients with a positive HUT test we observed that the LF spectral power decreased at 5 minutes before syncope. Observed changes in LF values, when compared to the rest position, were statistically significant ($P<0.05$). In patients with negative HUT, changes in LF bands were not statistically significant. There was a statistically significant increase in VLF bands with tilt and before syncope in positive HUT patients. In negative HUT patients increase in VLF spectral power was also significant before the end of the test.

Further analysis showed inter-individual variation in both groups. Nine patients in the positive HUT group exhibited decreased in LF values when tilted in contrast with the rest of the group who showed an increase in LF values. We observed the same individual pattern of LF changes in patients with negative HUT as well. However, all patients with positive HUT demonstrated decreased LF before the onset of syncope. (Tables 4.6, 4.7, and Figures 4.2, 4.3, 4.4, 4.5)

Study B There was a very significant decrease of HF and increase of LF/HF ratio in both CI and Mix groups with tilt and before syncope. In both subgroups (CI and Mix) LF was decreased before syncope. A significant increase in VLF was observed with tilt and before syncope in both CI and Mix groups. (Table 4.8).

In the VD group we noticed a slightly increase in HF power spectral with tilt in patient number 1 (P1) and a decrease in the patient number 2 (P2). Compared to rest position both patients show an increase in HF values before syncope. LF/HF ratio decreased with tilt. LF increased after tilt in one patient and increased in another one. Changes in the HRV indices during the test in this group were not significant compared to rest position. Table.4.9, shows the individual values of HRV indices in VD group.

Table 4. 6. HRV indices prior to and during HUT test in patients with positive HUT test.

Index	Rest	Tilt	5'BS
HF	26.35 ± 2.90	8.43 ± 1.29*	8.09 ± 2.21*
LF/HF	1.59 ± 0.19	7.47 ± 1.43*	7.02 ± 1.83*
LF	37.50 ± 3.10	38.40 ± 4.90	23.80 ± 2.43*
VLF	34.10 ± 3.55	51.40 ± 4.78*	67.10 ± 3.31*

Values are Mean ± SEM, * P <0.05, The p values refer to differences between each index and rest position

Table 4. 7. HRV indices prior and during HUT test in patients with negative HUT test.

Index	Rest	Tilt	10'BET	5'BET
HF	22.62 ± 2.48	7.85 ± 1.13*	6.90 ± 1.68*	5.98 ± 0.88*
LF/HF	2.36 ± 0.39	10.11 ± 2.16*	11.57±2.26*	10.81 ± 1.97*
LF	39.40 ± 3.14	43.00 ± 4.61	38.10± 3.84	39.40 ± 5.30
VLF	36.00 ± 3.11	44.10 ± 4.46	53.90 ± 3.56*	51.10 ± 5.03*

Values are Mean ± SEM, * P <0.05, compare to rest.

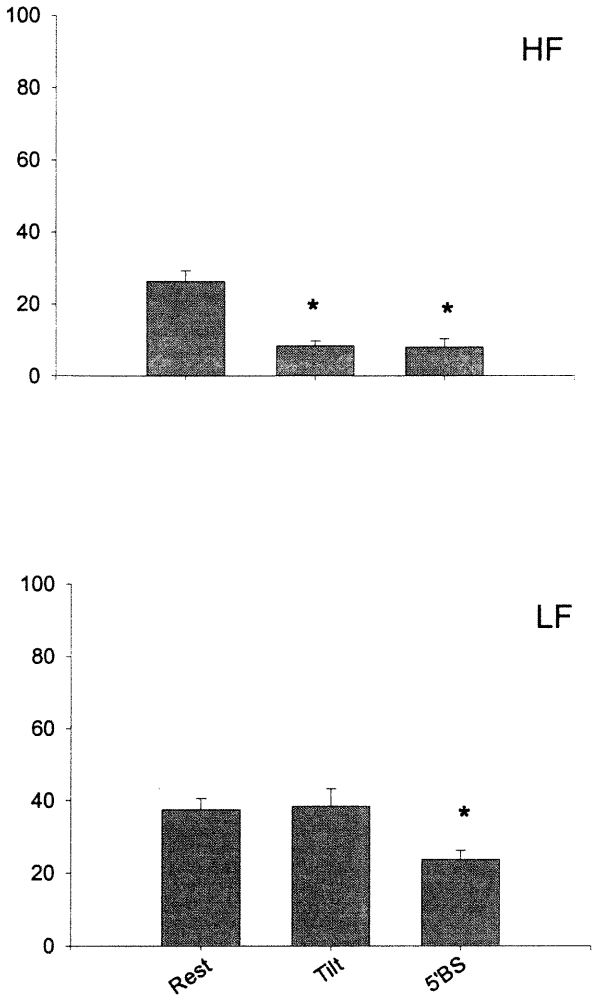


Figure 4. 2. Spectral analysis of HRV in patients with positive HUT test (Demonstration of changes in HF and LF bands during HUT)

Values are Mean ± SEM, * $p < 0.05$ compare to Rest. 5'BS: 5 minutes before Syncope.

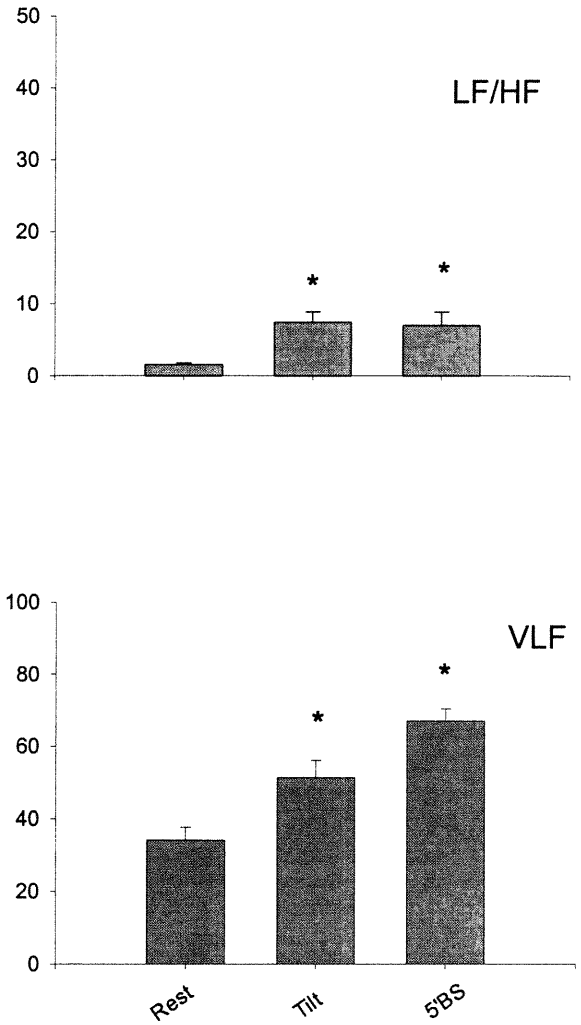


Figure 4.3. Spectral analysis of HRV in patients with positive HUT test (Demonstration of changes in VLF band and LF/HF during HUT)

Values are Mean ± SEM, * $p < 0.05$ compare to Rest. 5'BS: 5 minutes before Syncope.

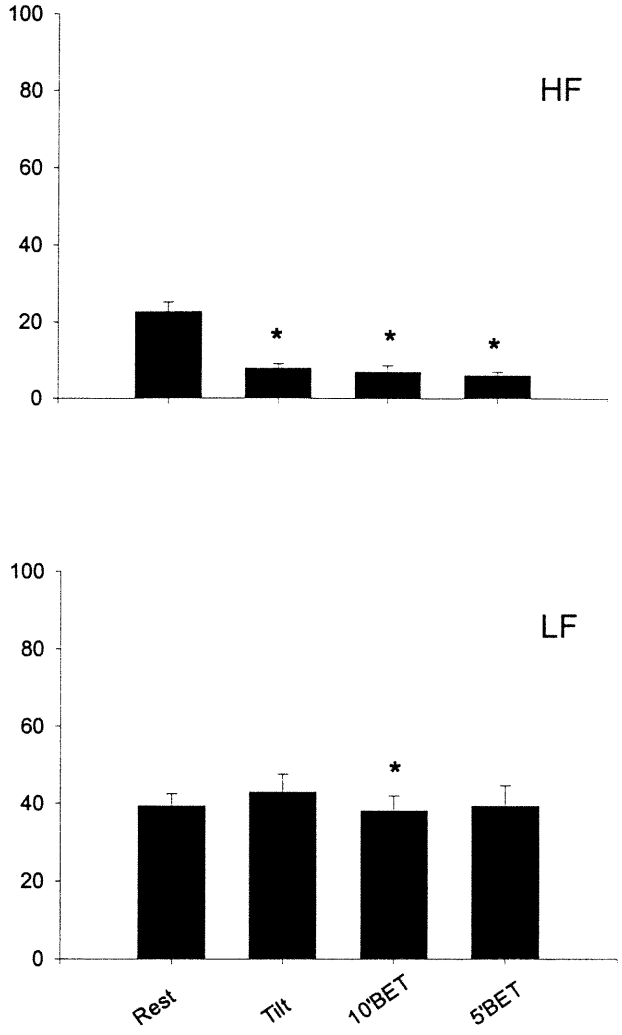


Figure 4.4. Spectral analysis of HRV in patients with negative HUT test

(Demonstration of changes in HF and LF bands during HUT test)

Values are Mean ± SEM, * $p < 0.05$ compare to Rest. 10'BET: 10 minutes before end of the test and 5'BET: 5 minutes before end of the test.

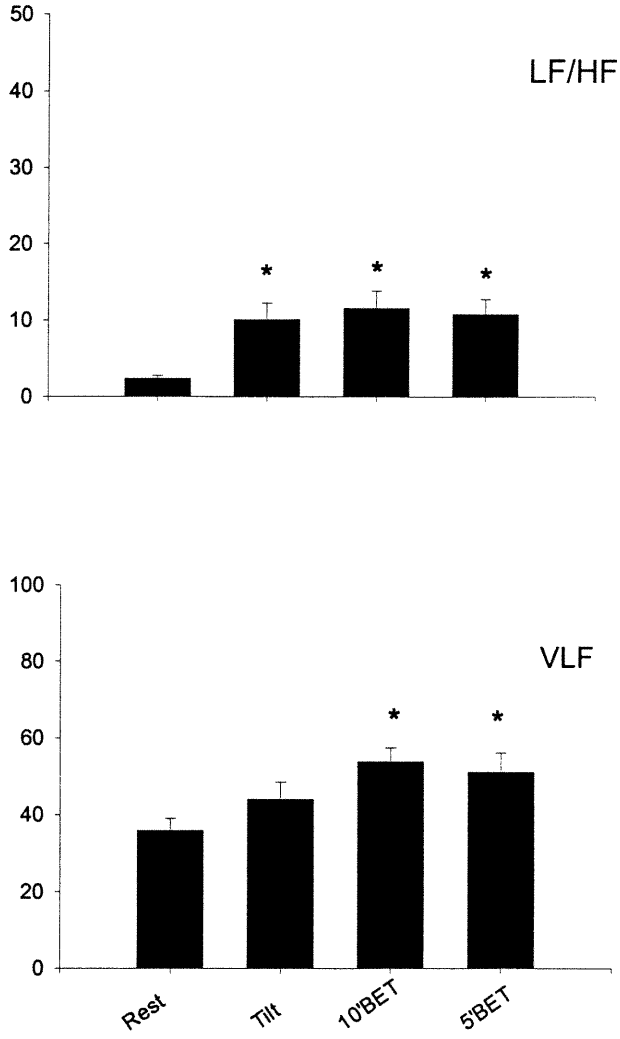


Figure 4.5. Spectral analysis of HRV in patients with negative HUT test (Demonstration of changes in VLF band and LF/HF during HUT)

Values are Mean ± SEM, * $p < 0.05$ compare to Rest. 10'BET: 10 minutes before end of the test. and 5'BET: 5 minutes before end of the test.

Table 4. 8. Mean values ± SEM of HRV indices during the test in subgroups of patients with positive HUT test.

	Index	Rest	Tilt	5'BS
CI	HF	32.38 ± 6.09	7.44 ± 1.54*	4.10 ± 0.86*
	LF/HF	1.24 ± 0.28	7.93 ± 2.08*	7.81 ± 2.04*
	LF	31.20 ± 5.81†	39.30 ± 7.28	23.50 ± 4.18
	VLF	34.30 ± 7.18	52.50 ± 7.64*	72.20 ± 4.67*
Mix	HF	22.77 ± 2.57	7.59 ± 1.61*	6.43 ± 1.95*
	LF/HF	2.24 ± 0.31	8.46 ± 2.20*	8.42 ± 3.18*
	LF	44.20 ± 1.64	42.90 ± 7.16	25.60 ± 3.28*
	VLF	31.00 ± 2.39	47.50 ± 7.21*	67.60 ± 4.31*

Values are Mean ± SEM, * $P < 0.05$, compared to rest , † $P < 0.05$, compared to Mix group.
5'BS: 5 minutes before Syncope.

Table 4. 9. Individual values of HRV Indices during the test in Patients with pure vasodepressive syncope

		Rest	Tilt	5'BS
HF	P1	23.50	24.40	24.20
	P2	16.80	8.65	40.60
LF/HF	P1	2.00	0.46	1.01
	P2	0.71	1.57	0.18
LF	P1	47.00	11.30	24.50
	P2	11.90	13.60	7.35
VLF	P1	27.80	58.80	40.40
	P2	69.70	74.50	48.60

P1: Patient number one, P2: Patient number 2.

4.4 Inter-group Comparison of HRV Indices

Study A The HF and LF/HF ratio at rest and after tilt did not show significant differences between the two groups. The LF value was higher at rest, tilt and at 5 minute before the end of the test in patients with a negative HUT compared to those with a positive HUT. This increase was statistically significant (P= 0.003) at 5 minutes before the end of the test. On the contrary, patients with negative HUT test had lower VLF values compared to the other group and this difference was statistically significant (p= 0.02) at 5 minutes before the end of the test. The distribution of the HRV indices in both groups showed no specific pattern to distinguish one group from the other. (Table 4.10 and Figures 4.6, 4.7)

Study B The HF value was higher at the rest position in the CI group compared to the Mix group. Tilting to 70 ° caused a significant decrease in HF at the time points immediately after the tilt and 5 min before the syncope in CI and Mix groups ($P<0.05$). In the VD group decrease in HF was observed in P2 but not in the P1. The HF values in the VD group showed an increase before the syncope in both cases (Table 4.9) while in the other groups at the same time point it decreased significantly. The values of HF in none of the groups went higher than the values in the rest position. All 3 groups seemed to have the same values of LF/HF at rest. LF/HF ratio increased significantly in CI and Mix groups ($P<0.05$) with tilt and before the syncope (which is matched with the pattern of changes in HF) but in VD this ratio had a minimal change compare to the other group specially before the syncope. Among all the groups Mix had a higher level of LF during the entire test period. At rest, LF power spectral was significantly lower in CI compared to Mix group. Figures 4.8 and 4.9, show statistically significant differences which were noticed in HRV indices between CI and Mix subgroups.

Table 4. 10. A comparison of HR and HRV measures in patients with negative HUT and patients with positive HUT test at rest and with tilt.

		Negative HUT	Positive HUT
		Mean ± SEM	Mean ± SEM
Rest	HR	73 ± 3	69 ± 3
	HF	22.62 ± 2.48	26.35 ± 2.90
	LF/HF	2.36 ± 0.39	1.75 ± 0.22
	LF	39.40 ± 3.14	37.50 ± 3.10
	VLF	36.00 ± 3.11	34.10 ± 3.55
Tilt	HR	79 ± 3	78 ± 3
	HF	7.85 ± 1.13	8.43 ± 1.29
	LF/HF	10.11 ± 2.16	7.50 ± 1.42
	LF	43.00 ± 4.61	38.40 ± 4.90
	VLF	44.10 ± 4.46	51.40 ± 4.78
5'BET	HR	90 ± 4	93 ± 4
	HF	5.98 ± 0.88	8.09 ± 2.21
	LF/HF	10.81 ± 1.97	7.02 ± 1.83
	LF	39.40 ± 5.30*	23.80 ± 2.43
	VLF	51.10 ± 5.03*	67.10 ± 3.31

* $P < 0.05$, compared to HUT positive group, $N_{pos} = 20$, $N_{neg} = 20$

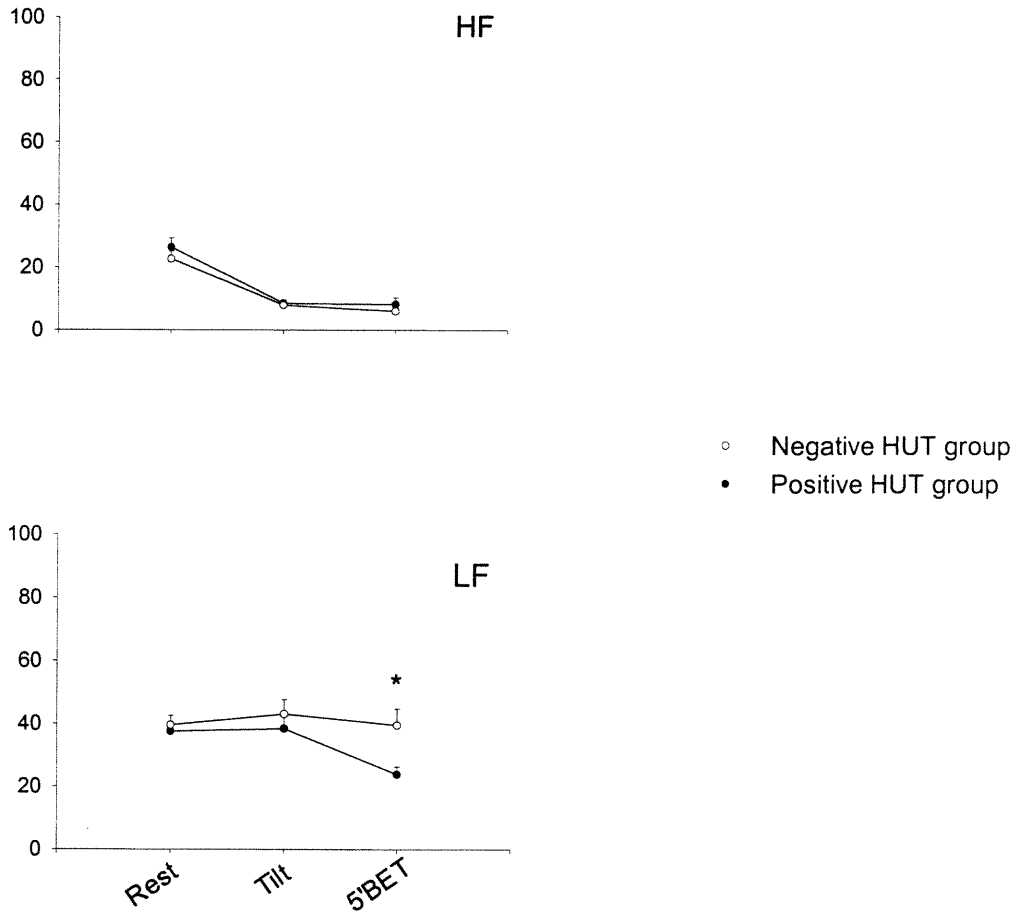


Figure 4. 6. A comparison of HRV indices (HF and LF bands) in patients with positive and negative HUT test.

Values are Mean ± SEM, * $p < 0.05$ compare to Positive group.

5'BET: 5 minutes before Syncope for positive group and 5 minutes before end of test for negative group.

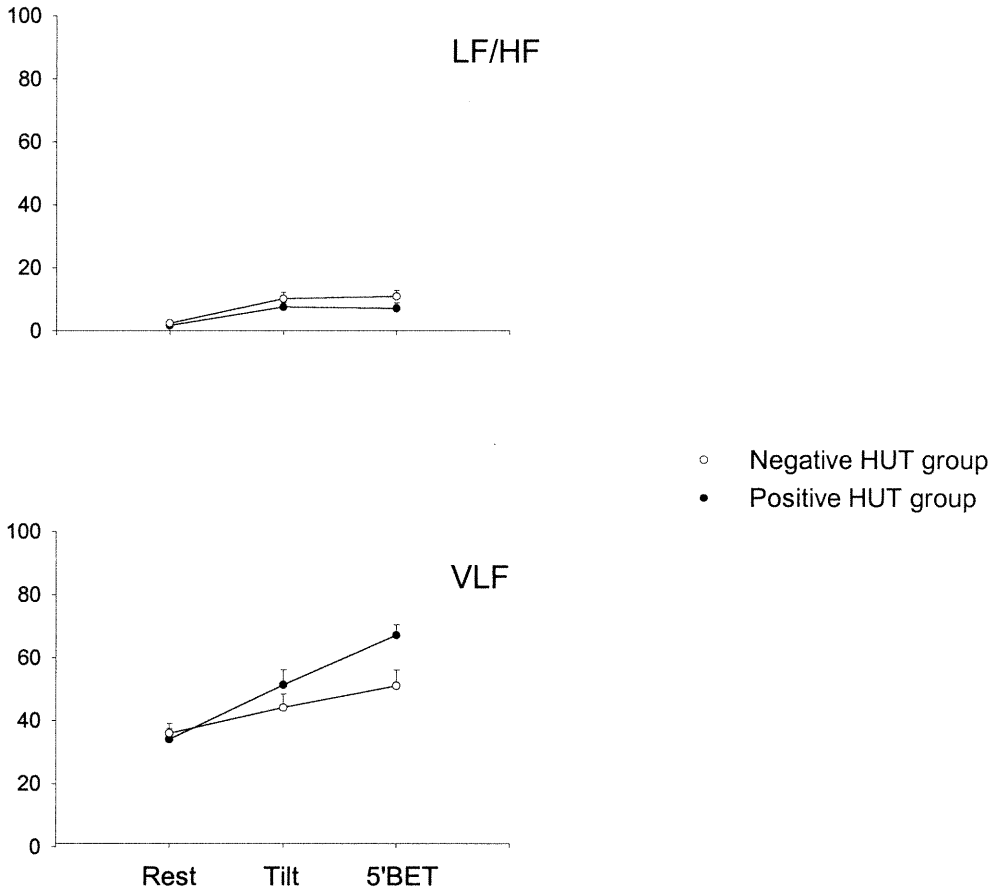


Figure 4. 7. A comparison of HRV indices (VLF band and LF/HF) in patients with positive and negative HUT test.

Values are Mean ± SEM, * $p < 0.05$ compare to Negative HUT group.

5'BET: considered 5 minutes before Syncope for positive group and 5 minutes before end of test for negative group.

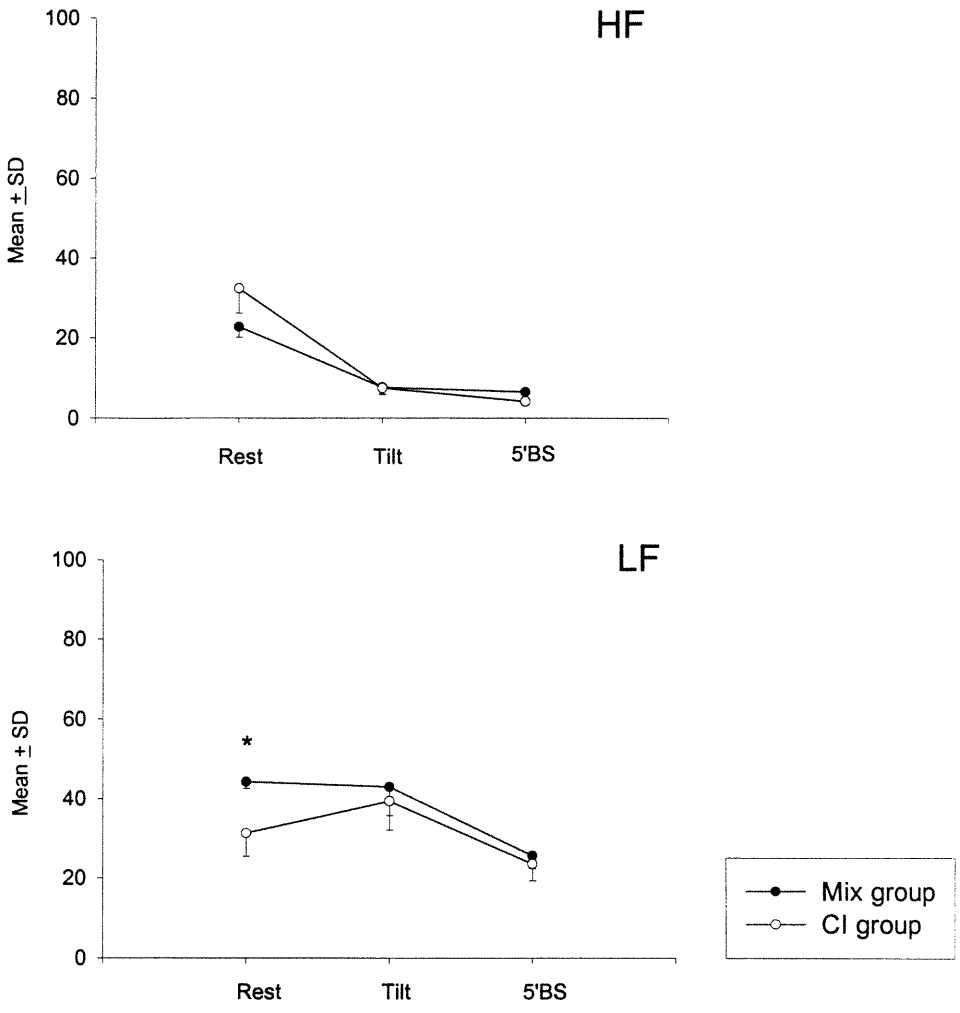


Figure 4.8. A comparison of HRV indices (HF, LF bands) between patients with predominant cardioinhibitory (CI) and mixed (Mix) reaction to HUT.

Values are Mean ± SEM, * $p<0.05$ compared to CI group.

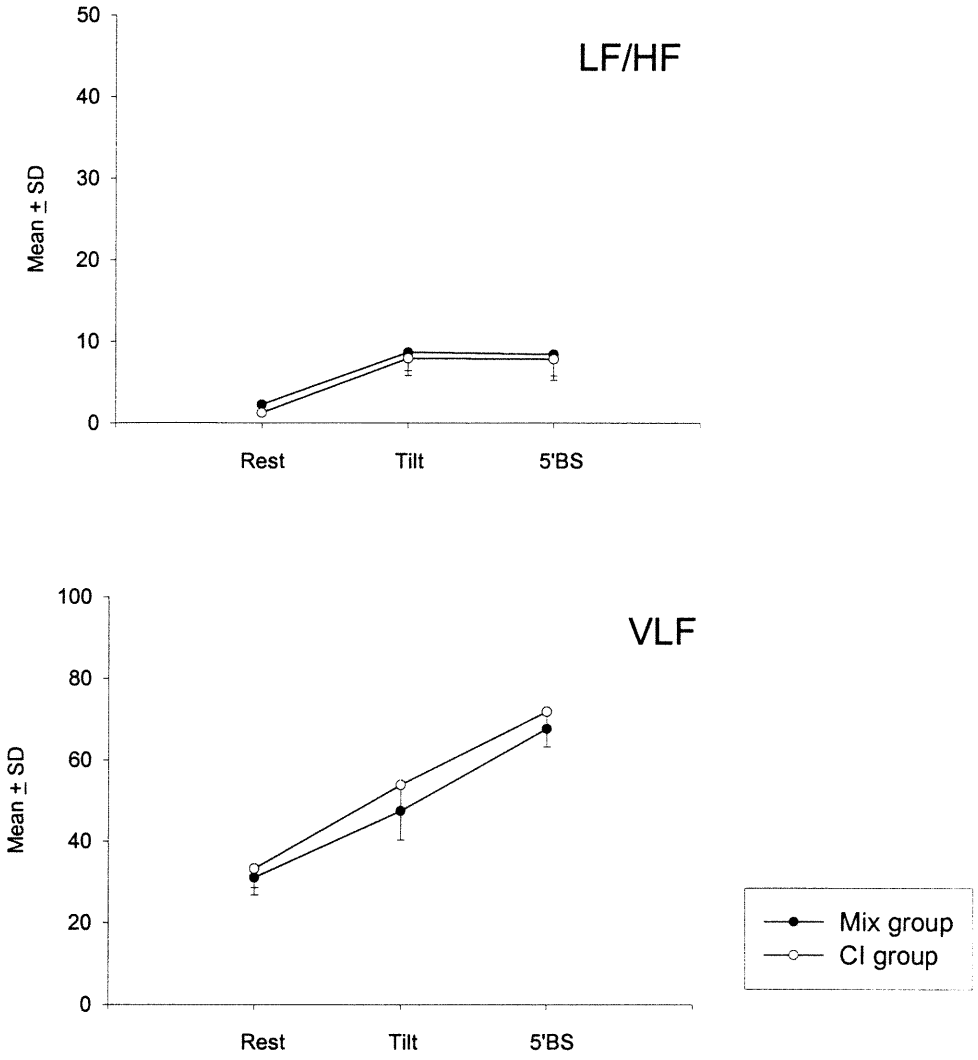


Figure 4.9. A comparison of HRV indices (LF/HF, VLF band) between patients with predominant cardioinhibitory (CI) and mixed (Mix) reaction to HUT.

Values are Mean ± SEM, * $p<0.05$ compared to Mix group.

CHAPTER V

DISCUSSION

In recent years, several studies have used temporal or spectral analysis to investigate HRV before and during tilt testing, mostly in normal individuals[75,76,77,78,79,80]. Only a few of these studies involved syncopal patients and no adequate comparisons were made between different categories of patients with vasovagal syncope, or between different stages of the tilting procedure. These studies tend to agree that, in normal subjects, a change in posture from lying to standing causes a decrease in vagal modulation of the RR interval and an increase in sympathetic nervous activity. However, there have been conflicting results with regard to the relationship between ANS behavior and syncope. Some investigators documented increased sympathetic drive just before syncope,[81,82] while others found reduced[74], [83]or unchanged[84] sympathetic tone.

Lipsitz et al.,[77]in a study of young normal individuals with no history of syncope but a positive tilt test, demonstrated a rise in the LF/HF ratio in response to upright tilt. They also reported an attenuated total spectral power and HF power at rest that persist during the tilt test, suggesting ANS imbalance with predominant sympathetic activity. In contrast, Morillo et al.[84] observed increased HF power, low LF/HF ratios, high rMSSD and pNN50 measures, during the first 5 minutes of tilt testing in 15 young syncopal patients with positive tilt test. They reported this as evidence of impaired sympathetic response and failure to withdraw parasympathetic tone under orthostatic stress. Both these studies compared HRV measures immediately after tilt with the baseline values. Lippman et al.[85] found that patients with a negative response, in contrast to patients with a positive tilt response, uniformly demonstrated withdrawal of parasympathetic tone when tilted upright.

Recently, Furlan et al.[90] identified two different patterns of cardiac autonomic changes on tilt table testing in patients presenting an occasional vasovagal event. They showed a marked cardiac sympathetic activation in a group of healthy volunteers who experienced a vasovagal reaction during a 90° HUT test and also a slow inversion of the cardiac sympathovagal balance with progressive sympathetic inhibition. They observed LF (the spectral marker of sympathetic modulation), suddenly dropped to nearly zero concomitantly with the onset of bradycardia, thus suggesting a persistent predominance of the sympathetic drive to the heart up to the vasovagal event. In the other group of fainters in that study, an initial marked predominance of LF, which, after having reached a maximum, slowly decreased before dropping down at the onset of bradycardia.

It can be seen from the above that in the upright position (or during passive tilt) the pattern of increase in LF and decrease in HF components, which has been considered to occur as a rule in the spectral profile[86] does not occur in all patients with the vasovagal response.

While both HRV and HUT testing are measures of autonomic function, HRV primarily reflects tonic vagal activity and HUT testing measures reflex autonomic activity. Lack of a general consensus as to the most appropriate time points for recording HRV indexes, few attempts[58,87] to study syncopal patients on the basis of the type of their hemodynamic response during the vasovagal reaction at HUT testing and to relate this to changes in ANS activity as well as the relatively small size of the study groups may explain the discrepancies in the above findings.

The current study employed spectral analysis of HRV to assess the behavior of the ANS during HUT testing in patients with vasovagal syncope and to compare the findings with those from patients with a history of syncope but a negative HUT result. We also addressed the hypothesis that the wide variety of clinical presentations of vasovagal events may somehow reflect different or even opposite changes in the cardiac autonomic profile of the syncopal subjects. The results of this investigation will be discussed as follows: (5.1) Assessment of resting autonomic Tone, (5.2) Autonomic tone changes during HUT testing, (5.3) Comparisons between subgroups.

5.1 *Assessment of Resting Autonomic Tone*

In our study, there were no significant differences in resting HR in patients with a positive tilt test when compared to patients with a negative test. We also observed no significant difference in HRV parameters at rest between tilt positive and tilt negative patients, a finding confirmed by Sneddon et al. [88] These findings are compatible with those of Yamanouchi et al.[89] who showed no significant difference in baseline plasma renin activity and aldosterone levels and in plasma epinephrine and norepinephrine levels in the supine posture at rest between syncopal patients with positive and those with negative HUT test. Furlan et al.[90] also reported no differences in the hemodynamic and spectral parameters under resting conditions between two groups of healthy subject with or without vasovagal syncope.

5.2 *Autonomic Tone Changes During Tilt Testing*

In our study, the pattern of changes in autonomic nervous activity during HUT testing in patients with positive HUT is not quite the same as the response of normal subjects who demonstrate a clear increase in sympathetic tone and a simultaneous withdrawal of parasympathetic tone immediately after tilt. Our results are in agreement with the findings of Lippman et al.[85] who reported withdrawal of parasympathetic tone uniformly only in patients with a negative response when tilted upright.

We found that, although the changes in HF spectral power and LF/HF ratio immediately after tilt have the same patterns in our study groups as in the normal subjects, the sympathetic response to tilting differs considerably. Overall, patients with a negative tilt test showed no significant changes in sympathetic tone

immediately when tilted. Patients with a positive HUT test however demonstrated a minimal increase in sympathetic activity when tilted but a significant decrease in sympathetic tone afterward which persisted until the onset of syncope and even after syncope when patients were returned to the supine position. Novak et al.[91] reported the same pattern of changes in low frequency bands in blood pressure of patients with positive test.

The increase in HR observed in both groups immediately after tilt and just before syncope in patients with vasovagal syncope was compatible mostly with parasympathetic withdrawal rather than an increase in sympathetic activity at the same time point and tended to be greater in vasovagal patients at 5 minutes before the syncope.

Looking at the individual variability of LF changes in response to tilt may raise the argument that LF fluctuations in RR interval variability may not accurately reflect changes in sympathetic activity.[92] However, if there is little doubt that sympathetic neural mechanisms contribute to the low frequency component, this does not necessarily mean that measuring LF is adequate " quantitative probe for sympathetic traffic."[93]

The tendency toward lower LF in the positive tilt patients when compared to negative tilt patients could be due to the lack of sympathetic activation in these patients. Furthermore these results reinforce the findings of Sneddon et al.[88] who considered that patients with vasovagal syncope demonstrated abnormalities in vascular control which lead to impaired vasoconstrictor response immediately after assumption of an upright posture. Kochiadakis et al.[87] reported a significant increase in the power of the LF band and the LF/HF ratio, and a decrease in the HF spectral power immediately after tilt in normal subjects. However, in contrast to the normal subjects, syncopal patients exhibited a significant decrease in LF spectral power and no changes in LF/HF ratio in response to tilt. They hypothesized that a decrease in sympathetic tone simultaneous with parasympathetic withdrawal could result in syncope. However, they did show a delayed increase in LF/HF ratio just before the onset of syncope.

We observed, in both positive and negative HUT test patients, an increase in LF/HF ratio after the tilt consisting of an absence of change in sympathetic tone and a very significant parasympathetic withdrawal. A higher LF and LF/HF ratio in patients with negative tilt test indicates sympathetic predominance in these patients compared to the positive tilt test patients. However, the fact that the mean values of the LF/HF ratio in positive HUT patients, though increasing significantly before syncope, do not reach the levels measured in normal subjects in the other studies, may be an indication that the sympathetic activation just before the onset of syncope is insufficient to produce an adequate increase in peripheral vascular resistance. The significantly lower systolic and diastolic blood pressures found[87] in syncopal patients shortly before the syncopal episode are compatible with this hypothesis. It is possible therefore that individual susceptibility to vasovagal syncope may be modulated by an impaired peripheral vascular resistance.

5.3 Comparisons between Subgroups

Sutton et al.[61] described three different subgroups of vasovagal syncope according to the patients' hemodynamic response at syncope induced by HUT table test: CI, VD, and mixed reaction. Studies comparing the changes in ANS activity in these subgroups of vasovagal syncope are few. Kochiadakis et al.[87] suggested a common pathophysiological mechanism but with different clinical presentations due to factors other than ANS in these 3 subgroups of patients. In contrast, Guzmán et al.[94] demonstrated two different manifestation of cardiac autonomic tone in neurally mediated syncope.

Our results support the existence of different patterns of changes in ANS activity during the HUT test. We demonstrated higher measures of HF spectrum at rest, in patients with predominant CI and mixed responses to tilt compared to the VD group. Further, the CI group compared to Mix group, had higher values of HF at rest and lower values of HF before the onset of syncope. Tilting to 70° caused a significant withdrawal in parasympathetic tone as evidenced by HF bands in CI and Mix groups. LF/HF values didn't show any differences with tilt or before syncope in

both CI and Mix groups. Significant decrease in HF values at tilt, while there has been no considerable changes in LF could be explained by marked parasympathetic withdrawal rather than an increased sympathetic activity. In both groups a decrease in LF power spectra before the syncope has been demonstrated but is significant only in the Mix group. In patients with a VD response however, we observed decreased LF spectral power in P1 and a slight increase in LF in P3 on tilting.

Although it seems evident that there is a different pattern of changes in HRV parameters in response to tilt in the 2 patients with VD compared to the CI and Mix groups, we have to remember that the VD group is very small and is not enough to draw definite conclusions. Recently, the hypothesis suggesting the existence of two different patterns of cardiac autonomic changes during tilt was proposed by Furlan et al.[90] They recognized that, in a group of 22 subjects with syncope, 13 patients had a progressive increase of cardiac sympathetic modulation up to the sudden onset of bradycardia, while 9 patients showed a gradual inhibition of sympathetic and a concomitant enhancement of vagal modulation of heart period. Our observations in HRV analysis in CI and Mix groups showed similar characteristics. Demonstration of progressive sympathetic inhibition in syncopal patients is another clue that vasovagal syncope may be promoted by an alternative pathophysiological mechanism other than enhancement of sympathetic activity and activation of cardiac mechanoreceptors.

5.4. Conclusions

The major findings of this study are first, patients with positive HUT test show variations in vagal autonomic tone but, compared to the negative test patients, the parasympathetic tone is higher both at rest and during tilt in patients with a positive test. Second, at least two main types of autonomic behavior exist in tilt induced syncope.

This study indicates that accentuation of sympathetic activity as a trigger factor for increase in cardiac contractility does not necessarily precede the tilt-induced vasovagal syncope. Thus, the classical theory of the pathophysiology of syncope that suggests that an increase of the sympathetic discharge and stimulation of the intra-myocardial mechanoreceptors is a triggering factor for vasovagal syncope seems unlikely to be able to explain all the cases of vasovagal syncope.

This observation may help explain the relative ineffectiveness of some therapeutic measures for example, ß-blockers, as the most commonly prescribed drugs in vasovagal syncope, among some patients. Their primary therapeutic benefit is believed to be a reduction in myocardial inotropy, which prevents the stimulation of left ventricular mechanoreceptors culminating in the Bezold-Jarisch-type reflex thought to be responsible for the vasovagal episode.

We also demonstrated that patients with vasovagal syncope are heterogeneous and show different patterns of ANS behavior in favor of a different pathophysiological mechanism involved in developing syncope.

The variability of the clinical outcome of HUT testing in vasovagal syncope could be in part related to parasympathetic and sympathetic activity fluctuations. Further studies need to be performed in a wide number of patients with syncope to establish whether a difference in basal autonomic tone in patients during a 24-hour period and during normal activity can predict their different reactions to HUT tilt.

We showed that at least two main types of autonomic behavior exist in tilt induced syncope. One in patients with predominant CI and mixed reaction to tilt is that of predominant parasympathetic activity, and the second, in the VD group which suggests decreased parasympathetic tone. These findings might have clinical implications in the management of patients with vasovagal syncope. The appropriate treatment of a patient with parasympathetic predominance may differ from that of the patient with predominance of sympathetic tone.

Further work is necessary to understand the normal physiology of the mechanoreceptors and chemoreceptors, the afferent and efferent limbs of reflexes, the central nervous system substrate as well as qualitative and quantitative humoral regulatory mechanisms prior to appreciating the pathophysiology of vasovagal syncope and confirmation of the role of ANS in mediating different responses.

Future studies, as regards the measurements themselves, with newer techniques for analysis of HRV which do not share some of the drawbacks of the traditional Fourier transform such as the lack of temporal information, the requirement for the signal to be stationary of the signal and the low frequency resolution of the analysis window, might give us more information about the role of ANS in pathophysiology of vasovagal syncope. A newer promising method of analysis, wavelet analysis which is not limited by the above mentioned constraints may provide new insights into the ANS changes preceding vasovagal syncope.

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