Correlation Analysis of Heart Rate Variability and Respiratory Frequency Under Sinus Arrhythmia Condition

Thesis submitted in partial fulfillment of the requirement for the award of degree of

Master of Engineering
in
Electronics Instrumentation and Control

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Declaration

*I hereby declare that the report entitled "**Correlation Analysis of Heart Rate Variability and Respiratory Frequency under Sinus Arrhythmia Condition** " is an authentic record of my own work carried out as requirements for the award of degree of M.E. (Electronic Instrumentation & Control) at Thapar University, Patiala, under the guidance of Dr. Mandeep Singh (AP, EIED) and Dr. Amit Kumar Kohli (AP, ECED) during January to July 2009.*

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Abstract

The heart is not just a muscular organ that serves to pump and make blood flow in the whole body, the heart, being connected to the brain and the autonomic nervous system, is emotional in its feelings and expression. The heart rate variability (HRV) test is designed to give an indication of the state of the biological systems that regulate cardiac activity. The cardiac system functions best when it is regulated by the autonomic circuit. When homeostasis is broken i.e. the natural balance is disturbed, higher levels of the central regulatory system dominate cardiac activity.

These changes in regulation are reflected in the variability of the heart rhythm**.** Beat-to-beat changes in cardiac signals or heart rate variability is controlled by the two branches of autonomic nervous system (ANS) in a very complex manner. It is clear that HRV analysis with and without respiratory information provides different results. The differences become more obvious when respiration rate is low. Furthermore, many standard ANS tests include deep breathing test, which is to stimulate parasympathetic branch of ANS. Therefore for accurate assessment of the ANS activity, one must include the effect of respiration in HRV analysis. This kind of a change is only observed when respiratory peak is used in HRV analysis to locate high frequency area then estimating the power. Employing respiratory signal in HRV analysis provides more accurate isolation of sympathetic and parasympathetic activity, which provides a better diagnostic tool in assessing human ANS.

Power spectral analysis of HRV measure changes in total ANS power and sympathetic and parasympathetic balance that occur during different emotional states. There are many situations where heart rate changes rapidly over time, and the control of those changes is of considerable interest.

Our thesis work focuses on analyzing the correlation between heart rate variability and respiratory frequency using MATLAB software tool. Pearson correlation coefficient is used for this purpose. Thereafter, various parameters like noise, high frequency component are varied to find the effect of respiration on heart rate variability. Hence, a better understanding is attained about autonomic control of rapidly changing signals. As a result of this methodology, pathophysiological conditions of paramount importance, such as arterial hypertension, myocardial ischemia, sudden cardiac death, and heart failure might soon undergo a novel scrutiny

with practical implications. It is generally accepted that RSA amplitude is a noninvasive marker of the activity of the parasympathetic nervous system, and it can therefore be used to infer relative changes in parasympathetic cardiac tone.

Keywords: Heart Rate Variability, Autonomic Nervous System, Respiratory Sinus Arrhythmia.

Organization of Thesis

The first chapter gives an overview of Heart. The second chapter provides literature review. The third chapter briefly introduces Heart rate Variability. The fourth chapter discusses Heart rate Variability in detail regarding its Power Spectrum. The fifth chapter gives information about arrhythmia. Effect of respiration on Heart rate Variability is discussed in chapter sixth. The seventh chapter discusses the implementation of various tools of Matlab software to analyse the correlation between Heart rate Variability and Respiratory signal. Finally, concluding thesis in eight chapter with future scope.

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Abbreviations

HRV	Heart Rate Variability
ANS	Autonomic Nervous System
RSA	Respiratory Sinus Arrhythmia
ECG(EKG)	Electrocardiogram
SA	SinoAtrial
AV	AtrioVentricular
MWSA	Mayer Wave Sinus Arrhythmia
SBP	Systolic Blood Pressure
VLF	Very Low Frequency
LF	Low Frequency
ULF	Ultra Low Frequency
SDNN	Standard Deviation of NN intervals
RMSSD	Root Mean Square Successive Difference
PNN50	Percentage of differences between adjacent normal RR intervals that are >50 ms
FD	Fractal Dimension
RF	Respiratory frequency
MWL	Mental Work Load
ILV	Instantaneous Lung Volume
CNS	Central Nervous System
PPG	Photoplethysmograph
PSD	Power Spectral Density
FFT	Fast Fourier Transform
AR	Autoregressive Spectrum
ARMA	Autoregressive moving average Spectrum
JTFA	Joint Time-Frequency Analysis
STFT	Short Time Fourier Transform
DFA	Detrended Fluctuation Analysis
DAN	Diabetic Autonomic Neuropathy
EPS	Electrophysiology Studies

ICD	Implantable Cardioverter Defibrillator
SNN	Sympathetic Nervous System
PNS	Parasympathetic Nervous System
tHRV	Traditional Heart Rate Variability
eHRV	Enhanced Heart Rate Variability
FRF	Fundamental Respiration Frequency

Chapter 1

Electrocardiogram

1.1 Structure of Heart

The Heart is an organ that supplies blood and oxygen to all parts of the body. There are four cavities, or open spaces, inside the heart that fill with blood. Two of these cavities are called atria. The other two are called ventricles. The two atria form the curved top of the heart. The ventricles meet at the bottom of the heart to form a pointed base which points toward the left side of your chest. The left ventricle contracts most forcefully, so you can best feel your heart pumping on the left side of your chest. The Heart is made up of a powerful muscle called Myocardium. The Myocardium is composed of cardiac muscle fibers that contracts and causes a wringing type of action. The location of the heart is about left-center of chest. The heart are two separate pumps that continuously sends blood throughout the body carrying nutrients, oxygen, and helping remove harmful wastes. The right side of the heart receives blood low in oxygen. The left side of the heart receives blood that has been oxygenated by the lungs. The blood is then pumped out into the Aorta and to all parts of the body [1]. The Structure of Heart is shown below:

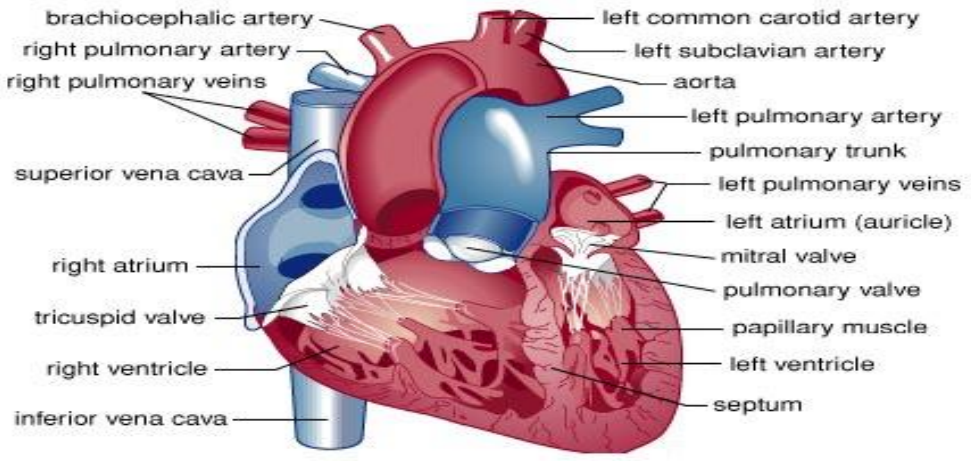


Figure 1.1: **Structure of Heart.**

- **Right Atrium:**

The Right Atrium is larger than the Left Atrium but has thinner walls. The Right Atrium has two major veins that return blood to the heart from all parts of the body. Two major veins returning the blood to the heart are the Superior Vena Cava and the Inferior Vena Cava. These two veins are sometimes called the "Great Veins". The Superior Vena Cava returns the deoxygenated blood from the upper part of the body and the Inferior Vena Cava returns the deoxygenated blood from the lower part of the body. The Right Atrium also receives blood back from the heart muscle itself. After the blood is collected in the Right Atrium it is pumped into the Right Ventricle through the Tricuspid Valve (three leaf valve).

- **Left Atrium:**

The Left Atrium receives blood from four Pulmonary Veins. The blood received from the lungs has been oxygenated. The oxygenated blood that is collected in Left Atrium is then pumped into the Left Ventricle through the Bicuspid Valve.

- **Right Ventricle:**

The Right Ventricle receives blood from the Right Atrium. When the Heart contract the blood is forced out through the Pulmonary Semilunar Valve into the Pulmonary Artery. The Pulmonary Semilunar Valve is a three flap valve that stops the backflow of blood. The walls of the Right Ventricle are a little thicker than the Right Atrium.

- **Left Ventricle:**

The chamber of the Left Ventricle has walls that are three times the thickness of the Right Ventricle. This is important because the oxygenated blood that it receives from the Left Atrium has to be pump throughout the body. The Bicuspid Valve closes and the blood is collected in the Left Ventricle. The closing of the Bicuspid Valve stops the backflow of blood. When the Heart muscle contracts the blood is forced through the Aortic Semilunar Valve which has the same features as the Pulmonary Valve. The blood then passes through the Aortic Semilunar Valve into the Aorta.

- **Aorta:**

The Aorta is the largest blood vessel in the body. The inner diameter of the Aorta is about 1 inch. The Aorta carries oxygenated blood to every other part of the body. The Aorta receives it's blood from the Left Ventricle.

- **Septum:**

The Septum is a partition that separates the right and left sides of the Heart. There are two separate regions of the Septum. They are the Interatrial Septum that separates the Atriums and the Interventrial Septurm that separates the Ventricles. The Interatrial Septum is only present in the fetal period and is open during this period. The Interatrial Septum closes at the time of birth. The Interventrial Septum is suppose to be closed all the time but sometimes an opening is present at birth. This would be considered a Congenital heart disease.

- **Superior Vena Cava:**

The importance of the Superior Vena Cava is to return blood back to the Right Atrium from the upper part of the body. It is one of the largest veins in the body.

- **Inferior Vena Cava:**

The Inferior Vena Cava is important for carrying the blood back to the Right Atrium from the lower part of the body.

- **Pulmonary Arteries:**

The Pulmonary Arteries carry the blood from the Right Ventricle to both of the lungs. There the blood is oxygenated and sent to the Left Atrium in the heart.

- **Pulmonary Veins:**

The Pulmonary Veins carry the oxygenated blood back to the Left Atrium in the heart. The left side of the heart houses one atrium and one ventricle. The right side of the heart houses the others. A wall, called the septum, separates the right and left sides

of the heart. A valve connects each atrium to the ventricle below it. The mitral valve connects the left atrium with the left ventricle. The tricuspid valve connects the right atrium with the right ventricle.

The top of the heart connects to a few large blood vessels. The largest of these is the aorta, or main artery, which carries nutrient-rich blood away from the heart. Another important vessel is the pulmonary artery, which connects the heart with the lungs as part of the pulmonary_circulation system. The two largest veins that carry blood into the heart are the superior vena cava and the inferior vena cava. They are called "vena cava" because they are the "heart's veins." The superior is located near the top of the heart. The inferior is located beneath the superior.

The heart's structure makes it an efficient, never-ceasing pump. From the moment of development through the moment of death, the heart pumps. The heart, therefore, has to be strong. The average heart's muscle, called cardiac muscle, contracts and relaxes about 70 to 80 times per minute without you ever having to think about it. As the cardiac muscle contracts it pushes blood through the chambers and into the vessels. Nerves connected to the heart regulate the speed with which the muscle contracts. When you run, your heart pumps more quickly.When you sleep, your heart pumps more slowly. Considering how much work it has to do, the heart is surprisingly small. The average adult heart is about the size of clenched fist and weighs about 11 ounces (310 grams) [1]. Located in the middle of the chest behind the breastbone, between the lungs, the heart rests in a moistened chamber called the pericardial cavity, which is surrounded by the ribcage. The diaphragm, a tough layer of muscle, lies below. As a result, the heart is well protected.The heart is responsible for pumping blood through the circulatory system. A brief description of the anatomy of the heart, the cardiac cycle, and factors affecting cardiac pumping efficiency and performance are described in the next sections.

The anatomy of the heart can be conveniently be divided into five functional units:

- The heart muscle (the 2 atria pump blood into the ventricles and the 2 ventricles pump blood out of the heart).

- The valves of the heart which maximize the pumping action of the heart (2 atrioventricular valves: the tricuspid and mitral; 2 semi lunar valves: the pulmonic and aortic)
- The electrical pacemaker and conduction system which sets the normal rhythm of the heart and coordinates the contraction of the heart (sinoatrial (SA) node, atrioventricular (AV) junction, His bundle, Purkinje fibers)
- The coronary circulation which distributes blood to the heart itself
- The autonomic nervous system innervations of the heart which regulates heart rate and contractility (sympathetic nerve endings in muscle of atria and ventricles, SA node, and AV junction; parasympathetic nerve endings mainly in atrial muscle, pacemaker, and the AV junction)

1.2 Functioning of the heart

The heart is a pump that distributes blood to the organs of the body. The heart is made of 4 chambers. The top 2 collecting chambers are called *atria*; the bottom 2 ejecting chambers are called *ventricles.* The right atrium receives blood deficient in oxygen from the body and sends it into the right ventricle. The right ventricle squeezes the blood out to the lungs to pick up fresh oxygen. The oxygenated blood returns from the lungs to the left atrium, which then funnels the blood into the left ventricle. The left ventricle ejects the oxygenated blood into the entire body via the aorta[2].

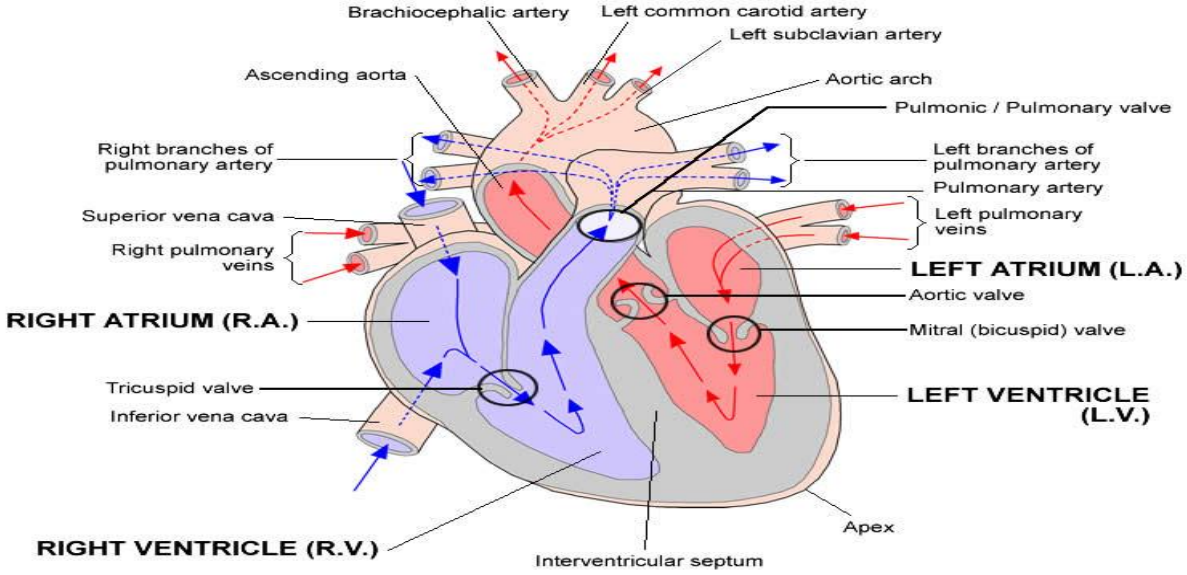


Figure 1.2: Functioning of Heart [3].

Every cell in your body needs oxygen in order to live and function. The role of the heart is to deliver the oxygen-rich blood to every cell in the body. The arteries are the passageways through which the blood is delivered. Functioning of Heart is shown in figure 1.2.

The largest artery is the aorta, which branches off the heart and then divides into many smaller arteries. The veins carry the deoxygenated blood back to the lungs to pick up more oxygen, and then back to the heart once again. Blood flows continuously through the circulatory system, and the heart muscle is the pump, which makes it all possible.

The normal human heart can be considered a two-stage pump, each containing two valves. The right side of the heart (with the blue arrows), in Figure 1.2, receives blood from the veins and pumps it through the lungs to collect oxygen, while the more powerful left side (red arrows), in Figure 1.2, ejects the oxygenated blood into the aorta. If a heart valve is congenitally defective or degenerates later in life, the heart cannot pump blood as efficiently. It must work harder to maintain the same cardiac output, enlarges and eventually fails. This degenerative process may take years and the quality of life for the patient diminishes severely.The proper functioning of the cardiac conduction system, with the consequent coordination of contraction and valve opening and closing in each region of the heart, is critical for efficient pumping of blood.

- An impulse arising from the SA node results in depolarization and contraction of the atria (the right atrium contracts slightly before the left atrium).
- The atrioventricular valves open and the ventricles are filled with blood.
- There is a short delay of the electrical impulse in the AV junction that allows the ventricles to fill completely.
- The electrical impulse is then propagated through the His bundle and Purkinje system to allow the ventricles to contract from the apex of the heart towards the base.
- As the ventricles contract and the pressure in the ventricles exceeds that in the atria, the atrioventricular valves close and the atria begin to relax and refill with blood.

- When the pressure in the ventricles exceed the pressure in the pulmonary artery and aorta, the pulmonic and aortic valves open, and blood is pumped into the pulmonary and systemic circulations, respectively.
- As the ventricles begin to relax after systole, the pulmonic and aortic valves close and diastole begins.

1.3 Electrocardiogram (ECG)

The electrocardiogram is a recording of the electrical activity of the heart as it undergoes excitation (depolarization) and recovery (polarization) to initiate each beat of the heart. This electrical activity is represented by a tracing showing the various phases of the activity above or below an isoelectric line (positive above and negative below) over time in a progressive fashion from the sinus node (the site of initiation of the electrical impulse in the cranial portion of the right atrium) to the AV node (in the right atrium) and then into the HIS-Purkinje bundle, where it spreads through both the left and right ventricular bundles (located on each side of the interventricular septum respectively). The activity spreads from these bundles out to each of the ventricles of the heart. This activity is recorded using an electrocardiographic machine connected to the patient with four electric leads (labelled 1, 11, 111, AVR, AVL, AVF) on the ankles and wrists and six on the front of the chest over the heart area (labelled V1-6). The normal pattern of the ECG allows analysis to determine whether there is any abnormality in any particular patient's ECG. The activity is classically represented by labelling the initial activity a P wave and in succession QRS, T and U waves. The P wave represents the electrical excitation of the atria, which causes contraction of both atria. The QRS complex represents the electrical excitation of the ventricles, which initiates the ventricular contraction (systole) shortly after the Q wave. The T wave represents the return of the ventricles from excitation to a normal state. The end of T wave marks the end of systole. The T wave represents the return to normal of the specialized muscle fibers that make up the pacemaker, which spreads the electrical signal throughout the ventricles. The interval between the onset of the P wave and the onset of the QRS is called the PR interval, which usually does not exceed 0.20 seconds. The QRS duration is from 0.08-0.10 seconds [4]. There is an isoelectric line separating the activity of the P wave from the QRS and the QRS from the T wave.

Counting the number of QRS complexes occurring per second gives the heart rate of the individual. The electrical axis (EA) of the heart is a vector originating in the centre of Einthoven's equilateral triangle and refers to the direction of the cardiac activation process as projected in the limb leads (1, 11, 111, AVR, AVL, AVF). The term "electrical axis" generally refers to the QRS complex.

1.3.1 Intervals and Peaks in ECG

The various peaks and intervals in ECG are as given in this ECG trace:

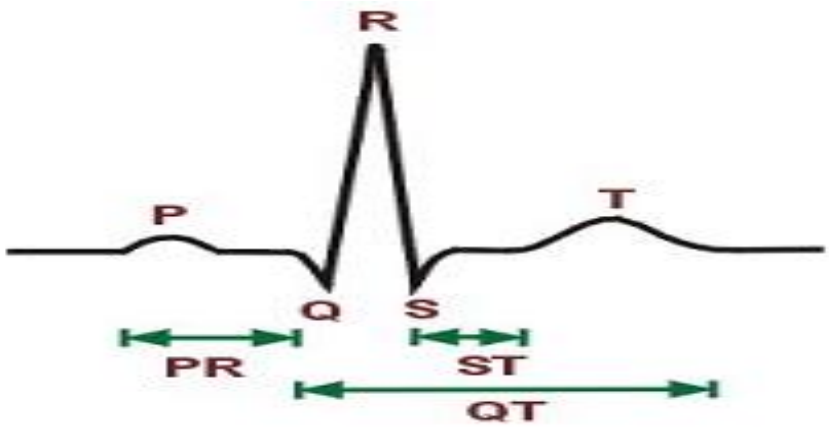


Figure 1.3 Typical ECG trace

As the heart undergoes depolarization and repolarization, the electrical currents that are generated spread not only within the heart, but also throughout the body. This electrical activity generated by the heart can be measured by an array of electrodes placed on the body surface. The recorded tracing is called an electrocardiogram (ECG, or EKG). A "typical" ECG tracing is shown above in figure 1.3. The different waves that comprise the ECG represent the sequence of depolarization and repolarization of the atria and ventricles. The **P wave** represents the wave of depolarization that spreads from the SA node throughout the atria, and is usually 0.08 to 0.1 seconds (80-100 ms) in duration. The brief isoelectric (zero voltage) period after the P wave represents the time in which the impulse is traveling within the AV node where the conduction velocity is greatly retarded.

The period of time from the onset of the P wave to the beginning of the QRS complex is termed the **P-R interval**, which normally ranges from 0.12 to 0.20 seconds in duration. This interval represents the time between the onset of atrial depolarization and the onset of ventricular depolarization. If the P-R interval is >0.2 sec, a conduction defect (usually within the AV node) is present (first-degree heart block).

The **QRS complex** represents ventricular depolarization. The duration of the QRS complex is normally 0.06 to 0.1 seconds. This relatively short duration indicates that ventricular depolarization normally occurs very rapidly. If the QRS complex is prolonged (> 0.1 sec), conduction is impaired within the ventricles. This can occur with bundle branch blocks or whenever a ventricular foci (abnormal pacemaker site) becomes the pacemaker driving the ventricle. Such an ectopic foci nearly always results in impulses being conducted over slower pathways within the heart, thereby increasing the time for depolarization and the duration of the QRS complex.

The isoelectric period (**ST segment**) following the QRS is the time at which the entire ventricle is depolarized and roughly corresponds to the plateau phase of the ventricular action potential. The ST segment is important in the diagnosis of ventricular ischemia or hypoxia because under those conditions, the ST segment can become either depressed or elevated.

The **T wave** represents ventricular repolarization and is longer in duration than depolarization (i.e., conduction of the repolarization wave is slower than the wave of depolarization).

The **Q-T interval** represents the time for both ventricular depolarization and repolarization to occur and therefore roughly estimates the duration of an average ventricular action potential. This interval can range from 0.2 to 0.4 seconds depending upon heart rate. At high heart rates, ventricular action potentials shorten in duration, which decreases the Q-T interval. Because prolonged Q-T intervals can be diagnostic for susceptibility to certain types of tachy arrhythmias, it is important to determine if a given Q-T interval is excessively long. In practice, the Q-T interval is expressed as a "corrected Q-T (**Q-Tc**)" by taking the Q-T interval and dividing it by the square root of the R-R interval (interval between ventricular depolarization). This allows an

assessment of the Q-T interval that is independent of heart rate. Normal corrected Q-Tc intervals are less than 0.44 seconds

There is no distinctly visible wave representing atrial repolarization in the ECG because it occurs during ventricular depolarization. Because the wave of atrial repolarization is relatively small in amplitude (i.e., has low voltage), it is masked by the much larger ventricular-generated QRS complex. ECG tracings recorded simultaneous from different electrodes placed on the body produce different characteristic waveforms.

1.3.2 Electrocardiogram Leads

As the heart undergoes depolarization and repolarization, electrical currents spread throughout the body because the body acts as a volume conductor. The electrical currents generated by the heart are commonly measured by an array of electrodes placed on the body surface and the resulting tracing is called an electrocardiogram (ECG or EKG). By convention, electrodes are placed on each arm and leg, and six electrodes are placed at defined locations on the chest. These electrode leads are connected to a device that measures potential differences between selected electrodes to produce the characteristic electrocardiographic tracings.

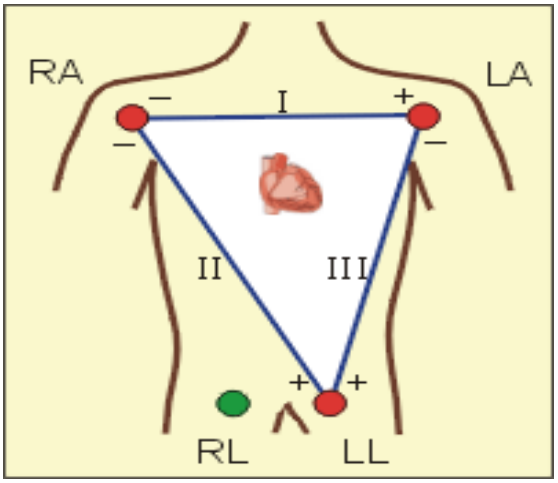


Figure 1.4: Bipolar Leads

There are two basic types of electrocardiogram (ECG) leads: bipolar and unipolar. Bipolar leads (standard limb leads) as shown in figure 1.4 utilize a single

positive and a single negative electrode between which electrical potentials are measured. Unipolar leads (augmented leads and chest leads) have a single positive recording electrode and utilize a combination of the other electrodes to serve as a composite negative electrode.

The three types of ECG leads are:

- Limb leads (Bipolar).
- Augmented Limb Leads (Unipolar).
- Chest Leads (Unipolar).

1.3.2.1 Standard Limb Leads (Bipolar)

By convention, lead I have the positive electrode on the left arm, and the negative electrode on the right arm, and therefore measure the potential difference between the two arms.

In this and the other two limb leads, an electrode on the right leg serves as a reference electrode for recording purposes.

In the lead II configuration, the positive electrode is on the left leg and the negative electrode is on the right arm.

Lead III has the positive electrode on the left leg and the negative electrode on the left arm. These three bipolar limb leads roughly form an equilateral triangle (with the heart at the center) that is called Einthoven's triangle shown in figure 1.5.

Whether the limb leads are attached to the end of the limb (wrists and ankles) or at the origin of the limb (shoulder or upper thigh) makes no difference in the recording because the limb can simply be viewed as a long wire conductor originating from a point on the trunk of the body.

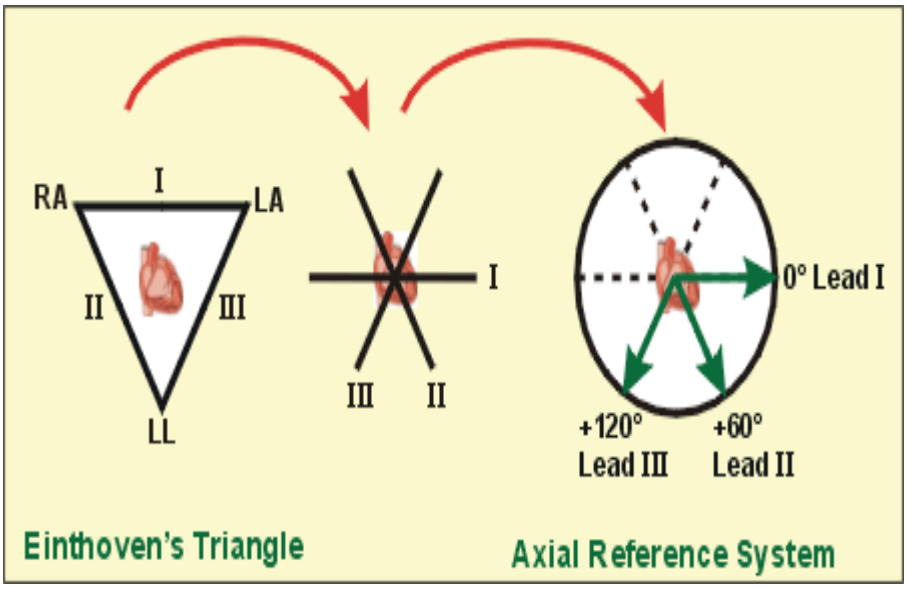


Figure 1.5: Einthoven's Triangle

Based upon universally accepted ECG rules, a wave a depolarization heading toward the left arm gives a positive deflection in lead I because the positive electrode is on the left arm. Maximal positive ECG deflection occurs in lead I when a wave of depolarization travels parallel to the axis between the right and left arms.

If a wave of depolarization heads away from the left arm, the deflection is negative. Also by these rules, a wave of repolarization moving away from the left arm is recorded as a positive deflection. Similar statements can be made for leads II and III in which the positive electrode is located on the left leg.

For example, a wave of depolarization travelling toward the left leg produces a positive deflection in both leads II and III because the positive electrode for both leads is on the left leg. A maximal positive deflection is recorded in lead II when the depolarization wave travels parallel to the axis between the right arm and left leg.

Similarly, a maximal positive deflection is obtained in lead III when the depolarization wave travels parallel to the axis between the left arm and left leg.

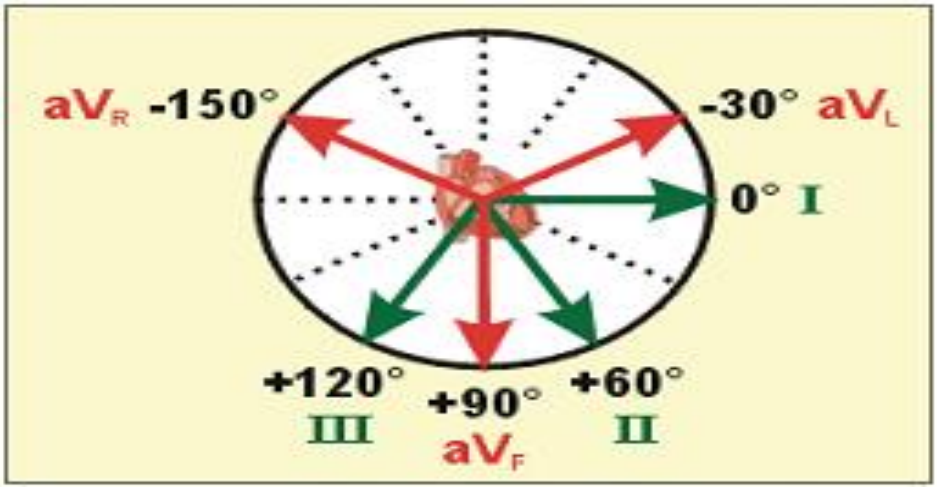


Figure 1.6: Axial Reference System

If the three limbs of Einthoven's triangle (assumed to be equilateral) are broken apart, collapsed, and superimposed over the heart, then the positive electrode for lead I is said to be at zero degrees relative to the heart (along the horizontal axis) (figure 1.6). Similarly, the positive electrode for lead II will be +60º relative to the heart, and the positive electrode for lead III will be +120º relative to the heart as shown to the right. This new construction of the electrical axis is called the axial reference system shown in figure 1.6. With this system, a wave of depolarization travelling at +60º produces the greatest positive deflection in lead II. A wave of depolarization-oriented +90º relative to the heart produces equally positive deflections in both lead II and III. In this latter example, lead I shows no net deflection because the wave of depolarization is heading perpendicular to the 0º, or lead I, axis.

1.3.2.2 Augmented Limb Leads (Unipolar)

In addition to the three bipolar limb leads described above, there are three augmented unipolar limb leads. These are termed unipolar leads because there is a single positive electrode that is referenced against a combination of the other limb electrodes. The positive electrodes for these augmented leads are located on the left arm (aV_L), the right arm (aV_R), and the left leg (aV_F). In practice, these are the same electrodes used for leads I, II and III. The aV_L lead is at -30º relative to the lead I axis; aV_R is at -150º and aV_F is at +90º. It is very important to learn which lead is associated with each axis. The three augmented unipolar leads, coupled with the three bipolar leads,

constitute the six limb leads of the ECG. These leads record electrical activity along a single plane, termed the frontal plane relative to the heart. Using the axial reference system and these six leads, it is simple to define the direction of an electrical vector at any given instant in time. If a wave of depolarization is spreading from right-to-left along the 0º axis, then lead I will show the greatest positive amplitude. If the direction of the electrical vector for depolarization is directed downwards (+90º), then aV_F will show the greatest positive deflection. If a wave of depolarization is moving from left-to-right at +150º, then aV_L will show the greatest negative deflection according to the rules for ECG interpretation.

1.3.2.3 Chest Leads (Unipolar)

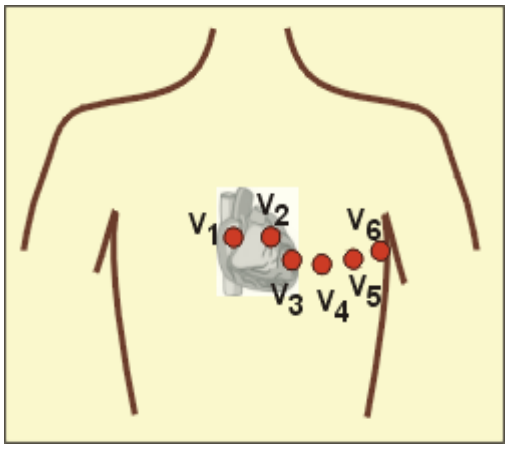


Figure 1.7: Chest Leads

The last ECG leads to consider is the precordial, unipolar chest leads. These are six positive electrodes placed on the surface of the chest over the heart in order to record electrical activity in a plane perpendicular to the frontal plane (figure in 1.7). These six leads are named V_1 - V_6. The rules of interpretation are the same as for the limb leads.

In summary, the twelve ECG leads provide different views of the same electrical activity within the heart. Therefore, the waveform recorded is different for each lead. To understand how cardiac electrical currents actually generate and ECG tracing and why the different leads display that electrical activity differently, it is necessary to understand volume conductor principles and vectors.

1.4 Tachycardia

Typically refers to the cardiac rhythm which produces a ventricular rate greater than 100 beats per minute, sometimes refers to the cardiac rhythm which produces an atrial rate greater than 100 beats per minute while the ventricular rate remains unaffected. The two main types of tachycardia are abnormal supraventricular tachycardias (which originate in the upper chambers of the heart, the atria) and ventricular tachycardias (which originate in the lower chambers of the heart, the ventricles).

The most common forms of tachycardias are:

1. Paroxysmal supraventricular tachycardia, which generally has a rate of 140 to 200 beats per minute, develops spontaneously, and stops and starts suddenly, but may reoccur.

2. Atrial flutter, in which the atria beat at 240 to 300 beats per minute, although the actual pulse rate is much slower, because not all of these impulses are translated into contractions of the ventricles.

3. Ventricular tachycardia, a very serious arrhythmia initiated in the ventricles, in which the heart rate is usually between 150 and 250.

4. Atrial fibrillation.

1.4.1 Causes and Risk Factors of Tachycardia

Sinus tachycardias are most likely to occur in those who are easily excitable, suffer anxiety, or drink a lot of caffeine-containing beverages. They may also been seen in people with thyroid disease, with fevers, or with certain drugs (especially asthma and allergy medications). The occurrence of tachycardias under any of these circumstances does not necessarily imply underlying heart disease. More severe types of tachycardia tend to occur in those who have underlying heart disease. They may be caused by an electrical disturbance within the heart without an anatomic deformity, or by congenital defects, coronary artery disease, chronic disease of the heart valves, or chronic lung

disease. Tachycardias may also occur in the course of a heart attack (or myocardial infarction).

1.4.2 Symptoms of Tachycardia

The main symptom is awareness of a rapid heartbeat, commonly called "palpitations." Depending on the cause and extent of the tachycardia, other symptoms may include shortness of breath, dizziness, actual syncope (fainting), chest pain, and severe anxiety.

1.5 Bradycardia

Having bradycardia means your heart beats very slowly. For most people, a heart rate of 60 to 100 beats a minute while at rest is considered normal. If heart beats less than 60 times a minute, it diagnose bradycardia. Healthy young adults and athletes often have heart rates of less than 60 beats a minute.

In other people, bradycardia is a sign of a problem with the heart's electrical system. It means that the heart's natural pacemaker is not working right or that the electrical pathways of the heart are disrupted. In severe forms of bradycardia, the heart beats so slowly that it does not pump enough blood to meet the body's needs.

1.5.1 Causes of Bradycardia:

- Changes in the heart that are the result of aging.
- Diseases that damage the heart's electrical system. These include coronary artery disease, heart attack, and infections such as endocarditis and myocarditis.
- Conditions that can slow electrical impulses through the heart. Examples include having a low thyroid level (hypothyroidism) or an electrolyte imbalance, such as too much potassium in the blood.
- Some medicines for treating heart problems or high blood pressure, such as beta-blockers, antiarrhythmics, and digoxin.

1.5.2 Symptoms of Bradycardia:

- Feel dizzy or lightheaded.

- Feel short of breath and find it harder to exercise.
- Feel tired.
- Have chest pain or a feeling that your heart is pounding or fluttering (palpitations).
- Feel confused or have trouble concentrating.
- Faint, if a slow heart rate causes a drop in blood pressure.

Chapter 2

Literature Review

2.1 Intercorrelation analyses among age, spectral parameters of heart rate variability and respiration in human volunteers:

In 1990, F. Weise, F. Heydenreich ,S. Kropf, D. Krell investigated interrelationship between age and heart rate, spectral parameters of heart rate variability, peak frequency of mid-frequency heart rate fluctuations, respiratory rate and coherence coefficient in healthy volunteers having normal blood pressure. Thereafter these parameters were correlated with each other in a young subject group to eliminate the effect of age. The peak frequency of mid-frequency heart rate fluctuations was significantly inversely related to age. The overall heart rate variability (0.01-.05 Hz) was reduced with aging due to the diminution of power spectral densities in the mid-frequency (0.05-0.15 Hz) and respiration related frequency band (heart rate spectral power around the mean respiratory rate). In the young subject group total power was positively related to the power of the discrete spectral components. The respiratory rate was inversely related to mid-frequency and respiration related frequency components of heart rate variability. Results appear to support on the one hand the hypothesis of age-related alterations in the autonomic cardiovascular control mechanisms. On the other hand data show significant correlations between spectral parameters of heart rate variability and respiration, which should be taken into consideration in the interpretation of heart rate power spectra in spontaneously breathing subjects [3].

2.2 Postural Effect on Respiratory Sinus Arrhythmia with Various Respiratory Frequencies:

In 1996,Hiromitsu Kobayashi studied Heart rate variations during steady state respiration with various frequencies on seven healthy male students at two different body positions. Respiration was controlled at four different frequencies (0.083, 0.100, 0.200, 0.250Hz), and the tidal volume was simultaneously controlled at 1500ml (0.083, 0.100Hz) or 1000ml (0.200, 0.250Hz:). A tilting bed was used for changing

body position, and the measurements were conducted at horizontal and vertical position. RSA (respiratory sinus arrhythmia) amplitude at 0.250Hz was significantly decreased at vertical position compared with horizontal position. At 0.200Hz the significant decrease could not be obtained although some tendency of decrease appeared. Contrary to these high frequencies, the amplitudes at low frequencies (0.083, 0.100Hz) were significantly increased ($p<0.01$) during vertical position. This postural effect on the low frequency RSA could be regarded as a similar result on MWSA (Mayer wave relate sinus arrhythmia) which reflects sympathetic nervous activity. Furthermore, the ratio between the amplitude at 0.100Hz and that at 0.250Hz was significantly correlated with mean heart rate ($n=56$, $r=0.73$). From these results it was assumed that the RSA amplitude at low frequency associate with not only parasympathetic nerves but also sympathetic nerves whereas the amplitude at high frequency was solely mediated by parasympathetic nerves.[4]

2.3 Effect of respiratory rate on the relationships between RR interval and systolic blood pressure fluctuations: a frequency-dependent phenomenon.

In 1997, Maria Vittoria Pitzalis determine the relationships between oscillations in systolic blood pressure and heart period at different breathing frequencies and investigate the role of sympathetic contribution to this relationship. Fourteen healthy volunteers underwent three randomized periods of controlled breathing at 6, 10 and 16 breaths/min. ECG (RR), respiratory signal (RESP) and systolic blood pressure (SBP) were continuously recorded. The component of RR and SBP oscillations related to respiration (RR_{Resp} and SBP_{Resp}) was defined by means of uni- and bivariate spectral analysis. The squared coherence (K^2) and phase between RR and RESP, and RR and SBP (RR-SBP) were also assessed. When the K^2 of RR-SBP in the respiratory band was >0.5, considered the phase and calculated the closed-loop gain between the two signals. Seven subjects were also studied after long lasting metoprolol treatment. Although the mean values of RR and SBP did not differ between the three periods of breathing, the higher the respiratory rate, the smaller the RR_{Resp} and SBP_{Resp}. The phase was always negative (SBP_{Resp} changes preceded RR_{Resp} changes), thus suggesting a baroreflex link. The higher the respiratory rate, the lower the gain and

phase. Pharmacological β-adrenoceptor blockade increased the gain and shifted the phase, but the relationships found at baseline between the respiratory rate and both the gain and phase remained unchanged. The effect of breath rate on the relationship between heart rate and systolic pressure variabilities is a frequency-dependent phenomenon that is also independent of the sympathetic drive.[5]

2.4 Effect of respiration rate on short-term heart rate variability:

In 1999, J. D. Schipke, M. Pelzer, G. Arnold studied the influence of the respiration rate on HRV. 15 volunteers performed controlled respiration at six different 6 min-intervals: below the low-frequency range (LF) of the power spectrum (0.03 Hz), within LF (0.08, 0.10 and 0.13 Hz), within the high-frequency range (HF; 0.25 Hz), and above HF (0.50 Hz). HRV was expressed in the time domain in terms of standard deviation (SDNN), root mean square successive difference (RMSSD) and the percentage of differences between adjacent normal RR intervals that are > 50 ms (pNN50). After fast Fourier transformation, HRV was expressed in the frequency domain in terms of LF power (0.05–0.15 Hz), HF power (0.15–0.45 Hz), and the ratio (R) of LF to HF. Heart rate (72 ± 11 min-1) remained unchanged throughout the protocol, indicating a steady state of circulation of blood. HRV differed up to 33 % in SDNN, 37 % in RMSSD and 75 % in pNN50 between the different respiration rates. LF power differed up to 72 % ($p < 0.10$), HF power up to 36 % and R up to 48 % ($p < 0.10$). Respiration clearly affected the frequency domain measurements of HRV via shifts in the respiratory sinus arrhythmia. The characteristic RSA-induced shifts in the frequency range could possibly be useful to determine respiration rate in freely moving individuals.[6]

2.5 Effect of Breathing Rate on Heart Rate Variability:

In 2004, T. PRINCI, A. ACCARDO, D. PETEREC investigate the relationship between sympatho-vagal modulation of cardiac function, expressed by heart rate variability (HRV), and spontaneous (as well as paced) breathing rate. This study was performed on 6 young females, characterized at rest by different heart rates (HRs) and different spontaneous breathing rates (8 and 15 breathing rate/min).The RR intervals, registered during spontaneous and paced respiratory rates, were elaborated and the

power spectral densities in very-low (VLF), low (LF) and high (HF) frequency bands were evaluated as well as the LF/HF ratio, the two standard deviations (SD_1 and SD_2) of the Poincaré plot, the γ values and the fractal dimension (FD). The results indicate no correlation between RR intervals and HRV parameters. On the other hand, an evident correlation between breathing rate, spontaneous or paced, and HRV parameters exists. Results show higher total power (absolute units), higher SD_1 and SD_2 (n. u.) parameters and lower FD values at lower breathing rate (8 br. r./min), independently from spontaneous breathing rate. In conclusion, the respiratory rate seems to be correlated to linear and non-linear parameters of HRV.[7]

2.6 Respiration And Heart Rate Variability :

In 2004 Lt Col KK Tripathi reviews the effects of various respiratory influences on different HRV estimates with the mechanisms involved therein. Certain examples are given, from the field of Aerospace Medicine, of the application of HRV analysis wherein respiration could be the main thing. Concerns expressed regarding effects of controlling the respiratory variables on HRV indices are given and, finally, the issue of susceptibility of non-linear HRV estimates to breathing is dealt with**.** The respiratory parameters which can affect HRV estimates, include- respiratory frequency (Rf), tidal volume, end tidal partial pressure of carbon di-oxide(PETco2) , the time ratio of expiration/inspiration and respiratory dead space.[8]

2.7 The Effect of Respiratory Frequency on Heart Rate Variability:

In 2004, S. V. Nesterov, V. P. Nesterov, and A. I. Burdygin found that the RF has a strong and regular influence on the parameters of HRV. RF-dependent changes in HRV are caused by two simultaneous processes: (a) a deeper respiration at a lower RF increases the RSA amplitude and (b) HRV parameters are influenced by a shift of the RSA peak along the frequency axis. Hence, under stable sympathetic influence on the cardiac rhythm, an increase in RSA in the range of HF leads to a higher power of this range and reduces the LF-to-HF ratio. This phenomenon is the most pronounced near the boundary between the LF and HF ranges. In the range of LF, a shift of the

increasing RSA peak under the conditions of decreasing RF leads to an increase in the power of this range and a higher LF-to-HF ratio.[9]

2.8 Heartbeat Synchronizes With Respiratory Rhythm Only Under Specific Circumstances:

In 2004, Yasuma and Hayano have theorized that respiratory sinus arrhythmia improves respiratory efficiency by the pairing of increases in heart rate with inhalation, when the concentration of oxygen in the alveoli is maximal. However, this phase relationship only occurs under specific circumstances.[10]

2.9 Model based and experimental investigation of respiratory effect on the HRV power spectrum:

In 2006 M Yildiz and Y Z Ider studied a comprehensive cardiorespiratory interaction model to test various hypotheses regarding the role of respiration in the LF peak of HRV. In this model, chest and abdomen circumference signals and lung volume signal are used as respiratory inputs. Simulations are made for periodic, spontaneous and slightly irregular respiratory patterns, and it is observed that the more low frequency (LF) power there in the respiratory signals, the more LF power there in the model predicted HRV. Experiments on nine volunteers were also performed for the same respiratory patterns and similar results were observed. Furthermore, the actual measured respiratory signals are input to the model and the model predicted and the actual HRVs are compared both in time domain and also with respect to their power spectra. It is concluded in general that respiration not only is the major contributor to the genesis of the HF peak in the HRV power spectrum, but also plays an important role in the genesis of its LF peak. Thus, the LF/HF ratio, which is used to assess sympathovagal balance, cannot be correctly utilized in the absence of simultaneous monitoring of respiration during an HRV test.[11]

2.10 Multiple window correlation analysis of HRV power and respiratory frequency:

In 2007, Hansson-Sandsten Maria, Jonsson Peter evaluate the correlation estimate, based on multiple window spectrum analysis, between the respiratory center frequency and the high-frequency band of the heart-rate variability (HRV) power. One aim is to examine whether a more restricted frequency range would better capture respiratory related HR variation, especially when the HR variation is changing rapidly. The respiratory peak is detected and a narrow-banded measure of the high-frequency (HF) band of the HRV is defined as the respiratory frequency ±0.05 Hz. After that, compare the mean square error of the correlation estimate between the frequency of the respiratory peak and the power of the HRV with the power in the usual 0.12-0.4 Hz frequency band. Different multiple window spectrum techniques were used for the estimation of the respiratory frequency as well as for the power of the HRV. They compared the peak-matched multiple windows with the Welch method while evaluating the two different HF-power estimates mentioned above. The results show that using a more narrow band for the power estimation gives stronger correlation which indicates that the estimate of the power is more robust [12].

2.11 Respiratory-phase domain analysis of heart rate variability can accurately estimate cardiac vagal activity during a mental arithmetic task:

In 2007 Kotani K, Takamasu K, Tachibana M. present a method to extract the amplitude of RSA in the respiratory-phase domain, to compare that with subjective or objective indices of the MWL (mental workload), and to compare that with a conventional frequency analysis in terms of its accuracy during a mental arithmetic task. HRV (heart rate variability), ILV (instantaneous lung volume), and motion of the throat were measured under a mental arithmetic experiment and subjective and objective indices were also obtained. The amplitude of RSA was extracted in the respiratory-phase domain, and its correlation with the load level was compared with the results of the frequency domain analysis, which is the standard analysis of the HRV. The subjective and objective indices decreased as the load level increased,

showing that the experimental protocol was appropriate. Then, the amplitude of RSA in the respiratory-phase domain also decreased with the increase in the load level. The results of the correlation analysis showed that the respiratory-phase domain analysis has higher negative correlations, -0.84 and -0.82, with the load level as determined by simple correlation and rank correlation, respectively, than does frequency analysis, for which the correlations were found to be -0.54 and -0.63, respectively. In addition, it was demonstrated that the proposed method could be applied to the short-term extraction of RSA amplitude. This method can estimate cardiac vagal activity more accurately than frequency analysis.[13]

2.12 Interaction between Heart Rate Variability and Respiration in Preterm Infants:

In 2008 P Indic1, EB Salisbury, D Paydarfar, EN Brown, R Barbieri have focused attention on cardiorespiratory function as an important indicator of development in infants. In the preterm infant, however, it remains unclear whether respiratory activity already affects heart beat variations at such an early development stage. In this work they investigate the presence of cardiorespiratory coupling in preterm infants by quantifying the interaction between heart rate variability and respiration using multivariate autoregressive analysis. They evaluated the frequency domain indices using standard methods. Results show a significantly higher coupling, as confirmed by surrogate data analysis, in the frequency range associated with regular breathing compared to other ranges. These observations indicate a mild, but present, respiratory sinus arrhythmia in preterm infants.[14]

2.13 Validity of Frequency Domain Method in Assessment of Cardia Autonomic Function During Controlled Breathing in Healthy Subjects:

In 2009 , NK Subbalakshmi, studied the correlation between heart rate variability measures derived from frequency domain and maximum-minimum method during one minute deep breathing at 6 respiratory cycles per minute. Ten healthy volunteers aged between 20-22 years of either sex took part in the study. Heart rate response to deep breathing was recorded with the subject in supine position connected to the limb

lead II. Simultaneously the ECG signals were picked up by the digital data acquisition system and fed in to a computer. Heart rate variability measures from maximum-minimum and frequency domain method were estimated by computer assisted method. The heart rate variability measures calculated for evaluation from frequency domain method was high and low frequency absolute power spectra. The values derived from maximum-minimum method were maximum R-R interval, minimum R-R interval and its ratio during deep breathing. Pearson correlation test was employed to find the correlation between heart rate variability measures. High and low frequency power spectra and ratio of maximum to minimum R-R interval during deep breathing were significantly correlating ($P<0.0001$). High and low frequency was significantly correlating with longest R-R interval during deep breathing ($P<0.0001$). Low and high frequency did not correlate with minimum R-R interval. The results of the present study suggests that either low or high frequency power spectra could be used to assess cardiac parasympathetic activity by employing deep breathing test.[15]

Chapter 3

Introduction

3.1 What is heart rate variability?

A healthy human heart does not beat – as most people assume – at a precisely regular rate, in terms of the length of time between beats, but rather slightly irregularly. In other words, it displays variation from one beat to the next. This is normal and shows that the organism, and thus also the heart, is being constantly influenced by external and internal stimuli, to which it must react in an adequate fashion. Thus, for example, a stress situation, brought on by bodily and/or mental strain, leads to an adjusted response of the heart. This can be seen in such signs as an increased heart rate, or, as a reduction of the variation range of the heart rate from beat to beat. This variation range of the heart rate from beat to beat is known as the heart rate variability (HRV).

The HRV results, among other things, from the influence of the nervous system (sympathetic and parasympathetic) on the sinuatrial node, the heart's internal "clock". The nervous system for its part is influenced by central mechanisms (brain) as well as feedback from the periphery (organs). The parasympathetic nervous system (vagus) assumes a mostly inhibitory effect, while the sympathetic nervous system has an activating function. Thus, a measurement of the HRV provides information not only about the central control mechanisms (brain) but also about the organ situation.

In a nutshell, this means that the higher the HRV the quicker and more flexibly the heart adapts to external and internal influences and the better the organism react to the environment. Accordingly, the ideal case is an optimum interplay between the sympathetic and parasympathetic nervous systems as an expression of an optimum capability for adaptation within the organism. A low HRV, on the other hand, indicates a reduced capacity for adaptation and may suggest serious health impairment, such as illnesses of the cardiovascular system, mental disorders, neuropathies or cancer. The HRV is comparable with the fever parameter: various illnesses can be indicated by fever, as with a reduction of the HRV, whereas many possible causes can be responsible for changes in both parameters.

Heart rate variability (**HRV**) is a measure of the beat-to-beat variations in heart rate (Figure in 3.1). It is usually calculated by analyzing a time series of beat-to-beat intervals from the ECG, of beat-to-beat intervals derived from an arterial pressure tracing or of beat-to-beat intervals derived from a pulse wave signal measured by means of a photoplethysmograph (PPG).[16] Under resting conditions, the ECG of healthy individuals exhibits periodic variation in R-R intervals. This rhythmic phenomenon, known as respiratory sinus arrhythmia (RSA), fluctuates with the phase of respiration -- cardio-acceleration during inspiration, and cardio-deceleration during expiration.

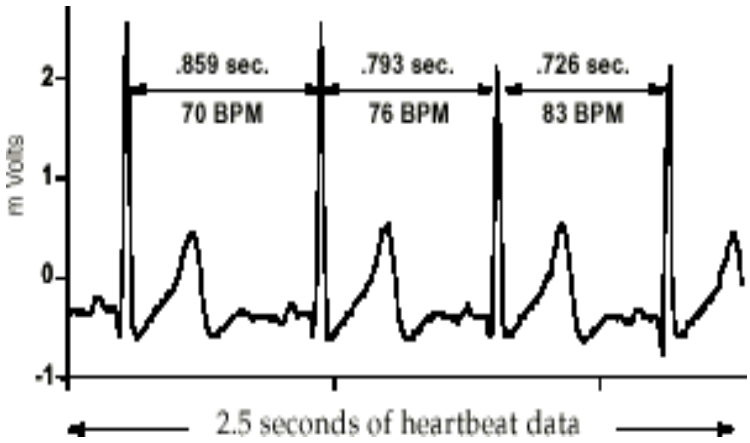


Figure 3.1 Heart rate variability is a measure of the beat-to-beat changes in heart rate.

Analysis of variations in the instantaneous heart rate time series using the beat-to-beat RR-intervals (the RR tachogram) is known as Heart Rate Variability (HRV) analysis. HRV analysis has been shown to provide an assessment of cardiovascular disease The heart rate may be increased by slow acting sympathetic activity or decreased by fast acting parasympathetic (vagal) activity. The balance between the effects of the sympathetic and parasympathetic systems, the two opposite acting branches of the autonomic nervous system, is referred to as the sympathovagal balance and is believed to be reflected in the beat-to-beat changes of the cardiac cycle. The heart rate is given by the reciprocal of the RR-interval in units of beats per minute. Spectral analysis of the RR tachogram is typically used to estimate the effect of the sympathetic and parasympathetic modulation of the RR-intervals. The two main frequency bands of interest are referred to as the Low-Frequency (LF) band (0.04 to

0.15 Hz) and the High-Frequency (HF) band (0.15 to 0.4 Hz). Sympathetic tone is believed to influence the LF component whereas both sympathetic and parasympathetic activity have an effect on the HF component. The ratio of the power contained in the LF and HF components has been used as a measure of the sympathovagal balance. Respiratory Sinus Arrhythmia (RSA) is the name given to the oscillation in the RR tachogram due to parasympathetic activity which is synchronous with the respiratory cycle. The RSA oscillation manifests itself as a peak in the HF band of the spectrum. For example, 15 breaths per minute corresponds to a 4 second oscillation with a peak in the power spectrum at 0.25 Hz. A second peak is often found in the LF band of the spectrum at approximately 0.1 Hz.

The HRV is based on the duration of the time interval between two R waves, graphically presented in the form of an RR interval tachogram. The functional value of the tachogram is the duration of an RR interval (in ms) at a certain point in time.

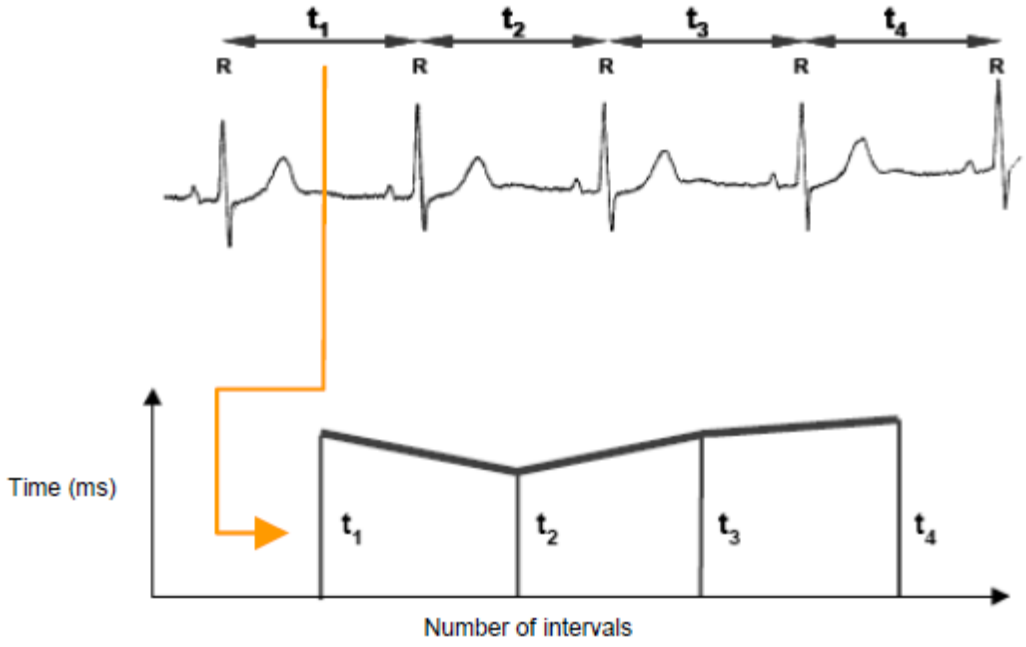


Fig. 3.2: Compilation of a tachogram from an ECG (t_n – duration of an RR interval).

Since heart rate is the simplest physiological index, it is extensively employed for studying work-load on the living system. Heart rate on a per min basis is generally represented. In a more detailed perspective, heart rate is analyzed on a beat by beat

basis(figure 3.2). In this case, the time interval of beat by beat may not be consistent and manifests a variation range of 10–30% even if the heart rate per min remains constant. This phenomenon is known as heart rate variability (HRV) as shown below:

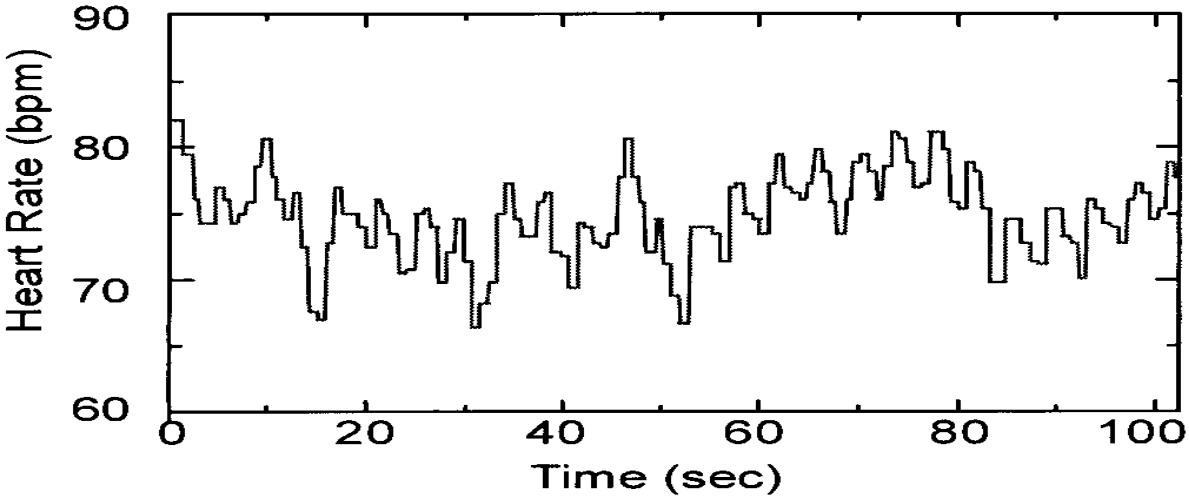


Fig. 3.3 Tachogram of heart rate variability. Periodic variations of heart rate are shown.

The *Autonomic Nerve System* (ANS) is responsible for short-term regulation of the blood pressure. The ANS is a part of the *Central Nervous System* (CNS). The ANS uses two subsystems - the *sympathetic* and *parasympathetic* systems. The *sympathetic* system is active during stressful situations, in order to provide a higher heart rate up to 180 beat per minute (bpm). Sympathetic fibers innervate the entire heart, including the sinus node, the AV conducting pathways and the atrial and ventricular myocardium. Increased activity of the sympathetic nerves increases heart rate (HR) and force of contraction. In addition, the rate of conduction through the heart is increased and the duration of contraction is shortened. When sympathetic activity increases, there is a latent period of up to 5 seconds before there is an increase in HR, which then reaches a steady level after about 30 seconds. In contrast, the parasympathetic system is active during rest and can reduces the HR down to 60 bpm. It innervates the atriventricular conducting pathways and the atrial muscle. The latency of the response of the sinus node is very short, just in the first of second beat after its onset. There is a linear relation between decreasing the HR and the frequency of parasympathetic stimulation..It has been noted that an imbalance between the

competing sympathetic and parasympathetic systems is an important indicator of many cardiac disorders. The HF component is in synchrony with respiration and is referred as respiratory sinus arrhythmia (RSA).

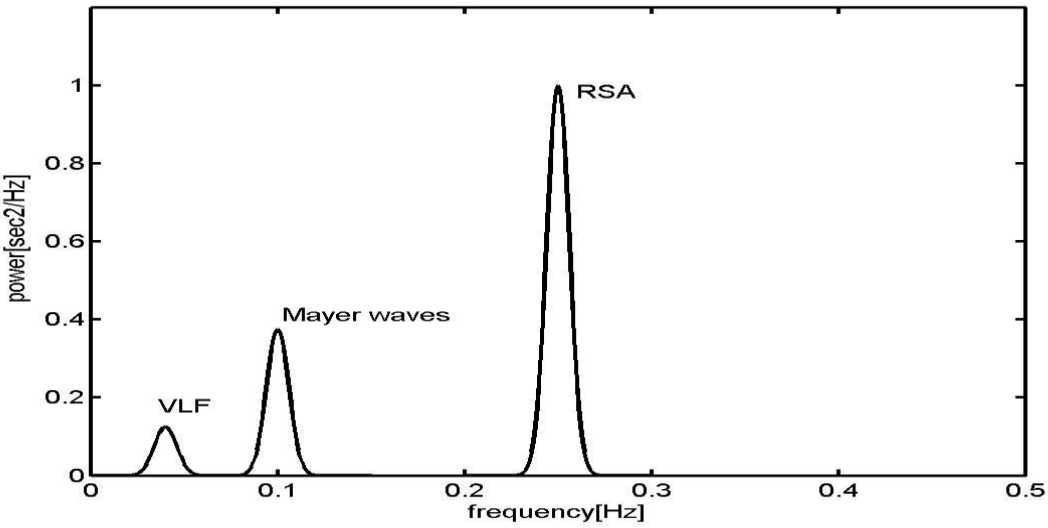


Fig. 3.4. A typical power spectrum of HRV

It is believed that under normal conditions the existence of at least three oscillatory systems are responsible for the generation of the Mayer waves, namely: (i) The baroreceptor or chemoreceptor feedback system; (ii) centrogenic rhythm in the brain stem with interconnection to the respiratory oscillator; (iii) the autorhythmicity of vascular smooth muscle. Fig 3.4 shows a typical power spectrum of HRV.

3.2 Background:

The connection between the state of health and the amount of variation in the heart rate was noted as early as the 3rd century AD by the Chinese doctor Wang Shuhe. He analysed various pulse types and gave the following prognosis: "When the heart is as regular as the tapping of the woodpecker or the dripping of the rain on the roof, the patient will die within four days." [17]. The clinical relevance of HRV was first appreciated in 1965 when Hon and Lee[18] noted that fetal distress was preceded by alterations in interbeat intervals before any appreciable change occurred in heart rate itself. Twenty years ago, Sayers[19]and others focused attention on the existence of physiological rhythms imbedded in the beat-to-beat heart rate signal. During the 1970s, Ewing et al[20] devised a number of simple bedside tests of short-term RR differences to detect autonomic neuropathy in diabetic patients. The association of

higher risk of postinfarction mortality with reduced HRV was first shown by Wolf et al in 1977 [21]. In 1981, Akselrod introduced power spectral analysis of heart rate fluctuations to quantitatively evaluate beat-to-beat cardiovascular control [22]. These frequency domain analyses contributed to the understanding of autonomic background of RR interval fluctuations in the heart rate record. The clinical importance of HRV became appreciated in the late 1980s, when it was confirmed that HRV was a strong and independent predictor of mortality after an acute myocardial infarction. With the availability of new, digital, high-frequency, 24-hour, multichannel ECG recorders, HRV has the potential to provide additional valuable insight into physiological and pathological conditions and to enhance risk stratification. In modern medicine HRV analysis has been used since the beginning of the sixties, where it was initially used in obstetrics for the early diagnosis of possible hypoxia in the foetus. Since the end of the eighties HRV measurement has become an ever more important tool in the diagnosis and prognosis of various illnesses.

- **Early detection and prognosis:**

In the area of intensive care HRV measurement is used for the early detection of possible complications – such as septicaemia (a generalised, life-threatening inflammatory condition of the whole body) – as well as a prognosis factor after the onset of illness. A connection between various sub-clinical inflammatory conditions and a reduced HRV has been shown in otherwise healthy people. It is possible to show a strong inverse relationship between the level of the HRV and the leukocyte count in the blood [23]. This is interesting inasmuch as it has been suggested that long-term inflammatory processes in the body favour the development of heart diseases. There is, therefore, a great deal of interest in measuring initial parameters that indicate inflammatory changes in the body, in order to be able to initiate effective preventative or therapeutic measures at an early stage. This is where measuring the HRV can provide useful information. Additionally, in high-risk patients with cardiovascular diseases a reduced HRV could be noted in addition to other inflammation markers (increase in interleukin-6, CRP)

- **Diagnosis:**

HRV can be used in the diagnosis of such diseases as diabetic neuropathy. A reduced HRV is considered a primary indicator of cardiovascular autonomic diabetic

neuropathy. In addition, patients suffering from depression have also been shown to have a reduced HRV along with an increased heart rate.

3.3 Analysis of Heart Rate Variability

Spontaneous variability of heart-rate has been related to three major physiological originating factors: quasi-oscillatory fluctuations thought to arise in blood-pressure control, variable frequency oscillations due to thermal regulation and respiration; frequency selective analysis of cardiac interbeat interval sequences allows the separate contributions to be isolated[24].

Heart rate variability refers to the regulation of the sinoatrial node the natural pacemaker of the heart by the sympathetic and parasympathetic branches of the autonomic nervous system. Our assumption, when we assess HRV, is that the beat-to-beat fluctuations in the rhythm of the heart provide us with an indirect measure of heart health, as defined by the degree of balance in sympathetic and vagus nerve activity. The heart rate variability analysis is a powerful tool in assessment of the autonomic function. It is accurate, reliable, reproducible, yet simple to measure and process. The source information for HRV is a continuous beat-by-beat measurement of interbeat intervals. The electrocardiograph (ECG or EKG) is considered as the best way to measure interbeat intervals. ECG is an electrical signal measured with special conductive electrodes placed on chest around heart area or limbs. It reflects minute changes in electrical field generated by heart muscle cells originating from its SA node. ECG signal has a very specific and robust waveform simple to detect and analyze. Because of that cardiac rhythm derived from ECG is the best way to detect not only true sinus rhythm but all types of ectopic heartbeats, which must be excluded from consideration of HRV analysis. Figure 3.5 shows baroreflex functionality.

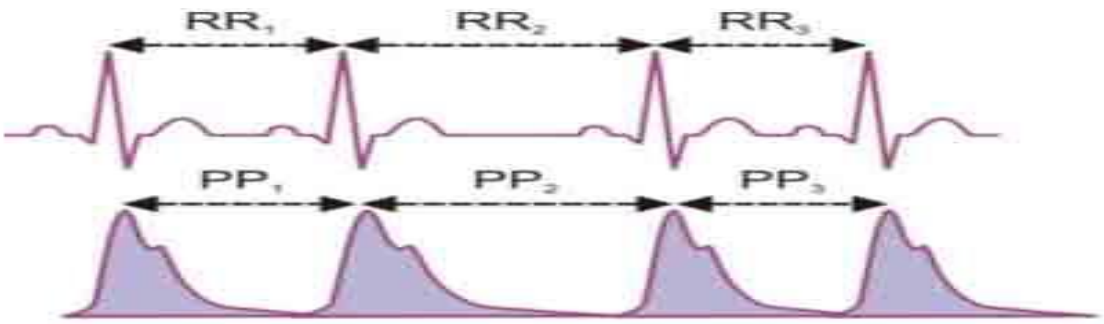


Figure 3.5 Schema showing the baroreflex functionality

The other approach to measure cardiac intervals is a measurement of pulse wave. It is less invasive and simple method of measurement based on photoplethysmograph. PPG is a signal reflecting changes in a blood flow detected when infrared light is emitted towards microcirculatory blood vessels. Depending on blood flow volume certain portion of that light is absorbed letting other part to pass or reflected. An optical sensor detects a quantity of light passed (or reflected from) the blood flow producing a waveform identifying pulse wave. Such waveform can also be processed to derive beat-by-beat interbeat intervals. Although PPG gives the summary information reflecting both cardiac and blood vessel components of HRV, some research studies showed a significantly high correlation between interbeat interval data measured by both ECG and PPG in short-term steady-state recordings.

One of the important issues when measuring either ECG or PPG is the absence of abnormal heartbeat used in interval detection. Only heartbeats originated in SA node can be processed to obtain HRV data. Whether there are ectopic heartbeats (PVCs or other types of extrasystolic heartbeats) or various movement artifacts on ECG (or PPG) considered as heartbeats, they must be excluded from consideration. There are various statistically-based algorithms of detection of such abnormal heartbeats (Figure 3.6) that minimize chances to get contaminated HR recordings. Nevertheless, for the sake of accuracy in HRV analysis it is important to be able to visually and verify all heartbeats automatically found, remove abnormal ones and include missing. The Heart Rhythm Scanner has an automatic detection of such movement artifacts and also gives the possibility to manually correct it.

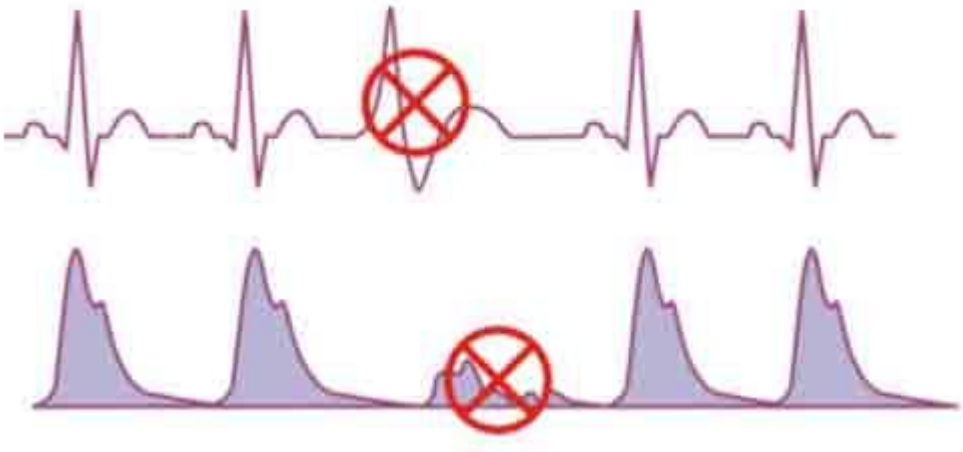


Figure 3.6 Example of abnormal heartbeats

3.4 Correlation:

If there is any relation between two variables i.e. when one variable changes the other also changes in the same or in the opposite direction, we say that the two variables are correlated. It means the study of existence, magnitude and direction of the relation between two or more variables. in technology and in statistics.

There are two points which one should remember while dealing with correlation. The first is that the value of the correlation coefficient is independent of the change in origin and scale. Secondly, the two independent variables are said to not be in correlation if the value of the covariance of the variable is zero. However, the converse of this property is not true. That is, the two variables that are not in correlation are not necessarily independent. The variables are not designated as dependent or independent. The two most popular correlation coefficients are: Spearman's correlation coefficient rho and Pearson's product-moment correlation coefficient. When calculating a correlation coefficient for ordinal data, select Spearman's technique. For interval or ratio-type data, use Pearson's technique.

3.5 Types of Correlation

1. Positive and negative correlation
2. Linear and non-linear correlation

A) If two variables change in the same direction (i.e. if one increases the other also increases, or if one decreases, the other also decreases), then this is called a positive correlation. For example : Advertising and sales.

B) If two variables change in the opposite direction (i.e. if one increases, the other decreases and vice versa), then the correlation is called a negative correlation. For example : T.V. registrations and cinema attendance.

1. The nature of the graph gives us the idea of the linear type of correlation between two variables. If the graph is in a straight line, the correlation is called a "linear correlation" and if the graph is not in a straight line, the correlation is non-linear or curvi-linear.

2. For example, if variable x changes by a constant quantity, say 20 then y also changes by a constant quantity, say 4. The ratio between the two always remains the same (1/5 in this case). In case of a curvi-linear correlation this ratio does not remain constant.

3.6 Degrees of Correlation

Through the coefficient of correlation, we can measure the degree or extent of the correlation between two variables. On the basis of the coefficient of correlation we can also determine whether the correlation is positive or negative and also its degree or extent.

1. Perfect correlation**:** If two variables changes in the same direction and in the same proportion, the correlation between the two is perfect positive. According to Karl Pearson the coefficient of correlation in this case is +1. On the other hand if the variables change in the opposite direction and in the same proportion, the correlation is perfect negative. its coefficient of correlation is -1.
2. Absence of correlation**:** If two series of two variables exhibit no relations between them or change in variable does not lead to a change in the other variable, then we can firmly say that there is no correlation or absurd correlation between the two variables. In such a case the coefficient of correlation is 0.
3. Limited degrees of correlation**:** If two variables are not perfectly correlated or is there a perfect absence of correlation, then we term the correlation as Limited correlation. It may be positive, negative or zero but lies with the limits 0 and 1.

   High degree, moderate degree or low degree is the three categories of this kind of correlation. The following table reveals the effect (or degree) of coefficient or correlation.

Table 3.1 Degrees of coefficient of correlation

Degrees	**Positive**	**Negative**
Absence of correlation →	Zero	0
Perfect correlation →	+ 1	-1
High degree →	+ 0.75 to + 1	- 0.75 to -1
Moderate degree →	+ 0.25 to + 0.75	- 0.25 to - 0.75
Low degree →	0 to 0.25	0 to - 0.25

The quantity *r*, called the *linear correlation coefficient*, measures the strength and the direction of a linear relationship between two variables. The correlation coefficient is a number between 0 and 1. If there is no relationship between the predicted values and the actual values the correlation coefficient is 0 or very low (the predicted values are no better than random numbers). As the strength of the relationship between the predicted values and actual values increases so does the correlation coefficient. A perfect fit gives a coefficient of 1.0. The main result of a correlation is called the correlation coefficient (or "r"). It ranges from -1.0 to +1.0. The closer r is to +1 or -1, the more closely the two variables are related. If r is close to 0, it means there is no relationship between the variables. If r is positive, it means that as one variable gets larger the other gets larger. If r is negative it means that as one gets larger, the other gets smaller (often called an "inverse" correlation).

- **Range of a Correlation Coefficient**

1. Perfect positive (all points fall on a straight line)

2. Perfect negative

3. No correlation

r =	±	(0 ↔ 1)
	Sign	Magnitude
	Gives direction	Gives strength

The value of r is such that $-1 \leq r \leq +1$. The + and – signs are used for positive linear correlations and negative linear correlations, respectively.

- **Positive Correlation:**

If *x* and *y* have a strong positive linear correlation, r is close to +1. An r value of exactly +1 indicates a perfect positive fit. Positive values indicate a relationship between *x* and *y* variables such that as values for *x* increase, values for *y* also increase.

- **Negative Correlation:**

If *x* and *y* have a strong negative linear correlation, r is close to -1. An r value of exactly -1 indicates a perfect negative fit. Negative values indicate a relationship between *x* and *y* such that as values for *x* increase, values for *y* decrease.

- **No Correlation:**

If there is no linear correlation or a weak linear correlation, r is close to 0. A value near zero means that there is a random, nonlinear relationship between the two variables r is a dimensionless quantity; that is, it does not depend on the units employed.

A Perfect Correlation of ± 1 occurs only when the data points all lie exactly on a

straight line. If r = +1, the slope of this line is positive. If r = -1, the slope of this line is negative.

A correlation greater than 0.8 is generally described as strong, whereas a correlation less than 0.5 is generally described as weak. These values can vary based upon the "type" of data being examined.

3.7 Methods of Determining Correlation

We shall consider the following most commonly used methods.(1) Scatter Plot (2) Karl Pearson's coefficient of correlation (3) Spearman's Rank-correlation coefficient.

1) **Scatter Plot (Scatter diagram or dot diagram):** In this method the values of the two variables are plotted on a graph paper. One is taken along the horizontal ((x-axis) and the other along the vertical (y-axis). By plotting the data, we get points (dots) on the graph which are generally scattered and hence the name 'Scatter Plot'.

The manner in which these points are scattered, suggest the degree and the direction of correlation. The degree of correlation is denoted by ' r ' and its direction is given by the signs positive and negative.

i) If all points lie on a rising straight line the correlation is perfectly positive and r = +1 (see fig.1)

ii) If all points lie on a falling straight line the correlation is perfectly negative and r = -1 (see fig.2)

iii) If the points lie in narrow strip, rising upwards, the correlation is high degree of positive (see fig.3)

iv) If the points lie in a narrow strip, falling downwards, the correlation is high degree of negative (see fig.4)

v) If the points are spread widely over a broad strip, rising upwards, the correlation is low degree positive (see fig.5)

vi) If the points are spread widely over a broad strip, falling downward, the correlation is low degree negative (see fig.6)

vii) If the points are spread (scattered) without any specific pattern, the correlation is absent. i.e. r = 0. (see fig.7)

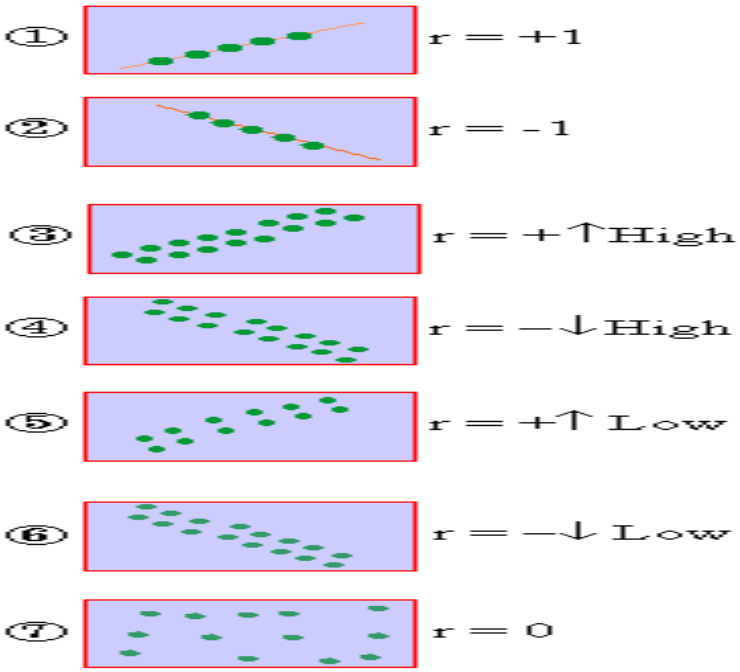


Figure 3.7: Different Patterns of Scatter Plot

Though this method is simple and is a rough idea about the existence and the degree of correlation, it is not reliable. As it is not a mathematical method, it cannot measure the degree of correlation.

2) **Karl Pearson's coefficient of correlation:** It gives the numerical expression for the measure of correlation. It is noted by 'r '. The value of 'r ' gives the magnitude of correlation and sign denotes its direction.

Assumptions:

- linear relationship between x and y
- continuous random variables
- both variables must be normally distributed
- x and y must be independent of each other

Termed *Pearson's Product Moment Correlation Coefficient*.

- Good with metric data.
- Probably the most popular correlation coefficient.
- It is required that both variables involved be normally distributed.
- Represents quantitatively the extent to which scores on two variables occupy the same relative position.

It is defined as

$$r = \frac{\sum x.y}{n\sigma_x\sigma_y}$$

$x = (x_i - \bar{x})$, $y = (y_i - \bar{y})$, $\sigma_x = s.d.ofx$ and $\sigma_y = s.d.ofy$

Where N = Number of pairs of observation R is also known as product-moment coefficient of correlation.

$$r = \frac{\sum x.y}{\sqrt{\sum x^2} \times \sqrt{\sum y^2}} \text{ Since } \sigma_x = \sqrt{\frac{\sum x^2}{n}} \quad \text{and} \quad \sigma_y = \sqrt{\frac{\sum y^2}{n}}$$

$$r = \frac{\sum x.y - \left(\frac{\sum x.\sum y}{n}\right)}{\sqrt{\sum x^2 - \frac{\sum x^2}{n}} \cdot \sqrt{\sum y^2 - \frac{\sum y^2}{n}}}$$

Now covariance of x and y is defined as

$$\text{cov}(x, y) = \frac{\sum (x_i - \bar{x})(y_i - \bar{y})}{n} \quad \text{Therefore} \quad r = \frac{\text{cov}(x, y)}{\sigma_x\sigma_y}$$

If the values of x and y are very big, the calculation becomes very tedious and if we change

the variable x to $u = \frac{x_1 - x_0}{c}$ and y to $v = \frac{y_1 - y_0}{d}$ where x_0 and y_0 are the assumed means for variable x and y respectively, then $r_{xy} = ruv$

The formula for r can be simplified as

$$r_{xy} = r_{uv} = \frac{\sum uv - \left(\frac{(\sum u)(\sum v)}{n} \right)}{\sqrt{\sum u^2 - \frac{(\sum u)^2}{n}} \times \sqrt{\sum v^2 - \frac{(\sum v)^2}{n}}}$$

The correlation coefficient stands in close relationship to linear regression. The square of r is called the goodness of fit and denotes the portion of total variance explained by the regression model.

Values of Pearson's correlation coefficient

Pearson's correlation coefficient (r) for continuous (interval level) data ranges from -1 to +1. Figure 3.8 shows different Patterns.

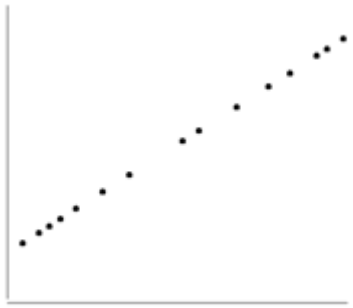
r = -1

Data lie on a perfect straight line with a negative slope.

r = 0

No linear relationship between the variables.

r = +1



Data lie on a perfect straight line with a positive slope.

Figure 3.8: Different Patterns of Pearson Correlation Coefficient.

3) Spearman's Rank Correlation Coefficient

This method is based on the ranks of the items rather than on their actual values. The advantage of this method over the others in that it can be used even when the actual values of items are unknown. For example if you want to know the correlation between honesty and wisdom of the boys of your class, you can use this method by giving ranks to the boys. It can also be used to find the degree of agreements between the judgements of two examiners or two judges.

A variant of Pearson's r which is used with rank data is called **Spearman's Rho (r_s)**. This correlation coefficient is appropriate when either of the following two conditions are met:

a. One variable is an ordinal scale and the other is an ordinal scale or higher.
b. One of the distributions is markedly skewed.

In either case, both scales must be converted to ranks. And if we computed Pearson's r on the ranked data, it would give Spearman's Rho.

The formula is :

$$R = 1 - \frac{6\sum D^2}{N(N^2 - 1)}$$

Where R = Rank correlation coefficient

D = Difference between the ranks of two items

N = the number of observations

Note: $-1 \leq R \leq 1$.

i) When $R = +1 \Rightarrow$ Perfect positive correlation or complete agreement in the same direction

ii) When $R = -1 \Rightarrow$ Perfect negative correlation or complete agreement in the opposite direction.

iii) When $R = 0 \Rightarrow$ No Correlation.

iii) When $R = 0 \Rightarrow$ No Correlation.

- **Important Issues With Correlation**

1. Factors Influencing the Correlation

- **Linearity**
  A linear (or monotonic) relationship is best characterized by a straight line.
- **Limited (Restricted & Truncated) Ranges**
  Refer to situations in which the sample is somehow limited. In both cases, it results in an underestimated r.
- **Extreme Groups**
  Results in an overestimated r.
- **An Extreme Score**
  Also results in an overestimated r. Is more of a problem when using small sample sizes.

2. Relation to Causality

Possible causal relationships between X and Y if they are correlated include:

Table 3.2 causal relationships

Possibility	Symbols	Explanation
a.	$X \rightarrow Y$	X causes Y
b.	$X \leftarrow Y$	Y causes X
c.	$X \leftarrow A \rightarrow Y$	A causes both X & Y
d.	$B \rightarrow C \rightarrow X$ $B \rightarrow Y$	Etc.

Main point is that correlation doesn't tell us much about causality. It should be noted that inferring causality from a correlation is an error that is all too common.

3. Some Specific Uses of Correlation

- **Determining Reliabilities:**
  Compare two rates (interobserver) or the same rates (intraobserver) observations of behaviour to see if they agree.
- **Determining Validities:**
  If first one variable is highly correlated with second one then that first variable is a valid predictor of second one and vice versa.
- **For Prediction:**
  A set of procedures similar to correlation called regression is used for predicting one variable from one or more other variables.

Chapter 4

Heart Rate Variability

4.1 Introduction

An electrocardiogram (ECG**)** is a graph, produced by electrocardiographs, that provides information about individual cardiac health. ECGs are commonly used in clinical applications to help doctors diagnose cardiac diseases such as tachycardia. Aside from directly analyzing the ECG signals, researchers and doctors also extract other indirect measurements from the ECG signals. One of the most popular measurements is heart rate variability (HRV). A normal one-cycle ECG signal is made up of several waves, as shown in Figure 4.1

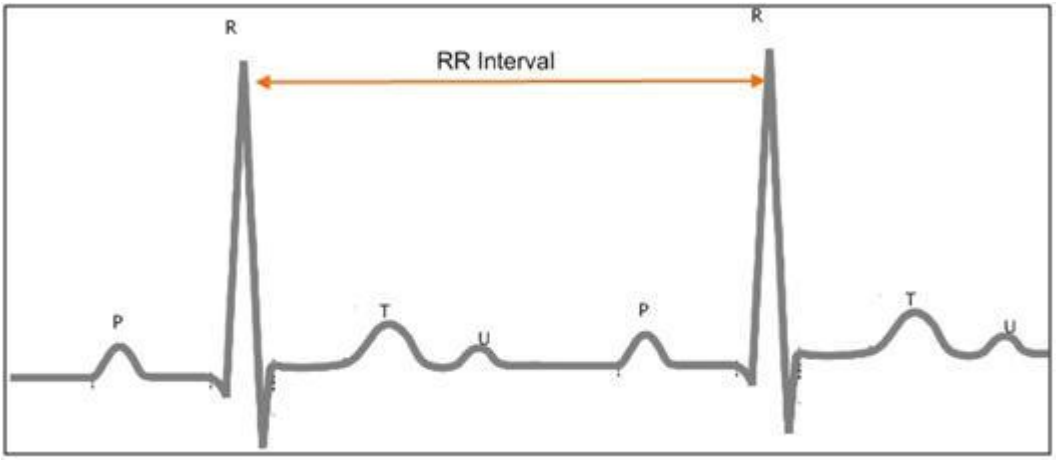


Figure 4.1 R Peaks of ECG Signal & RR Intervals

The peak with the highest amplitude is called the R wave. An RR interval is the time that elapses between two successive R waves. The lower peaks are the P wave; the T wave, and the U wave, respectively. Heart Rate Variability (HRV) measurements analyze how these RR intervals, which show the variation between consecutive heartbeats, change over time.

HRV analysis provides a quantitative marker of the autonomic nervous system (ANS) because the regulation mechanisms of HRV originate from the sympathetic and parasympathetic nervous systems [25]. To date, many researchers and engineers have made contributions to discover information which could be applicable to hospitals. In

the last ten years, over 2000 articles have been published about HRV [26]. These articles observe relationships between HRV and blood pressure, myocardial infarction, nervous system, cardiac arrhythmia, diabetes, respiration, renal failure, gender, age, fatigue, drugs, smoking, alcohols, and so on [27]. Various medical disciplines also have been researching HRV. It is believed that HRV analysis will become more popular in patient graphical and data analysis in the coming days.

4.2 Power Spectrum of HRV

Spectrum of HRV The mathematical transformation (Fast Fourier Transform) of HRV data into power spectral density (PSD) is used to discriminate and quantify sympathetic and parasympathetic activity and total autonomic nervous system activity. Power spectral analysis reduces the HRV signal into its constituent frequency components and quantifies the relative power of these components. Power Spectrum is shown in figure 4.2.

- Thoughts and even subtle emotions influence the activity and balance of the autonomic nervous system (ANS).
- The ANS interacts with our digestive, cardiovascular, immune and hormonal systems.
- Negative reactions create disorder and imbalance in the ANS.
- Positive feelings such as appreciation create increased order and balance in the ANS, resulting in increased hormonal and immune system balance and more efficient brain function.

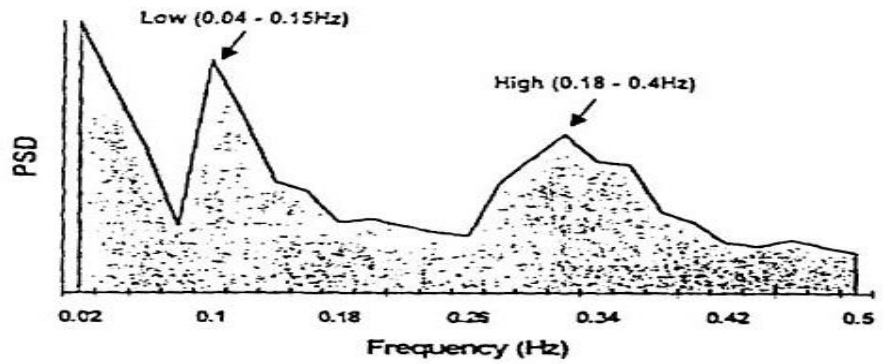


Fig 4.2 A typical power spectrum of HRV

The power spectrum is divided into three main frequency ranges. The very low frequency range (VLF) (0.0033 to 0.04 Hz), representing slower changes in heart rate, is an index of sympathetic activity, while power in the high frequency range (HF) (0.15 to 0.4 Hz), representing quicker changes in heart rate, is primarily due to parasympathetic activity. The frequency range around the 0.1 Hz region is called the low frequency (LF) band and is also often referred to as the baroreceptor band, because it reflects the blood pressure feedback signals sent from the heart back to the brain, which also affect the HRV waveform. The LF band is more complex, as it can reflect a mixture of sympathetic and parasympathetic activity. It has been shown in a number of studies that during mental or emotional stress, there is an increase in sympathetic activity and a decrease in parasympathetic activity. This results in increased strain on the heart as well as on the immune and hormonal systems. Increased sympathetic activity is associated with a lower ventricular fibrillation threshold and an increased risk of fibrillation, in contrast to increased parasympathetic activity, which protects the heart.

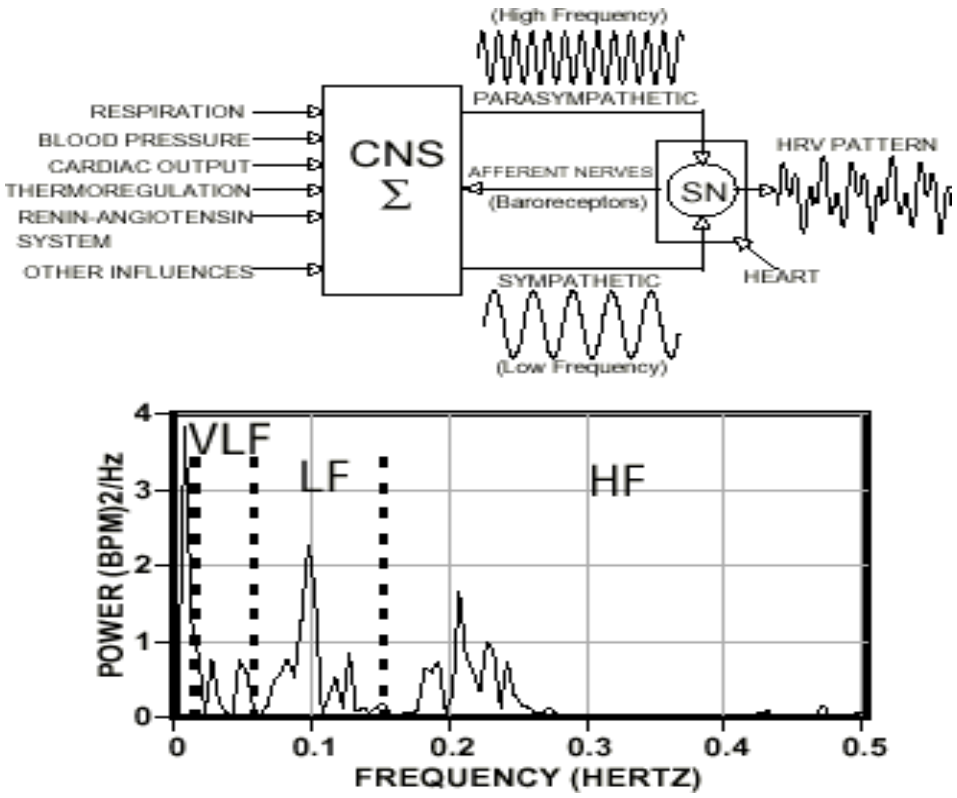


Figure 4.3 Nervous system links between heart and brain and power spectrum of heart rate variability.

The top diagram (Figure 4.3) illustrates the nervous system links between the heart and brain. The sympathetic branch speeds heart rate while the parasympathetic slows it. Heart rate variability is due to the interaction between the two branches of the nervous system and the signals sent from the heart to the brain (baroreceptor network). The bottom graph shows a power spectrum of the HRV waveform. The power (height of the peak) in each band reflects the activity in the different branches of the nervous system.

4.3 Methods of Measurement

HRV can be assessed by time domain or frequency domain indices. The time domain measures are based on the amount of time, in milliseconds, in the beat-to-beat intervals of the heart or from the differences between the normal beat-to-beat intervals. Technically, the beat-to-beat interval is defined as the time in milliseconds

between normal "R" to "R" waves on an EKG. The flowchart of HRV analysis is given below:

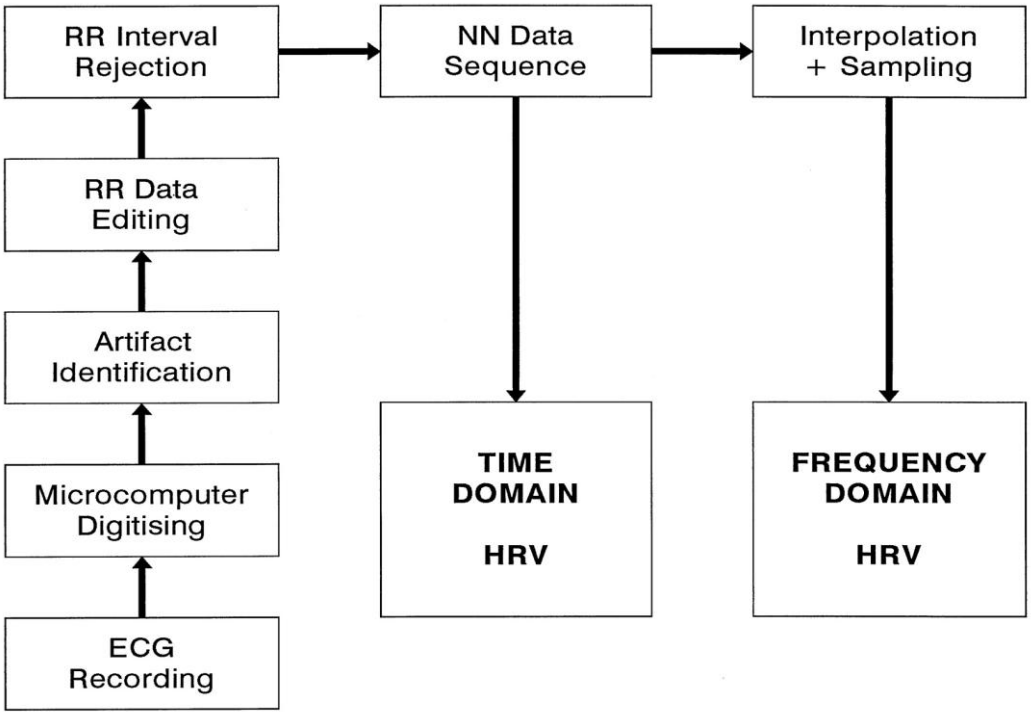


Figure 4.4 Flow chart summarizing individual steps used when recording and processing the ECG signal in order to obtain data for HRV analysis.

Frequency domain measures of HRV provide information on the frequency distribution of the components of HRV using power spectral density analysis. Spectral, analysis of HRV is characterized by four main components: the high frequency (HF) component (.15Hz -0.4Hz) measures the influence of the vague nerve in modulating the sinoatrial node. The low frequency (LF) component (.04Hz-.155 Hz) provides an index of sympathetic effects on the heart, particularly when these are measured in normalized units. The very low frequency (VLF) component (.003Hz -.04 Hz) reflects the influence of several factors on the heart, including chemoreceptors, thermareceptors, the renin-angiotensin system, and regular factors. Almost all of the variability from a short term spectral analysis of HRV is captured in these three components. An ultra low frequency (ULF) component (<.003 Hz) can also be observed in the HRV spectrum analysis of a longer sample [28].

4.3.1 HRV Analysis Methods

There are different methods of HRV analysis (Figure 4.5). One of the methods is time domain analysis. This method extracts a few special measures using only the temporal RR interval signals. Another method is spectral analysis. This method interpolates the RR interval at a certain rate and transforms this interval into the frequency domain. There are some standards for these two methods. Other methods are non-linear analysis and the time frequency analysis are also discussed later. To analyze HRV, we first must obtain the RR inter

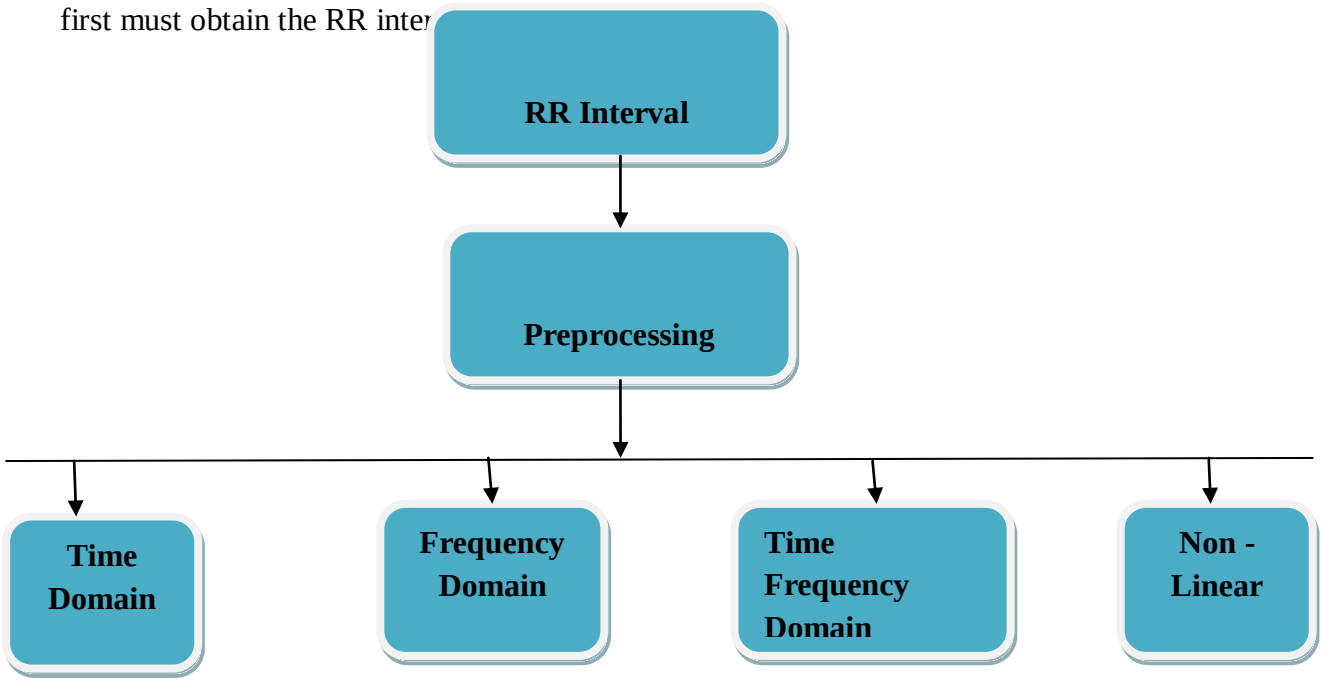


Figure 4.5 Show the entire process of HRV analysis.

- **Acquiring Raw ECG Signals**

ECG signals are acquired by various kinds of electrocardiographs.

- **Extracting RR intervals from ECG Signals**

RR interval signals are extracted from raw ECG signals. The extraction process usually involves the pre-processing step and the peak detection step. It is necessary to preprocess the raw ECG signals if they have noise corruption and have significant baseline trend. Then detect the R peaks by thresholding or using the wavelet-based peak detection method to compute the RR intervals.

- **Pre-processing**

RR interval signals might have some baseline wandering, which will result in inaccurate temporal and frequency analysis. we can choose whether to detrend the RR interval signals before analysis. The method to detrend RR interval signals is similar to the method of ECG signal processing.

- **Analyzing RR Interval Signals**

The following sections describe the different methods we can use to analyze the RR interval signals.

4.3.2 Analysis in the time range

The basis of the analysis in the time range is the absolute interval duration between two R waves, or their difference. A simple example of a time domain measure is the calculation of the standard deviation of beat-to-beat intervals. In other words the time intervals between heart beats can be statistically analyzed to obtain information about the autonomic nervous system.The higher the value of the median RR interval (ie the longer the RR interval), the lower the median heart rate. This can indicate an economical functioning of the heart. The higher the SDNN (as standard deviation of the RR med.), the greater the variability. A high variability indicate a good interplay between the sympathetic and parasympathetic nervous systems.

Time Domain methods include estimation of variables such as the standard deviation of the normal-to-normal (NN) intervals (sdNN), the square root of the mean of the sum of the squares of differences between adjacent NN intervals (rMSSD), NN50 or the number of normal to normal complexes that fall within 50 milliseconds, the percent of the number of pairs of adjacent NN intervals differing by more than 50 ms(pNN50). Although these variables provide useful information on HRV, they are not appropriate for short data records Their values are affected by data length and most of the time they provide information on only one branch of ANS [29].

- **Time domain measures of HRV**

(1) SDNN -standard deviation of durations of all NN intervals, (2)SDANN - standard deviation of 5-minute means of all NN intervals, **(3)** SDNN index - mean of the

standard deviations of all NN intervals for all 5-minute segments of a 24-hour recording, (4) rMSDD - root means square of differences between adjacent NN intervals in a 24-hour recording, ***(5)*** pNN50 - proportion of **NN** intervals which are shorter than 50 ms than the immediately previous NN interval, (6) HRV index - total number of NN intervals divided by the height of their histogram, **(7)** TINN-triangular interpolation of the histogram of NN interval durations where HRV is expressed as the baseline width of the triangle.

- **Time Domain Analysis**

For time series analysis, time domain measures are commonly used. Many measures can be extracted from the original RR interval signals to show the changes in the ANS.

Table 4.1 Time Domain Measures of HRV

Variables	Units	Descriptions
Statistical measures		
RR Mean & Std	s	Mean and standard deviation of all RR intervals.
HR Mean & Std	1/min	Mean and standard deviation of all heart hates.
RMSSD	ms	Square root of the mean of the sum of squares of differences between adjacent RR intervals.
NN50 count		Number of pairs of adjacent RR intervals differing by more than 50 ms in all the measurements.
pNN50	%	NN50 count divided by the total number of all RR intervals.
Geometric measures		

HRV triangular index		Total number of all RR intervals divided by the height of the histogram of all RR intervals.
TINN	ms	Baseline width of the minimum square difference triangular interpolation of the highest peak of the histogram of all RR intervals measured on a discrete scale with bins of 7•8125 ms (1/128 s).

4.3.3 Frequency domain measures of HRV

Three frequency domain measures are given: (1) high frequency power (0.15 - 0.40 Hz), reflecting modulation of vagal tone by breathing, (2) low frequency power (0.04 - 0.15 Hz), which reflects both parasympathetic and sympathetic modulation of heart rate, and (3) total power (0.003 - 0.40 Hz).[30]. There are three types of heart rate variation, providing an equivalent to the standard power spectrum: (1) high frequency peak, (2) medium frequency peak, and (3) low frequency peak.[31.]

- **Frequency domain**

A common frequency domain method is the application of the discrete Fourier transform to the beat-to-beat interval time series. This provides an estimation of the amount of variation at specific frequencies. Several frequency bands of interest have been defined in humans.

- Total Frequency Spectral Power shows the size of the entire area within all frequencies. This is regarded as the yardstick for the influence of the autonomic nervous system on the cardiovascular system
- High Frequency band (HF) between 0.15 and 0.4 Hz. HF is driven by respiration and appears to derive mainly from vagal activity or the parasympathetic nervous system. It shows the oscillations caused by the parasympathetic nervous system, in particular the respiratory sinus arrhythmia (RSA) and thus the respiration-synchronous heart rate fluctuations.
- Low Frequency band (LF) between 0.04 and 0.15 Hz. LF derives from both parasympathetic and sympathetic activity and has been hypothesized to reflect the delay in the baroreceptor loop.
- Very Low Frequency band (VLF) band between 0.0033 and 0.04 Hz. The origin of VLF is not well known, but it had been attributed to thermal regulation of the body's internal systems.
- Ultra Low Frequency (ULF) band between 0 and 0.0033 Hz. The major background of ULF is day/night variation and therefore is only expressed in 24-hour recordings.
- The ratio of low-to-high frequency spectra power(LF/HF) is used as an index of sympathetic to parasympathetic balance of heart rate fluctuation, but this remains controversial because of still little understanding of the LF component, which may be affected by centrally generated brainstem rhythms, baro-reflex influences, as well as both sympathetic and parasympathetic inputs, etc.

➢ **Frequency Domain Analysis**

The frequency domain analysis method of HRV analysis extracts frequency domain parameters, such as peak frequency and power in band, from the RR interval signals. The two components of ANS, sympathetic and parasympathetic, increase or decrease the heart rate and influence different bands in the spectrum of RR intervals. Therefore, we can use frequency domain analysis to monitor the state of the ANS.

Table 4.2 shows the common frequency domain measures of HRV, including peak frequency and power in the very low frequency (VLF), low frequency (LF), and high frequency (HF) bands.

Table 4.2 Frequency Domain Measures of HRV

Variables	**Units**	**Descriptions**
Peak Frequency	Hz	Peak frequencies of the power spectral density (PSD) estimate for the VLF, LF, and HF frequency bands.
VLF	ms^2	Power from 0–0.04 Hz.
LF	ms^2	Power from 0.04–0.15 Hz.
HF	ms^2	Power from 0.15–0.4 Hz.
LF Norm	n.u	LF power in normalized units: LF/(Total Power–VLF)*100.
HF Norm	n.u.	HF power in normalized units: HF/(Total Power–VLF)*100.
LF/HF Ratio		LF [ms^2]/HF [ms^2].

Frequency domain methods usually involve the following three steps:

1. Resample the RR interval signals.
2. Estimate the power spectral density (PSD) of the RR interval signals.
3. Compute frequency domain parameters from the PSD.

The RR interval signals extracted from ECG signals usually are not sampled at a regular interval. Therefore, the RR interval signals along the time axis are not spaced equally. Therefore it is necessary to convert the original RR signals into an evenly-sampled time series. PSD estimation are either nonparametric or parametric estimation methods. Nonparametric methods include FFT-based PSD, such as

Periodogram and Welch. Parametric methods include model-based PSD, such as autoregressive (AR) spectrum and autoregressive moving average (ARMA) spectrum.

4.3.4 Joint Time-Frequency Domain Analysis

The frequency domain analysis method works well for RR interval signals that do not vary much over time. However, in some applications such as long term HRV analysis, such as 24-hour RR intervals and drug pharmacodynamics research, RR interval signals vary significantly over time. In these situations, joint time-frequency analysis (JTFA) is used to analyze stationarity and time-frequency behavior. There are no standard measures for the joint time-frequency domain method. Short Time Fourier Transform (STFT), the Gabor expansion, or the Continuous Wavelet can be used to show the time-frequency plots and perform qualitative analysis.

4.3.5 Non-Linear Analysis

The RR interval signals are non-linear because they result from complex interactions of hemodynamics, electrophysiological, and humoral variables, as well as autonomic and central nervous regulations [32]. Very few studies have been done regarding non-linear analysis, so there are no standards. However, this is a promising area of research to discover tools that will help us better understand the complexity of the human system.

- **Poincare Plot:** It is an XY graph whose x's and y's are two consecutive RR intervals. The Poincare plot fits heart rate data points to an ellipse that is fitted to two intersecting lines. The ellipse is fitted onto the so called line-of-identity at 45◦ to the normal axis. The standard deviation of the points perpendicular to the line-of-identity denoted by SD1 describes short-term variability which is mainly caused by respiratory sinus arrhythmia (RSA). The standard deviation along the line-of-identity denoted by SD2 describes long-term variability.

- **Detrended Fluctuation Analysis:** The detrended fluctuation analysis (DFA) method quantifies the fractal scaling properties of RR interval signals. This

method avoids erroneous correlation by removing non-stationary artificial trends. Therefore, the DFA method shows the changes of long-term HRV correlation better than other methods. The DFA method uses linear fitting to analyze the DFA plot. The slope α of the fitted line indicates the correlation of HRV. If $\alpha = 0.5$, the signals are white noise and have no correlation. In some situations, the DFA plot is not strictly linear but made up of two lines at a certain break point. This situation suggests that there are two factors: a short range scaling exponent over short periods and a long-range exponent over long periods [32].

4.4 Comparison of HRV Analysis Method

Time Domain methods include estimation of variables such as the standard deviation of the normal-to-normal (NN) intervals (sdNN), the square root of the mean of the sum of the squares of differences between adjacent NN intervals (rmsSD), the percent of the number of pairs of adjacent NN intervals differing by more than 50 ms (pNN50). Although these variables provide useful information on HRV, they are not appropriate for short data records. Their values are affected by data length and most of the time they provide information on only one branch of ANS. Due to limitation of time domain methods, spectral analysis (SA) methods are introduced. SA methods allow the identification of oscillations in signals at their exact frequencies. One of the most common SA methods is Fourier Transformation (FT). FT has been used in HRV analysis extensively. Although FT enables researchers to quantify ANS activity, it also comes with some drawbacks. FT assumes stationarity while most of medical signals are not. That generates a problem especially when trying to detect transient changes over short period of time in clinical settings. Furthermore, because of the time and frequency resolution problems of FT, one can miss critical details in signals. Due to these issues, wavelet spectral analysis is proposed for HRV signals. For biological signals, wavelet analysis is more suited given its capability of adjusting to changes in signal characteristics. Window length in wavelet analysis is adjusted to the signal features and provides a better time frequency resolution. For slow changing signals, wavelets use longer windows. For fast changing signals, the window length is shorter.

4.5 Heart rate variability computation methods:

Heart rate variability (HRV) is a measure which expresses variations of the number of heartbeats per unit of time. A large value of this index reveals a complicated system which can respond better to a wide variety of conditions. Thus, a healthy person usually presents large values of HRV, while a decreased value may indicate a cardiac disease. Heart rate variability computation methods can be categorized as statistical, geometrical, those based on signal analysis in frequency or time domain, nonlinear ones, etc.[33]

The following ones are:

- Statistical: standard deviation, standard deviation of mean values of intervals, root mean square of successive differences, mean standard deviation of intervals, standard deviation of differences, percentage of differences greater than a given value and autocorrelation;
- Prediction and approximation: local linear prediction, least squares approximation and prediction with autoregressive moving average models;
- Time and frequency analysis methods: power spectral density and discrete wavelet transform; and
- Nonlinear: correlation dimension estimation and approximate entropy
- **Statistical method:**

  The most common statistical methods include standard deviation, standard deviation of mean values of intervals, root mean square of successive differences, mean standard deviation of intervals, standard deviation of differences, percentage of differences greater than a given value and autocorrelation.

  The standard deviation is defined as:

$$sdnn = \sqrt{1/N \sum_{j=1}^{N} (x_j - \bar{x})^2} - \sqrt{\sum_{j=1}^{N} x_j^2 / N - (\sum_{j=1}^{N} x_j / N)^2}$$

  where xi is a sample point (R-R interval), _x the mean value of all sample points and N the total number of sample points. The standard deviation of

mean values of intervals (sdann) is defined by the standard deviation of mean values of successive equal sized window intervals. A typical value of the window size is 5 min of recording.

The root mean square of successive differences is defined as:

$$rmssd = \sqrt{\frac{1}{N-1}\sum_{j=1}^{N-1}\left(x_{j+1} - x_j\right)^2}$$

where, again, xi is a sample point and N the total number of sample points.

The mean standard deviation of intervals (sdnni) is described by the mean standard deviation of successive equal sized window intervals, in a way similar to sdann. It defines a window size, but first calculate the standard deviation for every successive window and then computes the mean value of the standard deviations.

The percentage of differences greater than x (pNNx) calculates the percentage of the differences between successive samples that are greater than a given value of x. Typical values for x are 30 ms and 50 ms.

$$pNNx = \frac{\sum_{j=1}^{N-1}\Theta(\left(\left|x_{j+1} - x_j\right|\right) - x)}{N}$$

$$\Theta(i) = \{1, when i \geq 0$$

$$\Theta(i) = 0, otherwise$$

The standard deviation of differences is defined by the following formula:

$$sdsd = \sqrt{\frac{1}{N}\sum_{j=1}^{N}(dx_j - \bar{dx})^2},$$

Where $dx_i - |x_{i+1} - x_i|$, x_i is a sample point, $d\bar{x}$ the mean value of all $d\overline{x_i}$ and N the total no.of dx_i intervals.

Finally, the autocorrelation is given by the formula:

$$acorr(\tau) = \frac{\sum_{j=1}^{N-\tau}\left(x_j - \bar{x}\right)\left(x_{j+\tau} - \bar{x}\right)}{\sum_{j=1}^{N}\left(x_j - \bar{x}\right)^2},$$

Where τ is a time lag.

- **Prediction and approximation methods:**

There are two measures local linear prediction (llp) and least squares approximation (lsa). The local linear prediction [34,35] is a simple prediction method in which future samples of a timeseries $x_1, x_2, \ldots\ldots\ldots, x_i, \ldots\ldots x_N$ are predicted by using a linear combination of previous k samples.

$$\hat{x}_j = \frac{1}{K}\sum_{j=j-k}^{j-1} x_j$$

The index is calculated by the mean values of absolute differences between predicted and actual values:

$$llp = \frac{1}{N-K}\sum_{j=k}^{N}\left|\hat{x}_j - x_j\right|$$

In least squares approximation [34] the signal is divided in L successive windows of size k and each window is approximated by the least square method. Then calculate the mean approximation error for all approximated segments pi:

$$lsa = \frac{1}{L}\sum_{j=1}^{L}\left\|\overline{\hat{p}_j} - \overline{p_j}\right\|$$

ARMA (autoregressive moving average) models are usually used for prediction. The notation ARMA(p,q) refers to the model with p autoregressive terms and q moving average terms:

$$\hat{x}_j = \varepsilon_t + \sum_{j=1}^{q}\varphi_j \hat{x}_{t-j} + \sum_{j=1}^{q}\theta_j \varepsilon_{t-j}$$

The index is calculated by the mean values of absolute differences between predicted and actual values:

$$arma = \frac{1}{N - \max(p,q)}\sum_{j=\max(p,q)}^{N}\left|\hat{x}_j - x_j\right|$$

- **Time and frequency analysis methods:**

  There are two methods: power spectral density, which analyses the signal in the frequency domain, and discrete wavelet transform, which decomposes the signal in the time – frequency domain. Spectral analysis of the heart rate signal is typically used to estimate the effect of sympathetic and parasympathetic modulation of the RR-intervals. The heart rate may be increased by slow acting sympathetic activity or decreased by fast acting parasympathetic (vagal) activity. The two main frequency bands of interest are referred to as the low frequency (LF) band (0.04 to 0.15 Hz) and the high frequency (HF) band (0.15 to 0.4 Hz). Sympathetic tone is believed to influence the LF component whereas both sympathetic and parasympathetic activities have an effect on the HF component. In general, it is expected that normal ECGs, as more irregular, will demonstrate wider and more overlapped broadband frequency peaks in contrast to abnormal ECGs, where the spectrum is expected to be thinner, exposing a more regular behaviour. Figure 1 shows the power spectral density

of a normal ECG and an abnormal one.The power spectral density (psd) of a signal is given by the Fourier transform of its autocorrelation function $R(\tau)$

$$psd(f) = \int_{-\infty}^{\infty} R(\tau) e^{-j2\Pi f\tau} d\tau$$

The discrete wavelet transform dwt is a linear operation, which transforms a linear vector whose length is originally a power of two, to another vector of the same length. Given a signal x of length n, dwt consists of at most log2n stages. The first step produces two sets of coefficients—approximation coefficients (scaling coefficients) and detail coefficients (wavelet coefficients). The vectors are obtained by a low-pass filter for approximation and a high-pass filter for detail coefficients, followed by dyadic decimation. This process is applied repeatedly only to the resulting approximation coefficient vector, and then continues until the log2nth stage. The nature of the filters is dependent upon the family of wavelets used. For every signal processed, it is the scale-dependent statistics of the detail coefficients that provide the graphical diagnostic output. Specifically, once the detail coefficient vector has been computed at each scale, its standard deviation is calculated. The same is repeated for every scale, until the log2nth scale is reached. The detail coefficients of the wavelet transform are calculated as:

$$W_{m,k}^{wav} = 2^{\frac{-m}{2}} \sum_{j=0}^{n-1} x_j \psi_m (i - k2^m),$$

while the approximation coefficients may be calculated with:

$$S_{m,k}^{wav} = 2^{\frac{-m}{2}} \sum_{j=0}^{n-1} x_j \psi_m (i - k2^m),$$

In both equations, m is the scale variable (m-1,2, . . .) and k is the shift variable (n-. . . , -1, 0, +1, . . .). Functions $_{\psi_m}(i)$ and $\varphi_m(i)$ are the discrete-time mother wavelets for the mth scale in the calculation of the detail coefficients and approximation coefficients respectively. The variable n represents the total

number of samples being analysed. The m-scale dwt can be obtained by applying the one-scale dwt m times subsequently to the approximation components. The coefficients that are statistically manipulated and graphed are the detail coefficients. The choice of wavelet family applied to the signal through dwt is usually dependent upon the application.

- **Nonlinear methods:**

  There are two typical nonlinear methods—approximate entropy [36] and correlation dimension estimation method [37]. Presented here is approximate entropy (apen) [36], widely used for HRV computation. Given the original timeseries xt, construct a series of vectors:

$$\vec{x} = \left[x_{t,} x_{t+1,} x_{t+2,} ....., x_{t+m-1}\right]$$

  where m is a window size. Two vectors $\overrightarrow{x_i}$ and $\overrightarrow{x_j}$ are similar when

$$\left|x_i - x_j\right| < r, \left|x_{i+1} - x_{j+1}\right| < r, ..., \left|x_{i+m-1} - x_{j+m-1}\right| < r$$

  The threshold r is estimated heuristically.Typical values for m and r are m=2 and r=0.25std(xt), where std is the standard deviation. The quantity Cim(r) is the fraction of vectors of length m that are similar to the vectors of the same length that begins at interval i. We can calculate Cim(r) for each vector of size m and we define Cm(r) as the mean of these Cim(r) values. The approximate entropy is defined as:

$$\text{apen}=\ln\left[\frac{C_m(r)}{C_{m+1}(r)}\right]$$

- The delay times method, or the correlation dimension estimation, (cde) is an important tool in nonlinear analysis. It was first established by Grassberger and Procaccia [37]. From the original time series we construct a new series of vectors.

$$\overrightarrow{x_t} = \left[x_{t,} x_{t+\tau,} x_{t+2\tau,.} x_{t+(m-1)\tau}\right]$$

  For the construction of each of the vectors it is necessary to estimate two parameters, the embedding dimension m and the time lag τ . The time lag τ represents the window used for the computation of the coordinates of these

vectors. The parameter m is assigned increasing integer values, in a range that satisfies both the Taken criterion and the maximum admitted window length, according to basic nonlinear dynamics theory. Then, the correlation integral, C(m, r, τ) is computed for increasing values of m:

$$C(m,r,\tau) = \frac{2}{N-1}\sum_{i-1}^{N}\sum_{j-i+1}^{N}\Theta[r - \left\|\vec{x}_i - \vec{x}_j\right\|],$$

$$\Theta(i) = 1, when i \geq 0,$$
$$\Theta(i) = 0, otherwise$$

This integral basically computes how many of the above vectors have a distance between them less than r, where r is a ray in the vector space. We are then able to plot ln(C) vs. ln(r), where ln is the natural logarithm function. From this plot we select a scaling region and compute the slope of the curve in that region. This process is repeated for increasing values of the embedding dimension, m, and if the values of the slopes converge, then we have found the correlation dimension of the time series. The convergence value of the slope is an estimation of the correlation dimension.

4.6 Advantages of measuring HRV

1. To measure changes in total ANS power and sympathetic/parasympathetic balance that occurs during different emotional states.

2. The study of heart rate variability is a powerful, objective and noninvasive tool to explore the dynamic interactions between physiological, mental, emotional and behavioural processes.

3. HRV is an important indicator of both physiological resiliency and behavioral flexibility, reflecting the individual's capacity to adapt effectively to stress and environmental demands.

4. Provided proper isolation and more accurate detection of parasympathetic and sympathetic control of the heart.

5. HRV signals contain rhythms which include physiological information.

6. HRV biofeedback training appears to offer a more precise method for helping clients to moderate the heightened sympathetic activity that is associated with stress, anxiety and dysphonic mood.

7. It provides a window to observe the heart's ability to respond to normal Regulatory Impulses that affect its rhythm.

4.7 Applications of HRV

1. Heart Rate Variability, or HRV, is a non-invasive tool for the measurement of autonomic nervous system activity.

2. To detect any cardiovascular disease.

3. Diabetic Autonomic Neuropathy is characterized by a shift in autonomic tone. Heart Rate Variability (HRV) is a low cost, non-invasive tool for the early detection of DAN.

4. HRV has become a widely accepted tool to predict risk of cardiovascular events, particularly following myocardial infection.

5. HRV provides a clinical measurement tool for autonomic tone before and after a pain management or biofeedback program.

6. For better diagnosis of diseases associated with abnormal ANS activity.
7. The effects of drugs, and of external stimuli can be also better understood with analysis of HRV.

8. The most frequent clinical use of heart rate variability (HRV) is the identification of those survivors of acute myocardial infarction who are at risk of serious ventricular arrhythmias and/or sudden cardiac death.

9. Clinical applications are used in Arrhythmias, Autonomic Function, Congestive Failure, Diabetes Mellitus, Myocardial Infarction, Exercise Testing, Neonatal Sepsis, Sleep Apnea Syndromes, Sudden Cardiac Death.

Chapter 5

Respiratory Sinus Arrhythmia

5.1 Arrhythmia

An arrhythmia (also called dysrhythmia) is an abnormal rhythm of the heart, which can cause the heart to pump less effectively.

Arrhythmias can cause problems with contractions of the heart chambers by:

- Not allowing the chambers to fill with an adequate amount of blood, because an electrical signal is causing the heart to pump too fast.
- Not allowing a sufficient amount of blood to be pumped out to the body, because an electrical signal is causing the heart to pump too slowly or too irregularly.

In any of these situations, the heart may not be able to pump an adequate amount of blood to the body with each beat due to the arrhythmia's effects on the heart rate. The effects on the body are often the same, whether the heartbeat is too fast, too slow, or too irregular. The following are the most common symptoms of arrhythmia. However, each child may experience symptoms differently. Symptoms may include:

- weakness
- fatigue
- palpitations
- low blood pressure
- dizziness
- fainting

Another indication of an arrhythmia is a change in the electrocardiogram (EKG or ECG) pattern.

5.2 Different types of arrhythmias

An atrial arrhythmia is an arrhythmia caused by abnormal function of the sinus node, or by the development of another atrial pacemaker within the heart tissue that takes over the function of the sinus node.

A ventricular arrhythmia is an arrhythmia caused by abnormal function of the sinus node, an interruption in the electrical conduction pathways, or the development of another area within the heart tissue that takes over the function of the sinus node.

Arrhythmias can also be classified as slow (bradyarrhythmia) or fast (tachyarrhythmia). "Brady-" means slow, while "tachy-" means fast.

5.2.1 Atrial Arrhythmias

- **Sinus arrhythmia** - a condition in which the heart rate varies with breathing. Sinus arrhythmia is commonly found in children; adults may often have it as well. This is usually a benign condition - there may be no symptoms or problems associated with sinus arrhythmias.
- **Sinus tachycardia** - a condition in which the heart rate is faster than normal for the child's age because the sinus node is sending out electrical impulses at a rate faster than usual. This condition may cause symptoms such as weakness, fatigue, dizziness, or palpitations if the heart rate becomes too fast to pump an adequate supply of blood to the body. Sinus tachycardia is often temporary, occurring when the body is under stress from exercise, strong emotions, fever, or dehydration, to name a few causes. Once the stress is removed, the heart rate will usually return to its usual rate.
- **Sick sinus syndrome** - a condition in which the sinus node sends out electrical signals either too slowly or too fast. There may be alternation between too-fast and too-slow rates. This condition may cause symptoms if the rate becomes too slow or too fast for the body to tolerate.
- **Premature supraventricular contractions or premature atrial contractions (PAC)** - a condition in which the sinus node or another pacemaker site above the ventricles sends out an electrical signal early. The ventricles are unable to respond to this signal because they are still in the contraction phase (Figure 5.1).

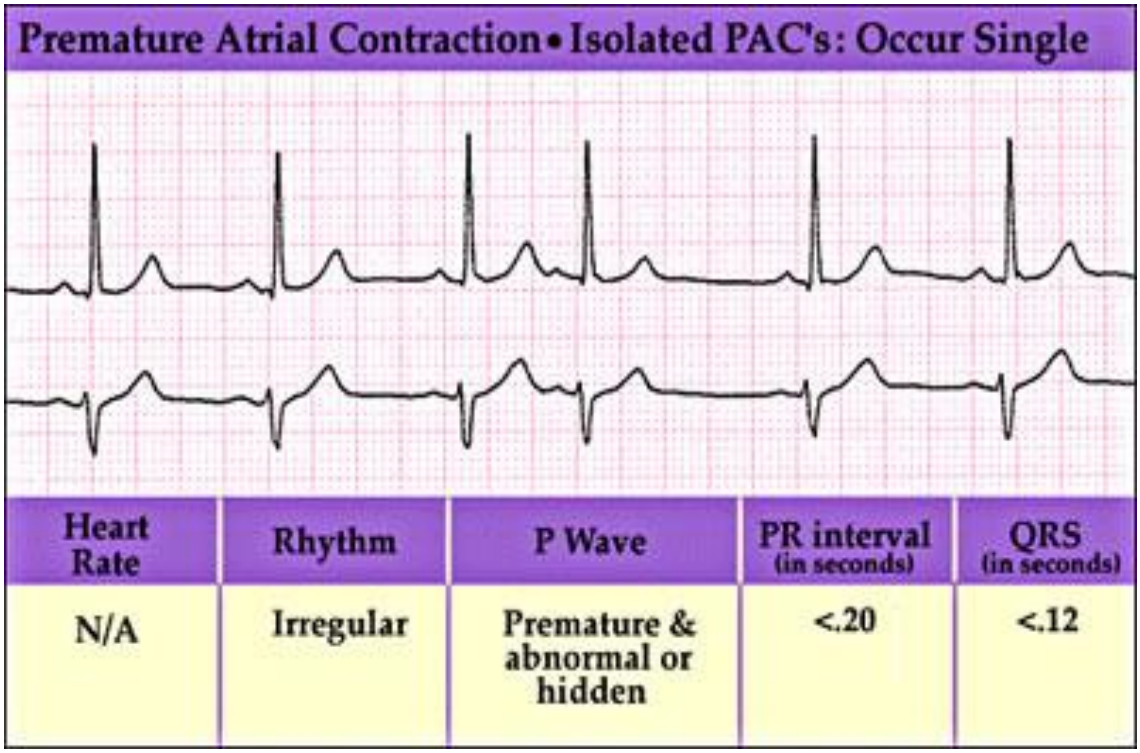


Figure 5.1 Premature atrial contraction

- **Supraventricular tachycardia (SVT) or paroxysmal atrial tachycardia (PAT)** - a condition in which the heart rate speeds up due to a series of early beats from the sinus node or another pacemaker site above the ventricles. PAT usually begins and ends rapidly, occurring in repeated periods. This condition can cause symptoms such as weakness, fatigue, dizziness, fainting, or palpitations if the heart rate becomes too fast.

- **Atrial flutter**: a condition in which the electrical signals come from the atria at a fast but even rate, thus causing the ventricles to contract faster and increase the heart rate. The heart rate maintains an even rate as it beats faster. When the signals from the atria are coming at a faster rate than the ventricles can respond to, the EKG pattern develops a signature "sawtooth" pattern, showing two or more P waves between each QRS complex. The number of P waves between each QRS complex is usually a constant number and is expressed as a ratio (i.e., a two-to-one atrial flutter means that two P waves are occurring between each QRS) (Figure 5.2).

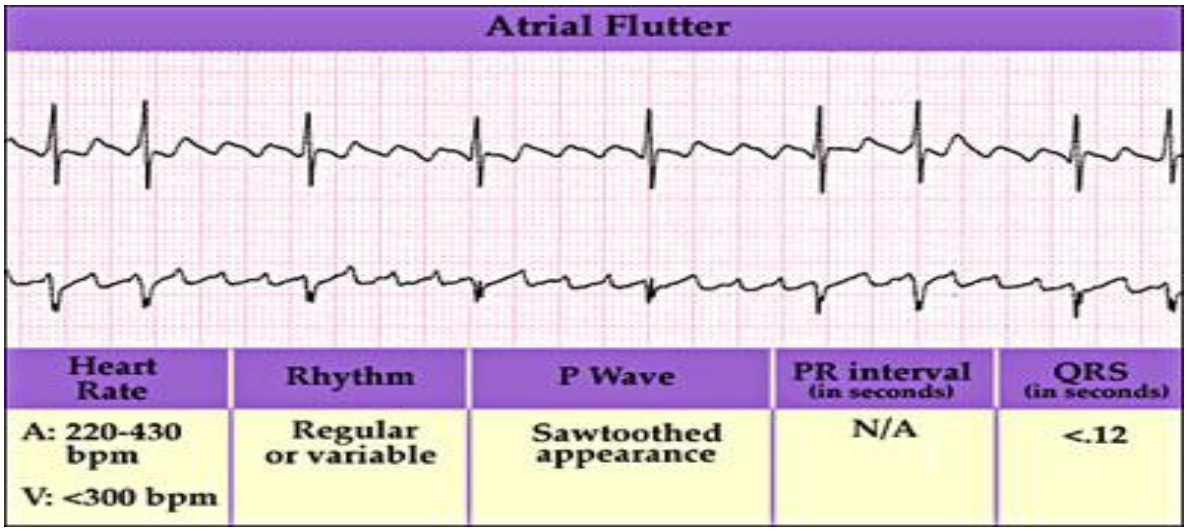


Figure 5.2 Atrial flutter

- **Atrial fibrillation** - a condition in which the electrical signals come from the atria at a very fast and erratic rate. The ventricles contract in an erratic manner because of the erratic signals coming from the atria (Figure 5.3).

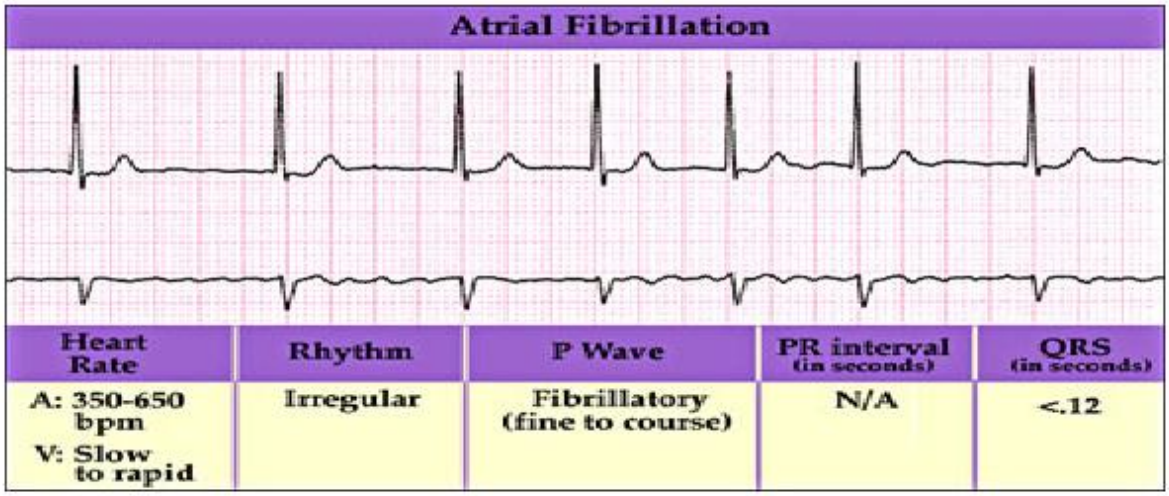


Figure 5.3 Atrial fibrillation

5.2.2 Ventricular Arrhythmias

- **Premature ventricular contractions (PVCs)** - a condition in which an electrical signal originates in the ventricles and causes the ventricles to contract before receiving the electrical signal from the atria. PVCs are not uncommon and often do not cause symptoms or problems. However, if the frequency of the PVCs

increases to several per minute, symptoms such as weakness, fatigue, dizziness, fainting, or palpitations may be experienced.

- **Ventricular tachycardia (VT)** - a condition in which an electrical signal is sent from the ventricles at a very fast but even rate. If the heart rate is sustained at a high rate, symptoms such as weakness, fatigue, dizziness, fainting, or palpitations may be experienced.

- **Ventricular fibrillation (VF)** - a condition in which an electrical signal is sent from the ventricles at a very fast and erratic rate. As a result, the ventricles are unable to fill with blood and pump it out, thus causing a very low blood pressure and symptoms such as weakness, dizziness, fainting, or loss of consciousness.

5.2.3 Diagonosis of arrhythmias: There are several different types of procedures that may be used to diagnose arrhythmias. Some of these procedures include the following:

- **Electrocardiogram (EKG or ECG)** - an electrocardiogram is a measurement of the electrical activity of the heart. By placing electrodes at specific locations on the body (chest, arms, and legs), a picture, or tracing, of the electrical activity can be obtained as the electrical activity is received and interpreted by an EKG machine. An EKG can indicate the presence of arrhythmias or other types of heart conditions. There are several variations of the EKG test, including the following:

    - **Resting EKG**

      For this procedure, the clothing on the upper body is removed and small, sticky patches called electrodes are attached to the chest, arms, and legs. These electrodes are connected to the EKG machine by wires. The EKG machine is then started and records the heart's electrical activity for a minute or so.

    - **Exercise EKG, or stress test**

      The child is attached to the EKG machine. However, rather than lying down, the child exercises by walking on a treadmill or pedalling a

stationary bicycle while the EKG is recorded. This test is done to assess changes in the EKG during stress such as exercise.

- **Signal-average EKG**
  This procedure is done in the same manner as a resting EKG, except that the heart's electrical activity is recorded over a longer period of time, usually 15 to 20 minutes. Signal-average EKG is done when arrhythmia is suspected but not seen on a resting EKG, since arrhythmias may be short-lived in nature and not seen during the short recording time of the resting EKG.

- **Holter monitor** - an EKG recording done over a period of 24 or more hours. Three electrodes are attached to the child's chest and connected to a small, portable EKG recorder by lead wires. The child goes about his/her usual daily activities (except for activities such as taking a shower, swimming, or any activity causing an excessive amount of sweating which would cause the electrodes to become loose or fall off) during this procedure. There are two types of Holter monitoring, including following:

  - **Continuous recording**
    The EKG is recorded continuously during the entire testing period.

  - **Event monitor, or loop recording**
    The EKG is recorded only when the patient starts the recording when symptoms are felt.

  Holter monitoring may be done when an arrhythmia is suspected but not seen on a resting or signal-average EKG.

- **Electrophysiologic study (EPS)** - an invasive test in which a small, thin tube (catheter) is inserted through the groin or neck and passed into the heart. This gives the physician the capability of finding the site of the arrhythmia's origin within the heart tissue, thus determining how to best treat it.

5.2.4 Treatment for Arrhythmias

Specific treatment for arrhythmias is based upon:

- child's age, overall health, and medical history
- extent of the condition
- child' s tolerance for specific medications, procedures, or therapies
- expectations for the course of the condition
- opinion or preference

Treatments may include:

- **Lifestyle modifications**

  Factors such as stress, caffeine, or alcohol can cause arrhythmias. Your child's physician may order the elimination of caffeine, alcohol (teens and young adults), or any other substance believed to be causing the problem. If stress is suspected as a cause, your child's physician may recommend stress-reduction measures such as an exercise program or family therapy.

- **Medication**

  There are various types of medications which may be used to treat arrhythmias. If your child's physician chooses to use medication, the decision of which medication to use will be determined by the type of arrhythmia, other conditions which may be present, and other medications already being used by your child.

- **Cardioversion**

  In this procedure, a small, electrical shock is delivered to the heart through the chest to stop certain, very fast, arrhythmias such as atrial fibrillation, supraventricular tachycardia, or sinus tachycardia. Your child is given medication to help him/her relax, and is then connected to an EKG monitor which is also connected to the cardioversion device. The small, electrical shock is delivered at a precise point during the EKG cycle.

- **Ablation**

  This is an invasive procedure done in the electrophysiology laboratory, and involves a small, thin tube (catheter) being inserted into the heart through a vessel in the groin or arm (Figure 5.4). The procedure is done in a manner similar to the electrophysiology studies (EPS) described above. Once the site of the arrhythmia has been determined by EPS, the catheter is moved to the

site. By use of a technique such as radiofrequency ablation (very high frequency radio waves are applied to the site, heating the tissue until the site is destroyed) or cryoablation (an ultra-cold substance is applied to the site, freezing the tissue and destroying the site), the site of the arrhythmia may be destroyed.

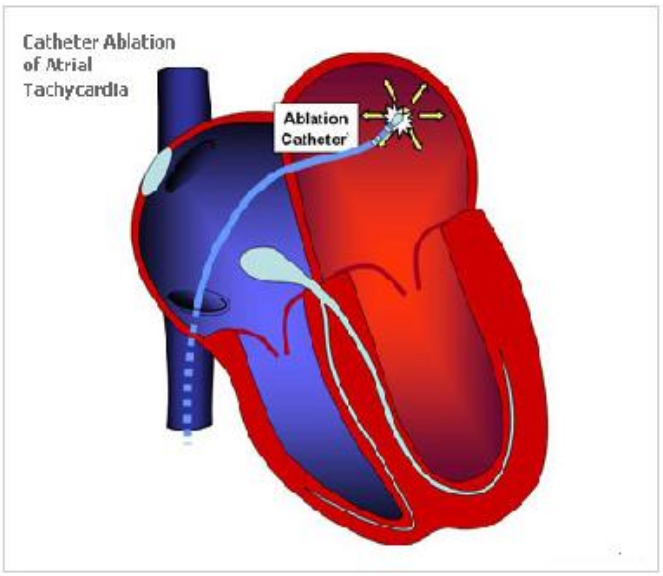


Figure 5.4 Ablation of atrial tachycardia

- **Pacemaker**

A permanent pacemaker is a small device that is implanted under the skin and sends electrical signals to start or regulate a slow heartbeat. A permanent pacemaker may be used to make the heart beat if the heart's natural pacemaker (the sinoatrial, or SA, node) is not functioning properly and has developed an abnormal heart rate or rhythm or if the electrical pathways are blocked. Pacemakers are typically used for slow arrhythmias such as sinus bradycardia, sick sinus syndrome, or heart block. In infants and young children, pacemakers are usually placed in the abdomen. The wires that connect the pacemaker to the heart are placed on the outside surface of the heart. This position is beneficial because the fat in the abdomen protects the pacemaker and pacemaker wires from injury that might occur during everyday childhood

activities such as climbing and falling. School-aged children and adolescents may have the pacemaker placed in the shoulder area just under the collarbone. The pacemaker wires are often placed inside the superior vena cava, a large vein that connects to the right atrium, and then guided inside the heart.

- **Implantable cardioverter defibrillator**

An implantable converter defibrillator (ICD) is a small device, similar to a pacemaker, that is implanted under the skin, often in the shoulder area just under the collarbone. An ICD senses the rate of the heartbeat. When the heart rate exceeds a rate programmed into the device, it delivers a small, electrical shock to the heart to slow the heart rate. Many newer ICDs can also function as a pacemaker by delivering an electrical signal to regulate a heart rate that is too slow. ICDs are typically used for fast arrhythmias such as ventricular tachycardia.

- **Surgery**

Surgical treatment for arrhythmias is usually done only when all other appropriate options have failed. Surgical ablation is a major surgical procedure requiring general anesthesia. The chest is opened, exposing the heart. The site of the arrhythmia is located, then destroyed or removed in order to eliminate the arrhythmia.

5.3 Respiratory Sinus Arrythmia

RSA is the natural cycle of arrhythmia that occurs through the influence of breathing on the flow of sympathetic and vagus impulses to the sinoatrial node. The rhythm of the heart is primarily under the control of the vagus nerve, which inhibits heart rate and the force of contraction. When we inhale, the vagus nerve activity is impeded and heart rate begins to increase. When we exhale this pattern is reversed. The degree of fluctuation in heart rate is also controlled significantly by regular impulses from the baroreceptors (pressure sensors) in the aorta and carotid arteries. When RSA is enhanced through biofeedback, the goal is usually to reinforce the natural feedback activity of the baroreceptors through our breathing pattern. **Respiratory sinus**

arrhythmia (RSA) is a naturally occurring variation in heart rate that occurs during a breathing cycle. Heart rate increases during inspiration and decreases during expiration. On an electrocardiogram this phenomenon is seen as subtle changes in the R-R interval synchronized with respiration. RSA is mediated through physiological mechanisms by which the R-R interval on the ECG is shortened during inspiration (heart rate increases) and prolonged during expiration (heart rate decreases). These mechanisms include central medullary generator, reflexes from the lungs, baroreflexes, chemoreflexes, as well as local mechanisms (stretching of the sinoatrial node etc.) Thus, the assessment of respiratory sinus arrhythmia is accepted as an index of cardiac vagal function. In humans, the magnitude of the RSA increases with physical conditioning and self-induced, relaxed breathing. RSA becomes less prominent with age, diabetes and cardiovascular disease.

RSA is the natural variation in heart rate that is primarily driven by breathing patterns and the regulating influence of the vagus nerve on the heart. For example, inhaling inhibits the activity of the vagus nerve, increases heart rate, and decreases HRV. Exhaling activates the vagus nerve, decreases heart rate, and increases HRV. RSA is also influenced by the baroreceptors (pressure sensors that help regulate your heart rate and blood pressure) and the limbic system in the brain (your emotion center). RSA is considered an accurate window into the autonomic nervous system (ANS). The greater the arrthymic variation in heart rate, the healthier the system. A simple way to think about this is, if at rest heart rate is varying between 80 and 60 beats per minute (bpm), that is better than varying between 65 and 70 bpm. High RSA (more variation) is indicative of resilience and health; low RSA is indicative of vulnerability to stress and disease. RSA naturally decreases with age. Interestingly, it is possible to increase RSA through slow breathing, meditation and exercise.

Respiratory sinus arrhythmia (RSA) is the change in heart rate (HR) due to respiration. Generally, inspiration causes HR to increase and expiration causes HR to decrease. RSA represents one frequency range of interest (0.15 to 0.3Hz) in the entire spectrum of heart rate variability (HRV). The RSA component of HRV has been used to study mental stress, cardiac aging, denervation & reinnervation after heart transplant, autonomic cardiac control and the effect of drugs on the sympathetic and parasympathetic systems. There is not just one index of RSA; it can be measured in a multitude of ways from the simple to the complex, and may be expressed in the

domains of time, frequency or phase. RSA can be quantified by various methods - the spectral analysis of heart rate variability or deep breathing test.

- **Deep breathing test**

Respiratory mediated heart rate changes are small during quiet breathing, then, it is more convenient to evaluate the respiratory sinus arrhythmia during deep breathing. Deep breathing test is considered as an index of cardiac vagal control.

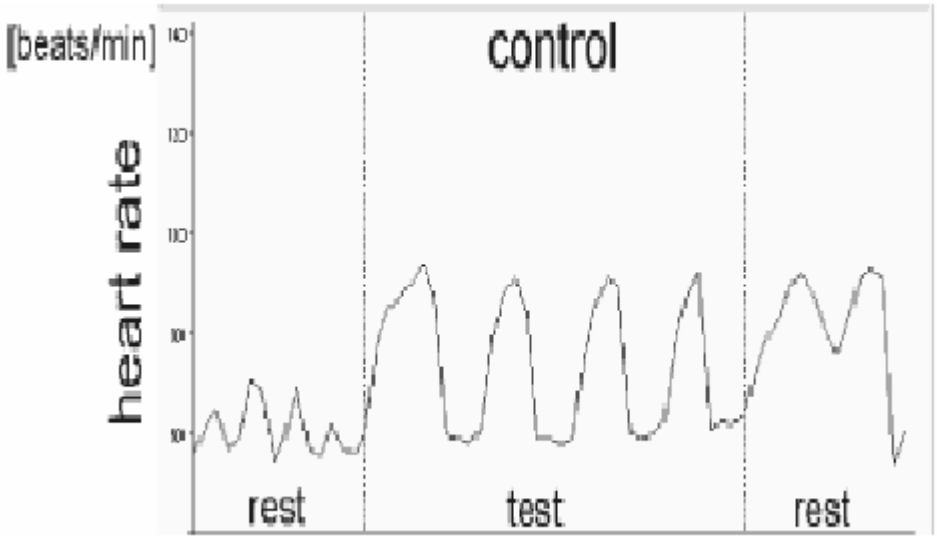


Fig.5.5.1 Deep breathing test in a healthy subject.

Fig. 5.5.2 Deep breathing test in an obese patients. Respiratory sinus arrhythmia is reduced compared with a healthy subject.

➢ **The heart rate variability analysis – high frequency (HF) band**

The high frequency spectral power of the heart rate variability analysis (0.04-0.15 Hz) reflects mainly respiratory sinus arrhythmia regarded as an index of the cardiac vagal modulation. The high-frequency (HF) spectral activity is decreased during manoeuvres associated with sympathetic activation (e.g. orthostatic test, mental load) and – vice versa –higher spectral activity in HF band is associated with parasympathetic activation (e.g.relaxation).

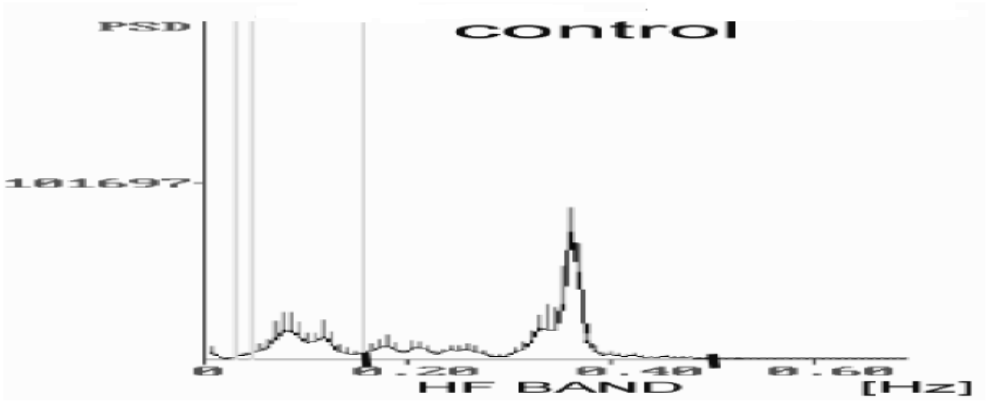


Fig. 5.6.1 The high frequency band in a healthy subject .

Fig. 5.6.2 The high frequency band in an obese patients. Spectral activity in HF band is reduced compared with a healthy subject.

Although RSA has been used as an index of cardiac vagal function, it is also a physiologic phenomenon reflecting respiratory-circulatory interactions.

The efficiency of pulmonary gas exchange can be improved by RSA. The matched timing of alveolar ventilation and its perfusion with RSA within each respiratory cycle could save energy expenditure by suppressing unnecessary heartbeats during expiration and ineffective ventilation during the ebb of perfusion.

RSA or heart rate variability in synchrony with respiration is a biological phenomenon, which may have a positive influence on gas exchange at the level of the lung via efficient ventilation/perfusion matching.

The fundamental function of respiration is to maintain homeostasis as an interface between the interior and exterior of the human body. The respiratory system is open to the outside through ventilation via the alveoli, while the circulatory system consists of two closed loops of pulmonary and systemic circulation (Fig 5.7). The neural network, mainly the autonomic nervous system, is known to play a major role in the interaction of respiration and circulation [10].

The respiratory system is open to the exterior of the human body through ventilation in the alveoli, while the circulatory system consists of two closed loops of pulmonary and systemic circulation.

Pulmonary circulation originates in the right ventricle and terminates in the left atrium. Systemic circulation originates in the left ventricle and terminates in the right atrium.

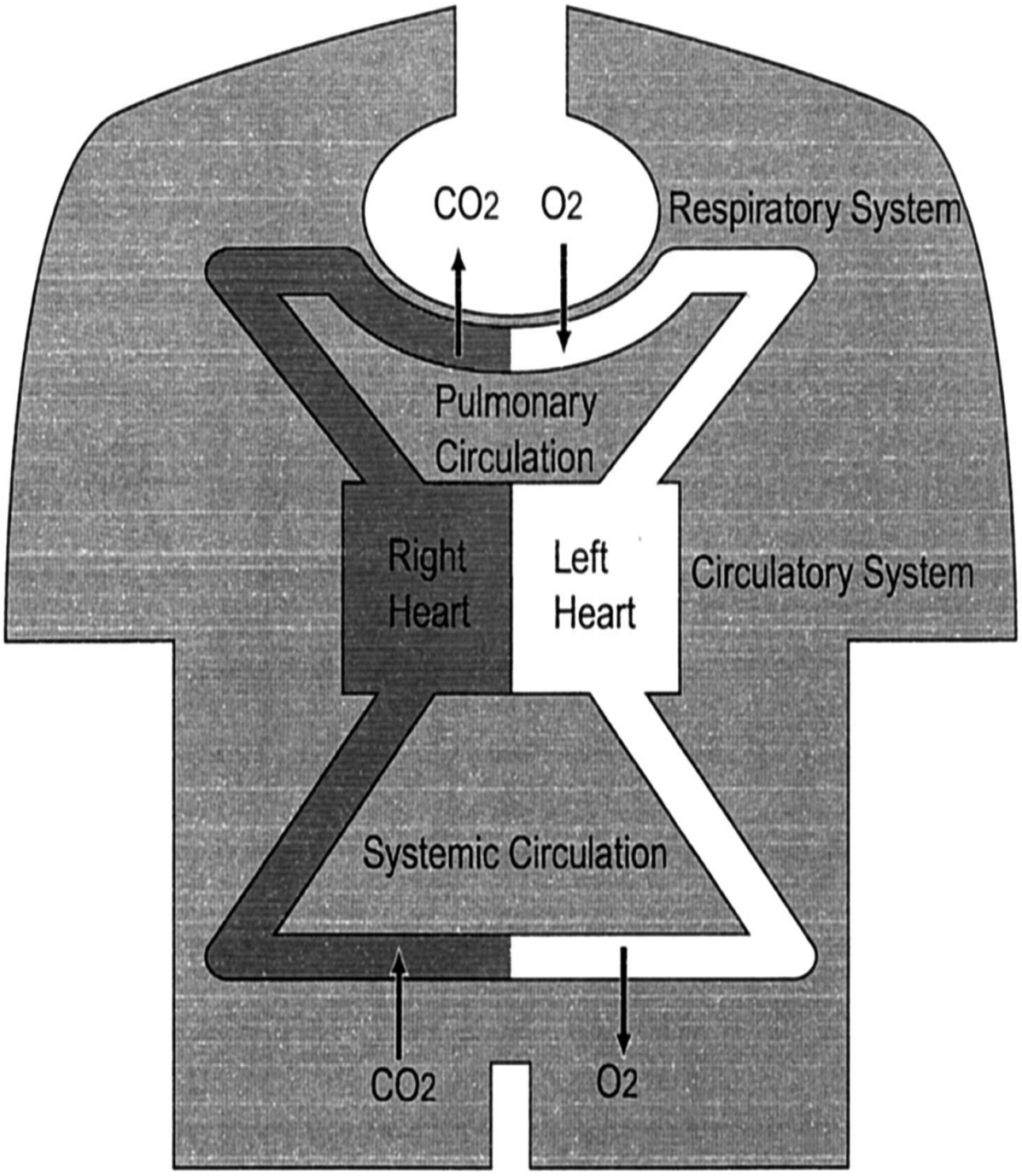


Figure 5.7: Respiratory and circulatory systems.

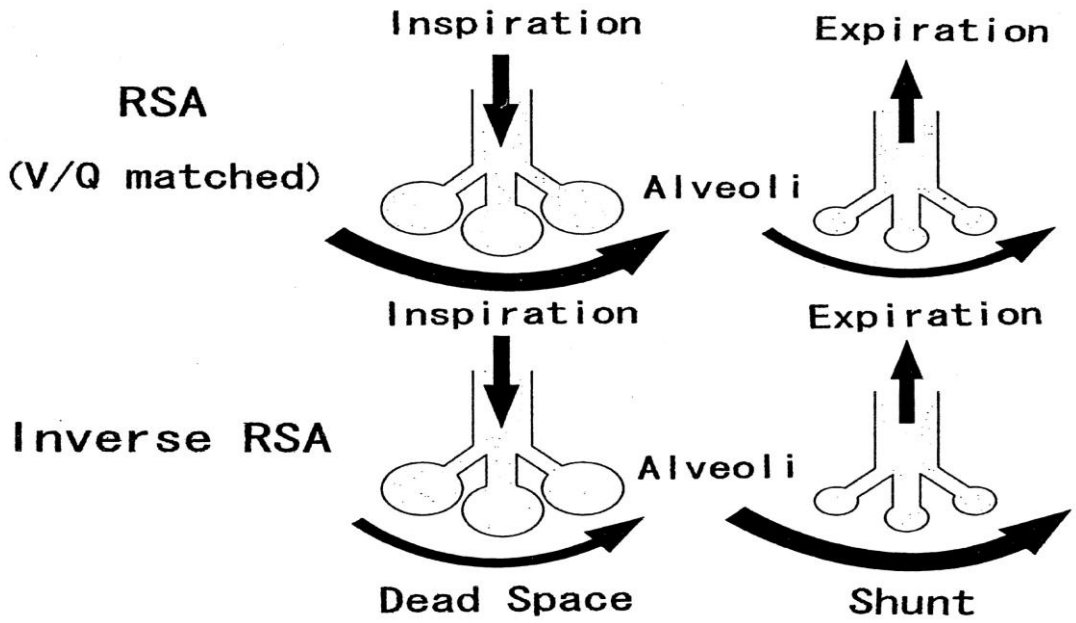


Figure 5.8: Scheme showing the conceptual effects of RSA (*top*) and its inversion (*bottom*) on the relationship between alveolar gas volume and capillary blood flow during inspiration (*left*) and expiration (*right*).

Curved horizontal arrows and vertical arrows indicate the volume of blood flow circulating in the pulmonary capillary bed and the direction of alveolar gas interfacing with the pulmonary capillary blood. V/Q = ventilation/perfusion.Common techniques for measuring RSA include time domain, or frequency domain methods

5.4 Determining RSA

RSA is derived from the R-wave of the electrocardiogram (ECG). Before any analysis takes place the ECG R-wave peaks must be detected with a high sampling rate, artefacts removed and abnormal beats replaced to give a series of interval times in milliseconds. The simplest RSA indexes include the difference in the maximum and minimum heart rate over a respiratory cycle, the absolute changes in successive beats, and statistical or geometrical measures of these. For successful time domain analysis,

RSA must be stable and normalised for respiratory volume, frequency and age. Further development links the time index with the respiratory cycle using either voluntary coupling of the breathing pattern or cosinor analysis.

Frequency domain measures use Fourier transforms and require special methods to work around problems associated with non-evenly spaced, non-stationary signals. Methods include a variety of interpolations, re-sampling and statistical tests. Shortening the measurement period to ensure stability of the signal can have an adverse effect on the sample obtained and can prevent valid analysis. Phase and wavelet analyses are alternatives to the Fourier transform. The multifractal nature of RSA allows the use of wavelet analysis to measure the dynamic properties of RSA, an advance on the other methods that can only measure stable properties [38].

RSA is a non-linear, non-stationary, irregular system with multiple inputs, outputs and feedback loops. When analysing this system with commonly used techniques the assumptions on which the techniques are based are often neglected. It is important that these assumptions are revisited and tested for the data being analysed, to ensure information is revealed rather than hidden by its analysis.

Chapter 6

Heart Rate Variability and Respiration

6.1 Effect of Respiration on Heart Rate Variability

Beat-to-beat changes in cardiac signals or heart rate variability (HRV) are controlled by the two branches of Autonomic Nervous System (ANS) in a very complex manner.

The autonomic nervous system has two major divisions: Sympathetic nervous system (SNS) and Parasympathetic nervous system (PNS). A balance between these two branches of ANS is essential for good health. Any type of dysfunction or imbalance between two branches of ANS is referred to as dysautonomia. Cardiac events such as variability in heart rate or blood pressure are affected by autonomic dysfunction. As a result of these changes, other diseases or events may occur, such as heart failure and myocardial infarction. Thus early sub-clinical detection of autonomic dysfunction by measurement of HRV is important for risk stratification and subsequent management.

Although traditional HRV (tHRV) analysis has shown to provide information on cardiac ANS control it is often fail to isolate the effect of two branches in HRV signals. This problem become more obvious especially at low respiratory rates since parasympathetic activity shifts into lower frequencies and overlaps the frequency interval where sympathetic region is defined. Enhanced HRV(eHRV) analysis provided proper isolation and more accurate detection of parasympathetic and sympathetic control of the heart.

HRV signals contain well defined rhythms which include physiological information [39]. Rhythms in the low frequency (LF) range, between 0.04 to 0.15 Hz, are usually considered as markers of sympathetic modulation. The high frequency (HF) range, between 0.15 to 0.4 Hz, can contain the rhythms regulated by parasympathetic activity[39][40]. Vagal activity is the major contributor to the HF component. Although many researchers considers LF area to involve sympathetic activity, some suggest that the LF area corresponds to both sympathetic and parasympathetic activity. On the other hand, an increase in normalized LF power is always observed as a result of sympathetic activation. Therefore, an increase in LF power is accepted as a sign of sympathetic activation by most authors. Similarly there are questions if HF

power of HRV signal is a true measurement of parasympathetic activity. There is a problem of isolating parasympathetic and sympathetic activity in traditional HRV analysis. Although there are predefined frequency intervals, there are many situations where the measurement of sympathetic is not pure sympathetic or measurement of parasympathetic is a mixed measure. For example respiration has a significant effect on the HR oscillations and parasympathetic activity is very closely related to respiratory sinus rhythm. Recent studies have shown that respiratory peak can be used as a quantitative measure of vagal control .Alcalay et al. has shown that respiratory peak in HR spectrum decreased as the dose of atropine increased when administered to human volunteers. [41] This type of behavior, a direct dose dependent change in vagal activity is a clear indication of the sensitivity of the respiratory peak as a tool for vagal control. Therefore if one uses traditional HRV (tHRV) analysis and ignores the effects of respiration in HRV spectra, problem of isolating two branches rises since respiration can entrain HR and Blood Pressure (BP) oscillations over a wide range of frequencies, from 0.01 to 0.5 Hz [42]. Slow respiration can cause a false-positive increase in LF power (an increase due to increased parasympathetic activity rather than sympathetic) in traditional HRV analysis. Related to the importance of respiration there is the logical conclusion that once the actual breathing rate is known, detection of the HF power should be centered around the fundamental respiration frequency (FRF) and not a default fixed frequency which is the case with traditional HRV analysis [42]. Uijtdehaage et al also found that "the changes in cardiac activity resulting from changes in sympathetic control cannot be interpreted accurately unless concurrent vagal activity is taken into account as well." Therefore, the respiratory peak can be used as a tool to estimate vagal activity, and isolate both branches of ANS (i.e., sympathetic and parasympathetic) [43]. Isolating both branches would eventually lead to more accurate evaluation of HRV and a better tool in diagnosing people with Autonomic Dysfunctions. The FRF is obtained from the power spectrum of the respiration signal and used in the independently computed HRV spectra to locate the HF area. The method which uses respiration information is called enhanced HRV (eHRV) analysis.

6.2 Traditional and enhanced HRV

In tHRV(Traditional HRV) analysis, standard LF, HF and LF/HF power parameters are estimated using previously determined fixed frequency ranges for these variables at each time. LF and HF power are estimated as the area under spectrum of HR in LF(0.04 Hz to 0.15Hz) and HF(0.15 Hz to 0.4 Hz)ranges. The LF/HF power is the mathematical ratio of LF power to HF power. Once all LF ,HF and LF/HF values are estimated from time-frequency plot at each time, they are averaged to determine the values for the whole signal.

In eHRV(Enhanced HRV) analysis, time-frequency representation of the respiratory signal is estimated using the same method as for the HR signal, and the highest peak is identified at each time. Before the time-frequency analysis, the respiratory signal is low pass filtered to remove very low frequencies. The frequency corresponding to highest peak in time-frequency plot at each time is called as the Fundamental Respiratory Frequency (FRF). This frequency ables to locate the HF area in time-frequency representation.

The respiratory parameters which can affect HRV estimates, include- respiratory frequency (Rf) ,tidal volume, end tidal partial pressure of carbon di-oxide(PETco2) the time ratio of expiration/inspiration and respiratory dead space. In a recent review of published evidence, Eckberg [44] summarised that respiratory fluctuations of muscle sympathetic nerve activity and electrocardiographic RR intervals result primarily from the action of a central ‘gate’ that opens during expiration and closes during inspiration. Parallel respiratory fluctuations of arterial pressures and R-R intervals are thought to be secondary to arterial baroreflex physiology- changes in systolic pressure provoke changes in the R-R interval. However, growing evidence suggests that these parallel oscillations result from the influence of respiration on sympathetic and vagal-cardiac motoneurones rather than from baroreflex physiology. Respiration can change HRV power spectra both in high and low frequency regions.

6.3 Control of respiration

The respiratory frequency approximates to 0.2–0.4 Hz during resting in general. In this case, although it is possible to separate the frequency band between MWSA (Mayer wave sinus arrhythmia) and RSA, the respiratory frequency may vary greatly

because of various factors, leading often to overlapping of band-widths of the LF component[45]. As a result, clear separation between MWSA(LF range) and RSA(HF range) cannot be realized. As low-frequency respiration in the vicinity of 0.1 Hz displays extremely high amplitudes [46] values of the LF component play an important role. This may be one of the factors contributing to HRV inconsistencies. From the above argument, it is therefore essential to impose control in conditioning a constant respiratory rhythm by using a metronome and other corrective procedures in measuring HRV. In fact, measurements of the HRV are often performed with regulatory control imposed on the subject to secure a constant respiratory frequency in recent times .Respiratory frequency is not the only factor of concern in HRV; the tidal volume and other factors have to be considered as well. As such, in a stricter sense, control of the respiratory frequency and other factors have to be regulated [47].

Stephen hales (Hales 1733) reported beat to beat heart rate variability to be synchronous with respiration (respiratory sinus arrhythmia).Respiration is a well known event that causes oscillations in the heart rate. Variation in heart rate is related to respiration due to the inspiratory inhibition of vagal tone, evoked by central impulses from the medullary and cardiovascular center.This parasympathethically mediated fluctuation can be abolished by atropine or vagotomy (Akselrod *et al.* 1985b). The variation in heart rate in relation to respiration is used as a noninvasive index of vagal nerve excitation in humans (Hayano *et al.* 1991). However respiration related to high frequency heart rate fluctuation has been shown to be somewhat imperfect index of vagal activity. There are situations in which high frequency changes of *RR* intervals may not reflect changes in the vagal modulation at all, but can be explained by the kinetics of sino-aterial node repose to acelylcholine (Saul *et al.* 1991). This respiration caused fluctuation occurs at both high and low frequency.

Sympathetic excitations have been suggested to correspond to RR intervals fluctuation at around 0.1 Hz frequency. However, most evidences does not support the notation that low frequency spectral power detects changes of sympathetic nerve activity (Hopf *et al.* 1985; Koh *et al.* 1994; Saul *et al.* 1990). One fluctuation loop affecting the heart rate variability is the vasometer part of the baroreflex loop, which is responsible for arterial pressure oscillation causing low frequency fluctuation. In addition, rapid control system of pressoreceptors and chemoreceptors maintain the cardiovascular homeostasis by altering the heart rate through small frequency adjustment. Heart rate fluctuation is also a result of various factors, which are often

difficult to discern from totals behaviour, which combine different waveforms. Thus one can study the cardiac dynamic behaviour influenced by the various endogenous and exogenous factors by studying heart rate variability.

Chapter 7

Problem Statement and Implementation

7.1 Introduction

The Heart Rate Variability gives an accurate view of the autonomic nervous systems and the variableness of the heart. It shows the state of relative health. Heart Rate Variability shows the correspondence between specific physiological components and the frequency spectrum. Reduction in HRV may represent increased isolation of the heart from its interactions with other organs. A primary focus of clinical work and research is in observing or modifying the balance in regulatory impulses from the vagus nerve and sympathetic nervous system. Some researchers are focussing attention on other factors that regulate the heart, such as chemoreceptor, thermo receptors, and the renin-angiotensin system. There are several prospective studies that have shown that HRV independently predicts mortality within the initial two years following a heart attack. HRV is regarded as an indicator of the activity of autonomic regulation of circulatory function. Alterations (mostly reductions) in HRV have been reported to be associated with various pathologic conditions such as hypertension, hemorrhagic shock, and septic shock. It also has some utility as a modest predictor of mortality after an acute myocardial infarction.

7.2 Problem statement:

During our thesis we have tried to analyse the correlation between Heart Rate Variability and Respiratory Frequency under Sinus Arrhythmia Condition in order to know the variation of heart rate w.r.t respiration. By this we can compare the heart rate variability of a healthy person and person suffering from arrhythmia condition and will help in detecting any cardiovascular disease.

7.3 Proposed Solution and Implementation:

We are using MATLAB software tool to analyse the correlation between heart rate variability and respiratory frequency.

- **MATLAB:**

MATLAB is a high-performance language for technical computing. It stands for matrix laboratory. It integrates computation, visualization, and programming in an easy-to-use environment where problems and solutions are expressed in familiar mathematical notation. Typical uses include Math and computation, Algorithm development, Data acquisition, Modelling, Simulation and Prototyping, Data analysis, exploration, and visualization, Scientific and engineering graphics, Application development, including graphical user interface building.

- The correlation estimate is defined as the covariance between two variables normalized by the square root of the variances. The correlation estimate will then always be between -1 and 1. The definition is

$$\hat{\rho}_{12} = \frac{C[\hat{f}_r, \hat{P}_h]}{\sqrt{C[\hat{f}_r, \hat{f}_r]C[\hat{P}_h, \hat{P}_h]}}$$

  Where C [,] denotes covariance, $\hat{f}_r$ is the estimated respiratory frequency and $\hat{P}_h$ is Power of the heart rate variability in a predetermined frequency band.
- We have used Pearson correlation coefficient to find the correlation between heart rate variability and respiratory frequency. Pearson correlation coefficient is used as it helps in determining the strength of the linear relationship more accurately.
- In case of finding correlation between heart rate variability i.e. jitter and respiratory frequency under normal conditions of a person different parameters are taken. These are Ao, Fo, Fvmin, Fvmax, Vn, NOP where Ao=amplitude of respiratory signal, Fo=frequency of respiratory signal, Fvmin=minimum value of respiratory signal, Fvmax=maximum value of respiratory signal, NOP=number of points.
- The jitter-signal is created from a sinusoidal disturbed by a low-frequency noise. The sinusoidal amplitude as well as the frequency are time-varying and the frequency of the jitter-signal follows the frequency of the respiratory signal, according to

$$x_{jitter}(n) = A_{jitter}(n)\cos(2\prod(\frac{f_r(n)}{1000})n) + v(n)$$

- First of all, Respiratory frequency is determined using $f_r(n) = f_0 - f_{\text{var}}(n)$, where $f_{\text{var}}(n)$ changing linearly from 0 to 0.075 Hz and $f_0 = 0.325\,\text{Hz}$.
- Jitter signal is created using $x_{jitter}(n) = A_{jitter}(n)\cos(2\prod(\frac{f_r(n)}{1000})n) + v(n)$ where $A_{jitter} = A_0 + A_{\text{var}}(n)$, $A_0 = 100$, $A_{\text{var}}(n)$ changing linearly from 0 to 75, $A_{\text{var}}(n) = 1000\,f_{\text{var}}(n)$, v(n) will change with every n. The low frequency noise is a white noise v(n) of variance σ_v^2.
- The correlation between respiratory frequency F_r and Jitter signal J i.e. index of heart rate variability is calculated by using

$$\overline{F_r} = \{F_{r_1}, F_{r_2} F_{r_3} .....F_{r_N}),\ \overline{J} = \{J_1, J_2, J_3.....J_N\}$$

$$Correlation(F_r, J) = \frac{1}{N}\sum_{i=1}^{N}(\frac{F_{r_i} - \overline{F_r}}{\sigma_{F_r}})(\frac{J_i - \overline{J}}{\sigma_J})$$

$$= \frac{\sum_{i=1}^{N}(F_{r_i} - \overline{F_r})(J_i - \overline{J})}{\sqrt{\sum_{i=1}^{N}(F_{r_i} - \overline{F})^2 \sum_{i=1}^{N}(J_i - \overline{J})^2}}$$

$$Mean - F_r = \overline{F_r} = \frac{1}{N}\sum_{i=1}^{N} F_{r_i}$$

$$Mean - J = \overline{J} = \frac{1}{N}\sum_{i=1}^{N} J_i$$

The standard deviation "SD" for each case is given by

$$\text{SD-}F_r = \sigma_{F_r} = \sqrt{\frac{1}{N}\sum_{i=1}^{N}(F_{r_i} - \overline{F_r})^2}$$

$$SD - J = \sigma_J = \sqrt{\frac{1}{N}\sum_{i=1}^{N}(J_i - \overline{J})^2}$$

The noise parameter is varied to find the effect of Pearson Correlation

Coefficient on it.

- **Under sinus arrhythmia condition:**
  - Synthetic cardiac and respiratory data with varying phase, amplitude, and frequency are created to test the algorithm.
  - The respiratory volume signal $S_{resp}(t)$ is synthesized by means of a sinusoid of frequency f_{resp}, amplitude a_1, and phase ϕ_{t0}, to which white noise was added.
  - All parameters can vary in time, corresponding to changes in breathing frequencies, phase drifts or "resets" of the respiratory cycle.
  - Instantaneous heart period variability, represented by the uniformly resampled RR-interval time series $S_{URRI}(t)$, is synthesized by summing a constant b_0 (representing the average heart beat interval) with three sinusoids of amplitudes b_{VLF} (very low frequency band), b_{LF} (low frequency component), b_{HF} (high frequency component) and of frequencies f_{VLF}, f_{LF}, f_{HF}. Because the HF component represents the RSA, f_{HF} is set equal to f_{resp}.
  - A phase parameter $\phi_{t0} + \Delta\phi_t$ is added in the HF component to model the phase difference between heart rate and respiratory signals.
  - White noise is added to the phase and to the signal.
  - The synthetic respiratory and heart-rate interval signals are thus given by

$$S_{resp}(t) = a_1 \cos(2\prod f_{resp}(t + \phi_{t0})) + noise(t)$$

$$S_{URRI}(t) = b_0 + b_{VLF} \cos(2\prod f_{VLF} t) + b_{LF} \cos(2\prod f_{LF} t) + b_{HF} \cos(2\prod f_{resp}(t + \phi_{t0} + \Delta\phi_t + noise_{\phi}(t))) + noise(t)$$

The various parameters taken are Amod, Td, Phit, Fmod, Fresp, Fvlf, Bvlf, Blf, Bhf, Vnt, Vn, NOP.

- **Time-varying respiratory frequency and phase delay**:
  - The sensitivity of the methods to respiratory frequency changes is evaluated on synthetic data with a sinusoidally modulated respiratory frequency.

- The variation range covers the frequency interval of normal breathing [0.15Hz, 0.35Hz]. The synthetic respiratory and heart rate interval signal are thus calculated by $f_{resp}(t) = \overline{f_{resp}}(1 + A_{\mathrm{mod}} \cos(2\prod f_{\mathrm{mod}} t))$, where $\overline{f_{resp}} = 0.25Hz$, $A_{\mathrm{mod}} = 0.4,$ and $f_{\mathrm{mod}} = 0.25Hz.$ The other parameters are $b_{VLF} = 0.07,\ b_{LF} = 0.1,$ $f_{LF} = 0.1,\ b_{HF} = 0.06, \phi_{t0} = 0.01, \Delta\phi_t = 0.01, noise_{\phi} = 0.01$ and noise(t) is a white noise with a maximal amplitude of 1sec.
- we have calculated the Pearson correlation coefficient by taking these parameters. The noise parameter and b_{HF} are varied to find the effect of correlation on these parameters. Pearson correlation coefficient is determined by same formula as above.

7.4 Results and Discussions:

The various parameters are varied to find the effect of respiratory signal on Heart Rate Variability.

[PrCor]=HRV_JITTER08(Amod,Td,phit,Fmod,Fresp,Fvlf,Flf,Bvlf,Blf,Bhf,Vnt,Vn,NOP)

[PrCor]=HRV_JITTER08(0.4,0.01,0.01,0.25,0.25,0.04,0.1,0.07,0.06,0.06,0.01,1,1000)

Under Sinus Arrhythmia Condition, Various parameters are varied to know the effect on correlation analysis between Heart Rate Variability and Respiratory Frequency. The effects are different for different parameters.

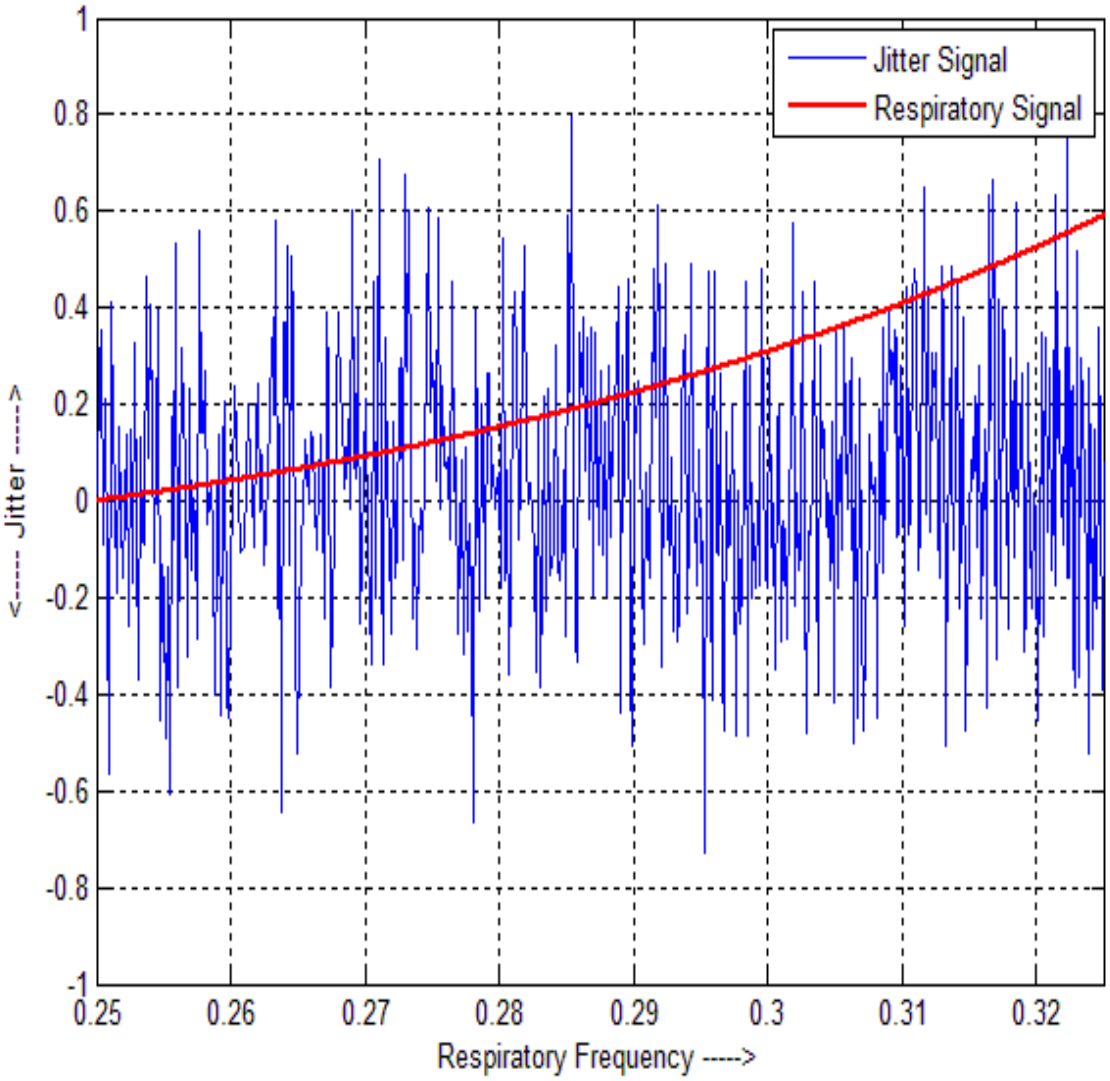


Figure 7.1 Correlation between Jitter i.e. an index of Heart Rate Variability and Respiratory Frequency Under Sinus Arrhythmia Condition.

Analysis: The blue line shows jitter signal having an irregular pattern whereas red line indicates respiratory signal showing increasing values.

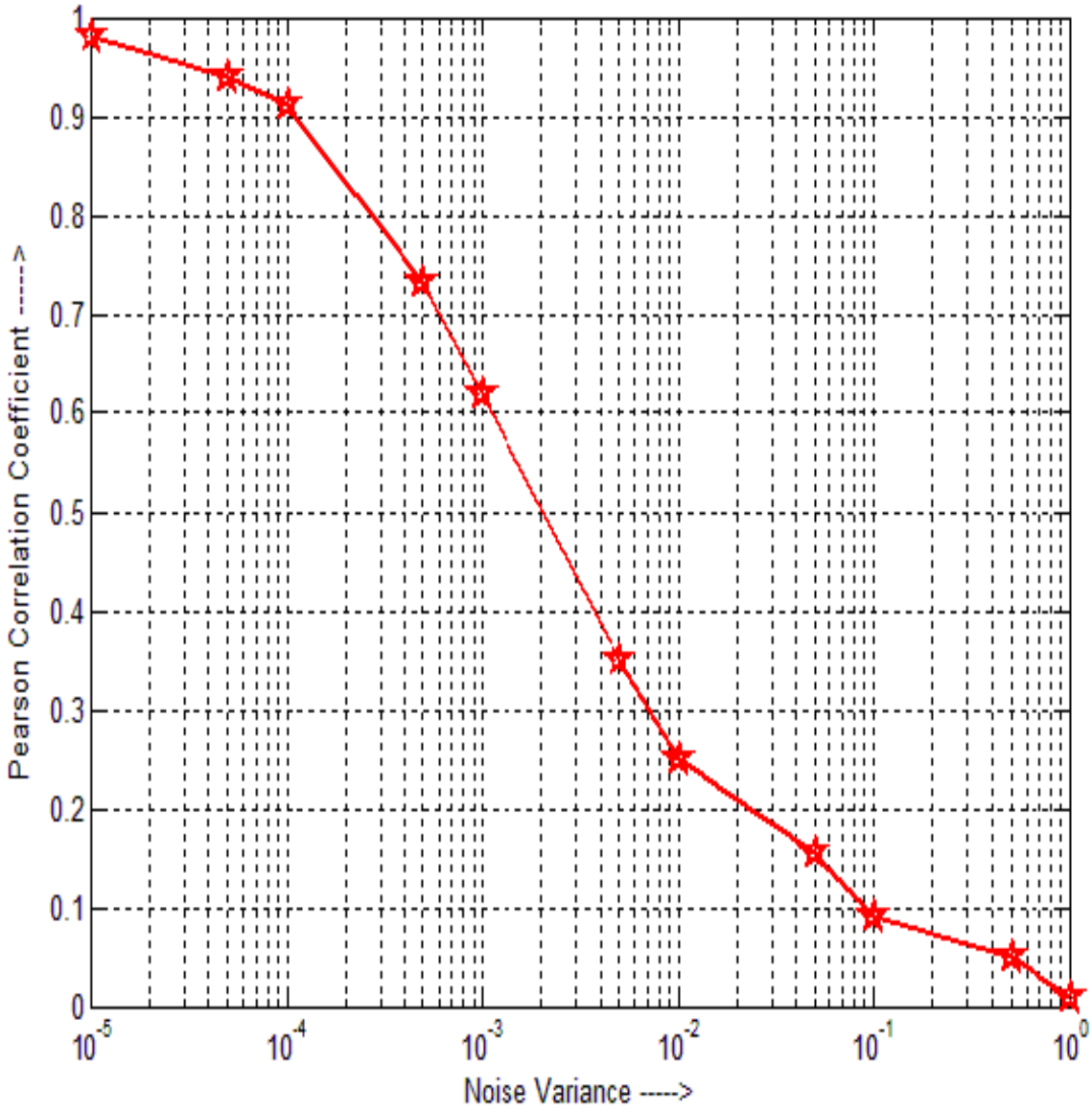


Figure 7.2 Variation of Pearson Correlation Coefficient w.r.t Noise Parameter Under Arrhythmia Condition.

Analysis: It shows a continuous decrease in correlation coefficient with increase in noise variance values.

[PrCor]=HRV_JITTER07(Ao,Fo,Fvmin,Fvmax,Vn,NOP)

[PrCor]=HRV_JITTER07(100,0.325,0,0.075,1,1000)

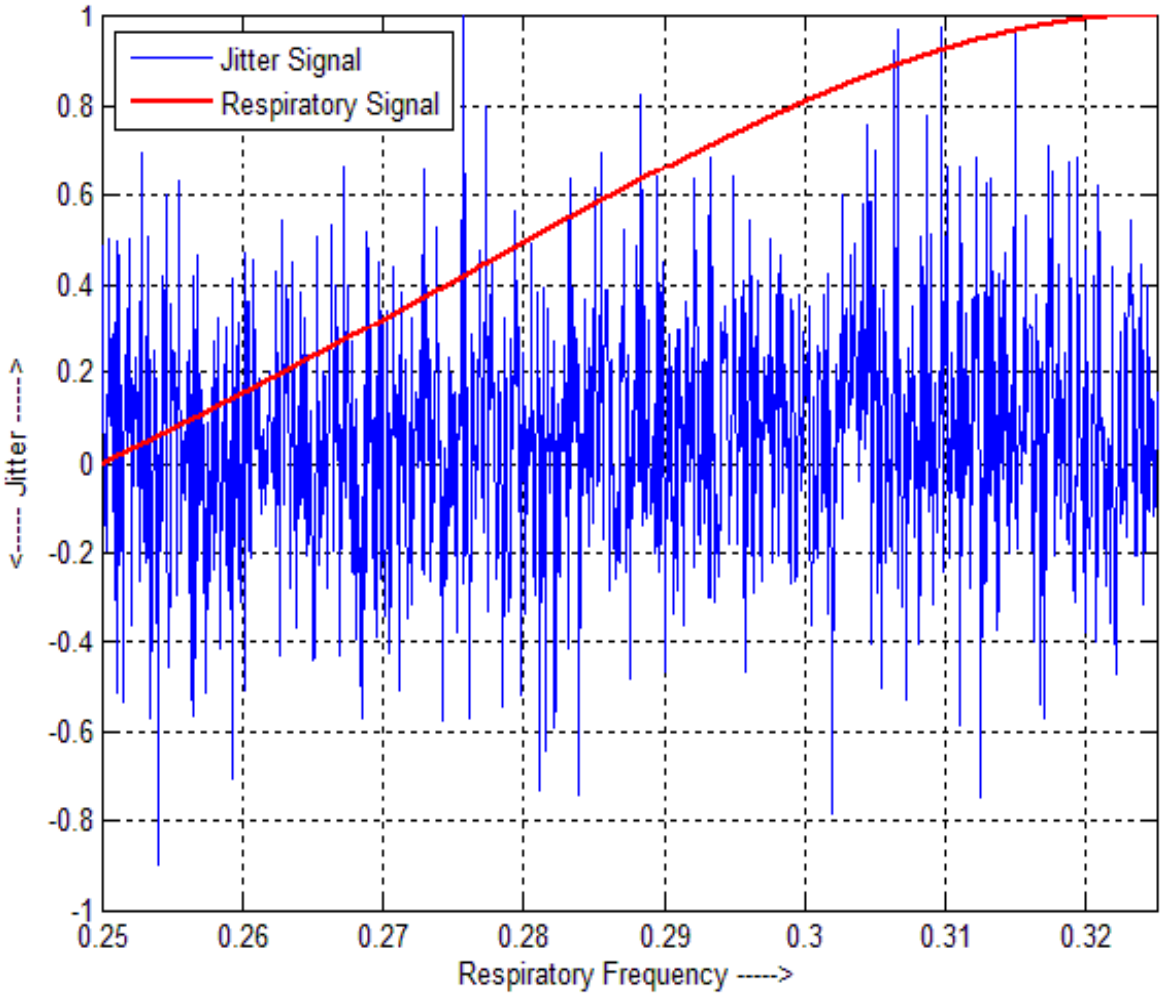


Figure 7.3 Correlation between Jitter and Respiratory Frequency Under Normal Conditions.

Analysis: The blue line indicates jitter signal and red line indicates respiratory signal. It shows a steep slope increase in respiratory signal whereas jitter signal is having an irregular pattern.

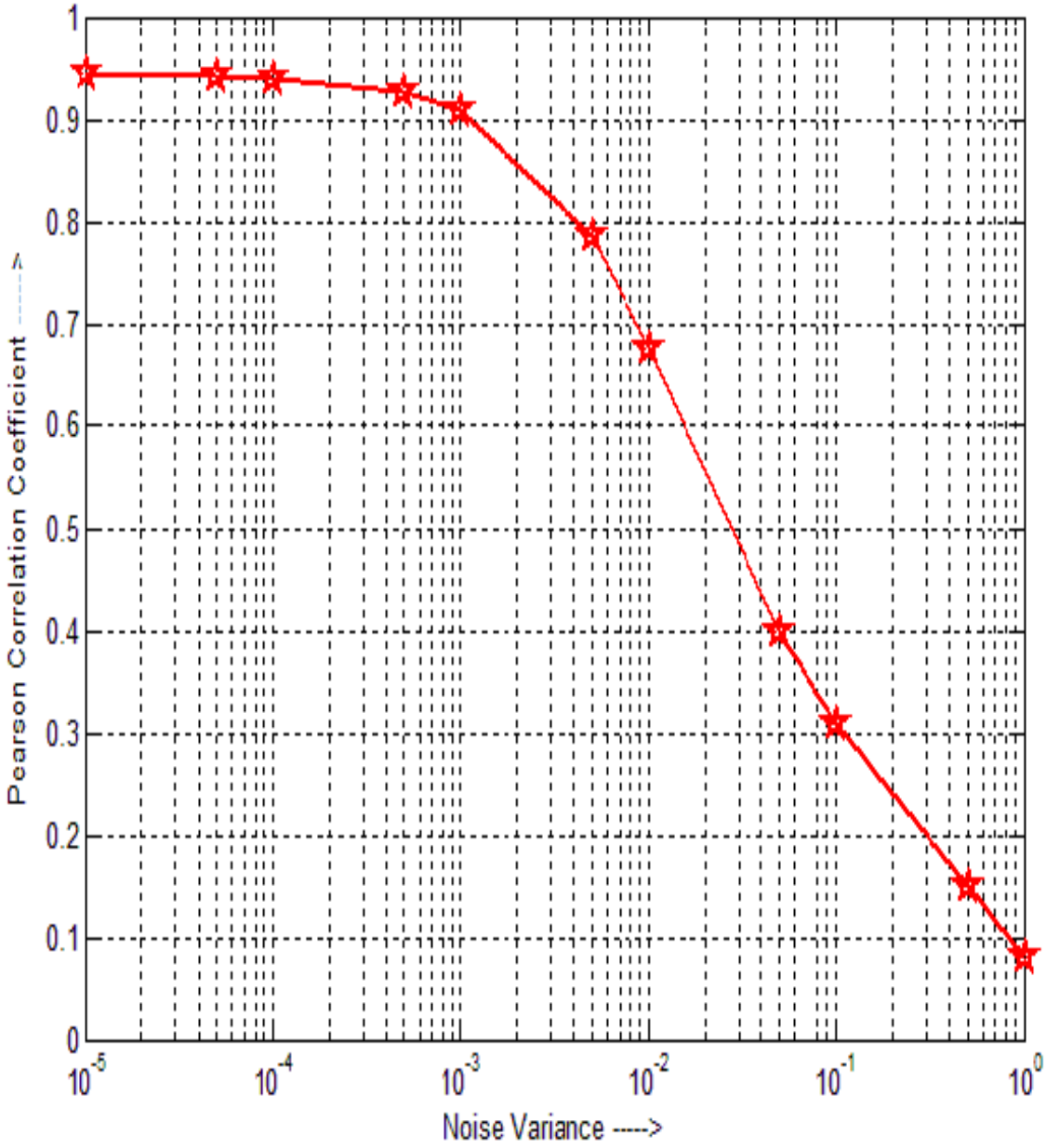


Figure 7.4 Variation of Pearson Correlation Coefficient w.r.t Noise Parameter

Analysis: During the first phase of graph it shows an almost constant value and in second phase it shows continuous decrease with an increase in noise variance parameter.

[PrCor]=HRV_JITTER08(0.4,0.01,0.01,0.25,0.25,0.04,0.1,0.07,0.06,0.01,0.01,0.001, 1000)

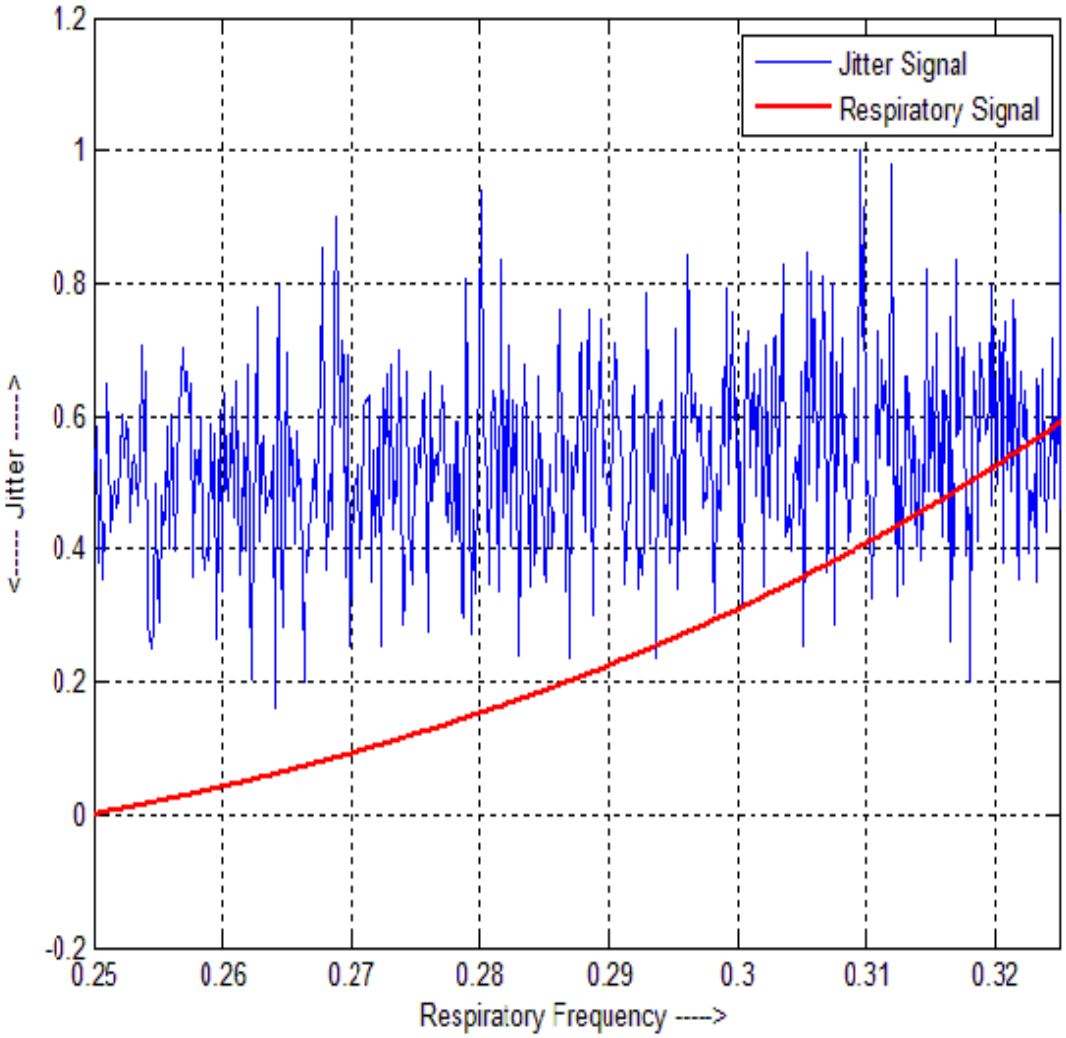


Figure 7.5 Correlation between Heart Rate Variability and Respiratory signal when $B_{hf} = 0.01$ and $V_n = 0.001$ Under Arrhythmia Condition.

Analysis: The red line shows respiratory signal and blue represents jitter signal. Respiratory signal shows continuous increase but up to a certain value.

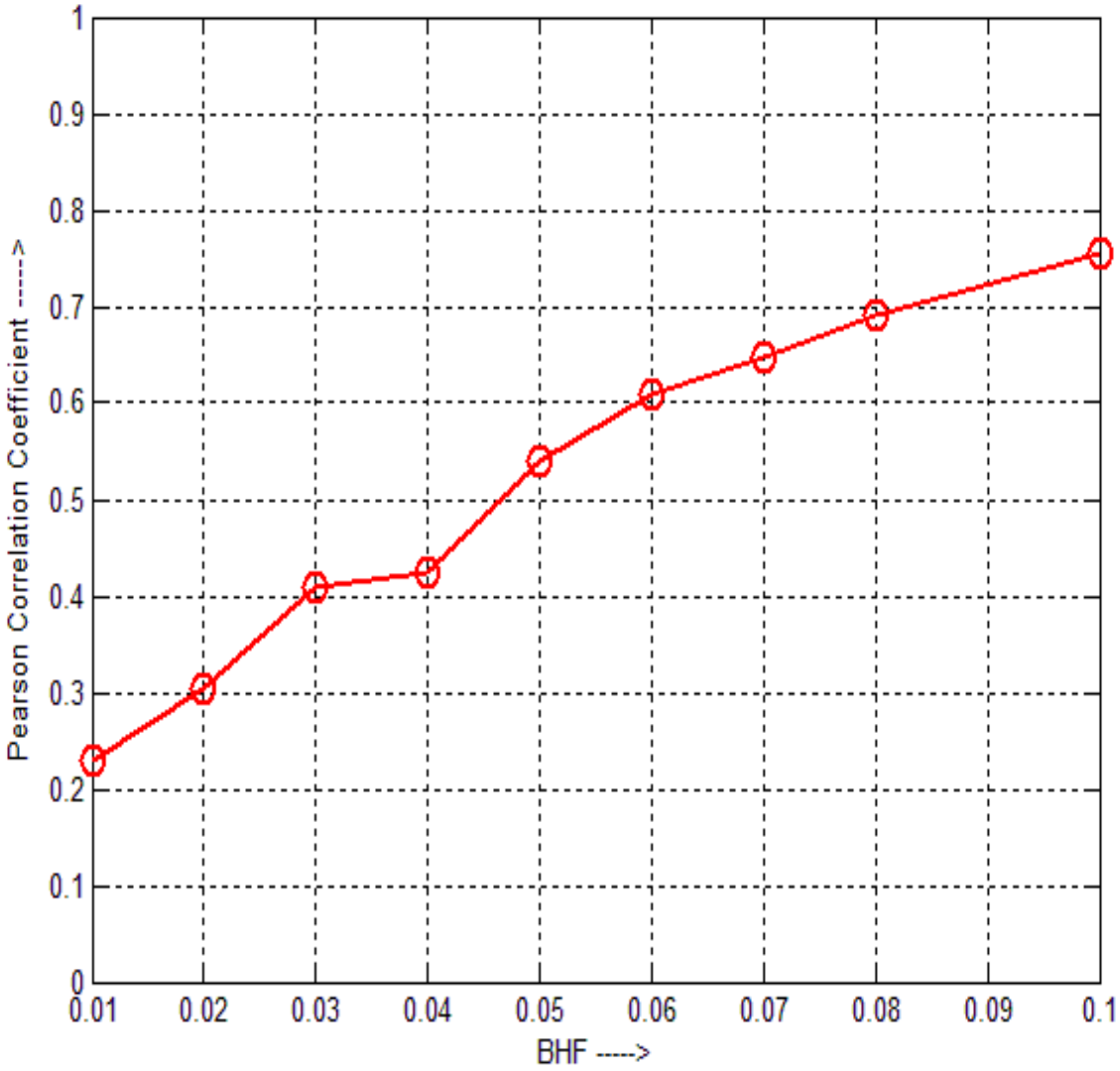


Figure 7.6 Variation of Pearson Correlation Coefficient w.r.t B_{HF} Parameter.

Analysis: It shows significant increase in correlation value with an increase in B_{HF} as high frequency component of heart rate variability power spectrum is an indicator of respiratory sinus arrhythmia condition.

Chapter 8

Conclusion and Future Scope

8.1 Conclusion

The Proposed method for finding correlation between heart rate variability and respiratory frequency is an effective method for detecting any cardiovascular disease. In medical and psychophysiological research, the study of RSA has become an increasingly common method to assess parasympathetic cardiac activity. Respiration clearly affected the frequency domain measurements of HRV via shifts in the respiratory sinus arrhythmia(RSA). The characteristic RSA-induced shifts in the frequency range could possibly be useful to determine respiration rate in freely moving individuals. RSA is the cyclic variation of instantaneous heart rate at the breathing frequency. In studies of cardio-respiratory interaction during sleep, paced breathing or postural changes, low respiratory frequencies, and fast changes can occur. RSA is an intrinsic resting function of the cardiopulmonary system. It is clear that RSA is an active physiological function that bears own biological roles. RSA magnitude measured as the HF component of HRV is widely used as an index of cardiac vagal function. RF has a strong and regular influence on the parameters of HRV. The results of our study suggest that the RF should be taken into account in HRV analysis lest the incorrect conclusions on the autonomic regulation of the cardiac rhythm be inferred. RSA plays a primary role in regulation of energy exchange by means of synchronizing respiratory and cardiovascular processes during metabolic and behavioral change. RSA magnitude was much more closely related to changes in respiratory parameters – particularly respiration rate – than to any changes in cardiac vagal tone .A high vagal tone or RSA is suggested to be associated with rapid regulation of cardiac output to promote disengagement and engagement with the environment and with good attentional capacities.On the other hand, a low RSA has been associated with anxiety disorders and cardiac failure. Thus, it is, of course, important to optimize the identification and assessment of the respiratory-related variation in the cardiac rhythm. By choosing a narrower HF band based on the respiratory peak, we found stronger correlation between the respiratory frequency and

HF HRV power. This provides an improvement in the estimation of RSA or HF HRV and consequently in assessing cardiac vagal traffic. Finally, one obvious drawback with our model is that it is not suitable when no respiratory data are present. Simulations show that HF band give a higher coherence between the respiratory frequency and the power of the HRV.

8.2 Future scope

In our thesis work, we have done analysis of finding correlation between heart rate variability and respiratory frequency under arrthymia condition. During our analysis, we have found that by varying noise parameter and high frequency component of heart rate variability, Pearson correlation coefficient is affected. This analysis will help in prognosis and treatment of patients whose heart loses its ability to respond to external environmental inputs. A method of measuring the 'instantaneous' temporal changes in HRV w.r.t respiration could provide both physiologic, diagnostic and prognostic information. This analysis can be used in hospitals to help diagnose various cardiac diseases. From this analysis we are able to find interesting relationships between HRV and diseases as well as drug pharmacodynamics. . For example,we may find some correlation between the ANS of a smoker versus a non-smoker. Correlation analysis of heart rate variability and respiratory frequency can be a powerful tool to assess autonomic nervous system function. It is not only useful when studying the pathophysiologic processes in certain diseases but also may be used in daily clinical practice.

In Future work, other parameters can also be varied and correlation of heart rate variability can be done w.r.t other respiratory parameters like tidal volume ,end tidal partial pressure of carbon di-oxide (PETco2) ,the time ratio of expiration/inspirationand respiratory dead space.

References

1. web.buddyproject.org/web019/web019/heart.html.
2. www.yourheartmadesimple.com/chapters/ch2/page1.cfm.
3. F. Weise, F. Heydenreich, S. Kropf, D. Krell, 1990, Intercorrelation analyses among age, spectral parameters of heart rate variability and respiration, Volume 21, pages 17 – 24.
4. Hiromitsu Kobayashi, 1996, Postural Effect on Respiratory Sinus Arrhythmia with Various Respiratory Frequencies, Vol. 15 (1996), No. 2 pp.87-91.
5. Maria Vittoria Pitzalis, 1997, Effect of respiratory rate on the relationships between RR interval and systolic blood pressure fluctuations, Volume 38, Number 2,Pp. 332-339.
6. J. D. Schipke, M. Pelzer, G. Arnold, 1999, Effect of respiration rate on short-term heart rate variability, *2: 92.*
7. T. Princi, A. Accardo, D. Peterec, 2004, Effect of Breathing Rate on Heart Rate Variability, pp 492-495.
8. Lt Col KK Tripathi, 2004, Respiration and Heart Rate Variability: A Review with Special Reference to Its Application in Aerospace Medicine, 64-75.
9. S. V. Nesterov, V. P. Nesterov, and A. I. Burdygin, August 9, 2004, The Effect of Respiratory Frequency on Heart Rate Variability.
10. Yasuma, F, Hayano, J (2004) Respiratory sinus arrhythmia: why does the heartbeat synchronize with respiratory rhythm? Chest 125,683-690
11. M Yildiz and Y Z Ider, 2006, Model based and experimental investigation of respiratory effect on the HRV power spectrum, 973–988.
12. Hansson-Sandsten Maria; Jonsson Peter; 2007, Multiple window correlation analysis of HRV power and respiratory frequency, IEEE transactions on biomedical engineering, vol. 54, pp. 1770-1779.
13. Kotani K, Takamasu K, Tachibana M, 2007, Respiratory-phase domain analysis of heart rate variability can accurately estimate cardiac vagal activity during a mental arithmetic task, 46(3):376-85.
14. P Indic1, EB Salisbury, D Paydarfar, EN Brown, R Barbieri, 2008, Interaction between Heart Rate Variability and Respiration in Preterm Infants, 35:57−60.

15. NK Subbalakshmi, 2009, Validity of Frequency Domain Method in Assessment of Cardiac Autonomic Function during Controlled Breathing in Healthy Subjects.
16. www.wikipedia.org
17. M.V. Kamath, E. L. Fallen, "Power spectral analysis of HRV: a non- invasive Signature of cardiac autonomic functions", Crit. Rev. Biomed. Eng. 1993; 21(3):245:311.
18. Hon EH, Lee ST. Electronic evaluations of the fetal heart rate patterns preceding fetal death, further observations. Am J Obstet Gynec 1965; 87: 814–26.
19. Sayers BM. Analysis of heart rate variability. Ergonomics 1973; 16: 17–32.
20. Ewing DJ, Martin CN, Young RJ, Clarke BF. The value of cardiovascular autonomic function tests: 10 years experience in diabetes. Diabetic Care 1985; 8: 491–8.
21. Wolf MM, Varigos GA, Hunt D, Sloman JG. Sinus arrhythmia in acute myocardial infarction. Med J Australia 1978; 2:52–3.
22. Akselrod S, Gordon D, Ubel FA, Shannon DC, Barger AC, Cohen RJ. Power spectrum analysis of heart rate fluctuation: a quantitative probe of beat to beat cardiovascular control. Science 1981; 213: 220–2.
23. Peng CK, Havlin S, Stanley HE, et al. Quantification of scaling exponents and crossover phenomena in nonstationary heartbeat time series.Chaos, 1995, 5 (1), pp. 82-87.
24. B. Mea. Sayers, "Analysis of Heart Rate Variability", Engineering ill Medicine Laboratory, Imperial College, London svv72bt, ergonomics, 1973, vol. 16, no.1, 17-32.
25. Juha-Pekka Niskanen, Mika P. Tarvainen, Perttu O. Ranta-aho, Pasi A. Karjalainen, Software for advanced HRV analysis, Computer Methods and Programs in Biomedicine, 2004, 76, pp.73-81.
26. Task force of the European society of cardiology and the North American society of pacing and electrophysiology, Heart rate variability—standards of measurement, physiological interpretation, and clinical use, Circulation 1996(93),5, pp. 1043—1065.
27. Rajendra Acharya U, Paul Joseph K, Kannathal N, Lim Choo Min and Jasjit Suri S, Heart Rate Variability, Advances in Cardiac Signal Processing, Springer-Verlag Berlin Heidelberg 2007,pp.121-165.

28. Han at, variability: Stand a roe of me as and m ant, physiological interpretation, and clinical use Task Force of The interest Society fCa,dl.i.n and Tin, North AT Steamy of Pacing end Electrophysiology European Read Journal (1996) 17, 354-381.
29. Task Force of the European Society of Cardiology and North American Society of Pacing and Electrophysiology, Heart Rate Variability: Standards of Measurement, Physiological Interpretation and Clinical Use, Circulation, vol.93, pp.1043-1065, 1996.
30. D. Singh, K. Vinod and S. C. Saxena, Sampling frequency of the RR interval time series for spectral analysis of heart rate variability, Journal of Medical Engineering & Technology, 2004(28), 6, pp. 263–272.
31. G. Manis, 01 February 2009, Comparison of the most common HRV computation algorithms from the systems designer point of view, Journal of Medical Engineering & Technology,33:2,110 — 118.
32. Michael J. Lewis, BSc, MSc, PhD, CPhys, MInstP, Heart Rate Variability Analysis: A Tool to Assess Cardiac Autonomic Function, CIN: Computers, Informatics, Nursing, 2005(23), 6, pp. 335-341.
33. G. Manis, 01 February 2009, Comparison of the most common HRV computation algorithms from the systems designer point of view, Journal of Medical Engineering & Technology,33:2,110 — 118.
34. Manis, G., Alexandridi, A. and Nikolopoulos, S., 2003, Diagnosis of cardiac pathology through prediction and approximation methods. In Seventh International Symposium on Signal Processing and its Applications, 29 October–1 November, 1998, Paris, France.
35. Manis, G., Nikolopoulos, S. and Alexandridi, A., 2004, Prediction techniques and HRV analysis. In: Medicon and Health Telematics (Naples, Italy).
36. Pincus, S.M., 1991, Approximate entropy: A complexity measure for biology timeseries data. In Proceedings of the IEEE 17th Annual Northeast Bioengineering Conference, 4–5 April 1991, New York.
37. Grassberger, P. and Procaccia, I., 1983, Characterization of strange attractors. Physical Review Letters, 50, 346 – 349.
38. Smith AL, Reynolds KJ, Owen H., Aug 2003, Respiratory Sinus Arrhythmia Measurement Techniques: A Review.

39. P.Novak, V. Novak, 'Time-frequency mapping of the heart rate, blood pressure and respiratory signals", Med. Biol. Eng. Comp, vol.31, pp.103-110, 1993.
40. B. Sayers, A. Mc, "Analysis of heart rate variability" Ergonomics 1973; 16:85-97.
41. M. Alcalay, S. Izraeli, R. Wallach, et al, Paradoxical Pharmacodynamic effect of atropine on parasympathetic control: a study by spectral analysis of heart rate fluctuations.1992; 52:518-527.
42. P. Low, Clinical Autonomic Disorders: Evaluation and Management, Lippincott-Raven, 1997, Philadelphia.
43. S. H. J. Uijtdehaage and J. F. Thayer, "Accentuated antagonism in the control of human heart rate", Clinical Autonomic Research 2000, 10:107-110.
44. Eckberg DL, Physiological basis for human autonomic rhythms, Ann Med 2000, 32: 341- 99.
45. Hiromitsu Kobayashi, Keita Ishibashi, and Hiroki Noguchi, 1999,Heart Rate Variability, An Index for Monitoring and Analyzing Human Autonomic Activities, Journal of Physiological Anthropology,*53-59*,
46. Angelone A, Coulter NA (1964) Respiratory sinus arrhythmia: a frequency dependent phenomenon. J Applied Physiology 19: 479-482.
47. Kobayashi H (1998) Normalization of respiratory sinus arrhythmia by factoring in tidal volume. Applied Human Science 17 (5): 207-213.

Appendix I

/* Matlab Code for Correlation between Heart rate variability and Respiratory frequency in normal conditions*/

```
function [PrCor]=HRV_JITTER07(Ao,Fo,Fvmin,Fvmax,Vn,NOP)
Vn=Vn*100000;
Fv=linspace(Fvmin,Fvmax,NOP);
Aj=zeros(1,NOP);
Fr=zeros(1,NOP);
Rs=zeros(1,NOP);
Ji=zeros(1,NOP);
noise=zeros(1,NOP);
noise=sqrt(Vn).*randn(1,NOP);
PrCor=0;
%
for m=1:NOP
    Aj(m)=Ao+1000*Fv(1,m);
end
%
for j=1:NOP
    Fr(j)=Fo-Fv(1,j);
end
%
for n=1:NOP
    Ji(n)=Aj(n)*cos(2*pi*n*Fr(n)/1000) + noise(n);
end
J=Ji/max(abs(Ji));
plot(Fr,J,'b');
% Signal is normalized with respect to its max abs value
hold on
%%%
for q=1:NOP
Rs(q)=cos(2*pi*Fr(q)*q/1000);
end
%%%
plot(Fr,Rs,'r');
hold off
%%%
MFr=mean(Fr);
MJ=mean(J);
SFr=std(Fr);
SJ=std(J);
%
for r=1:NOP
  PrCor=PrCor+(Fr(r)-MFr)*(J(r)-MJ)/(SFr*SJ);
end
PrCor=(1/NOP).*PrCor;
```

Appendix II

/* Matlab Code for Correlation between Heart rate variability and Respiratory frequency under Sinus Arrhythmia Condition*/

```
function[PrCor]=HRV_JITTER08(Amod,Td,phit,Fmod,Fresp,Fvlf,Flf,Bvlf,Blf,
Bhf,Vnt,Vn,NOP)
Fr=zeros(1,NOP);
Jj=zeros(1,NOP);
PrCor=0;
%%%
noise=sqrt(Vn).*randn(1,NOP);
noiset=sqrt(Vnt).*randn(1,NOP);
%%%
for m=1:NOP
    Fr(m)=Fresp*(1+Amod*cos(2*pi*Fmod*m/1000));
end
%%%
for j=1:NOP

Jj(j)=Bvlf*cos(2*pi*Fvlf*j/1000)+Blf*cos(2*pi*Flf*j/1000)+Bhf*cos(2*pi*
Fr(j)*(j+phit+Td+noiset(j))/1000);
end
%%%
Jj=Jj+noise;
J=Jj/max(abs(Jj));
plot(Fr,J,'b');
% Signal is normalized with respect to its max abs value
hold on
%%%
for q=1:NOP
Rs(q)=cos(2*pi*Fr(q)*(q+phit)/1000);
end
%%%
plot(Fr,Rs,'m');
hold off
%%%
MFr=mean(Fr);
MJ=mean(J);
SFr=std(Fr);
SJ=std(J);
%
for r=1:NOP
  PrCor=PrCor+(Fr(r)-MFr)*(J(r)-MJ)/(SFr*SJ);
end
PrCor=(1/NOP).*PrCor;
```