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ABSTRACT

THE ROLE OF SYMPATHOVAGAL IMBALANCE IN SYNCOPE USING HEART RATE VARIABILITY ANALYSIS

by
Jayadeep Krishnan Unni

One of the common and challenging problems confronting the physician in clinical practice is recurrent syncope. Despite extensive evaluations, the causes of these cases of syncope are not found in more than 40% of the patients.

It is thought that most patients who experience unexplained syncope do so because of transient, unpredictable episodes of vasovagally mediated hypotension and bradycardia. It is hypothesized that impaired inhibition of parasympathetic tone during stress accompanies the development of syncope. Head-up tilt table testing reportedly provokes vasovagal episodes effectively in susceptible persons.

This study attempts to explain the role played by the sympathetic and parasympathetic systems in the syncope condition. Heart Rate Variability, which has been demonstrated to be a reflection of the relative activities of sympathetic and parasympathetic systems, is utilized to compare the two groups of patients that took part in the study. The comparisons were performed between a set of normal subjects and patients with previous history of syncope. The syncope group was again categorized on the basis of their response to the tilt, i.e. positive or negative to tilt. Patients who experienced symptoms of syncope during the test were grouped positive and those who

did not as negative. Analysis was performed in the time domain as well as frequency domain. In the time domain the HF (parasympathetic) and LF (sympathetic + parasympathic) activity was analyzed before tilt and when in the tilted position, as a function of time. In the frequency domain, the LF and HF areas were compared between the two groups. The LF/HF ratio was a major parameter of interest in understanding the sympathovagal balance during the test.

It was found that in syncope patients the parasympathetic activity did not decrease when the patient was in the tilted position and also that their sympathetic activity did not pick up in response to the tilt as it does in normal subjects. This was clearly evident from the LF/HF analysis

THE ROLE OF SYMPATHOVAGAL IMBALANCE IN SYNCOPE USING HEART RATE VARIABILITY ANALYSIS

by
Jayadeep Krishnan Unni

A Thesis
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Department of Biomedical Engineering

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To God

and

my Parents

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CHAPTER 1

INTRODUCTION

1.1 Objective

The objective of this thesis is to try to unravel the possible role of the autonomic nervous system in the condition called syncope. In syncope the patient loses consciousness when in some physical or emotional stress. The most common cause of this is impaired perfusion of blood to the brain. It is thought that most patients who experience recurrent unexplained syncope do so because of transient, unpredictable episodes of vasovagally or neurally mediated hypotension and bradicardia. Headup tilt-table testing seems to be an effective method for provoking vasovagal episodes in susceptible persons. It is hypothesized that impaired inhibition of parasympathetic tone during stress accompanies the development of neurally mediated syncope in susceptible patients.

This study uses two attractive techniques to analyze the data acquired from a set of 10 subjects, of which 5 are normal and the other 5 had previous episodes of syncope. One is the HRView software package and the other Time Frequency Analysis utilizing Wigner code.

1.2 Back Ground Information

It is becoming increasingly evident that abnormalities in the functioning of the autonomic nervous system result in various cardiovascular disorders, syncope being one of these. Syncope is today one of the common and challenging problems that a physician is confronting. It is estimated that recurrent syncope accounts for 6% of all hospital admissions and 3% of all emergency room visits each year in the United States[1]. This has prompted more research work to uncover the role played by the autonomic nervous system in human physiology. Newer techniques to assess its functioning, in the frequency as well as time domains, are being developed. Most of these techniques utilize the heart rate variability or heart rate variation, which is believed to be influenced by the autonomic system, to study the latter.

1.2.1 Autonomic Nervous System

The autonomic nervous system (ANS) is that portion of the nervous system that controls the visceral functions of the body. This system helps control arterial pressure, gastrointestinal motility and secretion, urinary bladder emptying, sweating, body temperature, and many other activities, some of which are controlled almost entirely and some only partially.

The ANS is activated mainly by centers located in the spinal cord, brain stem and hypothalamus[5]. Portions of the cerebral cortex and especially of the limbic system can transmit impulses to the lower centers, and in this way influence autonomic control.

The autonomic signals are transmitted to the body through two major subdivisions

(1) Sympathetic nervous system

(2) Parasympathetic nervous systems

Sympathetic Nervous System

Figure 1.1 shows the general organization of the sympathetic nervous system.

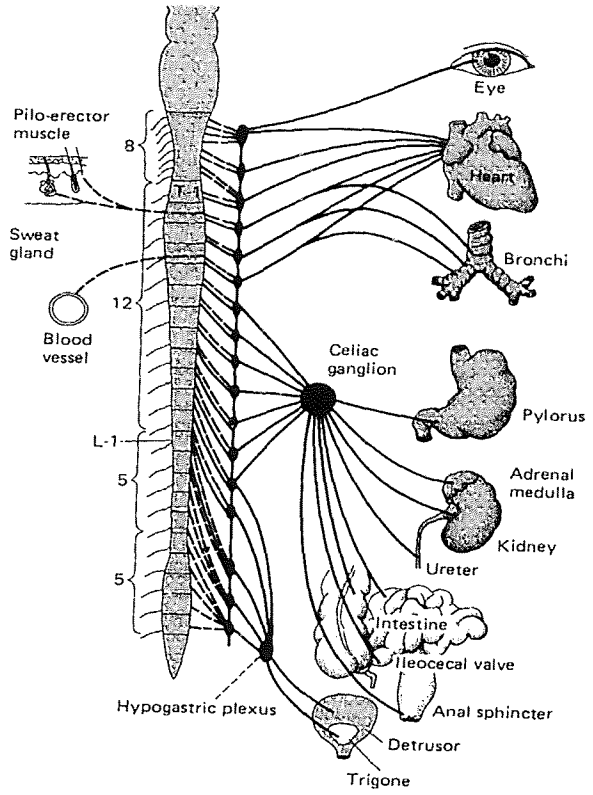

Figure 1.1. The sympathetic nervous system. Dashed lines represent postganglionic fibers. (Basic Neuroscience: Anatomy and Physiology; Guyton, 1987)

The sympathetic nerves originate in the spinal cord between the spinal segments T1 and L2 and pass from here first into the sympathetic chain, then to the tissues and organs that

are stimulated by the sympathetic nerves. Each sympathetic pathway from the cord to the stimulated tissue is composed of two neurons, a preganglionic neuron and a postganglionic neuron. The cell body of the preganglionic neuron lies in the spinal cord and its fiber passes through an anterior root of the cord into a spinal nerve. Immediately after the spinal nerve leaves the spinal column, the preganglionic sympathetic fibers leave the nerve and pass through the white ramus into one of the ganglia of the sympathetic chain. The post ganglionic neuron originates either in one of the sympathetic chain ganglia or in one of the outlying ganglia. From here the post ganglionic fibers travel to their destinations in the various organs. The symapathetic pathways originating in the different segments of the spinal cord are not necessarily distributed to the same part of the body as the spinal nerve fibers from the same segment. The sympathetic fibers from T1 generally pass up the sympathetic chain into the head; from T2 into the neck; T3, T4, T5 and T6 into the thorax; T7, T8, T9, T10 and T11 into the abdomen; and T12, L1 and L2 into the legs.

Parasympathetic Nervous System

Parasympathetic fibers leave the central nervous system through several of the cranial nerves, the second and third sacral spinal nerves and occasionally the first and fourth sacral nerves. About 75% of all parasympathetic nerve fibers are in the vagus nerves, passing to the entire thoracic and abdominal regions of the body. This is the reason parasympathetic activity is also referred to as vagal activity. The vagus nerve supplies parasympathetic nerves to the heart, the lungs, the esophagus, the stomach, the small

intestine, the liver, the gall bladder, the pancreas and the upper portions of the ureters. Parasympathetic fibers in the third nerve flow to the pupillary sphincters and ciliary muscles of the eye. Fibers from the seventh nerve pass to the lacrimal, nasal, and submandibular glands, and fibers from the ninth nerve pass to the parotid gland. The sacral parasympathetic fibers congregate and leave the sacral plexus on each side of the cord and distribute their peripheral fibers to the descending colon, rectum bladder, and lower portions of the ureters. This sacral group of fibers also supplies the external genitalia to control various sexual functions. The parasympathetic nervous system is shown in figure 1.2.

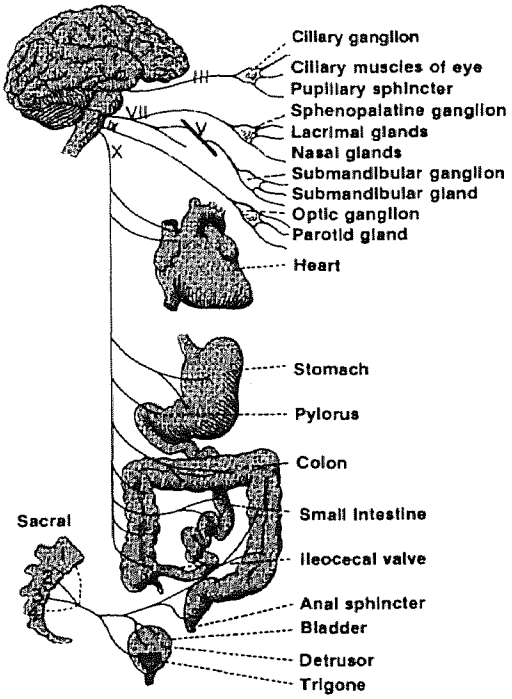

Figure 1.2. The Parasympathetic Nervous System (Basic Neuroscience: Anatomy and Physiology; Guyton 1987)

The sympathetic and parasympathetic nerve endings secrete one of the two synaptic transmitter substances, acetylcholine or norepinephrine. Those fibers that secrete acetylcholine are called cholinergic and those that secrete norepinephrine are called adrenergic, a term derived from adrenalin (British name of epinephrine). In general, the terminal nerve endings of the parasympathetic system secrete acetylcholine and most of the sympathetic nerve endings secrete norepinephrine. These hormones, in turn, act on the different organs to cause the respective parasympathetic and sympathetic effects.

Sympathetic stimulation causes excitatory effects in some organs but inhibitory effects in the others. Likewise, parasympathetic stimulation causes excitation in some organs but inhibition in others. Also, when sympathetic stimulation excites a particular organ, parasympathetic stimulation sometimes inhibits it, illustrating that the two systems usually act reciprocally to each other.

The sympathetic and parasympathetic systems are continually active, and the basal rates of activity are known respectively as sympathetic tone or parasympathetic tone. The value of the "basal" tone is that it allows a single nervous system to increase or decrease the activity of the stimulated organ. The heart is the principal driver or motor of blood in the human body, which is responsible for supplying blood to the different regions of the body, thus maintaining the blood pressure. The following sections attempt to explain the relation between the heart and the autonomic nervous system and the latter's role in influencing the performance of the former.

1.2.2 Conductive System of the Heart

Figure 1.3 shows the specialized excitatory cells and conductive system of the heart that controls the cardiac contractions.

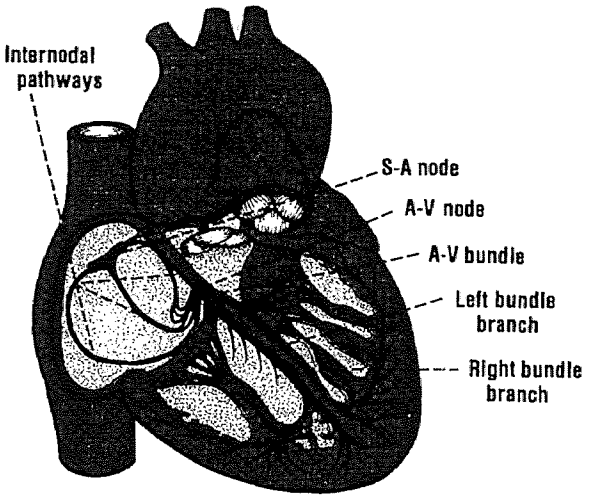

Figure 1.3: The SA node and the Purkinje system of the heart, showing also the AV node, the atrial internodal pathways and the ventricular bundle branches. (Basic Neuroscience: Anatomy and Physiology; Guyton 1987)

The following are the main components that have a role to play in the excitation and conduction mechanism occurring in the heart:

1) *The S-A node*, which is a small, ellipsoid strip of specialized cells, located in the anterosuperior wall of the right atrium. The S-A node is the portion of the heart's specialized conducting system that displays self-excitation property at the highest frequency. The normal rhythmic impulse that paces the heart is generated here.

2) *The internodal pathways* that conduct the impulse from the S-A node to the A-V node

3) *The A-V node*, located in the septal wall of the right atrium, that delays the transmission of the cardiac impulse from the atria into the ventricles. This delay allows time for the atria to empty their contents into the ventricles before ventricular contraction begins, thereby facilitating a coordinated and smooth pumping action.

4) *The A-V bundle*, which conducts the impulse from the atria into the ventricles, and

5) *The left and right bundles of Purkinje fibers*, which conduct the cardiac impulse to all parts of the ventricles.

1.2.3 Autonomic Nervous System and the Heart

The heart is supplied with both sympathetic and parasympathetic nerves as shown in Figure 1.4.

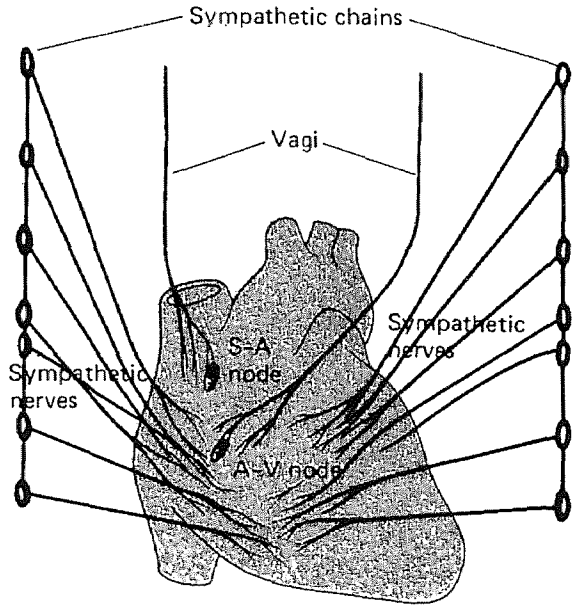

Figure 1.4: The Cardiac nerves. (Basic Neuroscience: Anatomy and Physiology; Guyton 1987)

The parasympathetic nerves are distributed mainly to the S-A and A-V nodes, to a lesser extent to the muscle of the two atria, and even less to the ventricular muscle. The sympathetic nerves, on the other hand, are distributed to all parts of the heart, with a strong representation to the ventricular muscle as well as to all other areas.

Autonomic Nervous System and the Pumping Efficiency of the Heart

The sympathetic and parasympathetic nerves have a strong influence on the pumping efficiency of the heart. The amount of blood pumped by the heart each minute, i.e. the cardiac output can often be increased more than 100% by sympathetic stimulation. It can also be decreased to almost zero by parasympathetic or vagal stimulation.

Effect of Sympathetic Excitation

Strong sympathetic stimulation can increase the heart rate in the humans to as high as 200 to 250 beats/min in young people[6]. Sympathetic stimulation can also increase the force with which the heart muscle contracts, thereby increasing the volume of blood pumped as well as increasing the ejection pressure. Sympathetic stimulation, thus, can often increase the cardiac output as much as twofold to threefold. During vigorous exercise it can even increase sevenfold.

Effect of Vagal Excitation

Strong vagal stimulation of the heart can even stop the heart beat for a few seconds. Strong parasympathetic stimulation, in addition, can decrease the strength of heart contraction by as much as 20 to 30%. The relatively modest decrease in cardiac contractility is primarily because the vagal fibers are distributed mainly to the atria and not much to the ventricles, where the power contraction of the heart occurs.

The effect of the sympathetic or parasympathetic stimulation on the cardiac output can be gauged from the cardiac function curve shown in Figure1.5.

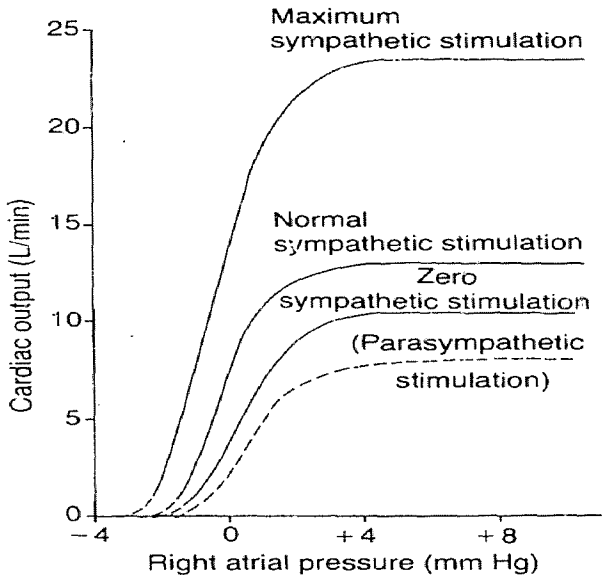

Figure 1.5 Effect on the cardiac output curve of different degrees of sympathetic and parasympathetic stimulation. (Textbook of Medical Physiology; Guyton; Eighth edition)

The curves demonstrate that at any given right atrial pressure, the cardiac output increases with increasing sympathetic stimulation and decreases with increasing

parasympathetic stimulation. But it is to be noted that nerve stimulation affects both the contraction strength of the heart as well as the heart rate, both of which play a role in determining the cardiac output. The following section examines the influence of ANS on heart rhythmicity and conduction.

Effect of ANS on the Heart Rhythmicity and Conduction

The parasympathetic nerves are distributed mainly to the SA node and AV node. Its presence in the muscles of the atria, as mentioned before, is less and to the ventricular muscles even lesser. The sympathetic nerves on the other hand are distributed to all parts of the heart with a strong presence in the ventricular muscles.

Stimulation of the parasympathetic fibers to the heart result in the hormone acetylcholine being released at the vagal endings. This hormone has two major effects on the heart. First, it decreases the rhythm rate of the sinus node, and second it decreases the excitability of the A-V junctional fibers between the atrial musculature and the A-V node, thereby slowing the transmission of the cardiac impulse into the ventricles. This results in slowing down the heart rate.

Stimulation of the sympathetic nerves releases the hormone norepinephrine. This hormone, firstly, increases the rate of sinus nodal discharge. Secondly, it increases the rate of conduction as well as the level of excitability in all portions of the heart. Thirdly, as described earlier, it increases greatly the force of contraction of all the cardiac musculature, both atrial and ventricular. In short, sympathetic stimulation increases both the heart rate and the strength of contraction.

Systemic blood vessels are one of the other organs affected by the ANS. Most blood vessels, especially those of the abdominal viscera and the skin of the limbs, are constricted by sympathetic stimulation. Parasympathetic stimulation generally has no effects on blood vessels but does dilate vessels in certain restricted areas. Since the sympathetic stimulation can increase both, the propulsion by the heart and resistance to flow of the blood through the blood vessels, the arterial pressure can increase greatly in response to sympathetic stimulation. On the other hand, parasympathetic stimulation decreases the pumping by the heart, which in turn lowers the arterial pressure by a moderate amount.

Due to the role played by the ANS in regulating all major organs in the body, diagnostic tests to assess the integrity of the ANS and its modulating effects on the heart have been developed. The basic objectives of such tests is to subject the ANS to a known stressor that activates a reflex and measure the response of the end organ, namely the heart. The heart rate response to such stressors as a change of position from supine to standing, deep breathing, valsalva, and lower body negative pressure has emerged as an index of autonomic control.

1.2.4 Syncope

Metabolism of the brain is extremely dependent on perfusion[2]. In contrast to skeletal muscle, storage of high-energy phosphates in the brain is limited, and energy supply depends largely on the oxidation of glucose extracted from the blood. Consequently, cessation of cerebral flow leads to loss of consciousness within approximately 10seconds.

Syncope[1] refers to loss of consciousness accompanied by muscle weakness and inability to stand upright most commonly due to the impairment (usually temporary) of cerebral perfusion. A typical episode is characterized by hypotension, pallor, and loss of consciousness in a motionless patient with depressed, shallow respirations. This, in turn, may be due to a reduction of systemic vascular resistance, an elevation of cerebrovascular resistance, hypovolemia, a variety of arrhythimias, and any other condition that results in a sudden reduction of cardiac output and therefore in cerebral blood flow.

The medical history of the patient is extremely valuable in the differential diagnosis of syncope. Several daily attacks of loss of consciousness which are abrupt and that occurs over one or two seconds suggest[1]

1) Stokes-Adams attacks, i.e., transient asystole or ventricular fibrillation in the presence of atrioventricular block.
2) Other cardiac arrhythmias
3) Epilepsy

A more gradual onset suggests vassodepressor syncope (i.e. the common faint) or syncope due to hyperventilation or rarely hyperglycemia. Unconsciousness for a few seconds suggests a vassodepressor syncope or syncope secondary to postural hypotension, while a longer period suggests aortic stenosis or hyperventilation. Syncope is most often associated with the upright posture because it is frequently a manifestation of postural hypotension. This type of syncope (vassodepressor) may be precipitated by physical or emotional stress. If postural hypotension is the cause of the syncope, cerebral

blood flow is usually restored promptly, and the consciousness regained when the patient falls or is placed in a horizontal position, and it is characteristically preceded by symptoms of autonomic hyperactivity such as dim vision, giddiness, yawning, sweating and nausea.

Vasovagal Hypotension and Syncope

This type of syncope is the most frequently encountered form. It is often precipitated by the sight of blood, sudden loss of blood, a sudden stressful or painful experience. This is most likely to occur in association with hunger, fatigue, or crowding, particularly in a hot room. Premonitory signs and symptoms are common, including pallor, yawning, sighing, hyperventilation, nausea, diaphoresis, blurred vision, impaired hearing, and a vague feeling of unawareness and sometimes a rapid heart rate. It generally occurs with the patient in the upright position. In this condition, the muscle vasodilator system becomes powerfully activated so that blood flow through the muscles increases severalfold. Intense vagal (parasympathetic) stimulation of the heart also occurs, causing the heart rate to slow markedly. This overall effect is called vasovagal syncope.

The Mechanism of Hypotension

Systemic arterial pressure is dependent on the product of cardiac output and systemic vascular resistance. Cardiac output is the product of heart rate and stroke volume. The autonomic nervous system plays a major role in the maintenance of arterial pressure because it influences both cardiac output and degree of constriction of the vessels of

resistance (arterioles) and capacitance (venules and veins). The afferent limbs of the autonomic reflex arcs that acutely regulate arterial pressure arise in stretch receptors in the aortic arch, the carotid sinuses, ventricles, and atria. Impulses are transmitted along afferent fibers in the glossopharyngeal and vagus nerves to extensive central connections in the medulla.

A reduction of arterial and intraventricular pressure diminishes the stimulation of pressoreceptors, which in turn activates sympathetic outflow and inhibits parasympathetic activity. As a result, vascular smooth muscle in arterioles and veins constricts, while heart rate and myocardial contractility are augmented. In addition, as arterial pressure falls, adrenal medullary secretion of norepinephrine increases, along with the output of antidiuretic hormone (ADH), adrenocorticotrophic hormone (ACTH), renin and aldosterone; all these effects restore the arterial pressure toward normal levels. Thus, the operation of these baroreceptors and a number of humoral systems normally serve to buffer the body from a variety of influences that would otherwise produce marked alterations in arterial pressure.

In a resting supine subject, the level of sympathetic discharge to the vasculature is low. Assumption of the upright posture is accompanied by venous pooling of approximately 700 ml of blood in the legs[4]. Systemic arterial pressure is maintained by venous and arterial constriction mediated by sympathetic stimulation. Even modest reflex changes of this type markedly facilitate maintenance of venous return and stroke volume. The initial gravitational effects associated with upright posture are compensated not only by reflex arteriolar and venous constriction but also by acceleration of heart rate and by

mechanical factors that limit venous pooling in the lower extremities. As a consequence of these compensatory mechanisms, when a normal person assumes the upright posture, there is only a transient, modest decline in systolic arterial blood pressure, generally of 5 to 15 mm Hg. Diastolic pressure tends to rise, and mean arterial pressure remains essentially unchanged; cardiac output and stroke volume decline; and there is a reflex tachycardia and vasoconstriction. In patients with orthostatic (upright posture) hypotension, by definition, the decline in arterial pressure is more profound and persists for a longer period of time than normal. Depending on the severity and duration of the hypotension it may be accompanied by symptoms of impaired cerebral perfusion such as dizziness, presyncope, or syncope.

Pathophysiology of Syncope

Despite intensive study of the phenomenon of syncope, its etiology has not been elucidated definitively. Early in the process, peripheral vasodilation appears to predominate. Blood pressure declines modestly, while blood flow to the limbs, cardiac output and heart rate remain essentially constant. Later the resistance in the skeletal muscular beds is reduced, and skeletal blood flow rises markedly while flow through other vascular beds such as cutaneous, renal and cerebral falls as arterial pressure falls rapidly. Although cardiac output does not usually decline markedly in vasodepressor syncope, the pathophysiological mechanisms must involve more than arteriolar dilation, since in normal individuals the fall in peripheral vascular resistance induced by vasodilation would be compensated for by a reciprocal and compensatory increase in

heart rate and cardiac output to maintain arterial pressure. In patients with vasodepressor syncope, however, cardiac output and heart rate fail to rise, presumably owing to some impairment of venous return. In addition it is reported that there is a diminished rise in plasma renin, and this reduces angiotensin mediated vasoconstriction.

The marked vasodilation in skeletal muscle beds may be mediated, in part, by reflexes triggered by stimulation of intracardiac receptors in a cycle that may involve hypotension due to peripheral vasodilation, reflex-increased sympathetic stimulation of the heart, increased intramyocardial wall tension and stimulation of intracardiac receptors. In many patients venoconstriction occurs and acts to protect the patient, in part, from the two major mechanisms responsible for vasovagal syncope, i.e., bradycardia and arteriolar dilation .

The hyperventilation that generally accompanies vasodepressor syncope results in a decline in arterial pCO2, which in turn produces cerebral vasoconstriction, thereby further impairing cerebral perfusion. Later, heart rate, arterial pressure, central venous pressure and cardiac output decline precipitously.

1.2.5 Heart Rate Variability

Resting heart rate (HR) varies widely in different individuals. During various physiological stresses, particularly exercise, it can increase by even threefold. The average value of heart rate in normal individuals in the resting state is around 72 beats/min. This value varies in the range of 60-90 beats/min in a day. During exercise this value could reach as high as 250 beats/min. By heart rate variability is meant the

continuous changes occurring in the beat to beat interval. Heart Rate Variability is mainly affected by respiration and by blood pressure. Respiration affects the heart rate through the parasympathetic nervous system only.

Heart rate is dependent, among other things, on the physical fitness, mental state and age. In addition, even in the absence of external perturbations, the normal heartbeat is not characterized by clockwork regularity[8-9]. Periodic changes in HR occur at a high frequency secondary to respiration through the day and night. In addition, very slow circadian changes occur that are mediated by neural and hormonal influences and various uncertain influences. Both the basic heart rate and its modulation are primarily determined by alterations in autonomic tone. As was discussed before, increased parasympathetic or vagal tone slows the HR, and increased sympathetic tone increases HR. It has been shown that normal ageing results in a reduction of autonomic control of the heart[11]. Changes in HR (heart rate variability) may be measured by a number of techniques, and since changes in HR are autonomically mediated, these measurements reflect autonomic tone. The techniques utilized for analysis involve both the frequency domain and the time domain.

Power spectral analysis of the heart rate has emerged as a powerful technique for the study of the ANS as it provides a window through which neurocardiac function can be assessed noninvasively. The power spectrum of either HR or BP variability yields three major bands. A low frequency peak that appears within the spectral band ranging from 0.05 Hz to 0.15 Hz is associated with baroreceptor-mediated blood pressure control. A high frequency peak in the range 0.15 to 0.4 Hz is strongly

correlated with respiratory sinus arrhythmia. The major activity in this band is due to respiration and a predominant peak usually occurs at the respiration frequency. A very low frequency peak below 0.05 Hz has been linked with vasomotor control and/or temperature control.

The high frequency band (HF) has been linked with parasympathetic activity; the greater the area under the HF peak, the more active is the parasympathetic system. The low frequency band (LF) is related to both parasympathetic and sympathetic activities. The power spectral data in this study was obtained using the HRView software package which is described below. The following is a typical power spectrum of heart rate.

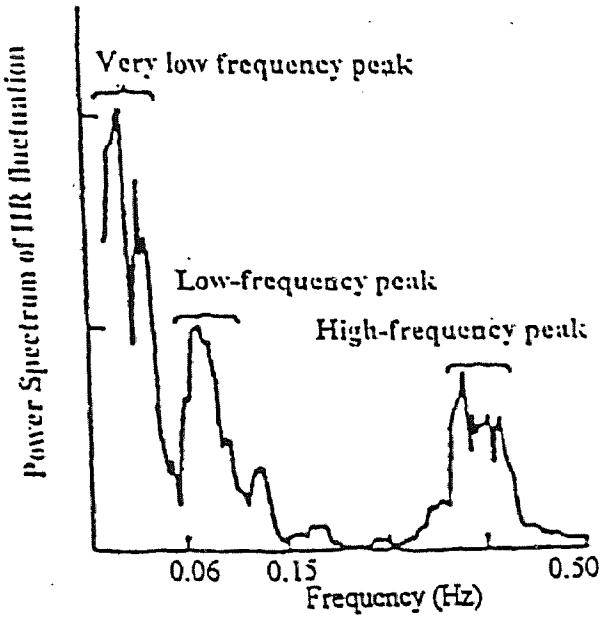

Figure 1.6 A typical power spectrum of heart rate variability (M.Kamath and E.Fallen, "Power spectral analysis of heart variability", *Crit. Rev in Biomed. Eng.*, 1993)

Table 1.1 Frequency range for each peak

Peak	Frequency Range
VLF	<0.05
LF	0.05-0.15
HF	0.15-0.40

1.2.6 HRView Software

This software package from Boston Medical Technologies was employed to acquire the physiological signals from the patient. The details about the software is presented in the Appendix.

HRView provides for the acquisition of up to three signals: Heart rate, Blood Pressure and Respiration. During the process of acquisition itself the R-wave in the ECG is identified and recorded. This can be done by suitably setting the parameters threshold, noise and lockout. An approximate time series which is a plot of the heart rate Vs time, is constructed and presented on the screen.The package provides the facility to go back and edit any improper R-wave detections that were made by the system.

HRView provides numerous options for interactive analysis of the recorded data. It uses accepted and referenced algorithms from the literature. It is also possible to customize algorithms for the user's needs. The following signals can be displayed and printed by HRView after analysis,

- Time Series and Power Spectral Density of

  Heart Rate (R-R interval or rate)

  Respiration

  Systolic and Diastolic blood pressure

  Average blood pressure

  Pulse blood pressure

- Transfer function (magnitude, phase and coherence) between any two spectra.

In addition the following statistics for any five frequency bands can be displayed,

- Total power spectral density in the specified band
- Peak power spectral density in the specified band
- Frequency at which the peak power spectral density occurs in the specified bands

This study utilized the HRView software to perform the frequency domain analysis. The time domain analysis was done using Time Frequency analysis utilizing the Wigner code.

1.2.7 Time Frequency Analysis

The fundamental idea of time-frequency analysis is to mathematically describe the situations where the frequency content of a signal is changing in time[16]. Time and frequency analyses are not good enough because they do not fully describe what is happening. Time analysis is among the standard methodologies used to study the signal x(t) as a function of time. Its main emphasis is on quantifying the energy, $|x(t)|^2\Delta t$, which

is the energy density in the small amount of time Δt, contained in that signal x (t)[17]. This does not yield information regarding the components that constitute the signal. To obtain this information, frequency analysis using the Fourier Transform needs to be performed. The Fourier Transform however tells us the frequencies that existed for the total duration of the signal not the frequency that exist at a particular time. However use of time-frequency analysis shows that one can fully describe the existence of a specific frequency at each instant of time.

Signals are characterized over a joint time-frequency plane in time-frequency signal representations. The combination of time domain and frequency domain analyses presents a more comprehensible and revealing picture of the temporal localization of a signal spectrum. One of the prominent methods of time-frequency analysis is short-time Fourier Transform (STFT). The basic idea of the STFT is that, to know what frequencies exist at a particular time, a small piece of the signal around that time is taken and Fourier analyzed. Since the time interval is short compared to the whole signal this process is called taking the short time Fourier transform. How large the time interval should be is decided by the choice of the window function. The window function serves to emphasize the times around the fixed time of interest 't'. The window function is multiplied with the signal and its Fourier transform taken. A different spectrum is obtained for each particular time as this process is continued. The totality of these spectra makes a time-frequency distribution.

If the window function is represented as $h(\tau-t)$, which emphasizes the times around the fixed time of interest t, then the Fourier transform of the piece of signal is given by[18],

$$S_t(f) = \int_{t-\Delta}^{t+\Delta} s(\tau)\, h(\tau-t)\, e^{-j2\pi f\tau} d\tau \qquad (1.1)$$

For each particular time as this process is continued, a different spectrum is obtained. The totality of these spectra makes a time-frequency distribution. The energy density of the signal at the fixed time t is,

$$\rho(t,f) = \left| \int_{t-\Delta}^{t+\Delta} s(\tau)\, h(\tau-t)\, e^{-j2\pi f\tau} d\tau \right|^2 \qquad (1.2)$$

where $\rho(t,f)$ is called the spectrogram.

The main motive of the time frequency analysis is to devise or to construct a distribution for time-frequency. Time-frequency distributions of signals map a one-dimensional function of time, x(t), into a two dimensional function of time and frequency, $\rho(t,f)$. The STFT was the first tool devised for analyzing a signal in the time-frequency domain. The advantage of the STFT is that it has an easily understandable interpretation and is positive everywhere. This is a desirable property when it is required to interpret the spectrogram as the signal energy distribution in the time-frequency plane. One of the shortcomings of the STFT is the trade off between time and frequency resolution. Take two extreme choices of the analysis window h(t). Consider in the first case a perfect time resolution where the analysis window is a dirac impulse,

$$h(t) = \rho(t) \Rightarrow \rho_{STFT}(t,f) = s(t)\, e^{-j2\pi ft} \qquad (1.3)$$

where s(t) and $\rho_{STFT}(t,f)$ are the signal and short time Fourier transform of the signal

respectively. In this case the STFT reduces to the signal, preserving all time variations of the signal but not providing any frequency resolution. In the second case when perfect frequency resolution is obtained with the all constant window h(t) = 1, then,

$$H(f) = \rho(f) \Rightarrow \rho_{STFT}(t,f) = S(f) \qquad (1.4)$$

where H(f) and S(f) are Fourier transforms of window and signal respectively. Here the STFT reduces to the Fourier transform and does not provide any time resolution. But the Uncertainty principle places a severe restriction on the widths of h(t) and H(f). According to this principle, BT >= (1/4π) where, 'B' is the bandwidth in Hertz and 'T' is the bandwidth in seconds. Thus both h(t) and H(f) cannot be made arbitrarily narrow.

As an alternative to overcome the shortcomings of the STFT the Wigner Distribution (WD) is employed. It possesses very high resolution in both time and frequency. The applicability of the WD for the analysis of blood pressure, respiratory and beat to beat fluctuations were assessed by Novak, 1993[15]. The instantaneous changes of spectral content of cardiovascular and respiratory signals, which characterize the autonomic nervous system responses, was shown to be followed well by the WD. Two of the main drawbacks of the WD are that it is not necessarily non-negative, and its bilinearity produces cross terms or interference between two signal components located at different regions in the time-frequency plane.

The equation for the Wigner distribution is,

$$\rho_w(t,f) = \int_{-\infty}^{\infty} e^{-j2\pi f\tau} s^*(t-1/2\tau)s(t+1/2\tau)d\tau \qquad (1.5)$$

where $s(t) = A(t)e^{j\phi(t)}$ represents the original time signal. A(t) is the amplitude and $\phi(t)$ is

the phase. τ is the time around the fixed time t. If the input signal consists of two group of signals with distinct characteristics, for example

$$\text{if } s(t) = s_0(t) + s_1(t) \tag{1.6}$$

then its WD can be expressed in terms of its components as

$$W_{s0+s1}(t,\omega) = W_{s0}(t,\omega) + W_{s1}(t,\omega) + W_{s0s1}(t,\omega) \tag{1.7}$$

where

$$W_{s0s1} = \int_{-\infty}^{\infty} e^{-j2\pi f\tau}[s_0(t+\tau/2)\, s_1^{*}(t-\tau/2) + s_0^{*}(t-\tau/2)\, s_1(t+\tau/2)]d\tau \tag{1.8}$$

is the WD of the cross terms of $s_0(t)$ and $s_1(t)$ which would cause an additional cross spectrum in the time-frequency representation. Figure 1.7 shows the Wigner distribution of a signal composed of the sum of two infinite duration sine waves. The oscillating term in the middle of the two frequencies is the cross term.

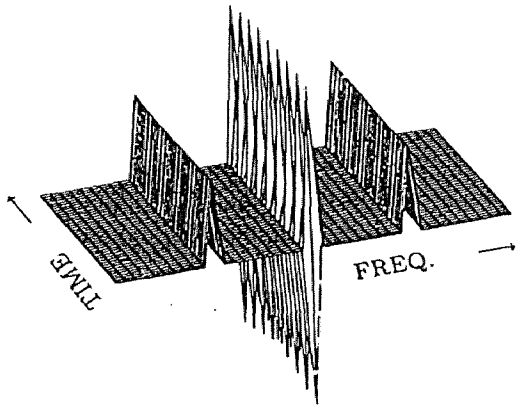

Figure 1.7 The Wigner distribution of the sum of two infinite duration sine waves. The oscillating middle term in the middle of the two frequencies is the cross term. (Amin, M. et al. "Methods and Applications for the Time-Frequency Analysis" Conference notes, University of Michigan 1993)

The smoothed pseudo WD was developed to overcome these drawbacks, which utilizes a smoothing window function in both the time and frequency domain. The complex mathematics operations involved in the analyses are not discussed.

1.2.8 Tilt Table Testing

Tilt table testing has emerged as an important test for heart rate variability studies. The test involves tilting the patient to an inclined position, usually 60 to 80^0, for a particular duration of time. When rising from the supine to standing position, reflex mechanisms are activated which prevent a fall in blood pressure. This procedure influences the functioning of the sympathetic and parasympathetic systems which is reflected as the change in heart rate. Thus, a response to a physiological stress, such as standing, is an attractive method for evaluating the autonomic nervous system. It has been demonstrated that the power under the low frequency peak significantly increases on standing due to the baroreceptor mediated efferent sympathetic outflow to the heart, and the power under the HF peak decreases in the standing position to reflect decreased parasympathetic activity.

Head-up tilt table testing is thought of as a valuable method for reproducibly provoking syncope in susceptible persons[14]. A strong orthostatic stimulus (prolonged upright posture) promotes maximal venous pooling

CHAPTER 2

TEST DETAILS

2.1 Overview

This study, approved by the Institutional Review Board at the UMDNJ and the Human Subjects Committee at NJIT, was aimed at uncovering the possible role of the autonomic nervous system in the condition called syncope using heart rate variability in subjects referred for tilt table testing. Data collection was done from subjects who were referred for tilt table test. All the subjects who took part in the study signed an informal consent form. These subjects had history of hypertension, syncope or other cardiac ailments. Data was also collected from subjects who were normal, i.e., without any kind of serious ailments. Since the number of syncope patients who came in for treatment during the

Table 2.1 Subject Distribution ('Positive for tilt' implies that the patient started experiencing symptoms of syncope while in the tilted state)

Syncope		Normal
Positive for tilt	Negative for tilt	
Female (39 years)	Female (73 years)	Female (35 years)
Male (36 years)	Female (78 years)	Female (48 years)
	Male (64 years)	Male (37 years)
		Male (28 years)

period of this study were not many, the data set of the number of syncope subjects for this study was limited. For the purpose of this study data of subjects who had previous history of syncope and who were normal were grouped. Except for one syncope patient (female aged 78) all the other subjects considered for the study were without hypertension. This study consisted of the following three phases.

1) Enrolling subjects who were willing, non-pregnant and fitted in the category of either syncope or normal. The study was based on two groups of patients, one with a history of syncope and the other normal, i.e., with no past incidence of syncope.

2) Subjecting the patient to tilt table testing while blood pressure, respiration and continuous ECG monitoring and recording is done. The test protocol was as follows,
    - The subject in the supine position for about 10 to 15 minutes.
    - The subject tilted to 80^0 for a maximum of 45 minutes or till the onset of syncope.
    - The subject brought back to supine state and made to remain so for 10 to 15 minutes.

3) The acquired signals (ECG, blood pressure and respiration) were analyzed using HRView software from Boston Medical Technologies (details about HRView in Appendix). Time Frequency Analysis technique utilizing the Wigner code is also

employed to analyze the same data so that more information regarding the role of sympathetic and parasympathetic nervous system in the syncope condition can be obtained.

2.2 Instrumentation

The study involved the use of the following equipment,

- An automatic tilt table (700 series Boston Gear).
- An ECG Monitor (Hewlett & Packard, HP 78532B)
- A blood pressure monitor (Finapres 2300)
- A respiration belt (RSP-01 respiration pneumogram amplifier from Boston Medical Technologies)
- An HRView Basic kit (HRView software, PC-LPM-16 data acquisition card, and HRV-A1 BNC Adapter).
- IBM Compatible computer- Pentium 100Mhz- 16MB RAM.

2.3 Signal Acquisition

The ECG signal acquisition was done using diagnostic ECG adhesive silver/silver chloride surface electrodes (Medtronics, Haverhill, MA). A monitor terminal HP 78532B was used to monitor the ECG signal. This signal was fed to the PC-LPM- 16 data acquisition board.

Blood pressure data was collected in real time using a Finapres Model 2300 Blood Pressure Monitor (Ohmeda, Englewood CO). The Finapres monitor provides continuous measurement of finger arterial blood pressure displaying the pressure waveform, digital readout of systolic, diastolic and mean pressure as well as pulse rate. The dynamic response required to accurately measure the arterial waveform is provided by the cuff's pressure servo valve and the pressure transducer located in the subject interface module at the end of the subject interface cable. A finger cuff containing photoelectronic components for measuring blood volume and a bladder for applying pressure to the finger, is wrapped around the subject's finger and connected to the subject interface module.

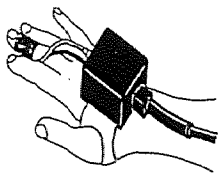

Figure 2.1 Finapres equipment connected to the subject's hand

The pressure readings obtained were not utilized for the analysis, as they were not accurate absolute measurements. But combined with the manual method of pressure measurement, it gave valuable indication of the trend of the pressure changes during the test.

The Respiration signal was acquired using the RSP-01 respiration pneumogram amplifier. An elastic belt containing a strain gauge sensor was placed around the subject's chest or abdomen to measure the expansion, which is a measure of the respiratory rate.

2.4 Data Analysis

The data collected in this study was analyzed using two prominent methods. The first involved the use of the HRView package and the other utilized the Time Frequency Analysis (TFA) using the Wigner code. Though both the techniques used the same data, collected using the HRView acquisition module, the data that was fed to the Wigner code required a slight change in the format. Of the two columns of data that were fed to the code, the first was the inter-beat interval multiplied by the sampling frequency and the second column was the time value. The sampling frequency used by HRView acquisition module is 1000. The analysis could be divided into the frequency domain and time domain. Frequency domain analysis mainly utilized the HRView, while for the time domain analysis the TFA seemed to provide more revealing and comprehensible results. HRView provides quantitative values of the LF and HF components over selected durations of time; but it does not give the nature of change in the LF and HF components over time during the test period. The following synopsis lists a brief description of the features of the analysis techniques used. For details refer to the appendix.

The HRVANLYS, which is the prominent module of the HRView system is one of the tools utilized for analysis. It can provide the following displays/records.

Time Domain

- Heart rate (R-R interval or rate)
- Respiration
- Systolic blood pressure
- Diastolic blood pressure
- Average blood pressure
- Pulse blood pressure

Frequency Domain

- Power Spectral Density

  Heart rate variability

  Respiration

  Systolic blood pressure

  Diastolic blood pressure

  Average blood pressure

  Pulse blood pressure

- Transfer function between any two spectra.
- Total Power Spectral Density in the specified band.
- Peak Power spectral density in the specified band.
- Frequency at which the peak power spectral density occurs in the specified band.

TFA, which is the other tool utilized, gives information about the roles played by the LF and HF components during the test as a function of time. It provides the following information after analysis from the collected data.

- LF activity as a function of time during the test period.
- HF activity as a function of time during the test period.
- LF/HF ratio as a function of time.
- The power spectrum of the test duration.

The following are the parameters analyzed for the study of the two groups of subjects (syncope and normal).

1) The heart rate variation as a function of time during the tilt test
2) The low frequency and high frequency activity as a function of time during the test.
3) A measure of the sympathetic-parasympathetic balance obtained by the ratio of the low frequency to the high frequency as a function of time during the duration of the test.
4) A quantitative measure of the low frequency and high frequency activity for a fixed duration of time in the supine state (before tilt) and the tilted or erect state.
5) The change in the activity of the low frequency and high frequency components between the supine and erect state.

CHAPTER 3

RESULTS

The following chapter presents the outcomes of the test performed on the subjects. The lack of enough number of subjects in the study, with the syncope condition is acknowledged. This was because the number of subjects referred for the tilt table test and who had previous history of syncope, were limited. A total of 5 subjects with previous history of syncope were studied. Of these, 2 subjects were positive for the tilt test. Positive implies that in the tilted position the subjects experienced the syncope condition. But before they slipped into the unconscious state they were brought back to the supine position.

Table 3.1 Subject Classification

SYNCOPE		NORMAL
Tilt Test Positive	Tilt Test Negative	
2	3	5

Of the two subjects who were positive to the tilt test one was a female, aged 39 and the other male, aged 36. The others who are grouped under syncope are one male,

aged 64, and two females aged 73 and 78. Except for the female aged 78 who was hypertensive, all the others were normotensives. Comparisons based on age, sex or race is not performed due to the small number of appropriate subjects.

The following sections show the results of the analysis, of the parameters mentioned in the previous chapter, for each of the subjects.

1) Heart Rate Variation

The following figures show the heart rate variation of the subjects as a function of time for the duration of the test. The heart rate values were obtained from the HRView acquired ECG signal which was subsequently processed by the analysis module of the HRView.

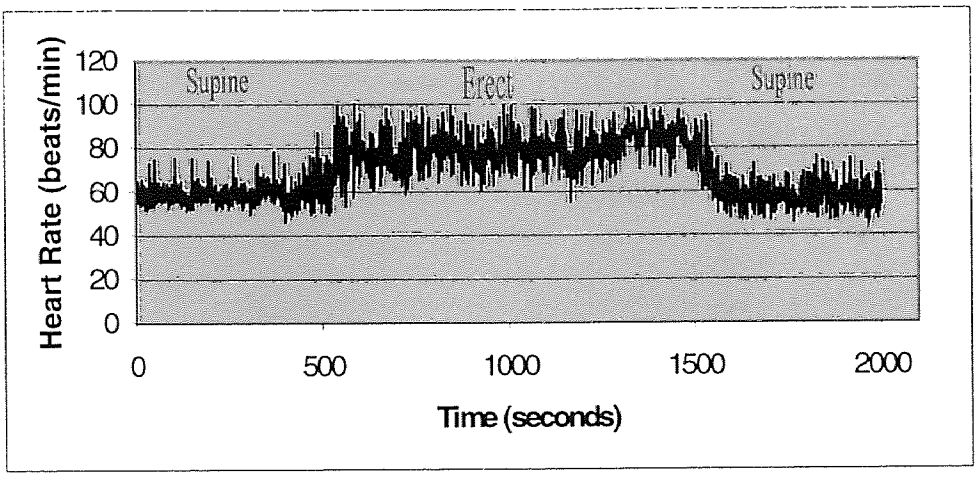

Figure 3.1 Heart Rate variation of 37 year old male (Normal)

It can be observed from Figure 3.1 that when the subject was tilted to the erect position at around 550 sec, the heart rate increased. It remained elevated for the duration the subject was in the tilted position. When he was brought back to the supine position the heart rate fell back to the initial levels.

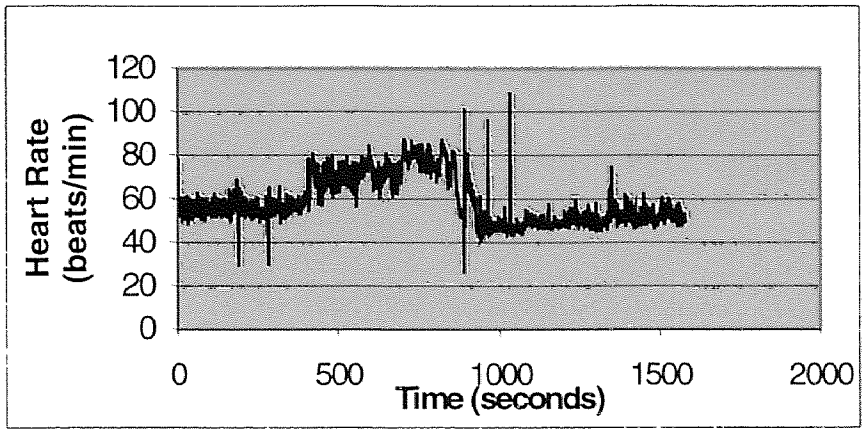

Figure 3.2 Heart Rate variation of 36-year-old male (syncope, positive for tilt test)

In the subject whose heart variation is shown in Figure 3.2, the tilt started at 400s. As the test progressed the subject started experiencing symptoms of syncope like giddiness, sweating etc (at around 870s). The heart rate decreased sharply during this time. Bradycardia i.e. slower heart rate than normal is, as was discussed in section 1.2.4, one of the symptoms of syncope.

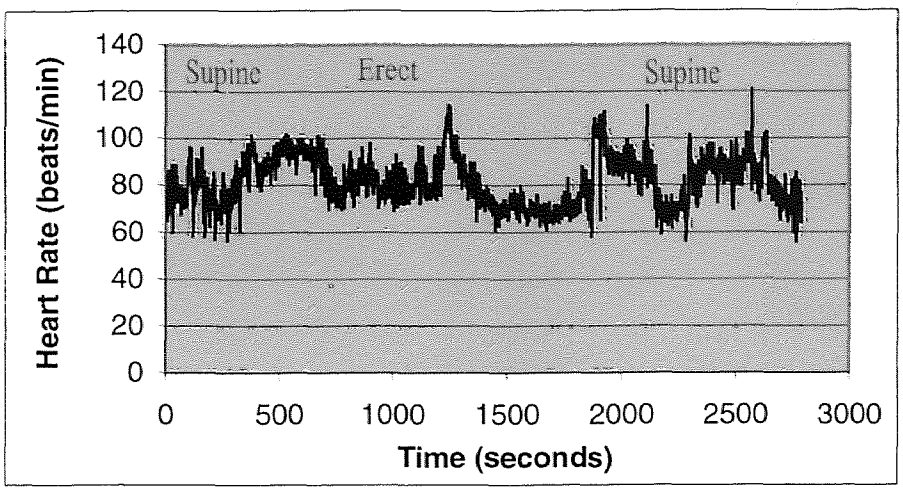

Figure 3.3 Heart Rate variation of 39-year-old female (Syncope, positive for tilt table test)

The heart rate variation shown in Figure 3.3 of the other subject who was positive for the tilt test, again indicates the drop in heart rate as she started experiencing syncope symptoms (at around 1310s).

The following figure (Figure 3.4) is the heart rate variation of the subject who had previous history of syncope but was not positive to the tilt test.

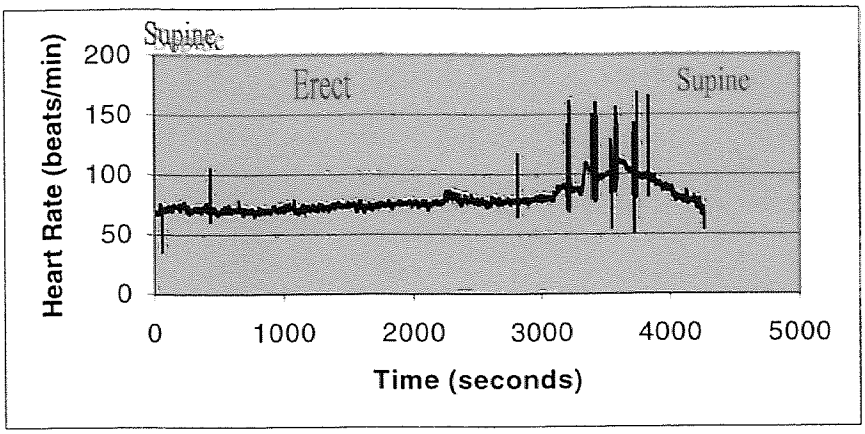

Figure 3.4 Heart Rate variation of female aged 73 (syncope, negative for tilt test)

Figure 3.4 indicates that there is no instance of bradycardia in the heart rate plot. The subject did not experience any of the symptoms characteristic of syncope during the course of the test. The same observation was made in the rest of the syncope subjects, who were negative to the tilt table test. The plot cannot be said to be normal also, as there is no increase in heart rate while the subject is in the erect position. But the notable observation here is that though the patient had previous history of syncope the plot does not show the occurrence of bradycardia which was characteristic of the syncope patients, who were positive to tilt.

2) High Frequency (Parasympathetic) Activity during the Test

The following figures give the high frequency (HF) activity as a function of time for the duration of the test, as obtained by the TFA method. This could give an indication of the role the parasympathetic nervous system plays in syncope. Figure 3.5 shows the HF (parasympathetic) activity of a normal subject during the test.

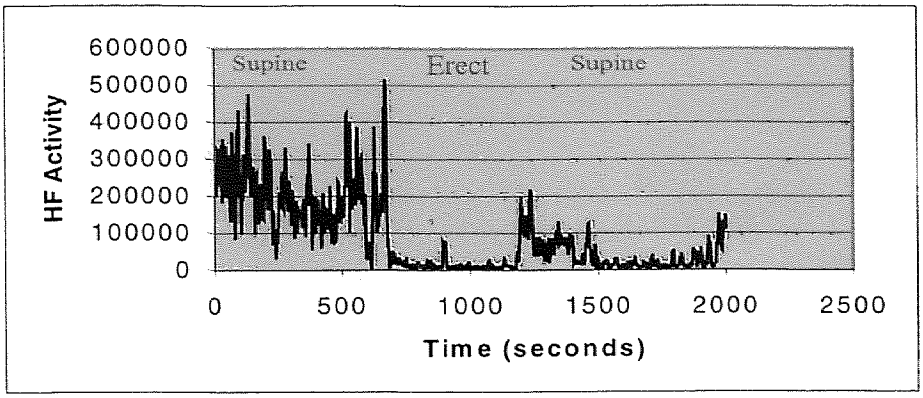

Figure 3.5 Parasympathetic Activity in 35-year-old female (Normal)

After the subject was elevated to the erect position at 678s, there was a definite fall in the parasympathetic activity. This decreased level of the HF activity continues till the subject is brought back to the supine state (at around 1180s). The parasympathetic activity again increases after the subject is back in the supine resting state.

Consider the following figure (Figure 3.6), showing the HF activity of the 39-year-old female with syncope.

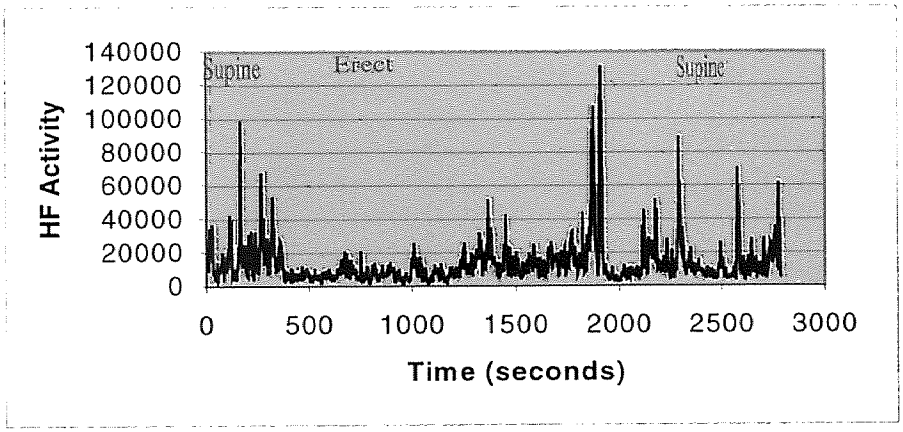

Figure 3.6 Parasympathetic activity in female aged 39 (Syncope, Positive for tilt test)

The parasympathetic activity decreases after the tilt starts, which is as expected. But as time progresses the parasympathetic activity begins increasing. When the subject started slipping into syncope the HF activity increased to levels that were observed prior to the tilt.

The following (Fig 3.7) is the parasympathetic activity of the 64-year-old male syncope patient. Here again, after the patient was brought to the erect position, the parasympathetic activity increases to levels as was before the tilt (i.e. when in supine state), which means the parasympathetic activity did not diminish as was expected, in the erect position.

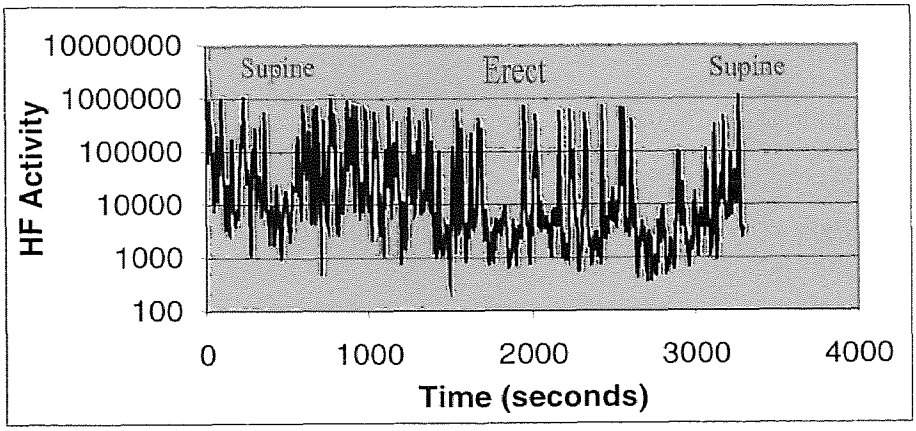

Figure 3.7 Parasympathetic activity in 64 year old male (Syncope, Negative for tilt test)

3) Low Frequency Activity (Parasympathetic + Sympathetic) during the Test

The low frequency activity (0.04 to 0.15 Hz), as was mentioned before, reflects the activity of both the sympathetic and parasympathetic nervous systems. The following section compares the LF activity occurring in the syncope group and the normal group as a function of time.

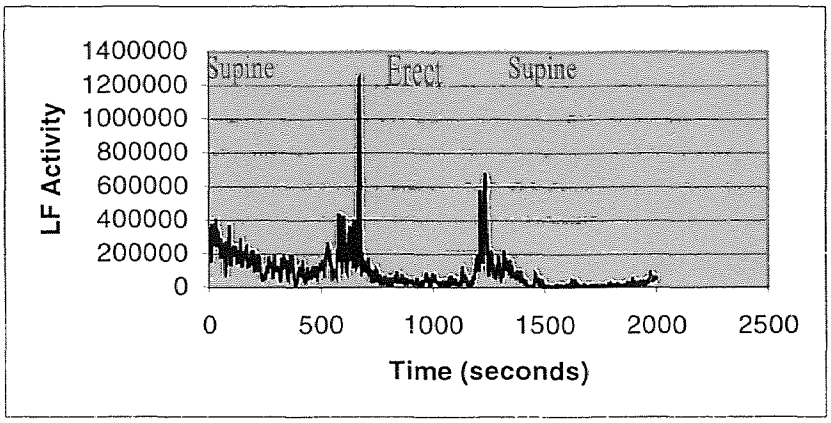

Figure 3.8 LF Activity (Parasymp + Symp) in 35 year old female (Normal)

From Figure 3.8, after the normal subject was brought to erect position at 678s, there is an increase in LF activity (Sympathetic + Parasympathetic). This activity goes on to decrease indicating that the patient is starting to stabilize or relax in the erect state. When the patient is brought back to the supine state there is an increase in the LF activity possibly due to the spurt in activity of the parasympathetic component trying to restore the balance affected by the postural tilt. This reflects the normal response to upright posture. The LF activity in the syncope patient with positive tilt response is as shown in fig 3.9.

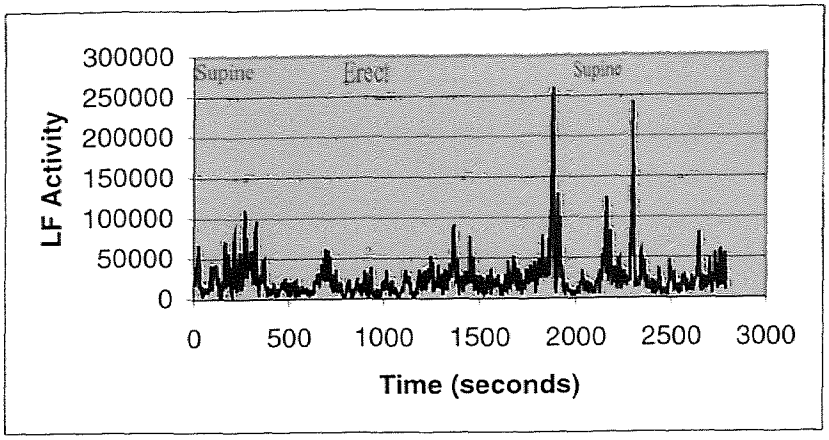

Figure 3.9 LF Activity (Parasymp + Symp) in 39 year old female (Syncope, Positive for tilt table test)

Unlike the normal subject considered in figure3.8, the LF activity in this subject after the start of the tilt (at 307s) is not very pronounced. This could imply that the sympathetic system is not as active as it should be when the patient is brought to the tilted position from supine.

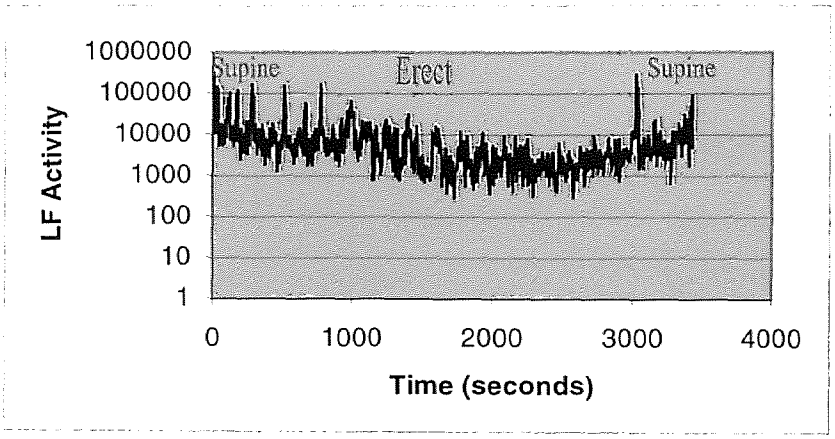

Figure 3.10: LF Activity (Parasymp + Symp) in 78 year old female (Syncope, Negative for tilt table test)

Figure 3.10 shows the LF activity of a 78-year-old female with syncope. She was also hypertensive. The patient was tilted at around 1000 sec. The LF activity is decreased after the start of the tilt.

4) LF/HF Ratio: A Measure of the Sympatho-Vagal Balance

The ratio LF/HF gives an estimate of the relative dominance of the sympathetic and parasympathetic systems. A high ratio may imply a higher sympathetic activity and a lower ratio, an increased parasympathetic activity. The trend of the LF/HF ratio for a subject during the test procedure could give more information regarding the relative activity of the two systems rather than quoting a value for the ratio as high or low. Though a clear change in the ratio could not be found in all subjects, a few of them did show a shift in the value of the ratios when they where brought to tilt from supine and then back.

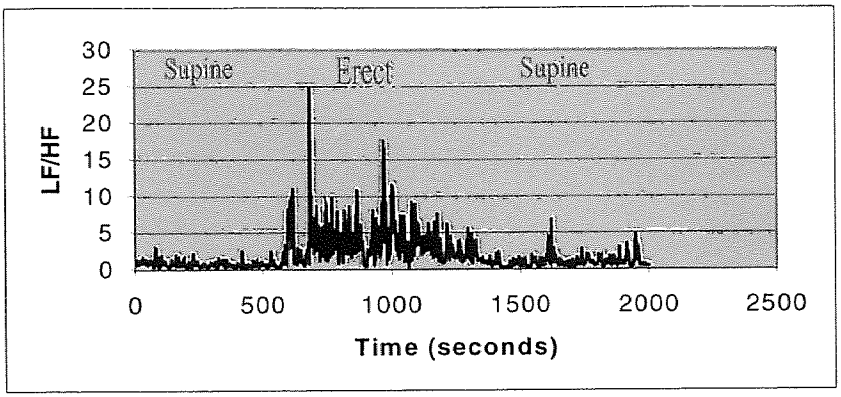

Figure 3.11 LF/HF in 35 year old female (Normal)

Figure 3.11 shows the plot of the LF/HF ratio of the normal 35 years old female subject. From the time the patient was brought to the erect position (at 678s) the ratio is increased and it remains so till the end of the tilt (at 1193s). This implies an increased sympathetic activity or decreased parasympathetic activity or both during the time the subject is in the tilted position. This is as expected.

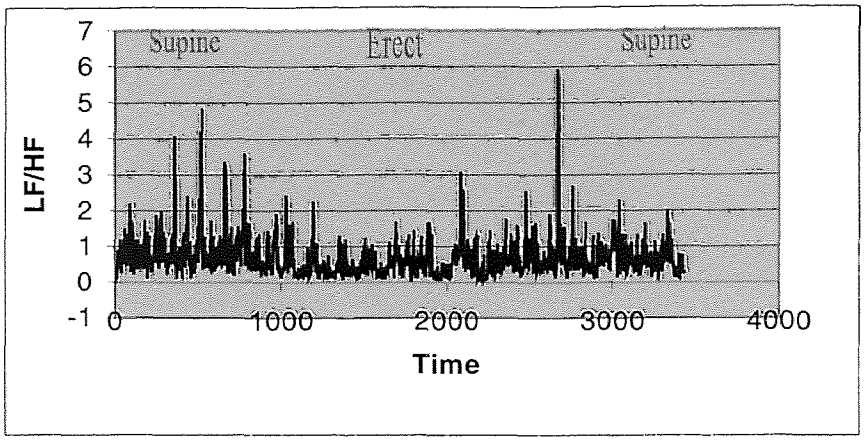

Figure 3.12 LF/HF in 78-year-old female (Syncope, Negative for tilt table test)

The plot shown above (fig 3.12) is that of 78 years old female syncope patient who was negative to the tilt test. After the patient is brought to the erect position (at 940s) there is a visible dip in the ratio during the tilted period. This could imply a lower sympathetic activity and a higher parasympathetic activity when the subject is in the erect position, which is not a normal response.

The following figure (fig 3.13) is the plot of the ratio in the case of 36 years old male syncope patient who was positive to the tilt test.

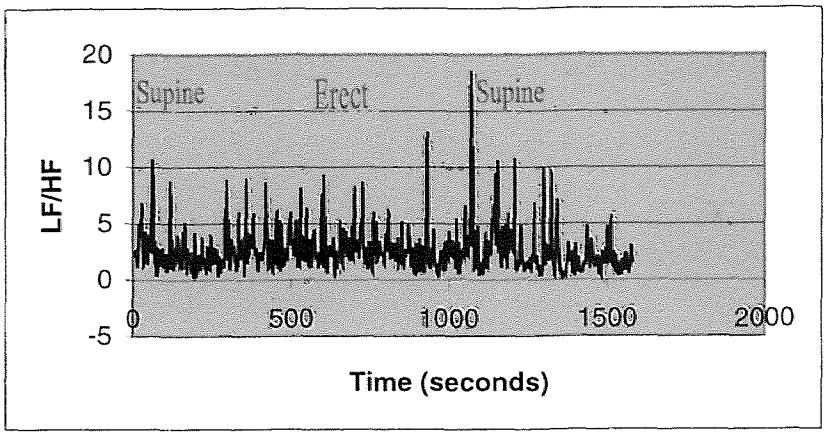

Figure 3.13 LF/HF in 36-year-old male (Syncope, Positive for tilt table test)

During the course of the tilt that started at 400s there is no noticeable change in the ratio even after the subject was tilted. Considering the fact that an increase in the sympathetic activity is expected in the tilted state, the above plot is not normal. It could indicate that either the parasympathetic activity did not decrease as it usually does when the subject is tilted, or the sympathetic activity did not increase or both. This observation was made in all the syncope patients irrespective of whether they were positive or negative for the tilt test.

5) Quantitative Measure of the LF/HF Change

The following section quantifies the LF/HF ratio when the subject is in the supine position and when in the tilted state. These results were obtained using HRView analysis. 5-minute periods before the tilt and after the tilt are considered for normal and syncope group of subjects. The following charts in fig 3.14 display the LF/HF ratio in normals. In the plots, 'after tilt' implies the period in which the subject is in the tilted position.

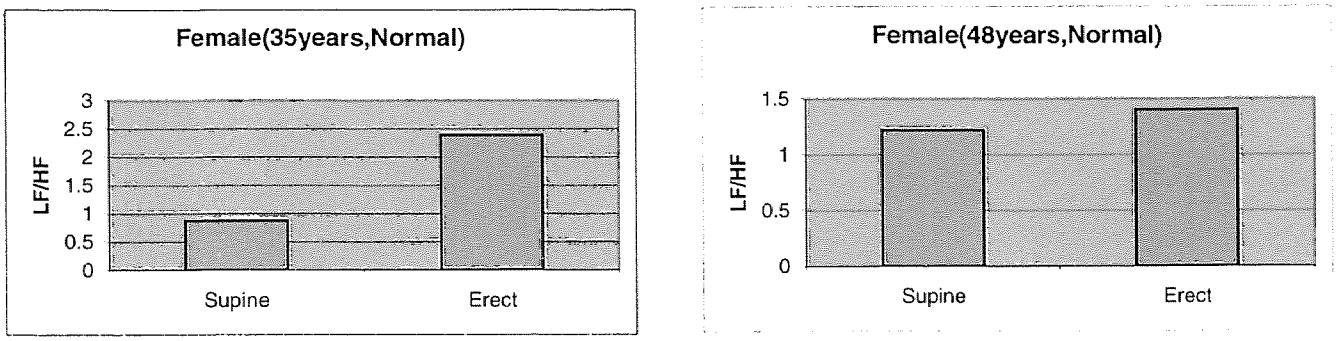

Figure 3.14 : The ratio of LF/HF before and after tilt in normals.(Obtained from HRView Analysis)

In the above plots as expected the LF/HF ratio in the erect position is higher than that in supine state. This is in agreement with the accepted fact that in the erect state the sympathetic activity increases and the parasympathetic activity decreases. As discussed before, it is this that enables the heart to increase the cardiac output thereby restoring the supply of blood to the upper regions of the body.

The following charts (figure 3.15) will bring out the effect of tilt on the sympatho-vagal balance in subjects with syncope.

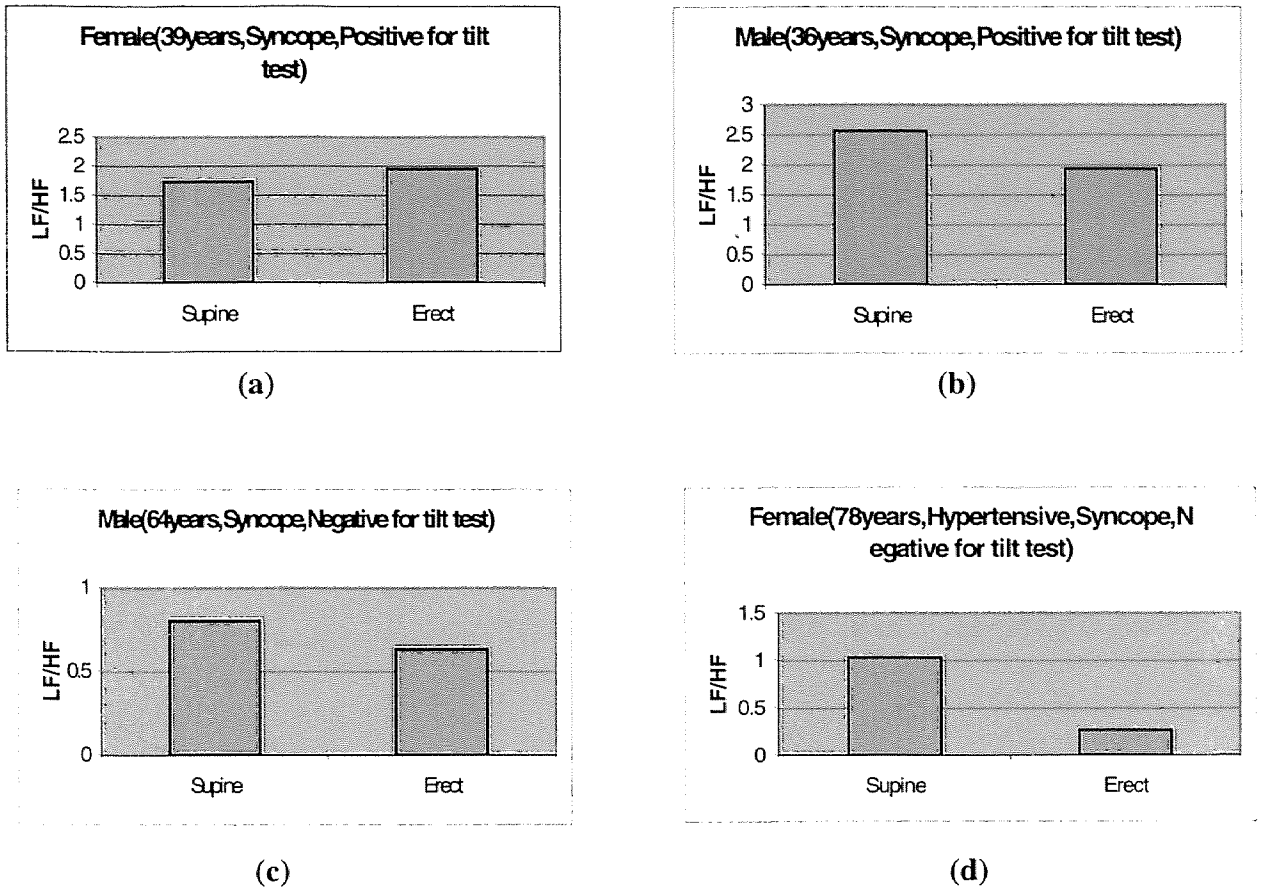

Figure 3.15 The LF/HF ratio before and after tilt in syncope patients (Obtained from HRView analysis)

The charts in Fig 3.15 illustrate a major difference when compared to the charts of the normal subjects. Except for the 39-year-old female subject (fig 3.15a), in all others there is a decrease in the LF/HF ratio in the erect state compared to that in the supine

position. This suggests a confirmation of the hypothesis that either the parasympathetic activity is not decreasing or sympathetic activity is not increasing or both, when the subject is brought to the erect position from the supine state.

4.3 Discussion

Although the pathophysiological mechanisms that lead to vasovagally mediated syncope have not been completely understood, a clearer picture is gradually emerging. The autonomic response to tilt table testing in normal subjects is well studied and documented. The results obtained during this study on the set of normal subjects are in agreement with these.

In the normal subjects, an upright posture result is gravity-mediated displacement of blood from the head and thorax. This displacement causes a gradual decrease in venous return, resulting in decreased filling of the ventricles and decreased stretch of the mechanoreceptors located there. The mechanoreceptors decrease their output of afferent impulses to the brainstem and thereby promote a reflex increase in sympathetic stimulation. Thus the normal subject has an increase in heart rate and an increase in diastolic pressure. As was shown in the previous section the upright posture elicits an increased LF and decreased HF activity. Also, there is an increased sympatho-vagal balance as indicated by the increased LF/HF ratio. Thus increased sympathetic tone and withdrawal of the parasympathetic tone characterize the normal response to upright posture.

Patients with syncope have a markedly different autonomic response to head-up tilt. This is evident from the various parameters that were analyzed during this study. The heart rate variability obtained in the time domain clearly indicated a drop in the heart rate just before the onset of syncope. But this instance of bradycardia was observed only in subjects, who were positive to the tilt table test. Subjects that were negative to the tilt test did not show any noticeable change in the rate. This is counterintuitive, because we expect the heart rate to increase in normals in response to upright posture. A possible explanation for this observation could be that the heart rate drop starts just before the patient slips into syncope and in the above mentioned syncope subjects, since they did not experience any of the symptoms that characterize syncope during the period of the test, the heart rate drop was also absent.

LF and HF activity during the course of the test was analyzed using both the HRView Analysis package and Time Frequency Analysis method utilizing the Wigner code. HF activity (Parasympathetic) which in normals diminishes in the erect position , did not do so in syncope patients. The LF activity which, on the other hand increases in normals in the erect position, decreased in syncope patients. This was a major finding in this study. This supports the hypothesis that impaired inhibition of parasympathetic tone during the upright tilt accompanies the development of syncope in susceptible patients. This is clearly seen in Fig 3.6 and Fig 3.7, where the HF activity is plotted as a function of time. The HF activity instead of dropping, remained at the same level as it was when the subjects were supine. This implies that the parasympathetic tone did not decrease while the subject was in the erect state.

The LF activity on the other hand showed a decrease in syncope patients in the erect state. This is evident from figures 3.9 and 3.10. This is in sharp contrast to what happens for normal patients. There is sufficient reason to suggest that in this LF decrease it is the sympathetic component that is actually decreasing, because during the same period the parasympathetic component does not decrease but maintains its activity as shown in the HF plot. These observations were made using the Time frequency analysis method.

The above result could also be obtained by the power spectral analysis using HRView. The results of the power spectral analysis of the different frequency bands enabled the computation of the LF and HF power. These power values were plotted as LF/HF ratio in figures 3.14 and 3.15. They indicate a clear HF (parasympathetic) dominance over the LF. This conclusion is reached because the LF/HF ratio is decreased in syncope patients while they are in the erect position. This could happen only if either the parasympathetic activity increases or if the sympathetic activity decreases or both. But the time domain analysis has revealed that the parasympathetic activity continues at the level before the tilt. This will lead to the conclusion that the sympathetic division in syncope patients is not responding well enough to the body's demands when they are brought to the upright position, resulting in the sensation of giddiness and syncope. It is suggested that in syncope patients, a sudden drop in venous return occurs as a result of excessive venous pooling. This causes vigorous contractions in the cardiac muscles, that activate a number of cardiac mechanoreceptors. This in turn produces a paroxysmal surge in neural input to the brain stem that somehow mimics the conditions seen in

hypertension and thus provokes an apparently paradoxical reflex bradycardia and peripheral vasodilation. As a result, both hypotension and bradycardia become profound enough to cause cerebral hypoxia and loss of consciousness.

CHAPTER 4

CONCLUSION AND FUTURE STUDIES

For any conclusion to be drawn on a study involving any system, especially the human system, it requires a adequate number of subjects. Even then a conclusive result cannot be arrived at because the human body is so amazingly complex. In that respect this study is inconclusive. But within the parameters of these limitations a reasonable hypothesis could be suggested from this study.

The frequency domain and the time domain analysis done using the HRView analysis package and the Time frequency Analysis respectively, arrived at a noteworthy conclusion. Unlike in normal subjects, where the upright position elicits a higher sympathetic response to meet the deficiency in blood supply to the upper regions of the body, in syncope patients it is found that the sympathetic system fails to respond adequately. In addition the parasympathetic activity, which normally is decreased owing to the body trying to meet the stressful situation, tends to be sustained at the value in the supine position before tilt, in the case of syncope patients. The combined effect of these two behaviors leads to hypotension and bradycardia, and subsequently to the loss of consciousness due to the reduced blood perfusion to the brain when the patient assumes upright position. As soon as the subject is returned to the supine state consciousness is restored.

Whereas the Time frequency analysis enabled the tracking of both the LF and HF activity with respect to time during the various stages of the test, the HRView enabled a frequency analysis of the contribution of the LF and HF components before and after the tilt. This in turn reflected the role of the sympathetic and parasympathetic system in syncope.

This study did not group the subjects based on age and sex. Though research in this field has so far not indicated the role of these two factors in syncope, it would be very interesting to study it because heart rate variability, which is the core of this study, is dependent on age and sex. The other important parameter, which had to be omitted though reluctantly, was the continuous blood pressure measurement. This was because pressure data was not collected from all the subjects owing to the inconvenience experienced by some due to the pressure monitoring device The pressure changes occurring during the test could be valuable data for analysis. As mentioned before, just before the onset of syncope the patient goes through a hypotensive phase. The magnitude and duration of this would make an interesting variable to study.

4.1 Comparison of the HRView and TFA Results

An attempt is made here to compare the results obtained using the two techniques from the data of two of the syncope patients. We expect the two results to be similar albeit the analysis in HRView is done in the frequency domain and TFA analysis by a combination of both the frequency and time domains. This will enable a reasonable validation of the

results and also would provide information regarding the relative accuracy of the two techniques, in analyzing the data.

Fig 4.1 shows the LF activity observed in the male syncope patient aged 36. The graphs show the plots obtained using both HRView and TFA technique. The amplitude scales for the two plots were different. Thus they were brought within the same range. The trend in the activity is of more concern than the magnitudes of the two plots. The power values were taken over a fixed window length of 171 seconds for both the techniques. This window length corresponds to the length of data HRView takes to calculate 512 point FFT. From the figure (Fig 4.1), the drop in the low frequency activity after the patient is brought to the erect position, at around 550s, can be seen. This is reflected in both the plots.

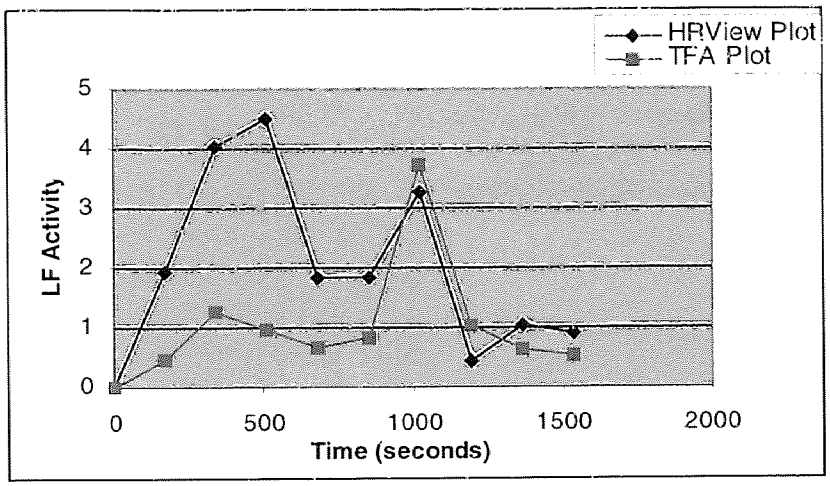

Figure 4.1 The LF activity as obtained using HRView and TFA Analysis of 36 year old male syncope patient).

The HF activity of the 36-year-old male syncope patient is as shown in figure 4.2. The activity obtained using both the techniques follow a similar trend. This suggests that both the techniques do arrive at similar conclusions on the changes occurring in the ANS activity during the course of the test.

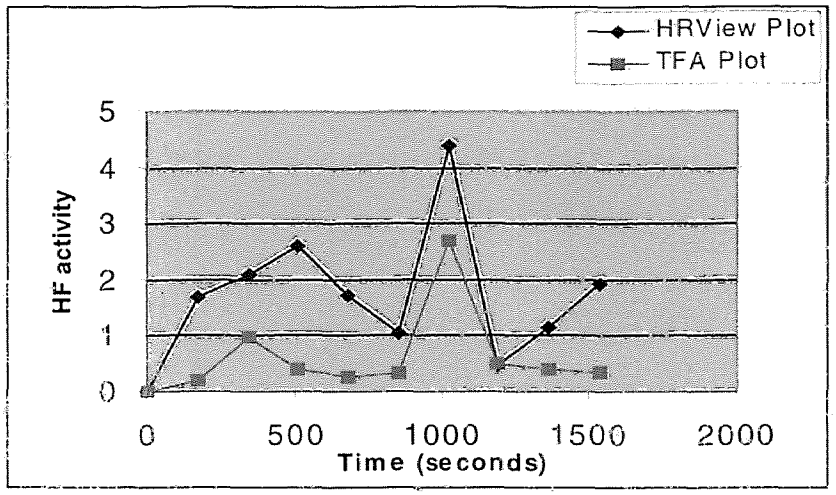

Figure 4.2 HF activity as obtained using the HRView and TFA Analysis of 36-year-old male syncope patient

Figures 4.3 and 4.4 shows the LF and HF activity respectively in 39-year-old female syncope patient. They again indicate the similar trend followed by the HF activity as analyzed by the two techniques.

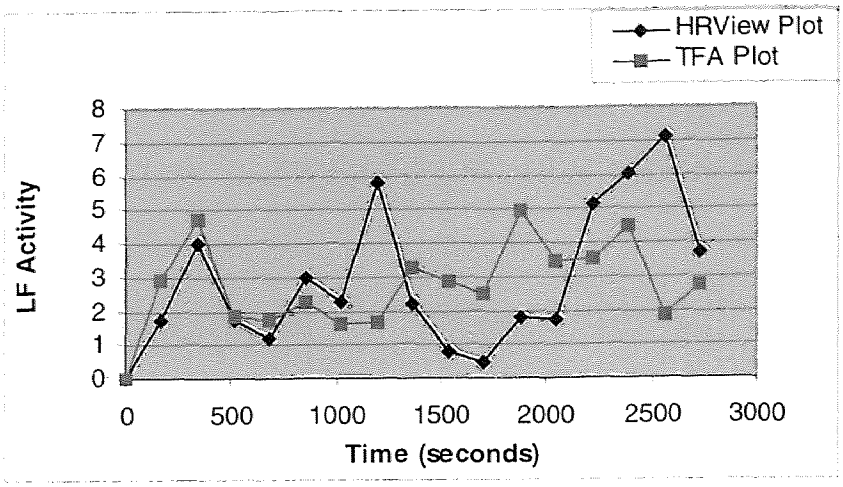

Figure 4.3 LF activity as obtained using the two techniques in 39-year-old female syncope patient.

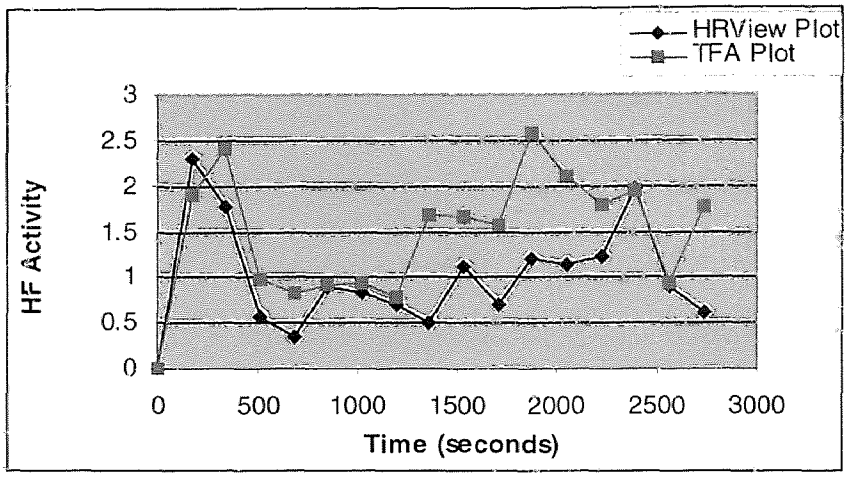

Figure 4.4 HF activity as obtained using HRView and TFA technique in 39 year old female syncope patient

The above plots thus not only support the conclusions arrived at earlier for the different patients in the study but also corroborates to an extent the validity of the two techniques.

APPENDIX

HRVIEW

HRView software, from Boston Medical Technologies, was utilized to acquire, edit and then analyze the ECG, respiration and pressure data collected from the patient. HRView provides for the acquisition, calibration, and analysis of up to three signals:

- Heart rate
- Blood pressure (Systolic and Diastolic)
- Respiration

HRView includes facilities for performing and analyzing standard time-domain autonomic function tests, including valsalva, metronomic deep breathing, standing 30/15, and other standard tests that analyze heart rate and blood pressure response to various challenges. Also included in this is the ability to interface to the industry-standard Dinamap 8100 to obtain and record cuff blood-pressure readings during testing.

Processed data (time series and spectral data) are directly available, without the need for the user to perform multiple, time-consuming, intermediate steps. HRView is interactive-during all steps, data are available for viewing. As parameters are changed (e.g., window length, spectral algorithm), the effects are observed immediately.

HRView runs under Microsoft Windows 3.1 and Windows 95, state-of-the-art, multitasking graphical operating system. HRview is an open system. All file format

descriptions are available. Source code is primarily written using National Instrument's LabVIEW, with many of the specialized HRV and math routines, such as R-wave detection, systolic detection, diastolic detection, and so forth, written in C. LabView source code is optionally available so that researchers can modify the system to their unique research needs.

The HRView system includes four major applications, which are,

1) HRVCAL, used for equipment calibration.
2) HRVACQ, used for acquiring HRV data.
3) HRVEDIT, used for editing HRV after acquisition.
4) HRVANALYS, used for analysing the acquired and edited HRVdata.

HRVCAL (Calibration)

The calibration procedure establishes the correspondence between the physical phenomena and the voltage output by the measuring device.

HRVACQ (Acquisition)

HRVACQ, the HRView acquisition application, displays and records the ECG, respiration and blood pressure signals. The first steps of data analysis are performed in real time. For each heart beat,

- The time of the ECG R-wave is identified and recorded. An approximate time series which is a plot of the heart rate Vs time, is constructed and presented on the screen.

- Systolic and diastolic blood pressure times and amplitudes are also identified and recorded. Time series are also constructed for these values.

ECG R-wave Detection:

The following parameters should be set to ensure proper R-wave detection:

- *Threshold*: This parameter sets the minimum expected R wave amplitude (above baseline). This prevents the false detection due to noise. The value of this parameter is adjusted according to the ECG amplitude of the patient.
- *Lock out*: After the systole is detected this amount of time must pass before a second systole can be detected. It is helpful for ensuring that T waves do not falsely trigger R wave detection. Its setting is dependant on the ECG being recorded from the patient. This is usually in the range of 300-500ms.
- *Noise*: This parameter determines the sensitivity of detection. Noise immunity is higher when this value is set higher. But high values also increases the chance of missing an R wave. A setting of 1/3 of R wave amplitude is generally employed.

Lowpass Filter Cut-off Setting:

Each signal can be low pass filtered (fifth-ordered, Butterworth response) prior to display and recording. A 40 Hz cut-off was employed for the filter as it is low enough to reject the 60 Hz noise, but high enough to preserve the signal characteristics.

Time-Series Frequency:

The TS Frequency parameter sets the frequency, in Hertz, at which the heart rate, systolic, and diastolic time series are generated. It is also the frequency at which the respiration signal is decimated. This frequency was set at 3 Hz for the study.

Run Length:

This control at the bottom of the application screen has two options for determining the length of recording to disk:

- the recording may be for a fixed period of time, say 600 seconds; after this period elapses, recording will automatically end.
- the recording may be run indefinitely (continuous setting) until manually stopped.

The continuous mode of recording was used for this study as the patient went through the test till the onset of syncope.

HRVEDIT (Editing)

User can rapidly scan data, view the R wave, systolic, and diastolic picks. If an improper pick is found, a section of the waveform may be zoomed (magnified on screen) and detection moved, added or deleted precisely using a cursor.

HRVANALYS (Analysis)

This is the heart of HRView. It provides numerous options for interactive data analysis. The user has maximum flexibility to set parameters, such as length of acquisition time,

length of analysis windows, filter cut-off frequencies, and spectral resolution. HRView uses accepted and referenced algorithms from the literature. It is possible to optionally customize algorithms to his or her needs. The HRVANALYS enable the display, printing and writing of the following signals:

- Time Series and Power Spectral Density of

  Heart Rate (R-R interval or rate)

  Respiration

  Systolic and Diastolic blood pressure

  Average blood pressure

  Pulse blood pressure

- Transfer function (magnitude, phase and coherence) between any two spectra.

In addition the following statistics for any five frequency bands of any or transfer function can be displayed,

- Total power spectral density in the specified band
- Peak power spectral density in the specified band
- Frequency at which the peak power spectral density occurs in the specified bands.

HRVANALYS does not analyse raw data files. It works with files that have been processed according to the Berger Algorithm[7], which have .tsd as an extension.

Spectral Adjusts:

From the spectral adjusts control panel various parameters can be adjusted to calculate the spectra and transfer function. Among the various important settings are,

Berger Interval:

Interval in seconds, between time series samples generated by the Berger algorithm[8], = (1/TS Frequency), the TS Frequency being set at acquisition time. TS frequency was set at 3 Hz for the entire study.

Nyquist Frequency:

This is the theoretical maximum frequency that can be analysed = 1/ 2(TS Frequency).

 # Pts FFT:

This sets the number of points in the time series used to develop each spectrum. This setting has several consequences,

- It determines the length of the time series used to generate each spectrum
- It determine the spectral resolution *Delta F*= Nyquist Frequency/ Points in spectra/2)

Spectra are generally calculated using 2^n points. Using 2^n points enables the use of FFT algorithm. If a custom number of points not equal to 2^n is selected, HRView must revert to DFT (Discrete Fourier Transform) which is a significantly slower algorithm.

The length and start times of windows of data to be analyzed are completely user-definable. Linear splining may be applied to heart rate data to compensate for events such

as ectopic beats and other artifact. Reports can be printed reports for spectral analysis and autonomic assessment. Data (graphs and statistics) are saved in a format that can be read by spreadsheet, database, and statistical software. This format permits the researcher to perform rapid (even automatic) custom analyses of data. New-Parameters and statistics for autonomic function tests are automatically computed. However, the user may examine all graphs, detections, and calculated values, overriding automatically obtained results where necessary.

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