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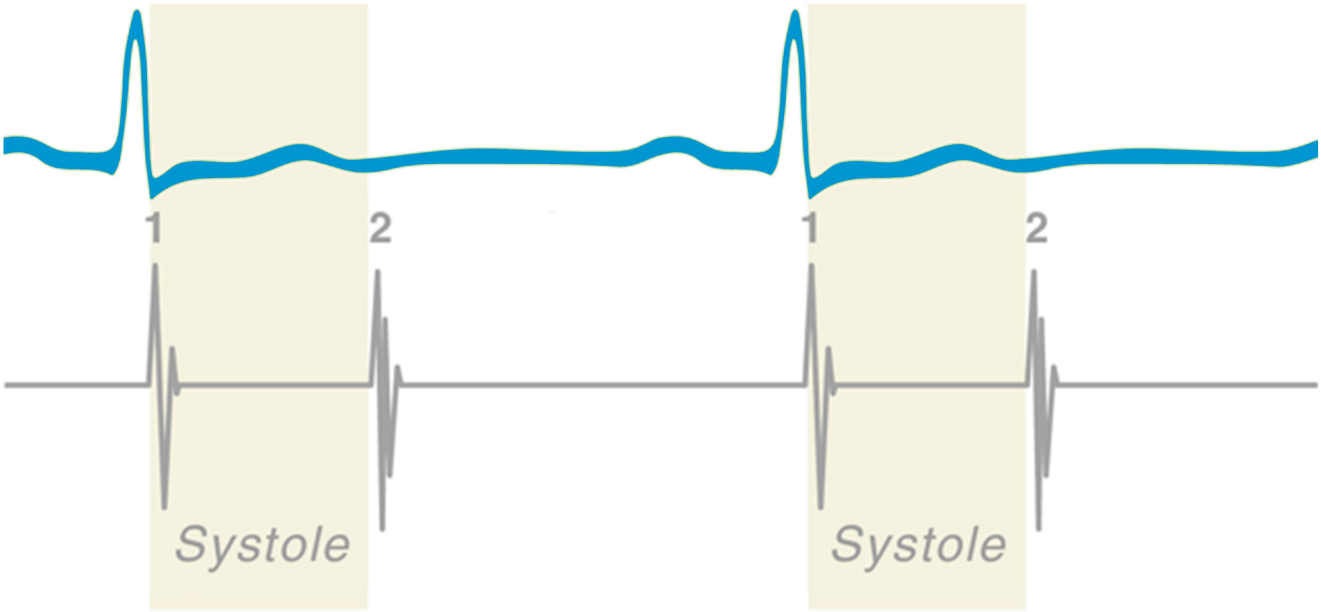
Electrical vs. Mechanical Systole In Heart Failure With Symptoms Of Systolic Dysfunction

Haiyong Liu



A MASTER'S THESIS IN BIOMEDICAL ENGINEERING AND INFORMATICS

AALBORG UNIVERSITY

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Synopsis:

In developed countries, the prevalence of heart failure ranges from 1% to 2% and rises to 10% or more among individuals over 70 years of age. Since the commonest cause of heart failure in industrialized societies is ischaemic heart disease, heart failure is usually associated with left ventricular systolic dysfunction. Systolic dysfunction in heart failure can lead to the worsening of symptoms, declining functional capacity, myocardial electrical instability and premature death. The five-year mortality of systolic heart failure remains 60% in men and 45% in women, even under advanced treatments. Since the ECG has a high negative predictive value of left ventricular systolic dysfunction, hence, a normal ECG also requires further process to the diagnosis of systolic heart failure. Therefore, PCG signal was also combined to detect the systolic dysfunction in this project. In normal case, the electrical systole (QT) is shorter than the mechanical systole (QS_2), but a $QT > QS_2$ syndrome was observed in patients with coronary artery disease. Therefore, the relationship between QT and QS_2 was focused among 10 subjects with systolic dysfunction. The result shows that $QT > QS_2$ can be observed among heart failure patients with systolic dysfunction, but it cannot be used as a criterion of the diagnosis in systolic heart failure.

Preface

This report was written as a Master Thesis, during the period of September 1st 2013 to January 3rd 2014 at Aalborg University, in the field of Biomedical Engineering and Informatics, under the supervision of Johannes Jan Struijk, Samuel Schmidt and Claus Graff. The theme for this semester was "Biomedical (information) systems". The project concerns an investigation of the relationship of QT and QS_2 in heart failure patients with symptoms of systolic dysfunction.

All citations in this report refer to the bibliography list at the end of the report. References are organized according to the Harvard method, [Author's last name, year of publishing].

This report was written by:

Haiyong Liu

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CHAPTER

1 Introduction

In developed countries, the prevalence of heart failure ranges from 1% to 2% and rises to 10% or more among individuals over 70 years of age [Remme and Swedberg 2001, McMurray 2010]. Since the commonest cause of heart failure in industrialized societies is ischemic heart disease, heart failure is usually associated with left ventricular systolic dysfunction [Remme and Swedberg 2001]. Other none ischemic factors, such as viral infection and hypertension, are also liked to contribute to systolic heart failure [McMurray 2010]. Systolic dysfunction in heart failure is commonly combined with diastolic dysfunction at rest and leads to the worsening of symptoms, declining functional capacity, myocardial electrical instability and premature death [Remme and Swedberg 2001, McMurray 2010]. The five-year mortality of systolic heart failure remains 60% in men and 45% in women, even under advanced treatments [Teeters and Alexis 2009].

Effective early diagnosis is essential to the treatment of heart failure with systolic dysfunction. The basis of effectual treatment of systolic heart failure is to interrupt the pathologic remodeling of the left ventricle and the systemic response to it [McMurray 2010]. The routine diagnosis of heart diseases is electrocardiogram (ECG). If other clinical symptoms and signs of heart failure co-exist, the contribution of anomalies on ECG rises significantly to the diagnosis of heart failure [Remme and Swedberg 2001]. However, the ECG has a high negative predictive value of left ventricular systolic dysfunction, hence, a normal ECG also requires further process to the diagnosis of systolic heart failure [Remme and Swedberg 2001].

ECG provides an electrical evidence of heart failure, while phonocardiogram (PCG) gives a better view of the mechanical process of the heart. The second heart sound (S_2) that caused by the closure of the aortic and the pulmonic valves can very well present the end of ventricular systole. Meanwhile, the electrical systole can be measured by the QT interval on ECG [Boudoulas et al. 1981a]. Therefore, QT interval and QS_2 interval respectively stand for the electrical and mechanical systole.

Based on the previous studies by Boudoulas and his colleagues, both QT and QS_2 perform a negative linear relationship to the heart rate in patients without symptoms of heart failure [Boudoulas et al. 1981a]. Moreover, the QT interval is always slightly shorter than the QS_2 under normal condition [Boudoulas et al. 1985a; 1981b]. However, a $QT > QS_2$ syndrome was observed in patients with coronary artery disease [Boudoulas et al. 1982]. As coronary artery disease causes two thirds of the total population of systolic dysfunction, the abnormal $QT > QS_2$ might also be observed in systolic heart failure.

Patients with long-QT syndrome have a high opportunity to perform the $QT > QS_2$ syndrome [Berul et al. 1998, Boudoulas et al. 1982]. But the case when $QT > QS_2$ occurs based on a normal QT interval is mainly focused in this project. Due to the impairment of systolic contractility of left ventricular, it is assumed that the mechanical systole (QS_2) might be abbreviated. Therefore, the purpose of this project is to figure out whether the relationship of $QT > QS_2$ can be used as a criterion of heart failure with systolic dysfunction, even though the ECG itself cannot effectively predict systolic heart failure.

8 male and 2 female patients with symptoms of systolic dysfunction were included as subjects in this study, and 2 healthy male subjects volunteered in this project as comparison. All the patient subjects were under Cardiac-Resynchronization Therapy with an implanted biventricular pacer. The ECG and PCG signal were detected from all the patients in different pacing situation at rest. The healthy subjects were also asked to be at the resting condition when recording the ECG and PCG signals.

CHAPTER

2 Problem Analysis

2.1 Cardiac amatomy

2.1.1 Internal anatomy of the heart

The human heart lies an oblique position in the thorax, with two-thirds to the left of the middle line and consists of 4 chambers: the right and left atrium, the right and left ventricular. The primary function of the heart is to collect oxygen-poor blood and pump it into the lungs to release carbon dioxide in exchange for oxygen, then collect the oxygen-rich blood and pump in to all tissues in the body to provide oxygen. The right part of the heart is responsible for collecting the oxygen-poor blood and pump it into the lungs, while the left part is in charge of collecting the oxygen-rich blood from the lungs and pump it to the whole body. Due to the function of the ventricles, which is to pump the blood away from the heart, the ventricles are much stronger [Iaizzo 2009, Weinhaus and Roberts 2005, Tortora and Derrickson 2008].

A lot of important structures locate on the smooth posterior wall of the right atrium. It receives the superior and the inferior vena cava and the coronary sinus, and also contains the fossa ovalis, the sinoatrial node (SA node) and the atrioventricular node (AV node). The ostium of the inferior vena cava and the coronary sinus lie on the inferior border of the right atrium. The coronary sinus receives almost all the deoxygenated blood from the vasculature of the heart, and it opens anteriorly into the right atrium and inferiorly to the ostium of the inferior vena cava. Moreover, there are valves cover the opening of both coronary sinus (Eustachian valve) and the inferior vena cava (Thebesian valve) to prevent backflow (Figure 2.1) [Iaizzo 2009, Weinhaus and Roberts 2005, Tortora and Derrickson 2008].

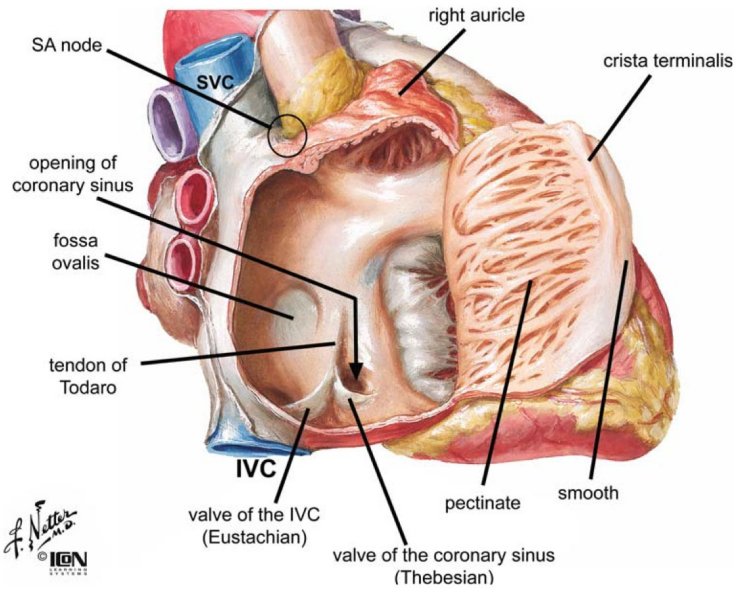

Figure 2.1. The right atrium of the heart [Weinhaus and Roberts 2005].

Most of the anterior surface of human heart is formed by the right ventricle, and it receives blood from the right atrium and pumps it to the lungs via pulmonary trunk and arteries. The blood is pumped into the right ventricle through the AV orifice from the right atrium and prevented from flowing back by the tricuspid valve. The valve is formed from the annulus, three valvular leaflets, three papillary muscles and three sets of chordae tendinae. The annulus is attached to the membranous ventricular septum and strengthens the AV orifice. In order to secure the three leaflets in place for the preparation of ventricular contraction, the leaflets are attached by three papillary muscles through chordae tendinae. During ventricular systole, the blood is pumped into the pulmonary trunk and arteries towards the lungs from the right ventricle, and similar to the AV orifice, there is also a valve that called pulmonary semilunar valve to prevent the backflow of the blood in diastole. The pulmonary semilunar valve consists of three symmetric and semilunar shaped cusps. The three cusps are attached to an annulus that is secured to the right ventricular infundibulum and the pulmonary trunk (Figure 2.2) [Iaizzo 2009, Weinhaus and Roberts 2005, Tortora and Derrickson 2008].

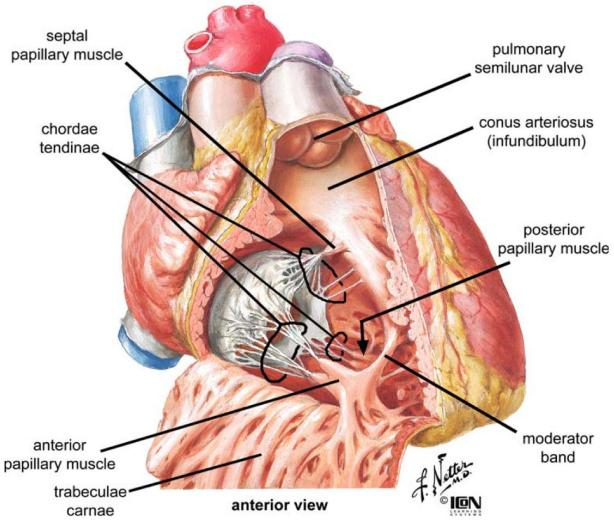

Figure 2.2. The right ventricle of the heart [Weinhaus and Roberts 2005].

The left atrium collects oxygenated blood from the lungs through the left and right pulmonary veins (Figure 2.3). Then the blood is pumped into the left ventricle and ejected from the left ventricle to all tissues in the body via aortic artery. The myocardium in the wall of the left ventricle is much thicker comparing to the right ventricle. There is also a left AV valve, or called bicuspid valve (also called mitral valve) to prevent the backflow of the blood during the contraction of left ventricle. Similar to the tricuspid, the bicuspid consists of the annulus, two leaflets, two papillary muscles and two sets of chordae tendinae. However, unlike annulus of the AV orifice in the right ventricle, the annulus fibrosus in the left ventricle only supports the posterior and lateral two-thirds of the annulus and the rest of it is renuforced by the attachment to the left atrium and by fibrosus support to the aortic semilunar valve. Besides, the function of the aortic semilunar valve is to prevent the blood from flowing back to the left ventricle during diastole [Iaizzo 2009, Weinhaus and Roberts 2005, Tortora and Derrickson 2008].

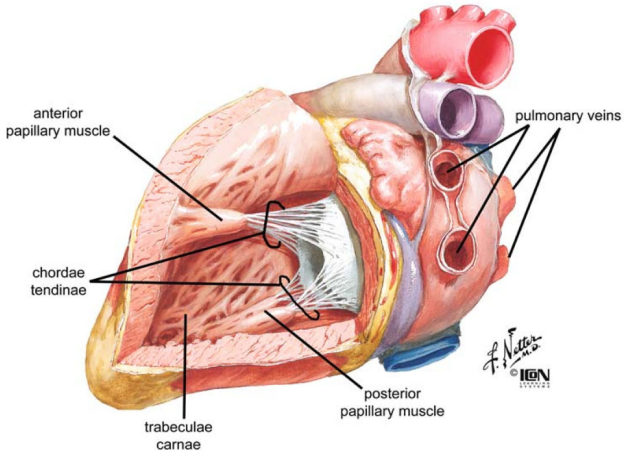

Figure 2.3. The left atrium and left ventricle of the heart [Weinhaus and Roberts 2005].

2.1.2 Vasculature of the heart

Like any other tissues in human body, the heart also needs nourishment and oxygen supply. The walls of the heart are too thick to be supplied only by diffusion, thus the tissues are supplied by a separate vascular supply committed only to the heart. The arterial supply of the heart starts from the base of the aorta as the right and left coronary arteries running in the coronary sulcus. The right coronary artery has two branches: the conus (arteriosus) artery runs to the conus arteriosus (right ventricular outflow tract), and the atrial branch to the right atrium. The left coronary artery emerges from the aorta and is superior and posterior to the right coronary ostium. It originates from the aorta and passes between the pulmonary trunk and the left atrial appendage. Moreover, the left coronary artery divides into the anterior interventricular (left anterior descending artery) and the left circumflex artery. The anterior interventricular artery is the major blood supply to the interventricular septum and the bundle branches of the conduction system. In addition, branches of the right coronary artery supply both the SA and AV node in at least 50% of the heart. Thus, it is easy to see that coronary artery diseases can lead to impairment or interruption of conducting system (Figure 2.4) [Weinhaus and Roberts 2005, Tortora and Derrickson 2008].

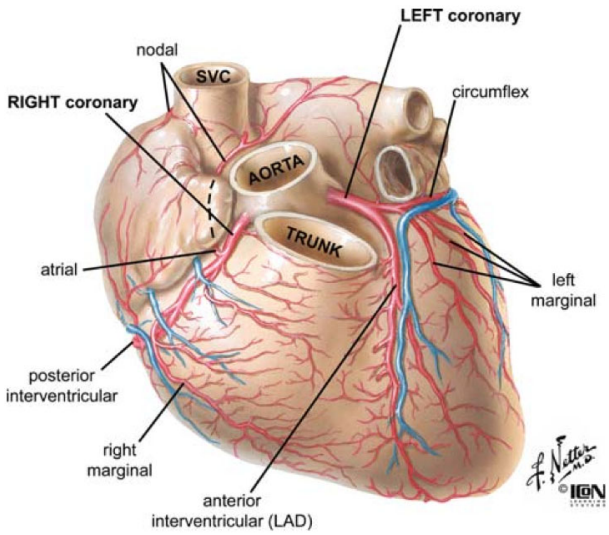

Figure 2.4. The vascular supply of the heart [Weinhaus and Roberts 2005].

Of course, the waste products and carbon dioxide need to be removed. The venous drainage of the heart is built by an extensive network of intercommunication veins and has three separate systems: the cardiac venous tributaries, the anterior cardiac veins and the smallest cardiac venous system. The cardiac venous tributaries consists of three large veins (the great, middle and small cardiac veins) that lie parallel to the coronary arteries and form the coronary sinus. About 85% of the venous drainage of the heart flow through the coronary sinus to the right atrium. The anterior cardiac veins is distinguished from the other systems due to the fact that the veins do not drain into the coronary sinus. Usually there are two to four veins in the anterior cardiac system, and the veins arise from the anterior right ventricular wall, pass across the right AV sulcus and enter the right atrium directly. The smallest cardiac venous system is composed of a multitude of small intramyocardial veins that are also called Thebesian veins.

They originate in the capillary beds of the myocardium and open directly into the chambers of the heart (Figure 2.5) [Weinhaus and Roberts 2005, Tortora and Derrickson 2008].

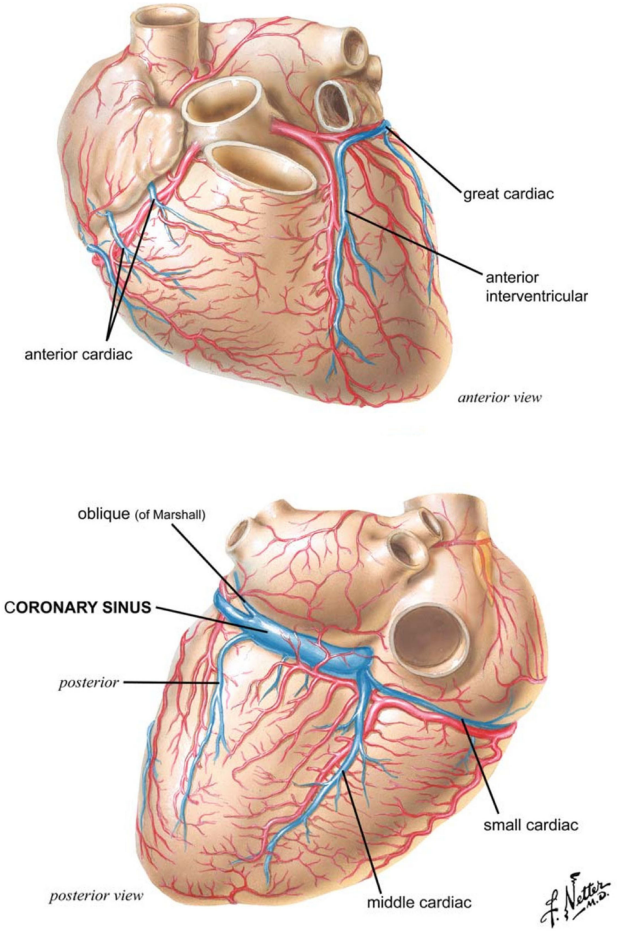

Figure 2.5. The venous drainage system of the heart [Weinhaus and Roberts 2005].

2.1.3 The cardiac conduction system

The sinoatrial node (SA node), which located in the right atrium, is the natural pacemaker that manifest spontaneous depolarizations. After the initial excitation from SA node, depolarization spreads throughout the atria. The depolarizations from the nodal cells go directly to the nearby myocardial cells and are rapidly passed via the right atrium to both the left atrium and the atrioventricular node (AV node). The AV node has a very complex structure, but the primary function is simple, that is to relay conduction between the atria and ventricles. Following the excitatory signals from AV node, depolarizations pass through His bundle and spread to both the left and right bundle branches. Finally, excitation travels through the Purkinje fibers and ventricular depolarization spreads (Figure 2.6) [Weinhaus and Roberts 2005, Laske et al. 2009, Tortora and Derrickson 2008].

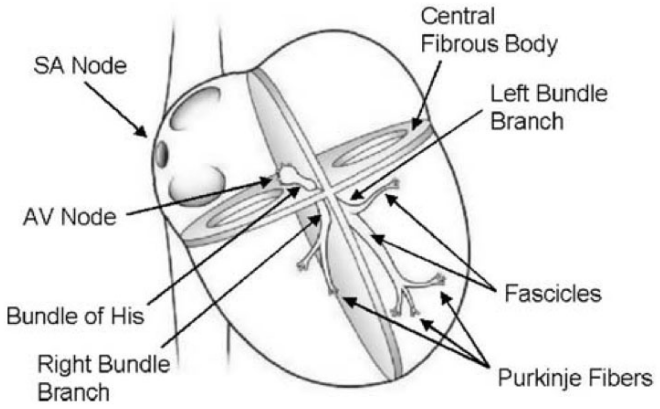

Figure 2.6. The conduction system of the heart [Laske et al. 2009].

In adults, the pacemaker rate of SA node is between 60 and 100$beats/min$. This is faster than any other regions of the heart. Not only the SA node, other specialized conduction system cells are also able to develop spontaneous diastolic depolarization, such as AV node and His-Purkinje system. Table 2.1 shows the conduction velocity and intrinsic pacemaker rate of various structures in the conduction pathway. Those lower rate rhythms are important for patient survival, as they maintain some degree of cardiac output in case the SA and/or VA node are not functional or functioning inappropriately [Iaizzo 2009, Laske et al. 2009, Tortora and Derrickson 2008].

Normal avtivation sequence	Structure	Conduction velocity(m/sec)	Pacemaker rate (beats/min)
1	SA node	<0.01	60 - 100
2	Atrial myocardium	1.0 - 1.2	None
3	AV node	0.02 -0.05	40 - 55
4	Bundle of His	1.2 - 2.0	25 - 40
5	Bundle branches	2.0 - 4.0	25 - 40
6	Purkinje network	2.0 - 4.0	25 - 40
7	Ventricular myocardium	0.3 - 1-0	None

Table 2.1. Conduction velocities and intrinsic pacemaker rate of various structures of the cardiac conduction pathway [Laske et al. 2009]. The structures are listed in the order of activation during a normal cardiac contraction, beginning with the sinoatrial node.

2.1.4 Heart tones

Heart tones are considered as one mechanical aspect of the cardiac performance [Bojanov 2009]. Several sounds can be heard from a normal heart. In a healthy person, two heart sounds can be heard: the first heart sound (S1) and the second heart sound (S2). The first heart sound is caused by the closure of the mitral valve (M1), and shortly by the closure of the tricuspid valve (T1). And the second heart sound arises from the closure of the aortic and the pulmonic valves. Normally the first components of S2 is due to the closure of aortic valve (A2) and followed by the pulmonic valve closure (P2) [Bojanov 2009, Iaizzo 2009, MacConnell and Branigan 2008].

In some circumstances, the physiological third and fourth heart sound can occur. The physiological third heart sound (S3) (Figure 2.7) is a low-pitched vibration caused by rapid ventricular filling during diastole. S3 sound can commonly occur in children, adolescents, and young adults. If it can be detected in individual over 30 years old, it usually a sign of ventricular gallop, which represents the diastole dysfunction associated with ventricular failure. Moreover, the S3 sound sometimes can be heard from individuals beyond age 40 and are more commonly found from women [Bojanov 2009, Iaizzo 2009]. The physiological fourth heart sound (S4) (Figure 2.8) is also soft and low-pitched, and is best heard in late diastole, just right before S1. S4 arises by rapidly ventricular filling during atrial systole, which causes vibrations of the left ventricular wall and the mitral apparatus. S4 is normally found in infants, small children and adults over 50 year-old [Bojanov 2009, Iaizzo 2009].

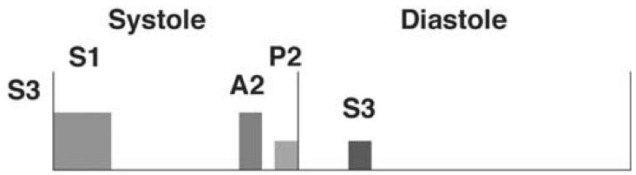

Figure 2.7. Third heart sound. A2 = aorticvalve closure; P2 = pulmonic valve closure; S1 = first heart sound; S3 = third heart sound [Bojanov 2009].

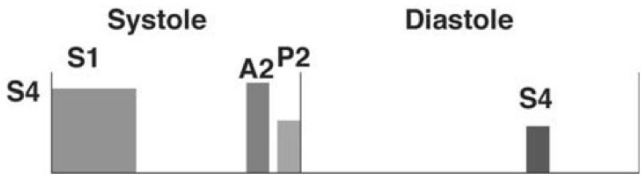

Figure 2.8. Fourth heart sound. A2 = aorticvalve closure; P2 = pulmonic valve closure; S1 = first heart sound; S4 = fourth heart sound [Bojanov 2009].

2.2 The Electrocardiogram (ECG)

2.2.1 The lead system

The electrocardiogram (ECG) is a measure of the changes about the electrical activity of the heart over time. More precisely, ECG measures the action potentials within each myocyte propagate throughout the heart as a whole during each cardiac cycle. Thus, ECG is not a direct measure of the cardiac cellular depolarization and repolarization but the recording of the cumulative signals of membrane potentials in populations of cells at a given point in time. The ECG has specific waveforms of electrical differences during the atrial and ventricular depolarization and repolarization [Macfarlane 2010, Laske et al. 2009]. Figure 2.9 shows the action potentials of different tissues that contribute to an ECG signal.

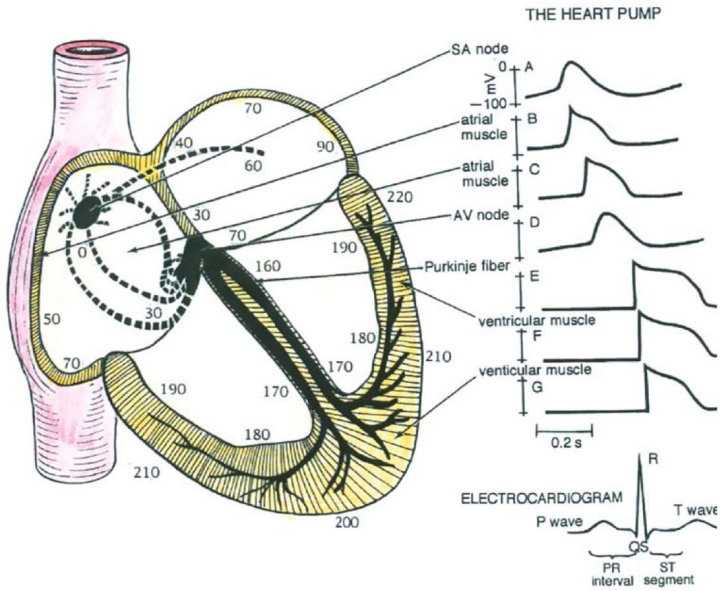

Figure 2.9. This figure shows how action potentials from different cardiac cells contribute to the ECG signal. The numbers on the figure shows how much time it delays from the original depolarization point (SA node) [Laske et al. 2009].

Nowadays, a 12-lead device is commonly used to measure the ECG. The 12-lead ECG includes three bipolar limb leads, three augmented unipolar limb leads and 6 unipolar chest leads. The three bipolar limb leads are used to measure the potential difference between right arm and

left arm (Lead I), right arm and left leg (Lead II), left arm and left leg (Lead III). Unlike the bipolar leads, the unipolar leads, which represent the potential variation at a single point, were introduced in 1934 by Wilson et al. [Wilson et al. 1934, Macfarlane 2010]. In order to obtain such a lead, a "central terminal" was produced. The Wilson Central Terminal (WCT) can be considered as a summation of the potentials at the right and left arms and left leg to form a single potential that is relatively constant throughout the cardiac cycle in practice. The three unipolar leads measure the potential difference between one limb (right and left arm and left leg) and the WCT. Later on, Goldberger modified the WCT in order to increase the voltage measured by the unipolar limb leads. Instead of using the WCT, he used the average of the other two limbs' potentials as the modified terminal, e.g., when measuring the potential from the right arm, the average of the potential from left arm and left leg is the modified terminal. These are the augmented unipolar limb leads: aVR, aVL and aVF [Goldberger 1942, Macfarlane 2010]. By using the WCT, it is possible to measure potentials on various points on the chest and six points are selected on the precordium in order to standardize recording. Electrodes locating on these positions are call unipolar chest leads (V_1-V_6) [Macfarlane 2010]. Table 2.2 shows the locations of the six unipolar chest leads.

Electrode	**Location of arrachment**
V_1	Right sternal margin, fourth intercostal space
V_2	Left sternal margin, fourth intercostal space
V_3	Midway between V_2 and V_4
V_4	Left midclavicular line, fifth intercostal space
V_5	Left anterior axillary line, V_4 level
V_6	Left midaxillary line, V_4 and V_5 level

Table 2.2. The locations of unipolar chest leads [Macfarlane 2010].

2.2.2 The ECG waveform

The normal ECG waveform consists of P-wave, QRS complex and the T-wave. As mentioned before, the cardiac cycle begins from the SA node, however, the firing of SA node cannot be detected by the ECG due to the small quantity of the cells that cannot create an electrical potential with an amplitude high enough to be recorded by the electrodes. The excitation from the SA node travels rapidly throughout both the right and left atria, and brings the P-wave. P-wave normally lasts around $80-100ms$ in duration and represents the depolarization of both atria and the onset of atrial contraction. When the P-wave ends, the signal returns to baseline while action potentials spread though AV node and bundle of His. Roughly $200ms$ after the start of P-wave, the depolarization of right and left ventricles occurs resulting in the QRS complex, which is approximately $100ms$ in duration. Take the normal ECG from lead II for instance (Figure 2.10), the first negative deflection is the Q-wave, the large positive deflection is the R-wave, and if there is a negative deflection after R-wave, it is called the S-wave. The end of the QRS complex means that the ventricles are completely depolarized and begin to contract [Macfarlane 2010, Laske et al. 2009]. In addition, the exact shape of the QRS complex depends on from which placement of electrodes is recording the signal [Laske et al. 2009]. Figure 2.11 shows a typical Lead II ECG combined with cardiac valve activities and ventricular systole and diastole [Laske et al. 2009]. After the QRS complex, the ventricular repolarization gives rise

to the T-wave. The T-wave is commonly the last detected potential in the cardiac cycle and followed by the P-wave of next cycle [Macfarlane 2010, Laske et al. 2009].

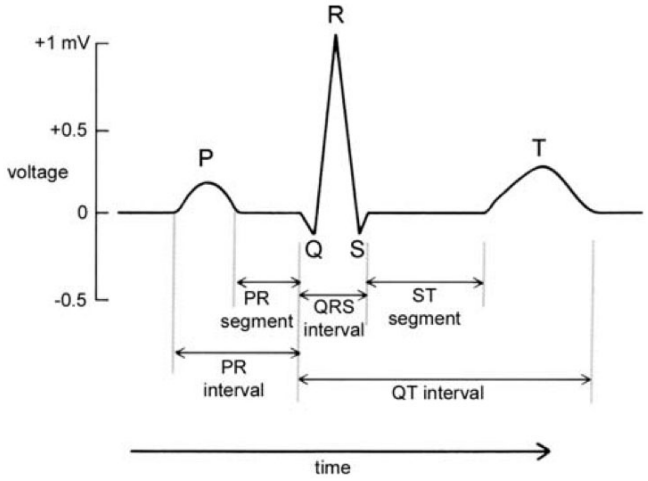

Figure 2.10. This figure shows the normal ECG from lead II [Laske et al. 2009].

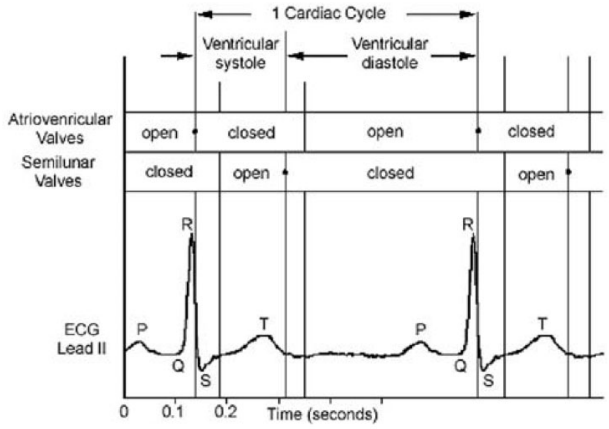

Figure 2.11. A typical Lead II ECG combined with the timing of atrioventricular and semiluna valve activity[Laske et al. 2009].

The direction and magnitude of the overall excitation of the heart are changing over time and known as the heart's "electrical axis". This is also the reason that the measurements of ECG are different from each lead (Figure 2.12). The ECG signals from different leads are the vector component of the electrical axis in specific directions [Laske et al. 2009]. Figure 2.13 shows the progress of ECG signal during one cardiac cycle in the three bipolar limb leads. The electrical axis can be used to explain the abnormal ECGs from patients who use implant pacemaker to trigger the cardiac cycles. The normal ECG signals obtained from the widely used 12-lead system are shown in Figure 2.14 [Macfarlane 2010].

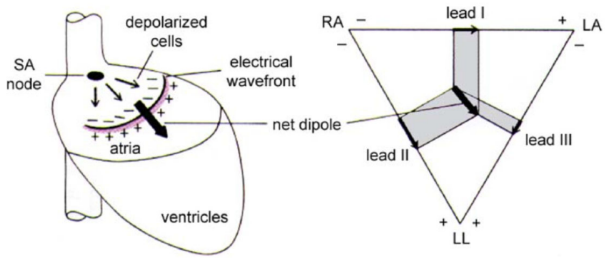

Figure 2.12. This figure shows the net dipole occuring in the heart at any one poing in time is detected by three bipolar limb leads in different directions [Laske et al. 2009].

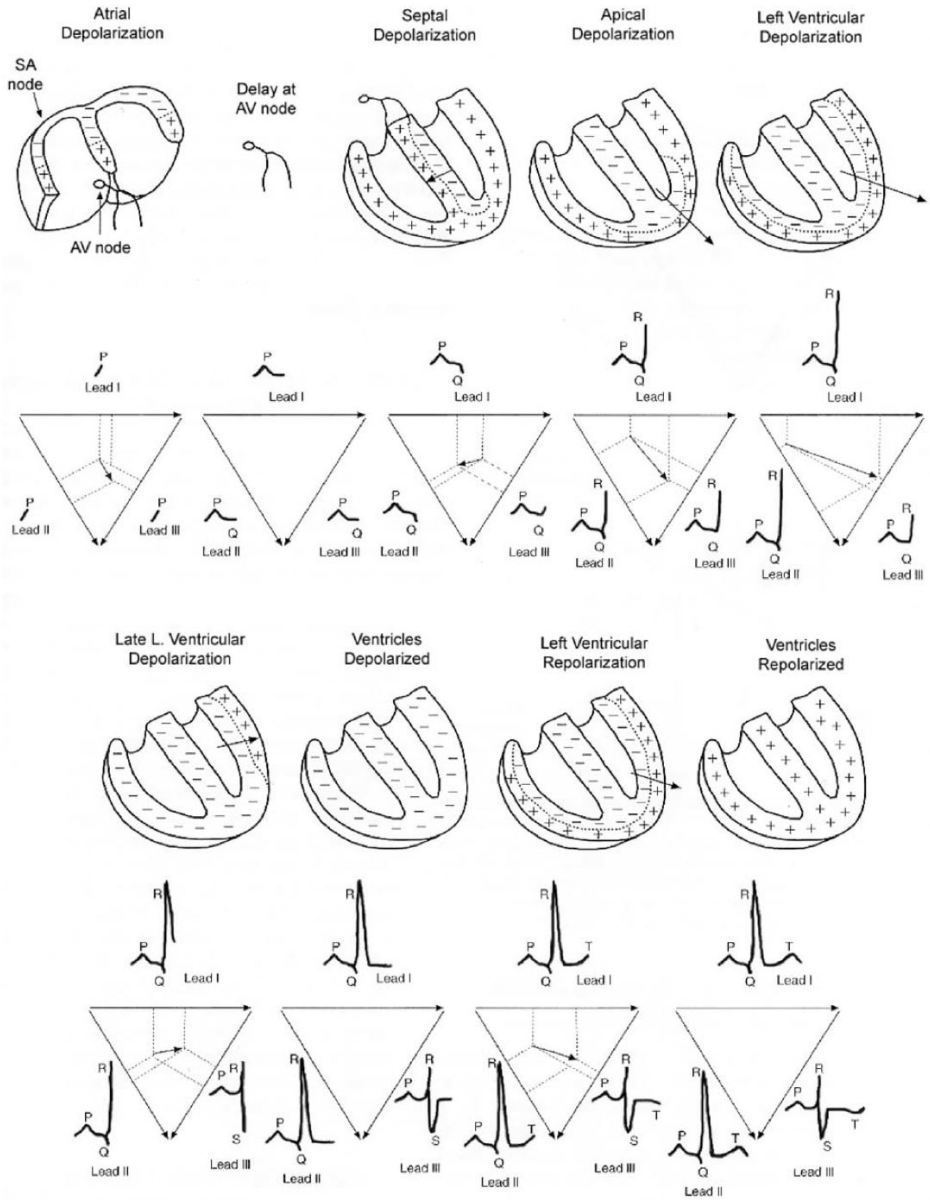

Figure 2.13. This figure shows the net dipole (indicated by the arrow) as it progresses through one cardiac cycle. It is detected by each of the three bipolar limb Leads I, II and III [Macfarlane 2010].

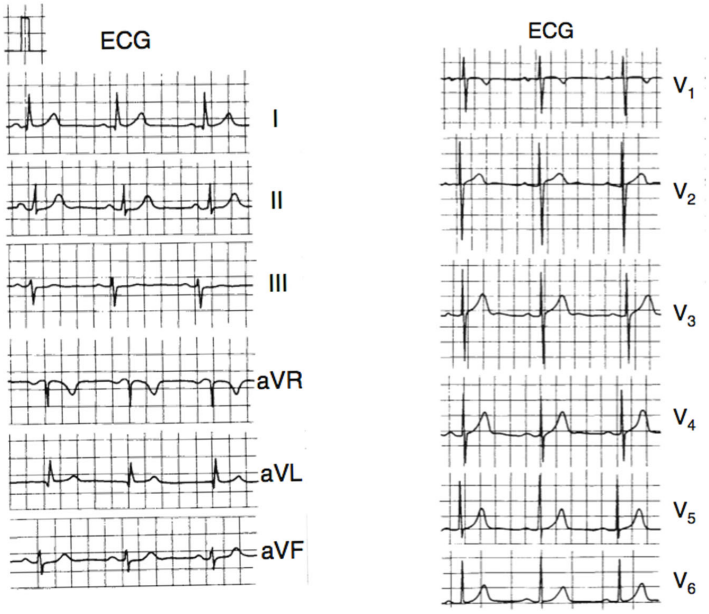

Figure 2.14. This figure shows the normal ECG signals from the 12-lead syetem [Laske et al. 2009].

2.3 General Information of Heart Failure

The prevalence of heart failure in Europe is up to 2% of the whole population, and increases rapidly with ages (the mean age of patients with heart failure is 74 year-old) [McMurray 2010]. Suggested by European Society of Cardiology, at least 10 million out of 900 million of the population are suffering heart failure. There are also similar amount of individuals with myocardial dysfunction, but without symptoms of heart failure [Remme and Swedberg 2001]. The prognosis of heart failure is generally poor. Nearly half of the patients diagnosed with heart failure will die within 4 years and no more than half of those with severe heart failure will survive for more than 1 year [Remme and Swedberg 2001].

2.3.1 The descriptive terms of heart failure

Acute heart failure and chronic heart failure

Acute heart failure (AHF) is defined as rapid onset of symptoms and signs secondary to abnormal cardiac function [Nieminen et al. 2005]. AHF is often used to state acute cardiogenic dyspnoea with signs of pulmonary congestion including pulmonary oedema [Remme and Swedberg 2001]. However, it could also be applied to oliguria and a cool periphery, which needs to be distinguished from pulmonary oedema, and cardiogenic shock [Nieminen et al. 2005]. AHF may occur with or without previous history of cardiac disease and is often life threatening and requires urgent treatment. Comparing to AHF, the definition of chronic heart failure (CHF) varies due to the complexity of this disease. However, selective features could be extracted.

One common but not completely satisfactory definition is: CHF is a pathophysiological state in which an abnormality of cardiac function is responsible for the failure of the heart to pump blood at a rate commensurate with the requirements of the metabolizing tissues [Remme and Swedberg 2001]. Unlike AHF, the diagnose of CHF relies on judgements of patients' history, physical tests and appropriate investigations [Remme and Swedberg 2001]

Systolic and diastolic heart failure
Most heart failure is triggered by ischemic heart disease with an evidence of left ventricular systolic dysfunction [Remme and Swedberg 2001]. The maladaptive changes that occur in myocytes and myocardial injury lead to pathologic remodeling of the left ventricle with dilatation and impaired contractility. If left untreated, these changes grow worse over time and finally lead to left ventricular systolic dysfunction. Much of the effective treatment of heart failure focuses on he interruption of left ventricular remodeling and the systemic responses to it [McMurray 2010]. Diastolic heart failure is usually present when symptoms of heart failure occur in the presence of a preserved left ventricular systolic function at rest (with normal ejection fraction or normal end-diastolic volume). Diastolic heart failure is uncommon in younger patients, but the chance increases in elder patients with cardiac dysfunction. Most patients with systolic dysfunction also have impaired diastolic function [Remme and Swedberg 2001].

Other descriptive terms in heart failure
There are also other terms which could be used in diverse situations, e.g., right and left heart failure, which refer to syndromes with congestion of the systemic or pulmonary veins. Moreover, mild, moderate and severe heart failure is also used as a clinical symptomatic description [Remme and Swedberg 2001].

2.3.2 Diagnosis of heart failure

Symptoms and signs of heart failure play an essential role in diagnosing heart failure. Breathlessness, ankle swelling and fatigue are common symptoms of heart failure, however, they might be difficult to explicate among elderly patients, patients with obesity and women [Remme and Swedberg 2001]. Although there is no standard questionnaire for the diagnosis of heart failure, some clinical or epidemiological studies have developed several scoring systems but need proper validation and cannot be used for clinical practice at the moment [Remme and Swedberg 2001, Marantz et al. 1988]. Table 2.3 is an example of a scoring system for heart failure by a study group in Boston [Marantz et al. 1988].

Criterion	Point value
Category I: History	
Rest dyspnea	4
Orthopnea	4
Paroxysmal nocturnal dyspnea	Phase 2
Dyspneaon walkingon	level 2
Dyspneaon climbing	l
Category II: Physical examination	
Heart rate abnormality (if 91- 110 beats/min, 1 point; if > 110 beats/min, 2 points)	1-2
Jugular-venous pressure elevation (if > 6cm H20, 2points; if > 6cm H20 plus hepatomegaly or edema, 3 points)	2-3
Lung crackles (if basilar, 1point; if more than basilar, 2points)	1-2
Wheezing	3
Third heart sound	3
Category I: Chest radiography	
Alveolar pulmonary edema	4
Interstitial pulmonary edema	3
Bilateral pleural effusions	3
Cardiothoracic ratio >0.50 (posteroanterior projection)	3
Upper zone flow redistributio	2

Table 2.3. Boston criteria for congestive heart failure [Marantz et al. 1988].

The characteristic signs of congestion of systemic veins, which can be commonly observed in heart failure, are peripheral oedema, a raised venous pressure and hepatomegaly [Butman et al. 1993, Remme and Swedberg 2001]. However, these cannot be applied as clinical signs of heart failure. Clinical signs of heart failure also acquire clinical examination including observation, palpating and auscultating the patients [Remme and Swedberg 2001]. A clinical diagnosis of heart failure may be convictive when multiple signs of heart failure and appropriate symptoms occur [Remme and Swedberg 2001].

The relationship between symptoms and the severity of cardiac dysfunction is usually poor, unlike other diseases [Marantz et al. 1988, Remme and Swedberg 2001]. But if a patient is diagnosed with heart failure, the symptoms may be used to classify the severity of heart failure and monitor the effects of treatment [Remme and Swedberg 2001]. A widely used classification of the severity of heart failure was established by the New York Heart Association (NYHA), which is shown in Table 2.4.

Class I.	No limitation: ordinary physical exercise does not cause undue fatigue, dyspnoea or palpitations.
Class II.	Slight limitation of physical activity: comfortable at rest but ordinary activity results in fatigue, palpitations or dyspnoea.
Class III.	Marked limitation of physical activity: comfortable at rest but less than ordinary activity results in symptoms.
Class IV.	Unable to carry out any physical activity without discomfort: symptoms of heart failure are present even at rest with increased discomfort with any physical activity.

Table 2.4. New York Heart Association Classification of Heart Failure [Remme and Swedberg 2001].

2.3.3 Possible methods for the diagnosis of heart failure in clinical practice

This section only provide a general view of available methods for diagnosing heart failure. Some of them will be discussed in details later in this report.

Electrocardiagram(ECG)
ECG changes can usually be observed in heart failure patients. It is crucial at detecting atrial fibrillation or flutter and ventricular arrhythmia as causative or contributing factors to heart failure based on ECG [Remme and Swedberg 2001]. However, more than 90% of ECG give negative predictive value of left ventricular systolic dysfunction, and it is suggested that left ventricular systolic dysfunction should be reconsidered in patient with a normal ECG[Gillespie et al. 1997, Remme and Swedberg 2001]. If the clinical symptoms and signs of heart failure co-exist, the accuracy of diagnosis based on an abnormal ECG largely increases [Remme and Swedberg 2001].

The chest X-ray
Chest X-ray should be part of the initial diagnosis in heart failure, suggested by European Society of Cardiology [Remme and Swedberg 2001]. Chest X-ray is effective for detecting the existence of pulmonary congestion and cardiac enlargement. An increased cardiac size, judged by a cardiothoracic ratio > 0.5, along with the existence of pulmonary congestion are useful factors to indicate abnormal cardiac function with decreased ejection fraction and/or elevated left ventricular filling pressure in patients with heart failure [Badgett et al. 1996]. Also interstitial and alveolar pulmonary oedema, which can be observed in chest X-ray, are reliable and crucial signs of severe left ventricular dysfunction. However, the radiographic findings alone cannot apply reliable estimations of pulmonary capillary pressure in individual patient. Therefore, chest X-ray cannot be used as the only basis for therapeutic decisions [KOSTUK et al. 1973, Remme and Swedberg 2001].

Echocardiography
Echocardiography is the preferred method to diagnose heart failure, suggested by European Society of Cardiology, due to the necessity of objective evidence on cardiac dysfunction at rest [Remme and Swedberg 2001]. Echocardiography allows the assessment of chamber

dimensions, wall thicknesses and geometry, indices of regional, global, systolic and diastolic ventricular function, and it is rapid and safe to apply. The evaluation of ventricular ejection can also be acquired by echocardiography, especially for mitral, tricuspid and aortic stenosis and regurgitation and grading of mitral regurgitation [Remme and Swedberg 2001].

There are also other tests that could be considered, such as stress echocardiography, nuclear cardiology, and cardiac magnetic resonance imaging. Pulmonary function should also be measured, due to the strong association between chronic obstructive airways disease and ischemic heart disease, one of the principal causes of heart failure [COOK and Shaper 1988, Sin et al. 2005, Remme and Swedberg 2001]. Moreover, exercise testing has been used for prognostic purposes and the result is an important component of the risk profile in chronic heart failure [Guyatt et al. 1985, Remme and Swedberg 2001].

2.4 Systolic heart failure

In the most basic terms, systolic heart failure is defined as the inability of the heart to supply the body tissues with enough blood to meet the metabolic demands [Teeters and Alexis 2009]. Coronary artery disease is the cause of about two thirds of cases of systolic heart failure, while hypertension and diabetes are also the causes in many cases [McMurray 2010].

2.4.1 Etiology and Pathophysiology

Systolic heart failure is mechanically due to decreased myocardial contractility leading to increased end-diastolic volumes and pressures, which adds more stress to the myocardial wall resulting in unconventional remodeling [Teeters and Alexis 2009, McMurray 2010]. Generally speaking, there are two etiologies for systolic dysfunction: ischemic cardiomyopathy and non-ischemic cardiomyopathy. Ischemic cardiomyopathy is commonly due to coronary artery disease with or without myocardial damage leading to reduced cardiac function. And non-ischemic cardiomyopathy has many more possible etiologies (shown in Table 2.5). To be noticed, the pathophysiology of systolic dysfunction may differ from the two kinds of etiology, however, the treatment is generally the same and both ischemic and non-ischemic cardiomyopathy are associated with significant morbidity and mortality [Teeters and Alexis 2009].

Ischemic	Non-Ischemic
Atherosclerosis	Viral
Diabetes	Tachycardia mediated
Vasospasm	Hypertensive
Arterial inflammation	Valvular
	Congenital
	Severe anemia
	Hyperthyroidism
	Hypothyroidism
	Post-partum
	Idiopathic
	Drug-induced

Table 2.5. Heart failure etiologies [Teeters and Alexis 2009].

The adaptive changes or injuries occurring in myocytes and the extracellular lead to pathologic remodeling of the left ventricle with dilatation and impaired contractility. These changes includes the size, shape and function of left ventricle and can lead to electrical instability, systemic processes resulting in many effects on other organs and tissues and further damages to the heart (e.g. pump failure and ventricular arrhythmia) (Figure 2.15). Therefore, interruption of left ventricular remodeling and the systemic responses to it is the basis of a lot of effective treatment to heart failure [McMurray 2010].

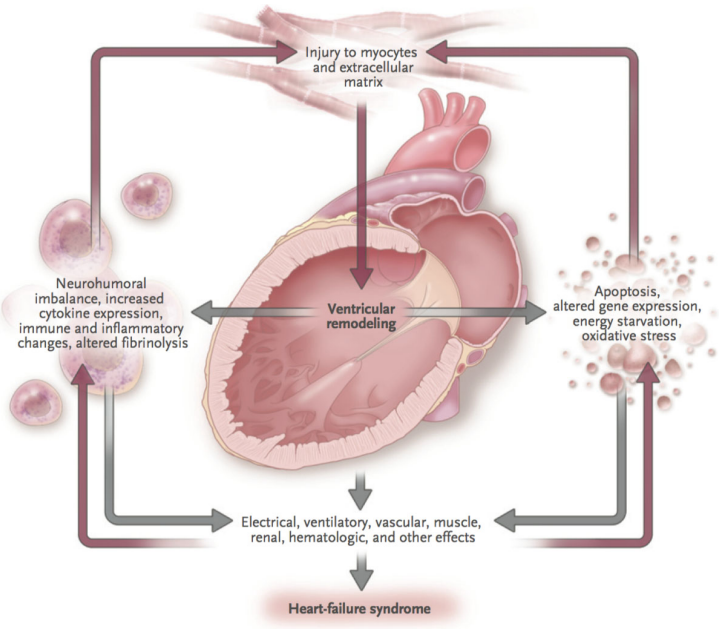

Figure 2.15. Damage and maladaptive changes to the myocytes and to the extracellular matrix leads to changes in the size, shape, and function of the left ventricle and the heart more generally. These changes, in turn, may lead to electrical stability, systemic processes resulting in many effects on other organs and tissues, and further damage to the heart. This cycle, along with intercurrent events, such as myocardial infarction, is believed to cause progressive worsening of the heart-failure syndrome over time [McMurray 2010].

2.4.2 Devices for treatment of systolic heart failure

Implantable Cardioverter-Defibrillators
Approximately half the deaths that happen to patients with systolic heart failure are due to ventricular arrhythmias, especially among patients with mild symptoms. For patients with severe heart failure, the cause of death is more likely to be pump failure [McMurray 2010]. The implantable cardioverter-defibrillators can reduce the risk of sudden death for patients with left ventricular systolic dysfunction, but the benefit will not be evident until one year or more after implantation [Bardy et al. 2005, McMurray 2010].

Cardiac-Resynchronization Therapy
In up to one third of severe systolic heart failure patients, intraventricular conduction delay can be observed. Intraventricular conduction delay is usually associated with dyssynchronous contraction of the left ventricle, leading to impaired emptying and mitral regurgitation [Bristow et al. 2004, Cleland et al. 2005, McMurray 2010]. Cardiac-resynchronization therapy (CRT) with atrial-synchronized biventricular pacing usually can improve the cardiac performance immediately by rising the stroke volume and reducing mitral regurgitation [Dickstein et al. 2008, McMurray 2010]. The therapy is to implant two electrodes on both left and right ventricle and trigger the contraction of both ventricles in proper time. One electrodes is usually via the vena cava and the right atrium into the right ventricle to stimulate the septum [McMurray 2010]. The electrode may or may not penetrate the myocardium, depends on the fixation of the electrode [McVenes and Stokes 2009]. The placement of the electrode for the left ventricle is transvenous. More specific, it goes via the coronary sinus and into a peripheral cardiac vein, and finally reaches the lateral wall of left ventricle [McVenes and Stokes 2009]. However, based on some anatomical studies, about 10% of the population has no suitable vein for LV pacing vis coronary sinus [Von Lüdinghausen 1987, McVenes and Stokes 2009].

2.5 Electrical and Mechanical systole

Electrical systole is always measured by QT interval on an ECG signal while Mechanical systole is usually presented by QS_2 from a combination of ECG and phonocardiogram (PCG) signal. For normal individuals, the QT is slightly shorter and parallels QS_2 [Boudoulas et al. 1981a] (Figure 2.16). Moreover, both QT and QS_2 have a negative linear relationship to heart rate even for patients without symptoms of heart failure [Boudoulas et al. 1981a].

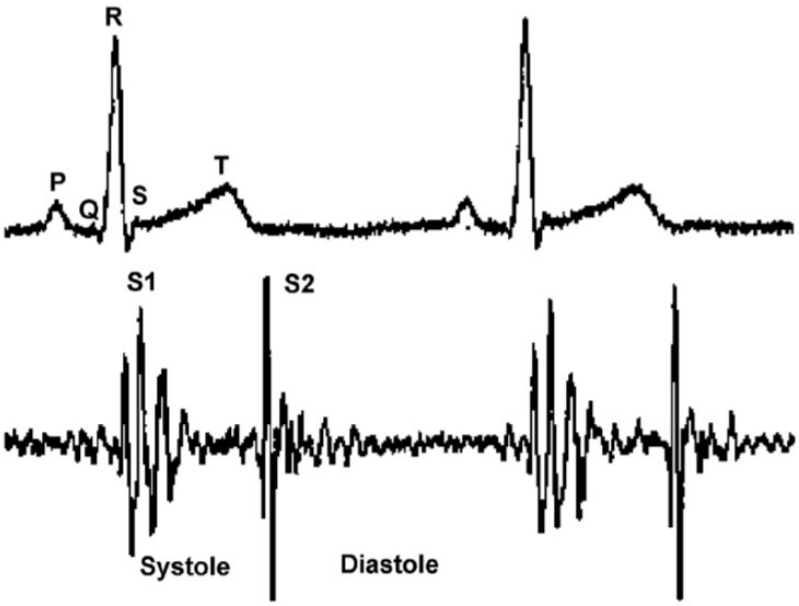

Figure 2.16. The relationship between the ECG signal and the PCG signal. The QT is slightly shorter than the QS_2 [Debbal and Bereksi-Reguig 2008].

However, an abnormal relationship of QT and QS_2 may occur. In coronary artery disease, the QT interval can be observed larger than QS_2. The possible reason is the dyssynchrony of the action potential within the ventricular myocardium that leads to QT prolongation [Boudoulas et al. 1982; 1985b]. Similar to coronary artery disease, patients with long QT syndrome also have QT > QS_2 [Vincent et al. 1991].

QT > QS_2 can also be caused by adrenergic stimulation. The adrenergic stimulation can cause the shortening of mechanical systole and therefore the abbreviation of QS_2 [Boudoulas et al. 1981b, De Caprio et al. 1984]. However, adrenergic stimulation does not produce a shortened QT interval but may prolong the QT [Boudoulas et al. 1981b]. Some diseases, such as acute myocardial infarction, can cause the excessive adrenergic activity [LEwis et al. 1972]. In this case, the QT > QS_2 is more likely because of the abbreviation of QS_2. The existence of QT > QS_2 is suggested as risk indicator of sudden death and need to be treated carefully [Boudoulas et al. 1985b].

CHAPTER

3 Problem Statement

Nowadays, the diagnosis of systolic heart failure must be evaluated by the combination of patient's history, examination findings and the appearance of clinical symptoms (e.g., dyspnea and fatigue) and signs (e.g., peripheral edema) [McMurray 2010, Teeters and Alexis 2009]. However, the onset of these symptoms could occur slowly and lead to the unawareness of some of the symptoms and signs [McMurray 2010]. Moreover, there are no imaging modalities or serum studies required to make the diagnosis, especially in mild disease [Teeters and Alexis 2009].

Some routine cardiac investigations (e.g., electrocardiography) are also insensitive for diagnosing systolic heart failure [Remme and Swedberg 2001]. The ECG is an essential method to detect atrial fibrillation or flutter and sometimes ventricular arrhythmia as the causative factor of heart failure [Iaizzo 2009]. Nonetheless, the ECG has a low predictive value on left ventricular hypertrophy that may be associated with systolic dysfunction [McMurray 2010]. And the European Society of Cardiology also suggested that even though a normal ECG has been observed, the diagnosis of chronic heart failure should still be carefully reviewed [Remme and Swedberg 2001].

The electrical systole is measured from in ECG signals. And the mechanical systole can be observed from a PCG signal combined with ECG. Under normal conditions, the duration of electrical systole (usually represented by QT interval) is slightly shorter than the duration of the mechanical systole (always represented by QS_2 interval) throughout the resting heart rate [Boudoulas et al. 1981b;a]. Both of QT and QS_2 interval shows a negative linear relationship to the heart rate and the QT parallels the QS_2 interval [Boudoulas et al. 1981a].

However, $QT > QS_2$ can be observed in coronary artery disease and long QT syndrome [Boudoulas et al. 1982, Vincent et al. 1991]. The presence of $QT > QS_2$ is a significant risk factor in patients who have myocardial infarction and it has been documented that the use of QS_2 as a normative reference provides a more sensitive prognostic index than QT interval [Boudoulas et al. 1982]. Moreover, any activities that enhance the adrenergic stimulation can also lead to a relative prolongation of QT in relation to QS_2 [Boudoulas et al. 1981b].

Based on the previous work done by Harisios Boudoulas and his colleagues, this phenomenon was described as the QT > QS_2 syndrome [Boudoulas et al. 1982; 1985b]. Nonetheless, they mainly introduced this syndrome with patients who have ventricular arrhythmia and coronary artery disease [Boudoulas et al. 1982]. Hence, the prolonged QT was mainly focused due to the fact that long QT is associated with rhythm disturbances and sudden death [Boudoulas et al.

1981b]. But for patients with systolic heart failure, the long QT interval may not be observed and the main focus is the QS_2 [Remme and Swedberg 2001].

Due to the systolic dysfunction leaded by pathologic remodel of the left ventricle in patients with systolic heart failure, the closure of aortic valves in left ventricle could be brought forward. Therefore, the duration of QS_2 could be shortened and the phenomenon of $QT > QS_2$ might be observed.

Therefore, the aim of this project is to find out,

whether the relation between QT and QS_2 can be used as a criterion for the diagnosis of heart failure with systolic dysfunction.

CHAPTER

4 Problem Solution

4.1 Data collection

10 subjects with heart failure participated during the collection of ECG and PCG data and each of them had been implanted a biventricular pacer. Among them were two female subjects and eight male subjects with the age ranging from 37 to 76. The basic information of these subjects were listed in Table 4.1. The pulse of each subjects were measured under rest condition with pacers on.

Subject	Gender (M/F)	Pulse(/min)
1	M	69
2	M	65
3	M	72
4	M	58
5	M	37
6	M	75
7	M	67
8	M	76
9	F	64
10	F	72

Table 4.1. Basic information of the subjects with heart failure. All the subjects were asked to keep in the rest situation during data collection.

The ECG signal was recorded by a 12 channel digital lang-term ECG recording device. Meanwhile the PCG signal was detected and recorded by microphone equipped acoustic device that provided by acarix ® for special academic uses. The sampling frequency was $5000HZ$. The devices were connected to a I-worx ® system (type IWX/228), which was set up to a computer to save the recorded data. Figure 4.1 shows the frame work of data collection.

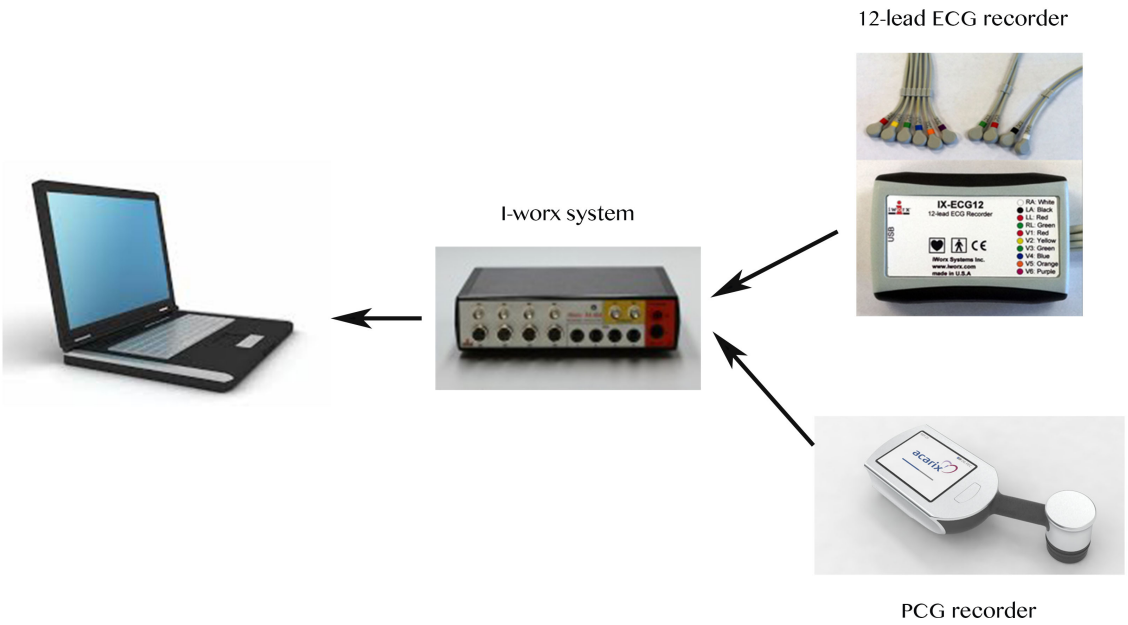

Figure 4.1. This figure shows the frame work of data collection. The ECG and PCG recorder detected and collected the signals and then transport the data via the I-worx ® system to a computer to save the data.

For the first 7 subjects, 8 leads of ECG signals were collected (I, II, and V_1 to V_6). And for the rest of the subjects, only 2 leads of ECG (I, II) were applied during data collection. But the PCG signals of all the subjects were recorded by the microphone equipped device. All the subjects were required to recording their ECG and PCG under four different situations:

- with both pacers on;
- only with left ventricular pacer on;
- only with right ventricular pacer on;
- with both pacers off.

However, some of the patients had severe heart failure and it would threaten their lives when turned both pacers off. Therefore, these subjects were only asked to turn down the stimulation of the pacers to simulate the both pacers off condition.

Besides the subjects with heart failure, two healthy subjects were also asked to record the ECG and PCG signal as a comparison group using the same data collection system. However, only 2 leads of ECG sensor were applied.

4.2 Data processing

In order to compare the duration of QT interval and QS_2 interval, the parameters below are required:

- the start point of QRS complex;
- the end of T-wave;
- the start of S_2.

To extract these parameters, one mean ECG and PCG of one cardiac cycle has be calculated from all the data of each subject. The details of the processing method will be introduced below.

To get rid of the high frequency noise produced by muscle activity during data collection, a Butterworth low pass filter was applied to the ECG signal. The cut-off frequency was set at $200HZ$, but can vary in order to obtain the closest ECG signal to the original one. It is important to announce that the high frequency noise is not the only kinds of noise that could appear on ECG signal. However, the other kinds of noise (e.g. base line wander) has slight influence on extracting the necessary parameters. Likely, a Butterworth bandpass filter was used to remove the noise in PCG signal with a passband from $30HZ$ to $175HZ$. Figure 4.2 shows the results after apply the filters on both ECG and PCG signal over time (/s).

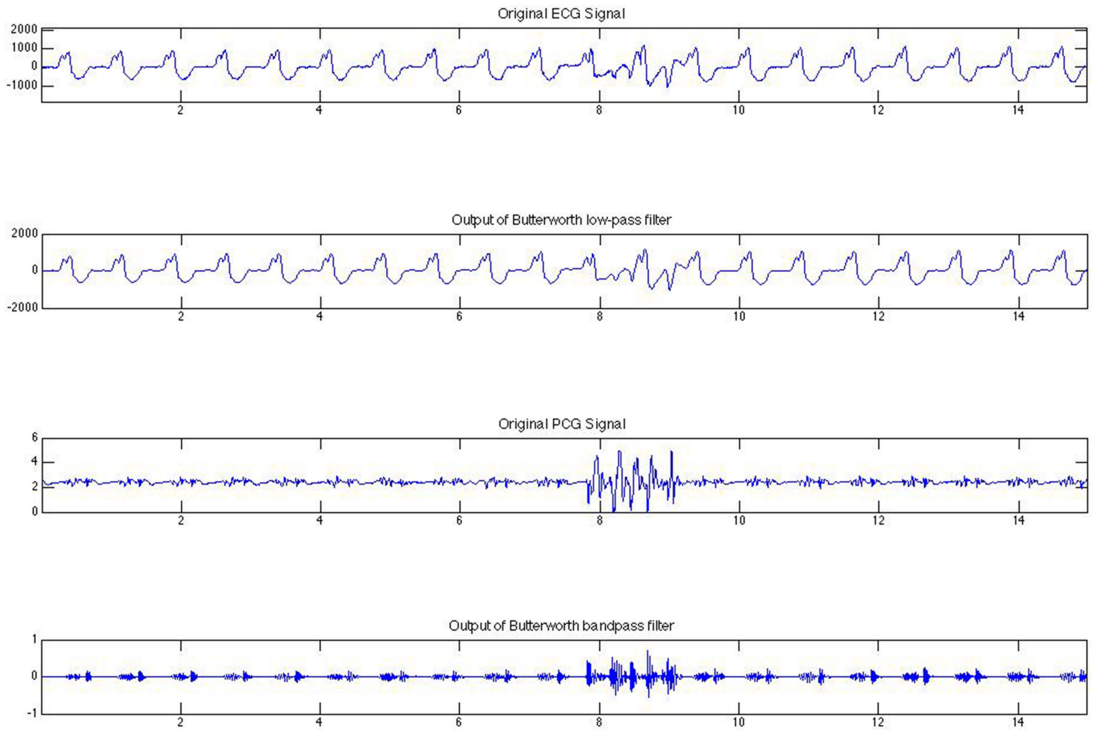

Figure 4.2. This figure shows one segment of ECG and PCG signal before and after applying the filter over time (/s).

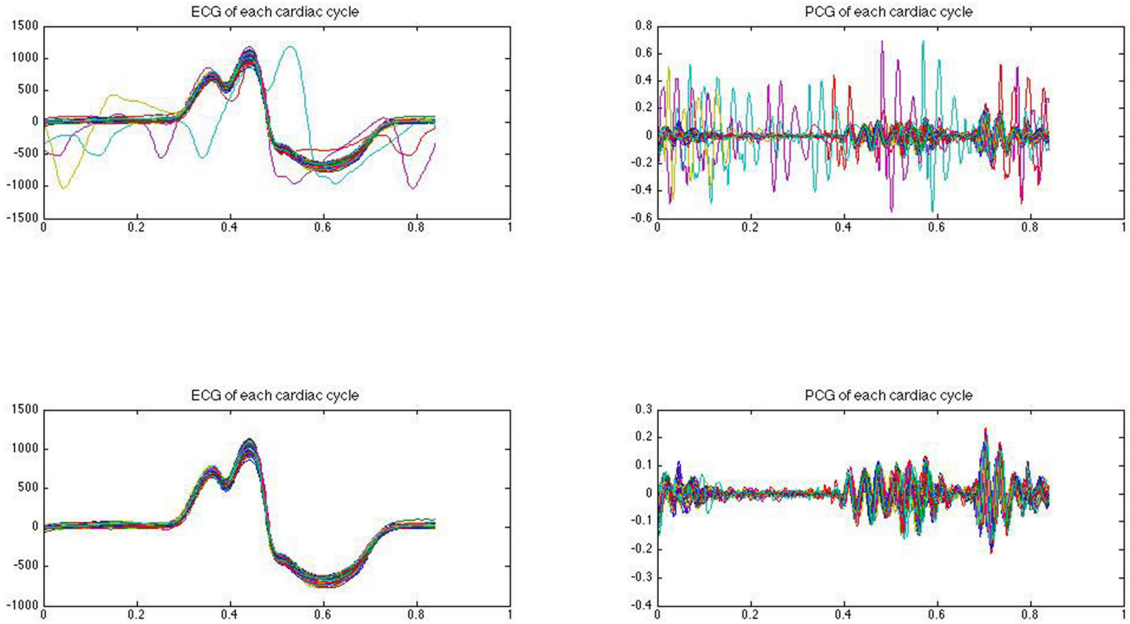

Figure 4.3. The two figures above are all the ECG and PCG cycls while the two figures below are the result after removing the noise contaminated cycles. The x-axis is time (/s).

Due to the fact that some cardiac cycles obtained during data collection have been contaminated with noise, it is easier to obtain the mean ECG and PCG signal of one cycle and remove those noise contaminated cycles. By doing this, the peak of R-wave in ECG signal of each cycle was found (could be positive or negative). Secondly, search forward and backward from the peak of R-wave to obtain an entire cardiac cycle. This is also done to the PCG signal with the same duration of time. After that, an average cardiac cycle was calculated (including the destroyed cardiac cycles). The correlation coefficient of each cardiac cycle in the ECG and the average cardiac cycle was calculated in order to remove the noise contaminated cardiac cycles. If the coefficient is less than 0.95 then this cycle was considered as cardiac cycle contaminated with noise and removed from the signals (Figure 4.3).

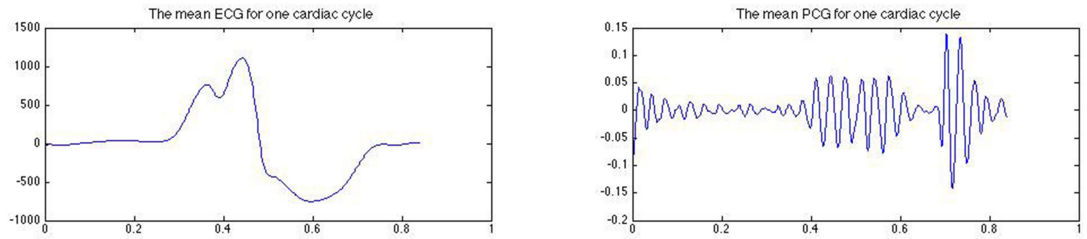

Figure 4.4. This figure shows the mean ECG and PCG signal of one cardiac cycle after removing the noise contaminated cycles over time (/s).

The mean ECG and PCG of one cardiac cycle were acquired after removing the useless cycles (Figure 4.4). The next step was to extract the useful parameters mentioned in the beginning of this section. To locate the start of QRS complex and the end of T-wave, the peak of Q-wave and T-wave were first found. Then two assistant lines were created from the start of the ECG signal to the first peak of QRS complex and from the end of the signal to the peak of T-wave (Figure 4.5). The vertical distance between the lines and the ECG signal was calculated ($H1$ and $H2$ in Figure 4.5) and the point in the the ECG signal that has the maximum distance in each part is the location of start of QRS complex and the end of T-wave.

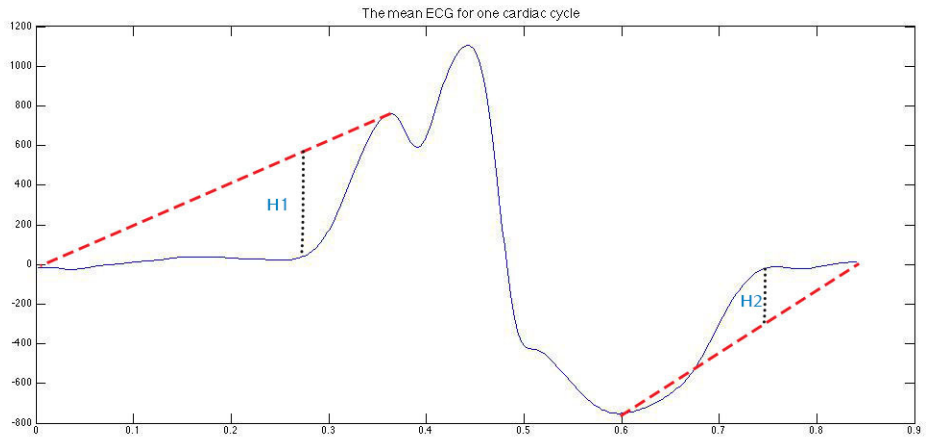

Figure 4.5. The two dotted red lines are the assistant lines drawn from the biginning of the signal to Peak of Q-wave and from the peak of T-wave til the end of the signal. The two dotted black lines $H1$ and $H2$ are the vertical distance between the signal to the assistant lines. The maximum distancec were found in order to locate the start of QRS-wave and the T-wave.

Since the left ventricle has systolic dysfunction in subjects with systolic heart failure, the dyssynchronous contraction of the left ventricle could happen. This leads to a relatively longer delay of the closure of the mitral valve. Therefore, the prolonged duration of S_1 sound could be observed and the time interval between the S_1 and S_2 was shortened. This increased the difficulty of finding the start of S_2. Hence, an envelope was make on the PCG signal. An envelope based on Hilbert transform was built by following the formula:

$$X = Xr + i * Xi \tag{4.1}$$

Xr is the original PCG signal and Xi stands for the Hilbert transform of Xr. X is the envelope and i is time. After applying the envelope, the first peak of the S_2 on the envelope was located and then the algorithm searched backwards on the envelope until the first point below the threshold was found. The threshold was set at 3% of the peak of S_2 sound. This point was considered as the start point of the S_2. Finally the parameters were all extracted (shown in Figure 4.6). Based on the parameters, the QT interval and the QS_2 interval were calculated.

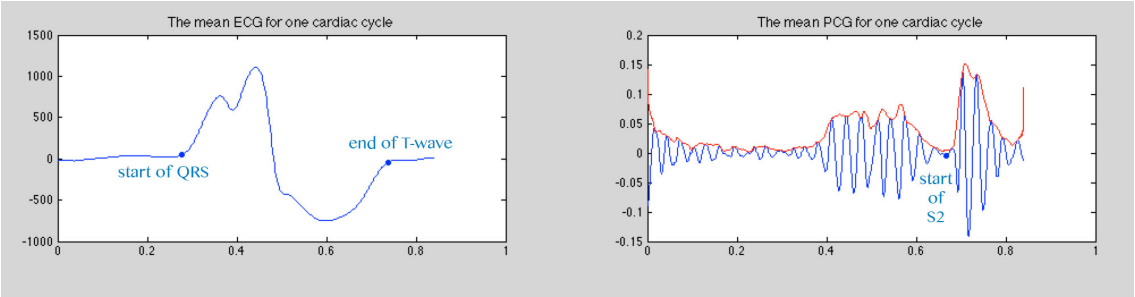

Figure 4.6. This figure shows the extracted parameters in both the ECG and PCG signal. The parameters needed were the start of QRS, the end of T-wave and the start of S_2. Based on that, the QT interval and the QS_2 interval were calculated.

Since the heart rate was only measured when the pacers were on for all the subjects, heart rate under the other conditions was calculated by measuring the RR interval in the ECG signals. The RR interval was extracted from the peaks of QRS complex after removing the noise contaminated signals. And the heart rate was calculated by this formula:

$$HR = 60/RR;$$

HR stands for heart rate (beats/min).

CHAPTER

5 Results

5.1 Data results

The analysis of data was done by the procedures introduced in section 4.2. The averages of ECG and PCG signal of one cardiac cycle were calculated and the QT interval and QS_2 interval were extracted. Table 5.1 on page 38 shows the QT and QS_2 intervals of all the subjects under the four conditions: with *both pacers on, left ventricular pacer on, right ventricular pacer on,* and *both pacers off.* To discuss the results in different aspects, these data will be arranged in several formats.

Time Difference between QT and QS_2

Table 5.2 shows the time difference between QT interval and QS_2 interval. The difference was calculated as $QT - QS_2$. For both of the healthy subjects, QT was shorter than QS_2. In subject 2, 7 and 8, the time difference could be observed to be positive under both conditions when one pacer was on.

Subject	Both Pacers On (ms)	LV Pacer On (ms)	RV Pacer On (ms)	Both Pacers Off (ms)
1	+2.6	+13.8	−10.2	+13.2
2	−1.4	+6.4	+2.0	+13.0*
3	−35.4	−6.4	-5.8	−25.6
4	−34.2	0.0	-32.4	−1.2
5	−11.8	−7.0	-1.8	−7.0
6	−65.6	+45.2	-72.8	−8.6
7	−4.2	+32.6	+31.8	+50.2
8	−4.4	+10.0	+13.6	−20.0 *
9	+9.2	−21.0	+102.6	−22.0
10	−34.4	−4.8	-2.6	−38.6
Healthy Sub 1	-	-	-	-18.0^{+}
Healthy Sub 2	-	-	-	-46.0^{+}

Table 5.2. This table shows the difference of QT and QS_2 of all the subjects. * means the pacers were not completely turned off due to the severity of heart failure in these subjects. $^{+}$ means data were measured from healthy subjects and no pacers were implanted.

Moreover, another 4 subjects (1, 4, 6 and 9) had the time difference positive under one of the two situations when the left or right ventricular pacer was on. When both of the pacers were

on, only subject 1 and 9 could be observed with QT > QS_2. Besides, subject 1, 2 and 7 had QT > QS_2 when both pacers were off.

QTc and QS_2 Index

To determine whether the QT was normal, one easy way is to calculate the QTc, which is by correcting the QT interval with heart rate. Followed by Bazzett equation:

$$QTc = QT * \sqrt{(RR)}$$

the QTc of all the subjects in all the four situations were calculated and shown in Table 5.3 on page 39. The normal QTc averages $390ms$ for male subjects and $415ms$ for female subjects with a range of $\pm 40ms$ [Bazett 1920, Boudoulas et al. 1982]. Therefore, any value of $QTc > 430ms$ in the male or $> 455ms$ in the female was considered abnormal [Boudoulas et al. 1982].

Subject	**Both pacers on**	**LV pacer on**	**RV pacer on**	**Both pacers off**
1	398.1	422.1	408.2	383.3
2	350.6	⋄458.2	366.0	370.1
3	387.1	417.5	416.0	393.9
4	403.0	⋄451.3	421.1	420.7
5	323.9	329.4	312.3	328.8
6	409.9	340.4	413.8	421.5
7	⋄442.0	⋄478.0	⋄451.2	⋄538.3
8	405.5	⋄465.7	⋄449.2	309.8
9	⋄467.8	451.9	⋄491.7	442.2
10	377.1	434.2	423.8	417.0

Table 5.3. The QTc (ms) of all the subjects. ⋄ stands for abnormal QTc values.

Introduced by Weissler, the QS_2 index (QS_2I) is one parameter to measure the systolic time interval in normal individuals associating with heart rate (HR) [Weissler et al. 1968]. The formula of QS_2 index is:

$$QS_2 = -2.1 * HR + QS_2I;$$

The normal QS_2 Index is 546ms in male and 549ms in female. Therefore, the normal QS_2 interval (QS_2n) was calculated as comparison.

Table 5.4 shows the QS_2n calculated from normal QS_2I in comparison with the QS_2 interval from the subjects. It is necessary to point out that the QS_2n was not calculated from the data of the subjects, but a prediction of normal individuals with the same heart rate. The difference was calculated as $QS_2 - QS_2n$ (ms). Six of all the subjects performed prolonged QS_2 interval in all the situations. However, subject 5 had shortened QS_2 interval when only RV pacer was on. Meanwhile, subject 8 showed shortened QS_2 interval when both pacers were off.

The Tendence of QT and QS_2 In Different Situations

The tendence of QT and QS_2 for all the patient subjects is shown in Figure 5.1. Half of the subjects (5,6,7,8 and 10) had the same tendence of QT and QS_2 under the four conditions. Among them, only subject 6 showed that QT and QS_2 were larger when only the pacer on right ventricle was on comparing with the situation when only the left ventricular pacer was on. Moreover, it is important to point out that the QT was always less than the QS_2 in subject 3,

4, 5 and 10. In the opposite, larger QS_2 could be observed from subject 2 and 7 under three conditions (except the condition with both pacers on).

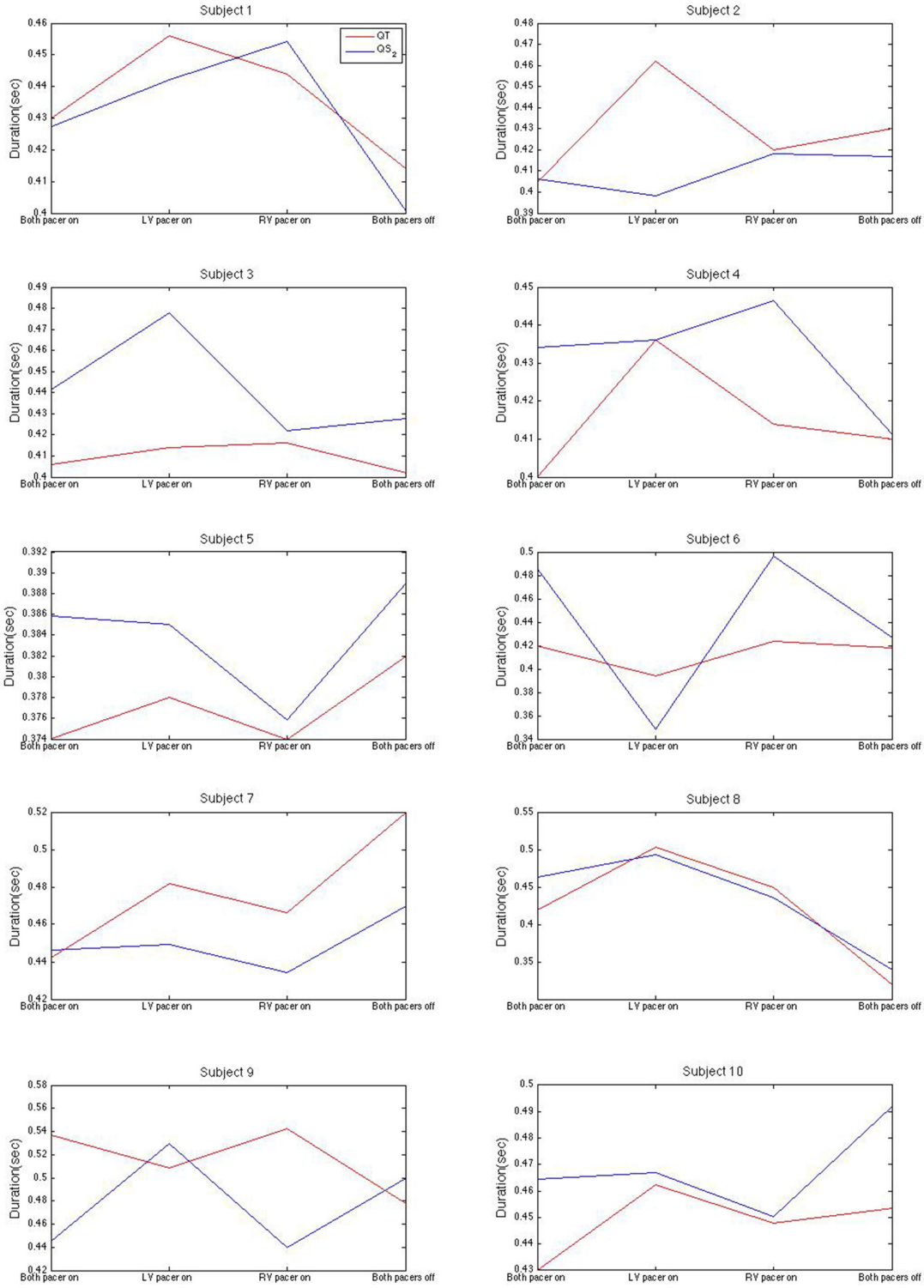

Figure 5.1. This figure shows the tendence of QT and QS_2 interval for 4 situations of all the patients subjects.

5.2 Statistical Analysis

5.2.1 Repeated measured ANOVA test

After obtaining the results of QT interval, QS_2 interval and the difference between them, whether the means of each value in four situations are statistical different should also be determined. The data were measured from all the patient subjects under four conditions: *both pacers on*, *left ventricular pacer on*, *right ventricular pacer on*, and *both pacers off*. Hence, the repeated measures ANOVA was chosen. The ANOVA test determines the differences between the means of three or more groups, and the null hypothesis is:

$$H_0 : \mu_1 = \mu_2 = \mu_3 = \mu_4; \tag{5.1}$$

This means all the means (μ) in the four sample groups are equal and there is not significant difference between the groups. Besides, an alternative hypothesis should also be established to describe an opposite situation. Therefore, the alternative hypothesis is:

H_A = *at least two means are significantly different.*

To accept or reject the null hypothesis, an F-statistic needs to be calculated by the following formula:

$$F_{\alpha(1),(n-k),(n-1)(k-1)} = \frac{MS_{groups}}{MS_{error}}, p = p-value; \tag{5.2}$$

The MS_{groups} stands for the mean square of the groups variability while MS_{error} refers to the mean square of error variability. $\alpha(1)$ is the confidence interval (95% was considered here), moreover, $(n-k)$, $(n-1)(k-1)$ are the degree of freedom of groups variability and error variability. n stands for the number of subjects and k means the number of groups.

First, the QT interval was focused and the F-statistic values:

$$F_{0.05(1),(3),(27)} = 1.75, p = 0.18; \tag{5.3}$$

By searching the Table of Critical Values of the F Distribution, $F_{0.05(1),(3),(27)} = 2.96$. And the p value is also larger than 0.05. Therefore, it is failed to reject the null hypothesis and there is no significant differences of QT interval between all the groups.

The F-statistic of QS_2 interval is shown below:

$$F_{0.05(1),(3),(27)} = 0.32, p = 0.81; \tag{5.4}$$

Therefore, the null hypothesis cannot be rejected. This means there is no significant differences of QS_2 interval between all the groups.

Al last, the F-statistic of the difference between QT and QS_2 is:

$$F_{0.05(1),(3),(27)} = 0.68, p = 0.57; \tag{5.5}$$

Hence, it is failed to reject the null hypothesis and there is no significant differences of the difference between QT and QS_2 in all the groups.

5.2.2 T test of the correlation between QT and QS_2

Not only the difference of means in each situation, but also the correlation between QT and QS_2 should be determined. A t-test of the correlation within each group was set and the R^2 correlation coefficient was calculated. The confidence interval was also set as 95%, and the formula of this t-test is:

$$t_{\alpha(1),(n-2)} = r * \sqrt{\frac{n-2}{1-r^2}} \tag{5.6}$$

n is the number of subjects and r is the correlation coefficient of the samples.

$$r = \frac{1}{n} * \frac{\sum (x_i - \bar{x}) * (y_i - \bar{y})}{SD_x * SD_y} \tag{5.7}$$

$$R^2 = r^2 \tag{5.8}$$

SD stands for the standard deviation of one group and $\bar{x}$, $\bar{y}$ are the means of group x and y.

The t-test was run for all the patient subject under the for conditions. To run the t-test, the null hypothesis was brought up as:

$$H_0 : \rho = 0 \tag{5.9}$$

This means there is no significant correlation between the two groups of samples (ρ is the population correlation coefficient). Hence, the alternative hypothesis, which stands for a significant relationship between the samples in the two groups, was:

$$H_1 : \rho \neq 0 \tag{5.10}$$

Table 5.5 shows the mean and SD of QT interval and QS_2 interval when both the pacers were on. Based on these information, r was calculated as: $r = 0.346$, therefore, $t_{0.05(1),8} = 1.046$ and $R^2 = 0.120$. However, the critical value of $t_{0.05(1),8}$ is 1.860. Hence, the null hypothesis cannot be rejected and there is no significant relationship between QT and QS_2 under this condition.

Both Pacers On		
.:	**QT**	**QS_2**
Mean	426.240	439.880
SD	43.309	28.926
n	10	10

Table 5.5. The mean and SD in the situation where both the pacers were on.

Table 5.6 shows the mean and SD of QT interval and QS_2 interval when the left ventricular pacer was on. Based on these information, r was calculated as: $r = 0.748$, therefore, $t_{0.05(1),8} = 3.188$ and $R^2 = 0.560$. However, the critical value of $t_{0.05(1),8}$ is 1.860. Hence, the null hypothesis is rejected and there is a significant relationship between QT and QS_2 when only the left ventricular pacer was on.

LV Pacer On		
.:	**QT**	**QS_2**
Mean	449.580	442.700
SD	43.977	53.906
n	10	10

Table 5.6. The mean and SD in the situation where only the left ventricular pacer was on.

Table 5.7 shows the mean and SD of QT interval and QS_2 interval when the right ventricular pacer was on. Based on these information, r was calculated as: $r = 0.324$, therefore, $t_{0.05(1),8} = 0.9687$ and $R^2 = 0.105$. However, the critical value of $t_{0.05(1),8}$ is 1.860. Hence, the null hypothesis cannot be rejected and there is no significant relationship between QT and QS_2 when only the right ventricular pacer was on.

RV Pacer On		
.:	**QT**	**QS_2**
Mean	439.740	437.300
SD	44.205	30.721
n	10	10

Table 5.7. The mean and SD in the situation where only the right ventricular pacer was on.

Table 5.8 shows the mean and SD of QT interval and QS_2 interval when both the pacers were off. Based on these information, r was calculated as: $r = 0.883$, therefore, $t_{0.05(1),8} = 5.321$ and $R^2 = 0.780$. However, the critical value of $t_{0.05(1),8}$ is 1.860. Hence, the null hypothesis is rejected and there is a significant relationship between QT and QS_2 under this condition.

Both Pacers Off		
.:	**QT**	**QS_2**
Mean	422.720	427.380
SD	54.140	48.765
n	10	10

Table 5.8. The mean and SD in the situation where both the pacers were on.

5.2.3 T test of the difference between QS_2 and QS_2n

In this project, it is also important to detect whether the QS_2 interval is prolonged, Therefore, another t test with 95% confidence interval was used to determine the difference between the means of QS_2 interval and QS_2n associated with the same heart rate. The null hypothesis is:

$$H_0 : \mu_{QS_2} = \mu_{QS_2 n}; \tag{5.11}$$

and the alternative hypothesis is:

$$H_0 : \mu_{QS_2} \neq \mu_{QS_2 n}; \tag{5.12}$$

still, μ is the mean value.

Table 5.9 shows the t value and p value of each condition. As the critical value of $t_{0.05(1),18}$ equals 1.734, only the null hypothesis in two cases (when both pacers were on and when the right ventricular pacer was on) is rejected. It means, when both pacers were on and when the right ventricular pacer was on, the means of QS_2 and QS_2n have significant difference.

.:	**Both pacers on**	**LV pacer on**	**RV pacer on**	**Both pacers off**
t	3.6753	0.4685	2.8230	1.2412
p value	0.0017	0.6450	0.0113	0.2305
df	18	18	18	18

Table 5.9. The result of t test on all the four cases. df is the degree of freedom that equals $(N-2)$. N is the number of samples.

Subject	Gender	Both Pacers On(ms)			Left Ventricular Pacer On(ms)			Right Ventricular Pacer On(ms)			Both Pacers Off(ms)		
		Heart rate	QT	QS_2	Heart rate	QT	QS_2	Heart rate	QT	QS_2	Heart rate	QT	QS_2
1	M	70	430.0	427.4	70	456.0	442.2	71	444.0	454.2	70	414.0	400.8
2	M	80	404.8	406.2	61	462.0	398.0	79	420.0	418.0	81	430.0*	417.0*
3	M	66	406.0	441.4	59	414.0	478.0	60	416.0	421.8	63	402.0	427.6
4	M	59	400.0	434.2	56	436.0	436.0	58	414.0	446.4	57	410.0	411.2
5	M	80	374.0	385.8	79	378.0	385.0	86	374.0	375.8	81	382.0	389.0
6	M	63	420.0	485.6	63	394.0	348.8	63	424.0	496.8	59	418.0	426.6
7	M	60	442.0	446.2	61	482.0	449.4	64	466.0	434.2	56	520.0	469.8
8	M	64	418.8	462.8	70	502.0	493.0	60	449.2	435.6	64	320.0*	340.0*
9	F	79	536.8	444.8	76	508.6	529.6	73	542.4	439.8	70	477.6	499.6
10	F	78	430.0	464.4	68	462.2	467.0	67	447.8	450.4	71	453.6	492.2
Mean Value	-	69.0	426.2	439.8	66.3	449.6	442.7	68.1	439.7	427.3	67.1	422.7	427.4
Healthy sub1	M	-	-	-	-	-	-	-	-	-	51	402.0^{+}	420.0^{+}
Healthy sub2	M	-	-	-	-	-	-	-	-	-	60	358.0^{+}	404.0^{+}

Table 5.1. This table shows the results of QT interval, QS_2 interval (ms) and heart rate under different conditions. * means the pacers were not completely turned off due to the severity of heart failure in these subjects. $^{+}$ means data were measured from healthy subjects and no pacers were implanted. M = Male, F = Female, Heart Rate (beat/min)

Subject	Gender	Both Pacers On (ms)			Left Ventricular Pacer On (ms)			Right Ventricular Pacer On (ms)			Both Pacers Off (ms)		
		QS_2	QS_2n	Difference	QS_2	QS_2n	Difference	QS_2	QS_2n	Difference	QS_2	QS_2n	Difference
1	M	427.4	399.0	28.4	442.2	399.0	43.2	454.2	396.9	57.3	400.8	399	1.8
2	M	406.2	378.0	28.2	398.0	417.9	−19.9	418	380.1	37.9	417.0	375.9	41.1*
3	M	441.4	407.4	34.0	478.0	422.1	55.9	421.8	420.0	1.8	427.6	413.7	13.9
4	M	434.2	422.1	12.1	436.0	428.4	7.6	446.4	424.2	22.2	411.2	426.3	−15.1
5	M	385.8	378.0	7.8	385.0	380.1	4.9	375.8	365.4	10.4	389.0	375.9	13.1
6	M	485.6	413.7	71.9	348.8	413.7	−64.9	496.8	413.7	83.1	426.6	422.1	4.5
7	M	446.2	420.0	26.2	449.4	417.9	31.5	434.2	411.6	22.6	469.8	428.4	41.4
8	M	462.8	411.6	51.2	493.0	399.0	94.0	435.6	420	15.6	340.0	411.6	−71.6*
Mean (male)	-	436.2	403.7	28.5	428.8	409.8	19.0	435.4	403.9	31.4	410.3	406.6	3.6
9	F	444.8	391.0	53.8	529.6	397.0	132.6	439.8	403	36.8	499.6	409.0	90.6
10	F	464.4	393.0	71.4	467.0	413.0	54.0	450.4	415.0	35.4	492.2	407.0	85.2
Mean (female)	-	454.6	392.0	62.6	498.3	405.0	93.3	445.1	409.0	36.1	495.9	408.0	87.9

Table 5.4. This table shows the QS_2n based on heart rate and QS_2I in normal individuals in comparison with the QS_2 interval of the subjects. The difference was calculated by QS_2 - QS_2n. * means the pacers were not completely turned off due to the severity of heart failure in these subjects.

CHAPTER

6 Discussion

The QT and QS_2 interval was measured from the ECG and PCG of heart failure patients taking cardiac-resynchronization treatment under four different conditions:

- with both pacers on;
- only with left ventricular pacer on;
- only with right ventricular pacer on;
- with both pacers off.

As observed in normal subjects, the QT was always shorter than QS_2, which has been proved by Boudoulas and his colleagues [Boudoulas et al. 1981a]. Six out of 10 subjects had larger QT interval than QS_2 interval in at least one of the four situations. This indicates that heart failure patients with systolic dysfunction may have relatively shorter mechanic systolic time interval due to the dilatation of left ventricle and impaired contractility [Teeters and Alexis 2009]. It is important to highlight that when there is an abnormal prolonged QTc, the QT has a large opportunity (75%) to be larger than QS_2. Based on previous study, the QT > QS_2 syndrome described in coronary artery disease, which is one common trigger of myocardial ischemia and finally leads to systolic dysfunction, often due to the prolongation of QT interval [Boudoulas et al. 1982, Teeters and Alexis 2009, McMurray 2010]. However, not all the QS_2 intervals were shortened while the QT intervals were prolonged. In fact, 90% of the samples showed a lengthening QS_2. Hence, this might explain that even though some subjects performed a prolonged QT, the QS_2 is still larger.

To discuss the possible reasons of prolonged QS_2, it is important to mention that systolic time interval has two components: pre-ejection period (PEP) and left ventricular ejection time (LVET) [Hassan and Turner 1983, Weissler et al. 1968]. PEP is the time interval from the beginning of electrical stimulation of the ventricles to the opening of the aortic valve while LVET is the time interval from the opening to the closing of the aortic valve. Therefore, QS_2 interval equals the sum of the two components [Weissler et al. 1968].

One possible reason of the prolonged QS_2 interval is the fact that systolic dysfunction is always combined with diastolic dysfunction [Remme and Swedberg 2001]. The mainly reason is the impaired LV systolic relaxation often causes an upward shift of the diastolic pressure and volume relation, thus leads to diastolic failure [Sys and Brutsaert 1995]. In turn, the mechanical systole can be prolonged in diastolic dysfunction [Weber et al. 2006]. The increasing systolic load in contraction phase in diastolic dysfunction induces the compensatory prolongation of

systolic duration[Weber et al. 2006]. Arterial stiffness is considered as a possible cause of the increased systolic load. Arterial stiffness can often be observed to increase in clinical diastolic dysfunction and it elevates aortic pulse wave velocity that leads to the earlier return of wave reflection. Therefore, the aortic pressure in late systole rises and late systolic load is increased [Nichols and O'Rourke 2011].

Another aspect to explain to lengthening of QS_2 interval is the prolongation of PEP. The changes in myocardial contractility and inotropic state can induce the variety in PEP, and PEP is usually prolonged in heart failure [Weissler et al. 1968, Hassan and Turner 1983]. Based on previous work of Thomas and Marks, elevated plasma norepinephrine levels in heart failure contributes to the lengthening of PEP [Thomas and Marks 1978]. Besides, the myocardial ischemic-induced differentiation in the physiology and biochemical properties of myocardial cells can also lead to prolonged PEP [Meiler et al. 1987]. This is because the myocardial cells adjust to anaerobic metabolism and high energy is depleted following by intracellular acidosis which interferes the availability of calcium ion to the contractile proteins [Meiler et al. 1987, Katz 1973]. Therefore, the myocardial contractility is limited and the prolonged PEP occurs.

Last but not least, all the subjects were at rest during the data collection and the heart rates were under normal range with pacers on. However, the QS_2 interval performs a negative linear relationship to the heart rate, hence, the abbreviated QS_2 might occur when the heart rate rises [Boudoulas et al. 1981a]. After exercise, the sympathetic system is activated and increases the adrenergic stimulation that can also lead to shortened QS_2 [De Caprio et al. 1984].

In this project, several different kinds of statistic studies were applied. A repeated measured ANOVA test was used to determine if there were significant differences between QT, QS_2 and QT - QS_2 in all the situations. The results showed that none of the variables had significant differences. This may indicate that the Cardiac Resynchronization Therapy (CRT) have improved the myocardial behavior and may interrupt the left ventricular remodeling. Also the relationship of QT and QS_2 under each condition was highly interested. Then a t test based on the correlation coefficient r was run to determine the relationship of QT and QS_2 and the result showed that they have strong relationship when the *left ventricular was on* and *no pacer was on*. Due to the fact that, even with impaired cardiac function, the changes of QT and QS_2 are both parallel with heart rate, it is assumed that pacer located on the septum in right ventricle interferes the spontaneous electrical and mechanical systole [Boudoulas et al. 1981a]. Moreover, because of the nonspontaneous stimuli, the incoordination between the electrical and mechanical systole produced by LV systolic dysfunction is reduced. Another aspect focused was the difference between the mean of QS_2 and QS_2n. The QS_2n was calculated by using the normal QS_2 index from healthy individuals. To determine the difference of mean value, an one way t test was applied. The results showed there were significant difference between the two sets of data: QS_2 and QS_2n in two conditions, which were *both pacers on* and *RV pacer on*. This also verifies that the pacer in right ventricle has an obvious influence on the LV mechanical systole.

The tendence of QT and QS_2 for the same subject during the four situation was also considered. 50% of all the patients subjects were observed to have the same tendence of QT and QS_2 as shown in Figure 5.1 on page 33. This may indicate that these subjects have a better prognosis after taking the CRT. However, there are some limitations to this assumption. In this project, patients with intraventricular conduction delays (e.g. left bundle branch block) were not

excluded. Meanwhile, the ECG signals from some patients did provide the proof of left bundle branch block due to the existence of QS or rS complex and RsR' wave or a wide QRS complex (Figure 4.4) [Sgarbossa et al. 1996, Nichols and O'Rourke 2011]. Therefore, the tendence of QT and QS_2 may perform differently for some patients due to the incoordinate delays in the conductive system. It is also important to mention that QS_2 also includes part of electrical activity of ventricular depolarization, thus it is more accurate to call it electromechanical systole interval [Boudoulas et al. 1982]. Any cardiac diseases which could lead to an abnormal lengthening of QRS complex can also prolong the interval of QS_2 [Weissler et al. 1968].

Besides, there might be error when extracting the features of ECG and PCG signals. To detect the start of QRS complex and the end of T-wave, two assistant lines were created from the start of the extracted cardiac cycle to the first peak of QRS complex and from the end of the cardiac cycle to the peak of T-wave (Figure 4.5). However, this method always finds the points that have the same slope as the assistant lines and these points may not be the exact turning points from the baseline of ECG to the QRS complex or from the T-wave to the baseline. By reducing the error, the start points of these two assistant lines need to locate further to the first peak of QRS complex and the peak of T-wave. The start of S_2 also needs further consideration. Commonly, the start of S_2 is chosen at the onset of the S_2 signal in PCG [Boudoulas et al. 1981a]. However, due to the advanced noise removal programs, the onset of S_2 will not be the same [Ari et al. 2010]. Therefore, in this project, a threshold was set as 3% of the maximum magnitude of S_2 after a simple bandpass filter. The threshold was chosen due to the magnitude of remained noise on the baseline after filtering, which varies from sample to sample. Hence, the threshold requires more evidence.

CHAPTER

7 Conclusion

The purpose of this project is to detect the change of relationship between QT interval and QS_2 interval in heart failure with systolic dysfunction. The results showed that $QT > QS_2$ could be observed in six subjects. However, QT is not always larger under all the four conditions in these subjects and only three subjects could be observed with $QT > QS_2$ when both pacers were off. For the rest subjects, the QT interval is always less than QS_2 which shows the same performance as in healthy individuals. Some subjects was detected to have prolonged QT and showed a high opportunity of the existence of $QT > QS_2$. Comparing with the abbreviated QS_2, long QT has more contribution to the $QT > QS_2$.

The QS_2 interval of all the subjects was stretched in comparison with QS_2n. The reason of this phenomenon can be explained by the accompanied diastolic dysfunction and the prolonged PEP in heart failure. Due to the fact that impaired LV systolic relaxation usually leads to diastolic failure, the influence of diastolic dysfunction can hardly be removed even although the systole was mainly focused.

All the subjects used implanted biventricular pacer as the treatment of heart failure. During this project, the statistic tests provided an evaluation of the CRT treatment. The CRT was reported to improve the life quality of patients, reduce the symptoms and increase survival [McMurray 2010]. The result of the repeated measured ANOVA tests showed that no significant changes of QT and QS_2 between the situations when both the pacers were on and both pacers were off. Moreover, it is also assumed the electrode implanted in the right ventricular has strong influences to the mechanical systole due to the significant changes in QS_2 when RV pacer was on comparing with other cases.

There were also several limitations of this project. Besides of the combination of diastolic failure, the existence of conductive block, such as left bundle branch block, was detected from the ECG signal. This factor can effect the relation of QT and QS_2 in different pacer evoking situations. Also, the start of S_2 need further research.

To summarize, $QT > QS_2$ can be observed from patients with systolic dysfunction, however, the mechanical systolic can be effected by the combined diastolic dysfunction and other myocardial changes in heart failure. The QS_2 interval could be prolonged and lead to a result of normal QT and QS_2 relationship. Therefore, patients with $QT > QS_2$ should to be suggested with further diagnosis of heart failure, but it cannot be used as a criterion of systolic dysfunction in heart failure.

CHAPTER

8 Perspectives

Under CRT, the QT interval could be under the normal range while the QS_2 is prolonged. As discussed before, this is due to the diastolic dysfunction. Since diastolic dysfunction is usually combined in systolic heart failure, the mechanical systole is better to be presented by LVET. In this case, even with prolonged QS_2 one can also argue that the mechanical systole might be shortened if an abbreviated LVET is detected.

Besides, any other diseases which may affect the electrical and mechanical systole need to be excluded. Such diseases as left bundle branch block and diabetes have significant influences on systolic time interval. Therefore, subjects with history of these diseases should be obviated.

All the subjects were under the rest situation while acquiring the data, but an experiment should also be brought with the heart rate after exercises. For example, the subjects can take the six minutes walk exercise before recording the ECG and PCG. The QS_2 is negative linear to heart rate, therefore, shortened QS_2 might occur after exercise. For normal subject, the QS_2 will not be shorter than QT after the exercise. However, for heart failure patients with mild symptoms, the QT and QS_2 may have the normal relation at rest but perform abnormal when heart rate increases.

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