國立交通大學

分子醫學與生物工程研究所

碩 士 論 文

台灣二尖瓣膜脫垂病人與正常族群心率變異性之性別與姿勢差異

Gender Differences and Posture change of Heart Rate Variability between Taiwanese Symptomatic Mitral Valve Prolapse Syndrome and Normal

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摘　要

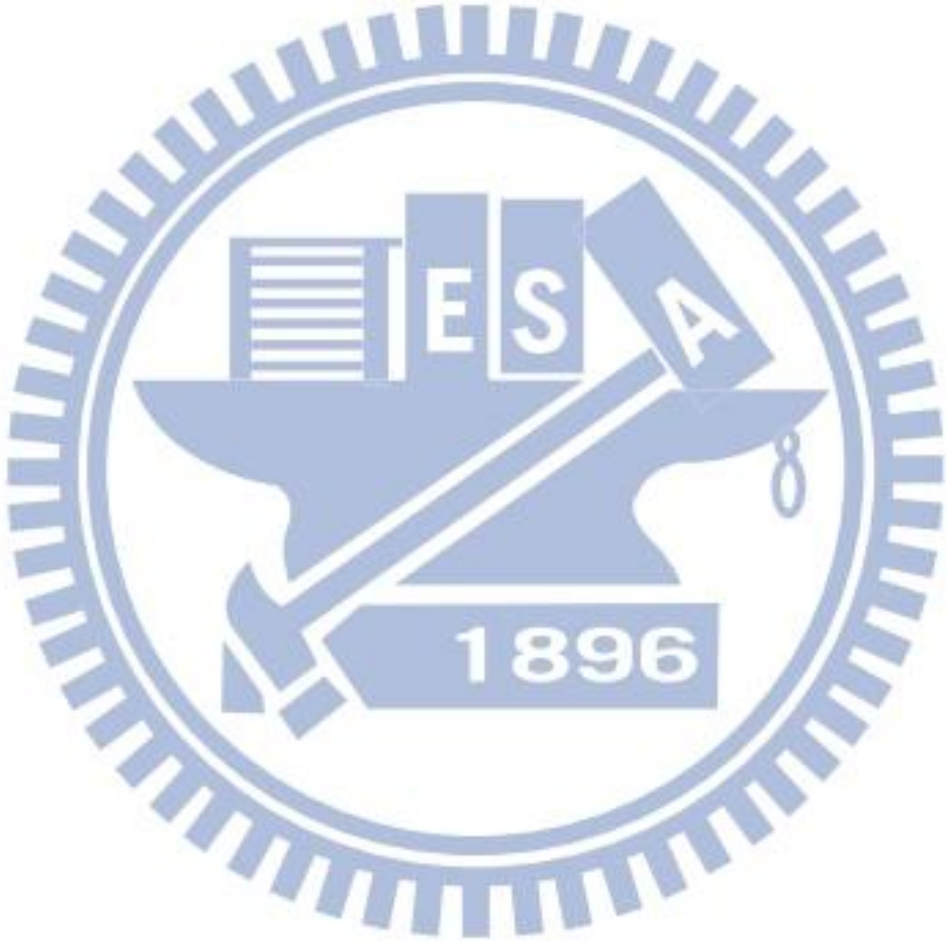
心率變異性(Heart rate variability, HRV)分析是一種測量連續心跳中，心搏與心搏之間變化程度的方法。過去二十年間對於自主神經系統(autonomic nervous system, ANS)和心血管疾病致死率的關係性有顯著增長的認識，包括心因性的猝死。HRV 的研究對於預測心肌梗塞、心臟瓣膜疾病、或是先天性心臟病的病人之長期存活率是有用的，HRV 的降低是危險因子，能預測致死與心律不整的併發。短時 HRV 能作為急性心肌梗塞預後的最初檢視。在標準的心電圖(electrocardiogram, ECG)中，兩個 R 波波峰之間稱為 R-R 間隔(R-R interval)，由連續的 R-R 間隔所構成的連續間距則定稱為 N-N 間隔(N-N interval)，心率變異性就是測量 N-N 間隔的變異性。正常的心跳會因為受到自主神經系統的調控而產生波動，因此當變異消失或明顯降低時，會產生沒有波動而完全規律的心率，這種心率被認為是心臟自主神經調節系統異常的表現。HRV 的目的在於測量心率快慢差異的規律，提供非侵入性的方式來測量自主神經系統的平衡性。本研究的目地是評估在台灣二尖瓣膜脫垂的病人及正常族群中，性別與姿勢的差異是否影響 HRV 數值。

參與實驗的二尖瓣膜脫垂病人總數 118 人，其中含 7 位男性及 111 位女性，在 2008 年十一月至 2013 年一月期間，於台北醫學大學附屬醫院經超音波診斷確

診為二尖瓣膜脫垂之病人；另有 148 名交通大學學生及新竹地區居民，其中含 54 位男性及 94 位女性，經過 12 導程心電圖檢查及確定無其他疾病者參加實驗，所有參加者皆為自願參與且簽下實驗同意書。本實驗所使用的機器為台灣達楷生醫科技所研發的 DailyCare BioMedical's ReadMyHeart® ，使用單導程 ECG (設定於第二導程)來做訊號的收集及分析，之後以人工編輯方式來檢查所收集到之訊號是否出現 R 波上的錯誤。實驗過程中，受測者需變化躺姿、坐姿、站姿三種姿勢以測量 HRV，而每一種 HRV 測量前受測者皆須休息五分鐘。所有的實驗皆於白天時間(早上九點至下午四點)進行，以避免日夜差異對自主神經系統造成影響。於時域分析上採用 SDNN、RMSSD 及 NN50 三項數值，頻域分析採用 TP、LF、HF 及 LF/HF 比值。

由實驗可得知，二尖瓣膜脫垂病人與正常人相比，於時域分析中只有 SDNN 在三種姿勢中都具有統計上的差異，且此結果與頻域分析中的 TP 差異情況相符。頻域分析中，除了躺姿測量不具有差異外，其餘姿勢的數值全部都顯示了病人與正常人在自主神經調控上的差異。在時域分析中，無論是二尖瓣膜脫垂病人還是正常人，男女之間在躺姿測量的 RMSSD 和 NN50 具有顯著差異。頻域分析中，除了與 SDNN 相符的 TP 以外，其餘在各姿勢測量中都具有男女差異，顯示男性與女性在自主神經調控上的不同。而各姿勢之間的差異，在正常族群中的時域分析都顯示姿勢上具有差異，除了坐姿和躺姿相比時僅 RMSSD 具有統計上差異。頻域分析也都具有意義，除了坐姿和躺姿相比時 TP 不具有顯著差異。而在頻域統計方面，全部都顯示具有姿勢上的差異，除了在坐姿和站姿的比較中，時域分析的 SDNN 和頻域分析的 TP 都不具有姿勢改變造成的顯著差異。從結果來看，我們可以得知 SDNN 數值相當於 TP，此結果與往昔發表的著作相符合。正常台灣人在性別上的 HRV 差異此前也由我們實驗室做過發表，此實驗更加一步推論在二尖瓣膜脫垂的病人測量 HRV 也應做性別的區分。未來我們應更多收集二尖瓣膜脫垂的男性病人以求完整這份研究。儘管時域分析或許不適合用來評估

二尖瓣膜脫垂病人的狀況，但頻域分析佐以姿勢變化的測量或許在評估二尖瓣膜脫垂的風險上將會是有效的工具。



Gender Differences and Posture change of Heart Rate Variability between Taiwanese Symptomatic Mitral Valve Prolapse Syndrome and Normal.

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Abstract

Heart rate variability (HRV) is the temporal variation between sequences of consecutive heartbeats. On a standard electrocardiogram (ECG), the duration between two adjacent R wave peaks is termed the R-R interval. The resulting period between adjacent QRS complexes resulting from sinus node depolarization is termed the N-N (normal-normal) interval, and HRV is the measurement of the variability of the N-N intervals. The last two decades have witnessed the recognition of a significant relationship between the autonomic nervous system and cardiovascular mortality, including sudden cardiac death. HRV investigation has its use in the prediction of long-term survival in patients who had suffered from congestive myocardial infarction, or had valvular or congenital heart disease. Depressed HRV is a predictor of mortality and arrhythmic complications independent of other recognized risk factors. HRV

assessed from short-term recordings may be used for initial screening of all survivors of an acute myocardial infarction. The purpose is to evaluate the gender and postural effects in HRV parameters between symptomatic MVPS patients and an apparently healthy population.

A total of 118 patients, 7 males and 111 females, who had been echocardiographically diagnosed as having MVPS at Taipei Medical University Hospital cardiology clinic from November 2008 to January 2013, and 148 healthy people (54 males and 94 females) with normal 12-lead ECG without previous history of medical disease from National Chiao-Tung University and residents in Hsinchu were recruited for the study. All subjects had sign an informed consent and agree to take part in the research.

A locally developed Taiwanese machine (DailyCare BioMedical'sReadMyHeart®) was used to record the HRV. One lead ECG (modified lead Ⅱ) was used for signals collection and analysis. The QRS complexes were detected and labelled automatically. The results of the automatic analysis were reviewed subsequently, and any errors in R-wave detection and QRS labelled were then edited manually. The subjects were asked to rest 5 minutes before each HRV recording (Lying, sitting and standing.) All the recordings were taken during the daytime (between 9:00 AM to 4:00 PM) to avoid

the diurnal influence of the autonomic difference.

For time-domain HRV measures, the mean N-N intervals and the standard deviation of N-N intervals during 5 minutes (SDNN) were then calculated. For frequency-domain HRV parameters analysis, spectral power was quantified by fast Fourier transformation and autoregressive method for the following frequency bands: 0.15-0.4 Hz (high frequency), 0.04-0.15 Hz (low frequency). Time domain parameters used were SDNN, RMSSD and NN50. Frequency domain parameters selected were TP, LF, HF and LF/HF. These parameters were defined in accordance with the 1996 ACC/AHA/ESC consensus. To make sure our data is normal distribution, Kolmogorov–Smirnov test was used at first. And then Paired Student t test was used to characterize differences in HRV variables. All HRV variables were expressed as mean ± SD. All statistical analyses were performed using Microsoft Excel 2007. A P value <0.05 was determined as statistically significant.

In Time domain only SDNN between MVPS and Normal was statistically significantly different in all positions, and so as Frequency domain's Total Power. In Frequency domain all Parameters were shown to have significant differences except in lying position. Between male and female in time domain, there were statistically

differences of RMSSD and NN50 at lying both in MVPS and Normal. In frequency domain, all parameters were statistically significantly different in all postures both in MVPS and normal except total power. For postural changes, in normal group that time domain parameters only RMSSD was statistically differences between lying and sitting, but in other postural compared, all parameters were significantly different. And it is the same as in frequency domain parameters, only TP in lying compared with sitting posture had no difference. In MVPS group, the result of time domain parameters and frequency domain were the same as in normal group, except in sitting compared with standing posture. SDNN of time domain, and TP of frequency domain had no significant difference.

From the results, we concluded that the SDNN is compatible with Total Power as demonstrated in the previous reports. Gender specific HRV variation had been reported in our previous study in normal Taiwanese. It is further strengthened the digenetic criteria for HRV should be gender specific in MVPS as well. Moreover, more male MVPS cases should be recruited for further clarification of this issue. Although time domain parameters might not be of use for the evaluation MVPS, frequency domain with postural changes might be a useful tool in MVPS diagnosis risk stratification.

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口試委員王雲銘老師及曲在雯老師在百忙中撥冗替學生進行口試，並給予意見及指導，使學生論文能更趨完備，在此也表達對兩位老師的謝意。

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Chapter 1 Introduction

1.1 Background

Heart rate variability (HRV) is a physiological phenomenon of temporal variation between sequences of consecutive heartbeats. On a standard electrocardiogram (ECG), the duration between two adjacent R wave peaks is termed the R-R interval. The resulting period between adjacent QRS complexes resulting from normal sinus node depolarization is termed the N-N (normal-normal) interval, and HRV is the measurement of the variability of the N-N intervals.

It has witnessed the recognition of a significant relationship between the autonomic nervous system and cardiovascular mortality, including sudden cardiac death [1]. HRV investigation has its use in the prediction of long-term survival in patients who had suffered from congestive heart failure, myocardial infarction, valvular or congenital heart disease. Depressed HRV is a predictor of mortality and arrhythmic complications independent of other recognized risk factors. HRV assessed from short-term recordings may be used for initial screening of all survivors of an acute

myocardial infarction. Short Term (5-15 min) HRV can provide non-invasive information on the autonomic nervous system(ANS), and was reported to be remarkably similar to 24 hour-HRV in post-MI patients and can provide predictive information for ventricular arrhythmias and sudden cardiac death (SCD). Physiological and pathological process may influence N-N interval variability[24]. Under normal conditions, the balance between sympathetic and parasympathetic activity favours the latter. Physiological influences may modulate central and peripheral receptor activity and hence the autonomic nervous activities.

In normal subjects, a variable heart rate is the normal physiological state. It has been suggested that the healthy heart has a long range 'memory' which prevents it from developing extremes of pace, and that this facility erodes as age or disease develops[5]. A loss of variability is associated with an increased mortality in patients post myocardial infarction[4]. Drug therapy may alter HRV; beta-blocker therapy has been shown to have a favorable effect on HRV[6][7] in patients with heart failure. However, changes in heart rate dynamics observed before ventricular tachyarrythmias (VTAs) in patients taking anti-arrhythmic drugs were independent of the drug regimen[8]. And postural change influence on the HRV parameters of normal Taiwanese has been reported by our group in the previous ICE Lund meeting.[12]

1.2 Research Propose

A normal range of HRV in the healthy asymptomatic population has still not been identified[2]. Without a normal range, changes in HRV are difficult to interpret and use in evaluating disease adjustments.

The purpose is to evaluate the gender and postural effects in HRV parameters between symptomatic Mitral Valve Prolapse Syndrome (MVPS) patients and an apparently healthy population.

1.2.1 Normal Range

If a set of amplitudes is obtained from a group of apparently healthy individuals within a well-defined age range, there will be a spread of measurements obtained with a predominance of values in the middle of the group and a smaller number at either side. In a classical situation, where there is an even spread of measurements around a central value with the distribution, there is said to be a normal distribution[27].

A point on the bell-shaped curve simply indicates the number of people in the group

who have an amplitude of a certain value[27]. When the distribution is symmetrical, the mean of the values will be in the middle of the range. Given the set of values, it becomes possible to calculate a mean and standard deviation (SD) for the parameter of interest. With a classical normal distribution, the mean plus or minus twice the standard deviation delineates approximately 95% of the range of values. Hence, if it could be shown that a set of values possessed a normal distribution, then one method of defining the normal range would simply be to calculate the mean and standard deviation and proceed to derive the upper and lower limits of the normal 95 percentile range. By taking such limits, where 2.5% of the values are excluded at either end of the distribution, so-called outliers can be excluded.

With respect to ECG measurements, however, it was pointed out by Simonson [28] many years ago that the range of measurements for most ECG parameters is not normal, it tends to have a skewed distribution, for the R-wave amplitude in V_5. The longer tail of the distribution is toward the higher values with the shorter tail being toward the lower values. To avoid this difficulty, an alternative approach for deriving the 95 percentile limits can be adopted.

The principal measurements of the ECG waveform note that these amplitudes and

durations are referred to well-defined onsets and terminations of the component waves[27]. In practice, the onset of the first wave in one lead does not need necessarily coincide with the apparent onset in other leads. This leads to the concept of introducing isoelectric segments within the QRS complex. The diagnostic significance of these segments has not yet been evaluated, but they have a relationship to vector orientations in a certain sense.

While the human eye at a glance may be able to say whether or not an ST segment is concave or convex upward, it requires several measurements to establish this when using a computer program. For this reason, Pipberger and co. [25] introduced the concept of time normalization. It was suggested [26] that the P wave be divided into four equal time-normalized segments. This approach has certain advantages, but it can suffer from errors in determining the onset and termination of the components[27].

1.2.2 Gender Difference

HRV might be effect by a lot of physical factors, some like illness, age, gender, racial or exercise. But nowadays we still do not have a HRV database all belonging to Taiwanese. Because of the differences in environment and life styles, Taiwanese

shouldn’t use the same HRV normal range data with other racial. We try to build the HRV normal range of Taiwanese in this research.

Gender differences in the autonomic nervous system may be present because of developmental differences or due to the effects of prevailing levels of male and female sex hormones[14]. Differences in the autonomic system may be due to differences in afferent receptor stimulation, in central reflex transmission, in the efferent nervous system and in post synaptic signaling. At each of these potential sites of difference, there may be effects due to different size or number of neurons, variations in receptors, differences in neurotransmitter content or metabolism as well as functional differences in the various components of the reflex arc[14].

In human beings, resting plasma concentrations and urinary excretion of Noradrenaline(NA) and adrenaline are generally not different between males and females[15–17]. However, males have been found to have higher resting sympathetic nerve activity to muscles, as determined by micro-neurography [17]. About in HRV, the majority of studies have found women to have a lower LF/HF power ratio than men, suggesting a preponderance of vagal over sympathetic responsiveness [18]. Higher LF power in men has been found in several studies [19–21]. These data

suggest that males have a preponderance of sympathetic over vagal control of cardiac function compared with females. Sato and Miyake[3] found that the male subjects were more sympathetic dominant than the female subjects. Our group has presented in 2010 ICE Lund meeting that gender difference will affect the result of HRV data[12].

1.2.3 Postural Changes

Autonomic Nervous System has a great effect in HRV. In this research we ask our case in three postures: lying, sitting and standing. These three postures mean the activity of sympathetic and parasympathetic nerves, and help us know how ANS work in different situation. In normal conditions, parasympathetic nerves are more active in lying position, and sympathetic nerves is much stimulated than parasympathetic nerves in standing position[12].

1.2.4 Mitral Valve Prolapse Syndrome and Normals

Patients with mitral valve prolapse syndrome (MVPS) may have a variety of cardiac and non cardiac abnormalities in addition to the characteristic valvular lesion with its mid-systolic click and late systolic murmur[9]. Symptoms such as atypical chest pain,

easy fatigability, abnormal cardiovascular and electrocardiographic responses to exercise, ST- and T wave changes on resting ECGs, and a variety of atrial and ventricular arrhythmias[10][11].

The presence of chest pain, ST-T-wave abnormalities, and arrhythmias suggests the possibility of a functional disorder involving the autonomic nervous system[9]. Many of the clinical features of the MVPS are found in other conditions which have been attributed to some type of autonomic dysfunction, e.g., neuro-circulatory or vaso-regulatory asthenia[13].

1.2.5 Age

Under the age of 50, sympathetic nerve activity was significantly greater in men than women [22]. In the study of Kuo et al.[23], the percentage LF power was significantly higher in the younger males than the younger females whilst the percentage HF power was significantly higher in the younger females than the younger males. Yamasaki et al.[18] also found a decline with age for both HF and LF power. The decline with age was more marked for men than for women.

Because of the data is not enough, we did not discuss about aging problem in this study.

1.3 Overview

In this study, it includes seven part. First chapter is introduction, and then chapter 2 is Electrocardiology. Chapter 3 is about Heart Rate Variability, and Chapter 4 is Mitral Valve Prolapse. In chapter 5 is the method and material about this study, and chapter 6 is result and discussion. The last chapter is about the future work.

Chapter 2 Electrocardiology

2.1 Synopsis of Electrocardiology

Electrocardiology in its broadest term is the study of the electric field generated by individual cells of the heart. Electrocardiology includes Electrophysiology and Biophysics. The most common subject is Electrocardiogram (ECG or EKG from the German Elektrokardiogramm). Electrocardiography is a transthoracic interpretation of the electrical activity of the heart over a period of time, as detected by electrodes attached to the outer surface of the skin and recorded by a device external to the body[29].

It was first proposed by Lempert in 1976[29] and just over one hundred years since the human electrocardiogram was first recorded by a physiologist Augustus D. Waller at the St. Mary's Hospital in London U.K.[32] and almost seventy years since the first unipolar electrocardiographic lead was introduced by Frank Wilson in the University of Michigan, U.S.A. (Wilson et al, 1934)[30]. Fisch[33] emphasized the fact that electrocardiography is a non-invasive technique which is relatively inexpensive and

simple to use. The electrocardiogram also provides unique information that cannot be obtained by any other investigative technique.

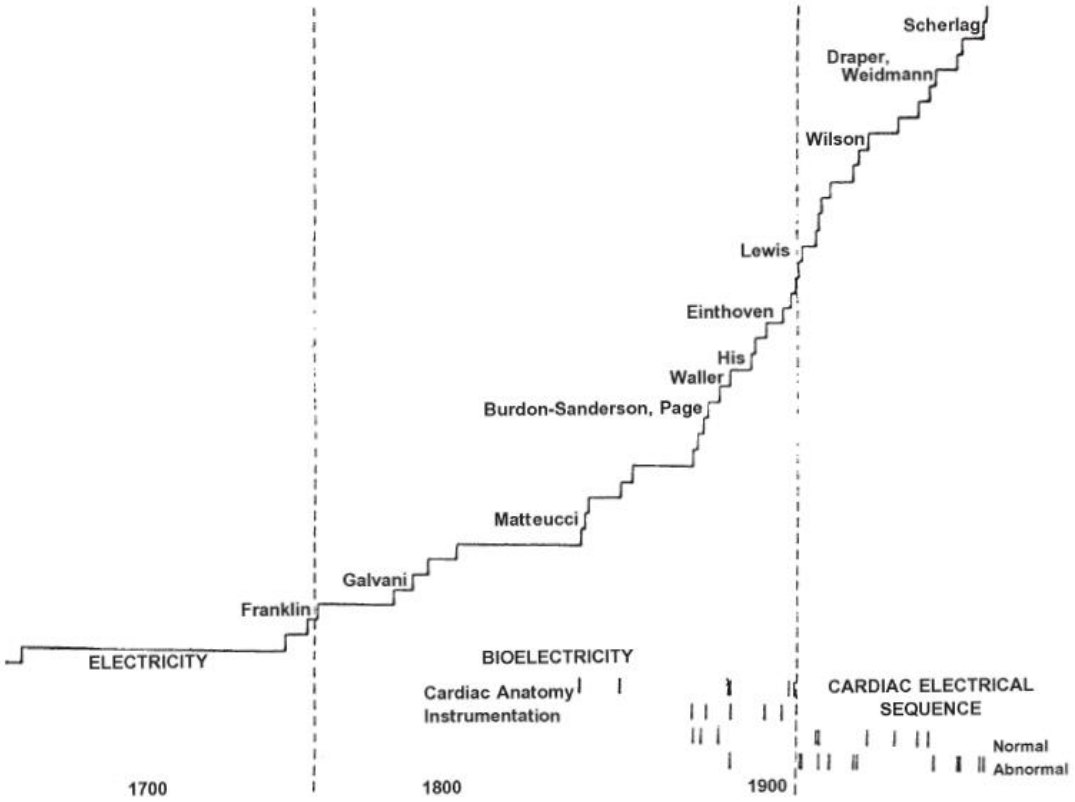
With the advent of computer techniques, the electrocardiogram can be recorded and interpreted with such equipments. So nowadays, it is more practical to use the electrocardiogram as an aid for clinical diagnosis. ECG is used to measure the rate and regularity of heartbeats, as well as the size and position of the chambers[29].

Nowadays, ECG becomes an important examination to aid clinical diagnosis. Some of the early work in electrocardiography was carried out in Europe, where today there are still considerable developmental efforts being expended, particularly in the field of computer-assisted electrocardiograms being recorded, there is a need for their automated analysis of ECGs. But the computer does not have the human emotional factor and distraction in the interpretation of electrocardiograms. Therefore, it provides the advantage of fast interpretation of ECG and significant improvement of signal processing technique[29].

2.2 History of Electrocardiology

L.G. Horan[31] has divided the history of electrocardiogram into three dedicate. “Era of Electricity”, it ended in 1750. And then started an “Era of Bioelectricity”, it was from 1750 to 1900. Finally, the “Era of Cardiac Electric Sequence” is from 1900 to nowadays.

Fig. 2.1 The developing of Cardiogram[31].

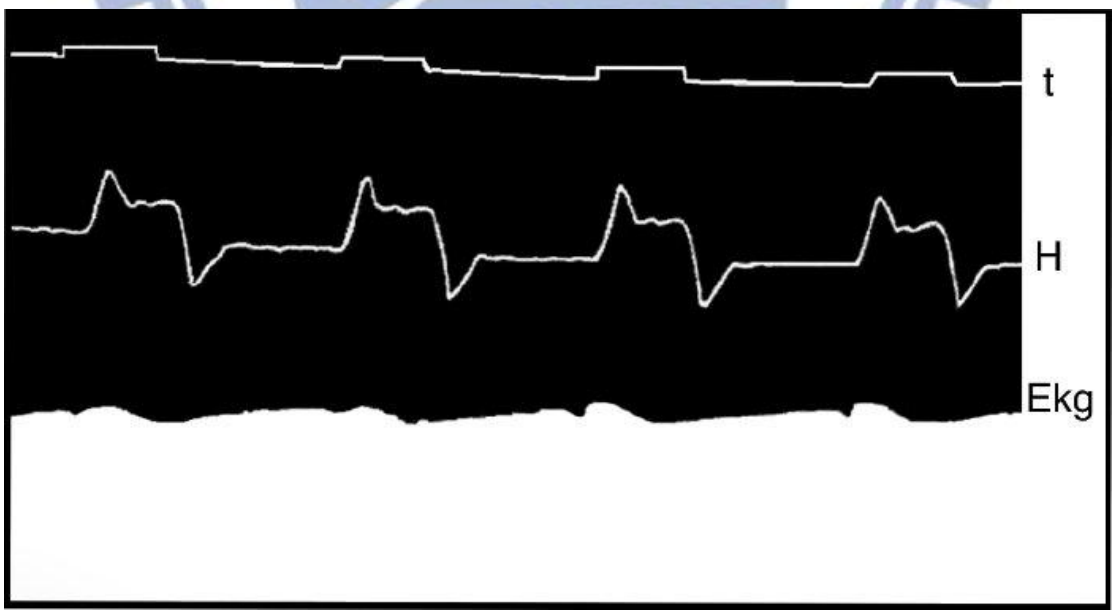


The first galvanometer had been invented by the mid 19th century. Physiologists were engaged in exploring the discharge from electric eels, the flow of electric current through frogs and the effects of injury. Electric current was initiated by Galvani, but

he was criticized by Volta who thought when different metals contact, it could generate electric current. Volta's work led to the development of batteries[34].

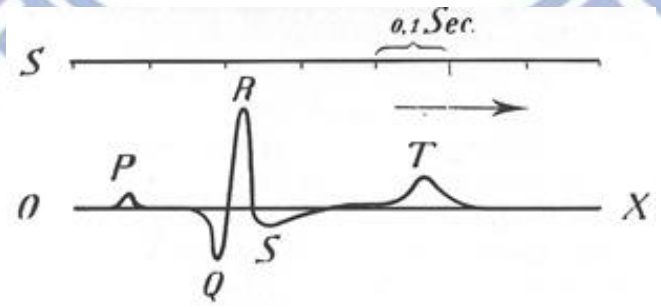
The first recording of cardiac electrical activity was performed in 1856 by Kölliker and Müller's demonstration of bioelectric potentials in the frog's heart[35]. It described a negative deflection measured by a galvanometer prior to each contraction. In 1876, Marey used the capillary electrometer to record the electric activity of the frog's heart on a photograph[36].

Fig. 2.2 The first human electrocardiogram recorded by Waller in 1887. t=time in seconds, Ekg=electrocardiogram, h=chest wall movement. [37]



Waller investigated that recording from the limbs of animals is the same with in man. He published his observations of the electrocardiogram recorded from his dog using the capillary electrometer in 1889. It was stated by Willem Einthoven in 1912 that Waller first introduced the term “electrocardiogram” into physiological science [38]. Einthoven designed a device to record cardiac electrical potentials from the surface of the body, and he introduced the concept known as “Einthoven’s triangle”. It means the body was represented in electrical terms by an equilateral triangle, from which the mean QRS axis can be calculated[39]. Einthoven also used the terminology of P, Q, R, S T to describe the deflection of the electrocardiogram (Fig 2.3) and developed a method called “Telecardiography” in 1906 for transmitting the electrocardiogram over telephone lines[32].

Fig. 2.3 Definition of the deflections of the electrocardiogram by Einthoven[40].
S=time in 0.1 second, Lower tracing shows P, Q, R, S & T deflection of the ECG.



Einthoven[38] introduced lead I, II, and III and a variety of different electrocardiographic abnormalities had been demonstrated.

The three limb leads, denoted I, II, and III can be represented as follows:

Lead I $= E_L - E_R$

Lead II $= E_F - E_R$

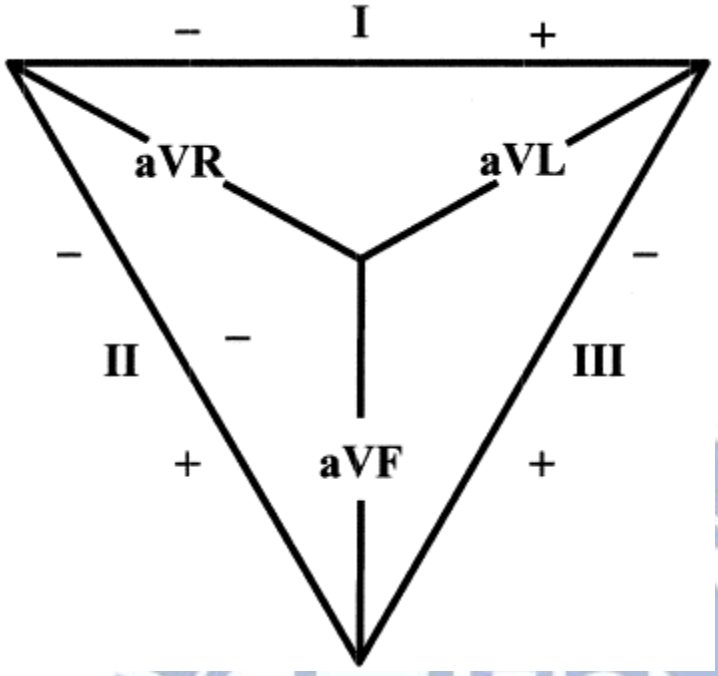
Lead III $= E_F - E_L$

Where E_L, E_R and E_F denote the potential at the left and fight arms and left leg. It follows that:

II $=$ I $+$ III

This is known as Einthoven's Law.

Fig. 2.4 Einthoven'sTriangle[53].



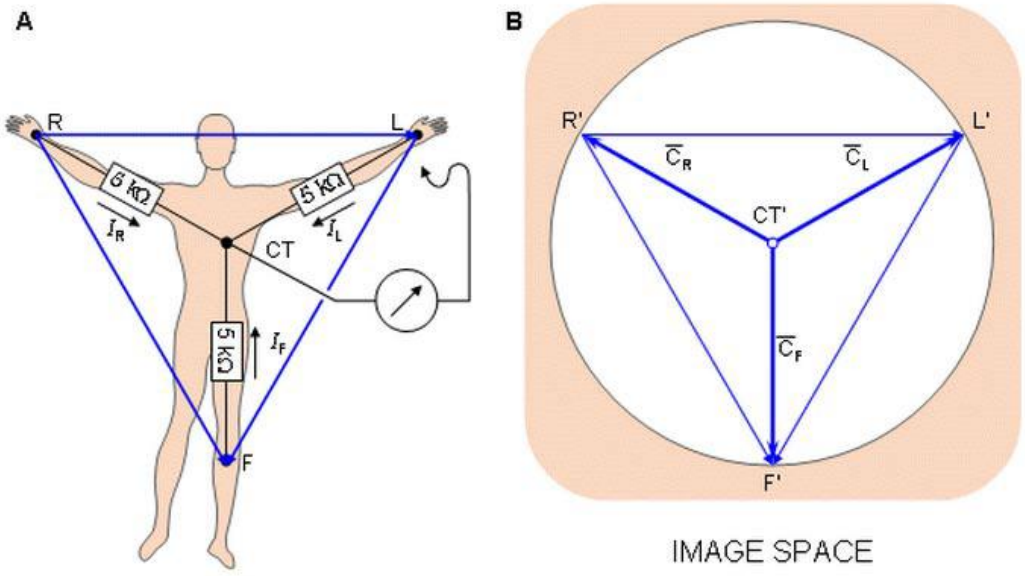
Sir Thomas Lewis had used bipolar chest leads in the studies of cardiac rhythmic disorders[41][42]. His measurement of epicardial activation established the hypothesis on the excitation of the myocardium.

During the 1920s, Frank Wilson undertook many studies correlating electrocardiographic findings (essentially limb leads I, II, and III) with abnormalities such as ventricular hypertrophy and bundle branch block. Their concept of "Ventricular Grandient" is still used in nowadays. Wilson's major contribution is his "central terminal"[43], which means unipolar chest leads can be recorded.

However, the concept allows the potential variation at a single point on the chest to be recorded with potential obtained by averaging the potentials of right and left arms and the left leg. This record is known as a “unipolar” lead. If the potential at the Wilson central terminal is denoted by EWCT then

$$E_{WCT} = 1/3 (E_R + E_L + E_F)$$

Fig. 2.5 (A) picture of Wilson central terminal; (B) image space of Wilson central terminal[44].



The next stage of the unipolar lead was to specify six precordial positions for the exploring electrodes, which were slightly different from the six leads V1-V6 used nowadays[45].

In 1942, Goldberger introduced the “augmented unipolar limb lead” to electrocardiography. He removed the Wilson central terminal connection from the limb on which the exploring lead was placed and this augmented the potential recorded by 50% [46]. Mathematically, the relationship between the modified unipolar right arm lead (modified VR), which is modified by the removal of the right arm connection to the Wilson central terminal, and the resultant potential of the modified Goldberger’s Terminal (EGT) for this lead is as follow:

$$VR = E_R - E_{WCT}$$

$$\text{Modified VR} = E_R - E_{GT}$$

$$= E_R - 1/2\,(E_L + E_F)$$

$$= 3/2\,E_R - 1/2\,(E_L + E_F + E_R)$$

$$= 3/2[E_R - 1/3\,(E_L + E_F + E_R)]$$

$$= 3/2\,[E_R - E_{WCT}]$$

$$= 3/2VR$$

The modified VR became known as aVR. Similar circuitry was introduced to record modified VL and VF, i.e. aVL and aVF.

The development of conventional 12-lead electrocardiography was then completed. There were three limb lead: I, II, and III from Einthoven; three augmented unipolar limb leads: aVR, aVL, and aVF from Goldberger's modification of Wilson's central terminal; and six praecordial leads V1-V6 arising out of Wilson's central terminal.

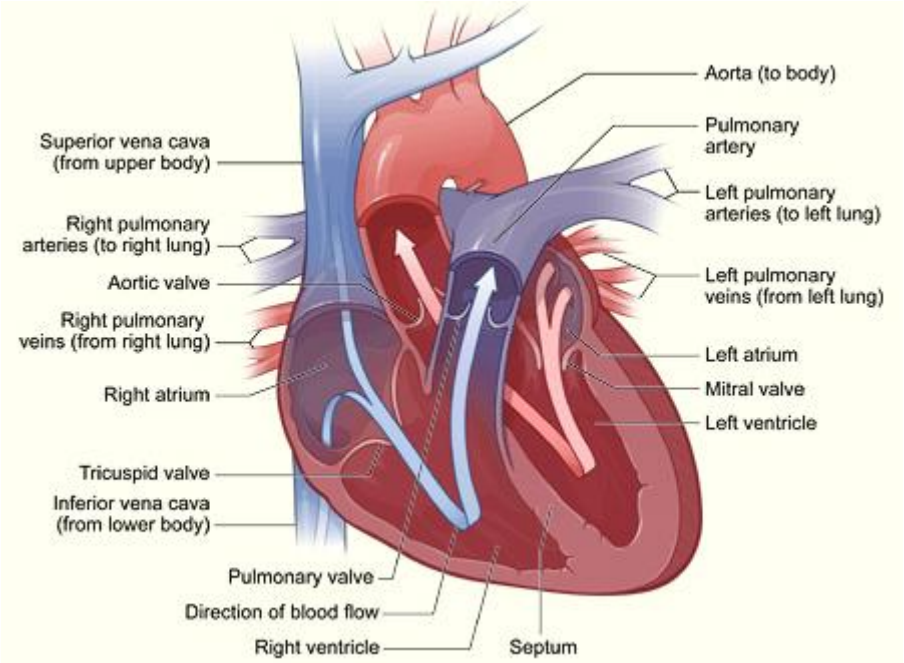
The development of electrocardiography continued in different ways and progressed through the research of several gifted electrocardiographers and electrophysiologists. The improvements in the techniques of measurement, recording, interpretation and modeling as well as the elaboration of many theories have contributed to the widening of electrocardiology.

2.3 Physiology of heart

The human heart has a mass of between 250 and 350 grams[47]. It has four chambers, two superior atria and two inferior ventricles. The atria are the receiving chambers and the ventricles are the discharging chambers.

The pathways of blood through the human heart are part of the pulmonary and systemic circuits. These pathways include the tricuspid valve, the mitral valve, the aortic valve, and the pulmonary valve[48]. The mitral and tricuspid valves are classified as the atrioventricular valves. The aortic and pulmonary semi-lunar valves separate the left and right ventricle from the pulmonary artery and the aorta respectively. The interatrioventricular septum separates the left atrium and ventricle from the right atrium and ventricle, dividing the heart into two functionally separate and anatomically distinct units.

Fig. 2.6 Blood flow diagram of the human heart[49].



Blood flows through the heart in one direction, from the atria to the ventricles, and out of the great arteries. Blood is prevented from flowing backwards by the tricuspid, bicuspid, aortic, and pulmonary valves.

The function of the right heart is to collect de-oxygenated blood, in the right atrium, from the body (via superior and inferior vena cavae) and pump it, via the right ventricle, into the lungs (pulmonary circulation) so that carbon dioxide can be dropped off and oxygen picked up. The left side collects oxygenated blood from the lungs into the left atrium. From the left atrium the blood moves to the left ventricle which pumps it out to the body (via the aorta). On both sides, ventricles are thicker and stronger than atria. The muscle wall surrounding the left ventricle is thicker than

the wall surrounding the right ventricle due to the higher force needed to pump the blood through the systemic circulation. Starting in the right atrium, the blood flows through the tricuspid valve to the right ventricle. It is pumped out of the pulmonary semilunar valve and travels through the pulmonary artery to the lungs. From there, blood flows back through the pulmonary vein to the left atrium. It then travels through the mitral valve to the left ventricle, from where it is pumped through the aortic semilunar valve to the aorta and to the rest of the body. The deoxygenated blood finally returns to the heart.

2.4 Conduction System of Heart

The normal electrical conduction in the heart allows the impulse that is generated by the sinoatrial node (SA node) be propagated to and stimulate the myocardium. It is the ordered stimulation of the myocardium that allows efficient contraction of the heart.

In order to maximize the efficiency of contraction and cardiac output, the conduction system of the heart has:

a) Substantial atrial to ventricular delay. It allows the atria to completely empty their contents into the ventricles. The atria connected only via the AV node which briefly delays the signal.

b) Coordinated contraction of ventricular cells. The ventricles must maximize systolic pressure to force blood through the circulation.

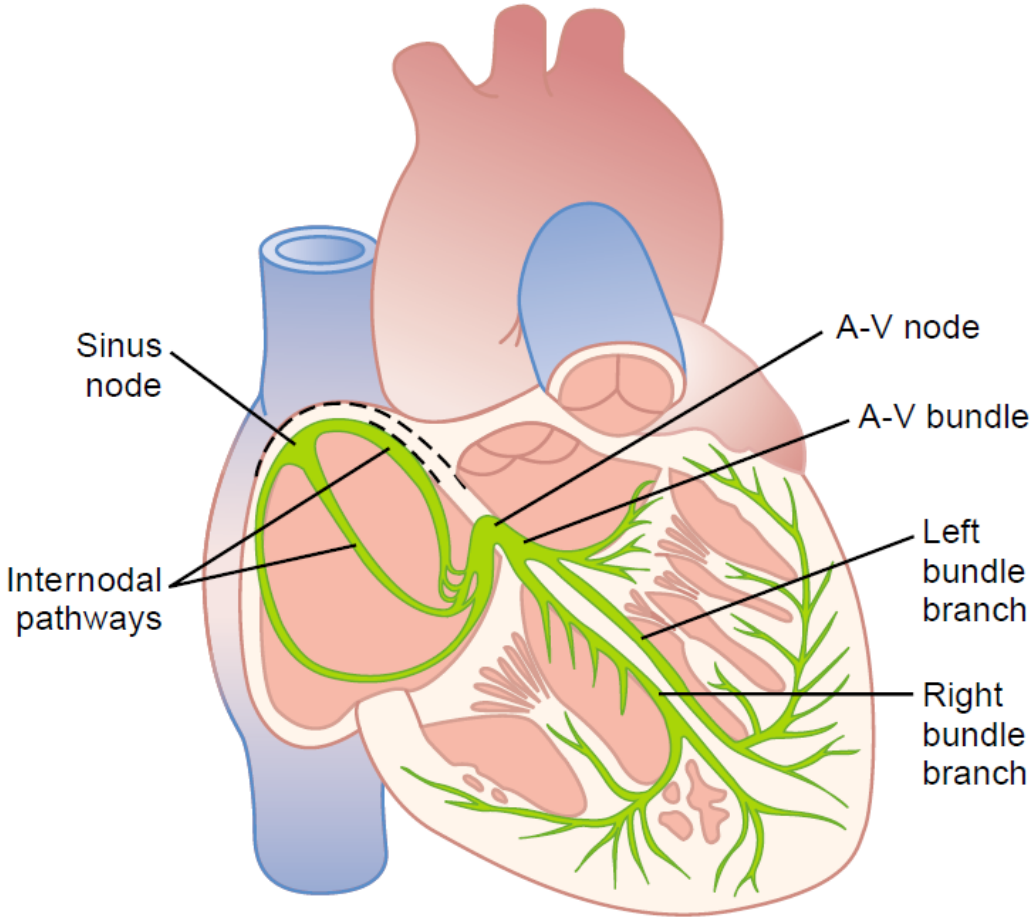
c) Absence of tetany. After contracting the heart must relax to fill up again.

Signals arising in the SA node stimulate the atria to contract and travel to the AV node. After a delay, the stimulus is conducted through the bundle of His to the Purkinje fibers and the endocardium at the apex of the heart, and then finally to the ventricular epicardium[50].

The heart is a functional syncytium. In a functional syncytium, electrical impulses propagate freely between cells in every direction, so that the myocardium functions as a single contractile unit. This property allows rapid, synchronous depolarization of the myocardium. While normally advantageous, this property can be detrimental as it

potentially allows the propagation of incorrect electrical signals. These gap junctions can close to isolate damaged or dying tissue, as in a myocardial infarction.

Fig. 2.7 conduction system of heart[22].



A typical ECG tracing of the cardiac cycle consists of a P wave, a QRS complex, a T wave, and a U wave.[50]

Table 2.1 wave and intervals. [52]

	description
RR interval	The interval between an R wave and the next R wave: Normal resting heart rate is between 60 and 100 bpm.
P wave	During normal atrial depolarization, the main electrical vector is directed from the SA node towards the AV node, and spreads from the right atrium to the left atrium. This turns into the P wave on the ECG.
PR interval	The PR interval is measured from the beginning of the P wave to the beginning of the QRS complex. The PR interval reflects the time the electrical impulse takes to travel from the sinus node through the AV node and entering the ventricles. The PR interval is, therefore, a good estimate of AV node function.
J-point	The point at which the QRS complex finishes and the ST segment begins, it is used to measure the degree of ST elevation or depression present.
ST segment	The ST segment connects the QRS complex and the T wave. The ST segment represents the period when the ventricles are depolarized. It is isoelectric.
T wave	The T wave represents the repolarization (or recovery) of the ventricles. The interval from the beginning of the QRS complex to the apex of the T wave is referred to as the absolute refractory period. The last half of the T wave is referred to as the relative refractory period (or vulnerable period).
ST interval	The ST interval is measured from the J point to the end of the T wave.
QT interval	The QT interval is measured from the beginning of the QRS complex to the end of the T wave. A prolonged QT interval is a risk factor for ventricular tachyarrhythmias and sudden death. It varies with heart rate and for clinical relevance requires a correction for this, giving the QTc.
U wave	The U wave is hypothesized to be caused by the repolarization of the interventricular septum. They normally have low amplitude, and even more often completely absent. They always follow the T wave and also follow the same direction in amplitude. If they are too prominent, suspect hypokalemia, hypercalcemia or hyperthyroidism usually[24].

In normal conditions, electrical activity is generated by the SA node. This electrical impulse is propagated throughout the right atrium, and through Bachmann's bundle to the left atrium, stimulating the myocardium of the atria to contract. The conduction of the electrical impulse throughout the atria is seen on the ECG as the P wave. As the electrical activity is spreading throughout the atria, it travels via specialized pathways, known as internodal tracts, from the SA node to the AV node.

The AV node functions as a critical delay in the conduction system. Without this delay, the atria and ventricles would contract at the same time, and blood wouldn't flow effectively from the atria to the ventricles. The delay in the AV node forms much of the PR segment on the ECG. And part of atrial repolarization can be represented by PR segment.

The distal portion of the AV node is known as the Bundle of His. The Bundle of His splits into two branches in the interventricular septum, the left bundle branch and the right bundle branch. The left bundle branch activates the left ventricle, while the right bundle branch activates the right ventricle. The left bundle branch is short, splitting into the left anterior fascicle and the left posterior fascicle. The left posterior fascicle is relatively short and broad, with dual blood supply, making it particularly resistant

to ischemic damage. The left posterior fascicle transmits impulses to the papillary muscles, leading to mitral valve closure. As the left posterior fascicle is shorter and broader than the right, impulses reach the papillary muscles just prior to depolarization, and therefore contraction, of the left ventricle myocardium. This allows pre-tensioning of the chordae tendinae, increasing the resistance to flow through the mitral valve during left ventricular contraction. This mechanism works in the same manner as pre-tensioning of car seatbelts.

The two bundle branches taper out to produce numerous Purkinje fibers, which stimulate individual groups of myocardial cells to contract. The spread of electrical activity through the ventricular myocardium produces the QRS complex on the ECG.

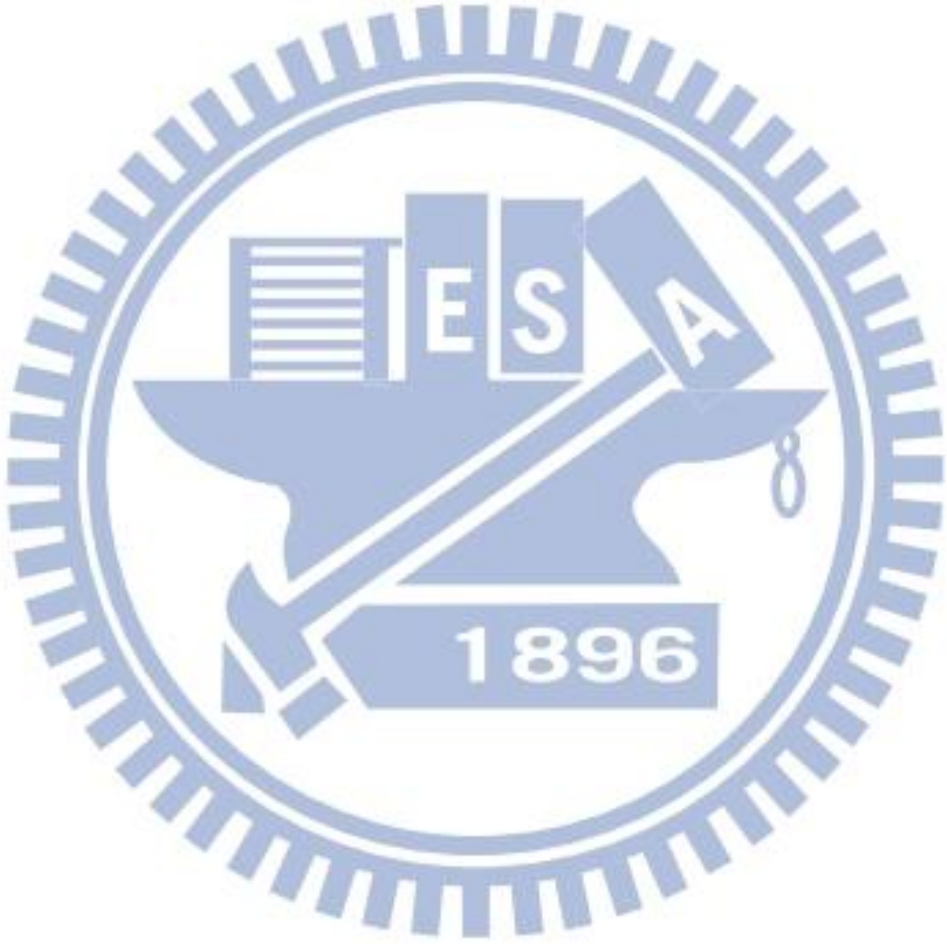
The last event of the cycle is the repolarization of the ventricles. It is the restoring of the resting state. In the ECG, repolarization includes the J wave, ST-segment, and T- and U-waves[51].

Cardiac muscle is a syncytium, and the heart is composed of two syncytiums: the atrial syncytium that constitutes the walls of the two atria, and the ventricular syncytium that constitutes the walls of the two ventricles[50]. The atria are separated

from the ventricles by fibrous tissue that surrounds the atrioventricular (A-V) valvular openings. Potentials are conducted only by way of a specialized conductive system: A-V bundle. This division of the muscle of the heart into two functional syncytiums allows the atria to contract a short time ahead of ventricular contraction, which is important for effectiveness of heart pumping. The action potential recorded in a ventricular muscle fiber, averages about 105 millivolts. The intracellular potential rises from a very negative value, about -85 millivolts, between beats to a slightly positive value, about +20 millivolts, during each beat. After the initial spike, the membrane remains depolarized for about 0.2 second, exhibiting a plateau, followed at the end of the plateau by abrupt repolarization.

In cardiac muscle, the action potential is caused by two types of channels[50]: (a) the fast sodium channels as the same in skeletal muscle and (b) another entirely different population of slow calcium channels, which are also called calcium-sodium channels. During this time, a large quantity of both calcium and sodium ions flows through these channels to the interior of the cardiac muscle fiber, and this maintains a prolonged period of depolarization, causing the plateau in the action potential. Further, the calcium ions that enter during this plateau phase activate the muscle contractile

process, while the calcium ions that cause skeletal muscle contraction are derived from the intracellular sarcoplasmic reticulum.



Chapter 3 Hear Rate Variability

3.1 Background

Heart rate variability (HRV) is the temporal variation between sequences of consecutive heartbeats. On a standard electrocardiogram (ECG), the maximum upwards deflection of a normal QRS complex is at the peak of the R wave, and the duration between two adjacent R wave peaks is termed the R-R interval. The ECG signal requires editing before HRV analysis can be performed, a process requiring the removal of all non-sinus-node-originating beats. The resulting period between adjacent QRS complexes resulting from sinus node depolarization is termed the N-N (normal-normal) interval[1], and HRV is the measurement of the variability of the N-N intervals. The last two decades have witnessed the recognition of a significant relationship between the autonomic nervous system and cardiovascular mortality, including sudden cardiac death[1]. HRV investigation as its use in the prediction of long-term survival in patients who has suffered from congenital myocardial infarction, or had valvular or congestive heart disease. Depressed HRV is a predictor of mortality and arrhythmic complications independent of other recognized risk factors[1]. HRV

assessed from short-term recordings may be used for initial screening of all survivors of an acute myocardial infarction.

In 1996, the European Society of Cardiology and the North American Society of Pacing and Electrophysiology to constitute a Task Force charged with the responsibility of developing appropriate standards. The goals of the Task Force were to: standardize nomenclature and develop definitions of terms; specify standard methods of measurement; define physiological and pathophysiological correlates; describe currently appropriate clinical applications, and identify areas for future research. 'Heart Rate Variability' has become the conventionally accepted term to describe variations of both instantaneous heart rate and RR intervals[1].

3.2 The history of HRV

The clinical relevance of heart rate variability(HRV) was first appreciated in 1965 when Hon and Lee[54] noted that fetal distress was accompanied by changes in beat-to-beat variation of the fetal heart, even before there was a detectable change in the rate. In the 1970s, Sayers and others[77] focused attention on the existence of physiological rhythms imbedded in the beat-to-beat heart rate signal. Ewing et al.

used short-term HRV (15 min) measurements as a maker of diabetic autonomic neuropathy[55]. In 1977, Wolf et al.[56] showed that patients with reduced HRV after a myocardial infarction had an increased mortality, and this was confirmed by studies showing that HRV is an accurate predictor of mortality post myocardial infarction (MI)[57-59]. In 1981, Akselrod et al. introduced power spectral analysis of heart rate fluctuations to quantitatively evaluate beat-to-beat cardiovascular control[60]. The clinical importance of HRV became apparent in the late 1980s when it was confirmed that HRV was a strong and independent predictor of mortality following an acute myocardial infarction[57-59].

HRV has also been investigated as a tool to predict the risk of sudden cardiac death(SCD)[61], and Low HRV is an independent risk factor for the development of later cardiac arrest in survivors of cardiac arrest[61]. Both reduced HF power and reduced LF power are independent predictors of later sudden death following survival from cardiac arrest[61]. Reduction in HF power appears superior at risk-stratifying patients[62].

3.3 Autonomic Nervous System and HRV relationships

HRV is affected by Autonomic nervous system. The ANS is part of the peripheral nervous system, it affects heart rate, digestion, respiratory rate, salivation, perspiration, pupillary dilation, urination, and sexual arousal[63].

The ANS included: sympathetic nervous system and the parasympathetic nervous system, which operate independently in some functions and interact co-operatively in others. In many cases they activate opponent where one activates a physiological response and the other inhibits it. The sympathetic division begins at the thoracic and lumbar (T1-L2/3) portions of the spinal cord. The parasympathetic division begins at the cranial nerves (CN 3, CN7, CN 9, CN10) and sacral (S2-S4) spinal cord. The sympathetic division typically functions in actions requiring quick responses. The parasympathetic division functions with actions that do not require immediate reaction. These two systems should be seen as permanently modulating vital functions[78].

3.3.1 Sympathetic nervous system

The sympathetic nervous system controls most of the body's internal organs. As in the flight-or-fight response, stress is thought to counteract the parasympathetic system, which generally works to promote maintenance of the body at rest. The functions of both the parasympathetic and sympathetic nervous systems are not so straightforward[64][65].

There are two kinds of neurons involved in the transmission through the sympathetic system: pre-ganglionic and post-ganglionic. The shorter preganglionic neurons originate from the thoracolumbar region of the spinal cord and travel to a ganglion, often one of the paravertebral ganglia, where they synapse with a postganglionic neuron. The long postganglionic neurons extend across most of the body from there[66]. At the synapses within the ganglia, preganglionic neurons release acetylcholine. In response to the stimulus, postganglionic neurons release norepinephrine[67].

The sympathetic nervous system is responsible for many homeostatic mechanisms in living organisms. It is perhaps best known for mediating the neuronal and hormonal

stress response commonly known as the fight-or-flight response. This response is also known as sympatho-adrenal response of the body, as the preganglionic sympathetic fibers that end in the adrenal medulla secrete acetylcholine (Ach) which activates the great secretion of epinephrine and to a lesser extent norepinephrine from it. Therefore, this response acts primarily on the cardiovascular system is mediated directly via impulses transmitted through the sympathetic nervous system and indirectly via catecholamines secreted from the adrenal medulla[78].

3.3.2 Parasympathetic nervous system

The parasympathetic system is responsible for stimulation of "rest-and-digest" or "feed and breed" activities that occur when the body is at rest, especially after eating, including sexual arousal, salivation, lacrimation, urination, digestion and defecation.

Sympathetic and parasympathetic divisions typically function in opposition to each other. This natural opposition is better understood as complementary in nature rather than antagonistic. The sympathetic division typically functions in actions requiring quick responses; whereas the parasympathetic division functions with actions that do not require immediate reaction.

The afferent fibers of the autonomic nervous system are not divided into parasympathetic and sympathetic fibers as the efferent fibers are[68]. Instead, autonomic sensory information is conducted by general visceral afferent fibers.

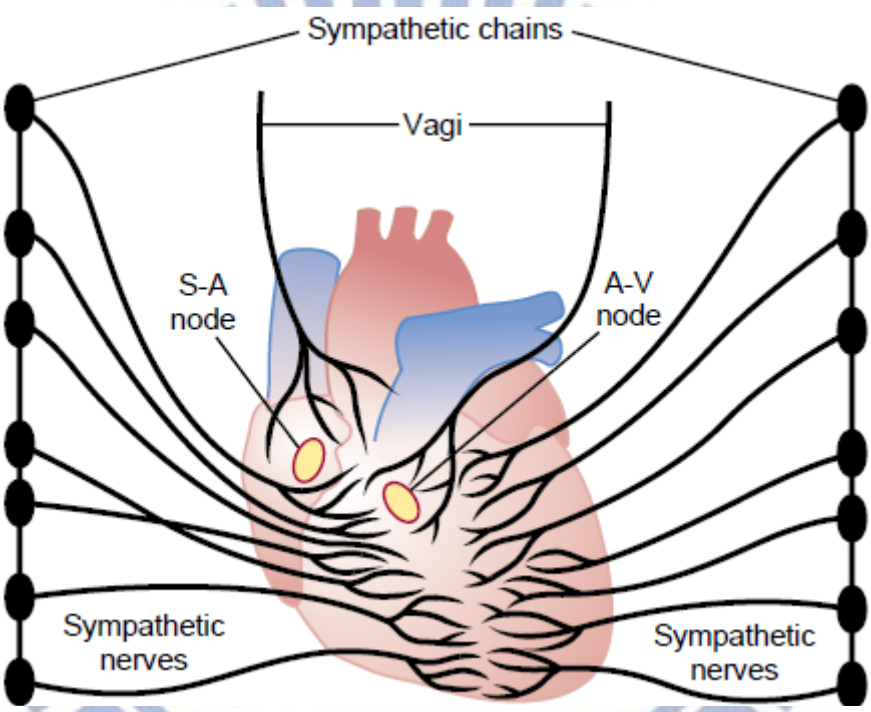
The parasympathetic nervous system uses chiefly ACh as its neurotransmitter, although some peptides (such as cholecystokinin) may act on the parasympathetic nervous system as a neurotransmitter[69][70]. Most transmissions occur in two stages: When stimulated, the preganglionic nerve releases ACh at the ganglion, which acts on nicotinic receptors of postganglionic neurons. The postganglionic nerve then releases ACh to stimulate the muscarinic receptors of the target organ.

3.3.3 Neurotransmitters and pharmacology

Sympathetic ganglionic neurons release norepinephrine at the effector organs and act on adrenergic receptors, with the exception of the sweat glands and the adrenal medulla: Acetylcholine is the preganglionic neurotransmitter for both divisions of the ANS, as well as the postganglionic neurotransmitter of parasympathetic neurons. Nerves that release acetylcholine are said to be cholinergic. In the parasympathetic system, ganglionic neurons use acetylcholine as a neurotransmitter to stimulate

muscarinic receptors. At the adrenal medulla, there is no postsynaptic neuron. The presynaptic neuron releases acetylcholine to act on nicotinic receptors. Stimulation of the adrenal medulla releases epinephrine into the bloodstream, producing a widespread increase in sympathetic activity.

Fig. 3.1 The distribution of sympathetic nerves and parasympathetic nerves in cardiac muscle[79].



3.4 Methods and measurements of heart rate variability parameters

Variations in heart rate may be evaluated by a number of methods. The most widely used methods can be grouped under time domain methods, frequency domain

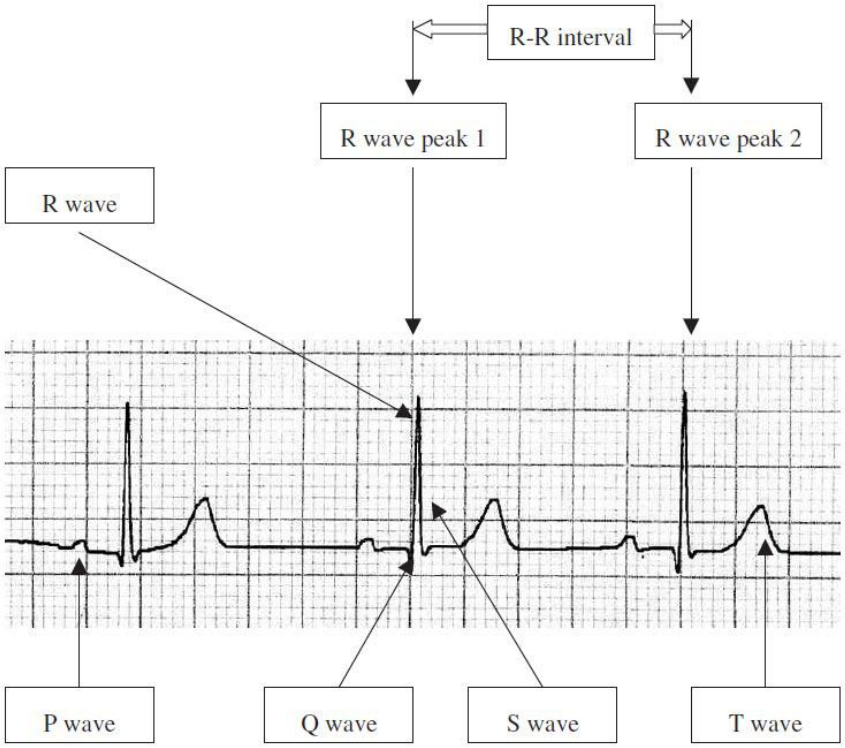
methods, and nonlinear methods.

3.4.1 Time domain methods

R is a point corresponding to the peak of the QRS complex of the ECG wave; and R-R interval is all intervals between adjacent QRS complexes resulting from sinus node depolarizations. The term "N-N interval" is used in place of R-R interval to emphasize the fact that the processed beats are "normal" beats[1].

Simple time domain variables that can be calculated include the mean NN interval, the mean heart rate, the difference between the longest and shortest NN interval, the difference between night and day heart rate, etc. Other time domain measurements that can be used are variations in instantaneous heart rate secondary to respiration, tilt, Valsalva manoeuvre, or secondary to phenylephrine infusion.

Fig. 3.2 Definitions of normal ECG waves[76].



3.4.1.1 Statistical methods

From a series of instantaneous heart rates or cycle intervals, more complex statistical time-domain measures can be calculated. These may be divided into two classes:

(a) those derived from direct measurements of the NN intervals or instantaneous heart rate.

(b) those derived from the differences between NN intervals.

Those variables may be derived from analysis of the total electrocardiographic recording or may be calculated using smaller segments of the recording period. All these measurements of short-term variation estimate high frequency variations in heart rate and thus are highly correlated.

SDNN(standard deviation of all normal to normal intervals) is the simplest variable to calculate. Since variance is mathematically equal to total power of spectral analysis, SDNN reflects all the cyclic components responsible for variability in the period of recording. The total variance of HRV increases with the length of analyzed recording[71].

SDANN(standard deviation of average normal to normal intervals) calculated over short periods, usually 5 min, which is an estimate of the changes in heart rate due to cycles longer than 5 min.

SDNN index (standard deviation of all normal to normal intervals index) is the mean of the 5-min standard deviation of the NN interval calculated over 24 h, which measures the variability due to cycles shorter than 5 min.

RMSSD (The square root of the mean of the sum of the squares of differences between adjacent NN intervals), the square root of the mean squared diVerences of successive NN intervals.

NN50 (Number of pairs of adjacent NN intervals differing by more than 50 ms in the entire recording), the number of interval differences of successive NN intervals greater than 50 ms.

pNN50 (NN50 count divided by the total number of all NN intervals), the proportion derived by dividing NN50 by the total number of NN intervals.

Table 3.1 Selected time domain measures of HRV[1].

Variable	Units	Description
SDNN	ms	Standard deviation of all NN intervals.
SDANN	ms	Standard deviation of the averages of NN intervals in all 5 min segments of the entire recording.
RMSSD	ms	The square root of the mean of the sum of the squares of differences between adjacent NN intervals.
SDNN index	ms	Mean of the standard deviations of all NN intervals for all 5 min segments of the entire recording.
SDSD	ms	Standard deviation of differences between adjacent NN intervals.
NN50 count		Number of pairs of adjacent NN intervals differing by more than 50 ms in the entire recording. Three variants are possible counting all such NN intervals pairs or only pairs in which the first or the second interval is longer.
pNN50	%	NN50 count divided by the total number of all NN intervals.

3.4.1.2 Geometrical methods

The NN intervals can also be converted into a geometric pattern[1], as the sample density distribution of NN interval durations, sample density distribution of differences between adjacent NN intervals, Lorenz plot of NN or RR intervals, etc.

The histogram assesses the relationship between the total number of NN intervals

detected and the NN interval variation[1]. The triangular HRV index considers the major peak of the histogram as a triangle with its baseline width corresponding to the amount of NN interval variability, its height corresponds to the most frequently observed duration of NN intervals. The triangular HRV index is an estimate of the overall HRV[1].

Three general approaches are used in geometric methods:

(a) a basic measurement of the geometric pattern (e.g. the width of the distribution histogram at the specified level) is converted into the measure of HRV.

(b) the geometric pattern is interpolated by a mathematically defined shape (e.g. approximation of the distribution histogram by a triangle, or approximation of the differential histogram by an exponential curve) and then the parameters of this mathematical shape are used.

(c) the geometric shape is classified into several pattern-based categories which represent different classes of HRV (e.g. elliptic, linear and triangular shapes of Lorenz plots).

Geometrical methods are less affected by the quality of the recorded data; however, the recording time should be at least 20 minutes[1], which means that short-term recordings cannot be assessed by geometric methods.

The HRV triangular index measurement is the integral of the density distribution (i.e. the number of all NN intervals) divided by the maximum of the density distribution. Using a measurement of NN intervals on a discrete scale, the measure is approximated by the value:

HRV triangular index= (total number of NN intervals) / (number of NN intervals in the modal bin)

And that is dependent on the length of the bin, i.e. on the precision of the discrete scale of measurement.

The triangular interpolation of NN interval histogram (TINN) is the baseline width of the distribution measured as a base of a triangle, approximating the NN interval distribution (the minimum square difference is used to find such a triangle). Both these measures express overall HRV measured over 24 h and are more influenced by

the lower than by the higher frequencies[59]. Other geometric methods are still in the phase of exploration and explanation.

The major advantage of geometric methods lies in their relative insensitivity to the analytical quality of the series of NN intervals[72].

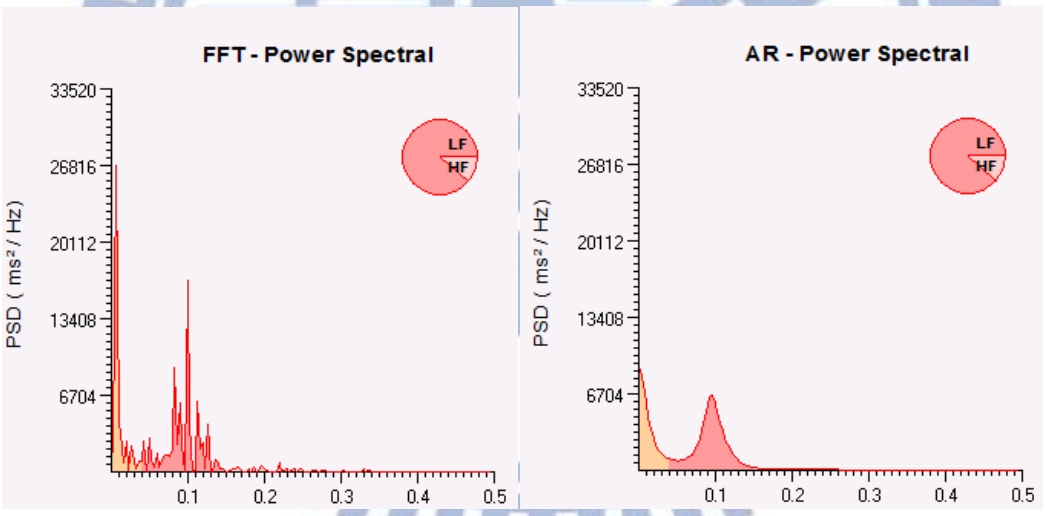
The major disadvantage is the need for a reasonable number of NN intervals to construct the geometric pattern. Recordings of at least 20 minutes and preferably 24 hours should be used to ensure the correct performance of the geometric methods.

3.4.2 Frequency domain methods

Several methods are available[74] since the late 1960s. Power spectral density (PSD), using parametric or nonparametric methods, provides basic information on the power distribution across frequencies. Methods for the calculation of PSD may be generally classified as nonparametric and parametric. In most instances, both methods provide comparable results. The advantages of the nonparametric methods are: (a) the simplicity of the algorithm employed (Fast Fourier Transform (FFT) in most of the cases) and (b) the high processing speed, while the advantages of parametric methods

are smoother spectral components that can be distinguished independent of preselected frequency bands, easy postprocessing of the spectrum with an automatic calculation of low-frequency and high-frequency power components with an easy identification of the central frequency of each component. Beside FFT, Auto-Regressiv (AR) model is another choice. These two kinds of models have different figures, but the consequences could be compared.

Fig. 3.3 Short-term HRV frequency domain methods.



In short-term recordings three main spectral components are distinguished in a spectrum calculated from the recordings: very low frequency(VLF), low frequency (LF), and high frequency (HF) components. Measurement of VLF, LF and HF power components is usually made in absolute values of power (ms^2), but LF and HF may

also be measured in normalized units (n.u.) which represent the relative value of each power component in proportion to the total power minus the VLF component. LF norm= LF/(Total Power–VLF) x 100, and HF norm= HF/(Total Power–VLF) x 100. The representation of LF and HF in n.u. emphasizes the controlled and balanced behavior of the two branches of the autonomic nervous system. Beside, normalization tends to minimize the effect on the values of LF and HF components of the changes in total power. Although HRV assessed from short-term recordings provides prognostic information, HRV measured in nominal 24-h recordings is a stronger risk predictor[1].

Long-term recordings Spectral analysis may also be used to analyze the sequence of NN intervals in the entire 24-h period. The result then includes an ultra-low frequency component (ULF), VLF, LF and HF components. The slope of the 24-h spectrum can also be assessed on a log–log scale by linear fitting the spectral values[1].

Because of the differences in the interpretation of the results, the spectral analyses of short-term and long-term electrocardiograms should always be distinguished. Frequency domain methods would be preferred to the time domain methods when investigating short term recordings[1]. In order to ensure the stability of the signal, the

recordings should not be substantially extended. Thus, recording of approximately 1 min is needed to assess the HF components of HRV while approximately 2 min are needed to address the LF component. In order to standardize short-term HRV, 5 min recordings of a stationary system are preferred[1].

Short-term recordings do have several advantages. First, they are quick to perform and to analyze. Second, short-term recordings can be made under controlled conditions to ensure standardization. Third, they can be made under a variety of conditions such as different postural, psychological or pharmacologic interventions. But in long-term recordings, physiological mechanisms of heart period modulations responsible for LF and HF power components cannot be considered stationary during the 24-h period[75]. But spectral analysis performed in the 24-h period as well as spectral results from shorter segments (e.g. 5 min) averaged over the entire 24-h period provide averages of the modulations attributable to the LF and HF components[1].

Vagal activity is the major contributor to the HF component, and disagreement exists in respect of the LF component[1][54]. When LF expressed in normalized units, it is a quantitative marker for sympathetic modulations. LF is reflecting both sympathetic

and vagal activity. Consequently, the LF/HF ratio is considered by some investigators to mirror sympatho/vagal balance or to reflect sympathetic modulations. Physiological interpretation of lower frequency components of HRV (VLF and ULF components) warrants further elucidation. It is important to note that HRV measures fluctuations in autonomic inputs to the heart rather than the mean level of autonomic inputs[1].

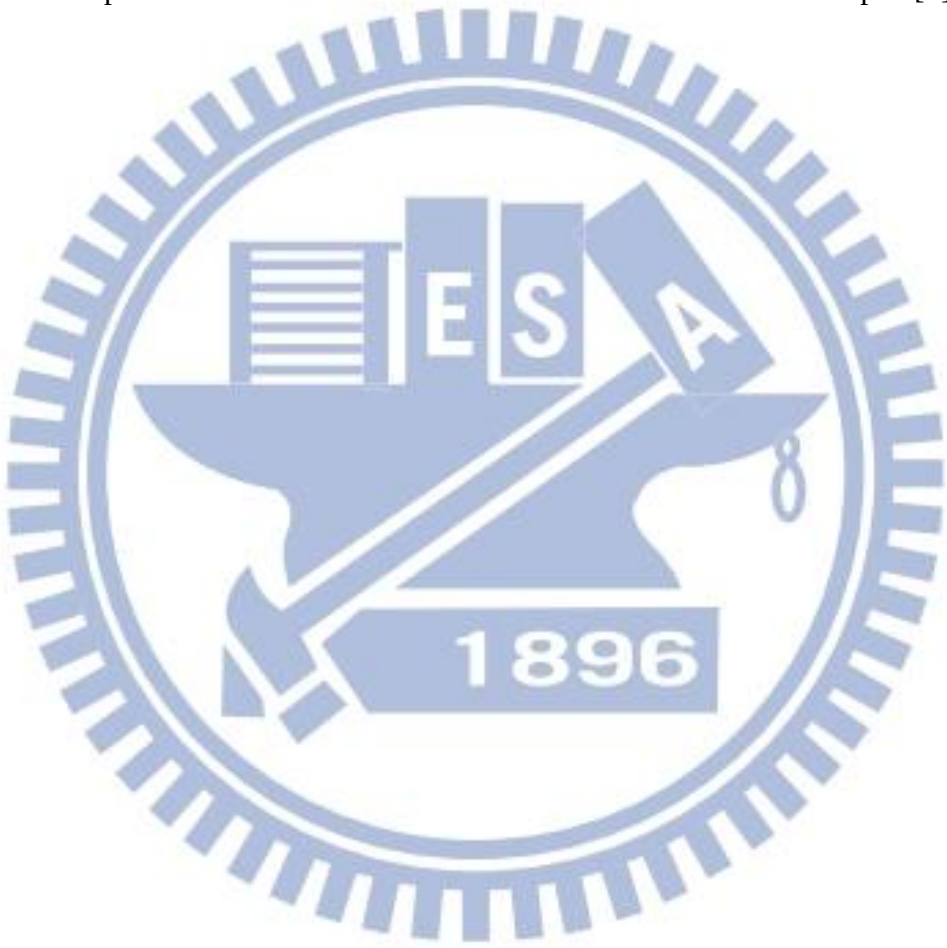


Table 3.2 Selected frequency domain measures of HRV[1].

Variable	Units	Description	Frequency range
		Analysis of short-term recordings (5 min)	
5 min total power	ms²	The variance of NN intervals over the temporal segment	approximately ≤0.4 Hz
VLF	ms²	Power in very low frequency range	≤0.04 Hz
LF	ms²	Power in low frequency range	0.04–0.15 Hz
LF norm	n.u.	LF power in normalised units LF / (Total Power–VLF) X 100	
HF	ms²	Power in high frequency range	0.15–0.4 Hz
HF norm	n.u.	HF power in normalised units HF / (Total Power–VLF) X 100	
LF/HF		Ratio LF [ms²] / HF [ms²]	
		Analysis of entire 24 h	
Total power	ms²	Variance of all NN intervals	Approximately ≤0.4 Hz
ULF	ms²	Power in the ultra low frequency range	≤0.003 Hz
VLF	ms²	Power in the very low frequency range	0.003–0.04 Hz
LF	ms²	Power in the low frequency range	0.04–0.15 Hz
HF	ms²	Power in the high frequency range	0.15–0.4 Hz
α	ms²	Slope of the linear interpolation of the spectrum in a log-log scale	Approximately ≤0.04 Hz

Table 3.3 Approximate correspondence of time domain and frequency domain methods applied to 24-h ECG recordings

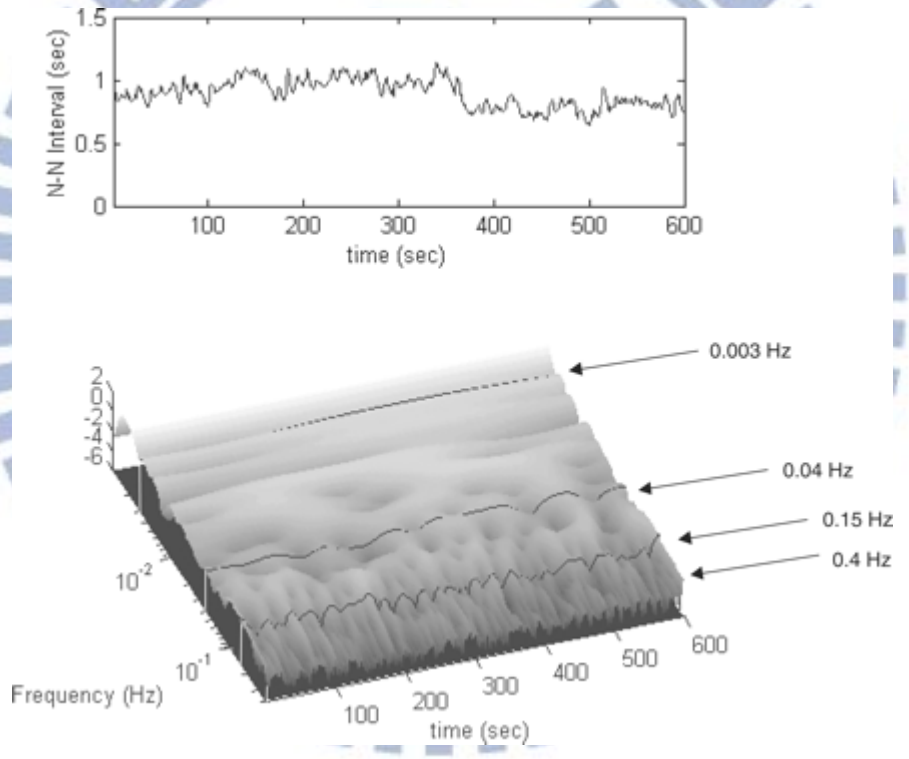
Time domain variable	Approximate frequency domain correlate
SDNN	Total power
HRV triangular index	Total power
TINN	Total power
SDANN	ULF
SDNN index	Mean of 5 min total power
RMSSD	HF
SDSD	HF
NN50 count	HF
pNN50	HF
Differenctial index	HF
Logarithmic index	HF

3.4.3 Time-frequency signal analysis methods

Recently, time-frequency signal analysis methods have been used[76]. These offer simultaneous interpretation of the signal in both time and frequency, which allows local, transient or intermittent components to be elucidated. Some time-frequency methods are available now, including the short time Fourier transform (STFT), Wigner-Ville transform (WVT), Choi-Williams distribution (CWD) and the continuous wavelet transform (CWT). The CWT become the most popular tool, as it

does not contain the cross-terms inherent in the WVT and CWD methods, and provides frequency-dependent windowing which allows for arbitrarily high resolution of the high frequency signal components[76].(Fig. 3.4) Accordingly, high frequency components are not lost to analysis.

Fig. 3.4 Consecutive sinus beat HRV intervals from a healthy subject (top) together with its associated wavelet transform plot (below). The boundaries of the HF, LF and VLF regions are plotted across the transform surface[76].



3.5 Clinical applications of HRV

Although there are many studies have reported on the clinical value of HRV, it still

has not been incorporated into clinical practice. Despite a number of commercial analytical systems, evaluation of HRV for each individual patient requires time consuming manual editing of artifacts. To make HRV analysis into the clinical stage, we should do more research to make HRV as a means of assessing cardiovascular risk in primary prevention.

3.5.1 HRV and autonomic diabetic neuropathy

Autonomic dysfunction has been related to a wide range of diabetic complications. Early detection of subclinical autonomic impairment through HRV measurements in diabetic individuals may be important for risk stratification, including pharmacologic and lifestyle interventions[80]. Previous work documents significant differences in both frequency and time domain measures of HRV between healthy populations and diabetic patients[81]. Diabetic subjects show parasympathetic impairment as assessed by frequency domain measures shifted towards the low frequency side and decline of the time domain measures namely SDNN, RMSDD, NN50 count, pNN50. Diabetic patients presenting with autonomic dysfunction have a poor cardiovascular prognosis with 8 year mortality up to 23%[82]. Early identification of cardiovascular autonomic neuropathy permits timely initiation of therapy.

3.5.2 HRV and post myocardial infarction

The Multicenter Post Infarction Research Group published a work demonstrating that reduced HRV was able of identifying a group of patients with increased cardiac mortality after myocardial infarction[58]. Low parasympathetic activity was found to be a marker for poor prognosis in patients presenting with unstable angina and non ST-elevation myocardial infarction[81].

3.5.3 HRV and sudden cardiac death

Cardiac death has been found to be often preceded by changes in autonomic activity[83]. And patients at risk of sudden cardiac death have decreased HRV[81]. Investigators have shown low HRV values in apparently healthy people who had ECG-Holter recordings prior to their sudden death, anginal patients who died suddenly while wearing a Holter monitor, and patients surviving from cardiac arrest[84]. The highest rate of death was reported among this population who has low HRV, independent of randomization either to drug or to placebo[85]. Beside of those factors, identification of patients at high risk for sudden death, who may benefit from an implantable cardioverter defibrillator, remains elusive[85].

Patients with ventricular hypertrophy appear to be at a higher risk of sudden cardiac death[87]. Beside, sudden death occurs more frequently in patients with impaired left ventricular function, in whom acute ischemia is usually less important than is the presence of a myocardial scar.

3.5.4 HRV and chronic heart failure

Kearney et al found that low serum sodium, low SDNN and high serum creatinine identify patients at increased risk of death because of progressive heart failure in ambulant outpatients[88]. The United Kingdom Heart Failure Evaluation and Assessment of Risk Trial105 (in 433 outpatients) found that reduced SDNN was able to predict death from progressive heart failure, but not sudden death[81]. Reduced short-term LF power during controlled breathing has been shown to be a powerful predictor of sudden death in patients with chronic heart failure independently[89]. A study has shown that HRV triangular index provides information on clinical status and prognosis in patients with chronic congestive heart failure[90]. But still, determining the cause of death in heart failure can be difficult.

Chapter 4 Mitral Valve Prolapse Syndrome

4.1 Background

Mitral Valve Prolapse Syndrome (MVPS) is a valvular heart disease characterized by the displacement of an abnormally thickened mitral valve leaflet into the left atrium during systole[92]. Prolapse is an abnormal displacement of the mitral leaflets relative to their surrounding structures. The overall prognosis of patients with mitral valve prolapse is excellent, but a small subset will develop serious complications. There are various types of MVP, broadly classified as classic and non-classic. In its non-classic form, MVP carries a low risk of complications. In severe cases, complications include mitral regurgitation, infective endocarditis, congestive heart failure, and, in rare circumstances, cardiac arrest from dysrhythmias, usually resulting in sudden death.[92] Mitral valve prolapse has been reported to be the leading cause of isolated mitral regurgitation and regurgitation requiring surgery[102]. Duren et al., found complications such as the need for mitral-valve surgery, stroke, infectious endocarditis, and sudden death in one third of patients with mitral valve prolapse[91]. Marks et al. reported complications in 27 percent of patients with classic mitral-valve prolapse[103].

The condition was first described by John Brereton Barlow in 1966[93]. Barlow first recognized the mitral origin of late-systolic murmurs often associated with clicks, thus it was termed Click-Murmur syndrome or Barlow syndrome. And then Criley termed this condition mitral valve prolapse [94]. In the 1980s, echocardiography became readily available and led to an apparent epidemic of MVPS diagnosed, especially among young women, and various non-specific symptoms were attributed to MVPS [92]. MVPS is a heterogeneous disorder with variability in its pathological, clinical, and echocardiographic manifestations. The prognosis of the condition is usually benign, but there can be serious sequelae, the most frequent of which is Cardiac dysrhythmias and sudden cardiac death.

4.2 Diagnosis

To ensure that the cases are all diagnosed as MVPS, we use physical examination and two-dimensional echocardiography. They are clinical diagnostic criteria for MVPS[91]. A careful physical examination is highly sensitive for echocardiographic mitral valve prolapse, although the specificity is limited [96]. Redundant leaflets or chordae may produce an audible click without echocardiographic prolapse, giving false positive physical findings. Additionally, multiple sources of non-prolapse related

systolic clicks have been documented, such as bicuspid aortic stenosis, atrial myxoma, and pericarditis. Echocardiographic prolapse may exist without significant auscultatory findings [96]. Echocardiography is the most useful and sensitive method of diagnosing a prolapsed mitral valve. Two-dimensional and three-dimensional echocardiography is particularly valuable as they allow visualization of the mitral leaflets relative to the mitral annulus [92].

MVPS has been classified into several subtypes, based on leaflet thickness, concavity, and type of connection to the mitral annulus. Subtypes can be described as classic, non-classic, symmetric, asymmetric, flail, or non-flail. All measurements below refer to adult patients.[95]

The thickness of the mitral leaflets during diastasis was measured from the leading to the trailing edge of the thickest area of the mid-portion of the leaflet, excluding focal areas of thickness and chordae. Each leaflet was measured and categorized according to the maximal thickness. Subjects were classified as having classic prolapse, if they displacement exceeded 2 mm and maximal thickness was at least 5 mm (Figure 1 and Figure 2). And as having non-classic prolapse if displacement exceeded 2 mm but the maximal thickness was less than 5 mm. [91]

Borderline degrees of displacement (≤2 mm) are not associated with increased leaflet thickness, mitral regurgitation, left atrial enlargement, valve-related complications, or progression over a period of 10 years and were not included in the definition of prolapsed[104]. The degree of mitral regurgitation was assessed as the ratio of the maximal regurgitant jet area to the area of the left atrium in the parasternal and apical long-axis and apical four-chamber views[105]. The degree of regurgitation was considered to be trace, mild, moderate, or severe on the basis of ratios of >0 to 10, >10 to 20, >20 to 40, and >40 percent, respectively[105].

Fig. 4.1 Classic Mitral-Valve Prolapse during Systole. [91]

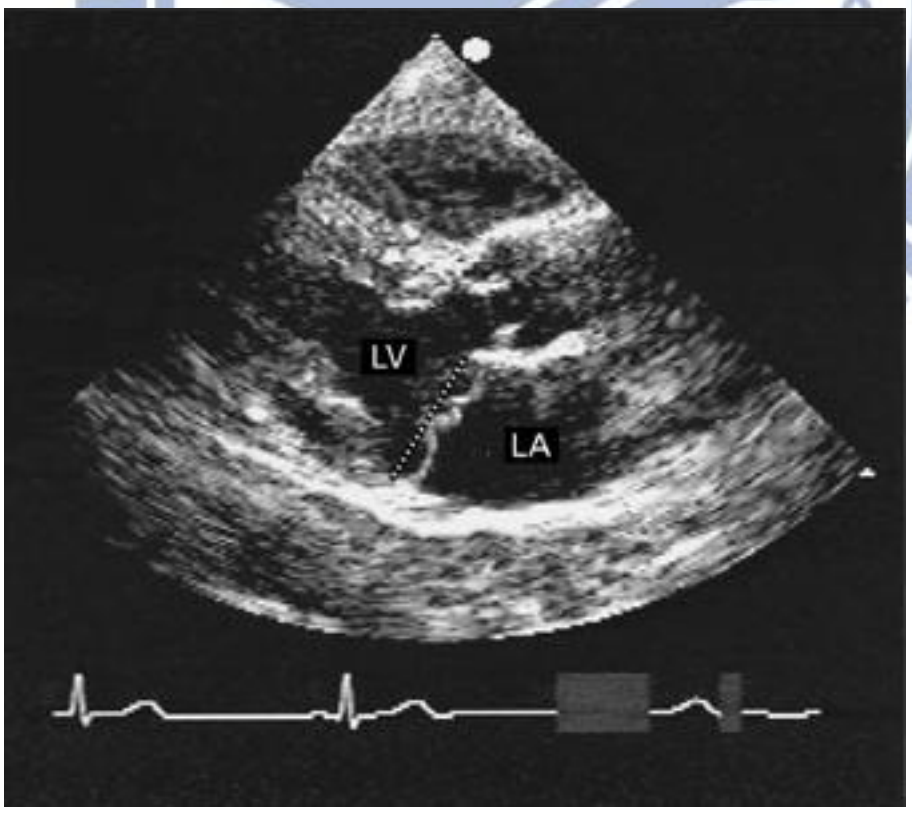
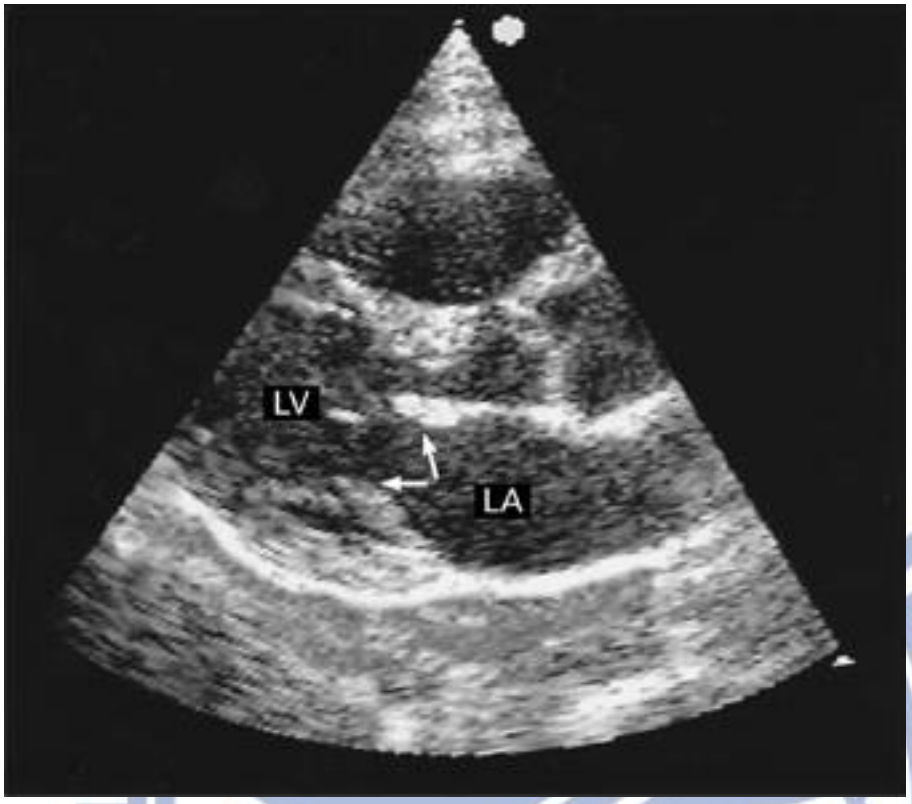


Fig. 4.2 Classic Mitral-Valve Prolapse with Leaflet Thickening (Arrows) during Diastole.[91]



Classical prolapse could be subdivided into symmetric and asymmetric, referring to the point at which leaflet tips join the mitral annulus [95]. In symmetric coaptation, leaflet tips meet at a common point on the annulus. Asymmetric coaptation is marked by one leaflet displaced toward the atrium with respect to the other. Patients with asymmetric prolapse are susceptible to severe deterioration of the mitral valve, with the possible rupture of the chordae tendineae and the development of a flail leaflet[95].

Asymmetric prolapse is further subdivided into flail and non-flail [95]. Flail prolapse occurs when a leaflet tip turns outward, becoming concave toward the left atrium, causing the deterioration of the mitral valve. The severity of flail leaflet varies, ranging from tip eversion to chordal rupture. Patients with flail leaflets have a higher prevalence of mitral regurgitation than those with the non-flail subtype [95].

4.3 Mitral Valve Prolapse Syndrome

Mitral valve prolapse syndrome (MVPS) has been applied to MVP associated with palpitations, atypical chest pain, dyspnea on exertion, low body mass index, and electrocardiogram abnormalities in the setting of anxiety, syncope, low blood pressure, and other signs suggestive of autonomic nervous system dysfunction [92].

Occasionally, supraventricular arrhythmias observed in MVP are associated with increased parasympathetic tone [98]. In this study, we prefer to collect MVPS patients' HRV data.

Mitral valve prolapse is usually diagnosed on the basis of a classic physical examination, discovered on an echocardiogram [91]. Various symptoms (like atypical

chest pain, exertional dyspnoea, palpitations, syncope, and anxiety) and clinical findings (including low blood pressure, leaner build, and electrocardiographic repolarisation abnormalities) have been associated with mitral valve prolapse and have been termed “mitral valve prolapse syndrome”[92]. The misperception that these symptoms frequently occur concomitantly with mitral valve prolapse has led to the practice of obtaining screening echocardiograms on patients who have atypical or nonspecific cardiovascular symptoms.

Abnormal autonomic function has been reported among symptomatic patients with mitral valve prolapse, including raised circulating concentrations of catecholamines, enhanced β-receptor affinity, increased vasoconstrictor tone, decreased plasma volume, and diminished vagal responsiveness [99,100]. Studies that included asymptomatic patients with mitral valve prolapse have shown no evidence of abnormal autonomic or neuroendocrine function either at rest or during tilt-table testing [101]. Thus, abnormal autonomic function might be responsible for symptoms in some patients with mitral valve prolapse, but it remains unclear whether their prolapse is directly related or incidental [102].

Chapter 5 Materials and Methods

5.1 Materials

We have total of 118 MVPS patients, 7 males and 111 females, who had been echocardiographically diagnosed as having MVPS at Taipei Medical University Hospital cardiology clinic from November 2008 to January 2013. And 148 healthy people (54 males and 94 females) with normal 12-lead ECG without previous history of medical disease from National Chiao-Tung University and residents in Hsinchu were recruited for the study. All subjects had sign an informed consent and agree to take part in the research.

Table 5.1 Age and Gender distribution with mean and standard deviation (SD).

	Symptomatic MVPS Average Age(years)		Normal Average Age(years)
Male (7)	39±7	Male (54)	28±4
Female (111)	42±13	Female (94)	26±6

We collected MVPS cases from the hospital, and most people aware of their medical needs normally in over 30 years old. And most our normal group are from university and company. That is to say, students, professors and office staffs are our main

resources. Their ages are most in 20 years old to 40 years old. Our cases amount is still not enough to classify them in group by age layer.

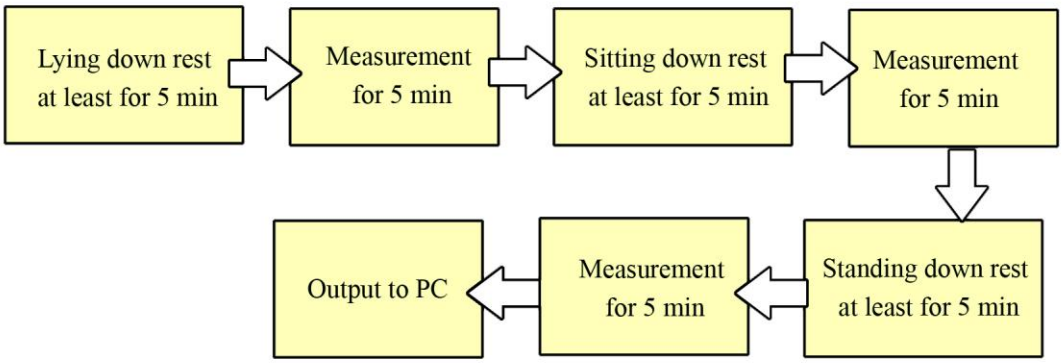
A locally developed Taiwanese machine (DailyCare BioMedical's ReadMyHeart®) was used to record the HRV. One lead ECG (modified lead Ⅱ, put the pad one in right shoulder and the other pad in left flank.) was used for signals collection and analysis. The QRS complexes were detected and labeled automatically. The results of the automatic analysis were reviewed subsequently, and any errors in R-wave detection and QRS labeled were then edited manually.

Fig. 5.1 The machine that we use in this study.

5.2 Methods of HRV Recording

Heart rate Variability is affected by Autonomic nervous system[66]. So before we do the test, there are some environmental factors have to be considered. The subjects were asked to rest 5 minutes before each HRV recording (Lying, sitting and standing.) (Figure 5.2) All the recordings were taken during the daytime (between 9:00 AM to 4:00 PM) to avoid the diurnal influence of the autonomic difference.

Fig. 5.2 Steps of the HRV experiment.



Methods for the calculation of power spectral density (PSD) can be classified as non-parametric and parametric[1]. Both methods provide comparable results. The advantages of the non-parametric methods are: (a) the simplicity of the algorithm employed (Fast Fourier Transform –FFT– in most of the cases) and (b) the high

processing speed, whilst the advantages of parametric methods are: (a) smoother spectral components which can be distinguished independently of preselected frequency bands, (b) easy post-processing of the spectrum with an automatic calculation of low and high frequency power components and easy identification of the central frequency of each component, and (c) an accurate estimation of PSD even on a small number of samples on which the signal is supposed to maintain stationary. The basic disadvantage of parametric methods is the need to verify the suitability of the chosen model and its complexity.

The present prospective study indicated that the FFT and autoregressive (AR) analyses provide significantly different estimates of heart rate variability in resting diabetic patients[107]. The spectral components of HRV calculated by using the two methods were not interchangeable and the FFT analysis must be preferred to AR for the following reasons: (a) all spectra components were obtained in each patient using FFT while numerous null or missing values were obtained using the AR method, (b) the AR results were more sensitive than FFT results to minor changes in the timing of the onset of analysis, (c) the day-to-day reproducibility of FFT was better than that of AR. Finally, by applying FFT over a 5-min resting period, the LF/HF ratio and LFnu and HFnu were essentially redundant in diabetic patients.

With FFT, the power is calculated by integration of the spectrum between the band lower and upper limits. Conversely, with AR, the criteria of assignment are based on the central frequency value of a well-defined oscillatory pattern, such a peak being not always observed. Furthermore, when two neighboring components are considered, the tails of each component could be assigned to one or another band depending on the method used[106]. FFT data should be interpreted in light of other indices quantifying the sympathovagal balance, namely time domain HRV indices.

5.3 Analysis of HRV

HRV was assessed automatically by the machine from the calculation of the mean R-R interval and its standard deviation measured on short-term 5 minute electrocardiograms, Normal-to-normal R-R interval data obtained from the edited time sequence of R-wave and QRS labeling were then transferred to a personal computer. In short-term HRV, frequency domain parameters has more clinical meanings than time-domain parameters[106].

For time-domain HRV measures, the mean N-N intervals and the standard deviation of N-N intervals during 5 minutes (SDNN) were then calculated. For

frequency-domain HRV parameters analysis, spectral power was quantified by fast Fourier transformation and autoregressive method for the following frequency bands: 0.15-0.4 Hz (high frequency), 0.04-0.15 Hz (low frequency).

Fig. 5.3 Steps of data analysis.

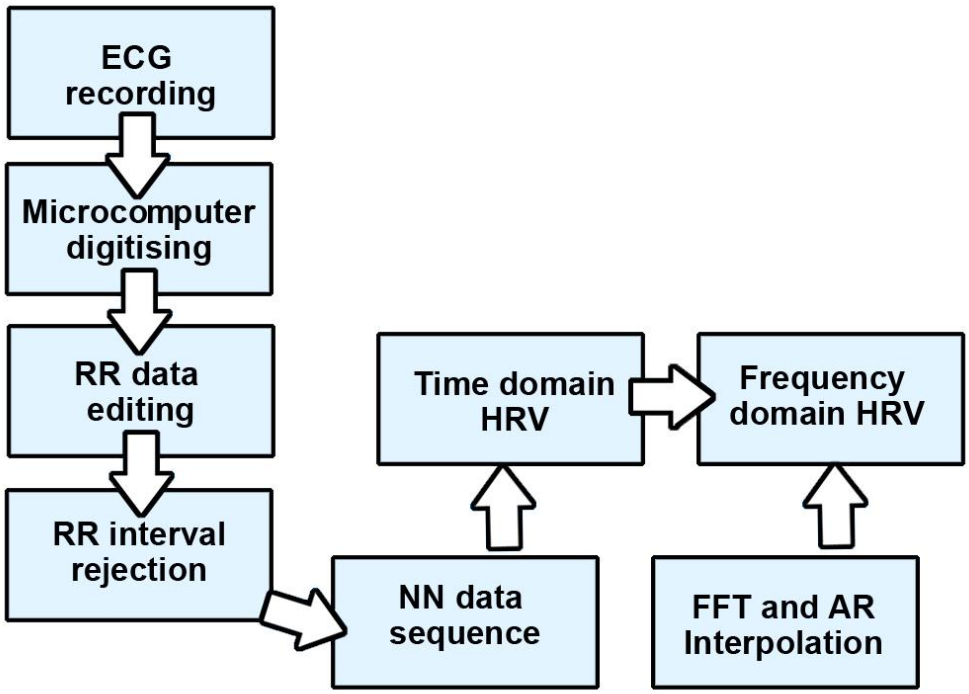


Table 5.2 Time domain parameters[1].

Variable	Units	Description
SDNN	ms	Standard deviation of all NN intervals.
SDANN	ms	Standard deviation of the averages of NN intervals in all 5 min segments of the entire recording.
RMSSD	ms	The square root of the mean of the sum of the squares of differences between adjacent NN intervals.
SDNN index	ms	Mean of the standard deviations of all NN intervals for all 5 min segments of the entire recording.
SDSD	ms	Standard deviation of differences between adjacent NN intervals.
NN50 count		Number of pairs of adjacent NN intervals differing by more than 50 ms in the entire recording. Three variants are possible counting all such NN intervals pairs or only pairs in which the first or the second interval is longer.
pNN50	%	NN50 count divided by the total number of all NN intervals.

Table 5.3 Frequency domain parameters[1]

Variable	Units	Description	Frequency range
Analysis of short-term recordings (5 min)			
5 min total power	ms^2	The variance of NN intervals over the temporal segment	approximately ≤0.4 Hz
VLF	ms^2	Power in very low frequency range	≤0.04 Hz
LF	ms^2	Power in low frequency range	0.04–0.15 Hz
LF norm	n.u.	LF power in normalised units LF / (Total Power–VLF) X 100	
HF	ms^2	Power in high frequency range	0.15–0.4 Hz
HF norm	n.u.	HF power in normalised units HF / (Total Power–VLF) X 100	
LF/HF		Ratio LF [ms^2] / HF [ms^2]	
Analysis of entire 24 h			
Total power	ms^2	Variance of all NN intervals	Approximately ≤0.4 Hz
ULF	ms^2	Power in the ultra low frequency range	≤0.003 Hz
VLF	ms^2	Power in the very low frequency range	0.003–0.04 Hz
LF	ms^2	Power in the low frequency range	0.04–0.15 Hz
HF	ms^2	Power in the high frequency range	0.15–0.4 Hz
α	ms^2	Slope of the linear interpolation of the spectrum in a log-log scale	Approximately ≤0.04 Hz

Table 5.4 Time domain parameters approximate frequency domain parameters[1].

Time domain variable	Approximate frequency domain correlate
SDNN	Total power
SDANN	ULF
SDNN index	Mean of 5 min total power
RMSSD	HF
SDSD	HF
NN50 count	HF
pNN50	HF

Time domain parameters used were SDNN, RMSSD and NN50. Frequency domain parameters selected were LF, HF and LF/HF. These parameters were defined in accordance with the 1996 ACC/AHA/ESC consensus[1].

5.4 Statistical Analysis

To make sure our data is normal distribution, Kolmogorov–Smirnov test was used at first. And then Paired Student t test was used to characterize differences in HRV variables. All HRV variables were expressed as mean ± SD. All statistical analyses were performed using Microsoft Excel 2007. A P value <0.05 was determined as statistically significant.

Chapter 6 Results

Figure 6.1 is the ECG signal cutting for 5 minutes. In below left picture means single wave of heart beats that you choose, PR interval, QRS complex, QT, QTc and so on. And right side is the waves of average value in 5 minutes, including PR interval, QRS complex, QT, QTc and ST segment.

Figure 6.2 is time domain analysis. It is including RRI histogram, HR histogram, RRI scatter, Mean RR, SDNN, RMSSD, NN50, pNN50 and so on.

Figure 6.3 is frequency domain analysis. It id including VLF power, LF power, HF power, Total power, LF norm, HF norm and LF/HF ratio.

Fig. 6.1 The ECG signal cutting for 5 minutes.

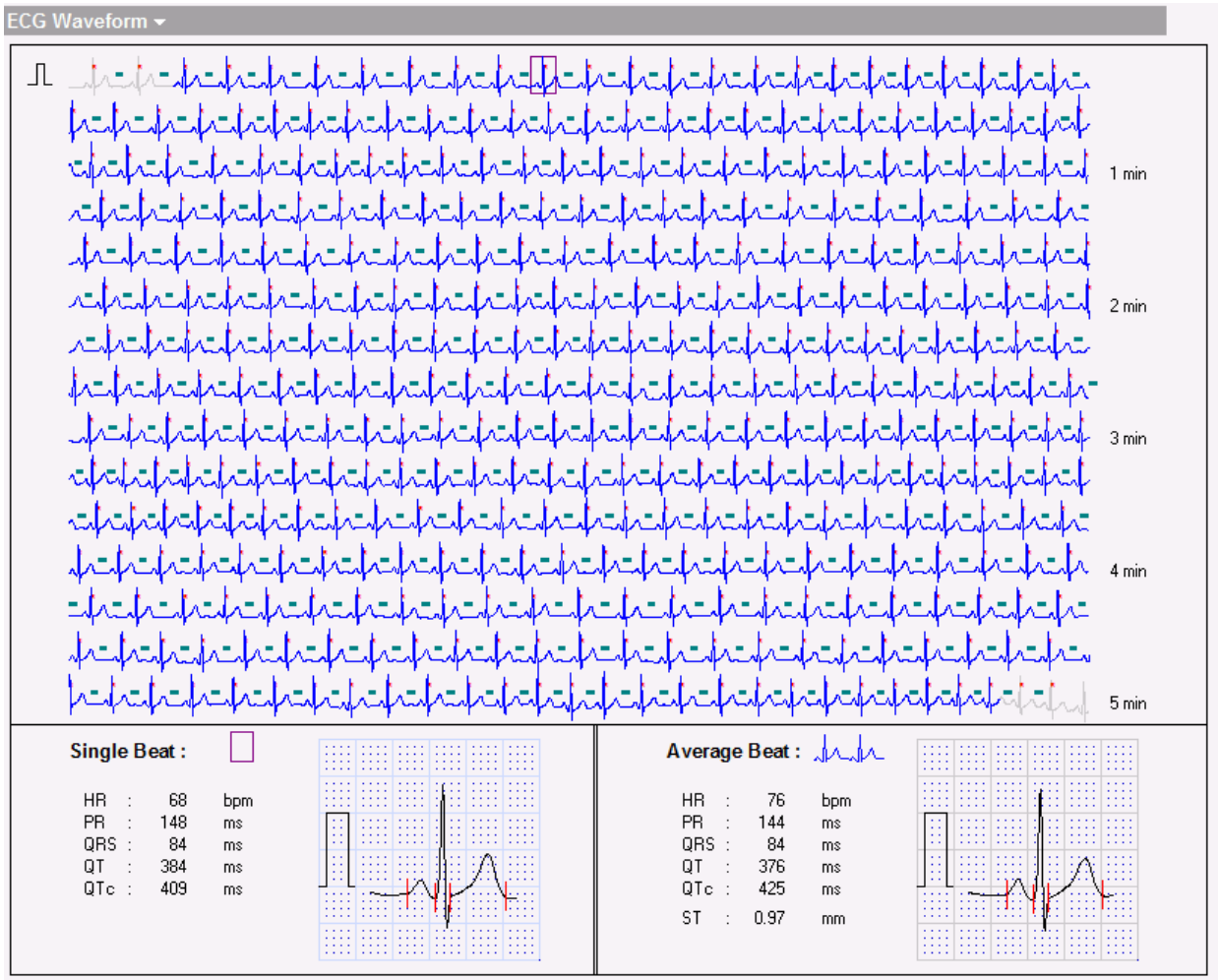
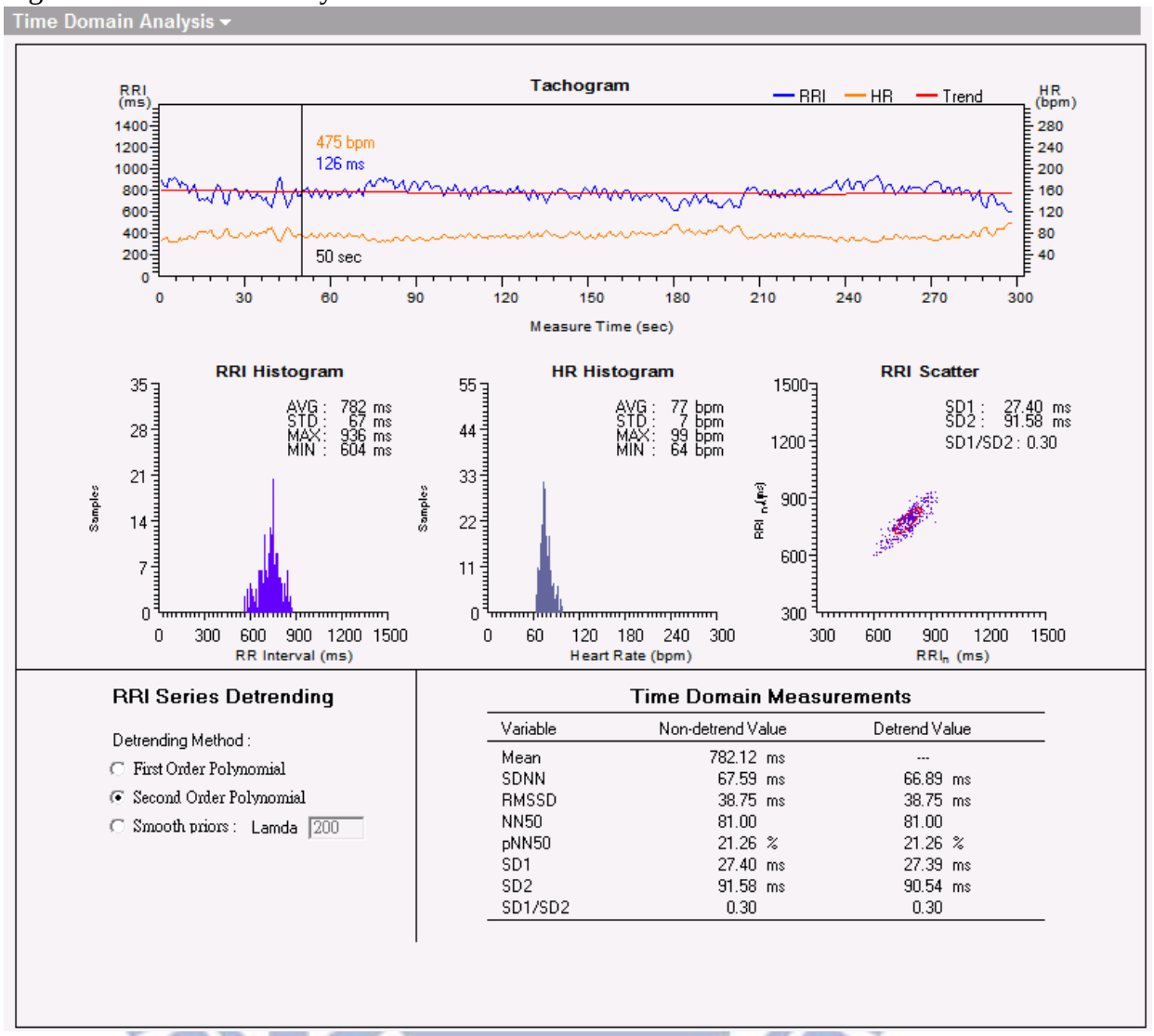
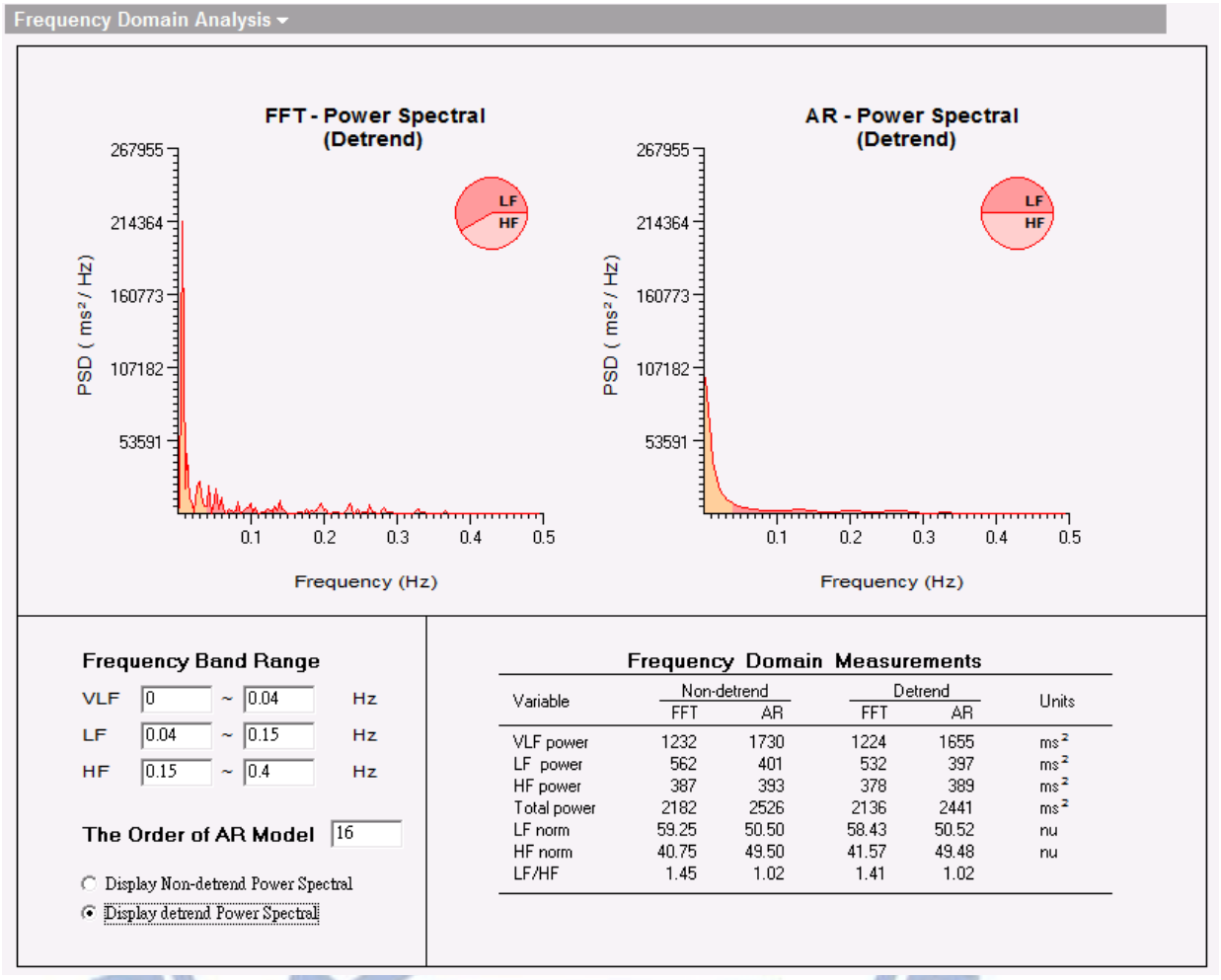


Fig. 6.2 Time domain analysis.



Variable	Non-detrend Value	Detrend Value
Mean	782.12 ms	---
SDNN	67.59 ms	66.89 ms
RMSSD	38.75 ms	38.75 ms
NN50	81.00	81.00
pNN50	21.26 %	21.26 %
SD1	27.40 ms	27.39 ms
SD2	91.58 ms	90.54 ms
SD1/SD2	0.30	0.30

Fig. 6.3 Frequency domain analysis.



6.1 Normal and MVPS

In table 6.1 and 6.2, we separate data into two groups in three different positions, we compared normal group with MVPS group.

Table 6.1 Time domain HRV Parameters between Symptomatic MVPS and Normal Group.[112][114-117][119]

HRV parameters	Posture	Symptomatic MVP (n=118)	Normal Group (n=148)	P value
SDNN(ms)	Lying	42.43 ± 37.75	51.06 ±33.75	0.03
	Sitting	36.67 ±17.35	50.67 ± 22.15	<0.01
	Standing	32.27 ±16.74	36.56 ±14.61	0.03
RMSSD(ms)	Lying	41.20 ± 50.84	46.84 ±43.83	NS
	Sitting	28.84 ±16.12	35.09 ±15.95	<0.01
	Standing	20.62 ±16.26	18.70 ± 9.55	NS
NN50	Lying	37.36 ± 53.89	60.24±57.75	<0.01
	Sitting	34.65 ±48.14	51.64 ±45.14	<0.01
	Standing	11.49±22.37	10.79 ±18.54	NS

*P<0.05 was statistically significant.

Table 6.2 Frequency domain HRV Parameters between Symptomatic MVPS and Normal Group.[112][114-117][119]

HRV parameters	Posture	Symptomatic MVP (n=118)	Normal Group (n=148)	P value
FFT				
TP	Lying	1213.50 ±719.13	1707.00 ± 241.83	<0.01
	Sitting	1379.50 ±1590.28	965.00 ±958.84	<0.01
	Standing	980.00 ±107.48	619.50 ±251.02	<0.01
HF(nu)	Lying	55.53 ± 15.90	53.96±16.11	NS
	Sitting	49.24 ±17.89	41.76 ±18.53	<0.01
	Standing	37.09 ±18.29	26.37 ±15.12	<0.01
LF(nu)	Lying	44.46 ± 15.90	45.95±16.11	NS
	Sitting	49.87 ±18.03	57.69 ±18.66	<0.01
	Standing	62.90 ±18.30	73.63 ±15.12	<0.01
LF/HF	Lying	1.03 ± 0.89	1.10 ±1.00	NS
	Sitting	1.34 ±1.08	2.00 ±1.89	<0.01
	Standing	2.97 ±4.19	4.45 ±3.55	<0.01
AR				
TP	Lying	1306.00 ± 650.54	1783.50 ± 256.68	<0.01
	Sitting	1400.00 ±1596.65	1121.00 ±1166.73	<0.01
	Standing	1344.50 ±581.95	627.50 ±252.44	0.04
HF(nu)	Lying	55.43 ± 15.99	53.91 ±16.32	NS
	Sitting	49.17 ±17.90	43.36 ±19.02	0.02
	Standing	37.02 ±18.33	26.41 ±15.94	<0.01
LF(nu)	Lying	44.56 ±15.98	46.08 ±16.33	NS
	Sitting	50.08 ±17.93	57.22 ±18.55	<0.01
	Standing	62.99 ±18.39	73.81 ±15.35	<0.01
LF/HF	Lying	1.04 ±0.90	1.11 ±0.99	NS
	Sitting	1.42 ±1.16	2.06 ±2.02	<0.01
	Standing	2.89 ±3.75	4.56 ±4.10	<0.01

*P<0.05 was statistically significant.

6.2 Gender difference

In table 6.3 to table 6.6, we compared male group with female group, and also in three different positions.

Table 6.3 Time domain HRV Parameters between Symptomatic MVPS male and female in all positions.[113-115][118-119]

HRV parameters	Posture	male (n=7)	female (n=111)	P value
SDNN(ms)	Lying	30.57 ± 47.00	43.17 ± 38.62	NS
	Sitting	51.51±25.33	35.83 ±16.66	NS
	Standing	36.63±17.40	32.02 ±16.80	NS
RMSSD(ms)	Lying	21.76 ± 35.95	42.42 ±52.07	<0.01
	Sitting	26.01 ±19.76	29 ±16.04	NS
	Standing	22.97±19.26	19.72 ±15.84	NS
NN50	Lying	15.43±35.03	38.73 ± 55.08	0.01
	Sitting	35 ± 56.06	34.63 ±48.12	NS
	Standing	9.75± 17.52	11.59 ±22.71	NS

*P<0.05 was statistically significant.

Table 6.4 Frequency domain HRV Parameters between Symptomatic MVPS Male and female in all positions.[113-115][118-119]

HRV parameters		male (n=7)	female (n=111)	P value
FFT				
TP	Lying	658.25±752.22	664.34±741.62	NS
	Sitting	799.00±978.64	668.71 ±605.27	NS
	Standing	514.33 ±409.80	501.36 ±432.93	NS
HF(nu)	Lying	28.60 ±9.99	56.49 ± 15.24	<0.01
	Sitting	31.35±6.14	50.25 ±17.82	<0.01
	Standing	23.87 ±7.52	37.83±18.46	0.01
LF(nu)	Lying	71.40±9.99	43.50 ±15.23	<0.01
	Sitting	68.66±6.14	48.81 ±17.91	<0.01
	Standing	76.13 ±7.52	62.15 ±18.47	0.01
LF/HF	Lying	2.07 ± 3.46	0.97±0.82	<0.01
	Sitting	2.29 ± 0.66	1.29±1.08	0.02
	Standing	3.60 ±1.80	2.93 ±4.29	NS
AR				
TP	Lying	680.00±768.69	703.56 ±767.00	NS
	Sitting	884.00 ±1090.36	714.65 ±686.83	NS
	Standing	537.00 ±423.22	558.33 ±536.96	NS
HF(nu)	Lying	28.46 ±10.18	56.39 ±15.33	<0.01
	Sitting	35.23 ±11.11	49.96±17.93	0.03
	Standing	21.84 ±6.29	37.87 ±18.43	<0.01
LF(nu)	Lying	71.54 ±10.18	43.59 ±15.32	<0.01
	Sitting	64.77 ±11.11	49.25 ± 17.93	0.03
	Standing	78.17 ±6.29	62.13 ±18.49	<0.01
LF/HF	Lying	2.12 ± 3.54	0.97 ±0.82	0.04
	Sitting	2.06 ±0.96	1.38 ±1.17	NS
	Standing	2.95±3.88	2.83 ±3.82	NS

*P<0.05 was statistically significant.

Table 6.5 Time domain HRV Parameters between normal male and female in all positions.[113-115][118-119]

HRV parameters		male (n=54)	female (n=94)	P value
SDNN(ms)	Lying	50.43 ±22.19	51.42 ±38.98	NS
	Sitting	51.81 ± 23.31	49.66±20.99	NS
	Standing	37.21 ±13.86	35.59 ±15.27	NS
RMSSD(ms)	Lying	37.44 ±18.50	52.23 ±52.54	<0.01
	Sitting	34.69±16.63	35.45±15.30	NS
	Standing	18.37±8.35	19±10.55	NS
NN50	Lying	50.09 ±45.52	66.07 ±63.22	0.04
	Sitting	46.94±42.82	55.84 ±46.74	NS
	Standing	11.25±16.56	10.36 ±20.23	NS

*P<0.05 was statistically significant.

Table 6.6 Frequency domain HRV Parameters between normal male and female in all positions.[113-115][118-119]

HRV parameters		male (n=54)	female (n=94)	P value
FFT				
TP	Lying	1447.49±1294.49	1438.30 ±1329.22	NS
	Sitting	1513.59 ±1783.71	1362.5±1433.58	NS
	Standing	778.14 ±607.27	720.24±736.91	NS
HF(nu)	Lying	42.81 ±14.03	60.37 ±13.58	<0.01
	Sitting	36.47 ±16.01	46.49±19.46	<0.01
	Standing	21.26 ±10.76	31.10±17.02	<0.01
LF(nu)	Lying	56.96 ±14.19	39.62 ±13.59	<0.01
	Sitting	63.52 ±16.03	52.46 ±19.43	<0.01
	Standing	78.74 ±10.76	68.89±17.02	<0.01
LF/HF	Lying	1.62 ± 0.97	0.81 ±0.89	<0.01
	Sitting	2.45 ±1.91	1.60±1.77	0.01
	Standing	5.09 ±3.34	3.86 ±3.62	0.04
AR				
TP	Lying	1524.24±1367.96	1511.06 ±1408.95	NS
	Sitting	1565.20 ±1820.76	1443.71 ±1530.34	NS
	Standing	1025.25 ±1035.84	782.48±812.72	NS
HF(nu)	Lying	42.55±14.06	60.44 ±13.81	<0.01
	Sitting	36.49 ±16.44	49.51 ±19.19	<0.01
	Standing	21.09±10.98	31.34 ±18.19	<0.01
LF(nu)	Lying	57.44 ±14.06	39.55 ±13.81	<0.01
	Sitting	63.48 ±16.52	51.62±18.60	<0.01
	Standing	78.91 ±10.98	69.08 ±17.30	<0.01
LF/HF	Lying	1.64 ± 0.95	0.81 ±0.88	<0.01
	Sitting	2.52±2.09	1.65 ±1.85	0.01
	Standing	5.38±4.08	3.79 ±3.97	0.02

*P<0.05 was statistically significant.

6.3 Postural changes

In table 6.7 to table 6.12, we try to compare different posture in lying, sitting and standing in normal group. And in table 6.8 to 6.12, we compared different posture in MVPS group.

6.3.1 Postural changes in normal

Table 6.7 Time domain HRV Parameters between lying and sitting position in normal group.

HRV parameters	Lying (n=148)	Sitting (n=148)	P value
SDNN(ms)	51.06 ± 33.75	50.67 ± 22.15	NS
RMSSD(ms)	46.84 ± 43.83	35.09 ± 15.95	<0.01
NN50	60.24 ± 57.75	51.64 ± 45.14	NS

*P<0.05 was statistically significant.

Table 6.8 Frequency domain HRV Parameters between lying and sitting position in normal group.

HRV parameters	Lying (n=148)	Sitting (n=148)	P value
FFT			
TP	1707.00 ± 241.83	965.00 ± 958.84	NS
HF(nu)	53.96 ± 16.11	41.76 ± 18.53	<0.01
LF(nu)	45.95 ± 16.11	57.69 ± 18.66	<0.01
LF/HF	1.10 ± 1.00	2.00 ±1.89	<0.01
AR			
TP	1783.50 ± 256.68	1121.00 ± 1166.73	NS
HF(nu)	53.91 ± 16.32	43.36 ± 19.02	<0.01
LF(nu)	46.08 ± 16.33	57.22 ±18.55	<0.01
LF/HF	1.11 ±0.99	2.06 ±2.02	<0.01

*P<0.05 was statistically significant.

Table 6.9 Time domain HRV Parameters between lying and standing position in normal group.

HRV parameters	Lying (n=148)	Standing (n=148)	P value
SDNN(ms)	51.06 ± 33.75	36.56 ±14.61	<0.01
RMSSD(ms)	46.84 ± 43.83	18.70 ± 9.55	<0.01
NN50	60.24 ± 57.75	10.79±18.54	<0.01

*P<0.05 was statistically significant.

Table 6.10 Frequency domain HRV Parameters between lying and standing position in normal group.

HRV parameters	Lying (n=148)	Standing (n=148)	P value
FFT			
TP	1707.00 ± 241.83	619.50 ± 251.02	<0.01
HF(nu)	53.96 ± 16.11	26.37 ± 15.12	<0.01
LF(nu)	45.95 ± 16.11	73.63 ± 15.12	<0.01
LF/HF	1.10 ± 1.00	4.45 ±3.55	<0.01
AR			
TP	1783.50 ± 256.68	627.50 ± 252.44	<0.01
HF(nu)	53.91 ± 16.32	26.41 ±15.94	<0.01
LF(nu)	46.08 ± 16.33	73.81 ±15.35	<0.01
LF/HF	1.11 ±0.99	4.56 ± 4.10	<0.01

*P<0.05 was statistically significant.

Table 6.11 Time domain HRV Parameters between sitting and standing position in normal group.

HRV parameters	Sitting (n=148)	Standing (n=148)	P value
SDNN(ms)	50.67 ± 22.15	36.56 ±14.61	<0.01
RMSSD(ms)	35.09 ± 15.95	18.70 ± 9.55	<0.01
NN50	51.64 ± 45.14	10.79±18.54	<0.01

*P<0.05 was statistically significant.

Table 6.12 Frequency domain HRV Parameters between sitting and standing position in normal group.

HRV parameters	Sitting (n=148)	Standing (n=148)	P value
FFT			
TP	965.00 ± 958.84	619.50 ± 251.02	<0.01
HF(nu)	41.76 ± 18.53	26.37 ± 15.12	<0.01
LF(nu)	57.69 ± 18.66	73.63 ± 15.12	<0.01
LF/HF	2.00 ±1.89	4.45 ±3.55	<0.01
AR			
TP	1121.00 ± 1166.73	627.50 ± 252.44	<0.01
HF(nu)	43.36 ± 19.02	26.41 ±15.94	<0.01
LF(nu)	57.22 ±18.55	73.81 ±15.35	<0.01
LF/HF	2.06 ±2.02	4.56 ± 4.10	<0.01

*P<0.05 was statistically significant.

6.3.2 Postural changes in MVPS

Table 6.13 Time domain HRV Parameters between lying and sitting position in Symptomatic MVPS group.

HRV parameters	Lying (n=118)	Sitting (n=118)	P value
SDNN(ms)	42.43 ± 37.75	36.67 ± 17.35	NS
RMSSD(ms)	41.20 ± 50.84	28.84 ± 16.12	<0.01
NN50	37.36 ± 53.89	34.65 ± 48.14	NS

*P<0.05 was statistically significant.

Table 6.14 Frequency domain HRV Parameters between lying and sitting position in Symptomatic MVPS group.

HRV parameters	Lying (n=118)	Sitting (n=118)	P value
FFT			
TP	1213.50 ± 719.13	1379.50 ± 1590.28	NS
HF(nu)	55.53 ± 15.90	49.24 ± 17.89	<0.01
LF(nu)	44.46 ± 15.90	49.87 ± 18.03	0.02
LF/HF	1.03 ± 0.89	1.34 ± 1.08	0.02
AR			
TP	1306.00 ± 650.54	1400.00 ± 1596.65	NS
HF(nu)	55.43 ± 15.99	49.17 ± 17.90	<0.01
LF(nu)	44.56 ± 15.98	50.08 ± 17.93	0.02
LF/HF	1.04 ±0.90	1.42 ± 1.16	<0.01

*P<0.05 was statistically significant.

Table 6.15 Time domain HRV Parameters between lying and standing position in Symptomatic MVPS group.

HRV parameters	Lying (n=118)	Standing (n=118)	P value
SDNN(ms)	42.43 ± 37.75	32.27 ± 16.74	<0.01
RMSSD(ms)	41.20 ± 50.84	20.62 ± 16.26	<0.01
NN50	37.36 ± 53.89	11.49 ± 22.37	<0.01

*P<0.05 was statistically significant.

Table 6.16 Frequency domain HRV Parameters between lying and standing position in Symptomatic MVPS group.

HRV parameters	Lying (n=118)	Standing (n=118)	P value
FFT			
TP	1213.50 ± 719.13	980.00 ± 107.48	0.03
HF(nu)	55.53 ± 15.90	37.09 ± 18.29	<0.01
LF(nu)	44.46 ± 15.90	62.90 ± 18.30	<0.01
LF/HF	1.03 ± 0.89	2.97 ± 4.19	<0.01
AR			
TP	1306.00 ± 650.54	1344.50 ± 581.95	0.04
HF(nu)	55.43 ± 15.99	37.02 ± 18.33	<0.01
LF(nu)	44.56 ± 15.98	62.99 ± 18.39	<0.01
LF/HF	1.04 ±0.90	2.89 ± 3.75	<0.01

*P<0.05 was statistically significant.

Table 6.17 Time domain HRV Parameters between sitting and standing position in Symptomatic MVPS group.

HRV parameters	Sitting (n=118)	Standing (n=118)	P value
SDNN(ms)	36.67 ± 17.35	32.27 ± 16.74	NS
RMSSD(ms)	28.84 ± 16.12	20.62 ± 16.26	<0.01
NN50	34.65 ± 48.14	11.49 ± 22.37	<0.01

*P<0.05 was statistically significant.

Table 6.18 Frequency domain HRV Parameters between sitting and standing position in Symptomatic MVPS group.

HRV parameters	Sitting (n=118)	Standing (n=118)	P value
FFT			
TP	1379.50 ± 1590.28	980.00 ± 107.48	NS
HF(nu)	49.24 ± 17.89	37.09 ± 18.29	<0.01
LF(nu)	49.87 ± 18.03	62.90 ± 18.30	<0.01
LF/HF	1.34 ± 1.08	2.97 ± 4.19	<0.01
AR			
TP	1400.00 ± 1596.65	1344.50 ± 581.95	NS
HF(nu)	49.17 ± 17.90	37.02 ± 18.33	<0.01
LF(nu)	50.08 ± 17.93	62.99 ± 18.39	<0.01
LF/HF	1.42 ± 1.16	2.89 ± 3.75	<0.01

*P<0.05 was statistically significant.

6.4 Results

For normal group versus MVPS group, in time domain only SDNN between symptomatic MVPS and Normal group was statistically significantly different in all positions. And they can be significantly differentiated by Time domain's SDNN and Frequency domain's Total Power. In Frequency domain, all Parameters were shown to have significant differences except in lying position. And there is significantly statistically differences of frequency domain HRV parameters in sitting position[119].

For gender difference, in time domain there were statistically differences in RMSSD

and NN50 at lying both in MVPS and Normal. And in frequency domain, all parameters were statistically significantly different in all postures both in MVPS and normal except total power and LF/HF in standing position.

For postural changes, in normal group that time domain parameters only RMSSD was statistically difference between lying and sitting, but in other postural compared, all parameters were significantly different. And it is the same as in frequency domain parameters, only TP in lying compared with sitting posture had no difference. In MVPS group, the result of time domain parameters and frequency domain were the same as in normal group, except in sitting compared with standing posture. SDNN of time domain, and TP of frequency domain had no significant difference. These results and conclusions have been published in the 40th International Congress on Electrocardiology (ICE), Scotland, 2013.[119]

Chapter 7 Conclusions and Discussions

In conclusions,

1. There are differences between normal and MVPS, and the most significant posture is sitting position.
2. In short-term HRV, it is prefer frequency domain analyze than time domain analyze.
3. There are differences between male and female whether in normal or MVPS, especially in frequency domain.
4. Both MVPS and normal cases are affected by postural changes.

Different machines and software were used to analyze in different researches, so there is no official standard normal value in HRV. We hope this study will help to build the database in Taiwanese.

According to 1996 ACC/AHA/ESC consensus[1], short term HRV is suit for frequency domain parameters to analyze. HF presents how parasympathetic nerves control heart rate, LF presents activity of sympathetic nerves and LF/HF presents the balance between sympathetic and parasympathetic nerves.

Normal group and symptomatic MVPS can be significantly differentiated by Time domain's SDNN and Frequency domain's Total Power. And there are significantly statistically different of frequency domain HRV parameters in sitting position.

MVPS patients' ECGs show the changing ST-T wave[10][11] so their sympathetic nerves are more active than normal people. But in this study result show that normal data is lower than MVPS data in HF, and higher than MVPS in LF. That is to say, sympathetic system is more active in normal than in MVPS. But if it classifies into male and female, then the result in female would be normal group's HF is higher than MVPS group, and LF is lower. For female, vagal nerves are more active in normal than in MVPS, and it is the same with clinical study. Male has no significant difference between normal and MVPS. Maybe it is because male data is not enough and the data has extreme values.

The results show the statistically changing of ANS in MVPS cases. In clinical use, we should consider of not only the analysis of Ultrasound, but also nerve system of patients.

Gender specific HRV variation had been reported in our previous study in normal

Taiwanese[108]. It is further strengthened the digenetic criteria for HRV should be gender specific in MVPS as well. Although the results show that time domain parameters might not be of use for the evaluation MVPS, frequency domain with postural changes might be a useful tool in MVPS diagnosis risk stratification in Taiwanese.

ANS was affected by female hormones, so in female, sympathetic tone will decline and parasympathetic will elevate if comparing with male[109]. Although time domain parameters have no statistically difference could be refer, but in frequency domain, the parameters show that female is higher than male in HF, and is lower in LF and LF/HF ratio. It conforms to our suppose whether in normal group or in MVPS group.

There is no significant difference between lying and sitting posture, but between lying and standing, which have bigger difference in posture, the data exist significant difference. It shows that postural changes will affect ANS, whether in normal group or MVPS group. So it might be implied that postural changes should be included in the future HRV research both on symptomatic MVPS and normal controls.

In lying posture has the higher RR interval. That means it has a lower heart rate and

will have higher SDNN value. That result is the same with the result from Gamelin FX and the group[111]. In frequency domain parameters, lying posture is the highest in HF and the lowest in LF both in normal and MVPS group; whereas standing posture is the lowest in HF and the highest in LF. It means when people in lying posture, their parasympathetic nerves are more active than sympathetic nerves. On the contrary, sympathetic nerves have more activity in standing position.

Our normal cases resource is the university in Hsin-Chu area, and MVPS cases are the patients mostly from hospital in Taipei area. So most normal cases are in 20 ~ 25 years old range, and MVPS cases are in 30 ~ 60 years old range. In the future, we should set an age level group for 10 years to classify the data. We already know in normal case, the older one has a lower HRV value. We also need to collect more data in every age level, especially male in MVPS.

This study is trying to build a HRV standard value for Taiwanese. Nowadays researches are mostly for Caucasian and African[110]. There is rarely for Asian, even for Taiwanese. People live in different area and environment might have different factor to affect their ANS, and different ethnicity may have some differences in their ANS in nature. Use the standard for Caucasian in other race is not a good choice.

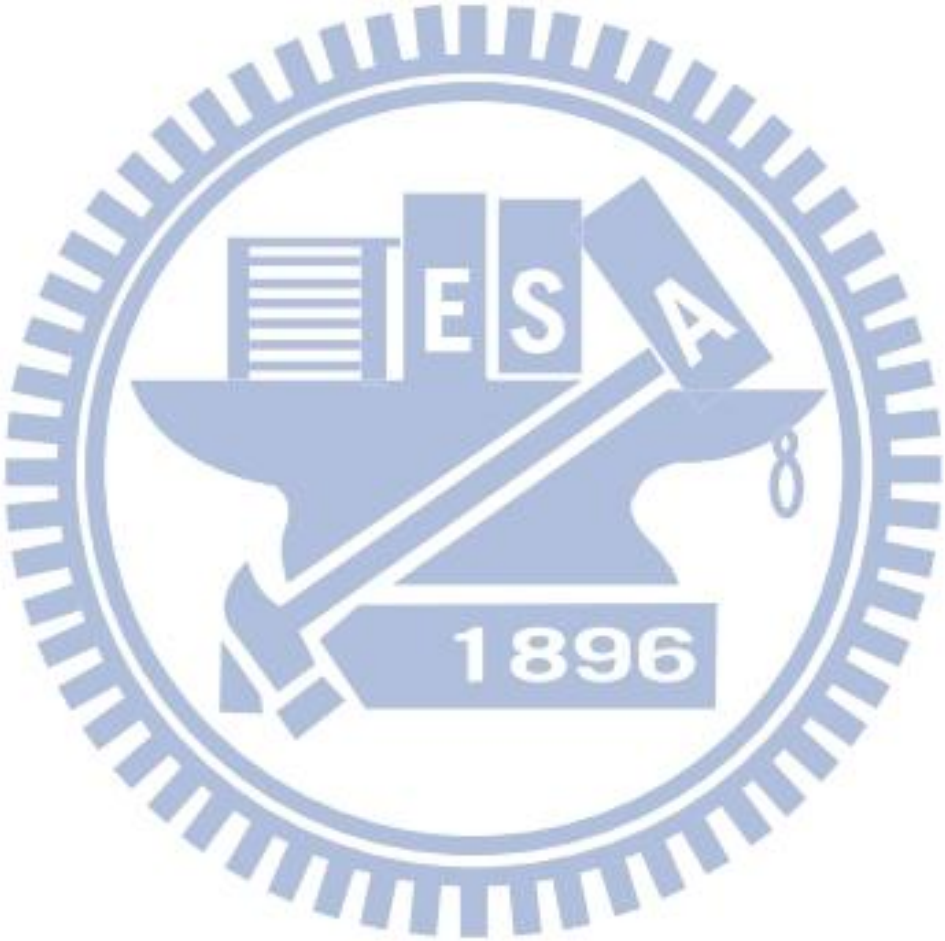
Although Taiwan has no broad land, but there are many mountains. Numerous people live in the high altitude place, and they might be one of our case. This factor that where the case live in flat or in mountain might affect their ANS. In future work, maybe we should consider this factor and collect more cases to prove this suppose.

The HRV measurements are processing form 9:00 A.M to 4:00 P.M, this period might be too long for HRV study because of the diurnal of ANS in humans. Maybe we can try to shorten the experimental time to reduce the mistakes. But also we need more data to be collected that we can exactly classify the data.

Height and weight might also affect the HRV results. The gender different of HRV might not only affected by female hormone, but BMI value. In the future work, we can try to classify data with BMI.

General to say, compared to female, male have more exercise habits. Exercises will also affect HRV results. And we should notice in what vocations the cases are. Some particular jobs need to work at night, and some student groups are used to stay night. Diurnal is also an important changing factor in ANS. Besides, some people may have great pressure about their jobs, academic performance or their own personal

relationship problems. Mental situation will also affect ANS activity. When people are happy or exited, sympathetic tone is more active. And when they are in low tension, that parasympathetic tone is more active than sympathetic tone. Before we process the test, we should have a discussion with our cases about their life style to make sure the errors are reduced to minimum.



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116. Ya-Chu Chen, Lung-Wen Tsai, Ing-Fang Yang, Chung-Kai Tseng, Ten-Fang Yang. “A Research of Heart Rate Variability between Symptomatic Mitral Valve Prolapse Syndrome and Normal”, The 13th International Society for Applied Cardiovascular Biology (ISACB), London, United Kingdom, 12-15, September, 2012.

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Electrocardiology and Cardiovascular Bioinformatics Laboratory

國立交通大學

12 導程心電圖與心率變異性研究計劃 受檢者同意書

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受檢者姓名：	聯絡電話：
受檢者性別：□男　□女	通訊地址：
身分證號碼：	身高：　　cm
出生日期：西元　　年　　月　　日	體重：　　kg
年齡：	血壓：　　mmHg

1. 研究目的：

本研究目的收集生理表現正常個案及二尖瓣脫垂症候群的 12 導程 ECG 及 HRV 之 Data base 建立，統計出適用於台灣人的 12 導程心電圖及心率變異分析，作於臨床診斷規則。

12 導程心電圖(ECG)	心率變異分析(HRV)
心電圖(ECG)是記錄心臟組織電壓變化的一個圖形，利用心臟傳導系統發出電波，興奮整個心臟肌肉纖維而產生收縮。電波的產生及傳導，皆會產生微弱的電流分佈全身，若將心電圖記錄器的電極連接到身上不同的部位，就可記錄出「心電圖」。 在臨床診斷價值如下：心房及心室肥大、心房及心室電波的傳導遲延、心肌缺血或梗塞、心律不整、心包膜炎、使用心臟藥物、電解質代謝障礙、及評估心臟節律器。	心率變異分析(HRV)是記錄連續性的心跳速率變化的程度，計算方式是藉由心電圖所得到的心跳與心跳間隔的時間序列，運用數學方法加以計算得到的參考數據，應用於判斷自律神經系統之功能。 在臨床診斷價值如下：心因性猝死、高血壓、出血性休克、敗血性休克，及可做為預測心肌梗塞後的預後指標。

2. 受檢程序：

ECG	HRV(躺、坐、站)
A. 請放鬆心情，臥姿時請平躺。 B. 將四肢及胸前導極放置部位以酒精棉片擦拭。 C. 導極放置部位如下： 四肢導極：左腳、右腳、左手、右手 胸前導極：V1：右側第四肋間胸骨線 V2：左側第四肋間胸骨線	A. 為時共 30 分鐘的測量，期間請勿走動及說話。 B. 受檢步驟：　休息 5 分鐘 ↓ 平躺測量分鐘 ↓ 休息 5 分鐘

V3：在 V2-V4 之中點 V4：左側第五肋間鎖骨中線上方 V5：左側第五肋間前腋線上，於 V4-V6 之中點 V6：左側第五肋間中腋線上 D.接上導極。	↓ 坐姿測量 5 分鐘 ↓ 休息 5 分鐘 ↓ 站姿測量 5 分鐘

3.其他：

A. 整個檢查過程約需 30~45 分鐘，身體不會有任何不適的感覺，請放鬆且平緩的呼吸。

B. 檢查 12 導程心電圖，女生須把胸罩鬆開往上掀，可不必完全拿掉。

C. 受試者佩戴金屬項鍊、手錶或腕飾，則請受試者取下以免影響測量。

4.參與此實驗可獲得之幫助：

※主動告知受檢者試驗之結果。

※提供受檢者試驗結果之諮詢服務。

※提供受檢者相關醫學資訊。

※此檢測無須擔付任何受檢費用。

5.受檢者聲明

以上資訊已向我說明，我有機會詢問此研究的相關問題，我已了解且同意此研究計畫，若我以後有問題，可與心臟電氣學及心血管生物資訊學實驗室(BA108)聯絡。

受檢者簽名：_____(正楷)

身分證字號：

受檢日期：西元　　年　　月　　日

6.研究者聲明：

我保證我本人，已對上述人士解釋過本研究，包括本研究目的、受檢程序與參加本研究可能的相關注意事項。所有被檢者提出之疑問，均已予以答覆；對於受檢者之基本資料均以保密。

測試者簽名：_____

主要主持人：Professor Ten-Fang YANG〔楊騰芳 博士〕MD,MSc,PhD

7.備註：

Appendix 2 Publication List

2012 TSOC

Ya-Chu Chen, Lung-Wen Tsai, Ing-Fang Yang, Chung-Kai Tseng, Ten-Fang Yang. Short Term Heart Rate Variability might be useful for the evaluation of Taiwanese symptomatic mitral valve prolapse syndrome. *The 42th Taiwan Society of Cardiology (TSOC)*. Taipei, Taiwan. 4-6, May, 2012. P19, p202, Acta Cardiologica Sinica Vol. 28.

Ya-Chu Chen, Lung-Wen Tsai, Ing-Fang Yang, Chung-Kai Tseng, Ten-Fang Yang. A research on Gender Differences in Taiwanese Symptomatic MVPS and Normal. *The 42th Taiwan Society of Cardiology (TSOC)*. Taipei, Taiwan. 4-6, May, 2012. P20, p202, Acta Cardiologica Sinica Vol. 28.

2012 ICE Beijing

Ya-Chu Chen, Lung-Wen Tsai, Ing-Fang Yang, Chung-Kai Tseng, Ten-Fang Yang. HRV can be used as a non-invasive tool to evaluate symptomatic MVPS. *The 39th International Congress on Electrocardiology (ICE)*. Beijing, China. 9-12, August, 2012. Oral presentation.

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Ya-Chu Chen, Lung-Wen Tsai, Ing-Fang Yang, Chung-Kai Tseng, Ten-Fang Yang. Heart Rate Variability With Postural Changes Might Be Useful For Detection Of Symptomatic Mitral Valve Prolapse Syndrome In Taiwanese. *The 13th International Society for Applied Cardiovascular Biology (ISACB)*. London, United Kingdom. 12-15, September, 2012. P12, p31, ISACB's 2012 scientific program.

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2013 TSOC

Ya-Chu Chen, Chih-hao Shu, Lung-Wen Tsai, Ing-Fang Yang, Chung-Kai Tseng, Ten-Fang Yang. A study of postural effect on Heart Rate Variability in Symptomatic Taiwanese Mitral Valve Prolapse Syndrome. *The 43th Taiwan Society of Cardiology (TSOC)*. Taipei, Taiwan. 17-19, May, 2013. P19, p207, Acta Cardiologica Sinica Vol. 29.

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Chih-hao Hsu, Ya-Chu Chen, Lung-Wen Tsai, Ing-Fang Yang, Chung-Kai Tseng, Ten-Fang Yang. Standard 12 lead ECG interval in mitral valve prolapsed syndrome in Taiwan. *The 43th Taiwan Society of Cardiology (TSOC)*. Taipei, Taiwan. 17-19, May, 2013. P14, p206, Acta Cardiologica Sinica Vol. 29.

Chih-hao Hsu, Ya-Chu Chen, Lung-Wen Tsai, Ing-Fang Yang, Chung-Kai Tseng, Ten-Fang Yang. Gender difference of ECG QT interval between MVPS and normal. *The 43th Taiwan Society of Cardiology (TSOC)*. Taipei, Taiwan. 17-19, May, 2013. P14, p206, Acta Cardiologica Sinica Vol. 29.

2013 ICE Glasgow

Ya-Chu Chen, Chih-hao Shu, Lung-Wen Tsai, Ing-Fang Yang, Chung-Kai Tseng, Ten-Fang Yang. Gender Differences of Heart Rate Variability between Taiwanese Symptomatic Mitral Valve Prolapse Syndrome and Normal. *The 40th International Congress on Electrocardiology (ICE)*. Glasgow, Scotland. 7-10, August, 2013. In press.

Chih-hao Hsu, Ya-chu Chen, Lung-Wen Tsai, Ing-Fang Yang, Chung-Kai Tseng, Ten-Fang Yang. ECG interval might be useful for the detection of normal valve prolapse syndrome in Taiwan. *The 40th International Congress on Electrocardiology (ICE)*. Glasgow, Scotland. 7-10, August, 2013. In press.

Appendix 3 Poster of 42nd Taiwan Society of Cardiology (1)

A research on Gender Differences in Taiwanese Symptomatic MVPS and Normal

Ya-chu Chen[1], Lung-Wen Tsai[2], Ing-Fang Yang[4], Chung-Kai Tseng[3], Ten-Fang Yang[1, 2]
(1) National Chiao Tung University, Hsin Chu, Taiwan (2) Taipei Medical University Hospital, Taipei, Taiwan (3) China Medical University Hospital, Taichung, Taiwan (4) Jen Chi General Hospital, Taipei, Taiwan

Abstract

Introduction:
Short term Heart Rate Variability (HRV) recording was claimed to be similar to 24 hour HRVs. Mitral Valve Prolapse Syndrome (MVPS) was reported to be associated with significant Autonomic Nervous System (ANS) dysfunction in Caucasians. Sexual variation of HRV was also previously reported.
Objective:
The aim is to evaluate if gender differences can be used for the detection of MVPS from normals.
Materials and Methods:
A total of 72 symptomatic echocardiographically documented MVPS patients (4 males and 68 females) from TMUH and 101 healthy NCTU students (51 males and 50 females) were recruited as normals for this study. A local HRV system with one modified lead II was used. All recordings were taken during daytime to avoid diurnal ANS influences. The subjects were asked to rest 5 minutes before recording and the postural alterations (lying, sitting and standing).
Results:
For MVPs, no difference was found in time domain between male and female.
For normal male and female, frequency domain was statistically significantly different only in LF/HF ratio; Whereas, postural changes were shown to have significant effects in LF/HF ratio in all postures in frequency domain.

Table: Frequency domain HRV: FFT and AR LF/HF ratio

HRV parameters	MVP male (n=4)	MVP female (n=68)	P value	Normal male (n=51)	Normal female (n=50)	P value
FFT LF/HF (lying)	2.84 ± 2.84	1.18 ± 0.97	0.04	1.65 ± 0.97	0.96 ± 1.16	0.0009
AR LF/HF (lying)	2.89 ± 2.89	1.19 ± 0.97	0.04	1.67 ± 0.95	0.96 ± 1.15	0.0006
FFT LF/HF (sitting)	2.29 ± 2.29	1.31±1.10	0.03	2.45 ±1.91	1.60 ±1.77	0.01
AR LF/HF (sitting)	2.06 ±2.06	1.34 ±1.17	NS	2.52±2.09	1.64 ±1.86	0.01
FFT LF/HF (standing)	3.60 ±1.80	2.95±4.38	NS	5.09 ±3.34	3.64 ±3.53	0.02
AR LF/HF (standing)	2.95±3.88	2.89 ±3.89	NS	5.38±4.08	3.91 ±4.09	0.04

*P<0.05 statistically significant.

Conclusion:

1. For time domain, HRV cannot be used to differentiate male from female in all positions, but the sample size is not large enough.
2. For frequency domain, HRV LF/HF ratio might be a useful tool in all three postures for the detection of gender differences in symptomatic MVPS and normal group.

Appendix 4 Poster of 42nd Taiwan Society of Cardiology (2)

Short Term Heart Rate Variability might be useful for the evaluation of Taiwanese symptomatic mitral valve prolapse syndrome

Ya-chu Chen[1], Lung-Wen Tsai[2], Ing-Fang Yang[4], Chung-Kai Tseng[3], Ten-Fang Yang[1, 2]
(1) National Chiao Tung University, Hsin Chu, Taiwan (2) Taipei Medical University Hospital, Taipei, Taiwan (3) China Medical University Hospital, Taichung, Taiwan (4) Jen Chi General Hospital, Taipei, Taiwan

Abstract

Introduction:
Short Term (5-15 min) Heart Rate Variability (HRV) has been reported to be similar to 24 hour HRV measurements. MVPS has been documented to be associated with significant Autonomic Nervous System (ANS) dysfunction. HRV can be used as a non-invasive tool for the detection of ANS dysfunction.
Objective:
The purpose is to evaluate if HRV with postural changes can be used to differentiate between symptomatic MVPS and normal.
Materials and Methods:
A total of 72 symptomatic patients (4 males and 68 females) had been echocardiographically diagnosed as having MVPS from the cardiology clinic and 101 healthy university students (51 males and 50 females) were recruited as normal controls for the present study. A Taiwanese HRV system with single modified lead II ECG was used to record and analyse the tracing. All the recordings were taken during the daytime to avoid the diurnal ANS influence of diurnal changes. All subjects were asked to rest at least 5 minutes before taking the records and the postural changes (lying, sitting and standing).

Results:

Table: Time domain HRV Parameters

HRV parameters	Symptomatic MVP (n=72)	Normal Group (n=101)	P value
SDNN(ms) lying	37.42±24.45	51.50 ±21.38	0.000068
RMSSD(ms)	29.91±24.58	41.41 ±18.38	0.00053
NN50	28.65±36.99	64.68 ±49.99	0.000000095
SDNN(ms) sitting	36.87±17.43	50.50±22.36	0.0000065
RMSSD(ms)	28.78±16.05	35.74 ±16.02	0.0028
NN50	36.06±48.64	53±45.22	0.011
SDNN(ms) standing	32.21±16.95	36.23 ±14.41	0.05
RMSSD(ms)	20.22±16.11	18.47 ±9.51	NS
NN50	11.93±22.73	11.23 ±18.79	NS

$P<0.05$ was regarded as statistically significant.

Conclusion:

1. Symptomatic MVP group is statistically significant different to normal control in lying and sitting positions in time domain HRV.
2. For frequency domain, HRV might not be useful to detect the MVPs.

Appendix 5 Oral presentation of 39th International Congress on Electrocardiology, Beijing

HRV can be used as a non-invasive tool to evaluate symptomatic MVPS

Ya-chu Chen[1], Lung-Wen Tsai[2], Ing-Fang Yang[4], Chung-Kai Tseng[3], Ten-Fang Yang[1, 2]
(1) National Chiao Tung University, Hsin Chu, Taiwan (2) Taipei Medical University Hospital, Taipei, Taiwan (3) China Medical University Hospital, Taichung, Taiwan (4) Jen Chi General Hospital, Taipei, Taiwan

Abstract

Background:
The purpose is to evaluate HRV parameters in symptomatic MVP patients and an apparently healthy population.
Materials and Methods:
A total of 119 MVP patients (7 males and 112 females) had been echocardiographically documented at cardiology clinic and 101 healthy students from University (51 males and 50 females) were recruited for the study. A local HRV with modified lead II ECG was used. HRV was performed during the daytime to avoid diurnal effects. The subjects were asked to rest at least 5 minutes before recording with lying posture.
Results:
Only time domain SDNN between MVPS and Normal Group was statistically significantly different; Whereas, frequency domain parameters between MVPS and Normal Group were shown to have significant differences. (Vide infra Table 1)
Conclusion:
1. Symptomatic MVPS can be significantly differentiated by Time domain SDNN and Frequency domain parameters from normal.
2. This study reconfirmed the previous Caucasian reports of abnormal ANS status in MVP.

Table 1 Frequency domain HRV Parameters between Normal and Symptomatic MVP in lying position.

HRV parameters	Normal (n=101)	MVPS (n=119)	P value
SDNN(ms)	51.50 ±21.49	42.43 ±37.75	0.01
FFT			
HF(nu)	464.76 ±405.50	277.49 ±947.37	0.03
LF(nu)	477.20 ±559.58	236.27±770.27	0.004
LF/HF	1.31 ±1.13	1.03±0.89	0.02
AR			
HF(nu)	471.19 ±410.56	279.44 ±968.61	0.03
LF(nu)	484.38 ±581.49	279.55 ±1115.98	0.04
LF/HF	1.32 ±1.12	1.04 ± 0.90	0.02

*P<0.05 was statistically significant.

Appendix 6 Poster of 13th International Society for Applied Cardiovascular Biology (1)

Heart Rate Variability With Postural Changes Might Be Useful For Detection Of Symptomatic Mitral Valve Prolapse Syndrome In Taiwanese

Ya-chu Chen, National Chiao Tung University, Hsin Chu City, Taiwan; Lung-Wen Tsai, Taipei Medical University Hospital, Taipei City, Taiwan; Ing-Fang Yang, Jen Chi General Hospital, Taipei City, Taiwan; Chung-Kai Tseng, China Medical University Hospital, Taichung City, Taiwan; Ten-Fang Yang*, National Chiao Tung University, Hsin Chu City, Taiwan. Taipei Medical University and Hospital, Taipei City, Taiwan
*Senior member of ISACB

Abstract

Purpose: To evaluate if HRV parameters with postural changes can be used to differentiate between symptomatic MVPS patients and normal controls.

Methods: A total of 72 symptomatic patients (4 males and 68 females) had been echocardiographically diagnosed as having MVPS from the cardiology clinic and 101 healthy university students (51 males and 50 females) were recruited as normal control for the present study. A locally developed HRV system with one modified lead II ECG was used to record the tracing. All the records were taken during the daytime to avoid the influence of diurnal changes. The subjects were asked to rest at least 5 minutes before taking the records and postural alterations(lying, sitting and standing).

Results: Time domain Parameters between MVPS and Normal Group was statistically significantly different in lying and sitting position ($P < 0.05$); Whereas, Frequency domain Parameters with postural changes were shown to have no significant differences in all postures.

Conclusion: For time domain, HRV symptomatic MVP group is statistically significant different to normal control in lying and sitting positions. Lying and sitting female MVP Time domain parameters were statistically significant different to normal; whereas male only lying RMSSD and NN50 were significantly different. For frequency domain, HRV cannot significantly differentiate symptomatic MVP group from normal control.

Table 1 Time domain HRV Parameters

HRV parameters	Symptomatic MVP (n=72)	Normal Group (n=101)	P value
SDNN(ms) lying	37.42±24.45	51.50 ±21.38	0.00
RMSSD(ms)	29.91±24.58	41.41 ±18.38	0.00
NN50	28.65±36.99	64.68 ±49.99	0.00
SDNN(ms) sitting	36.87±17.43	50.50±22.36	0.00
RMSSD(ms)	28.78±16.05	35.74 ±16.02	0.00
NN50	36.06±48.64	53±45.22	0.01
SDNN(ms) standing	32.21±16.95	36.23 ±14.41	0.05
RMSSD(ms)	20.22±16.11	18.47 ±9.51	NS
NN50	11.93±22.73	11.23 ±18.79	NS

P<0.05 was regarded as statistically significant.

Appendix 7 Poster of 13th International Society for Applied Cardiovascular Biology (2)

A Research of Heart Rate Variability between Symptomatic Mitral Valve Prolapse Syndrome and Normal

Ya-chu Chen, National Chiao Tung University, Hsin Chu City, Taiwan; Lung-Wen Tsai, Taipei Medical University Hospital, Taipei City, Taiwan; Ing-Fang Yang, Jen Chi General Hospital, Taipei City, Taiwan; Chung-Kai Tseng, China Medical University Hospital, Taichung City, Taiwan; Ten-Fang Yang*, National Chiao Tung University, Hsin Chu City, Taiwan. Taipei Medical University and Hospital, Taipei City, Taiwan
*Senior member of ISACB

Abstract

Purpose: To evaluate if HRV parameters is different between MVPS and normal.
Methods: A total of 72 symptomatic echocardiographically documented MVPS patients (4 males and 68 females) and 101 healthy students (51 males and 50 females) were recruited as normals for this study. A local HRV system with one modified lead II was used. All recordings were taken during daytime to avoid diurnal ANS influences. The subjects were asked to rest 5 minutes before recording and postural alterations (lying, sitting and standing).
Results: For MVPs, no difference was found in time domain between male and female. For normal male and female, frequency domain was statistically significantly different only in LF/HF ratio; Whereas, postural changes were shown to have significant effects in LF/HF ratio in all postures in frequency domain.

Table: Frequency domain HRV: FFT and AR LF/HF ratio

HRV parameters	MVP male (n=4)	MVP female (n=68)	P value	Normal male (n=51)	Normal female (n=50)	P value
FFT LF/HF (lying)	2.84 ± 2.84	1.18 ± 0.97	0.04	1.65 ± 0.97	0.96 ± 1.16	0.0009
AR LF/HF (lying)	2.89 ± 2.89	1.19 ± 0.97	0.04	1.67 ± 0.95	0.96 ± 1.15	0.0006
FFT LF/HF (sitting)	2.29 ± 2.29	1.31±1.10	0.03	2.45 ±1.91	1.60 ±1.77	0.01
AR LF/HF (sitting)	2.06 ±2.06	1.34 ±1.17	NS	2.52±2.09	1.64 ±1.86	0.01
FFT LF/HF (standing)	3.60 ±1.80	2.95±4.38	NS	5.09 ±3.34	3.64 ±3.53	0.02
AR LF/HF (standing)	2.95±3.88	2.89 ±3.89	NS	5.38±4.08	3.91 ±4.09	0.04

*P<0.05 statistically significant.

Conclusion: For time domain, HRV cannot be used to differentiate male from female in all positions, but the sample size is not large enough. For frequency domain, HRV LF/HF ratio might be a useful tool in all three postures for the detection of gender differences in symptomatic MVPS and normal group.

Appendix 8　Poster of 43rd Taiwan Society of Cardiology (1)

A study of postural effect on Heart Rate Variability in Symptomatic Taiwanese Mitral Valve Prolapse Syndrome

Ya-chu Chen[1], Chih-hao Shu[1], Lung-Wen Tsai[2], Ing-Fang Yang[3], Chung-Kai Tseng[4], Ten-Fang Yang[1, 2]

(1) National Chiao Tung University, Hsin Chu, Taiwan (2) Taipei Medical University and Hospital, Taipei, Taiwan (3) Jen Chi General Hospital, Taipei, Taiwan (4) China Medical University Hospital, Taichung, Taiwan

Abstract

Introduction:

Heart rate variability (HRV) is a physiological phenomenon of variation in the time interval between heartbeats measured by the variation in the beat-to-beat interval. Short Term (5-15 min) HRV can provide non-invasive information on the autonomic nervous system(ANS), and was reported to be remarkably similar to 24 hour-HRV in post-MI patients and can provide predictive information for ventricular arrhythmias and sudden cardiac death (SCD). Postural change influence on the HRV parameters of normal Taiwanese has been reported by our group in the previous ICE Lund meeting. The purpose is to evaluate the influence of postural change of HRV parameters in symptomatic Mitral Valve Prolapse (MVP) patients.

Methods:

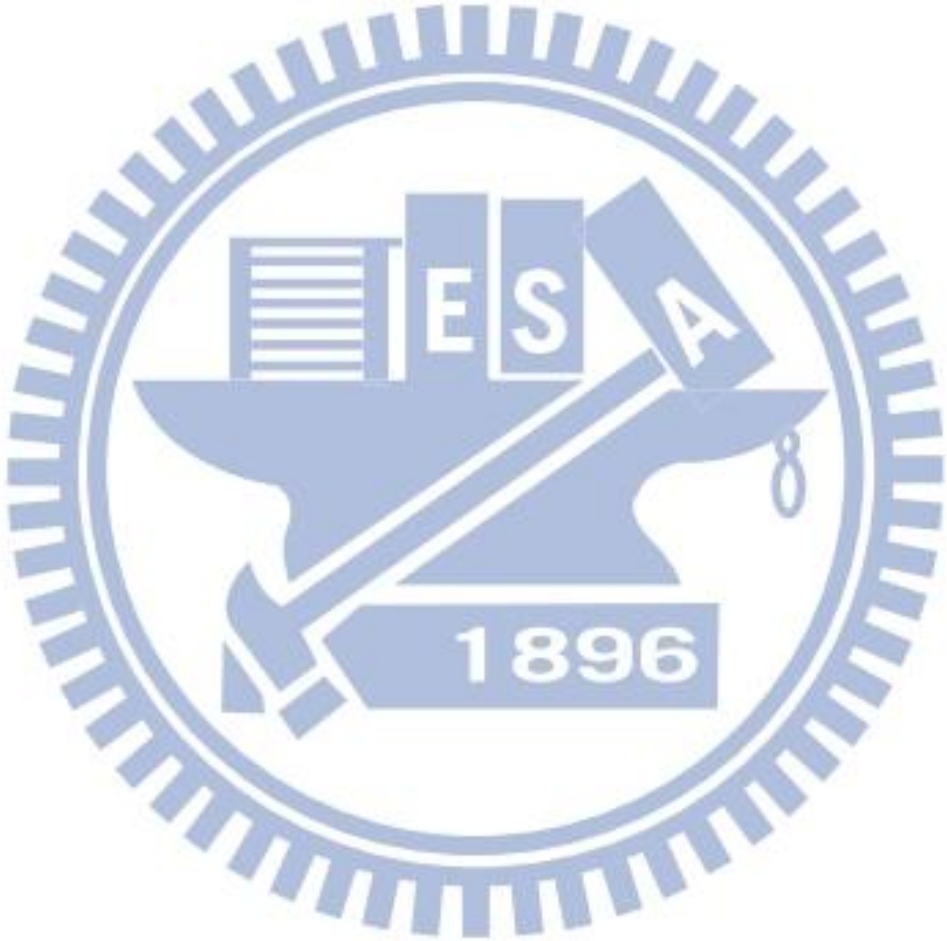
A total of 118 MVP patients (7 males and 111 females) had been echocardiographically documented at cardiology clinic and 148 healthy university students (54 males and 94 females) were recruited for the study. A local HRV system with modified lead II ECG was used. HRV was performed during the daytime to avoid diurnal effects. The subjects were asked to rest at least 5 minutes before recording HRV with lying, sitting and standing posture. Paired Student t test was used to characterize changes in HRV variables between MVP patients and normals. All HRV variables were expressed as mean ± SD. All statistical analyses were performed using Microsoft Excel 2007. A P value <0.05 was determined as statistically significant.

Results:

In Time domain only SDNN between MVPS and Normal was statistically significantly different in all positions; Whereas, in Frequency domain all Parameters were shown to have significant differences except in lying position.

Conclusion:

1. Normal group and symptomatic MVPS can be significantly differentiated by Time domain's SDNN and Frequency domain's Total Power.
2. There is significantly statistically differences of frequency domain HRV parameters in sitting position.



Appendix 9　Poster of 43rd Taiwan Society of Cardiology (2)

A Research of Gender influence of Heart Rate Variability between Taiwanese Symptomatic Mitral Valve Prolapse Syndrome and Normal

Ya-chu Chen[1], Chih-hao Shu[1], Lung-Wen Tsai[2], Ing-Fang Yang[3], Chung-Kai Tseng[4], Ten-Fang Yang[1, 2]

(1) National Chiao Tung University, Hsin Chu, Taiwan (2) Taipei Medical University and Hospital, Taipei, Taiwan (3) Jen Chi General Hospital, Taipei, Taiwan (4) China Medical University Hospital, Taichung, Taiwan

Abstract

Introduction:

Short term Heart rate variability (HRV) can provide non-invasive information on the autonomic nervous system(ANS), including its vagal and sympathetic components, which has a strong association with the pathogenesis of ventricular arrhythmias and sudden cardiac death (SCD) in the general population, short term HRV were claimed to be similar to 24 hour HRVs in men and can provide predictive information similar in strength to entire record. Mitral Valve Prolapse Syndrome (MVPS) was reported to be associated with significant ANS dysfunction in Caucasians. Sexual variation of HRV was also previously reported. The aim is to evaluate gender effect on HRV parameters in Taiwanese symptomatic MVP patients.

Methods:

A total of 118 MVP patients (7 males and 111 females) had been echocardiographically documented at cardiology clinic and 148 healthy university students (54 males and 94 females) were recruited for the study. A local HRV system with modified lead II ECG was used. HRV was performed during the daytime avoid diurnal effects. The subjects were asked to rest at least 5 minutes before recording HRV with lying, sitting and standing posture. Paired Student t test was used to characterize changes in HRV variables between MVP patients and a normal Taiwanese population. All HRV variables were expressed as mean ± SD. All statistical analyses were performed using Microsoft Excel 2007. A P value <0.05 was determined as statistically significant.

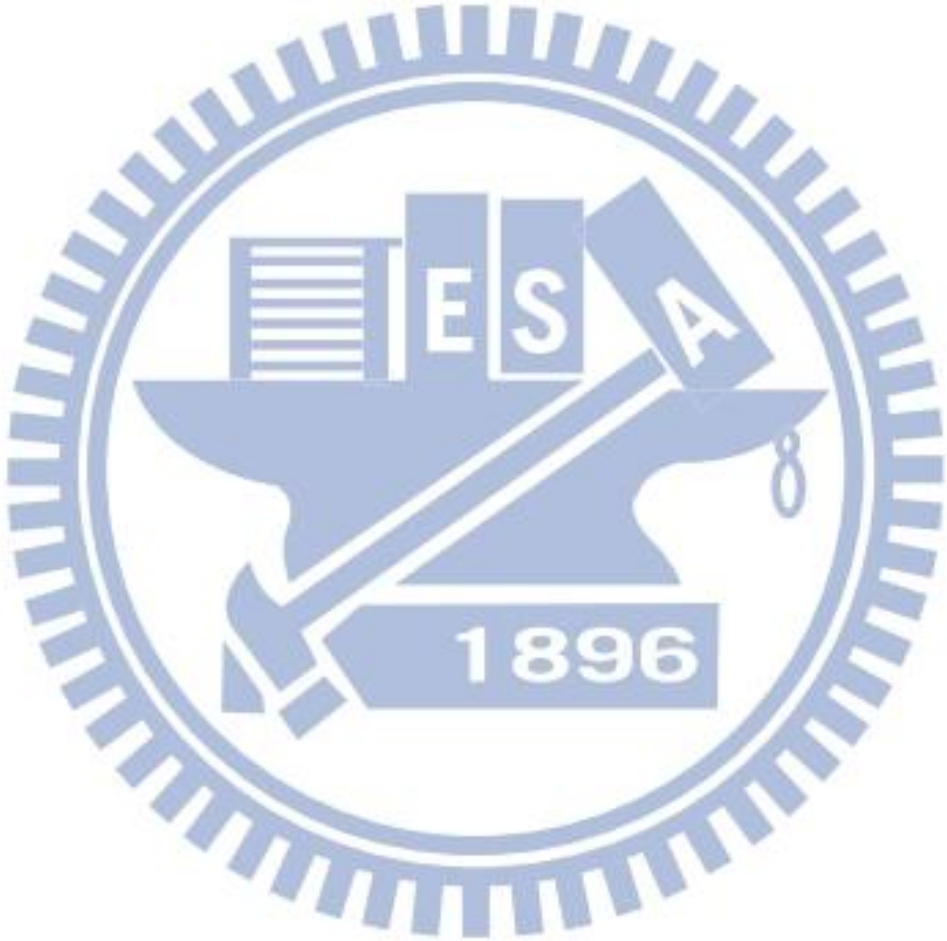
Results:

For MVPs, no difference was found in time domain between male and female except lying position.

For normal, all frequency domain parameters were statistically significantly different except total power.

Conclusion:

1. Gender specific HRV diagnostic MVPS criteria should be established in Taiwanese.
2. For frequency domain, HRV might be a useful tool in all three postures for the detection of gender differences in symptomatic MVPS and normal group.



Appendix 10　40th International Congress on Electrocardiology, Glasgow (1)

Gender Differences of Heart Rate Variability between Taiwanese Symptomatic Mitral Valve Prolapse Syndrome and Normal.

Ya-chu Chen[1], Chih-hao Shu[1], Lung-Wen Tsai[2], Ing-Fang Yang[3], Chung-Kai Tseng[4], Ten-Fang Yang[1, 2]

(1) National Chiao Tung University, Hsin Chu, Taiwan (2) Taipei Medical University Hospital, Taipei, Taiwan (3) China Medical University Hospital, Taichung, Taiwan (4) Jen Chi General Hospital, Taipei, Taiwan

Abstract

Introduction:

Short Term (5-15 min) Heart rate variability (HRV) can provide non-invasive evaluation of the autonomic nervous system (ANS), and was reported to be remarkably similar to 24 hour-HRV in post-MI patients as an independent predictor for ventricular arrhythmias and sudden cardiac death occurrence. Postural change influence on the HRV parameters of normal Taiwanese has been reported by our group in the previous ICE Lund meeting. The purpose is to evaluate the gender effect and influence of postural changes in symptomatic MVPS and normal.

Materials and Methods:

A total of 118 MVPS and 148 healthy university students were recruited for the study. A local HRV system with modified lead II ECG was used. HRV was performed during the daytime to avoid diurnal effects. The subjects were asked to rest at least 5 minutes before recording HRV with lying, sitting and standing posture. Paired Student t test was used to characterize changes in HRV variables between MVPS and normal. All statistical analyses were performed using Microsoft Excel 2007.

Results and conclusion:

1. Normal group and symptomatic MVPS can be significantly differentiated by Time domain's SDNN and Frequency domain's Total Power.
2. In Frequency domain all Parameters were shown to have significant differences except in lying position.
3. Although time domain parameters might not be of use for the evaluation MVPS, frequency domain with postural changes might be a useful tool in MVPS diagnosis risk stratification.

Appendix 11　40th International Congress on Electrocardiology, Glasgow (2)

ECG QT INTERVAL MIGHT BE USEFUL FOR THE DETECTION OF MITRAL VALVE PROLAPSE SYNDROME IN TAIWAN

Chih-hao Hsu[1], Ya-chu Chen[1], Lung-Wen Tsai[2], Ing-Fang Yang[3], Chung-Kai Tseng[4], Ten-Fang Yang[1, 2].

National Chiao Tung University, Hsin Chu City[1] , Taipei Medical University and Hospital, Taipei City[2] , Jen Chi General Hospital, Taipei City[3] , China Medical University Hospital, Taichung City[4], Taiwan.

Abstract

Introduction:

Four corrected QT (QTc) formulae, namely Bazett, Fridericia, Framingham and Hodges, can be easily calculated by modern ECG to improve the detection of ventricular arrhythmia (VA) and Sudden Cardiac Death. MVPS has been reported to have significantly more VA than normal. There was no study about the Taiwanese MVPS and normal QTc ranges published.

Objective:

The aim of this study is to evaluate if the gender difference can be a factor for the QTc correction formulae in Taiwanese normal and MVPS.　.

Materials and Methods:

The ECG data measured with ECG machine were analyzed in 581 normal subjects and a total of 86 MVP patients. The 12-lead ECG signal is measured and recorded by the ECG machine BURDICK Atria 6100® . All the ECG signals were collected to a desktop pc for statistical analysis. Two tail student-t test was adopted to differentiate the QT corrected formulae. SPSS-19 software was used to do the statistical analysis.

Results and Conclusion:

In Normal, all QTc were significantly longer in women than men. In MVPS, significant gender difference was only shown in Framingham and Hodges. There is no significant difference of QTc between MVPS and normal in women. But in men, significant difference only exists in Bazett and Fridericia. QTc might be used to differentiate MVPS from normal. Therefore, gender dependent QTc criteria should be established for the diagnosis of MVPS.