Cardiac Dyssynchrony in Heart Failure

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To my wife, Mona, and my parent, S.G. and Flora, for their unconditional love and wholehearted support.

Declaration of Originality

I declare that this thesis represents my own original work, except where due acknowledgement is made. My contribution to the studies described in this thesis includes formulation of the specific research questions and hypotheses, study design, patient recruitment, performance and analysis of echocardiography, data analysis, and writing of the manuscripts. My work was supported by a group of researchers who are listed as authors of the publications. They have helped in patient recruitment, performance of echocardiography, and analysis of echocardiographic data. Prof CM Yu has provided important input in terms of overall support and guidance of the project, supervision of data collection and analysis, as well as final approval of the manuscripts.

This work has not been previously included in a thesis, dissertation or report submitted to this University or to any other institution for a degree, diploma or other qualifications.

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List of Abbreviations

ACS	Acute coronary syndrome
ADHF	Acute decompensated heart failure
CAD	Coronary artery disease
CRT	Cardiac resynchronization therapy
CSHF	Chronic stable heart failure
ECG	Electrocardiogram
EF	Ejection fraction
Em	Mean basal myocardial early diastolic velocity
HFPEF	Heart failure with preserved ejection fraction
HT	Hypertension\
LBBB	Left bundle branch block
LV	Left ventricle
LVH	Left ventricular hypertrophy
RBBB	Right bundle branch block
Sm	Mean basal myocardial peak systolic velocity
TDI	Tissue Doppler Imaging
Te-SD	Diastolic dyssynchrony index
Ts-SD	Systolic dyssynchrony index

Publications

The following publications are derived from the original studies described in this thesis. The full manuscripts have been published in scientific indexed journals.

1. Lee PW, Zhang Q, Yip GW, Wu L, Lam YY, Wu EB, Yu CM. Left ventricular systolic and diastolic dyssynchrony in coronary artery disease with preserved ejection fraction. Clinical science. 2009;116:521-529.
2. Lee AP, Zhang Q, Yip G, Fang F, Liang YJ, Xie JM, Lam YY, Yu CM. Lv mechanical dyssynchrony in heart failure with preserved ejection fraction complicating acute coronary syndrome. JACC. Cardiovascular imaging. 2011;4:348-357.
3. Lee AP, Song JK, Yip GW, Zhang Q, Zhu TG, Li C, Chan A, Yu CM. Importance of dynamic dyssynchrony in the occurrence of hypertensive heart failure with normal ejection fraction. Eur Heart J. 2010;31:2642-2649.
4. Lee AP, Zhang Q, Looi JL, Sun JP, Fang F, Liu YT, Liang YJ, Xie JM, Li RJ, Yu CM. Left ventricular systolic dyssynchrony in acute decompensated heart failure. International journal of cardiology. 2013;168:4285-4286.
5. Sun JP, Lee AP, Grimm RA, Hung MJ, Yang XS, Delurgio D, Leon AR, Merlino JD, Yu CM. Optimisation of atrioventricular delay during exercise improves cardiac output in patients stabilised with cardiac resynchronisation therapy. Heart. 2012;98:54-59.

Abstract

Like any muscle, cardiac contraction is evoked by action potentials. In the healthy heart, atrial and ventricular activation occur through impulse conduction via the rapid conduction system. Normal cardiac function requires a highly synchronized series of mechanical events occurring in the atria and the ventricles. This synchronization is achieved by rapid conduction of action potentials through the electrical conduction system, which leads to coordinated mechanical activation and deactivation of the myocardium — a process known as electromechanical coupling. As a result of this coordinated electromechanical coupling, the left ventricle functions efficiently as a pump. On the contrary, asynchronous electrical activation leads to asynchronous contraction. The presence of a bundle branch block or other intraventricular conduction delay can worsen heart failure due to systolic dysfunction by causing ventricular dyssynchrony, thereby inducing regional loading disparities and reducing the efficiency of contraction. Consistent with the idea that ventricular dyssynchrony exacerbates left ventricular dysfunction is the observation that a variety of hemodynamic benefits follow the correction of dyssynchrony with cardiac resynchronization therapy (CRT) using biventricular pacing. With decades of research on electromechanical coupling in the heart, it is now recognized that (1) cardiac dyssynchrony worsens ventricular efficiency and contributes to the progression of systolic heart failure; (2) cardiac dyssynchrony can be accurately assessed by echocardiography; (3) cardiac dyssynchrony independently predicts worse prognosis in patients with systolic heart failure; and (4) CRT has established as an effective treatment for systolic heart failure, leading to improved symptomatic status and better survival.

Concerning the subject of cardiac dyssynchrony there are still a lot of unanswered questions which are important to complete understanding of disease mechanisms of heart failure and hence to develop better treatment strategies. First, patients with heart failure but with a preserved ejection fraction (HFPEF) constitutes about half of the heart failure occurrence. Yet, it is not completely understood whether cardiac dyssynchrony, as a potential pathogenic

mechanism and therapeutic target, is present in these patients. Second, the heart and circulation is a dynamic system. Nevertheless, scarce data exists on how cardiac dyssynchrony alters in response to exercise and other hemodynamic stressors in patients with heart failure. The potential clinical significance of dynamic dyssynchrony is unknown. Furthermore, identification of precipitating factors of acute hemodynamic decompensation in heart failure is important to prevent recurrent acute exacerbation and hospitalization. Cardiac dyssynchrony has been suspected to be an insidious, potentially correctable trigger of acute decompensated heart failure (ADHF), but scientific evidence is limited. Last but not least, about 30% of the CRT recipients did not respond to the treatment. It was proposed that inadequate optimization of atrioventricular (AV) synchronization is the most common contributory factor, hence the routine practice of AV optimization after CRT implantation. But again, electromechanical coupling is a dynamic process. It is uncertain, however, whether AV optimization should be performed at rest or during exercise to achieve optimal hemodynamic and clinical benefit.

In Part I of this thesis, I will review the literature on heart failure, cardiac dyssynchrony, and exercise impact on the cardiovascular system. In Chapter 1, the definition, clinical classification, and epidemiology of heart failure, as well as the biomechanical model for heart failure progression will be discussed. In Chapter 2, the literature on the normal and pathological electromechanical coupling mechanism, the clinical implication of dyssynchrony in heart failure, and the effect of CRT will be reviewed. In Chapter 3, I will discuss the current understanding of the physiologic effect of exercise, heart rate and stress on cardiac function and synchronicity. In Part II, the hypotheses (Chapter 4) and general objectives (Chapter 5) of the studies included in this thesis will be specified. In Part III, I will describe in detail the general methodology used in these studies including the study population involved (Chapter 6), the echocardiographic techniques (Chapter 7), and the exercise/pharmacological stress protocols (Chapter 8) used in these studies.

Part IV will be a thorough and logical reporting of the background, methods, findings, discussion, and conclusion of each of the clinical studies of this thesis. Chapter 9, 10 and 11 will focus on patients with preserved ejection fraction and Chapter 12 and 13 will attempt to fill the gap of knowledge of cardiac dyssynchrony in patients with systolic heart failure.

In the study discussed in Chapter 9, the prevalence of left ventricular mechanical dyssynchrony in coronary artery disease with preserved ejection fraction was evaluated. Ninety-four consecutive patients with chronic coronary artery disease and preserved ejection fraction (≥50%) were evaluated using echocardiography with tissue Doppler imaging and compared to 217 patients with depressed ejection fraction and (<50%) and 117 healthy subjects. Left ventricular systolic and diastolic dyssynchrony were determined by measuring the standard deviations of peak systolic (Ts-SD) and early diastolic myocardial (Te-SD) velocities, respectively, using a six-basal/six-mid-segmental model. In patients with coronary artery disease and preserved ejection fraction, both Ts-SD (32.2±17.3 compared with 17.7±8.6 ms; $p<0.05$) and Te-SD (26.2±13.6 compared with 20.3±8.1 ms; $p<0.05$) were significantly prolonged when compared with controls, although they were less prolonged than patients with coronary artery disease and depressed ejection fraction (Ts-SD, 37.8±16.5 ms; and Te-SD, 36.0±23.9 ms; both $p<0.005$). Patients with preserved ejection fraction who had no prior myocardial infarction had Ts-SD (32.9±17.5 ms) and Te-SD (28.6±14.8 ms) prolonged to a similar extent (p=NS) to those with prior myocardial infarction (Ts-SD, 28.4±16.8 ms; and Te-SD, 25.5±15.0 ms). Patients with class III/IV angina or multi-vessel disease were associated with more severe mechanical dyssynchrony ($P<0.05$). Furthermore, the majority of patients with mechanical dyssynchrony had narrow QRS complexes in those with preserved ejection fraction. This is in contrast with patients with depressed ejection fraction in whom systolic and diastolic dyssynchrony were more commonly associated with wide QRS complexes.

In Chapter 10, focus will be shifted to patients with acute coronary syndrome complicated by acute HFPEF. One hundred two patients presenting with acute coronary syndrome (ejection fraction ≥50%) and 104 healthy controls were studied using tissue Doppler imaging: group 1 (n=55) had HFPEF on presentation and group 2 (n=47) had no clinical HFPEF. Te-SD was found to be greater in group 1 (33±13 ms) than group 2 (21±9 ms) ($p<0.001$), and diastolic mechanical dyssynchrony was evident in 35% of patients in group 1 but in only 9% in group 2 ($p<0.001$). Worsening of the diastolic dysfunction grade was associated with a parallel increase in Te-SD (grades 0, 1, 2, and 3: 16±3 ms, 21±5 ms, 28±9 ms, and 41±17 ms, respectively; $p<0.001$). Te-SD correlated negatively with mean early diastolic basal myocardial velocity (Em) ($r=-0.56$, $p<0.001$) and positively with peak mitral inflow velocity of the early rapid-filling wave/Em ($r=0.69$, $p<0.001$). Multivariate analysis identified peak mitral inflow velocity of the early rapid-filling wave/Em as the only variable independently associated with HFPEF [odds ratio (OR)=1.48, $p=0.001$]. When peak mitral inflow velocity of the early rapid-filling wave/Em was excluded from the model, Te-SD (OR=1.13, $p<0.001$) and mean Em (odds ratio=0.37, $p<0.001$) became independently associated with HFPEF.

In Chapter 11, I will evaluate the impact of hemodynamic stress on left ventricular dyssynchrony and the relationship and predictive value of dynamic changes of left ventricular dyssynchrony on hypertensive HFPEF. In this study, a total of 131 subjects including 47 hypertensive HFPEF patients, 34 hypertensive patients with left ventricular hypertrophy without HFPEF, and 50 normal controls were studied by dobutamine stress echocardiography with tissue Doppler imaging. In normal controls, systolic and diastolic dyssynchrony did not develop during stress. The prevalence of resting systolic (36.2% vs. 38.2%, $p=0.85$) and diastolic (34.0% vs. 29.4%, $p=0.66$) dyssynchrony was similar in patients with HFPEF and left ventricular hypertrophy. During stress, the prevalence of systolic and diastolic dyssynchrony increased dramatically to 85.1% and 87.2%, respectively, in patients with HFPEF, but only 52.9% and 58.8% in patients with left ventricular hypertrophy ($p<0.005$). In HFPEF group, stress-induced

increase in mean systolic basal myocardial velocity (Sm) was significantly blunted (2.8±2.0 vs. 4.2±2.4 cm/s, p=0.004), and the increase was abolished for mean Em (-0.3±2.5 vs. 2.4±3.4 cm/s, p<0.001). On multivariate analysis, stress-induced changes in mean Em (OR=0.69, p=0.004) and mean Sm (OR=0.56, p=0.004), and diastolic (OR=4.6, p=0.005) and systolic dyssynchrony during stress (OR=4.3, p=0.038) were independent determinants for occurrence of HFPEF.

In Chapter 12, the role of dyssynchrony in patients with systolic heart failure presentating with acute decompensation (ADHF) will be studied. In this study, it was hypothesized that acute left ventricular systolic dyssynchrony might be a hidden triggering mechanism for ADHF. Echocardiography with tissue Doppler imaging was performed in 145 subjects with systolic heart failure (ejection fraction <50%), including 84 consecutive patients presented with ADHF requiring hospitalization, comparing them to 61 chronic stable heart failure patients who had no heart failure exacerbation or hospitalization in the past 6 months. The ADHF group was observed to have higher heart rate on admission than patients with stable heart failure (82±15 vs 68±13 bpm, P<0.001), greater left ventricular wall thicknesses and mass (all P<0.05), and mitral regurgitation was more common (71% vs 46%, P<0.0001; ERO=0.12±0.11 vs 0.02±0.04 cm2, P<0.0001), but the overall severity of mitral regurgitation was mild or moderate. Despite no difference in ejection fraction, the ADHF group had significantly lower mean Sm (2.7±0.9 cm/s vs 3.0±0.9 cm/s, P=0.04). The Ts-SD was significantly prolonged in the ADHF group compared to patients with stable heart failure (44.7±16.6 vs 33.4±17.7 ms, P=0.0001). Significant left ventricular systolic dyssynchrony was evident in 75% (63 of 84) of patients of the ADHF group, compared to only 44% (27 of 61) of patients with chronic stable heart failure (P=0.0002).

In Chapter 13, I will focus on the role of dynamic AV dyssynchrony during exercise in patients with systolic heart failure who receive CRT. AV delay in CRT recipients are typically optimised at rest. However, there are limited data on the impact of exercise-induced changes in heart rate on the optimal AV delay and left ventricular function. In this study, AV delays were

serially programmed in 41 CRT patients with intrinsic sinus rhythm at rest and during two stages of supine bicycle exercise with heart rates at 20 bpm (stage I) and 40 bpm (stage II) above baseline. The optimal AV delay during exercise was determined by the iterative method to maximise cardiac output using Doppler echocardiography. Results were compared to physiological change in PR intervals in 56 normal controls during treadmill exercise. The optimal AV delay was progressively shortened ($p<0.05$) with escalating exercise level (baseline: 123±26 ms vs. stage I: 102±24 ms vs stage II: 70±22 ms, $p<0.05$). AV delay optimisation led to a significantly higher cardiac output than without optimisation did during stage I (6.2±1.2 l/min vs. 5.2±1.2 l/min, $p<0.001$) and stage II (6.8±1.6 l/min vs. 5.9±1.3 l/min, $p<0.001$) exercise. A linear inverse relationship existed between optimal AV delays and heart rates in CRT patients (AV delay=241-1.61 x heart rate, $R^2=0.639$, $p<0.001$) and healthy controls ($R^2=0.646$, $p<0.001$), but the slope of regression was significantly steeper in CRT patients ($p<0.001$).

In conclusion, the works included in this thesis provide new evidence that left ventricular mechanical dyssynchrony is common in patients with coronary artery disease and preserved ejection fraction, even in patients without prior myocardial infarction or evidence of eletromechanical delay. In particular, left ventricular diastolic mechanical dyssynchrony may impair diastolic function and contribute to the pathophysiology of HFPEF during acute coronary syndrome. Moreover, dynamic dyssynchrony and impaired myocardial longitudinal function reserve during stress may contribute importantly to the pathophysiology of hypertensive HFPEF. In patients with heart failure and reduced ejection fraction, a high prevalence of left ventricular systolic dyssynchrony during acute decompensation suggests that acute or dynamic left ventricular systolic dyssynchrony may be an important precipitating factor and a potential therapeutic target. Progressive shortening of hemodynamically optimal AV delay with increasing heart rate during exercise suggests that dyssynchrony is dynamic and there may be a need for programming of rate-adaptive AV delay in CRT recipients to optimise clinical

response. I believe this work will provide new understanding of the prevalence, mechanism, and clinical significance of cardiac dyssynchrony in heart failure.

Part I Introduction and Literature Review

Chapter 1 Heart Failure: An Overview

1.1 Definition of heart failure

Heart failure is a clinical syndrome caused by a cardiac structural or functional disorder that impairs the capability of the ventricle to fill with or eject blood commensurate with the demands of the body, or precludes it from accomplishing so without an increase in filling pressures. Heart failure manifests clinically as fatigue, dyspnoea, fluid retention, and reduced exercise capacity, and can result from disorders of any components of the heart including the pericardium, myocardium, heart valves, and blood vessels (Hunt et al. 2009). However, heart failure is usually discussed primarily in relation to myocardial dysfunction, as valvular, vascular, and pericardial diseases are usually readily correctable by surgical or other definitive treatment.

1.2 Clinical classification and staging of heart failure

1.2.1 Heart failure with reduced ejection fraction (or Systolic heart failure) vs heart failure with preserved ejection fraction

It is practically helpful to divide patients having heart failure into individuals with heart failure with reduced ejection fraction (EF) and the ones with preserved EF (HFPEF). Patients with heart failure having a low left ventricular (LV) EF, usually defined as <45-50%, are categorized as having systolic heart failure. Typically these individuals have dilatation of the LV cavity and a reduced cardiac output because of diminished contractility in the myocardium. In comparison, patients with HFPEF (EF typically considered to be ≥50%) are generally considered having heart failure syndrome as a result of a complex pathophysiologic interplay of systolic (Yu et al. 2002) and diastolic dysfunction, left atrial dysfunction, arterial and venous stiffening, increased plasma volume, and skeletal muscle abnormalities (Sanderson 2014).

1.2.2 Acute vs chronic heart failure

Chronic, clinically stable heart failure may easily decompensate. Acute decompensated heart failure (ADHF) often manifests as a worsening of the signs and/or symptoms, typically dyspnoea, oedema, and fatigue, in a patient with existing chronic heart failure (Adams et al. 2005, Zile et al. 2008, Greenberg 2012). It is often a common and potentially fatal condition, which may be new or an exacerbation of chronic disease. This is most commonly triggered by an intercurrent illness (such as pneumonia), myocardial infarction, uncontrolled hypertension, arrhythmias, anemia, increased fluid or salt absorption, renal impairment, renal artery stenosis, as well as medications that cause fluid retention such as NSAIDs and thiazolidinediones. Acute decompensated heart failure also can present as a low cardiac output state, characterized by fatigue, notable exercise intolerance, anorexia, in addition to cognitive impairment. Classification of heart failure into acute versus chronic heart failure is useful to encourage physicians focusing on different aspects of the therapeutic approach in different clinical scenarios. In patients with chronic stable heart failure, treatment objectives will usually be focusing on improving symptoms and long-term survival, while in patients presenting with acute decompensation the immediate goals are on hemodynamic stabilization, identification of potential triggers, and prevention of recurrent exacerbation.

1.2.3 Stages in the development of heart failure

As outlined by the American College of Cardiology/American Heart Association (ACC/AHA) guideline (Hunt et al. 2005, Hunt et al. 2009), heart failure should be considered as a progressive disease and there are several stages in the evolution of heart failure:

Stage A - At high risk for heart failure but without structural heart disease or symptoms

Stage B - Structural heart disease but without signs or symptoms of heart failure

Stage C - Structural heart disease with prior or current symptoms of heart failure

Stage D - Refractory heart failure requiring specialized interventions

1.3 Epidemiology of heart failure

A 2014 update from the AHA estimated that there were 5.1 million people with HF in the United States in 2006 (Go et al. 2014). There are an estimated 23 million people with HF worldwide (McMurray et al. 1998). The actual reported prevalence of heart failure varies among population-based studies and is dependent on the population being analyzed and methodology used. Over the past decade, there has been a significant rise in the prevalence of heart failure, which has been associated with a rise in the rate of heart failure hospitalization (McCullough et al. 2002). The rise in prevalence of heart failure is probably attributed to aging population (Stewart et al. 2003, Vigen et al. 2012), as the occurrence of coronary artery disease and hypertension is the highest in these patients. Moreover, increasing survival following myocardial infarction can result in a higher incidence of heart failure later in life. The mortality of heart failure has remained high, reflecting that contemporary therapies for heart failure may only delay disease progression but are not curative.

The relative incidence of systolic heart failure and HFPEF was evaluated in the PREVEND study among community-based, middle-age subjects (Brouwers et al. 2013). In this study, 34% of patients had HFPEF and 66% had systolic heart failure. According to a local study conducted in our institution, HFPEF appears to be more common (66% of patients with a clinical diagnosis of heart failure had EF>45%) than systolic heart failure in Chinese patients with the symptoms of heart failure (Yip et al. 1999). This may be related to older age at presentation and the high prevalence of hypertension in this community. The prognosis of HFPEF seems to be better than systolic heart failure in some reports (annual mortality 8 to 9 versus 19 %) (Lam et al. 2011), but comparable mortality rates were reported by other researchers (Bursi et al. 2006). In a recent meta-analysis of 31 studies involving nearly 42,000 patients with heart failure reported that mortality of HFPEF is lower than that of systolic heart failure by about 30% (Meta-analysis Global Group in Chronic Heart 2012). Prognosis remained grim for both HFPEF and systolic heart failure after hospitalization for the first episode of heart failure. These data calls for an urging clinical need for development of new treatment strategies for heart failure, and such goal

cannot be accomplished without a thorough understanding of the pathophysiology of the heart failure syndrome.

1.4 Pathogenic models in heart failure and their therapeutic implications

The clinical syndrome of heart failure can be explained in terms of several different clinical model systems. In the classical “cardio-renal” model, heart failure can be viewed as a problem of excessive salt and water retention caused by abnormalities of renal blood flow (Packer 1992). In the “hemodynamic” model, heart failure is thought to arise largely as a result of abnormalities of the pumping capacity of the heart and excessive peripheral vasoconstriction (Packer 1992). The “cardio-renal” model provided the rational basis for the use of diuretics to control the volume status of patients with heart failure, and the “hemodynamic" model provided the rational basis for the use of inotropes and intravenous vasodilators to augment cardiac output. The observation that medical therapies including ACE inhibitors and β-adrenergic blocking agents have a beneficial effect on the natural history of LV dysfunction, despite initially unimpressive (Currie et al. 1984) or even adverse (Hall et al. 1995) hemodynamic effects has led to the conceptualization of the “neurohormonal model”, in which heart failure progresses as a result of the over-expression of biologically active molecules that are capable of exerting deleterious effects on the heart and circulation (Bristow 1984).

Finally, heart failure progression can also be viewed as a “biomechanical" model. In this model, heart failure develops as a consequence of the cardiac remodelling after initial pathological insults (e.g. myocardial infarction, hypertension, electromechanical dyssynchrony, etc) which is characterized by the maladaptive change in LV structure and geometry leading to mechanical disadvantages including increased end-diastolic wall stress, subendocardial ischemia, and increased oxygen utilization. The major insights gained from this model are that (i) deleterious effects of cardiac remodelling can, at some point, sustain itself resulting in a vicious cycle of progressive LV remodelling and dysfunction beyond the effect of neurohormonal activation; and (ii) cardiac remodelling can be a reversible process which means

that the relentless progression of heart failure can be halted or reversed by appropriate therapies (Mann et al. 2005). Conceptualization of the heart failure syndrome as a biomechanical model provides important therapeutic insights into the development of new treatments that target at the cardiac remodelling per se, instead of merely the hemodynamic or neurohormonal consequences of LV dysfunction, allowing for a greater potential to break the vicious cycle of disease progression in heart failure. An important clinical example is observed in the use of cardiac resynchronization therapy, which, by correcting myocardial resynchronization, promotes cardiac reversed remodelling, resulting in not just improvement of symptoms but also favourable alteration or even reversal of the natural disease course of heart failure (Yu et al. 2002). The biomechanical view of heart failure progression is crucial for the realization of a paradigm shift in the therapeutic strategy of heart failure from the largely palliative to potentially curative one. Therefore, an in-depth understanding of the pathogenic role of cardiac dyssynchrony in the progression of heart failure at different clinical stages and in acute exacerbation will have significant therapeutic implication.

Chapter 2 Cardiac Synchronicity and Dyssynchrony

2.1 Electrical and mechanical activation of the normal heart

In the normal heart, electrical activation originates from the sinus node which is located near the epicardial surface in the high sulcus terminalis, at the junction of the superior vena cava and the right atrium (James 1961). Like any muscle, cardiac contraction is evoked by action potentials. There is a time delay between depolarization and mechanical force generation owing to the time required for action potential-triggered calcium influx, cytosolic release, transport, and binding to the intracellular contractile machinery. This delay, amounting to approximately 30ms, is known as electromechanical delay and can be observed on a global basis as the delay between the R-wave of the ECG and the rise in LV pressure (Prinzen et al. 1992). In the healthy heart, atrial and ventricular activation occur through impulse conduction via the rapid conduction system. During normal sinus rhythm in hearts without conduction abnormalities the electrical activation is relatively synchronous (activation of the ventricles occurring within 70ms), occurring earliest in the LV septal endocardium and latest in the epicardium of the LV lateral wall (Durrer et al. 1970). The consequence of this synchronous electrical activation is a highly synchronous contraction sequence of the ventricle. In order to comprehend the pathophysiologic mechanisms governing dyssynchrony in heart failure, it is useful to appreciate that structurally normal hearts also exhibit certain degree of heterogeneity in contractile function in relation to its complex geometric construction. Early studies involving myocardial dissection and histological examination revealed that ventricular myocardial fibres within the epicardial and endocardial regions are oriented along the longitudinal axis of the heart, whereas fibres within the midwall region are oriented circumferentially (Streeter et al. 1969, Greenbaum et al. 1981). These findings in isolated regions of the excised heart were recently corroborated by in a more global scale of the heart using diffusion tensor magnetic resonance imaging as well as speckle tracking

echocardiography (Helm et al. 2005). Helm et al. demonstrated that the myocardial fibre comprised of two primary orientations (circumferential and longitudinal) that transition smoothly from one direction to another. Electrical activation through the His–Purkinje system results in a ventricular electrical wave front that starts in the endocardium and apex and ends in the epicardium and base with resultant regional disparities in electrical activation by as much as 80 to 100 ms from start to finish. This effects in a temporal mechanical activation of myocardial fibres especially between the endocardial and the epicardial layers as well as the apex and base regions. Such unique arrangement of myocardial fibres allows for a complex contractile motion that involves both circumferential motion and longitudinal shortening from apex to base. On the other hand, there is evidence of the presence of a regional difference in electromechanical delay between endocardium and epicardium, as well as between the LV free wall and the septum. As a result of this highly coordinated heterogeneity in electromechanical coupling and myocardial architecture, the left ventricle functions synchronously and efficiently as a pump.

2.2 Abnormal cardiac function and the prevalence of dyssynchrony

Normal physiologic consequence of electrical activation can be disturbed during ventricular pacing as well as in diseases affecting the rapid conduction system. In heart failure patients, conduction defects due to LBBB or slow intra-myocardial conduction are common and result in regionally delayed electrical activation. Under these circumstances the electrical impulse is conducted through the slowly conducting working myocardium, rather than through the rapidly conducting specialized conduction system. Reduced speed and abnormal sequence in electrical activation of the complex myocardial fibre architecture leads to asynchronous contraction and reduces pump efficiency. As a result, the time required for activation of the entire ventricular muscle, expressed as QRS duration, is prolonged. Nevertheless, this is not always the case and patients with heart failure may have LV dyssynchrony in the absence of regionally delayed electrical activation. Patients with systolic heart failure and a narrow QRS complex exhibit mechanical dyssynchrony with a prevalence ranging from 30 to 50% (Yu et al.

2003, Bleeker et al. 2005, Haghjoo et al. 2007). Similarly, 30–40% of patients with HFPEF have also been shown to frequently have mechanical dyssynchrony(Wang et al. 2007, Yu et al. 2007). The explanation for this may rest on an appreciation that dyssynchrony can result from both electrical and non-electrical mechanisms. First, dyssynchrony may be the result of temporal delay in electrical activation of one region vs. another. The classic example is LBBB where electrical activation occurs first in the septum and then propagates slowly via intra-myocardial conduction to the lateral wall. Improving the activation phase difference with biventricular pacing, one can achieve more synchronous mechanical contraction and enhance ventricular performance. A second mechanism of dyssynchrony occurs in the setting of apparently normal temporal electrical activation. In normal dogs, clamping of aorta results in acute increase of afterload and regional ventricular myocardial shortening becomes dyssynchronous and relaxation time constant is prolonged (Yano et al. 1994). Furthermore, abnormal loading of the heart, ischemia, or interstitial fibrosis can induce mechanical delay and dyssynchrony in heart failure. These types of dyssynchrony, however, may not be directly amenable to electrical resynchronization, but could be improved by vasodilators and diuretics (Wang et al. 2007).

2.3 Methods for dyssynchrony assessment

Advances in cardiac imaging technologies have made direct assessment of cardiac dyssynchrony clinically feasible. Various imaging modalities have been evaluated as tools for quantifying LV dyssynchrony. Echocardiography including tissue Doppler imaging (TDI) has been the most widely studied (Yu et al. 2003, Bax et al. 2004, Bordachar et al. 2004, Notabartolo et al. 2004, Penicka et al. 2004, Cho et al. 2005, Yu et al. 2005). However, controversies exist in the literature regarding whether TDI-based parameters for mechanical dyssynchrony can predict CRT response (Chung et al. 2008, Chung et al. 2008). Recommendations for performance and reporting of echocardiography for CRT were provided in the 2008 American Society of Echocardiography (ASE) consensus statement, advising that dyssynchrony reports should not include a recommendation for whether a patient should undergo CRT, which should be a case-

by-case clinical decision (Gorcsan et al. 2008). Nevertheless, CRT response depends on multiple factors including the presence of scar tissues, the site of late ventricular activation, the pacemaker lead position, and the dynamic nature of dyssynchrony, such that it is not surprising that baseline dyssynchrony assessment by TDI, even accurately reflecting mechanical dyssynchrony, may not always predict CRT response. The clinical significance of TDI-based assessment of mechanical dyssynchrony in terms of its robustness in independently predicting long-term prognosis of HF patients has been consistently reported (Fauchier et al. 2002, Cho et al. 2005, Penicka et al. 2007).

Additional methods for assessing dyssynchrony that have been investigated include cardiac magnetic resonance imaging (Bleeker et al. 2006, Chalil et al. 2007), myocardial strain imaging (Suffoletto et al. 2006, Miyazaki et al. 2008), and electrical activation patterns assessed by electrophysiologic mapping (Fung et al. 2007). Echocardiography with TDI has been the most widely studied modality for assessment of mechanical dyssynchrony. It has the unique advantage of high temporal resolution (frame rate>100Hz), which is important for the assessment of regional differences in timing of myocardial motion in the scale of milliseconds. Detail discussion of the relative advantages and disadvantages of other imaging modalities for dyssynchrony assessment is beyond the scope of this work.

2.4 Effect on mechanical work and clinical prognosis

In heart failure, conduction defects such as LBBB result in regionally delayed electrical activation. Asynchronous electrical activation in turn leads to asynchronous and discordant contraction. Typically, the septal region is activated early via an intact right bundle, whereas the basal LV posterolateral region is activated late as excitation propagates slowly via intra-myocardial conduction. Accordingly, regions with the earliest electrical activation also start to contract first. Because the rest of the muscle fibres are still in a relaxed state, the early-activated fibres can shorten rapidly before the onset of the ejection phase. This rapid early systolic shortening is followed by minimal mid ejection systolic shortening and premature relaxation. On

the contrary, in late-activated regions the fibres are stretched passively during early systole, which is followed by a doubling of the net systolic shortening and by delayed relaxation (Prinzen et al. 1990, Prinzen et al. 1999). These differences in contraction patterns as a result of asynchronous activation imply that opposing regions of the ventricular wall are out of phase and that the energy generated by one region is dissipated in opposite regions. Therefore, cardiac dyssynchrony not merely reduces cardiac output but reduces myocardial efficiency with work performed on one side of the heart being wasted by its stretching of the contralateral side, resulting in a low or near zero net work for this region (Prinzen et al. 1999). Workload is much greater in the late contracting lateral wall, which operates at a higher initial stretch and contracts against higher stress. It is these inefficient energy uses that delay intra-cavitary pressure rise. Furthermore, late activation of the posterolateral papillary muscle results in suboptimal mitral valve closure and mitral regurgitation, further decreasing cardiac output. Regionally dissipated energy correlates with regional heterogeneity in coronary perfusion and ischemia, further jeopardizing myocardial energetics in the already failing dysfunctional ventricles (Baller et al. 1981, Park et al. 1985, Baller et al. 1988).

The impact of dyssynchronous contraction can be described using regional elastance curves with regional stiffness plotted as a function of time (Figure 2-1A). Differences in timing of activation between the early-activated septum and the late-activated lateral wall result in a rightward shift of the lateral wall curve relative to that of the septum. The vertical difference between the curves reflects the degree of septum-to-lateral wall volume shift. The volume shift is great during isovolumic contraction, which is the reason of reduction in dP/dt_{max} and is even greater in late systole/early diastole, impairing ejection and relaxation. The net effect of LV dyssynchrony is reduction in the cardiac output. As shown on the plot of pressure–volume loops (Figure 2-1B), dyssynchrony results in a shift of end-systolic pressure–volume relationship to the right that represents a load-independent compromise of LV function. In addition, stroke volume (width of loop) is reduced, leading to increased LV end-systolic volume and increased

end-systolic wall stress (Park et al. 1985). In the early-activated septal region, the workload is low owing to a figure-8-shaped stress–strain relationship. In early systole, the region contracts against low load, and in late systole, it is stretched at a higher load.

Although the most common conduction defect is LBBB, regionally delayed electrical activation may occur with right bundle branch block (RBBB). However, RBBB is associated with less LV dyssynchrony globally than LBBB (Byrne et al. 2007). This discrepancy is largely related to the geometric asymmetry of the LV. Although the lateral free wall is principally dependent on LV loading conditions, the septum is loaded from both the RV and the LV. In RBBB, the early-activated lateral wall contracts against a quiescent septum; yet, RV loading may reduce significant pre-stretch and ventricular dyssynchrony. This may explain why the observed effect on LV intra-cavity pressure development is less than that with LBBB. This pattern of mechanical dyssynchrony may be the reason why the impact of CRT in RBBB is less than that in LBBB (Bilchick et al. 2010).

The Framingham study found a significant association between LBBB and increased mortality and cardiac morbidity. About 50% of patients with LBBB died of cardiovascular disease within 10 years of onset of LBBB, compared with only 11.6% of similar-aged controls. The association between LBBB and cardiovascular mortality remains significant after statistical adjustment for the influence of diabetes, systolic blood pressure, age, coronary artery disease, and heart failure (Schneider et al. 1979). In patients with cardiomyopathy, strong evidence exists to suggest that LBBB is associated with a significantly high mortality. In the study by Xiao et al, a QRS duration of >160ms was found in 8 out of 10 patients who died, but only 5 of the 39 stable patients (Xiao et al. 1996) and the QRS duration tended to prolong over time. Shamin et al studied 241 heart failure patients, dividing them into three groups based on their QRS duration: QRS <120ms, QRS 120-160ms, and QRS >160ms. The corresponding mortality rates at 36 months of the 3 groups of patients were 20%, 36%, and 58.3% (Shamim et al. 1999). Bader et al used tissue Doppler echocardiography to assess dyssynchrony in 104 patients with systolic heart

failure without prior myocardial infarction. They found that the presence of intra-LV (but not inter-ventricular) dyssynchrony was an independent predictor of severe cardiac events, independent of the LVEF and QRS width. QRS width correlates poorly with mechanical dyssynchrony. Of the 57 patients with a QRS width <120ms, 56% presented with intra-LV dyssynchrony. Intra-LV dyssynchrony was observed in 84% of LBBB patients, but also in 83% of RBBB patients (Bader et al. 2004). Accordingly, such patients should be more actively identified for early intensive treatment and survey.

In summary, LBBB results in significant intra-LV and inter-ventricular dyssynchrony. Clinical consequences include significant impairment in systolic and diastolic function, as well as decreased cardiac efficiency. These changes are generally well tolerated in patients with normal LV function, but in patents with severe LV dysfunction and symptomatic heart failure, the results can be profound and can contribute significantly to the increased morbidity and mortality. Mechanical dyssynchrony can also occur without prolongation of QRS duration on ECG and is also independently associated with poorer clinic outcome in patients with systolic heart failure.

2.5 Effects of CRT

Consistent with the notion that ventricular dyssynchrony exacerbates LV dysfunction is the observation that a variety of hemodynamic and clinical benefits follow the correction of dyssynchrony with CRT. A number of randomized controlled trials have shown improved outcomes with CRT in appropriately selected patients with systolic heart failure who have an intraventricular conduction delay or LBBB (St John Sutton et al. 2003, Cleland et al. 2005). Potential mechanisms of benefit include improved indices of LV myocardial performance and reverse ventricular remodelling (Yu et al. 2002, St John Sutton et al. 2003). CRT improves LV systolic performance in patients with heart failure associated with an LBBB, leading to greater coordination of global contraction. At the molecular level, preliminary data from an experimental model suggest that CRT reduces regional and global molecular remodelling,

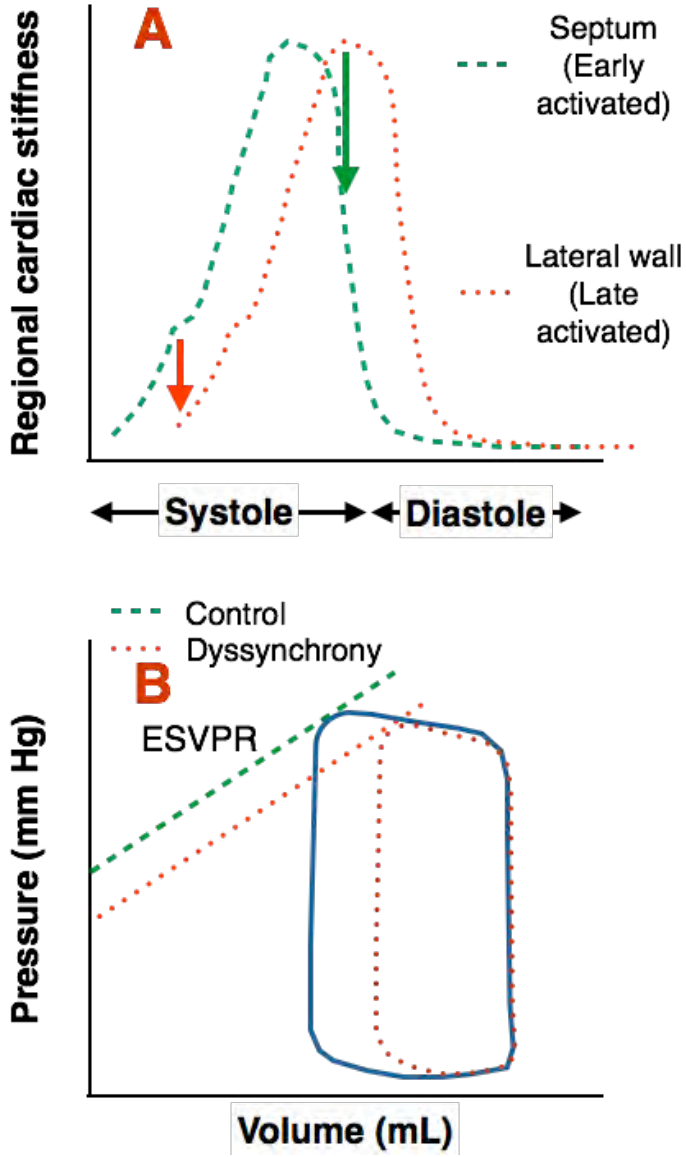
generating more homogeneous activation of stress kinases and reducing apoptosis (Chakir et al. 2008). The magnitude of the beneficial effect of CRT can be illustrated by the observations from two randomized trials. In the CARE-HF trial in which the median baseline LVEF was 25%, the LVEF in the CRT compared to no CRT group increased by 3.7% at three months and 6.9 % at 18 months (Cleland et al. 2005). The increase in systolic ventricular performance was associated with a rise in systolic pressure of approximately 6 mm Hg compared to no CRT (median baseline 110 mmHg) and a reduction in plasma N-terminal-pro-brain natriuretic peptide of 225 pg/mL at three months and 1122 pg/mL at 18 months (median baseline 1800 to 1900 pg/mL). A similar improvement was demonstrated in an analysis from the MIRACLE trial in which the LVEF in 323 patients was measured at baseline and at three and six months of therapy. At six months, there was a significantly greater increase in LVEF with CRT than without (3.6 versus 0.4%) (St John Sutton et al. 2003). Several mechanistic studies demonstrated that the improvements in global measures of LV function are accompanied by additional benefits. With CRT, increased ventricular performance is associated with no change or a mild reduction in myocardial energy demands and myocardial oxygen consumption, indicating improved myocardial efficiency (Ukkonen et al. 2003, Sundell et al. 2004). This finding is in contrast to the effects of inotropic therapy, which increases myocardial energy demand. In addition, CRT restores the normal increase in the rate of LV pressure rise in early systole (dP/dt) associated with higher heart rates, a phenomenon that is blunted or reversed in many patients with advanced HF (Kass 2006, Vollmann et al. 2006). These additional benefits may contribute to the improved metabolic reserve and enhanced exercise capacity during biventricular pacing. More importantly, CRT is associated with reverse ventricular remodelling in patients with heart failure. In the CARE-HF and MIRACLE trials, CRT produced significant reductions in LV end-systolic and end-diastolic dimensions, mitral regurgitant jet area, and, in MIRACLE, LV mass, all of which are signs of reverse remodelling (Breithardt et al. 2003, St John Sutton et al. 2003, Cleland et al. 2005, Zhang et al. 2006). In a follow-up study from the MIRACLE trial, these favourable

changes persisted at 12 months (Sutton et al. 2006). Reverse remodelling was also observed in the CONTAK CD, PATH-CHF, and VIGOR CHF trials (Stellbrink et al. 2001, Saxon et al. 2002, Higgins et al. 2003). Tissue Doppler echocardiography suggests that the main mechanism of benefit is improved mechanical synchrony (Stellbrink et al. 2001, Yu et al. 2002). The relationship between reverse remodelling and long-term clinical outcomes was evaluated in a study of 141 patients with advanced heart failure treated with CRT (Yu et al. 2005). Serial echocardiograms, including tissue Doppler imaging, were performed at baseline and three and six months after biventricular pacemaker implantation. Responders with reverse remodelling were defined as those patients with ≥10 % reduction in LV end-systolic volume. At a mean follow-up of almost two years, the 87 patients (62%) who were defined as responders with evidence of reverse remodelling had lower all-cause mortality compared to nonresponders (7 versus 31%), and lower cardiovascular mortality (2.3 versus 24%), as well as fewer heart failure events compared to nonresponders (12 versus 33%). In multivariate analysis, among a number of clinical and echocardiographic parameters, only a reduction in LV end-systolic volume was an independent predictor of all-cause or cardiovascular mortality. These findings support the hypothesis that reverse remodelling is an important component of the benefit from CRT, although the accepted definition of reverse remodelling based on percentage reduction of LV volumes may be problematic as there may be differences in the ability to attain such remodelling in different sizes, shapes, and pathologies of the ventricles. On the other hand, the lack of change in an observable reduction of LV volumes does not necessarily indicate the absence of reverse remodelling as changes in shape, geometry, wall thickness, and physiology may not be accounted for by a change in global volumes. Although it is generally thought that reverse remodeling, symptomatic improvement, and prognostic benefit correlate with each other, it may not be always the case (Yu et al. 2005).

CRT is also associated with an acute increase in cardiac index and a reduction in pulmonary capillary wedge pressure compared to normal sinus rhythm or right ventricular

pacing (Cazeau et al. 1994, Blanc et al. 1997, Leclercq et al. 1998, Auricchio et al. 1999, Kass et al. 1999), increased ability to tolerate more aggressive medical therapy and neurohormonal blockade (especially beta-blockade) (Aranda et al. 2005), improved diastolic function among responders (Waggoner et al. 2005) and improvement in heart rate variability (Fantoni et al. 2005). The benefit of CRT on reduction of atrial and ventricular arrhythmia was, however, somewhat controversial, with some studies suggested CRT reduces ventricular (Ermis et al. 2005) and atrial (Yannopoulos et al. 2007) arrhythmia, while larger trials did not confirm these observations (Young et al. 2003, Hoppe et al. 2006).

Figure 2-1. (A) Regional elastance plots of a dyssynchronous heart and (B) Pressure–volume loops showing effect of dyssynchrony on ESPVR.



(A) Plots of early (dashed) and late (dotted) activated myocardial regions are time-delayed. Vertical distance between the curves reflects transfer of forces from one region to the other. This difference is significant in early systole (red arrow) during isovolumic contraction reducing pressure development and this difference is even greater in late systole/early diastole (green arrow) reducing ejection and relaxation. (B) The ESPVR shifts rightward (dotted line), end-systolic volume increases, and stroke volume and work declines.

Chapter 3 Exercise, Stress, and Cardiac Function

3.1 Exercise physiology

Exercise is a common physiological stress used to elicit cardiovascular abnormalities not present at rest and to determine adequacy of cardiac function (Gibbons et al. 2002, Myers et al. 2009). Muscular exercise imposes three tasks on the circulation: pulmonary blood flow must be increased to enhance gaseous exchange in the lung, blood flow through working muscle must be raised, and a reasonably stable blood pressure must be maintained (Francis 1987, Shepherd 1987). The first requirement, a rise in pulmonary perfusion, is met by an increase in right ventricular output. The second requirement, an increase in muscle perfusion, is met by locally mediated vasodilatation which reduces the resistance to blood flow through the working muscle (Clausen 1976). In addition, an increase in LV output is necessary to supply the extra flow (Blomqvist et al. 1983, Weber et al. 1985). The third requirement, arterial pressure stability in the face of huge changes in system vascular resistance and cardiac output, is achieved by controlled vasoconstriction in non-active tissues (Skinner et al. 1969). The net effect of these changes is the diversion of an increasing fraction of the raised LV output into working muscles.

The magnitude of hemodynamic response during exercise depends on the severity of the exercise and the amount of muscle mass involved (Shephard et al. 1988). Anticipation of dynamic exercise results in an acceleration of ventricular rate due to vagal withdrawal, increase in alveolar ventilation, and increased venous return primarily as a result of sympathetic venoconstriction (Francis 1987). The net effect is to increase resting cardiac output before the start of exercise. In the early phase of exercise in the upright posture, cardiac output is increased by an augmentation in stroke volume mediated throughout he use of the Frank-Starling mechanism and heart rate (Manyari et al. 1983); the increase in cardiac output in the later phase of exercise is primarily due to a sympathetic-mediated increase in heart rate (Gerstenblith et al.

1976). At fixed submaximal workloads below anaerobic threshold, steady-state conditions are usually reached after the second minute of exercise, following which heart rate, cardiac output, blood pressure, and pulmonary ventilation are maintained at reasonably constant levels. During strenuous exercise, the pulmonary vascular bed can accommodate as much as a six fold increase in cardiac output with only modest increases in pulmonary artery pressure, pulmonary capillary wedge pressure, and right atrial pressure (Reeves et al. 1988); in normal individuals, this is not a limiting determinant of peak exercise capacity. Cardiac output can increase by four- to six fold above basal levels during strenuous exertion in the upright position, depending on genetic endowment and level of training (Blomqvist et al. 1983). The maximum heart rate and cardiac output are decreased in older individuals, partly because of decreased beta-adrenergic responsively. Maximum heart rate can be estimated from the formula 220 - age in years, with a standard deviation of 10 to 12 beats per minute (Gerstenblith et al. 1976, Tanaka et al. 2001). In the post exercise phase, hemodynamic return to baseline within minutes of termination of exercise. Vagal reactivation is an important cardiac deceleration mechanism after exercise and is accelerated in well-trained athletes but blunted in patients with chronic heart failure. Intense physical work or significantly cardiorespiratory impairment may interfere with achievement of a steady state, and an oxygen deficit occurs during exercise. The total oxygen uptake in excess of the resting oxygen uptake during the recovery period is the oxygen debt.

In summary, intense exercise can elicit a rapid, 15-fold increase in whole body oxygen uptake. This is accomplished by 10-fold increase in minute ventilation, a 5-fold increase in cardiac output, and a 3-fold increase in systemic oxygen extraction along with microvascular adaptations, which serve to increase the delivery of oxygen to muscles where it is most needed. Cardiopulmonary adaptations are tightly coupled to changes in skeletal muscle metabolism. Maximal cardiac output normally limits aerobic exercise capacity, while unused ventilatory and skeletal muscle function is measurable at peak exercise. Training enhances virtually every step of exercise gas exchange from the lung to the skeletal muscle mitochondrion.

3.2 Effect of heart rate, exercise and dobutamine on cardiac dyssynchrony

Mechanical dyssynchrony is augmented as heart rate increased by right atrial pacing in patients with heart failure and normal QRS duration. Kurita et al. performed a study to assess mechanical dyssynchrony in 20 heart failure patients with normal QRS duration, 12 heart failure patients with LBBB, and 20 control subjects at baseline and then followed by a 40 beat per minute increase in heart rate induced by right atrial pacing. Mechanical dyssynchrony in heart failure patients with normal QRS duration or LBBB was higher than that found in control subjects. In heart failure patients with normal QRS duration, mechanical dyssynchrony increased with increased heart rate. The resultant degree of mechanical dyssynchrony was similar to that at baseline in heart failure patients with LBBB. Increased heart rate did not affect dyssynchrony in the control patients (Kurita et al. 2007).

Lafitte et al. studied 65 consecutive heart failure patients and 50 matched healthy control patients undergoing exercise echocardiography. Conventional and tissue Doppler parameters were measured before and during symptom-limited exercise. In patients with normal LV function, exercise did not modify the extent of LV dyssynchrony. In contrast, in heart failure patients, LV dyssynchrony increased by at least 20% in about one third of the subjects, decreased by at least 20% in another third, and remained stable in the rest of the patients. Moreover, 26% of heart failure patients had either exercise induction or normalization of ventricular dyssynchrony. A significant association was found between exercise-induced changes in dyssynchrony and the presence of ischemic cardiomyopathy. Rest-exercise differences in ventricular dyssynchrony were correlated with changes in cardiac output and mitral regurgitation. These findings suggested that exercise can alter the magnitude of ventricular dyssynchrony in heart failure patients. Some patients have a response to exercise with induction of ventricular dyssynchrony, whereas others show normalization, and changes in ventricular dyssynchrony during exercise correlate with alterations in cardiac output and mitral regurgitation (Lafitte et al. 2006).

D’Andrea et al. describe a series of 60 patients with idiopathic dilated cardiomyopathy and narrow QRS complex duration who were submitted to supine bicycle exercise echocardiography and cardiopulmonary exercise testing. Cardiac synchronicity was measured at rest and during exercise. The standard deviation of time intervals between the onset of the QRS complex and the peak myocardial systolic velocity of 12 LV segments (six at basal level and six at mid level) was calculated. The effective regurgitant orifice of mitral regurgitation was obtained at rest and exercise by the proximal flow convergence technique. Dynamic LV dyssynchrony unmasked by exercise was found in more than half of the patients. Increased LV dyssynchrony during exercise was independently associated with increased functional mitral regurgitation, reduced exercise capacity, and lower forward stroke volume at peak exercise stress (D'Andrea et al. 2007). Lancellotti et al. have distinguished three groups of changes in dyssynchrony with exercise: patients without difference between rest and exercise, patients with dyssynchrony at rest that normalized at exercise, patients without dyssynchrony at rest that appeared at exercise (Lancellotti et al. 2005). These studies strengthen the concept of dynamic dyssynchrony during exercise.

Dynamic dyssynchrony was also observed in studies using pharmacological agent such as dobutamine as stressor. The onset of action of intravenous infusion of dobutamine is about one to two minutes, and the half-life is two minutes. Similar to exercise, dobutamine increases heart rate, myocardial contractility, and myocardial oxygen demand. The increment in systolic blood pressure is much less with dobutamine compared with exercise. Exercise stress is more physiologic and provides important information in relation to exercise capacity which is an important predictor of outcome.

Chattopadhyay et al. have shown that in patients with LV dysfunction, the prevalence and severity of dyssynchrony increases during dobutamine stress (Chattopadhyay et al. 2008). Dobutamine-induced dyssynchrony was subsequently reported in patients with dilated cardiomyopathy by other investigators (Parsai et al. 2009, Yagishita-Tagawa et al. 2013).

Dynamic dyssynchrony during dobutamine echocardiography appears to be associated with adverse cardiovascular outcome (Matsumoto et al. 2013) and may be a better predictor of CRT response compared to resting dyssynchrony (Parsai et al. 2009, Suma et al. 2012). Parsai et al. showed that low-dose dobutamine increases and unmasks LBBB-induced dyssynchronous motion, easing its detection in systolic heart failure patients. The degree of clinical and echocardiographic response correlated with the extent of peak "septal flash" motion in isovolumic contraction time seen during low-dose dobutamine (Parsai et al. 2009). Cardiac resynchronization may not improve LV dyssynchrony in patients in whom LV dyssynchrony disappears at stress in contrast to those in which stress increases LV dyssynchrony. Valzania et al. have shown that CRT-induced improvement of LV synchronicity is also maintained during stress in responders to resynchronization (Valzania et al. 2007).

LV dilation, remodelling, and dyssynchrony are linked to functional mitral regurgitation in patients with systolic heart failure. There is an association between exercise-induced changes in mitral valve deformation, severity of mitral regurgitation, LV remodelling, and dyssynchrony. Dynamic mitral regurgitation is probably both a cause for progressive LV dyssynchrony and a result of it. Dynamic mitral regurgitation is also a determinant of rapid QRS widening, and predicts short-term and long-term mortality and hospitalization for cardiac decompensation (Lancellotti et al. 2003, Lancellotti et al. 2004, Pierard et al. 2004, Lancellotti et al. 2005). Because of the link between dynamic LV dyssynchrony and dynamic mitral regurgitation, it can be hypothesized that exercise-induced increase in dyssynchrony can be associated with a worse outcome and that conversely exercise-induced normalization of LV dyssynchrony can predict a better outcome. Therefore, assessment of dyssynchrony during exercise or dobutamine infusion could provide incremental and unique information that are important for prognostication and guidance of treatment including, but not limited to, biventricular pacing in patients with heart failure.

Part II Objectives And Hypothesis Of The Thesis

Chapter 4 Unanswered Questions In Cardiac Dyssynchrony

Recognition of the clinical significance of cardiac dyssynchrony in systolic heart failure opens a new horizon of cardiovascular research with many ensuing questions that are new and clinically relevant. In this thesis, we will try to address these questions.

4.1 Is cardiac dyssynchrony present in HFPEF and/or early stage of heart failure?

Patients with heart failure but with a preserved ejection fraction (HFPEF) constitutes about half of the heart failure occurrence. We do not know whether cardiac dyssynchrony, which has been well described for systolic heart failure, is also present in patients with HFPEF. As HFPEF has yet no proven effective treatment, identifying potential novel therapeutic targets such as cardiac dyssynchrony will be important for future development of new treatment strategies. Furthermore, in patients at risk of, but not yet have, heart failure (i.e. stage A or B heart failure according to the AHA/ACC classification; for instance, patients with coronary artery disease without symptoms or signs of heart failure), the prevalence and significance of cardiac dyssynchrony remains unknown.

4.2 Does cardiac dyssynchrony contribute to ADHF?

Both systolic heart failure and HFPEF can be subcategorized as chronic versus acute. ADHF is a worldwide leading cause of hospital admission and mortality. Many such decompensated episodes have no clinically obvious triggers. Transient acute increase of cardiac dyssynchrony has been suspected to be a potential trigger of ADHF, but scientific evidence is limited. Confirming the pathogenic role of cardiac dyssynchrony in ADHF has important therapeutic implications as CRT may have a specific role in preventing hospitalization or mortality due to acute cardiogenic pulmonary oedema.

4.3 Is cardiac dyssynchrony in HFPEF a dynamic phenomenon?

The heart is a dynamic organ. In the previous chapter, we discussed the evidence that showed conduction and mechanical dyssynchrony of the heart can be precipitated or worsened with increase in heart rate and by exercise or pharmacological stress in patients with systolic heart failure. In patients with HFPEF, however, we do not know whether and how cardiac dyssynchrony alters in response to hemodynamic stressors as we usually assess dyssynchrony with our patients at a resting state; and therefore there is little data of the potential clinical significance of dynamic cardiac dyssynchrony in HFPEF.

4.4 What is the therapeutic implication of dynamic dyssynchrony?

Although CRT has proven to reduce mortality and improve symptomatic status in patients with HF, about 30% of the CRT recipients did not respond clinically. Among many factors, inadequate optimization of the CRT settings to achieve LV and atrioventricular (AV) synchronization appears to be an important cause for the lack CRT response in some patients. In current clinical practice, assessment of cardiac dyssynchrony in CRT recipients is performed at rest only. We do not know whether optimization of the CRT settings should be performed according to the dyssynchrony status at rest or during exercise. The latter, though being more difficult to perform, is physiologically more sound as most patients are up and about and usually not in a resting state. The impact of exercise dyssynchrony on CRT optimization to improve treatment response is not completely understood and may have important impact on improving response rate of CRT.

Chapter 5 General Objectives and Hypotheses of The Thesis

5.1 General Objectives

The general objectives of this thesis include the followings:

(i) To evaluate the prevalence and characteristics of LV mechanical dyssynchrony (both systolic and diastolic) in patients with coronary artery disease (CAD) with preserved or depressed LVEF.

(ii) To elucidate the impact of LV mechanical dyssynchrony on ventricular function and its relationship with the occurrence of acute HFPEF in patients presenting with ACS.

(iii) To examine whether LV mechanical dyssynchrony would change dynamically during dobutamine stress in hypertensive patients with HFPEF and the potential importance of dynamic dyssynchrony as a determinant for the development of HFPEF.

(iv) To examine the relationship between LV mechanical dyssynchrony and acute decompensation of systolic heart failure.

(v) To examine the impact of heart rate increase during different levels of exercise on the hemodynamically optimal AV delay.

(vi) To evaluate the magnitude of change in optimal AV delay during exercise in CRT patients comparing to the physiological change of AV delay in healthy controls.

5.2 Hypotheses to be tested

The following hypotheses are tested in the five clinical studies included in this thesis:

(i) LV mechanical dyssynchrony is prevalent in CAD patients with preserved EF without signs or symptoms of HF.

(ii) LV mechanical dyssynchrony in CAD patients may impair LV function despite preserved EF and is more severe in patients presenting with HFPEF that complicates ACS.

(iii) LV mechanical dyssynchrony changes with stress and dynamic exaggeration of LV mechanical dyssynchrony is associated with impaired myocardial functional reserve and the clinical occurrence of HFPEF in patients with chronic essential hypertension.

(iv) Patients who presented with acute decompensated systolic heart failure may have more LV mechanical dyssynchrony than those who had chronic stable heart failure without recent exacerbation.

(v) In CRT recipients, AV dyssynchrony optimization at rest may not be adequate to maximize the hemodynamic benefit of CRT during exercise when cardiac demand is increased.

Part III General Methodology

Chapter 6 Study Populations

6.1 Patients with structural heart disease at risk of heart failure

6.1.1 Chronic CAD without heart failure:

A total of 311 consecutive patients referred to a cardiac specialty clinic in a tertiary university hospital with the diagnosis of chronic CAD were prospectively recruited. Electronic medical records including medical history, physical findings, ECG, stress testing and coronary angiography of patients with a referral reason of evaluation of chest pain or suspected CAD were reviewed. The diagnosis of chronic CAD was established by the presence of chest pain plus one or more of the following objective evidence of CAD: (i) documented prior MI (myocardial infarction) based on the presence of pathological Q waves in two or more contagious leads on an ECG; (ii) coronary stenosis on invasive coronary angiography of at least 70%; and (iii) in very few patients by the presence of myocardial ischemia on functional stress testing. Study patients were considered to have preserved EF if EF was ≥50% (n=94) as measured by echocardiography using biplane Simpson's method. Those who had an EF<50 % were considered as having depressed EF (n=217). Patients who had atrial fibrillation, previous pacemaker implantation, restrictive cardiomyopathy, aortic or mitral stenosis, prosthetic valves, severe mitral annular calcification, recent evidence of acute myocardial schema or revascularization within the past 6 months were excluded.

6.1.2 Acute coronary syndrome (ACS) without heart failure

A total of 47 consecutive patients presented to the emergency department with ACS in whom symptoms or signs of heart failure did not develop during the hospital stay and had a normal EF (≥50%) on echocardiography on presentation were studied. All subjects presented to the emergency department with acute chest pain >30 min and had ischemic changes on the electrocardiogram (ST-segment depression or elevation ≥0.1 mV and/or T-wave inversion on at

least 2 contiguous leads) and/or elevated serum cardiac biomarker (troponin T) within 6 h of presentation. Patients with EF <50%, atrial fibrillation, pacemaker implantation, more than a mild degree of valvular dysfunction, a prosthetic valve, pericardial constriction, and myocardial rupture were excluded.

6.1.3 Hypertensive left ventricular hypertrophy (LVH) without heart failure

A total of 34 patients with hypertensive LVH but without symptoms or signs of heart failure were identified from our outpatient echocardiography database of hypertensive patients and the lack of clinical HFPEF was confirmed by formal history and physical examination. All patients had EF ≥50%. LVH was defined as left ventricular mass index (LVMI) >95 g/m^2 for women and >115 g/m^2 for men as calculated from LV linear dimensions according to recommendations from the American Society of Echocardiography. Exclusion criteria include known significant CAD, recent ACS or revascularization within 6 months, prior myocardial infarction, prior history of a positive stress test, primary cardiomyopathy, significant valvular disease, chronic pulmonary disease, chronic renal failure, permanent atrial fibrillation, and those who had received pacemaker implantation.

6.2 Patients with systolic heart failure

6.2.1 Acute decompensated systolic heart failure

A total of 84 consecutive patients who presented to our emergency department with ADHF with depressed EF requiring hospitalization were studied. ADHF was defined as a clinical syndrome of acute respiratory distress associated with elevated jugular venous pressure, peripheral oedema, pulmonary rales, and radiographic evidence of alveolar pulmonary oedema, in association with an EF<50%. Two cardiologists verified the diagnosis of acute decompensated heart failure independently. The index hospital admission may be the first time presentation of newly diagnosed HF or acute exacerbation of prior heart failure. Patients with EF≥50%, ACS, primary valvular disease, atrial fibrillation, and pacemaker implantation were excluded.

6.2.2 Chronic stable systolic heart failure

A total of 61 patients with chronic stable systolic heart failure (EF<50%) was selected by means of a review of our outpatient clinic database of patients who had no evidence of decompensation or hospitalization for heart failure over the past 6 months. Exclusion criteria were the same as its acute counterpart.

6.2.3 CRT recipients for dynamic exercise dyssynchrony assessment

A total of 41 patients with heart failure previously implanted with a CRT device for more than 6 months, who are able to complete a supine bicycle exercise stress protocol, being in sinus rhythm and having had intact AV conduction, were recruited. In order to ensure physiological sinus rate response to exercise, we specifically excluded patients if previous device interrogations indicated that they required atrial rate support at rest. Other exclusion criteria were chronotropic incompetence, atrial fibrillation and prior valvular surgery.

6.3 Patients with HFPEF

6.3.1 HFPEF patients with ACS

Fifty-five consecutive patients who were admitted to a tertiary care hospital for ACS complicated by acute heart failure with preserved EF (≥50%) on presentation were prospectively studied. Definition of ACS was discussed as above. The diagnosis of acute heart failure was made clinically by the attending physicians during acute hospitalization and independently verified by a cardiologist based on documented symptoms of HF (acute onset or worsening of dyspnoea), signs of fluid retention (elevated jugular venous pressure and dependent oedema), in addition to radiological evidence of pulmonary vascular congestion. Patients with EF <50%, atrial fibrillation, pacemaker implantation, more than a mild degree of valvular dysfunction, a prosthetic valve, pericardial constriction, and myocardial rupture were excluded from the study.

6.3.2 HFPEF patients with hypertension

A total of 47 hypertensive HFPEF patients were prospectively identified from consecutive patients admitted to the hospitals with the admission diagnosis of heart failure and a prior history

of hypertension. Heart failure was rigorously defined by Framingham criteria and independently adjudicated by two cardiologists. All patients had an EF >50% on echocardiography performed within 24–72 h of index admission. Exclusion criteria include known significant CAD, recent ACS or revascularization (<6 months), prior myocardial infarction, prior history of a positive stress test, primary cardiomyopathy, significant valvular disease, chronic pulmonary disease, chronic renal failure, permanent atrial fibrillation, and those who had received pacemaker implantation

6.4 Normal subjects

A total of 120 normal subjects (>18 year-old) were recruited as the reference group. Normal subjects had no history of cardiovascular or systemic disease, and had normal physical examination, ECG and echocardiographic results. Age and gender matching to the comparing study populations was performed in various studies as appropriate. Healthy subjects referred for exercise or stress test evaluation but had otherwise normal history, physical examination, electrocardiography, resting and stress echocardiography were recruited as normal controls for studies involving exercise or dobutamine stress echocardiography as part of the investigation protocol.

Chapter 7 Echocardiography

Echocardiography is the main imaging tool for the assessment of LV function and mechanical dyssynchrony in our studies. Transthoracic echocardiography with 2D, Doppler and tissue Doppler imaging was performed to all participating subjects at rest, and, in studies involving evaluation of dynamic dyssynchrony and myocardial functional reserve, echocardiography was performed at rest as well as during exercise or dobutamine infusion. For studies including subjects presenting with acute decompensated heart failure or ACS, echocardiography was performed within 72 hours of clinical presentation to capture the LV function and dyssynchrony status in the acute phase.

7.1 Assessment of LV dimensions and ejection fraction

Linear and volumetric measurements of LV chamber size were performed according to the recommendations issued by the American Society of Echocardiography. Linear measurements of LV dimensions are made by measuring the internal dimensions the LV minor axis at the level of mitral leaflet tips in the parasternal long-axis view of 2D echocardiography. Quantitative volumetric measurements of the LV were obtained by tracing of the endocardial border in apical 4- and 2-chamber views in end-diastole and end-systole using the biplane method of disks (modified Simpson's rule). The investigators were experienced echocardiographers who were familiar with the Simpson's method. The reproducibility of LVEDV and LVESV, measured by coefficients of variation, ranged from 3-9% for experienced investigators (Otterstad et al. 1997). The LV is mathematically divided along its long axis into a series of disks of equal height. Individual disk volume is calculated as height × disc area (assuming circular disks). LV volume is then represented by the sum of disk volumes. LVEF was calculated as the proportion of the end-diastolic volume (EDV) ejected by the LV with each contraction:

$$EF = 100\% \times (EDV - ESV) / EDV.$$

7.2 Assessment of global longitudinal function and mechanical dyssynchrony

7.2.1 Tissue Doppler imaging (TDI)

TDI uses the Doppler principles to measure tissue velocities. A wall filter is used to distinguish between signals originating from moving tissue (high amplitude, low velocities) and blood flow (low amplitude, high velocities). TDI was performed at apical views (apical 4-chamber, 2-chamber, and long-axis) for the long-axis/major-axis motion of the LV as previously described (Yu et al. 2002, Yu et al. 2003). 2D echocardiography with TDI-colour imaging views (apical 4-chamber, 2-chamber, and long-axis views) were optimized for pulse repetition frequency, colour saturation, sector size, and depth, that maximized a highest possible frame rate of ≥100 Hz. At least 3 consecutive beats were stored, and the images were analyzed off-line with the aid of a customized software package (EchoPac PC, Vingmed-General Electric). Myocardial velocity curves were reconstituted off-line using the 6 basal and 6 mid-segmental model, which consisted of septal, lateral, anteroseptal, posterior, anterior, and inferior segments at both basal and mid-levels in the LV. The basal segments were sampled just above the mitral annulus level, and the middle segments were sampled at the mid-level of the LV. The time to peak myocardial systolic velocity during the ejection phase (Ts) and the time to peak myocardial early diastolic velocity (Te) were measured with reference to QRS complex.

7.2.2 Assessment of global LV longitudinal myocardial function

The architecture of LV myocardial fibres has a unique spiral pattern, with the subendocardial and subepicardial fibres oriented mainly longitudinally and the mid fibres circumferentially. The systolic velocity of the mitral annulus (s') correlates well with LVEF and SV, with important prognostic implications. In this thesis, the LV longitudinal systolic myocardial function was assessed by averaging the peak systolic myocardial velocities at the six basal segments (mean Sm) by offline TDI analysis with the sample volumes placed just above the mitral annulus. Similarly, the LV longitudinal early diastolic myocardial function was

assessed by averaging the early diastolic myocardial velocities of the six basal segments (mean Em).

7.2.3 Indices of LV mechanical dyssynchrony

The timings of beginning and end of ejection (aortic valve opening and closure) and those of diastole (mitral valve opening and closure) were derived from continuous-wave Doppler of aortic forward flow and pulse-wave Doppler of mitral inflow. Markers with valve opening and closing events would appear on the electrocardiogram (ECG) recordings during off-line TDI analysis to ensure only the peak myocardial systolic (Sm) and peak myocardial early diastolic (Em) velocities with their corresponding Ts and Te were measured accurately during ejection and early diastolic phases. The time to peak myocardial systolic velocity during the ejection period (Ts) and the time to peak myocardial early diastolic velocity (Te) were measured for each segment with reference to the onset of QRS complex. The ECG lead showing the largest amplitude of the QRS complex with a readily distinguishable onset point of the complex was used. The standard deviation (SD) of Ts (Ts-SD) and Te (Te-SD) of the 12 LV segments were calculated. The inter- and intra-observer variability for measuring dyssynchrony were compared in 60 consecutive measurements and were 4.7 and 3.2% respectively (Figure 7-1).

It is important to understand the differences between regional wall motion abnormality that is conventionally described on 2D echocardiography or cineangiography (Gibson et al. 1978) and mechanical dyssynchrony described on TDI. Electrical dyssynchrony refers to a prolonged conduction time in the ventricles resulting in a prolonged QRS duration. Mechanical dyssynchrony is the mechanical discoordination, usually associated with simultaneous contraction and stretch in different regions of the LV as well as delays in the time to peak contraction from one segment to another. Wall motion analysis measures the amplitude of the regional LV myocardial motion, while dyssynchrony analysis measures the dispersion of the timing (TDI) of myocardial motion. Regional wall motion abnormality (e.g. due to ischemia or infarction) can be present without significant dispersion of the timing of peak myocardial

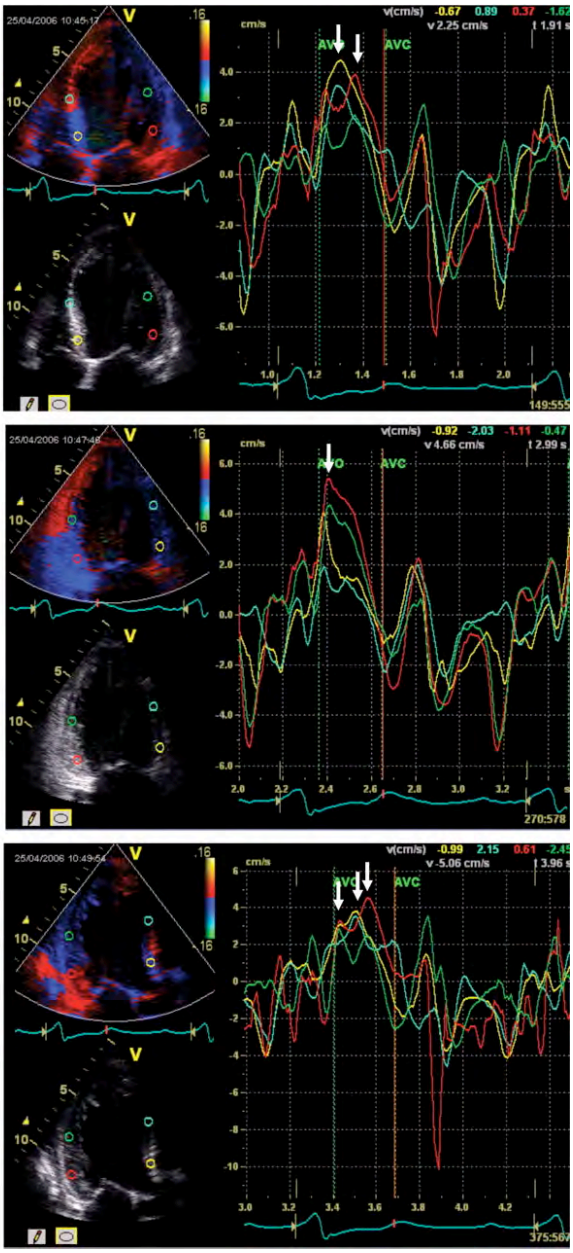
contraction. On the other hand, mechanical dyssynchrony (abnormality in regional timing of myocardial motion), sometimes even in the absence of a significantly prolonged QRS duration, can be present without significant hypo-, a-, or dyskinesia of the regional wall motion (abnormality in regional amplitude of myocardial motion). Moreover, systolic displacement (cineangiography) and/or thickening (2D echocardiography) of the left ventricular myocardium are assessed in regional wall motion analysis, whereas the rate of change of the myocardial motion (velocity, strain rate) is typically assessed in dyssynchrony analysis using TDI. Therefore, dyssynchrony assessment of LV myocardium using TDI assess the dispersion of the rate of rise of contractile force with regional myocardium rather than the regional position of endocardium, and may therefore better reflect the inefficiency in energy use during dyssynchronous myocardial contraction (and relaxation). Because of its high temporal resolution, TDI is useful for dyssynchrony assessment to demonstrate subtle heterogeneity in the timing of regional myocardial motion.

7.3 Assessment of LV diastolic filling

Mitral inflow velocities were measured using spectral Doppler echocardiography by placing the pulse-wave Doppler cursor at the tips of the opened mitral valve in the apical 4-chamber view. To assess diastolic function, peak mitral inflow velocity of the early rapid-filling wave (E), peak velocity of the late filling wave due to atrial contraction (A), and deceleration time of early mitral inflow velocity (DT) of the early filling were measured. The mean Em was assessed by averaging the myocardial early diastolic velocities at the 6 basal segments at offline TDI analysis. Diastolic dysfunction was graded with reference to a classification scheme previously described (Lester et al. 2008). Normal diastolic function was defined as E/A = 0.9 to 1.5, DT = 160 to 240 ms, and E/Em <10; grade 1 (abnormal relaxation) if E/A <0.9 and DT >240 ms; grade 2 (pseudonormal) if E/A = 0.9 to 1.5, DT = 160 to 240 ms, plus either E/Em ≥10 or E/A reversal on Valsalva manoeuvre; and grade 3 (restrictive filling) if E/A >2, DT <160 ms

and E/Em ≥15. The diastolic function in patients that did not fall into any category and was classified as undetermined.

Figure 7-1. An example of dyssynchrony assessment using color-coded tissue Doppler imaging in a 12-segment model.



Myocardial velocity curves of the 6 basal and 6 mid segments of the left ventricle were reconstituted from the color-coded TDI images obtained at the 3 apical views. The time to peak systolic (arrows) velocities of each segment is measured and their dispersion in terms of standard deviation is calculated. Reprinted with permission from Oxford University Press, Yu CM, Sanderson JE, Gorcsan J 3rd. Echocardiography, dyssynchrony, and the response to cardiac resynchronization therapy. Eur Heart J. 2010;31:2326-37.

Chapter 8 Exercise and pharmacological stress protocols

Dynamic dyssynchrony and LV functional reserve were examined by exercise or pharmacological stress echocardiography using the following stress protocols.

8.1 Exercise protocol

A symptom-limited graded bicycle exercise test was performed with the patient in the semi-supine position on a tilting exercise table. The patient's feet were secured to the pedals of the recumbent bicycle, and the patient was instructed to slowly begin pedalling. In order to achieve a target sinus rate of 20 beats above the patient's baseline rate, we instructed patients to increase the speed of their pedalling and/or we gradually increased the levels of bicycle resistance based on the cardiologist's estimate of the patient's target workload. The patient's atrial rate was maintained to within 10 bpm of his or her target rate by continually adjusting the resistance of the bicycle and coaching the patient to alter the pedalling speed as necessary. After the patient achieved the first target rate (stage I), AV delays were reprogrammed at the elevated rate by the same iterative method as performed at baseline. After completion of the first exercise stage, patients began the second stage of the exercise protocol with a target sinus rate of 40 bpm above his or her baseline rate (stage II). This second stage was performed immediately after the first stage by gradually increasing the resistance of the bicycle. The patient's heart rate was again maintained to within 10 bpm of his or her targeted rate during the imaging procedure by adjusting the resistance of the bicycle as required, and the Doppler images were acquired as previously described. Doppler images from three consecutive intrinsic cardiac cycles were recorded and averaged. All echocardiographic data were analyzed by two experienced sonographers, with disagreements settled by consensus.

8.2 Pharmacological stress protocol

Dobutamine infusion was started at 5 μg/kg/min and increased every 3 min to 10, 20, 30, and 40 μg/kg/min. The test was terminated if any of the following endpoints was reached:

achieved the target heart rate [85% × (220 − age in years)], new regional wall-motion abnormality, significant arrhythmia, persistent hemodynamic compromise, angina or intolerable symptoms. In the absence of contraindications, atropine (0.3–1.0 mg intravenously) was given if the target heart rate was not reached. Image acquisition with 2D and coded-coded TDI was performed at rest and at peak stress using the apical four-chamber, two-chamber, and long-axis views.

Part IV Clinical Studies

Chapter 9 Study 1: Left Ventricular Dyssynchrony in Coronary Artery Disease with Preserved Ejection Fraction

9.1 Introduction

We have previously discussed that, in patients with heart failure and LV systolic dysfunction, LV dyssynchrony is a common phenomenon (Yu et al. 2003). In this chapter we shall establish the existence of, and evaluate the associated factors that may contribute to, cardiac dyssynchrony in patients with structural heart disease, exemplified by CAD, but no symptoms or signs of heart failure. It is believed that the presence of LV dyssynchrony in patients with stage C or D heart failure can impair the function of a failing ventricle further, resulting in worsening of symptoms and clinical outcomes (Baldasseroni et al. 2002, Duncan et al. 2004). The patients that we are going to study in this chapter belongs to the clinical group of stage A or B heart failure according to the AHA/ACC classification and the aim of this chapter is to extend our view of cardiac dyssynchrony from as being a pathogenic mechanism that worsen LV function in patients with established heart failure to a pre-existing (and potentially correctable) condition that occur earlier in the clinical progression of heart failure even before clinical signs or symptoms of heart failure develop.

Electrical dyssynchrony refers to the asynchronous electrical activation of the LV in association with intraventricular conduction disturbance (e.g. bundle branch block), whereas the term mechanical dyssynchrony is often used to describe the mechanical effects of asynchronous ventricular contraction and relaxation, which may or may not be associated with electrical conduction delay. Although LV dyssynchrony was initially recognized as a phenomenon related only to electrical conduction delay in systolic heart failure with widened QRS complexes, previous studies have reported that it also exists in approximately 30–40% of patients with a

normal QRS duration (Yu et al. 2003) and in a significant number of patients with heart failure and preserved EF (Wang et al. 2007, Yu et al. 2007). CAD is one of the commonest causes of heart failure; however, there are limited results about mechanical dyssynchrony in CAD patients with preserved EF. Several previous studies in animals and patients have suggested that myocardial ischemia results in a delay in relaxation (Bonow et al. 1985, Garcia-Fernandez et al. 1999, Pislaru et al. 2001, Abraham et al. 2002, Wang et al. 2005) and contraction (Pislaru et al. 2001, Lin et al. 2004, Lyseggen et al. 2005, Zwanenburg et al. 2005) without producing a regional wall motion abnormality on conventional echocardiography. As discussed in the previous chapters, TDI has been validated for assessment of the timing of regional myocardial motions from which indices of systolic and diastolic dyssynchrony can be derived (Yu et al. 2002, Yu et al. 2003, Yu et al. 2004). In the present study, we examined the presence and characteristics of mechanical dyssynchrony (both systolic and diastolic) in CAD patients with preserved EF in comparison with CAD patients with depressed EF and healthy controls.

9.2 Methods

9.2.1 Subjects

A power analysis was conducted to determine the number of participants needed in this study. An ANOVA examined the null hypothesis that the dyssynchrony indices (Ts-SD and Te-SD) were not different among the 3 groups of subjects: (i) CAD patients with preserved EF, (ii) CAD patients with depressed EF, and (iii) healthy controls. Based on previous comparable data, mean Te-SD of the normal population and that of patients with systolic heart failure were approximately 20ms and 38ms, respectively (Yu et al. 2007). Assuming the mean Te-SD of CAD patients with depressed EF but no heart failure symptoms to be lower than those with systolic heart failure (e.g. 30ms), and Te-SD of CAD patients with preserved EF to be equal to the grand mean of the 3 groups (25ms), and the standard deviation of Te-SD within each group to be 15ms (Yu et al. 2002, Yu et al. 2003, Yu et al. 2007), the effect size f was calculated to be 0.272. The alpha for the ANOVA was set at 0.05. To achieve power of 0.8, a minimal sample

size of 135 is required to detect a significant model. Based on similar statistical consideration for Ts-SD, to detect an effect size of f=0.311, alpha=0.05, power=0.8, a minimum sample size of 105 was needed.

A total of 311 consecutive patients referred to a cardiac specialty clinic in a tertiary university hospital with the diagnosis of CAD and 117 age- and gender-matched healthy subjects were prospectively recruited into the present study. The diagnosis of CAD was established by the presence of chest pain plus one or more of the following objective evidence of CAD: (i) documented prior MI (myocardial infarction) based on the presence of pathological Q waves in two or more contagious leads on an ECG; (ii) coronary stenosis on invasive coronary angiography of at least 70%; and (iii) in very few patients by the presence of myocardial ischemia on functional stress testing. Of the 311 patients in the present study, 115 had documented coronary stenosis on coronary angiography, of which 57 had an EF ≥50% and 58 had an EF <50%. Prior MI was evident in 208 patients. In 22 patients, CAD was diagnosed based on typical angina symptoms and positive stress testing. These patients either refused or were considered not to be clinical candidates for coronary revascularization due to co-morbid conditions. Patients who had atrial fibrillation, previous pacemaker implantation, restrictive cardiomyopathy, aortic or mitral stenosis, prosthetic valves, severe mitral annular calcification or revascularization within the past 6 months were excluded.

Study patients were considered to have preserved EF if EF was ≥50% (preserved EF group; n=94) as measured by echocardiography using biplane Simpson's method. Those who had an EF <50% were considered as having depressed EF (depressed EF group; n=217). Control subjects had no history of cardiovascular or systemic disease, and had normal physical examination, ECG and echocardiographic results. The study was approved by the ethics committee for clinical research at our institution, and written informed consent was obtained from all subjects.

9.2.2 Echocardiography:

Transthoracic echocardiography was performed for all subjects (Vivid 7; Vingmed-General Electric). LV volumes and EFs were assessed by biplane Simpson's method using the apical four- and two-chamber views. At least three consecutive beats in sinus rhythm were measured, and the average values were taken. Regional wall motion abnormalities were evaluated by visual assessment of systolic wall thickening on two-dimensional echocardiography (Lang et al. 2005).

TDI was performed at apical views (apical four-chamber, two-chamber and long-axis views) for assessing the longitudinal motions of the left ventricle (Yu et al. 2002, Yu et al. 2003, Yu et al. 2004). Two-dimensional echocardiography with colour TDI optimized for pulse repetition frequency, colour saturation, sector size and depth were obtained to maximize the frame rate to 100 Hz or higher. At least three consecutive beats were stored, and the images were analyzed offline using customized software (EchoPac-PC, version 6.1.0; Vingmed-General Electric). Myocardial velocity curves were reconstituted offline using the six-basal/six-mid-segmental model, which consisted of septal, lateral, anteroseptal, posterior, anterior and inferior segments at both basal and mid-levels of the left ventricle (Yu et al. 2002, Yu et al. 2003, Yu et al. 2004). The investigators who performed the TDI analysis were blinded from the clinical information of the subjects. Two-dimensional image and TDI analyses were performed separately such that the investigator who analyzed the TDI curves was blinded from the two-dimensional information, such as EF and regional wall motion abnormalities. The basal segments were sampled just above the mitral annulus level, and the mid-segments were sampled at the midlevel of the left ventricle. Ts (time to peak myocardial systolic velocity during the ejection period) and Te (time to peak myocardial early diastolic velocity during the filling period) were measured with reference to the onset of the QRS complex. The timings of the beginning and the end of LV ejection (aortic valve opening and closure) and filling (mitral valve opening and closure) periods were determined by continuous-wave Doppler of the aortic forward flow and pulse-wave Doppler of the mitral inflow. Markers with valve opening and closing

events would appear on the ECG recordings during offline TDI analysis to ensure only the peak myocardial systolic and early diastolic velocities with their corresponding Ts and Te were measured accurately. For the assessment of LV intra-ventricular dyssynchrony, Ts-SD (SD of Ts) and Te-SD (SD of Te) as well as Ts-diff (maximal difference in Ts) and Te-diff (maximal difference in Te) of all at the 12 LV segments were calculated (Yu et al. 2003, Yu et al. 2004).

9.2.3 Statistical analysis

Data were analyzed using SPSS (version 13.0). For the comparison of mechanical dyssynchrony and other parametric data among the various groups, independent Student's t tests and one-way ANOVAs with post-hoc Scheffe's test for inter-group differences were employed, where appropriate. Linear regression was employed to investigate the relation between two parametric variables. Comparison of categorical data was performed using a Pearson χ^2 test. Continuous data are expressed as means±SD. A P value <0.05 was considered statistically significant.

9.3 Results

Among the preserved EF, depressed EF and control groups, there were no significant differences in age (63.5±10.1, 64.8±11.6 and 64.2±9.4 years respectively) and gender distribution (76, 74, and 71% male respectively). The clinical and demographic characteristics of the two groups of CAD patients are shown in Table 9.1. The prevalence of hypertension, diabetes and MI were similar. However, more patients with depressed EF were prescribed loop diuretics, ACEIs (angiotensin-converting enzyme inhibitors) and/or ARBs (angiotensin receptor blockers).

Table 9-1. Comparison of clinical and demographic characteristics between CAD patients who had preserved and depressed EF

	CAD patients with			
	Preserved EF (*n*=94)	**Depressed EF (*n*=217)**	**χ^2**	***P* value**
Age (years)	63.5±10.1	64.8±11.6	–	NS
Male gender (%)	76	74	1.35	NS
CCS angina class (%)			67.5	<0.001
I	57	9		
II	35	42		
III	8	44		
IV	0	5		
Hypertension (%)	53	55	0.07	NS
Diabetes mellitus (%)	39	44	0.52	NS
MI (%)	60	70	3.25	NS
QRS duration (ms)	84.0±15.7	120.2±32.6	–	<0.001
QRS >120 ms (%)	6	30	20.68	<0.001
EF (%)	61.7±8.3	34.8±9.7	–	<0.001
Coronary angiography (%)			18.5	<0.001
SVD/DVD	86	46		
TVD/LMD	14	54		
Medication (%)				
Antiplatelet agent	93	73	15.29	<0.001
ACEI or ARB	54	71	8.15	<0.01
β-Blocker	73	40	29.11	<0.001
Loop diuretic	24	65	48.18	<0.001

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CCS, Canadian Cardiovascular Society; DVD, double-vessel disease; LMD, left main stem disease; NS, not significant; SVD, single-vessel disease; TVD, triple-vessel disease.

9.3.1 Systolic mechanical dyssynchrony in CAD patients with preserved and depressed EF

Compared with normal controls, systolic mechanical dyssynchrony was highly prevalent in CAD patients with preserved EF. Both Ts-SD and Ts-diff were significantly prolonged in the preserved EF group, but were more so in the depressed EF group (Table 9.2). Using a cut-off value of Ts-SD >33 ms derived from the upper 2 SD of the mean from normal subjects [8], 41% (39 out of 94) of patients in the preserved EF group and 57% (123 out of 217) in the depressed EF group had systolic dyssynchrony (χ^2=6.07, P=0.01) (Figure 9.1A). Using Ts-diff >100 ms as the cut-off value derived from the upper 2 SD of the mean from normal subjects [8], a similar prevalence was found in the preserved and depressed EF group [39% (37 out of 94) compared with 58% (126 out of 217); χ^2=9.20, P=0.002].

Table 9-2. Comparison of systolic and diastolic dyssynchrony in CAD patients who had preserved or depressed EF and normal controls.

Variable	CAD patients with			*P* value		
	Controls	Preserved EF	Depressed EF	Controls compared with preserved EF	Controls compared with depressed EF	Preserved compared with depressed EF
Ts-SD (ms)	17.7±8.6	32.3±17.3	37.8±16.5	<0.001	<0.001	0.002
Ts-diff (ms)	53±24	95±49	109±45	<0.001	<0.001	0.004
Te-SD (ms)	20.3±8.1	26.2±13.6	36.0±23.9	0.026	<0.001	<0.001
Te-diff (ms)	66±28	85±47	111±69	0.016	<0.001	<0.001
LVEF (%)	70.7±8.0	61.7±8.3	34.8±9.7	<0.001	<0.001	<0.001

P values are Scheffe-corrected.

9.3.2 Diastolic dyssynchrony in CAD patients with preserved and depressed EF

Likewise, diastolic dyssynchrony was evident in the preserved EF group. Both Te-SD and Te-diff were significantly prolonged in the preserved EF group, but were more severe in the depressed EF group (Table 9.2). Using a cut-off value of Te-SD >34 ms, as derived from the upper 2 SD of the mean from normal subjects [8], diastolic dyssynchrony was present in 20% (19 out of 94) of patients in the preserved EF group and 38% (83 out of 217) in the depressed EF group (χ^2=9.68, P=0.002) (Figure 9.1B). Similarly, when Te-diff >113 ms was used as the cut-off value [8], the prevalence of diastolic dyssynchrony was significantly lower in the preserved EF group than the depressed EF groups [19% (18 out of 94) compared with 37% (81 out of 217); χ^2=9.99, P=0.002].

9.3.3 Clinical and coronary angiographic findings in relation to mechanical dyssynchrony

Angina was more severe in patients with depressed EF (Table 9.1) using the Canadian Cardiovascular Society classification. Patients with class III/IV angina had significantly higher Ts-SD (36.4±16.3 compared with 31.4±17.6 ms; P=0.01) and Te-SD (37.3±24.3 compared with 29.4±17.1 ms; P<0.001) than those with class I/II angina.

Coronary angiography was performed in 57 patients in the preserved EF group and 58 in the depressed EF group. More patients with depressed EF had coronary angiograms showing triple-vessel or left main CAD (Table 9.1). Patients with triple-vessel/left main diseases had significantly higher Ts-SD (48.9±12.9 compared with 21.6±9.7 ms; P<0.001) and Te-SD (36.2±19.1 compared with 21.7±6.2 ms; P<0.001) than those with single/double-vessel diseases.

9.3.4 Prior MI and mechanical dyssynchrony

A total of 208 patients had had a prior MI. These patients had ECG evidence together with akinesia of the corresponding LV segments on echocardiography. Among patients with preserved EF, LV mechanical synchrony was abnormal when compared with healthy controls (Table 9.3 and Figure 9.2), and was increased to a similar extent irrespective of whether or not there had been a prior MI (examples of mechanical dyssynchrony in patients with CAD and preserved EF without and with a prior MI are shown in Figure 9.3). On the contrary, in patients with depressed EF, mechanical dyssynchrony was significantly higher in those with a prior MI (Table 3).

Among all CAD patients, those with an anterior MI (n=118) had slightly lower EF values (45.6±14.2 compared with 52.1±15.8%; P<0.05) than others who had inferior MI (n=90). However, there was no significant difference in Ts-SD (28.7±15.7 compared with 31.8±18.5 ms) and Te-SD (26.6±14.1 compared with 28.5±20.5 ms) between patients with an anterior or inferior MI.

Table 9-3. Comparison of mechanical dyssynchrony in CAD patients with respect to the absence or presence of a prior MI.

Variable	CAD patients with preserved EF			CAD patients with depressed EF		
	Prior MI (*n*=56)	No prior MI (*n*=38)	*P* value	Prior MI (*n*=152)	No prior MI (*n*=65)	P value
Ts-SD (ms)	28.4±16.8	32.9±17.5	NS	37.7±17.4	30.1±15.2	0.003
Ts-diff (ms)	83.0±47.0	93.2±44.9	NS	110.0±42.3	95.0±44.1	0.02
Te-SD (ms)	25.5±15.0	28.6±14.8	NS	37.2±25.2	29.0±18.0	0.02
Te-diff (ms)	81.3±48.9	92.8±54.8	NS	112.5±68.0	90.2±51.7	0.02
LVEF (%)	62.4±8.7	65.1±8.6	NS	37.4±7.4	38.6±8.4	NS

NS, not significant.

QRS duration and mechanical dyssynchrony: Only 6% (6 out of 94) of patients in the preserved EF group had wide QRS complexes of >120 ms, as opposed to 30% (65 out of 217) in the depressed EF group (χ^2=19.2, P<0.001) (Figure 4). Among patients with preserved EF, the vast majority of systolic (37 out of 39) and diastolic (16 out of 19) dyssynchrony were in the narrow QRS complexes subgroup. In contrast, among patients with depressed EF, the prevalence of systolic dyssynchrony in patients with wide QRS complexes (52 out of 65) was significantly higher (χ^2=19.2, P<0.001) than those with narrow QRS complexes (71 out of 152). Likewise, diastolic dyssynchrony was more common in patients with wide QRS (50 out of 65) than narrow (33 out of 152) QRS complexes (χ^2=56.4, P<0.001).

9.4 Discussion and conclusions

To our knowledge, this is one of the largest studies to date that has examined the prevalence and patterns of systolic and diastolic dyssynchrony in CAD patients with a wide range of LVEF. The study demonstrated that systolic and diastolic dyssynchrony were highly prevalent even in patients with preserved EF, irrespective of the status of prior MI and QRS duration.

9.4.1 Relationship between myocardial ischemia and mechanical dyssynchrony in CAD

In our present study, mechanical dyssynchrony was associated with higher angina class and multi-vessel disease, suggesting an important role of myocardial ischemia in the pathogenesis of mechanical dyssynchrony in CAD. As changes in timing of regional mechanical events may precede local motion abnormalities during myocardial ischemia, mechanical dyssynchrony could be present when LVEF is relatively preserved. This phenomenon has been observed in an animal model by Wang et al. (Wang et al. 2005). When resting myocardium was subjected to progressive coronary stenosis, a delayed onset of subendocardial thinning was demonstrated in the early stage of hypoperfusion before the development of regional wall motion abnormalities. In another clinical study, the time to peak systolic velocity measured by TDI was found to be associated with coronary stenosis in patients with chest pain who had no apparent ventricular wall motion abnormalities on echocardiography (Lin et al. 2004). In addition, Fan et al. (Fan et al. 1997) found that mechanical dyssynchrony was affected by regionally stunned myocardium in porcine hearts.

9.4.2 Relationship between prior MI and mechanical dyssynchrony in CAD

Another major finding of our present study was that mechanical dyssynchrony was highly prevalent even in the absence of a prior MI. This observation supports that factors other than the presence of a prior MI, such as ischemia and stunning, may contribute to mechanical dyssynchrony in CAD patients with preserved EF. In addition, it highlights that mechanical dyssynchrony can be present without a regional wall motion abnormality on resting echocardiography. The lack of accuracy of the visual assessment of regional wall motion dyssynergy has been reported previously by Kvitting et al. (Kvitting et al. 1999). In contrast, TDI allows quantitative evaluation of mechanical dyssynchrony with high temporal resolution and is more objective.

The relationship between prior MI and mechanical dyssynchrony also appeared to be different in patients with preserved and depressed EF. In the present study, the presence of a prior MI worsened mechanical dyssynchrony in patients with depressed EF, a finding consistent

with previous reports by Zhang et al. (Zhang et al. 2005) and Fahmy Elnoamany et al. (Fahmy Elnoamany et al. 2006). However, among patients with preserved EF, the status of a prior MI apparently did not alter the degree of mechanical dyssynchrony. The present study was not intended to explore the mechanisms contributing to the difference, although this might be related to the larger infarct size or scar tissues as well as more severe peri-infarct ischemia in patients with depressed EF, resulting in worsening of regional dyssynchrony, or alternatively the reduced EF is a marker of more severe myocardial ischemia, which has a contributory role to mechanical dyssynchrony.

9.4.3 Relationship between QRS duration and mechanical dyssynchrony in CAD

The majority of patients with preserved EF who had mechanical dyssynchrony had narrow QRS complexes. This is in contrast with patients with depressed EF, where mechanical dyssynchrony was more commonly associated with wide QRS complexes. These observations are consistent with our previous study (Yu et al. 2007), and may imply that an abnormality other than an electromechanical coupling delay, such as a delay in myocyte contraction and relaxation or myocardial scarring, may have more important contributions to mechanical dyssynchrony in CAD patients with preserved EF.

9.4.4 Comparison with previous studies

In 138 heart failure patients (60 patients with preserved EF), De Sutter et al. (De Sutter et al. 2005) found a relatively low prevalence (17%) of systolic dyssynchrony in patients with preserved EF, but the prevalence was higher in patients with a QRS duration >120 ms (50%). In that particular study, 20% of the patients had non-ischemic cardiomyopathy. Moreover, the use of pulse-wave TDI in only four basal left ventricle segments in that study (Zwanenburg et al. 2005) is likely to have underestimated the prevalence of mechanical dyssynchrony.

It has been reported previously that systolic and diastolic dyssynchrony occurred in 36 and 39% respectively, of patients with heart failure and normal EF (Yu et al. 2007). In the present study, however, the prevalence of diastolic dyssynchrony in patients with CAD and preserved

EF appeared to be lower (20%), although the prevalence of systolic dyssynchrony was similar (42%). This discrepancy may be explained by the differences in the clinical characteristics of the patients. In the previous study, all patients had a prior history of heart failure and preserved EF, and among them 62% had a non-ischemic aetiology. It is possible that, in patients with diastolic heart failure, the more impaired LV filling may have induced diastolic dyssynergy, resulting in a higher prevalence of diastolic dyssynchrony.

9.4.5 Limitations

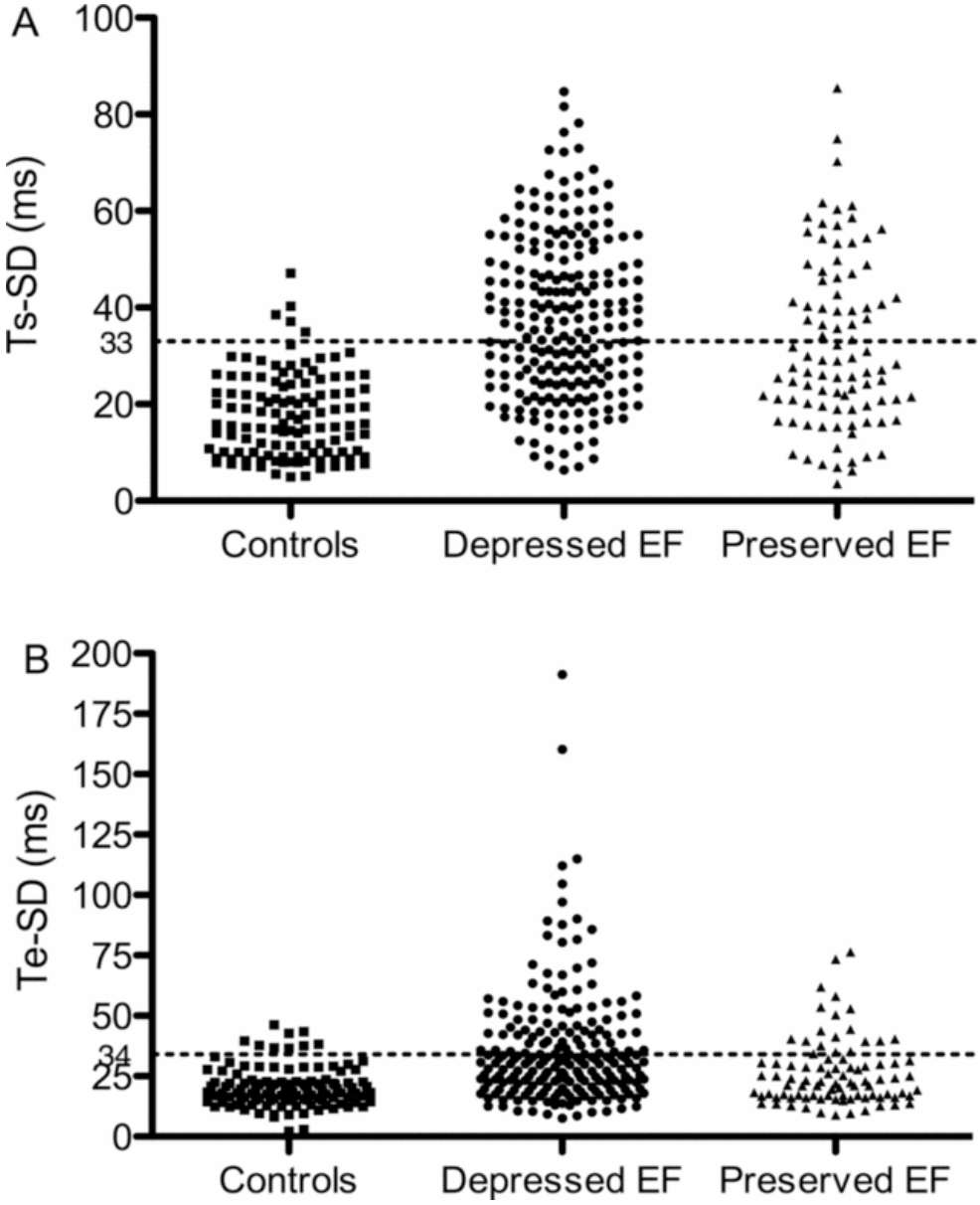
The present study has several limitations. Only longitudinal myocardial motion and dyssynchrony were examined in the present study, whereas radial and circumferential motions were not evaluated. However, as subendocardial muscle fibres are oriented longitudinally (Greenbaum et al. 1981) and are more vulnerable to ischemia than the circumferentially arranged mid-wall fibres, evaluation of longitudinal motions would be a sensible measure to characterize mechanical dyssynchrony in CAD. The reproducibility and usefulness of TDI in the evaluation of mechanical dyssynchrony has been questioned recently (Chung et al. 2008). However, we believe that the technique is highly dependent on the adequate training of operators and its reproducibility remains high in experienced laboratories (Yu et al. 2007). Although all patients in the present study had chest pain and most had angiographic or ECG evidence of CAD, myocardial ischemia was documented by functional stress testing in only few patients.

9.4.6 Conclusions

Mechanical dyssynchrony has been shown to be associated with impaired LV diastolic filling in CAD with preserved systolic function [25] and to be an independent predictor of morbidity and mortality in patients with depressed EF [26]. The present study has demonstrated a high prevalence of both systolic and diastolic dyssynchrony in patients with CAD and preserved EF. Unlike those with depressed EF, mechanical dyssynchrony in patients with preserved EF mainly occurs in those with narrow QRS complexes and was independent of the

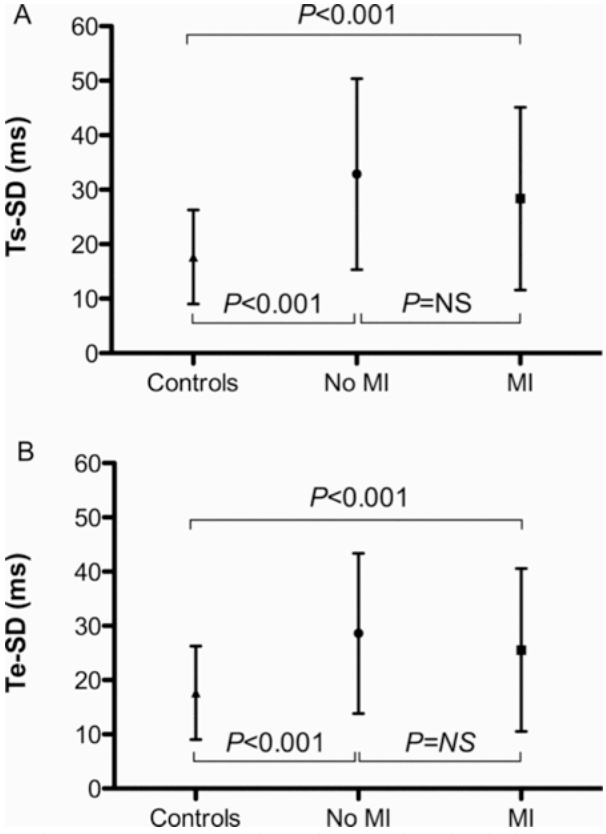
presence of a prior MI. Nonetheless, both systolic and diastolic dyssynchrony were more prevalent in CAD patients with depressed EF.

Figure 9-1. Scatter plots of Ts-SD (A) and Te-SD (B)



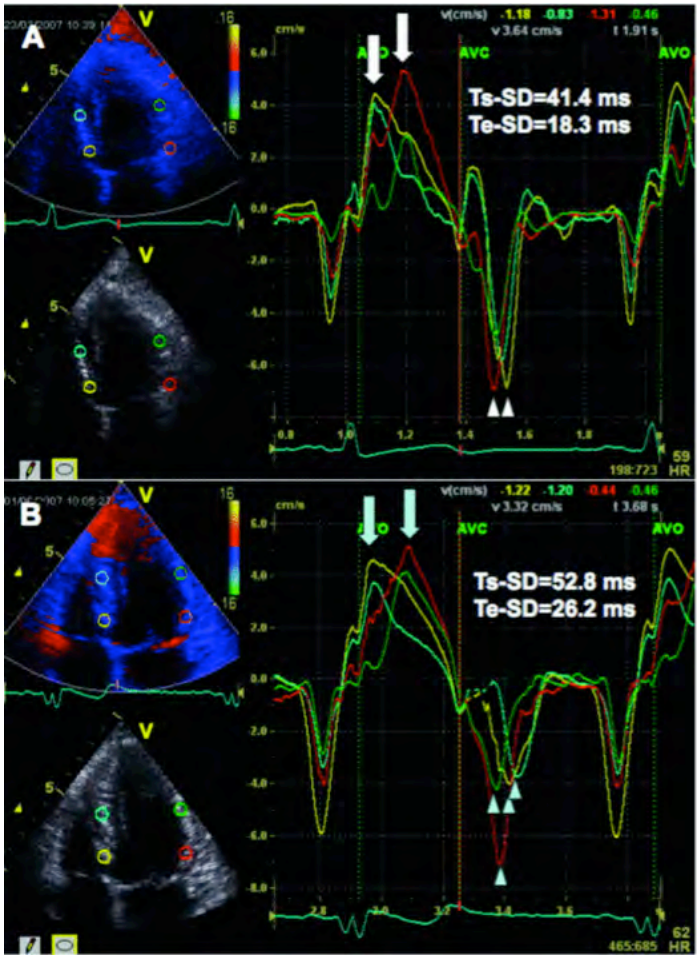
The dotted lines denote the cut-off values for systolic and diastolic dyssynchrony derived from normal controls. Mechanical dyssynchrony in CAD was most severe in patients with depressed EF, but was also evident in patients with preserved EF.

Figure 9-2. Ts-SD (A) and Te-SD (B) in CAD with or without prior MI.



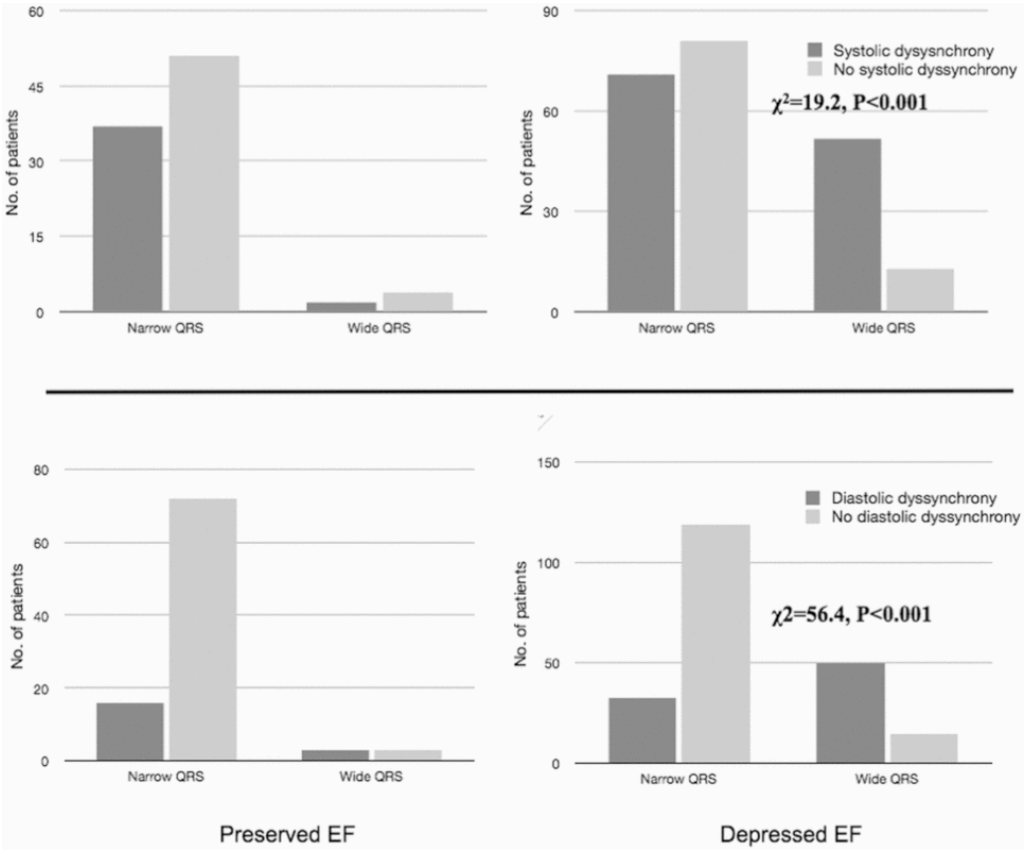
Values are means (S.D.). Mechanical dyssynchrony was present in patients with preserved EF, irrespective of the status of prior MI. P values are Scheffe-corrected.

Figure 9-3. Examples of dyssynchrony in CAD patients with preserved EF.



TDI with myocardial velocity curves reconstructed at apical four-chamber views are shown. A similar measurement was made in apical two-chamber and long-axis views. (A) A patient with a prior anterior MI (EF = 62 %) had systolic dyssynchrony with delayed time to peak systolic velocity in the antero-lateral wall (arrows). (B) A patient (EF = 65 %) without a prior MI had a comparable degree of systolic dyssynchrony (arrows). The two cases also illustrate that systolic dyssynchrony can occur without significant diastolic dyssynchrony (arrow heads).

Figure 9-4. Distribution of dyssynchrony according to QRS group.



Chapter 10 Study 2: LV Mechanical Dyssynchrony in Heart Failure With Preserved Ejection Fraction Complicating Acute Coronary Syndrome

10.1 Introduction

In the previous chapter we have established that LV mechanical dyssynchrony is not only present but highly prevalent in patients with CAD with preserved EF without heart failure irrespective of prior MI status or QRS duration. In this chapter, we are going to explore the potential role of LV mechanical dyssynchrony in CAD patients with preserved HF who have clinical signs and symptoms of heart failure (HFPEF). There is growing recognition that HFPEF is common and is associated with significant morbidity and mortality (Owan et al. 2006). CAD, in addition to hypertension, diabetes, and ageing, is a frequent risk factor for HFPEF (Choudhury et al. 2002). In the setting of acute coronary syndrome (ACS), HFPEF often complicates the acute clinical course. Although LV performance can be impaired as a result of ischemia-induced systolic dysfunction, infarct-related increase in myocardial stiffness, and/or ischemic mitral regurgitation, the pathogenic mechanisms of acute ischemic HFPEF are not completely understood.

Mechanical dyssynchrony in LV contraction has been established as an important pathogenic mechanism in systolic HF. In the setting of acute ischemic HFPEF, acute myocardial ischemia leads to delayed onset and slower rate of contraction and relaxation in regional myocardial segments and thus may generate LV mechanical dyssynchrony (Pislaru et al. 2001, Abraham et al. 2002), which may in turn compromises LV systolic and diastolic performance and leads to clinical HF. In the present study, we sought to elucidate the impact of LV mechanical dyssynchrony on ventricular function and its relationship with the occurrence of acute HFPEF in patients presenting with ACS.

10.2 Methods

10.2.1 Patients

A power analysis was conducted to determine the number of participants needed in this study. An ANOVA examined the null hypothesis that the dyssynchrony indices (Ts-SD and Te-SD) were not different among 3 groups of subjects: (i) ACS patients with HFPEF, (ii) ACS patients without HFPEF, and (iii) healthy controls. Based on previous comparable data, mean Te-SD of the normal population was about 20 ms (Yu et al. 2002, Yu et al. 2003, Yu et al. 2007), with a standard deviation of about 15ms. The mean Te-SD of ACS patients with HFPEF was assumed to be greater than the normal mean by 0.8 SD (i.e. at least 32ms), and the mean Te-SD of ACS patients without HFPEF to be equal to the grand mean of the 3 groups (i.e. 26ms). The alpha for the ANOVA was set at 0.05. To achieve power of 0.8 and an effect size of 0.327, a minimal sample size of 96 is required to detect a significant model. With similar statistical consideration for Ts-SD (normal mean=18ms, SD=15ms) (Yu et al. 2007), to detect an effect size of f=0.327, alpha=0.05, power=0.8, a minimum sample size of 96 was needed.

One hundred two consecutive patients (age 64 ± 10 years, 76 men) who were admitted to a tertiary care hospital for ACS and had a normal ejection fraction (EF) (≥50%) were prospectively studied. All subjects presented to the emergency department with acute chest pain >30 min and had ischemic changes on the electrocardiogram (ST-segment depression or elevation ≥0.1 mV and/or T-wave inversion on at least 2 contiguous leads) and/or elevated serum cardiac biomarker (troponin T) within 6 h of presentation. Patients with a depressed EF (<50%), atrial fibrillation, pacemaker implantation, more than a mild degree of valvular dysfunction, a prosthetic valve, pericardial constriction, and myocardial rupture were excluded from the study. The diagnosis of HF was made clinically by the attending physicians during acute hospitalization and independently verified by a cardiologist based on documented symptoms of HF (acute onset or worsening of dyspnoea), signs of fluid retention (elevated jugular venous pressure and dependent oedema), in addition to radiological evidence of pulmonary vascular congestion. There were 55 patients who had HFPEF during hospitalization

(group 1) and 47 patients in whom HFPEF did not develop during the hospital stay (group 2). Patients underwent cardiac catheterization and invasive revascularization if clinically indicated. One hundred and four age- and sex-matched healthy subjects were studied as controls. They had no history of cardiovascular or systemic diseases, had normal findings on a physical examination and electrocardiogram, and had an echocardiogram showing no evidence of structural heart disease. The study was approved by the ethics committee of the institution, and written informed consent was obtained from all subjects.

10.2.2 Echocardiography

Echocardiography (Vivid 7, Vingmed-General Electric, Horten, Norway) was performed within 72 h after hospital admission and before any coronary revascularization procedures were performed. As described in chapter 7, two-dimensional and Doppler echocardiography was performed in standard parasternal, apical, and subcostal views. Tissue Doppler imaging (TDI) was performed in apical 4-chamber, 2-chamber, and long-axis views for evaluation of LV longitudinal function. Colour-coded TDI optimized for pulse repetition frequency, colour saturation, and sector size and depth were obtained to maximize the frame rate to 100 Hz or higher. At least 3 consecutive beats in sinus rhythm were stored, and the images were analyzed offline using customized software (EchoPac-PC, Vingmed-General Electric). All measurements were averaged over at least 3 consecutive cardiac cycles. The echocardiographers who obtained the images and the investigators who performed the offline analysis were blinded to the clinical information of the subjects.

10.2.3 Evaluation of LV volumes and systolic and diastolic function

LV end-diastolic volume, end-systolic volume, and EF were assessed using the modified Simpson method in the apical 4- and 2-chamber views. Regional wall-motion abnormality was evaluated, and a wall motion score index (WMSI) was determined according to the recommendations by the American Society of Echocardiography (Cerqueira et al. 2002). Longitudinal LV systolic function was assessed by averaging the peak myocardial systolic

velocities at the 6 basal segments (Sm) obtained by offline TDI analysis with the sample volumes placed just above the mitral annulus (Yu et al. 2007).

To assess diastolic function, peak mitral inflow velocity of the early rapid-filling wave (E), peak velocity of the late filling wave due to atrial contraction (A), and deceleration time of early mitral inflow velocity (DT) of the early filling were recorded by using Doppler echocardiography. The longitudinal LV diastolic function was assessed by averaging the myocardial early diastolic velocities at the 6 basal segments (mean Em) at offline TDI analysis. Diastolic dysfunction was graded with reference to a classification scheme previously described (Lester et al. 2008). As discussed in chapter 7, normal diastolic function was defined as E/A = 0.9 to 1.5, DT = 160 to 240 ms, and E/Em <10; grade 1 (abnormal relaxation) if E/A <0.9 and DT >240 ms; grade 2 (pseudo-normal) if E/A = 0.9 to 1.5, DT = 160 to 240 ms, plus either E/Em ≥10 or E/A reversal on Valsalva manoeuvre; and grade 3 (restrictive filling) if E/A >2, DT <160 ms and E/Em ≥15. The diastolic function in 10 patients did not fall into any category and was classified as undetermined.

10.2.4 Evaluation of LV mechanical dyssynchrony

To assess LV mechanical dyssynchrony in both systole and diastole, myocardial velocity curves obtained from coded-coded TDI were reconstituted offline using the 12-segment (6 basal, 6 mid) model that consisted of the anterior, inferior, anteroseptal, inferoseptal, anterolateral, and inferolateral segments at both basal and mid-levels of LV (Yu et al. 2003). The basal segments were sampled just above the mitral annulus, and the mid-segments were sampled at the mid-level of LV. The time to peak myocardial systolic velocity during the LV ejection period (Ts) and the time to peak myocardial early diastolic velocity (Te) during the early LV filling period were measured for each segment with reference to the onset of QRS complex. Continuous-wave Doppler imaging of the aortic and mitral flow was used to determine the timing of aortic and mitral valve opening/closure, respectively. Markers of valve opening and closing events would appear on the electrocardiographic recordings during offline TDI analysis to assist in accurate

measurement of Ts and Te. The SD of Ts (Ts-SD) and of Te (Te-SD) of the 12 LV segments were calculated to measure systolic and diastolic mechanical dyssynchrony, respectively. Using the upper 2 SDs of normal controls as a cut-off, systolic mechanical dyssynchrony was defined as Ts-SD >33 ms and diastolic mechanical dyssynchrony as Te-SD >34 ms, as previously reported (Yu et al. 2003, Yu et al. 2007). Post-systolic shortening, defined as myocardial contraction occurring after aortic valve closure (positive velocity greater than the peak ejection velocity), was distinguished from myocardial early diastolic velocity by their different timing and opposite directions. Post-systolic shortening, albeit considered to be a marker of ischemia, may not be a marker of mechanical dyssynchrony in ischemic cardiomyopathy (Yu et al. 2004). Therefore, in the present study, post-systolic shortening was not included in the assessment of LV mechanical dyssynchrony.

10.2.5 Statistical analysis

Data were analyzed using statistical software (SPSS for Windows, SPSS Inc., Chicago, Illinois). Results were presented as mean ± SD or number and percentage of patients. Comparisons among patient groups and among various grades of diastolic dysfunction were performed using 1-way analysis of variance with Scheffé test or Pearson chi-square test as appropriate. Pearson coefficient was used for correlation analysis. Univariate analysis was performed for all clinical and echocardiographic variables including age, sex, type of ACS, hypertension, diabetes, systolic and diastolic blood pressures, heart rate, QRS duration, LV end-diastolic volume, LV end-systolic volume, LV ejection fraction, mean Em, mean Sm, E/Em, E/A, DT, WMSI, Ts-SD, and Te-SD. Variables with $p < 0.1$ on univariate analysis were tested in the multivariate logistic regression with the forward stepwise method to identify independent associations with HFPEF. A value of $p < 0.05$ was considered significant.

10.3 Results

10.3.1 Patients

The clinical and demographic characteristics of group 1 and group 2 ACS patients are shown in Table 10.1. Patients in group 1 were significantly older ($p = 0.03$) and had a higher prevalence of anterior myocardial infarction ($p = 0.02$) than those in group 2. The vast majority (96%) of patients in both groups had a QRS duration <120 ms. Other clinical characteristics and medications before admission were similar in the 2 groups.

10.3.2 LV volumes and systolic and diastolic function

Both groups of ACS patients had normal EF and similar WMSI (Table 10.2). Yet there were subtle abnormalities in systolic parameters in both ACS groups compared with controls; namely, ACS patients had a greater end-systolic volume ($p < 0.05$), lower EF ($p < 0.001$), higher WMSI ($p < 0.001$), and lower mean Sm ($p < 0.001$) than normal controls (Table 2). Of note, the extent of systolic abnormality was similar in group 1 and group 2 leading to the absence of intergroup differences. On the other hand, diastolic dysfunction was more severe in group 1, which had a higher prevalence of pseudo-normal and restrictive filling patterns ($p < 0.001$) and, in particular, a lower mean Em and a higher E/Em ratio by TDI (all p values <0.001 vs. group 2 or controls).

Table 10-1. Comparison of demographic and clinical characteristics between ACS patients with HFPEF (group 1) versus those without HFPEF on presentation (group 2)

	ACS Group 1 With HFPEF (n = 55)	ACS Group 2 Without HFPEF (n = 47)	Chi-Square	p Value
Age, yrs	66 ± 11	61 ± 9	NA	0.03
Male sex	41 (75)	35 (75)	0.0	NS
Type of ACS			7.42	0.02
Anterior STEMI	16 (29)	4 (8)	NA	NA
Inferior STEMI	8 (15)	12 (26)	NA	NA
NSTE ACS	31 (56)	31 (66)	NA	NA
Hypertension	31 (56)	24 (51)	0.29	NS
Diabetes	16 (29)	20 (43)	2.00	NS
Smoker	24 (44)	19 (40)	0.11	NS
SBP, mm Hg	140 ± 22	144 ± 16	NA	NS
DBP, mm Hg	81 ± 9	78 ± 8	NA	NS
Heart rate, beats/min	89 ± 11	89 ± 10	NA	NS
QRS duration, ms	90 ± 20	89 ± 11	NA	NS
QRS ≥120 ms	2 (4)	2 (4)	0.03	NS
Medications				
ACEI or ARB	23 (42)	16 (34)	0.65	NS
Beta-Blocker	17 (31)	20 (43)	1.49	NS
Nitrates	30 (55)	26 (55)	0.01	NS
Calcium channel blocker	13 (24)	7 (15)	1.23	NS
Statin	30 (55)	26 (55)	0.01	NS
Aspirin	36 (65)	32 (68)	0.08	NS
Diuretics	10 (18)	6 (13)	0.56	NS

Values are mean ± SD or n (%).
ACEI = angiotensin-converting enzyme inhibitor; ACS = acute coronary syndrome; ARB = angiotensin receptor blocker; DBP = diastolic blood pressure; NA = not applicable; NSTE = non–ST-segment elevation; SBP = systolic blood pressure; STEMI = ST-segment elevation myocardial infarction.

10.3.3 Systolic and diastolic mechanical dyssynchrony

Ts-SD was increased in both ACS groups compared with controls ($p < 0.001$), but it did not differentiate group 1 from group 2 (Table 10.2). The prevalence of systolic mechanical dyssynchrony (i.e., Ts-SD >33 ms) was similar in group 1 and group 2 (47% vs. 43%; p = NS) (Fig. 10.1). In contrast, Te-SD was significantly increased in group 1 ($p < 0.001$ vs. the other 2 groups) (Table 10.2). Diastolic mechanical dyssynchrony (i.e., Te-SD >34 ms) was evident in 19 of 55 patients (35%) in group 1 but in only 4 of 47 patients (9%) in group 2 ($p < 0.001$) (Fig.10.1).

Combining the 2 ACS groups, comparisons of echocardiographic variables among various diastolic function grades are shown in Table 10.3. As expected, mean Em decreased, whereas E/Em increased progressively with escalating severity of diastolic dysfunction ($p < 0.001$ for all comparisons). Although conventional systolic parameters including EF and WMSI showed no significant differences among the 4 grades, mean Sm was relatively preserved in patients with grade 0 (normal) diastolic function ($p < 0.001$ vs. other grades). Nevertheless, there was no intergroup difference (p = NS) in mean Sm from grade 1 to grade 3 diastolic dysfunction.

Interestingly, Te-SD increased progressively from grade 1 to grade 3 diastolic dysfunction ($p < 0.001$) (Fig. 10.2). This was in contrast to Ts-SD, which showed no significant differences across diastolic function grades. There was a significant correlation between Te-SD and E/Em ($r = 0.69$, $p < 0.001$) (Fig. 10.3) and, inversely, with mean Em ($r = -0.56$, $p < 0.001$), but not between Ts-SD and E/Em ($r = 0.08$, p = NS) or mean Em ($r = 0.08$, p = NS). On the other hand, mean Sm correlated significantly with mean Em ($r = 0.56$, $p < 0.001$), Ts-SD ($r = -0.42$, $p < 0.001$), and Te-SD ($r = -0.23$, $p = 0.001$). Ts-SD and Te-SD correlated significantly with each other, albeit modestly ($r = 0.16$, $p = 0.019$). Examples of dyssynchrony TDI curves and mitral Doppler inflow patterns in controls and group 1 and group 2 ACS patients are shown in Figure 4.

10.3.4 Coronary angiography

Fifty-seven patients (30 in group 1 and 27 in group 2; p = NS) underwent cardiac catheterization and revascularization as clinically determined, and all of them had >70% luminal stenosis in at least 1 major epicardial coronary artery. To examine the relationship between coronary anatomy and mechanical dyssynchrony, a subset of patients with single-vessel disease were studied (n = 35). The distribution of the most delayed segments on echocardiography with regard to the coronary artery anatomy on angiography is shown in Figure 10.5. Interestingly, the segments with the most delayed contraction or relaxation (i.e., segments with the latest Ts or Te) in a patient did not always correspond anatomically to the coronary vascular territory on

angiography. The most delayed contraction or relaxation was observed in the remote segments with normal coronary arteries in 25.7% and 28.5% of cases, respectively (Fig. 10.5).

Table 10-2. Comparison of echocardiographic parameters among ACS patients presenting with HFPEF (group 1), ACS patients without HFPEF (group 2), and normal controls

	ACS patients		Controls	P value		
	Group 1 With HFPEF	Group 2 Without EFPEF		Group 1 vs. Controls	Group 2 vs. Controls	Group 1 vs. Group 2
LV volumes, ml						
LVEDV	89 ± 21	88 ± 9	74 ± 18	NS	NS	NS
LVESV	39 ± 9	37 ± 7	28 ± 8	0.009	0.02	NS
LV systolic function						
LVEF, %	69 ± 11	67 ± 11	78 ± 6	<0.001	<0.001	NS
WMSI	1.1 ± 0.2	1.1 ± 0.1	1.0 ± 0.0	<0.001	<0.001	NS
Mean Sm, cm/s	5.1 ± 1.1	5.3 ± 1.6	6.5 ± 1.1	<0.001	<0.001	NS
LV diastolic function						
E/A	1.2 ± 0.4	0.9 ± 0.3	1.0 ± 0.3	NS	NS	0.02
DT, ms	185 ± 54	221 ± 48	168 ± 32	NS	<0.001	0.003
Em, cm/s	4.6 ± 1.4	6.5 ± 1.5	7.6 ± 1.6	<0.001	<0.001	<0.001
E/Em	18.3 ± 7.3	10.5 ± 3.7	10.2 ± 2.7	<0.001	NS	<0.001
Grade				<0.001	<0.001	<0.001
0	0	11 (23)	64 (62)			
1	5 (9)	24 (51)	40 (38)			
2	29 (53)	8 (17)	0			
3	15 (27)	0	0			
Undetermined	6 (10)	4 (9)	0			
LV mechanical dyssynchrony, ms						
Ts-SD	34 ± 16	32 ± 18	17 ± 8	<0.001	<0.001	NS
Te-SD	33 ± 13	21 ± 9	20 ± 7	<0.001	NS	<0.001

Values are mean ± SD or n (%). *p value is Scheffé-corrected.
A = peak velocity of the late filling wave due to atrial contraction; ACS = acute coronary syndrome; DT = deceleration time of early mitral inflow velocity; E = peak mitral inflow velocity of the early rapid-filling wave; Em = mean early diastolic velocity of 6 basal left ventricular myocardial segments; LV = left ventricular; EDV = end-diastolic volume; ESV = end-systolic volume; LVEF = ejection fraction; Mean Sm = mean of peak systolic velocity of 6 basal left ventricular myocardial segments; Te-SD = SD of time to peak early diastolic velocity of 12 myocardial segments; Ts-SD = SD of time to peak systolic velocity of 12 myocardial segments; WMSI = wall motion score index.

10.3.5 Associating factors of HFPEF in ACS on multivariate analysis

Several clinical and echocardiographic variables were associated with HFPEF on univariate analysis including age, type of ACS (anterior ST-segment elevation myocardial infarction), E/A, DT, mean Em, E/Em, and Te-SD ($p < 0.1$) (Table 10.4). E/Em was the only variable independently associated with HFPEF on multivariate analysis (odds ratio: 1.48; 95% confidence interval: 1.17 to 1.88; $p = 0.001$). If E/Em was excluded from the model, Te-SD

(odds ratio: 1.13; 95% confidence interval: 1.10 to 1.20; p < 0.001) and mean Em (odds ratio: 0.37; 95% confidence interval: 0.25 to 0.55; p < 0.001) were independently associated with HFPEF.

Table 10-3. Echocardiographic parameters by diastolic function grades in ACS patients.

	Grades of Diastolic Dysfunction				
	Normal (n=11)	Grade 1 (n=29)	Grade 2 (n=37)	Grade 3 (n=15)	ANOVA P
LVEF, %	64 ± 8	62 ± 9	61 ± 7	60 ± 9	NS
WMSI	1.1 ± 0.2	1.1 ± 0.1	1.1 ± 0.1	1.2 ± 0.2	NS
Mean Em, cm/s	8.1 ± 0.9	6.3 ± 0.4*	4.8 ± 0.9*†	3.6 ± 1.2*†‡	<0.001
Mean Sm, cm/s	6.6 ± 1.6	5.1 ± 1.1*	5.0 ± 1.2*	4.6 ± 1.1*	<0.001
E/A	1.27 ± 0.18	0.69 ± 0.07*	0.94 ± 0.19*†	2.27 ± 0.13*†‡	<0.001
DT, ms	181 ± 27	254 ± 44*	200 ± 36†	134 ± 10†‡	<0.001
E/Em	8.1 ± 1.8	10.2 ± 2.9*	14.8 ± 5.5*†	24.7 ± 4.6*†‡	<0.001
Te-SD, ms	16 ± 3	21 ± 5*	28 ± 9*†	41 ± 17*†‡	<0.001
Ts-SD, ms	29 ± 14	33 ± 18	37 ± 17	29 ± 17	NS

Sm = peak systolic velocity of 6 basal left ventricular myocardial segments; other abbreviations as in Table 10.2.
∗Scheffé-corrected p < 0.05 compared with normal diastolic function.
†Scheffé-corrected p < 0.05 compared with grade 1 diastolic dysfunction.
‡Scheffé-corrected p < 0.05 compared with grade 2 diastolic dysfunction.

10.4 Discussion and conclusions

The present study demonstrated that patients with ACS complicated by acute HFPEF had significantly increased temporal dispersion in the regional timing of myocardial relaxation detectable by TDI. The results of this study show that diastolic mechanical dyssynchrony is closely linked to diastolic dysfunction grade and noninvasive estimates of filling pressure (E/Em), suggesting that LV diastolic dyssynchrony may be a contributing factor for acute ischemic HFPEF. Interestingly, such an association was not apparent for systolic mechanical dyssynchrony.

10.4.1 Role of LV mechanical dyssynchrony in the pathogenesis of HFPEF complicating ACS

HF is a frequent complication of ACS and is associated with poor prognosis (Khot et al. 2003, Steg et al. 2004). Many patients with ACS complicated by acute HF on presentation have relatively preserved LV systolic dysfunction. In the Global Registry of Acute Coronary Events,

for instance, only 48.7% of the HF patients had depressed EF (Steg et al. 2004). However, the pathogenic mechanisms of HFPEF in these patients are not completely understood.

The presumed pathophysiological abnormality leading to HFPEF is diastolic dysfunction, a common finding in patients with coronary artery disease (Bonow et al. 1981). Normal diastolic function is characterized by rapid decrease in LV pressure during the isovolumic and the early ventricular filling phases, as well as high compliance of LV walls during the late diastolic filling phase (Brutsaert et al. 1989). The active process of myocardial relaxation that generates the rapid LV pressure decrease is normally homogeneous in all regional segments. Increase in the temporal heterogeneity in this process with some fibres lengthening later than the others may jeopardize normal ventricular filling (Bonow et al. 1988). Further prolongation of early myocardial relaxation could delay diastolic LV minimum pressure well into late diastole and could therefore contribute to the elevation of LV filling pressure (Zile et al. 2004). In other studies of this thesis, we also demonstrated that LV systolic and diastolic mechanical dyssynchrony were prevalent in patients with chronic coronary artery disease (Lee et al. 2009) and HFPEF (Yu et al. 2007, Lee et al. 2010). Wang et al. (Wang et al. 2007) observed that LV diastolic mechanical dyssynchrony had inverse correlations with the time constant of relaxation and pulmonary capillary wedge pressure in chronic hypertensive HFPEF. In the present study, parallel increase in diastolic mechanical dyssynchrony with increasing severity of diastolic dysfunction supported this hypothesis. E/Em was calculated in this study as a surrogate measure of LV filling pressure. There have been controversies in the literature with regard to whether the ratio of early transmitral velocity to tissue Doppler mitral annular (E/e') or mean basal myocardial early diastolic velocity (E/Em) is a reliable estimate of ventricular filling pressure (Ommen et al. 2000, Ommen et al. 2003, Mullens et al. 2009, Bhella et al. 2011, Nagueh et al. 2011). The accuracy of E/e' or E/Em in reflecting LVEDP has been challenged based on the fact that the two measurements is made in early diastole during a time of rapid early filling whereas LVEDP is measured at end-diastole. Nevertheless, the initial study (Ommen et al. 2000) that

established the correlation between E/e' and LV filling pressure actually used the mean LV diastolic pressure as the surrogate of mean LA pressure, rather than LVEDP. There are certainly many factors that can modulate the relationship between E/e' (and E/Em) and LV filling pressures, including the degree of ventricular remodeling, prevalence of mitral regurgitation, atrial fibrillation (when E and e' cannot be measured simultaneously), presence of dyssynchrony, or previous cardiac resynchronization therapy. Careful interpretation of E/e' or E/Em alone as surrogates for LV filling pressures is therefore warranted when confounding factors that may affect their accuracy and reliability in HF patients encountered during day-to-day clinical practice. It is, however, safe to conclude that the ASE/EAE algorithm including E/e′ (or similarly E/Em) can be used to categorize patients into clinically significant groups of LA pressure (PCWP <15 and >18), with a middle group that requires assessment by the comprehensive approach considering multiple parameters including the deceleration time of the E wave, the early and late velocities of the mitral annulus measured by tissue Doppler (e′ and a′), the LA volume, the pattern of pulmonary vein flow, and the duration of reversed flow into the pulmonary veins during atrial contraction in the suitable clinical context (Nagueh et al. 2009). On the other hand, the present study has excluded patients with most of the confounding factors mentioned above and therefore E/Em could still be considered a parameter with reasonably good correlation with the LV filling pressure in this study population. E/Em was apparently the single most important associating factor of HFPEF on multivariate analysis, which is probably not surprising because any mechanisms that lead to acute HFPEF should eventually increase the LV filling pressure with resultant pulmonary oedema. However, Te-SD and mean Em became independently associated with HFPEF after excluding E/Em from the regression model. These results, together with the close correlation between E/Em and Te-SD, support the hypothesis that diastolic mechanical dyssynchrony may contribute to HFPEF through elevation of the LV filling pressure.

As myocardial ischemia is often a regional phenomenon, it is possible that regional delay in relaxation leads to diastolic mechanical dyssynchrony during ACS. Among patients with chronic coronary artery disease and preserved LV systolic function, diastolic mechanical dyssynchrony has been shown to predict exercise-induced ischemia with resultant impairment of early ventricular filling (Perrone-Filardi et al. 1991). In the present study, the location of coronary stenosis and the site of regional mechanical delay were, in general, concordant with each other. However, a dissociation of coronary stenosis and mechanical delay did occur in some patients. Several possible explanations exist. First, myocardial perfusion is modified by physiological factors such as vasomotor tone and microvascular resistance, which are not well appreciated on coronary angiography. Microvascular ischemia may be present in diabetic and hypertensive patients, who were prevalent in our study population. On the other hand, nonischemic factors such as electrical delay may lead to mechanical dyssynchrony. Although a wide QRS complex of >120 ms was uncommon, electrical delay that was not manifested on surface electrocardiography could not be entirely excluded in our study population.

In this study, we observed that the mean Sm correlated significantly with mean Em, Ts-SD, and Te-SD. Longitudinal motion of the LV base toward LV apex during systole is largely a result of torsional deformation of the spirally arranged LV myofibres. The potential energy stored by LV torsion during the systolic phase is reinstituted during LV untwisting and aids in diastolic suction. An abnormal activation sequence of the ventricles (e.g., due to right ventricular pacing, regional ischemia, distortion of myofibril architecture, electrical conduction delay) can result in dyssynchronous LV contraction, with reduced torsion and longitudinal shortening (Delgado et al. 2009). Recent studies pointed out that LV dyssynchrony was inversely related to LV torsion in advanced HF patients with prolonged QRS duration (Sade et al. 2008, Bertini et al. 2009), underscoring that LV torsion (and associated longitudinal function) may be a parameter that reflects the extent of LV dyssynchrony. The relationships of mean Sm with mean Em, Ts-SD, and Te-SD in our study lent further support that systolic and diastolic mechanical events of

the LV are closely coupled, and mechanistic links may exist between LV longitudinal systolic function and LV dyssynchrony in patients with ACS. Intriguingly, although systolic mechanical dyssynchrony was evident in ACS patients, it did not appear to be associated with an acute occurrence of HFPEF. We postulate that systolic mechanical dyssynchrony may be common in the setting of ACS but per se might not be enough to cause acute HFPEF when the global systolic function is relatively preserved and diastolic dysfunction is mild.

10.4.2 Study limitations

First, although this study demonstrated a strong association between LV mechanical dyssynchrony and HFPEF in the setting of ACS, a causal relationship cannot be directly assumed because of the cross-sectional design of the study. A longitudinal study to demonstrate that ACS patients with dyssynchrony at baseline are more likely to develop future HFPEF would help to further confirm the findings of the present study. Further studies should focus on elucidating the mechanism (e.g. ischemia, fibrosis, cardiomyopathy, or subtle electrical conduction abnormality) of mechanical dyssynchrony observed in ACS patients, which would form the basis for future randomized controlled trials to test the efficacy of potential therapeutic strategy that targets to correct the mechanical dyssynchrony in treating or preventing HFPEF in ACS patients. Second, there is a possibility of undetected transient systolic dysfunction, or mitral regurgitation, because echocardiography was performed within 72 h but not immediately after the onset of acute symptoms. Third, the findings of this study may not be extrapolated to patients with atrial fibrillation who were excluded owing to technical difficulty in evaluating dyssynchrony in this group of patients. Finally, clinical outcomes of ACS patients with or without HFPEF were not assessed due to the relatively small sample size and short follow-up period in this study. However, the clinical significance of HFPEF in ACS was established (9 and 10), and the present study aimed to provide insight into the pathophysiological mechanisms underlying this disorder.

In this study, a higher extent of diastolic dyssynchrony was observed in patients with ACS who presented with HFPEF when compared to those who did not have HF symptoms on presentation. Limited by its cross-sectional design, this study provided evidence of association between diastolic dysfunction and dyssynchrony in the study population, but not direct evidence of causal link. From a biological plausibility point of view, it is more likely that the heterogeneity in timing of LV myocardial relaxation (i.e. diastolic dyssynchrony) leads to inefficient generation of the suction force during early rapid filling and hence contribute to impaired diastolic function, rather than the reverse. Furthermore, the strong correlation and the presence of a "dose-response" relationship between Te-SD and the severity of diastolic functional grade imply a causal link between the two.

10.4.3 Conclusions

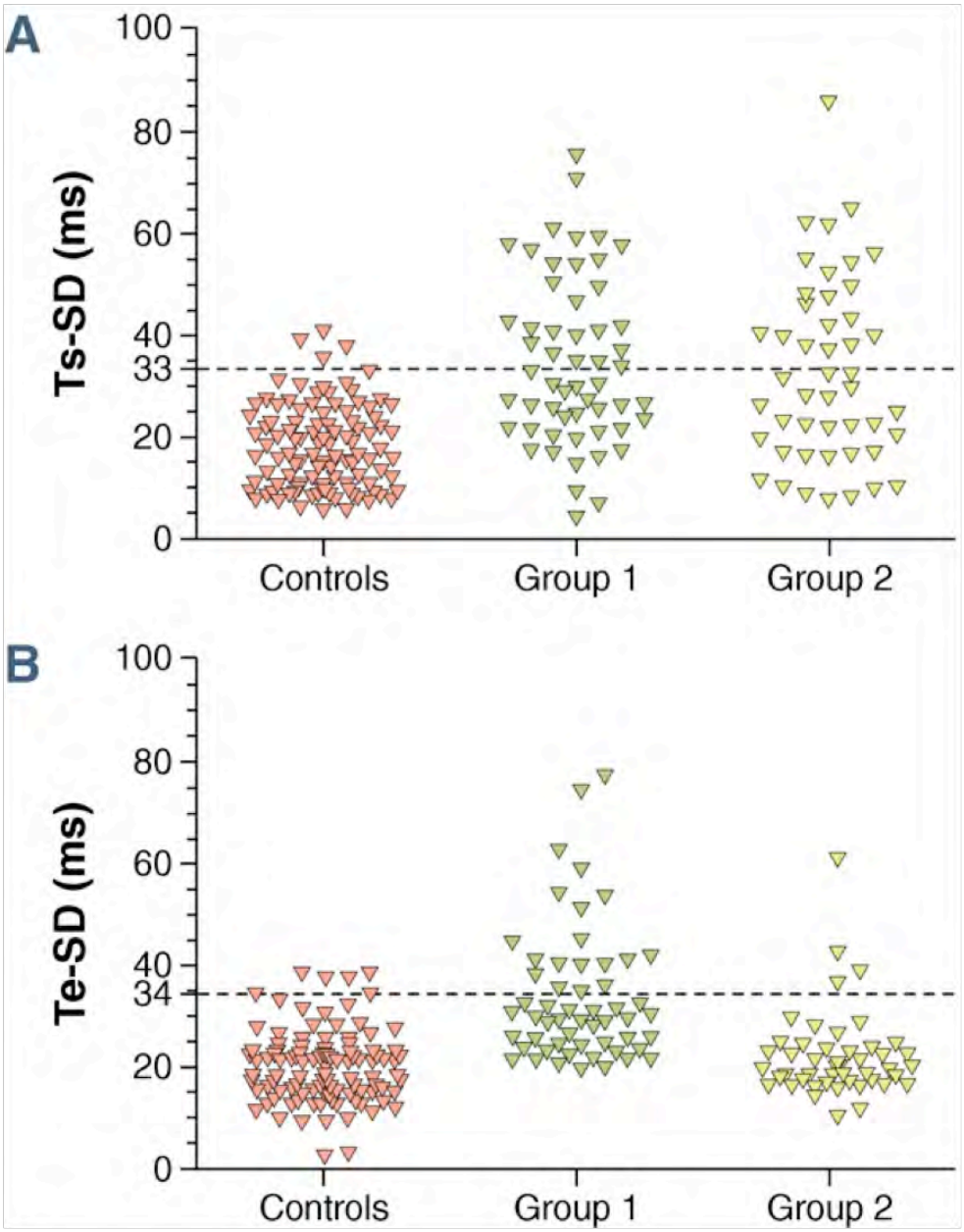
The present study demonstrated that LV diastolic mechanical dyssynchrony is associated with global diastolic dysfunction and may be a predisposing factor of HFPEF in acute ischemic patients. This finding may provide a new therapeutic target for ischemic HFPEF. Whether LV diastolic mechanical dyssynchrony can be reversed or modified by medication, revascularization, or even cardiac resynchronization therapy warrants further investigations.

Table 10-4. Multivariate analysis for associating factors of HFPEF in ACS patients

Univariate Analysis p Value	Multivariate Analysis (E/Em Included in the Regression Model)		Multivariate Analysis (E/Em Excluded From the Regression Model)		
	OR (95% CI)	p Value	OR (95% CI)	p Value	
Age	0.027	NA	NS	NA	NS
Anterior STEMI	0.03	NA	NS	NA	NS
E/A	0.011	NA	NS	NA	NS
DT	0.006	NA	NS	NA	NS
Em	<0.001	NA	NS	0.37 (0.25–0.55)	<0.001
E/Em	<0.001	1.48 (1.17–1.88)	0.001	NA	NA
Te-SD	<0.001	NA	NS	1.13 (1.10–1.20)	<0.001

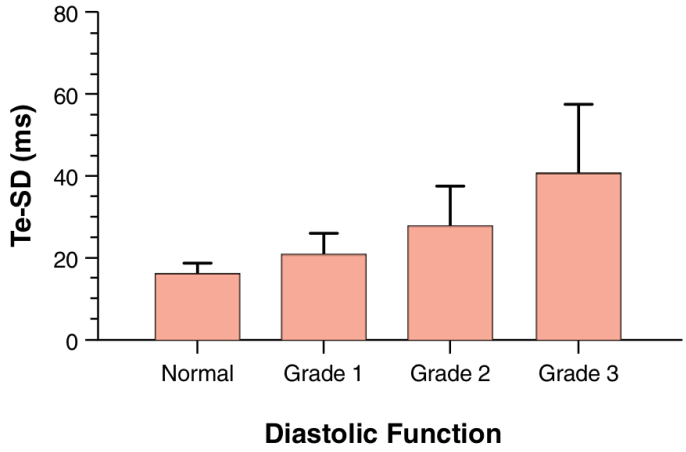
CI = confidence interval; HFPEF = heart failure with preserved ejection fraction; OR = odds ratio; other abbreviations as in Table 10.1 and Table 10.2.

Figure 10-1. Scatter plots of Ts-SD (A) and Te-SD (B) in ACS patients and controls.



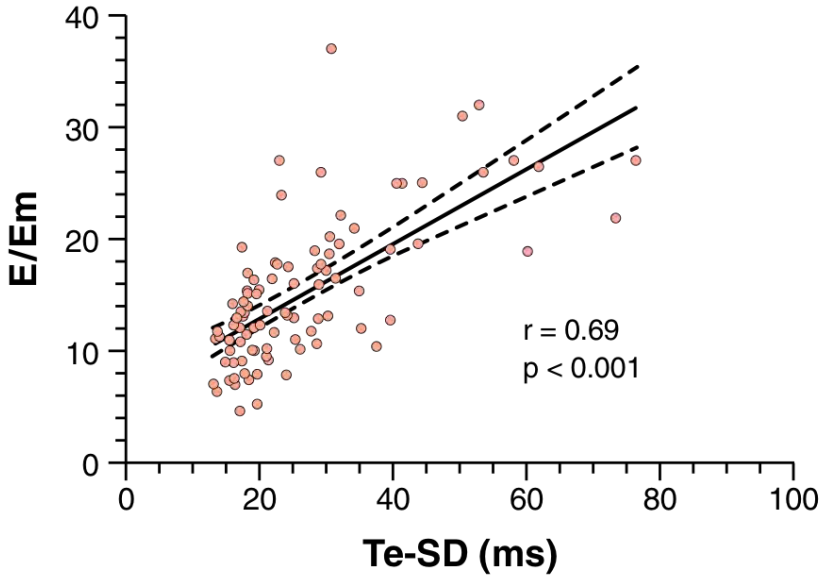
Using the SD of the time to peak systolic velocity of 12 myocardial segments (Ts-SD) **(A)** 33 ms and the SD of the time to peak early diastolic velocity of 12 myocardial segments (Te-SD) **(B)** 34 ms, respectively, as cut-offs for systolic and diastolic mechanical dyssynchrony (derived from the upper 2 SDs of normal controls), the prevalence of systolic mechanical dyssynchrony was similar between the acute coronary syndrome (ACS) group 1 and group 2, whereas the prevalence of diastolic mechanical dyssynchrony was significantly higher in group 1 (35% vs. 9%).

Figure 10-2. Bar charts showing relationship between diastolic dyssynchrony and diastolic function.



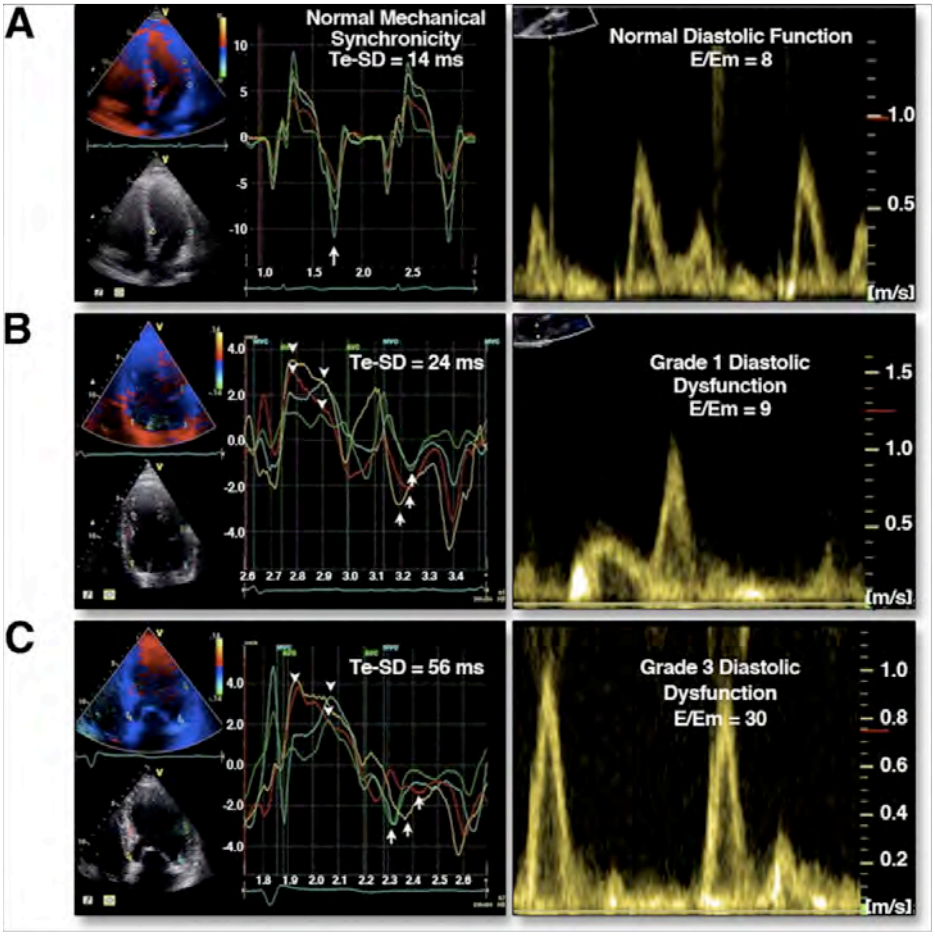
Te-SD increased progressively in parallel to the diastolic dysfunction grade (Scheffé-corrected p value <0.05 for all intergrade comparisons). **Error bars** represent SD. Abbreviations as in Figure 10.1.

Figure 10-3. Scatter plots of Te-SD and E/Em in ACS patients.



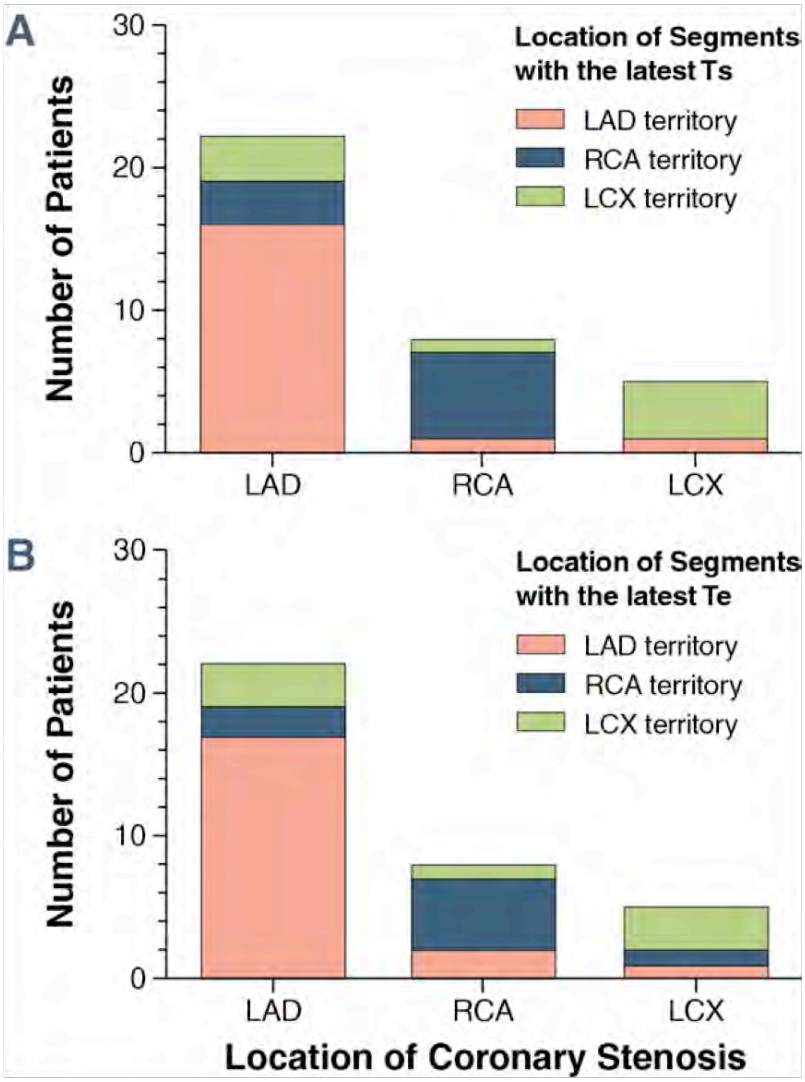
The scatterplot demonstrates the significant correlation ($r = 0.69$, $p = 0.001$) between the echocardiographic parameters for diastolic mechanical dyssynchrony and left ventricular filling pressure. The error lines (dotted lines) represent 95% confidence intervals of the regression line (solid line). E/Em = peak mitral inflow velocity of the early rapid-filling wave/mean early diastolic velocity of 6 basal left ventricular myocardial segments; other abbreviations as in Figure 10.1.

Figure 10-4. Examples of myocardial velocity curves and mitral inflow patterns.



In a control subject **(A)**, homogeneous relaxation of myocardial segments **(arrow)** is associated with normal rapid ventricular filling. In a patient in the ACS group 2 **(B)**, timings of peak early diastolic velocity (Em) in various myocardial segments are less homogeneous. Te-SD was slightly prolonged to 24 ms, which was associated with grade 1 diastolic dysfunction. E/Em was 9, suggesting that left ventricular filling pressure was not elevated in this patient who did not have acute heart failure symptoms. In contrast, in a patient from ACS group 1 in whom heart failure with preserved ejection fraction developed, Te-SD was significantly prolonged to 56 ms, indicative of diastolic mechanical dyssynchrony. This was associated with restrictive mitral filling and markedly increased E/Em, consistent with extremely elevated filling pressure. Of note, systolic mechanical dyssynchrony **(arrowheads)** could be present with **(C)** or without **(B)** diastolic mechanical dyssynchrony. Abbreviations as in Figures 10.1 and 10.3.

Figure 10-5. Distribution of locations of the most delayed myocardial segments in single-vessel LAD, RCA, or LCx stenosis



Left anterior descending artery (LAD) territory: basal and mid-anterior, anteroseptal, and anterolateral segments; right coronary artery (RCA) territory: basal and mid-inferior, inferoseptal segments; left circumflex artery (LCX) territory: basal and mid-lateral, inferior (for dominant left system) segments. Te, time to peak myocardial early diastolic velocity; Ts, time to peak myocardial systolic velocity during the left ventricular ejection period.

Chapter 11 Study 3: Stress-Induced Dynamic Left Ventricular Dyssynchrony in Heart Failure with Preserved Ejection Fraction

11.1 Introduction

Apart from CAD as discussed in previous chapters, hypertension is another important and frequent risk factor for HFPEF (Owan et al. 2005). Despite the high prevalence, morbidity and mortality of HFPEF, its fundamental pathophysiology remains controversial. As discussed in previous chapters, in systolic heart failure, LV mechanical dyssynchrony has been recognized as an important factor associated with poor prognosis (Penicka et al. 2007). A high prevalence of LV dyssynchrony also exists in patients with HFPEF as demonstrated by our data in chapter 9 and 10 as well as by other studies (Wang et al. 2007, Yu et al. 2007). However, it is unsure if LV mechanical dyssynchrony plays a role in its pathophysiologic process. While previous studies only measured LV dyssynchrony at rest, patients with HFPEF often develop symptoms during exertion or stress. It is largely unknown whether the status of LV mechanical dyssynchrony would change with hemodynamic stress in HFPEF, and whether this plays a contributory role in the pathophysiology. Therefore, the objective of the study discussed in this chapter is to examine whether LV systolic and diastolic dyssynchrony would change during hemodynamic stress in patients with hypertensive HFPEF using dobutamine as a stressor, and decide whether dynamic dyssynchrony is an important determinant for the development of HFPEF in hypertensive patients. In order to achieve these objectives, patients with hypertensive HFPEF were compared with age- and gender-matched hypertensive patients with left ventricular hypertrophy (LVH) but without history of HFPEF, and with normal healthy controls.

11.2 Methods

11.2.1 Study population

This multicentre prospective study consists of three groups of subjects: (1) hypertensive patients with HFPEF; (2) hypertensive patients with LVH but without clinical features or past

history of HFPEF; and (3) age- and gender-matched healthy controls. The HFPEF patients were prospectively identified from consecutive patients admitted to the hospitals with the admission diagnosis code of heart failure (ICD-10 code: I50). Heart failure was rigorously defined by Framingham criteria and independently adjudicated by two cardiologists. All HFPEF patients, who have been hospitalized for pulmonary congestion diagnosed by chest radiogram and clinical examination, had a prior history of hypertension and EF > 50% on echocardiography within 24–72 h of index admission (Vasan et al. 2000). The LVH group was identified from our outpatient echocardiography database of hypertensive patients and the lack of clinical HFPEF was confirmed by formal history and physical examination. Left ventricular hypertrophy was defined as left ventricular mass index (LVMI) >95 g/m2 for women and >115 g/m2 for men as calculated from LV linear dimensions according to recommendations from the American Society of Echocardiography (Lang et al. 2005).

A power analysis was conducted to determine the number of participants needed in this study. An ANOVA examined the null hypothesis that Ts-SD during stress were not different among the 3 groups of subjects: (1) hypertensive HFPEF; (2) hypertensive LVH without HFPEF; and (3) age- and gender-matched healthy controls. Based on previous data, mean Ts-SD of the normal population at rest was about 20 ms (Yu et al. 2002, Yu et al. 2003, Yu et al. 2007). Previous data suggested that the mean Ts-SD in normal subjects did not change with exercise (Lafitte et al. 2006). The standard deviation of Ts-SD during dobutamine stress was unknown and was assumed to be 20ms, greater than that for Ts-SD measured at rest (15ms). The study was set to detect a stress-induced increase of Ts-SD in hypertensive HFPEF patients by at least 1 SD compared to normal subjects (i.e. at least 35ms); the mean Ts-SD of hypertensive LVH patients without HFPEF was assumed to be equal to the grand mean of the 3 groups (i.e. 27.5ms). The alpha for the ANOVA was set at 0.05. To achieve power of 0.8 and an effect size of 0.306, a minimal sample size of 108 was required.

A total of 105 patients (60 patients with HFPEF and 45 patients with asymptomatic LVH) were screened. Coronary angiogram was performed in 31 patients (19 patients in the HFPEF group and 12 patients in the LVH group) as a result of positive stress tests or at the discretion of physicians. Eight of them (five with HFPEF and three with LVH) had ≥50% epicardial coronary artery stenosis and were excluded from the study. The remaining 23 patients had no or mild (<50%) coronary stenosis and were included in this study for analysis. Other exclusion criteria include recent acute coronary syndrome or revascularization (<6 months), prior myocardial infarction, prior history of a positive stress test, primary cardiomyopathy, significant valvular disease, chronic pulmonary disease, chronic renal failure, permanent atrial fibrillation, and those who had received pacemaker implantation. After excluding these subjects, 47 patients with HFPEF (HFPEF group) and 34 with asymptomatic LVH (LVH group) were recruited for this study. Fifty sex- and gender-matched healthy subjects referred for evaluation of atypical chest pain but had otherwise normal history, physical examination, electrocardiography, echocardiography and stress test were recruited as normal controls. The study protocol was approved by ethics committee of the institution and informed consent was signed by all subjects.

11.2.2 Echocardiography

All subjects underwent dobutamine stress echocardiography (DSE) (Vivid 7, Vingmed-General Electric, Horten, Norway) with tissue Doppler imaging (TDI). The HFPEF group underwent DSE 3 months after acute hospitalization when they were in compensated clinical state without active HF symptoms. Dobutamine infusion was started at 5 μg/kg/min and increased every 3 min to 10, 20, 30, and 40 μg/kg/min. The test was terminated if any of the following endpoints was reached: achieved the target heart rate [85% × (220 − age in years)], new regional wall-motion abnormality, significant arrhythmia, persistent hemodynamic compromise, angina or intolerable symptoms. In the absence of contraindications, atropine (0.3–1.0 mg intravenously) was given if the target heart rate was not reached. Image acquisition with

2D and coded-coded TDI was performed at rest and at peak stress using the apical four-chamber, two-chamber, and long-axis views.

11.2.3 Assessment of systolic and diastolic functions

All the echocardiographic measurements were performed offline by the core echocardiographic laboratory in a blinded manner by an operator who was unaware of the diagnostic groups. The LV end-diastolic volume (LVEDV), LV end-systolic volume (LVESV) and LVEF were measured from the apical four-chamber and two-chamber views using the modified Simpson method.6 The LV longitudinal systolic myocardial function was assessed by averaging the peak systolic myocardial velocities at the six basal segments (mean Sm) by offline TDI analysis with the sample volumes placed just above the mitral annulus. Similarly, the LV longitudinal early diastolic myocardial function was assessed by averaging the early diastolic myocardial velocities of the six basal segments (mean Em) (Wang et al. 2003). Doppler-derived mitral inflow velocities were determined at rest and diastolic function classification grade (I–IV) was assigned as previously described (Lester et al. 2008). In eight patients, diastolic function was classified as undetermined.

11.2.4 Assessment of arterial elastance

Effective arterial elastance was estimated as end-systolic pressure divided by stroke volume. The stroke volume was calculated from the difference between LVEDV and LVESV. End-systolic pressure was estimated as systolic pressure times 0.9, as previously validated (Chen et al. 2001).

11.2.5 Assessment of left ventricular dyssynchrony

To evaluate LV systolic and diastolic dyssynchrony, myocardial velocity curves obtained from coded-coded TDI were reconstituted offline using the six-basal–six-mid-segment model consisting of the anterior, antero-septal, infero-septal, inferior, posterior, and lateral segments at basal- and mid-ventricular levels (Yu et al. 2004). Pulse repetition frequency, colour saturation, sector size and depth were optimized to maximize the frame rate to 100 Hz or higher. At least

three consecutive beats in sinus rhythm were stored, and the images were analyzed offline by an investigator blinded from clinical information using a customized software (EchoPac-PC, Vingmed-General Electric). All measurements were averaged over at least three consecutive cardiac cycles. The time to peak myocardial systolic velocity during the ejection period (Ts) and the time to peak myocardial early diastolic velocity (Te) were measured for each segment with reference to the onset of QRS complex. The standard deviation (SD) of Ts (Ts-SD) and Te (Te-SD) of the 12 LV segments were calculated. The intra- and inter-observer variability of the dyssynchrony parameters was determined in 40 consecutive measurements. The intra-observer variability for Ts-SD at rest was 3.6%, Te-SD at rest 3.3%, Ts-SD during stress 5.4%, and Te-SD during stress 5.2%. The corresponding figures for inter-observer variability were 4.3%, 4.4%, 6.5%, and 6.9%.

11.2.6 Statistical analysis

Data were analyzed using a statistical software (SPSS for Windows, SPSS Inc., Chicago, IL). Results were expressed as mean ± SD or number of patients (%) as appropriate. Paired t-test was used for within-group comparisons of continuous variables between rest and stress. Between-group differences were assessed by one-way analysis of variance with post hoc Scheffe's test or Pearson χ^2 test as appropriate. Correlations of continuous variables were tested by Pearson's coefficient. Multivariate logistic regression analysis with forward stepwise method was performed to identify independent predictors of HFPEF. Variables tested in the model included age, gender, co-morbidities (i.e. the presence or absence of diabetes, smoking, hyperlipidemia or prior stroke, tested as categorical variables), heart rate, blood pressures, QRS duration, LV volumes, LVEF, LVMI, diastolic function classification grade, effective arterial elastance, Δmean Em, Δmean Sm, and systolic and diastolic dyssynchrony at rest and stress. These factors were previously reported to be associated with development of HFPEF (Yip et al. 2002, Yu et al. 2002, Kawaguchi et al. 2003, Aurigemma et al. 2006, Wang et al. 2007, Yu et al.

2007). A variable is entered into the model if $P < 0.05$ and is removed if $P > 0.10$. P-values are two-sided with $P < 0.05$ considered to be statistically significant.

11.3 Results

11.3.1 Clinical characteristics and hemodynamic responses to stress

There were no differences in age (HFPEF: 57 ± 14 years vs. LVH: 61 ± 14 years vs. controls: 58 ± 13 years; $P = 0.377$) and gender [HFPEF: 21 men (45%) vs. LVH: 15 men (44%) vs. controls: 27 men (54%); $P = 0.956$] distribution among the three groups. The prevalence of cardiovascular risk factors and co-morbidities, including smoking, diabetes, hyperlipidemia, and prior stroke, and the medications were similar between the two hypertensive patient groups. The majority of patients had normal QRS duration (<120 ms) with no significant stress-induced changes (Table 11.1). The hemodynamic and echocardiographic characteristics were shown in Table 11.2. Systolic blood pressure during stress was significantly higher in the HFPEF group compared with the LVH group ($P < 0.001$), despite being similar between the two groups at rest. Effective arterial elastance was significantly higher in the hypertensive patients. It increased significantly during stress with the greatest exaggeration in the HFPEF group ($P < 0.001$). The HFPEF group had significantly greater LV wall thickness and LVMI than the LVH group ($P < 0.001$). The resting LVESV, LVEDV, LVEF, and diastolic function classification grade were similar. During stress, LV volumes decreased and LVEF increased ($P < 0.01$) in both hypertensive patient groups (Table 11.2).

Table 11-1. Comparison of clinical and demographic characteristics between patients with hypertensive left ventricular hypertrophy and HFPEF

	LVH group (*n* = 34)	HFPEF group (*n* = 47)	*P*
Age (years)	61 ± 14	58 ± 13	0.377
Male gender [*n* (%)]	15 (44%)	21 (45%)	0.956
Risk factors/co-morbidities [*n* (%)]			
Diabetes mellitus	7 (21%)	9 (19%)	0.872
Smoking	5 (15%)	7 (15%)	0.975
Hyperlipidemia	11 (34%)	14 (30%)	0.805
Stroke	3 (9%)	5 (11%)	0.787
QRS duration (ms)			
Rest	89 ± 13	83 ± 9	0.564
Stress	90 ± 10	87 ± 9	0.162
QRS ≥ 120 ms [*n*(%)]	3 (9%)	7 (15%)	0.412
NYHA class [*n*(%)]			
II	–	42 (89%)	
III	–	5 (11%)	
Diastolic function classification grade [*n*(%)]			
I	12 (35%)	16 (34%)	0.535
II	18 (53%)	24 (51%)	
III	–	2 (4%)	
IV	–	1 (2%)	
Medications [*n*(%)]			
Calcium channel blockers	26 (76%)	36 (77%)	0.800
Beta-blockers	23 (68%)	32 (68%)	0.964
ACEI or ARB	23 (68%)	33 (70%)	0.805
Diuretics	32 (94%)	44 (94%)	0.924

ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blocker; HFPEF, heart failure with preserved ejection fraction; LVH, left ventricular hypertrophy; NYHA, New York Heart Association.

11.3.2 Comparisons of left ventricular dyssynchrony at rest and stress

The standard deviation of Ts and Te did not significantly differ between rest and stress in normal subjects (Table 11.3). At rest, Ts-SD was significantly greater in both hypertensive patient groups (both $P < 0.05$ vs. normal controls), but similar between the two groups. Interestingly, Ts-SD increased significantly after stress in both hypertensive groups ($P < 0.05$), but the magnitude of change (ΔTs-SD) was significantly greater in the HFPEF group compared with the LVH group ($P < 0.001$) (Table 11.3). We defined systolic dyssynchrony as two SD above the mean Ts-SD of normal controls. As the mean and distribution of Ts-SD did not

change with stress in normal subjects, the cut-off for systolic dyssynchrony was >33 ms both at rest and stress. At rest, 36.2% of patients in the HFPEF group and 38.2% in the LVH group had systolic dyssynchrony (χ^2 = 0.036, P = 0.85). Upon stress, the prevalence of systolic dyssynchrony increased dramatically to 85.1% in the HFPEF group, but to only 52.9% in the LVH group (χ^2 = 10.04, P = 0.002) (Figure 11.1).

Table 11-2. Comparison of demodynamic and echocardiographic parameters among patients with hypertensive left ventricular hypertrophy, HFPEF, and normal controls

	Normal controls (*n* = 50)	LVH group (*n* = 34)	HFPEF group (*n* = 47)	ANOVA *P*
Heart rate (b.p.m.)				
Rest	70 ± 14	72 ± 14	69 ± 14	0.761
Stress	129 ± 22*	124 ± 24*	126 ± 18*	0.469
Systolic blood pressure (mmHg)				
Rest	129 ± 8	156 ± 11†	156 ± 11†	<0.001
Stress	164 ± 10*	196 ± 13*†	214 ± 17*†‡	<0.001
Diastolic blood pressure (mmHg)				
Rest	75 ± 7	86 ± 7†	86 ± 7†	<0.001
Stress	92 ± 8*	104 ± 7*†	104 ± 5*†	<0.001
LVMI (g/m^2)	51 ± 13	114 ± 9†	129 ± 9†‡	<0.001
IVST (mm)	8 ± 1	12 ± 1†	15 ± 1†‡	<0.001
PWT (mm)	8 ± 1	10 ± 1†	15 ± 1†‡	<0.001
LVEDV (mL)				
Rest	108 ± 18	109 ± 15	111 ± 17	0.783
Stress	112 ± 17*	105 ± 15*	105 ± 19*	0.490
LVESV (mL)				
Rest	42 ± 9	40 ± 8	42 ± 11	0.432
Stress	29 ± 7*	27 ± 6*	29 ± 12*	0.403
LVEF (%)				
Rest	61 ± 5	64 ± 5	62 ± 7	0.111
Stress	74 ± 5*	74 ± 5*	73 ± 8*	0.690
Effective arterial elastance (mmHg/mL)				
Rest	1.81 ± 0.39	2.08 ± 0.39†	2.11 ± 0.51†	0.002
Stress	2.02 ± 0.39	2.34 ± 0.45*†	2.59 ± 0.46*†‡	<0.001

*P < 0.01 vs. resting value; †P < 0.05 vs. normal controls; ‡P < 0.05 vs. LVH group. IVST, interventricular septal thickness; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume; LVMI, left ventricular mass index; PWT, posterior wall thickness.

For diastolic dyssynchrony, Te-SD was also significantly prolonged in both hypertensive patient groups compared with normal controls (both P < 0.001 vs. controls) (Table 11.3).

However, there was no significant difference between the two groups at rest. Upon stress, Te-SD increased in both hypertensive patient groups, but the change (ΔTe-SD) was significantly greater in the HFPEF group ($P < 0.001$) (Table 3). We defined diastolic dyssynchrony as the upper two SD of normal controls, i.e. >34 ms (similar to systolic dyssynchrony, the cut-off remained the same at rest and stress). Resting diastolic dyssynchrony was evident in 34.0% of the HFPEF group and 29.4% of the LVH group ($\chi^2 = 0.194$, $P = 0.66$). During stress, the prevalence of diastolic dyssynchrony increased significantly in the HFPEF group to 87.2%, which became significantly higher than the 58.8% in the LVH group ($\chi^2 = 8.564$, $P = 0.003$) (Figure 11.1).

The pattern of change in dynamic dyssynchrony was illustrated in Figure 11.2. Stress-induced systolic dyssynchrony was observed in 51.1% of patients in the HFPEF group, but only 23.5% in the LVH group ($\chi^2 = 11.165$, $P = 0.011$). Also, persisting systolic dyssynchrony occurred in 34.0% in the HFPEF group, but only 29.4% in the LVH group. Conversely, persistent synchronous contraction both at rest and stress was more frequently observed in the LVH group (38.2% vs. 12.8%). Likewise, stress-induced diastolic dyssynchrony was more commonly observed in the HFPEF group (57.4% vs. 35.3%; $\chi^2 = 9.566$, $P = 0.023$), while more patients in the LVH group had persistently synchronous relaxation at rest and stress (35.3% vs. 8.5%).

11.3.3 Comparisons of mean Sm and mean Em at rest and stress

Both hypertensive patient groups had lower resting mean Sm than normal controls (both $P < 0.001$), although it was further reduced in the HFPEF group ($P < 0.001$ vs. LVH group) (Table 11.3). During stress, the mean Sm increased in all three groups ($P < 0.001$ vs. rest for all groups) but the increment (ΔSm) was the smallest in HFPEF ($P < 0.05$ vs. LVH; $P < 0.001$ vs. controls) (Table 11.3, Figure 11.3). For diastolic function, both hypertensive patient groups had lower resting mean Em than normal controls (both $P < 0.001$), but it was lower in the HFPEF group ($P < 0.001$ vs. LVH group) (Table 11.3). The mean Em increased significantly during stress in both the LVH group and normal controls ($P < 0.001$ vs. rest), but it was unchanged in

the HFPEF group (P = 0.468) (Table 11.3, Figure 11.3). Patients with diastolic dyssynchrony (n = 61) during stress had significantly more blunted ΔEm (0.4 ± 2.9 vs. 2.1 ± 3.5 m/s, P = 0.037) than those without (n = 20).

Table 11-3. Comparison of TDI-derived myocardial longitudinal function and dyssynchrony among patients with hypertensive left ventricular hypertrophy, HFPEF, and normal controls

	Normal controls (*n* = 50)	LVH group (*n* = 34)	HFPEF group (*n* = 47)	ANOVA *P*
Mean Sm (cm/s)				
Rest	8.7 ± 1.9	6.6 ± 2.2†	5.4 ± 1.5†‡	<0.001
Stress	16.4 ± 4.3*	11.0 ± 3.8*†	8.2 ± 2.2*†‡	<0.001
ΔSm	7.7 ± 3.3	4.4 ± 2.4†	2.8 ± 2.0†‡	<0.001
Mean Em (cm/s)				
Rest	11.8 ± 3.1	6.8 ± 3.0†	4.6 ± 1.8†‡	<0.001
Stress	13.8 ± 3.4*	9.4 ± 4.1*†	4.3 ± 2.0†‡	<0.001
ΔEm	1.9 ± 3.3	2.4 ± 3.4	−0.3 ± 2.5†‡	<0.001
Ts-SD (ms)				
Rest	23.2 ± 5.1	31.8 ± 4.2†	31.3 ± 5.0†	<0.001
Stress	24.1 ± 4.3	34.1 ± 3.6*†	37.2 ± 3.5*†‡	<0.001
ΔTs-SD	1.9 ± 4.5	2.3 ± 4.2	5.9 ± 4.2†‡	<0.001
Te-SD (ms)				
Rest	22.9 ± 5.7	31.6 ± 4.2†	32.9 ± 4.5†	<0.001
Stress	23.3 ± 5.4	35.4 ± 6.5*†	41.2 ± 8.9*†‡	<0.001
ΔTe-SD	0.6 ± 2.9	3.8 ± 6.7	8.3 ± 9.9†‡	<0.001

*P < 0.05 vs. resting value; †P < 0.05 vs. normal controls; ‡P < 0.05 vs. LVH group.

11.3.4 Independent factors associated with HFPEF on multivariate analysis

Multivariate analysis was performed to identify independent factors associated with of HFPEF. Of all tested variables, ΔEm [Odds ratio (OR) = 0.69, 95% confidence interval (CI): 0.54–0.89, P = 0.004], ΔSm (OR = 0.56, 95% CI: 0.37–0.83, P = 0.004), diastolic dyssynchrony during stress (OR = 4.6, 95% CI: 1.9–20.9, P = 0.005), and systolic dyssynchrony during stress (OR = 4.3, 95% CI: 1.1–16.7, P = 0.038) emerged as independent factors associated with of HFPEF.

11.4 Discussion and conclusions

The present study provides novel data on the dynamic property and impact of LV dyssynchrony in hypertensive patients with LVH and HFPEF. Despite a similar severity of resting LV dyssynchrony in both disease groups, both systolic and diastolic dyssynchrony during stress were more prevalent and profound in patients with hypertensive HFPEF. Furthermore, despite apparently normal stress-induced increase in LVEF, the HFPEF group had severely

blunted augmentation in long-axis myocardial systolic function and absence of increment in long-axis myocardial diastolic function during stress. These findings are suggestive of impairment in systolic reserve and almost absence of diastolic reserve. Finally, independent determinants for the occurrence of HFPEF included diastolic and systolic dyssynchrony during stress as well as reduced augmentation in diastolic and, to a lesser extent, systolic longitudinal myocardial function.

11.4.1 Dynamic dyssynchrony in HFPEF and asymptomatic hypertensive heart disease

Several recent studies reported a high prevalence of resting LV dyssynchrony in patients with HFPEF (Wang et al. 2007, Yu et al. 2007). Importantly, in one study (Wang et al. 2007), abnormal LV systolic indices including stroke work and myocardial contractility were found to be associated with increased systolic dyssynchrony in HFPEF. A few previous studies reported abnormal systolic function in patients with LVH and HFPEF (Yip et al. 2002, Yu et al. 2002, Aurigemma et al. 2006). The concept of resting diastolic dyssynchrony and its contribution to diastolic dysfunction has been reported in severe hypertrophic conditions including aortic stenosis and hypertrophic obstructive cardiomyopathy (Villari et al. 1996, Park et al. 2002). More recently, diastolic dyssynchrony was examined in a clinical study of HFPEF patients, which found that both time constant of relaxation and mean wedge pressure increased in parallel with the prolongation of the diastolic regional time delay (Wang et al. 2007). However, most previous studies investigating LV dyssynchrony in HFPEF were performed at resting condition. Intuitively, as the symptoms of HFPEF are often precipitated by hemodynamic stress, evaluation of dyssynchrony during stress is likely to be clinically and pathophysiologically relevant. Indeed, in systolic heart failure, recent studies showed that magnitude of LV dyssynchrony could be altered by stress and the dynamic response of dyssynchrony is variable among individuals (Lafitte et al. 2006, Kang et al. 2008).

In the present study, although LV dyssynchrony was evident in hypertensive patients with and without clinical HFPEF, it did not differ between the two groups at rest. However,

hemodynamic challenge revealed significant worsening of LV dyssynchrony mainly in the HFPEF group, implicating a higher vulnerability of developing stress-induced dynamic dyssynchrony in hypertensive HFPEF. Interestingly, a shift from resting dyssynchrony to disappearance during stress is very rare, which suggests that the dynamic change is not a random event. Using the same method as ours to assess systolic dyssynchrony, a recent study found that 6 min treadmill exercise test led to deterioration in systolic dyssynchrony only in HFPEF patients but not asymptomatic hypertensive patients with diastolic dysfunction; systolic dyssynchrony during exercise was associated with higher plasma N-terminal pro-BNP levels (Wang et al. 2007). Nevertheless, diastolic dyssynchrony was not evaluated in that particular study. In fact, the current study suggested that diastolic dyssynchrony during stress is also a strong predictor of HFPEF in hypertensive heart disease.

A number of mechanisms may account for the occurrence of stress-induced dynamic dyssynchrony. One possible factor is myocardial ischemia. In one study, coronary heart disease was associated with diastolic dyssynchrony, which improved after revascularization (Bonow et al. 1985). However, coronary heart disease may not be a common precipitating factor of HFPEF, and indeed angiographically confirmed coronary disease was uncommon in the present study. Left ventricular hypertrophy is another potential cause of dyssynchrony. Patients in the HFPEF group had higher LVMI than those in the LVH group. It is well known that LVH is associated with increased myocardial oxygen demand and abnormal coronary flow reserve that may result in sub-endocardial ischemia and regional dysfunction during stress (Vatner et al. 1993).

11.4.2 Systolic and diastolic myocardial function reserve in HFPEF

Another distinguishing feature of patients with HFPEF in this study was the severely blunted response of mean Sm and, in particular, the lack of increment of mean Em during stress. In the LVH group, stress-induced augmentation of mean Sm and mean Em was also blunted, but less severe than that observed in the HFPEF group. Using TDI (Yip et al. 2002, Yu et al. 2002) and speckle strain techniques (Wang et al. 2008), recent studies demonstrated the presence of

resting long-axis systolic dysfunction in HFPEF patients. Arguably, as patients with HFPEF will predominantly have exertional symptoms, the current study supports the hypothesis that impaired systolic and diastolic function reserves are important in the pathogenesis of HFPEF (Tan et al. 2009, Wang et al. 2009). Kawaguchi et al. has suggested that systolic and diastolic reserve in HFPEF may be impaired during exercise as a result of systolic ventricular and arterial stiffening (Kawaguchi et al. 2003). Consistently, a higher arterial elastance was observed in the HFPEF group, even though it may be underestimated in the present study owing to the vasodilatory effect of dobutamine. Dynamic dyssynchrony during DSE has been reported in other afterload mismatch conditions. In one report, dynamic dyssynchrony was implicated as a contributory factor to the lack of contractile reserve in a patient with aortic stenosis (Lancellotti et al. 2009). We postulated that stress-induced LV dynamic dyssynchrony, impaired myocardial function reserve, and exaggerated arterial afterload mismatch may all be mutually interacting factors in the complex pathophysiology of HFPEF.

11.4.3 Limitations

Since coronary angiography was not performed in all patients, the possibility of silent ischemia in the study population cannot be entirely excluded. However, DSE is sensitive in detecting functionally significant ischemia, and subjects with obstructive coronary artery disease were excluded from the study. Although the reproducibility of the TDI techniques has recently been challenged by the PROSPECT study (Chung et al. 2008), it should be recognized that, like any other techniques, a learning curve exists for dyssynchrony analysis. In trained and experienced centres of performing dyssynchrony analysis, a high beat-to-beat reproducibility of myocardial velocity profile has been ascertained and a low inter- and intra-observer variability has been observed (Yu et al. 2009).

Increased heart rate during stress may influence the exact definition of dyssynchrony. Nevertheless, the definition of dyssynchrony in this study was derived from age-, gender-matched normal controls, with similar heart rate both at rest and stress among the three study

groups. Interestingly, when using the absolute measure of time delay to assess dyssynchrony, the cut-offs remain unchanged between rest and stress when derived from two SD above mean from normal controls. Consistently, normal controls did not develop dyssynchrony during stress. Therefore, the same cut-offs were applicable during rest and stress in these patients.

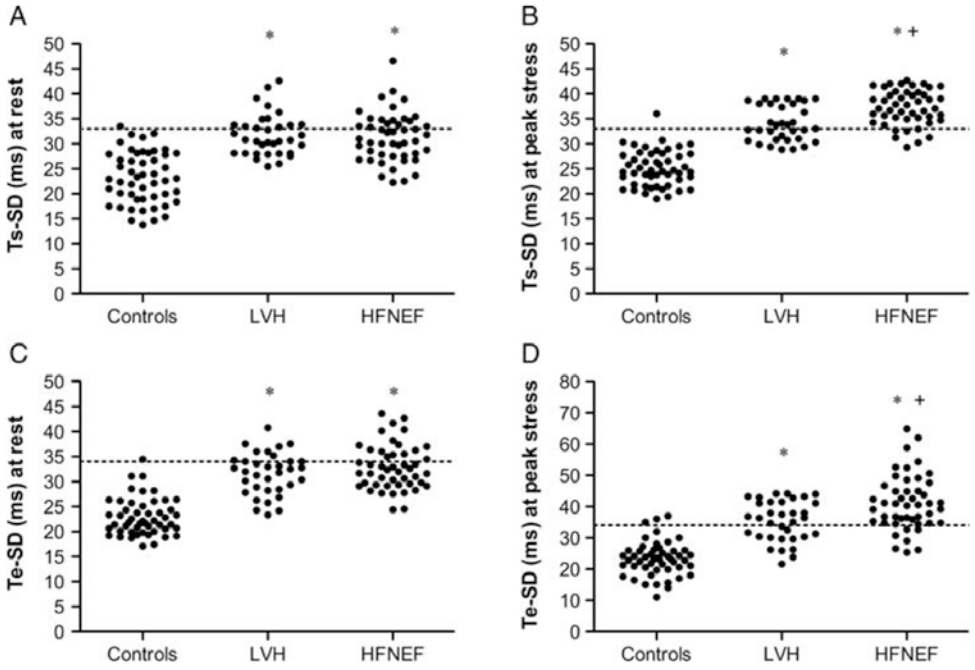
Owing to the angle dependency of TDI, radial, rotational, and apical information regarding dyssynchrony was not included in this study. Recently, the use of 2D speckle strain techniques in evaluating myocardial mechanics has been reported (Delgado et al. 2008). However, the main limitation of speckle tracking is a lower frame rate at the outset, resulting in possible under-sampling of peak values, which may be a problem in tracking in high heart rate during stress.

Finally, it is important to note that the present study, limited by its cross-sectional design, albeit finding a strong association between dynamic dyssynchrony and hypertensive HFPEF, does not confirm causality, which can only be defined from a longitudinal study.

11.4.4 Conclusions

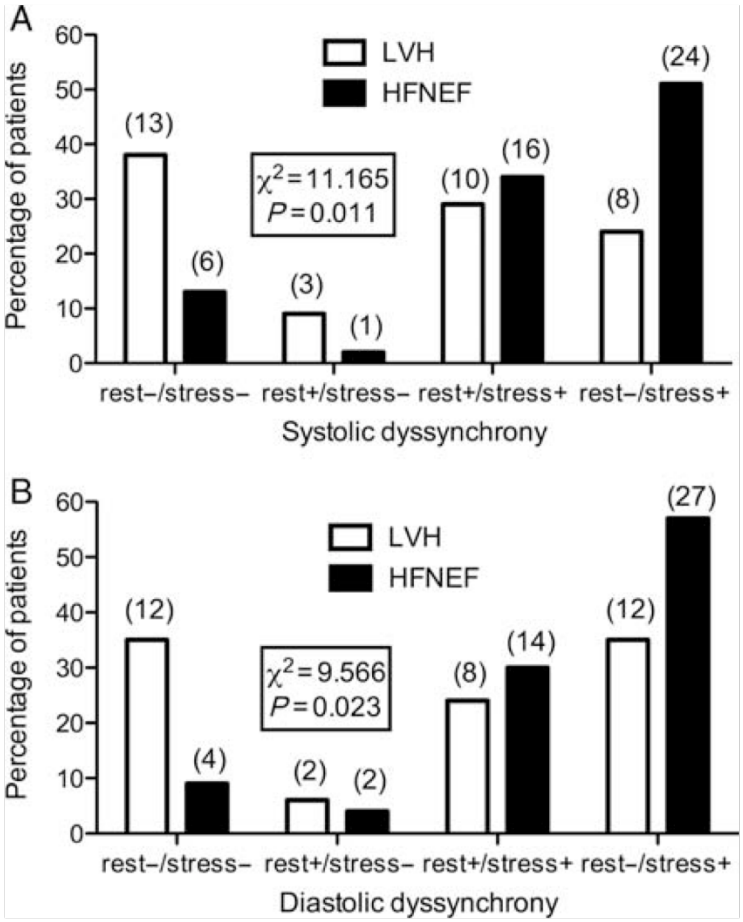
Our study demonstrated that LV dyssynchrony is highly dynamic in HFPEF patients. Systolic and diastolic dyssynchrony during stress, along with impaired systolic and diastolic reserves, appeared to be independent predictors for the development of clinical HFPEF in hypertensive heart disease. These findings contribute to a better understanding of the pathophysiology of HFPEF and add insights to plan on treatment strategies. As LV dyssynchrony could be absent at rest but provoked by stress, evaluation of dynamic dyssynchrony using stress test may help identifying patients at a higher risk of developing HFPEF. Finally, whether therapies targeting at LVH regression (Brilla et al. 2000) would reverse dynamic dyssynchrony and leads to improvement of symptomatic status and myocardial function reserve warrants further investigations.

Figure 11-1. Scatter plots of Ts-SD and Te-SD at rest (A, C) and after stress (B, D).



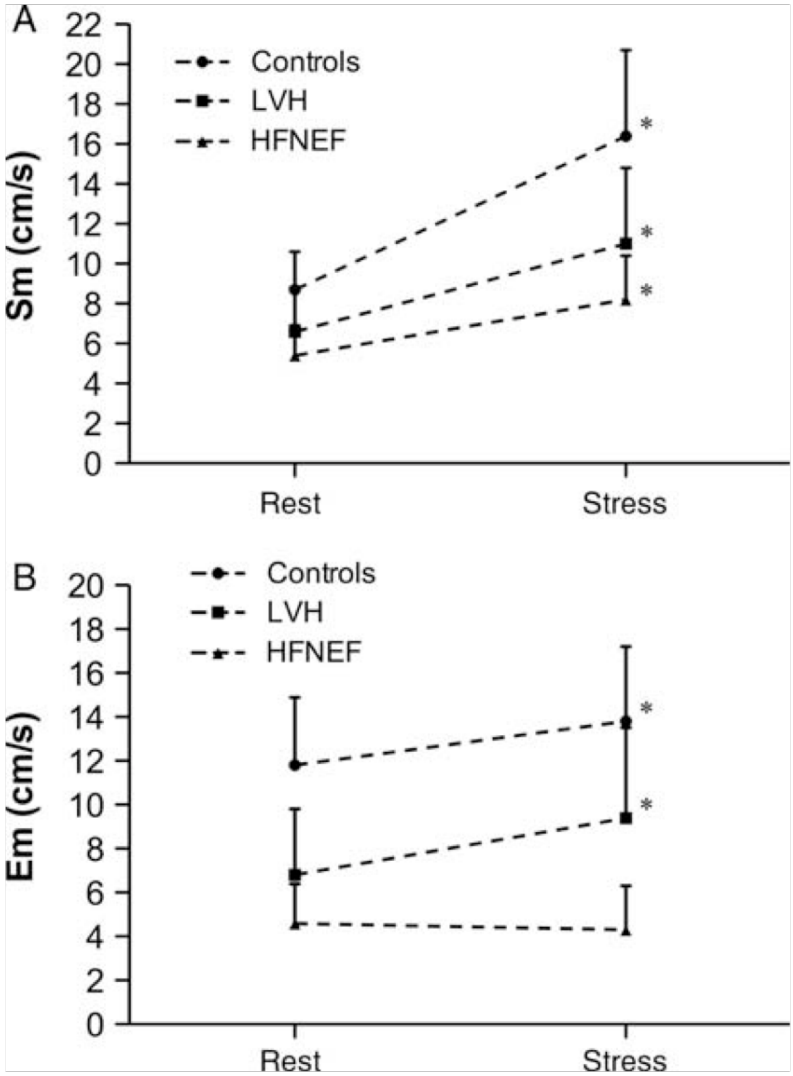
*P < 0.001 vs. normal controls. $^{+}$P < 0.001 vs. LVH group. Dotted lines denote cut-off values for systolic (>33 ms) and diastolic (>34 ms) dyssynchrony.

Figure 11-2. Change of systolic (A) and diastolic (B) dyssynchrony status from rest to stress.



Rest-/stress-, persistent synchrony; rest+/stress-, stress-induced synchrony; rest+/stress+, persistent dyssynchrony; and rest-/stress+, stress-induced dyssynchrony. Numbers in parentheses indicate the number of patient in each category.

Figure 11-3. Change of mean Sm (A) and mean Em (B) on stress test.



Stress-induced increases in mean Sm and mean Em were blunted significantly in the heart failure with normal ejection fraction group. *P < 0.001 rest vs. stress.

Chapter 12 Study 4: Left Ventricular Dyssynchrony in Acute Decompensated Heart Failure with Depressed Ejection Fraction

12.1 Introduction

The previous chapters established the role of LV mechanical dyssynchrony in patients with structure heart disease and preserved LV systolic function and those with HFPEF. In patients with LV systolic dysfunction or depressed EF, acute decompensated heart failure (ADHF) is a common and potentially fatal cause of acute respiratory distress. However, its pathogenesis is incompletely understood. Although acute myocardial ischemia, hypertensive crisis, fluid retention, and tachyarrhythmia are recognized triggers (Gandhi et al. 2001, Yu et al. 2003), many patients do not have clinically apparent precipitating factors. LV systolic mechanical dyssynchrony is an important pathogenic factor in chronic systolic heart failure and can exists without electrical conduction delay on surface electrocardiogram (Yu et al. 2003). Evaluation of LV dyssynchrony in heart failure is often based on assessment when patients are in stable compensated state. Nevertheless, LV dyssynchrony can change dynamically with exercise (Ennezat et al. 2006) and, as shown in the previous chapter (Lee et al. 2010) and by others (Chattopadhyay et al. 2008), pharmacological stress. Patients can have transient episodes of increased LV dyssynchrony leading to elevation of LV filing pressure, precipitating or worsening mitral regurgitation and eventually acute pulmonary oedema. The cardiovascular system is constantly exposed to external factors that impose hemodynamic stress: drugs, change in loading conditions, anemia, and infection, etc. In this chapter, we test hypothesis that patients who presented with ADHF may have increased LV dyssynchrony as compared to those who had chronic stable heart failure (CSHF) without recent exacerbation. We prospectively performed echocardiography with TDI in a consecutive series of patients during episodes of ADHF with comparison to patients with CSHF. With TDI, LV dyssynchrony can be examined by evaluation

of the regional timing of LV contraction during the acute episodes of ADHF, providing a better appreciation of the dynamic characteristics of LV dyssynchrony.

12.2 Methods

12.2.1 Patient population

A power analysis was conducted to determine the number of participants needed in this study. A Student t-test examined the null hypothesis that there was no difference in Ts-SD between patients with ADHF and those with CSHF. Based on previous comparable data, mean Ts-SD of patients with CSHF (with reduced EF, including both narrow and wide QRS duration) was about 35 ms (Yu et al. 2002, Yu et al. 2003, Yu et al. 2007), with a standard deviation of about 15ms. The alpha value was set at 0.05. To achieve power of 0.8 and a medium effect size of d=0.5, a minimal sample size of 128 was required to detect a significant model.

A total of 145 subjects consisting of 84 consecutive patients who presented to our emergency department with ADHF requiring hospitalization were prospectively recruited and 61 patients with CSHF identified from our outpatient database. ADHF was defined as a clinical syndrome of acute respiratory distress associated with elevated jugular venous pressure, peripheral oedema, pulmonary rales, and radiographic evidence of alveolar pulmonary oedema. The diagnosis of ADHF was verified independently by two cardiologists. The index hospital admission may be the first time presentation of newly diagnosed HF or acute exacerbation of prior HF. Eligible patients were those with LV ejection fraction (EF) <50%. Exclusion criteria included acute coronary syndrome, primary valvular lesions, atrial fibrillation during dyssynchrony assessment, chronic kidney disease, congenital and pericardial diseases. A comparison group was selected by means of a review of our data set of patients with CSHF who had no evidence of decompensation or HF hospitalization over the past 6 months. The ADHF and CSHF groups were matched for age, gender, and LVEF. The study was approved by the local ethics committee of the Institution and informed consents were obtained from all subjects.

12.2.2 Echocardiography

Echocardiography (Vivid 7, Vingmed-General Electric, Horten, Norway) was performed in all subjects. For the ADHF group, echocardiography was performed within 48 hours of hospital admission. Two-dimensional and Doppler echocardiography was performed in standard parasternal, apical and subcostal views. TDI was performed at apical 4-chamber, 2-chamber, and long-axis views. Coded-coded TDI optimized for pulse repetition frequency, colour saturation, sector size and depth were obtained to maximize the frame rate to 100 Hz or higher. At least 3 consecutive beats in sinus rhythm were stored, and the images were analyzed offline using customized software (EchoPac-PC, Vingmed-General Electric). All measurements were averaged over at least 3 consecutive cardiac cycles. The echocardiographers who obtained the images and the investigators who performed the offline analysis were blinded from the clinical information of the subjects.

LV wall thickness and mass were measured according to guideline recommendations (Lang et al. 2005). LV end-diastolic volume, end-systolic volume, and EF were assessed using the modified Simpson method in the apical 4- and 2-chamber views (Lang et al. 2005). Left atrial dimension was measured on the parasternal long-axis view. Longitudinal LV function was assessed by averaging the peak myocardial systolic (mean Sm) and early diastolic (mean Em) velocities at the 6 basal segments obtained by offline TDI analysis with the sample volumes placed just above the mitral annulus. The severity of any mitral regurgitation was quantitatively assessed by the proximal isovelocity surface area method. The effective regurgitant orifice (ERO) was calculated with use of standard formula (Zoghbi et al. 2003).

12.2.3 Assessment of LV dyssynchrony

Myocardial velocity curves obtained from coded-coded TDI were reconstituted offline using the 12-segment (6-basal 6-mid) model which consisted of the anterior, inferior, anteroseptal, inferoseptal, anterolateral and inferolateral segments at both basal and mid-levels. The basal segments were sampled just above mitral annulus, and the mid segments were sampled at mid LV. Time to peak systolic velocity during ejection (Ts) was measured for each

segment with reference to the onset of QRS complex. Continuous-wave Doppler of the aortic and mitral flow was used to determine the timings of aortic and mitral valve opening/closure, respectively. Markers of valve opening and closing events would appear on the electrocardiogram during offline TDI analysis to assist accurate measurement of Ts. The standard deviation of Ts (Ts-SD) of the 12 LV segments was calculated to evaluate LV systolic dyssynchrony. Significant LV systolic dyssynchrony was defined as Ts-SD >33ms.

12.2.4 Statistical analysis

Data were analyzed using statistical software (SPSS, SPSS Inc., Chicago, Illinois). Results were presented as mean±SD or number of patient (%). Group comparisons were performed by independent student's t test or Pearson χ^2 test as appropriate. Pearson coefficient was used for correlation analysis. A value of $P<0.05$ was considered significant.

12.3 Results

12.3.1 Patient characteristics

Clinical and echocardiographic characteristics of the study population were shown in Table 12.1. As expected, patients with ADHF had higher heart rate measured on hospital admission than those with CSHF measured at a clinically stable state (82±15 vs 68±13 bpm, $P<0.001$). Otherwise, there was no significant difference in age, gender, blood pressure, etiologist of HF, co-morbidities, QRS duration, and medications between the 2 groups.

12.3.2 Conventional echocardiographic parameters

There was no significant difference in LV volumes, ejection fraction and left atrial dimension between patients presenting with ADHF vs those with CSHF (P=NS). However, patients presenting with ADHF had significantly increased LV septum and posterior wall thickness and calculated LV mass (all $P<0.05$; Table 12.1). Mitral regurgitation was more frequently present in patients with ADHF than those with CSHF [60 of 84 (71%) vs 28 of 61 (46%), $P<0.0001$] and the degree of mitral regurgitation was more severe in the ADHF group,

but the overall severity of mitral regurgitation was only mild to moderate (ERO=0.12±0.11 vs 0.02±0.04cm^2, P<0.0001).

12.3.3 TDI and LV mechanical dyssynchrony

Despite no intergroup difference in LVEF, the mean Sm was reduced among patients of the ADHF group compared to those of the CSHF group (2.7±0.9 cm/s vs 3.0±0.9 cm/s, P=0.04). On the other hand, the mean Em was similar between the 2 groups. The Ts-SD was significantly prolonged in the ADHF group compared to the CSHF group (44.7±16.6 vs 33.4±17.7 ms, P=0.0001) (Figure 12.1, Table 12.1). Significant LV systolic dyssynchrony, defined as Ts-SD>33 ms, was evident in 75% (63 of 84) of patients of the ADHF group, compared to only 44% (27 of 61) of the CSHF group (P=0.0002). Notably, patients with Ts-SD >33 ms were significantly more likely to have an elevated E/Em >20 (84% vs 43%; χ^2=16.1, P<0.0001), signifying a severely elevated LV filling pressure. There was only a weak correlation of Ts-SD with ERO (r^2=0.12, P<0.0001).

Table 12-1. Comparisons of clinical characteristics of patients with acute decompensated heart failure and chronic stable heart failure

Variables	ADHF (n = 84)	CSHF (n = 61)	P value
Clinical			
Age, year	65 ± 11	61 ± 11	0.83
Men, n (%)	67 (80%)	50 (82%)	0.93
Systolic blood pressure, mm Hg	136 ± 22	129 ± 25	0.08
Diastolic blood pressure, mm Hg	78 ± 13	77 ± 14	0.67
Heart rate, bpm	82 ± 15	68 ± 13	< 0.0001
QRS duration, ms	123 ± 29	123 ± 27	1.0
Smoking, n (%)	14 (17%)	12 (19%)	0.5
Diabetes mellitus, n (%)	63 (75%)	41 (68%)	0.15
Hypertension, n (%)	50 (60%)	26 (43%)	0.064
Ischemic cardiomyopathy, n (%)	45 (53%)	24 (40%)	0.096
History of revascularization, n (%)	8 (8%)	1 (2%)	0.08
Drug therapy, n (%)			
Loop diuretics	79 (94%)	56 (92%)	0.74
ACE inhibitors or ARB	77 (82%)	49 (80%)	0.08
Beta-blocker	64 (76%)	48 (78%)	0.84
Echocardiography			
IVST, mm	1.05 ± 0.25	0.88 ± 0.27	0.035
PWT, mm	1.01 ± 0.21	0.87 ± 0.12	0.001
LVM, g	267 ± 90	228 ± 74	0.04
LVEDD, mm	6.1 ± 0.9	6.3 ± 1.0	0.51

LVESD, mm	5.1 ± 1.0	5.2 ± 1.1	0.74
LVEF, %	31 ± 9	34 ± 9	0.15
Left atrial diameter, mm	4.8 ± 0.7	4.5 ± 0.7	0.13
Mitral E/A	1.7 ± 1.2	1.2 ± 1.0	0.22
ERO, cm^2	0.12 ± 0.11	0.02 ± 0.04	< 0.0001
Mean Em, cm/s	3.2 ± 1.3	3.5 ± 1.3	0.31
Mean Sm, cm/s	2.7 ± 0.9	3.0 ± 0.9	0.04
Ts-SD, ms	44.7 ± 16.7	33.3 ± 17.6	0.0001

Values are expressed as mean ± SD or number (%). ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; ADHF, acute decompensated heart failure; CSHF, chronic stable heart failure; IVST, interventricular septal thickness; PWT, posterior wall thickness; LVM, LV mass; LVEDD, left ventricular end-diastolic dimension; LVESD, left ventricular end-systolic dimension; LVEF, left ventricular ejection fraction; ERO, effective regurgitant orifice. Mean Em, mean basal myocardial early diastolic velocity; Mean Sm, mean basal myocardial systolic velocity; Ts-SD, standard deviation of peak systolic myocardial velocity in the 6-basal, 6-mid segmental model.

12.4 Discussion and conclusions

12.4.1 Acute LV systolic dyssynchrony and exacerbation of systolic dysfunction

Our study showed that among patients with systolic heart failure presenting with acute decompensation requiring hospitalization a high prevalence of LV systolic dyssynchrony was evident during the first 1-2 days of hospital admission. LV systolic dyssynchrony is the mechanical effect of asynchronous ventricular contraction, which is a recognized contributory factor of progressive worsening of the LV function in chronic heart failure. LV systolic dyssynchrony carries worse prognosis in patients with heart failure due to LV systolic dysfunction (Shamim et al. 1999). Our study fills the gap of knowledge about the role of LV systolic dyssynchrony in the acute decompensation of systolic heart failure. The ERO of functional mitral regurgitation was significantly larger in patients with ADHF, which may have contributed to acute increase in LA pressure and increased preload to the LV. Although exercise-induced changes in LV systolic dyssynchrony strongly correlated with those in functional mitral regurgitation in patients with chronic ischemic LV dysfunction (Ennezat et al. 2006), our study demonstrated only a mild degree of regurgitation and a weak correlation with LV systolic dyssynchrony in the acute setting.

12.4.2 Potential mechanisms of LV systolic dyssynchrony in ADHF

Several mechanisms such as arrhythmia, ischemia, hypertension, or exercise may exacerbate dyssynchrony. However, patients admitted with arrhythmias or evidence of acute ischemia were excluded from our study. None of our patients had chest pain, ischemic ST-segment changes, or echocardiographic evidence of ischemia during the acute episode, which suggests that the acute LV systolic dyssynchrony was unlikely to be related to myocardial ischemia in this study. High systolic blood pressure on admission could have contributed to the exacerbation of LV systolic dyssynchrony through an increase in afterload. Nevertheless, this is unlikely the cause of LVSD in our study as there was no significant difference in blood pressure measured on admission in patients with ADHF compared to that measured in patients at a stable clinical state.

LV and left atrial dimensions did not differ significantly between the ADHF and the CSHF groups. However, patients of the ADHF group had greater LV wall thickness and LV mass than those of the CSHF group. Rosen et al. demonstrated that in asymptomatic individuals, age, increased LV mass, and decreased myocardial perfusion were related to delayed regional myocardial contraction and greater extent of dyssynchrony (Rosen et al. 2009). LV hypertrophy is associated with the development of HF and increased incidence of other major cardiovascular events, including sudden death. LV concentric remodelling initially is associated with decreased LV function manifested as reduced midwall circumferential shortening despite preserved ejection fraction. Eventually patients with LV hypertrophy will tend to develop global systolic dysfunction. In this study, patients in the ADHF group had worse LV hypertrophy compared to the CSHF group, suggesting that the presence of LV hypertrophy in concert with LV systolic dyssynchrony may predispose systolic heart failure patients to acute exacerbation.

LV systolic dyssynchrony may be heart rate dependent. In ADHF, activation of renin–angiotensin and sympathetic systems results in tachycardia and an elevation in vascular resistance which may contribute to exacerbation of LV systolic dyssynchrony. Dyssynchrony may worsen with tachycardia because of non-homogenous distribution of ultrastructural

changes, potential myocardial ischemia, or calcium handling abnormalities within the myocytes secondary to cardiac disease, leading to further impairment of the force–frequency relation in the whole heart (Spragg et al. 2003).

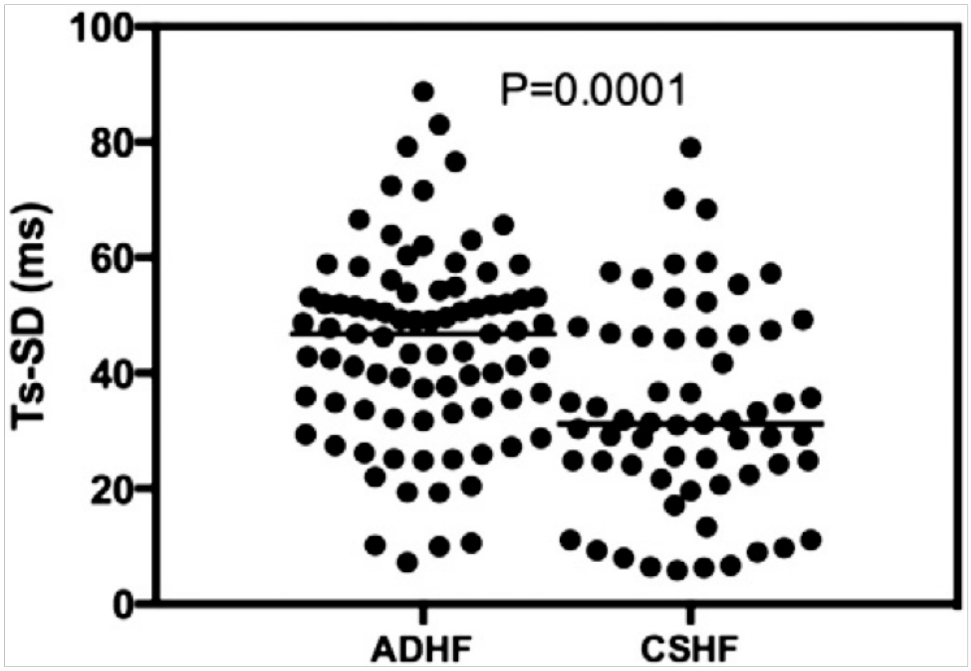
12.4.3 Limitations

A limitation of this study is that echocardiography was not performed in the emergency department at admission. When patients with ADHF arrive at the hospital, they usually have already received treatment including loop diuretics, which may have affected cardiac loading and the degree of LVSD. Another limitation is that we did not assess whether the increased severity in LV systolic dyssynchrony during ADHF is predictive of clinical outcome. However, increase in the severity of LV systolic dyssynchrony in acute decompensated heart failure as compared to chronic patients is a new and important finding and should trigger future studies to define whether systolic HF patients with LV systolic dyssynchrony at rest or during stress may be more prone to acute heart failure exacerbation.

12.4.4 Conclusions

In patients presenting with ADHF due to LV systolic dysfunction, we demonstrated in this study a high prevalence of LV systolic dyssynchrony during the acute phase of hospitalization. With TDI our study has demonstrated that LV systolic dyssynchrony in an acute setting was associated with a high E/Em indicative of significantly elevated LV filling pressure. We conclude that LV systolic dyssynchrony may be an important precipitating factor of acute decompensated heart failure.

Figure 12-1. Scatter plots of Ts-SD in ADHF and CSHF.



Scatter plots of Ts-SD (mean values indicated by horizontal lines) showing significantly higher degree of left ventricular systolic dyssynchrony in ADHF patients than CSHF patients.

Chapter 13 Study 5: Effect of Exercise on Hemodynamically Optimal Atroventricular Delay in Heart Failure Patients Receiving Cardiac Resynchronization Therapy

13.1 Introduction

In previous chapters, we established the existence of LV dyssynchrony in patients with cardiac diseases with or without heart failure, and the existence and clinical significance of dynamic LV dyssynchrony in patients with HFPEF. In this chapter, we evaluate the potential therapeutic implications of dynamic atrio-ventricular (AV) dyssynchrony in patients with systolic heart failure. Despite the successful introduction of cardiac resynchronisation therapy (CRT) for treatment of patients with heart failure with prolonged QRS duration, post-implant optimisation of the device remains a clinical challenge. In particular, the optimisation of AV delay is an integral part of follow-up care to maintain the highest percentage of biventricular pacing, maximise LV diastolic filling time and abolish presystolic mitral regurgitation, but it must be long enough to avoid truncation of atrial filling (Freedman et al. 1986, Buckingham et al. 1992, Leonelli et al. 1997). Large-scale randomised clinical trials establishing the overall efficacy of CRT have differed widely in their approaches to AV optimisation, ranging from the use of out-of-the-box settings for AV delay (Cazeau et al. 2001), to AV optimisation guided by Doppler echocardiography (Auricchio et al. 1999, Abraham et al. 2002, Cleland et al. 2005), to the use of either algorithms based on intrinsic AV intervals and QRS durations or device-based measurement of intracardiac conduction timings (Bristow et al. 2004). However, it remains controversial as to which method is superior. Previous studies suggested the potential clinical and cardiac functional benefits of AV optimisation on CRT recipients (Khairy et al. 2001, Kedia et al. 2006, Kerlan et al. 2006), while a more recent randomised trial reported that its routine use might not be warranted (Ellenbogen et al. 2010). On the other hand, in real-life experience, a

CRT registry has demonstrated that the suboptimal programming of AV delay is the commonest reason for the lack of favourable CRT response (Mullens et al. 2009).

In the current practice, AV optimisation was performed with the patients typically in supine resting condition. However, with the improvement of LV function and gain in exercise capacity, it becomes increasingly important to consider optimisation of AV delay during exercise when tachycardia develops and diastolic filling intervals are considerably shortened. In normal hearts, AV intervals shorten instantly with increased heart rate, a physiological adaptation with recognised haemodynamic advantage during exercise. In patients with heart failure, it is recently recognised that cardiac dyssynchrony alters dynamically with stress (Lafitte et al. 2006, Lee et al. 2010). Little is known, however, about the haemodynamic effect of AV delay during exercise in CRT patients. We therefore hypothesised that AV optimisation at rest may not be adequate to maximise the hemodynamic benefit of CRT during exercise when cardiac demand is increased. The primary objective of the current study was to examine the impact of heart rate increase during different levels of exercise on the optimal AV delay when assessed by Doppler echocardiography, as recommended by the American Society of Echocardiography (Gorcsan et al. 2008). Our secondary objective was to evaluate the magnitude of change in optimal AV delay during exercise in CRT patients, when compared to the physiological change of AV delay (PR intervals) in healthy controls.

13.2 Methods

13.2.1 Study population

A power analysis was conducted to determine the number of participants needed in this study. A linear regression with repeated measures examined the null hypothesis that there were no differences in the optimal AV delay at different levels of exercise in CRT patients and healthy subjects. A small to medium effect size f=0.25 was assumed. The alpha value was set at 0.05. To achieve power of 0.8, a minimal sample size of 86 was required to detect a significant model.

Patients with heart failure previously implanted with a CRT device for more than 6 months were recruited. Inclusion criteria were as follows: the patients who are able to complete a supine bicycle exercise stress protocol (the selected population may, therefore, be better responders to CRT because of this criterion), being in sinus rhythm and having had intact AV conduction. In order to ensure physiological sinus rate response to exercise, we specifically excluded patients if previous device interrogations indicated that they required atrial rate support at rest. Other exclusion criteria were chronotropic incompetence, atrial fibrillation and prior valvular surgery. The control group was composed of age- and gender-matched healthy subjects who underwent treadmill exercise with no clinical evidence of cardiovascular disease and with normal ECG and negative stress tests. All ECGs of healthy subjects were analysed to measure the heart rates and the corresponding PR intervals during each stage of exercise.

13.2.2 Echocardiography and AV optimisation

Experiments were conducted in dedicated exercise echocardiographic imaging laboratories at three participating university hospitals. A cardiologist, a sonographer, a research assistant and a device field engineer were present at all times during the study. Prior to acquiring images, the programmer head was secured over the CRT device so that marker channel and ECG signals could be continuously viewed and recorded throughout the study. The VV interval was set at 0 ms for all subjects. A 12-lead ECG was connected to the patient, and with the patient supine and at rest, a full baseline echocardiographic examination was performed (Vivid 7; VingMed Ultrasound, General Electric, Milwaukee, Wisconsin, USA).

Pulsed-wave Doppler images of transmitral flow velocity were recorded by placing the sample volume at the tips of the mitral valve leaflets and using a sweep speed of 100 mm/s. If required, the sample volume was moved closer to the mitral valve annulus to visualise the A-wave termination more clearly. Pulsed-wave Doppler sampling of LV outflow tract (LVOT) was recorded by placing the sample volume 1 cm below the aortic valve from the apical five-chamber view, and the LVOT velocity–time integral (VTI) was measured at a sweep speed of

100 mm/s. The LV end-diastolic and end-systolic volumes and the LV ejection fraction were measured using the modified biplane Simpson's method (Lang et al. 2005). Baseline echocardiography was performed with the patient supine and at rest during biventricular pacing triggered to intrinsic sinus activity. A resting AV optimisation procedure was performed by programming the device into an atrial tracking mode (DDD). The sensed AV interval was programmed at rest, starting with an interval of 30 ms, which was then increased iteratively at 20–30-ms intervals until loss of ventricular capture. The optimal AV delay was defined as the delay that produced maximum LVOT-VTI associated with maximal E- and A-wave separation and without truncation of the A wave. A representative case is illustrated in figure 13.1. We paid extra attention to avoid the truncation of the A wave during AV optimisation. Moreover, if the AV delay is optimal according to LVOT-VTI, there should be no truncation of the A wave.

13.2.3 Exercise protocol

The exercise portion of the protocol began after AV optimisation was completed at baseline. The patient's feet were secured to the pedals of the recumbent bicycle, and the patient was instructed to slowly begin pedalling. In order to achieve a target sinus rate of 20 beats above the patient's baseline rate, we instructed patients to increase the speed of their pedalling and/or we gradually increased the levels of bicycle resistance based on the cardiologist's estimate of the patient's target workload. The patient's atrial rate was maintained to within 10 bpm of his or her target rate by continually adjusting the resistance of the bicycle and coaching the patient to alter the pedalling speed as necessary. After the patient achieved the first target rate (stage I), AV delays were reprogrammed at the elevated rate by the same iterative method as performed at baseline. After completion of the first exercise stage, patients began the second stage of the exercise protocol with a target sinus rate of 40 bpm above his or her baseline rate (stage II). This second stage was performed immediately after the first stage by gradually increasing the resistance of the bicycle. The patient's heart rate was again maintained to within 10 bpm of his or her targeted rate during the imaging procedure by adjusting the resistance of the bicycle as

required, and the Doppler images were acquired as previously described. Doppler images from three consecutive intrinsic cardiac cycles were recorded and averaged. All echocardiographic data were analysed by two experienced sonographers, with disagreements settled by consensus.

13.2.4 Statistical methods

Descriptive statistics for baseline demographics are presented as means±SD for continuous variables and as percentages for discrete variables, unless otherwise specified. Linear regression for repeated measures was employed for intraindividual comparison of the optimal AV delays and other haemodynamic variables at the three testing periods. Correlation between the optimal AV delays and heart rates was tested by linear regression analyses. The regression equation derived from the patient population was compared to that derived from the PR intervals across all heart rates of healthy controls during treadmill test by using the analysis of covariance method. All statistical analyses were conducted using statistical software (SAS Institute Inc.). A p value <0.05 was considered statistically significant. The study has been approved by the local ethics committee, and informed consents were signed by all subjects.

13.3 Results

A total of 41 patients who previously received a CRT pacemaker (Medtronic Models 8040 and 8042; Medtronic Inc., Minneapolis, Minnesota, USA) or defibrillator (Models 7289 and 7303) and 56 healthy subjects were enrolled. These patients had received CRT for a mean duration of 2±2 years. Five patients could not achieve the target heart rate of the stage I exercise, and nine could not achieve that of the stage II exercise due to reported symptoms of fatigue and inability to increase atrial rates. Baseline demographics of the patient population (collected on the day the patients participated in the study, before exercise) are provided in table 13.1.

Table 13-1. Baseline characteristics of patients implanted with cardiac resynchronization therapy before exercise

Parameter	Baseline value (n=41)
Age, years	57±19
Men, n (%)	24 (59)
Time from implant, median days (range)	528 (124–1218)
Systolic blood pressure, mm Hg	128±22
Diastolic blood pressure, mm Hg	72±10
Resting heart rate, bpm	70±10
Ischemic origin, n (%)	11 (27)
Non-ischemic origin, n (%)	30 (73)
NYHA class III, n (%)	11 (26)
LVEDV, ml	168±90
LVESV, ml	99±62
LVEF, %	43±13
β Blockers, n (%)	35 (86)
Diuretics, n (%)	41 (100)
ACE inhibitors, n (%)	38 (92)

ACE, angiotensin converting enzyme; EDV, end-diastolic volume; EF, ejection fraction; ESV, end-systolic volume; LV, left ventricular; NYHA, New York Heart Association.

The AV delay was measured from the device from sensed AV to sensed right ventricle (RV). At rest, the 'non-optimised AV delay' was the AV delay setting already programmed when the patients came to the laboratory. During exercise, the non-optimised AV delay was the rate-dependent AV conduction according to the intrinsic algorithm programmed in the device. Our results showed that the device-programmed AV delay was generally not short enough for optimisation of cardiac output during exercise, and the associated Doppler measures are shown in table 13.2. At baseline, the optimal AV delay in CRT patients was 123±26 ms. The optimal AV delay became progressively shortened with each increasing exercise stage ($p<0.05$). As a result, the optimised AV delay at each stage of exercise was significantly shorter than the non-optimised counterpart ($p<0.01$) (Table 13.2). Importantly, the optimal AV delay was associated with significantly higher LVOT-VTI and cardiac output at each stage of exercise ($p<0.01$) when compared with non-optimised AV delay setting. By linear regression analysis, there is a close negative correlation between optimal AV delay and heart rate ($r^2=0.639$), and this is best described by the linear equation:

Optimal AV delay (ms) = 241 - 1.61 × Heart rate (bpm)

Table 13-2. Hemodynamic effects of exercise on CRT recipients as a function of echo-derived optimal AV delay versus non-optimized AV delay at the three testing periods.

	Rest		Stage I exercise		Stage II exercise	
	Non-optimised AV delay	Optimal AV delay	Non-optimised AV delay	Optimal AV delay	Non-optimised AV delay	Optimal AV delay
Heart rate, bpm	70±10		88±10*		106±15†	
Programmed AV delay, ms	125±40	123±26	115±30	102±24‡ *	106±26*	70±22‡ †
LVOT-VTI, cm	17±4	21±4.0‡	18±5	21±5.0‡	16±4.0	19±4.0‡
Cardiac output, l/min	3.9±0.8	4.8±0.9‡	5.2±1.2*	6.2±1.2‡ *	5.7±1.5	6.7±1.2‡ *

*p<0.05 versus baseline.
†p<0.05 versus stage I and baseline.
‡p<0.01 versus non-optimised AV delay.
AV, atrioventricular; CRT, cardiac resynchronization therapy; LVOT, left ventricular outflow tract; VTI, velocity time integral.

A total of 185 ECGs recorded from 56 healthy controls who underwent the treadmill exercise test were analysed. The PR interval decreased significantly as heart rate increased in healthy subjects (r^2=0.646). An inverse linear relationship between PR intervals and heart rates was found in healthy subjects:

PR interval (ms) = 231 - 0.84 × Heart rate (bpm)

The slopes of the two data sets were significantly different (p<0.001) (figure 13.2).

13.4 Discussion and conclusions

13.4.1 Dynamic AV delay in healthy individuals vs CRT recipients

In the present study, we demonstrated that hemodynamically optimal AV delay in CRT patients progressively shortened with increasing heart rate during exercise. A significant linear inverse relationship exists between optimal AV delays and heart rates in CRT patients. Intriguingly, our results suggested that the magnitude of change in the AV delays with increasing heart rates in CRT patients appeared to be significantly greater than the physiological exercise-induced change of PR intervals observed in healthy subjects.

The contribution of AV synchrony to maintaining physiological cardiac performance is well established (Daubert et al. 1986, Barbieri et al. 1990). Conduction time through the AV

node normally decreases due to sympathetic activity with physiological increase in heart rate, resulting in shorter AV intervals at high heart rate. Any variation in heart rate has been demonstrated to result in an immediate, precise and inversely proportional variation in the AV interval in normal hearts (Barbieri et al. 1990). In patients with heart failure, modern CRT devices allow rate-adaptive AV delay shortening during exercise. However, current rate-adaptive algorithms are based on data derived from patients who had preserved LV systolic function (Sheppard et al. 1993, Melzer et al. 2007). It is controversial whether AV delay should be shortened, kept constant or prolonged as heart rate increases, and little is known about the magnitude of AV delay shortening with increased heart rate in patients with heart failure.

A majority of previous studies have indicated the need to shorten delays with increased rates (Mehta et al. 1989, Sheppard et al. 1993, Bordachar et al. 2006, Stockburger et al. 2006), while another recent study suggested that optimal AV delays lengthened with increased heart rates (Scharf et al. 2005). In a study performed by Melzer et al, (Melzer et al. 2007) submaximal exercise conditions revealed a significant shortening of optimal AV delay in CRT patients during DDD pacing, but not during VDD pacing. Valzania et al (Valzania et al. 2008) reported that optimal AV delay did not change in CRT patients during exercise. However, these studies were limited by a relatively small sample size and the lower heart rate achieved (about 20 bpm above baseline) during exercise. Thus, significant shortening of optimal AV delay at higher heart rate could not be excluded. The present study represents the first attempt to investigate the magnitude of change in optimal AV delay in response to exercise-induced increased heart rates with comparison to a group of age- and gender-matched healthy controls. With a larger sample size and a more comprehensive exercise protocol, our study suggested that optimal AV delays shorten at higher heart rate during exercise in patients with heart failure who received CRT.

We believe that by studying a normal control group, we could have a better reference with which the direction and magnitude of exercise-induced changes in optimal AV delay in CRT patients can be compared. In this study, we showed that the direction of change (shortening of

AV delay) is the same in both healthy and CRT patients, but the magnitude of shortening of AV delay required to produce the best hemodynamic outcome appeared to be greater than that observed in healthy controls from which we could generate a hypothesis for the development of better AV optimisation algorithm.

13.4.2 Potential mechanisms of dynamic AV delay

Although the exact underlying mechanisms are unclear, possible explanations can be speculated. First, there is a systematic timing difference between the sensed AV interval programmed on CRT devices (which begins with atrial depolarisation) and the PR interval measured on surface ECG (which begins with the onset of P wave). Beyond that, pacemaker programming bypasses further atrial conduction delays. Such discrepancy is a function of intra-atrial and interatrial conduction time, which may be prolonged in patients with heart diseases (Levin et al. 2011). On the other hand, there may be fundamental differences in the heart rate response of optimal AV delay between patients with heart failure and healthy individuals, which was suggested by the diverging, rather than parallel, discrepancy between the two regression lines observed in CRT patients and healthy subjects, respectively. It has been previously shown that, when compared to healthy individuals, patients with dilated cardiomyopathy have an abnormal shortening of LV diastole at rest that is accentuated during exercise (Plehn et al. 2007, Plehn et al. 2008). Lastly, in subjects with heart failure, LV diastolic dysfunction is invariably present, which will impair active and passive components of early diastolic filling and possibly atrial contraction. This can only be compensated by maximising diastolic filling time, which is being shortened more substantially than systolic time during tachycardiac condition. Thus, a ‘more than physiological’ shortening of AV delays during exercise in patients with heart failure who received CRT may have haemodynamic benefits by preserving diastolic time and maintaining cardiac output. Finally, without adaptation during exercise in the failing hearts, the intrinsic AV delay through conduction over the right bundle may shorten, while the paced (left) ventricular AV delay remains unchanged. This may change VV timing considerably and

reintroduce LV dyssynchrony during exercise. Shortening the AV delay may restore synchrony of the left ventricle, hence increasing the LV stroke volume.

13.4.3 Clinical implication of dynamic AV delay

Previous studies mostly focused on the role of AV optimisation performed at rest in patients who received CRT, and programming was performed and mostly started at pre-hospital discharge after device implantation. The recently announced optimal AV delay (SMART-AV) study (Ellenbogen et al. 2010) that compared device-based, echo-based or empirical programming of AV delay did not find significant difference in LV volume and LV ejection fraction. In addition, the FREEDOM - A Frequent Optimization Study Using the QuickOpt Method study (Abraham et al. 2010) that employed device-based optimisation of AV and VV delay (QuickOpt) did not show its superiority to conventional methods of optimisation when clinical composite score was compared. However, the methods of optimization used in these studies measured AV delay at rest. Of note, with improvement of LV function and reverse remodelling, which typically becomes obvious after treatment for 3–6 months, and the progressive increase in exercise capacity, it becomes crucial whether optimal AV delay is programmed during exercise. The augmentation of cardiac output with optimal shortening of AV delay, as observed in our study, may further improve the exercise capacity and functional status of these patients. Furthermore, it is a sensible approach to perform such optimisation at least 3–6 months after CRT when initial improvement of clinical status is achieved.

13.4.4 Limitations

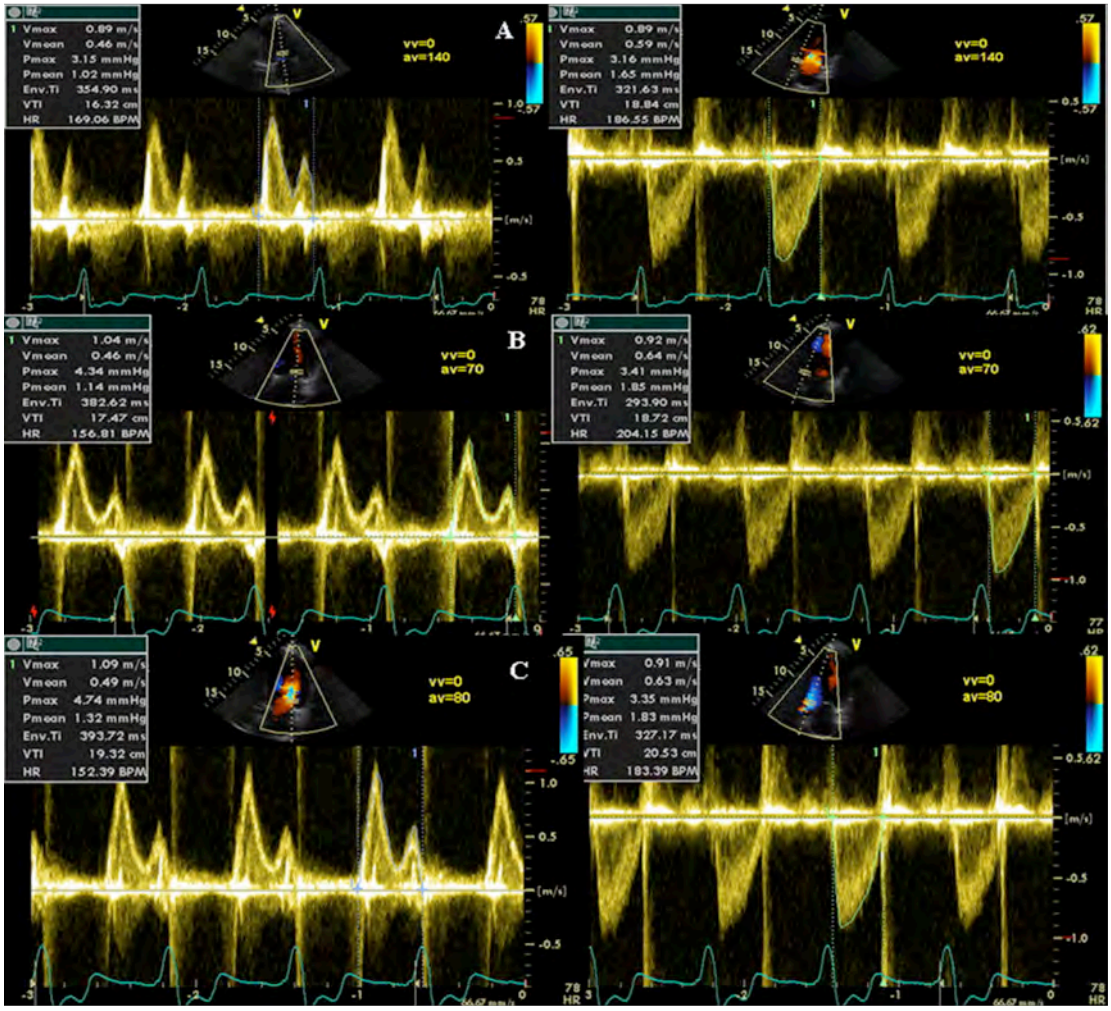
The findings of our study may be limited to patients with preserved intrinsic atrial rhythm without AV conduction disorders. For patients with chronotropic incompetence who are dependent on atrial pacing, additional studies are needed to address dynamic changes in AV delay, although this condition is uncommon in a population with heart failure. However, in real-life experience, most of the patients had preserved sinoatrial node function. Also, the study

design did not intend to determine whether the hemodynamic benefits observed in exercise-induced AV interval shortening would be translated into long-term clinical response to CRT.

13.4.5 Conclusions

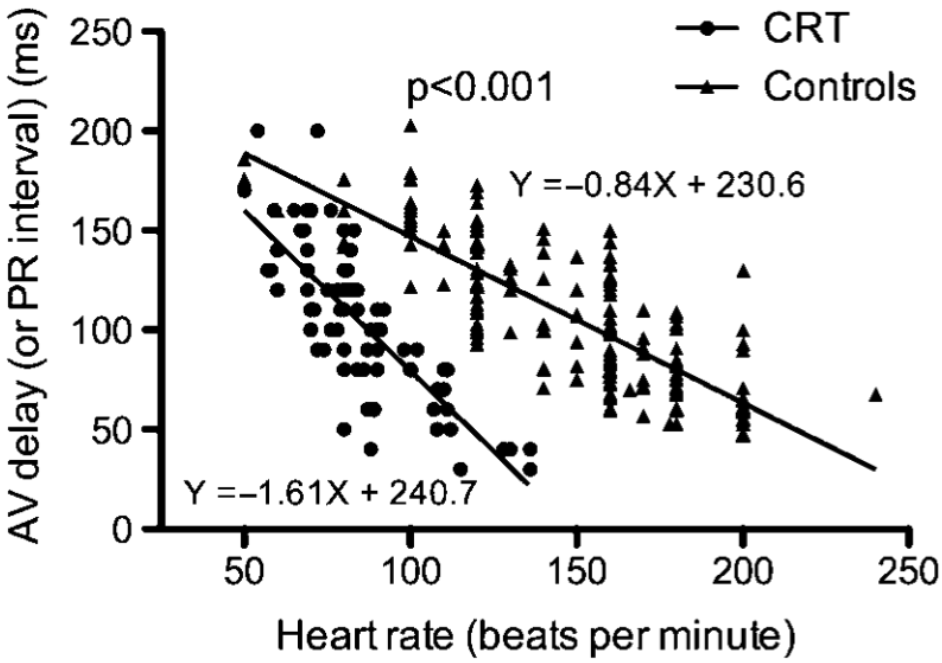
The results of this study suggested that echocardiographic AV optimisation during exercise improves cardiac performance in CRT patients. Therefore, it may be clinically beneficial to program the rate-adaptive shortening of AV intervals during exercise. We suggest physicians to adjust the optimal AV delay for each patient with a CRT device and to check the optimal AV delay regularly with exercise echocardiography, as illustrated in this study. This may be of particular importance in patients who are initial non-responders or who remain symptomatic during exercise after CRT. The appropriate timing for AV delay programming is yet to be defined, but evaluation with exercise echo at 3–6 months post-implant may be a suitable time. Our findings also suggest that current rate-adaptive algorithms, which are derived from patients with normal LV function, may need to be modified if they are to be applied to patients with heart failure receiving CRT, that is, by a steeper slope. Finally, whether AV optimisation during exercise will improve responder rate in CRT recipients warrants further investigation.

Figure 13-1. Examples of the hemodynamic effect of changing the AV delay at rest and during exercise in CRT.



(A) Mitral inflow at a heart rate of 78 bpm with longer atrioventricular (AV) delay (140 ms); note that the A wave ends early (the left ventricular (LV) filling time was 274 ms) in relation to the QRS on the mitral inflow image; velocity time integral (VTI) was measured at 16.32 cm (left); the VTI of aortic outflow was 18.84 cm (right). (B) At the same heart rate with a shorter (70 ms) AV delay, the mitral inflow image shows that the LV filling time was 350 ms, and the VTI was measured at 17.47 cm (left). This aortic VTI was measured to be 18.72 cm. Due to the short AV interval, there is partial truncation of the A wave. (C) At same heart rate with an AV delay of 80 ms, the mitral inflow Doppler shows that the A wave ends in the middle of the QRS and immediately prior to mitral valve closure; the VTI was measured at 19.32 cm (left); the aortic VTI was measured at 20.53 cm. As compared with those at shorter or longer AV delay pattern, the LV filling time was the longest (388 ms) and the VTIs were the largest in this setting; this AV delay time was defined as the optimal value.

Figure 13-2. Scatter plots of optimised AV delay in patients who received CRT and the change in PR interval in healthy controls in relation to heart rate.



The optimised AV delay in CRT patients was significantly shorter than the PR intervals in healthy controls, with the discrepancy accentuated with increasing heart rate. Solid lines represent best-fit lines for linear regression models. The difference in the slopes of the two regression lines was statistically significant ($p<0.001$).

Part V Discussion

Chapter 14 Clinical Implications

14.1 Ubiquitous existence of cardiac dyssynchrony in heart failure

The first evidence for detrimental mechanical effects of dyssynchronous electrical activation was described more than 80 years ago by Carl J. Wiggers (Wiggers 1925). Information on cardiac mechanics has been rapidly increasing owing to the development of non-invasive imaging techniques for the assessment of regional myocardial function. We have since learnt that cardiac dyssynchrony by no means exists only in patients with systolic heart failure and bundle branch block. Yu et al. was among the first groups to report the high prevalence of LV systolic (51%) and diastolic (46%) dyssynchrony in symptomatic chronic systolic heart failure patients with narrow QRS complexes (Yu et al. 2003). Subsequently this finding was replicated by other studies reporting a prevalence of LV mechanical dyssynchrony ranging from ~30% to 50% (Bleeker et al. 2005, Haghjoo et al. 2007, Wang et al. 2007, Zhang et al. 2011). In the studies included in this thesis, we have extended our discovery of the existence of cardiac dyssynchrony from patients with symptomatic chronic systolic heart failure to (i) patients with structural heart disease (CAD, hypertensive LVH) but preserved EF and no heart failure, (ii) patients with acute decompensated systolic heart failure, and (iii) patients with ischemic and hypertensive HFPEF. The prevalence of resting LV systolic and diastolic dyssynchrony, defined using TDI-derived cut-off values, were 38%~43% and 9%~29%, respectively, in patients without heart failure but established structural heart disease (pre-heart failure stage B cardiac disease). On the other hand, the prevalence of resting LV systolic and diastolic dyssynchrony in patients with HFPEF were 36%~47% and 34%~35%, respectively. It is clear from our data that LV mechanical dyssynchrony is a very common phenomenon in all stages and clinical subtypes of heart failure (Figure 14-1). The degree of LV systolic and diastolic mechanical dyssynchrony as measured by the Ts-SD and Te-SD indices appeared to increase continuously across the clinical spectrum of heart failure (Figure 14-2).

As discussed in the section 1.4 of chapter 1, the “biomechanical” model of heart failure progression predicts that mechanical disadvantage induced by cardiac dyssynchrony can initiate and perpetuate maladaptive remodelling of the cardiac structure, leading to dilatation, dysfunction and failure of the ventricles. In patients with systolic heart failure receiving CRT, Zhang et al. demonstrated that while acute reduction in LV volume after CRT is mediated by hemodynamic benefits, regression of LVH and reduction of regional LV wall thickness were demonstrated at 3-months, representing structural reverse remodelling. Such benefit was only observed in volumetric responders but was absent in non-responders (Zhang et al. 2006). There is little reason to believe that structural remodelling in response to dyssynchrony only happens in late stage of heart failure. In the studies included in this thesis, demonstration of the high prevalence of LV mechanical dyssynchrony and its association with LV mass and function in patients with non-failing hypertensive and coronary heart disease suggested that maladaptive remodelling in response to dyssynchronus contraction and relaxation of the LV is present in early stages of heart disease and may contribute to disease progression to clinical heart failure. The results of REVERSE (Daubert et al. 2009) and MADIT-CRT (Moss et al. 2009) show beneficial effects of CRT very similar to those observed for severe HF cohorts, with improvement in functional status, reduces HF hospitalizations, and promotes reverse remodelling, providing strong support to expand the use of CRT to patients with mild HF and dyssynchrony. We have demonstrated in this thesis that the pathogenic role of cardiac dyssynchrony may start even earlier in patients with asymptomatic structural heart diseases and those with HFPEF, providing a strong rationale to find novel therapeutic strategy targeting dyssynchrony in these groups of patients. Given the fact that the majority of the patients with preserved EF do not have strong electrical evidence of conduction delay despite having echocardiographic evidence of significant LV mechanical dyssynchrony, CRT, which stimulates the heart electrically to affect the timing of LV regional contraction, may not reverse mechanical dyssynchrony in these groups of patients. Nevertheless, treatment to resynchronise the

mechanical function of the heart may not necessarily be CRT (Takemoto et al. 2007, Wang et al. 2007). The findings of our works and works done by others suggested that increase in LV afterload, hypertrophy, regional sympathetic denervation, and interstitial fibrosis appeared to be important factors associated with mechanical dyssynchrony (Wang et al. 2007, Leong et al. 2012, Gimelli et al. 2014). Cardiac fibrosis is a hallmark of cardiac diseases (Biernacka et al. 2011). Recent data suggested that there may be a complex interactions among myocardial sympathetic innervation, perfusion, and mechanical dyssynchrony assessed with nuclear cardiac imaging techniques (Gimelli et al. 2014). Myocardial mechanical dyssynchrony is frequently associated with greater alterations in myocardial perfusion, contractile function and adrenergic innervation. The region of the latest mechanical activation showed a greater impairment of sympathetic tone. In patients with dilated cardiomyopathy, the extent of myocardial fibrosis as quantified by late-gadolinium enhanced magnetic resonance imaging is associated with inter- and intra-ventricular dyssynchrony, and contributes to the lack of response to medical therapy in newly diagnosed dilated cardiomyopathy (Leong et al. 2012). Anti-hypertensive drugs, anti-fibrotic agents, and agents that modulate myocardial sympathetic nervous activity may therefore have indirect favourable effect on mechanical dyssynchrony (Takemoto et al. 2007, Ito et al. 2009, Leask 2010, Kwon et al. 2012).

14.2 Exercise and pharmacological stress-induced dynamic dyssynchrony in heart failure

We have demonstrated that dyssynchrony is a dynamic condition that changes in response to stress or exercise. Although resting dyssynchrony and diastolic dysfunction are present in hypertensive LVH patients with or without heart failure, dynamic exaggeration of dyssynchrony during stress and diminished myocardial longitudinal function reserve are characteristics of hypertensive HFPEF. On the other hand, we have shown that exercise may shorten the hemodynamically optimal AV delay for systolic heart failure patients who receive CRT. These findings suggest that clinical evaluation of cardiac dyssynchrony at rest may not be sufficient in terms of risk stratification and optimization of therapy, and assessment of dynamic

dyssynchrony during exercise or pharmacological stress may provide important addition information.

14.3 Cardiac dyssynchrony in acute decompensated systolic heart failure

We have shown that significant LV systolic dyssynchrony was evident during the acute decompensated state of systolic heart failure in up to 75% of cases, much more common than in patients with chronic stable heart failure. While LV dyssynchrony in chronic heart failure is important in clinical progression and structural remodelling in heart failure over periods of months or years, acute LV dyssynchrony may be a dynamic transient phenomenon that precipitates acute deterioration of hemodynamic stability in heart failure. There seems to be no predictable relationship between dyssynchrony at rest and dyssynchrony during exercise or stress. The current practice of assessing dyssynchrony and CRT parameters at rest is therefore problematic and may not effectively prevent ADHF precipitated by acute dyssynchrony. Our studies provide new evidence to support the clinical significance of dyssynchrony evaluation both at rest and during exercise or stress conditions.

Figure 14-1. Prevalence of LV dyssynchrony in various clinical subtypes and stages of heart failure as reported in the current thesis.

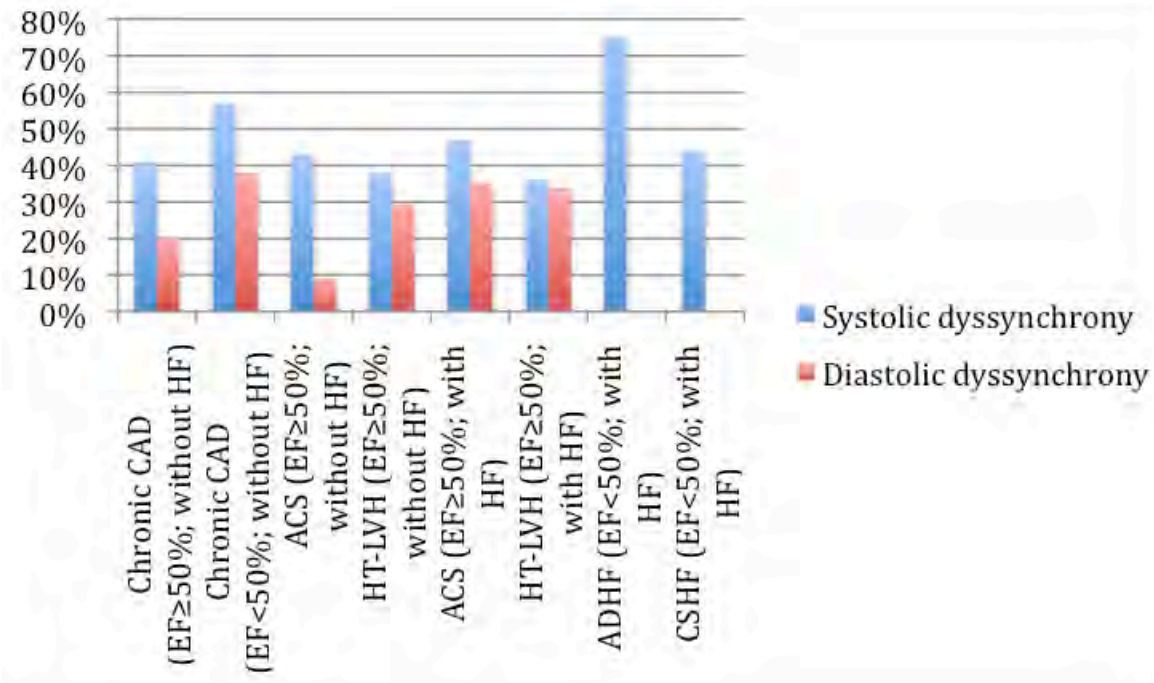
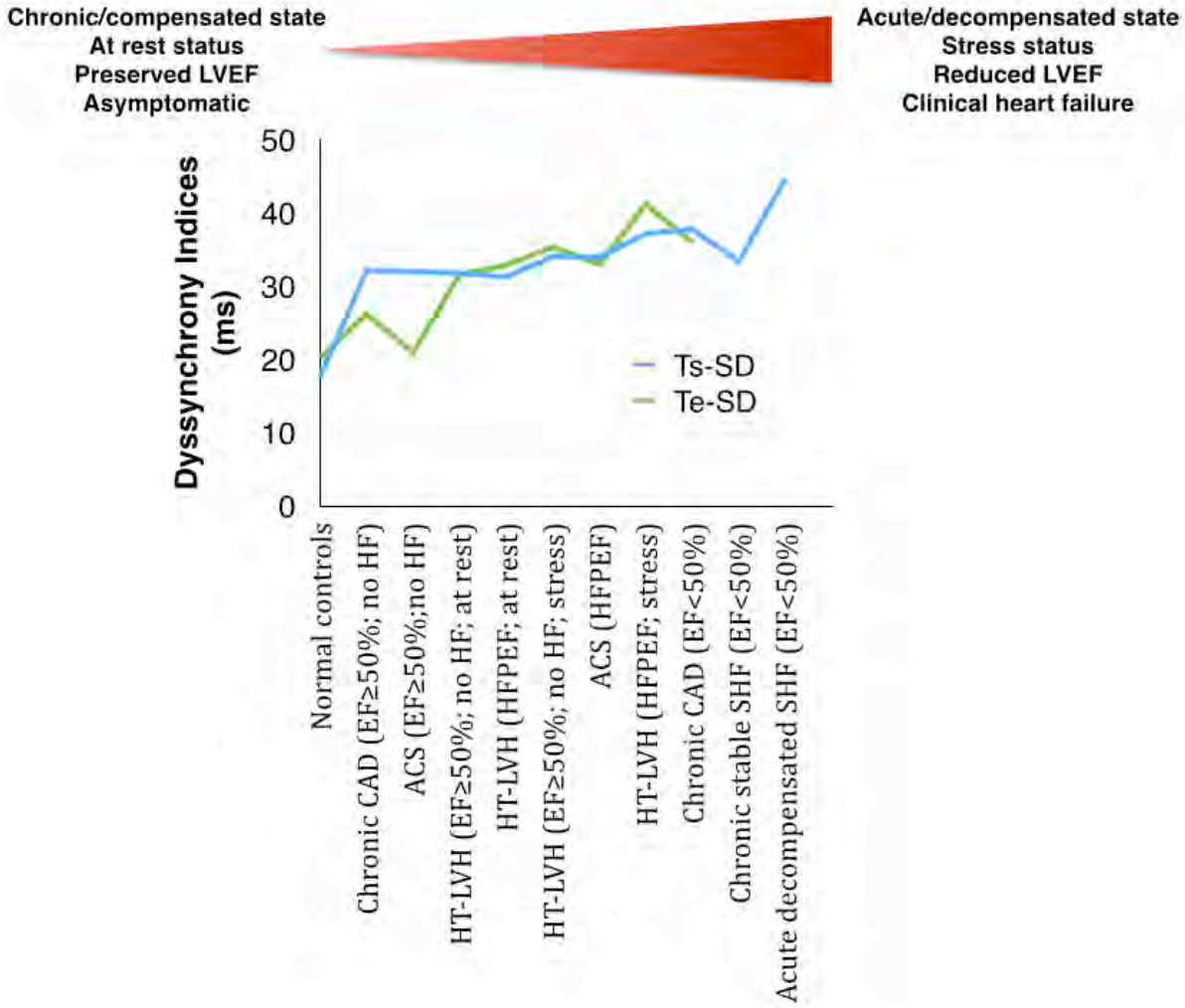


Figure 14-2. Systolic and diastolic mechanical dyssynchrony across the clinical spectrum of heart failure.



Chapter 15 Limitations

In addition to the limitations addressed in each of the clinical studies discussed in this thesis, a common limitation of these studies is that the pathogenic role of chronic, acute and dynamic cardiac dyssynchrony in various forms of heart failure is supported merely by a case-control study design. Therefore, one may argue that any associations, how strong they may be, between cardiac dyssynchrony and clinical occurrence or decompensation of heart failure are not cause and effect relationships. Nevertheless, we believe our studies have generated some intriguing and important hypotheses to be tested by future investigations using a prospective study design.

We used TDI as the main investigational tool to assess dyssynchrony. The well-known limitations of TDI to assess cardiac mechanics are its angle dependency and inability to differentiate deformation from translational motion. TDI is also not useful for examination of cardiac mechanics other than those occurring in longitudinal direction, and therefore circumferential and twist mechanics were not assessed in our studies. Recent advance in cardiac mechanic imaging using speckle tracking algorithm has overcome most of these limitations, allowing assessment of true myocardial deformation in multiple directions independent of the angle of incidence of the ultrasound beams, and may be more useful to evaluate the dyssynchronous contraction and relaxation of the ventricles in heart failure patients (Mor-Avi et al. 2011).

Chapter 16 Future direction and conclusions

Our studies have established the prevalence and potential clinical significance of resting and dynamic dyssynchrony in various forms and stages of heart failure. Future investigations should be conducted to confirm the pathogenic role of cardiac dyssynchrony and its clinical significance as a potential therapeutic target in patients with progressive LV remodelling at an earlier stage, HFPEF and ADHF. Larger observational studies and randomized controlled trials would be needed to confirm the speculations generated from our previous studies.

Novel imaging techniques such as speckle tracking echocardiography should be used in future studies to confirm that cardiac mechanics observed in our studies are true deformation and to evaluate cardiac mechanics other than longitudinal function. Longitudinal velocities, strain and strain rate reflect only longitudinal contraction of the myocardium. LV wall is composed of 3 layers of fibres: endocardial, epidcardial, and mid layers. Endocardial and epicardial fibres have longitudinal direction, whereas mid-layer fibres are circumferential. Circumferential strain can be calculated by speckle tracking imaging from the short axis views at all myocardial levels: base, mid level and apex. Contraction of longitudinally and circumferentially oriented fibres results in systolic myocardial thickening, which can be characterized by radial strain. Torsion is base-to-apex gradient in the rotation angle along the long axis of the LV and is measured in degrees per sm. Torsion has an important role in cardiac mechanics. This complex motion is determined by dominant contraction of epicardial fibres with larger radius of arm of moment. During diastole untwisting occurs. Rotation can be measured with speckle tracking imaging from the short-axis view images. The association of cardiac dyssynchrony with LV twist and untwist, which are important motions of cardiac mechanics, can be examined at rest and during exercise with speckle tracking imaging. Indeed, a recent study was performed to assess torsional dyssynchrony in patients with HFPEF during exercise (Tan et al. 2013). Patients with HFPEF

have proportionally greater temporal dispersion and uncoupling of systolic LV twist and longitudinal motion on exercise, when patients became breathless. Torsional dyssynchrony correlated negatively with changes in stroke volume and with peak oxygen consumption on cardiopulmonary exercise testing, corroborating and extending the work described in this thesis that demonstrated the presence of stress-induced dynamic dyssynchrony and impaired longitudinal functional reserve in HFPEF patients.

The prognostic significance of dynamic and resting mechanical dyssynchrony should be established in patients with HFPEF and even those with pre-failure structural diseases. It is important for clinicians to know whether dyssynchrony at rest or during stress predicts earlier occurrence of heart failure, more frequent heart failure hospitalization, and increased mortality. In a recent prospective study conducted by D'Andrea et al., dynamic dyssynchrony induced on bicycle exercise is associated with increased risk of death, heart transplantation, or LV-assist device implantation in patients with narrow-QRS dilated cardiomyopathy over a median follow-up of 48 months (D'Andrea et al. 2013).

In conclusions, our studies provided important, new data supporting that LV mechanical dyssynchrony in both systole and diastole is common in various clinical forms and stages of heart failure, including chronic systolic heart failure, acute decompensated systolic heart failure, HFPEF, and even non-failing structural heart diseases due to hypertension and CAD. LV mechanical dyssynchrony is dynamic and may alter in occurrence and severity with exercise and pharmacological stress. Acute LV diastolic dyssynchrony may be an important contributory factor of HFPEF complicating ACS, whereas acute LV systolic dyssynchrony may be a trigger of acute decompensation of systolic heart failure. Dynamic exaggeration in LV mechanical dyssynchrony in association with diminished longitudinal myocardial functional reserve appears to be important in the pathogenesis of HFPEF in hypertensive patients. The pathogenic role of cardiac dyssynchrony in heart failure extends far beyond that described in chronic stable heart failure with low EF. The studies included in this thesis have increased our understanding of the

clinical significance of cardiac dyssynchrony and have laid down the framework for further investigations into its role as new prognostic marker and therapeutic target in heart failure.

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