LEFT VENTRICULAR MECHANICS DURING RIGHT VENTRICULAR PACING

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ABSTRACT

Despite the routine use of right ventricle (RV) pacemakers to treat sinus node dysfunction, atrioventricular (AV) block, and other electrical abnormalities in the heart, recent studies have demonstrated that chronically RV-paced patients have an increased the risk of hospitalization, heart failure (HF), and death (1, 2). Dyssynchronous electrical and mechanical activation of the left ventricle (LV) has been demonstrated in animal models of acute RV pacing (3-5). In humans, acute and chronic RV pacing have been demonstrated to impair LV systolic function (6, 6-12) and induce longitudinal or radial mechanical dyssynchrony (8, 13, 14). However, the 3-dimensional LV mechanics that result from acute and chronic RV pacing have not been fully explained. Recent advances in echocardiographic image analysis, including tissue Doppler imaging (TDI) and speckle tracking echocardiography (STE), can quantify LV motion in multiple planes throughout the LV. This dissertation will examine the effects of RV pacing on LV mechanics and synchrony in longitudinal, radial, and rotational planes of motion. We hypothesize that acute RV pacing will result in reduced and dyssynchronous longitudinal, radial and rotational LV function. We further hypothesize that these alterations to normal LV function may lead to HF during chronic RV pacing, and that this type of HF is structurally and functionally different than HF due to other causes. These results may provide insight into the mechanisms responsible for pacing-induced LV dysfunction, and enable physicians to better track cardiac function in paced patients, and modify treatments or design new therapies for patients requiring ventricular pacing.

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CHAPTER 1. INTRODUCTION

Since the development of the first wearable cardiac pacemaker by Earl E. Bakken and Dr. C. Walton Lillehei at the University of Minnesota in 1957, electrical pacemaker devices have become common treatment options for a number of cardiac conditions. The right ventricular (RV) apex is a relatively accessible location to implant a pacemaker lead in cases where ventricular pacing is required. In the United States, approximately 180,000 RV pacemakers are implanted each year (15). Cases of sinus node dysfunction account for 58% of these procedures, while 31% are due to atrioventricular (AV) block (due to ablation procedures, or other causes) (15). RV pacing has been shown to improve symptoms, exercise capacity, quality of life and survival in these patients (16-18). However, recent studies have demonstrated that RV pacing may also impair LV systolic function and increase the risks of hospitalization, heart failure (HF), and death in some patients (1, 2, 6, 7, 10-12). These findings demonstrate the need for a better understanding of the implications of RV pacing on cardiac function.

The mechanisms responsible for RV-pacing induced HF remain unclear. However, since RV pacing induces a slow myocyte-to-myocyte propogation of the electrical activation wavefront throughout both the RV and LV (rather than rapid propagation through the Purkinjie network), surface electrogardiograms exhibit a wide QRS complex and bundle branch block pattern, characteristic of electrical dyssynchrony. Locations nearest to the pacing lead might be mechanically activated significantly earlier than more distant areas of the LV, compromising efficient pumping function of the heart. This pattern of dyssynchronous electrical and mechanical activation of

left ventricle (LV) has been demonstrated in animal models of acute RV pacing (3-5). Over time, this may lead to the reduced LV function and increased incidence of HF that have been reported in chronically RV-paced humans. This dissertation will focus on the role of RV pacing in altering to LV function and mechanical dyssynchrony as assessed by tissue Doppler echocardiography (TDI) and speckle tracking echocardiography (STE). Specifically, the following hypotheses will be addressed:

1) Acute RV pacing, as compared to native AV conduction, will result in greater systolicdysfunction and dyssynchrony throughout the LV in longitudinal, radial, and rotational planes of motion.
2) Chronically RV-paced patients will have impaired longitudinal, radial and rotational LV function compared to non-paced controls of similar age.
3) Chronically RV-paced patients with HF will exhibit different LV mechanics than HF patients with the same ejection fraction (EF) that are not paced.

The second chapter of this dissertation reviews the current literature concerning LV function, methods of assessing that function, and the effects of RV pacing on LV mechanics. The anatomic structure of the LV will be described, with an emphasis on its relationship to electrical and mechanical functions. Echocardiographic methods of assessing mechanical function and dyssynchrony of the LV, and the impact of RV pacing on these assessments, will be discussed.

The acute effects of ventricular pacing on hearts with normal systolic function will be addressed in chapter three. LV systolic motion and synchrony will be described in the longitudinal, radial, circumferential and rotational planes during three different acute ventricular pacing modalities. The mechanics during pacing from the RV apex, the LV free wall, or both sites simultaneously will be compared to the mechanics observed during atrial pacing with native AV conduction. This chapter is currently in review at *The Journal of the American Society of Echocardiography*.

Echocardiographic differences between chronically RV-paced patients and age-matched non-paced control subjects will be explored in the fourth chapter. All paced subjects included in this study will have had normal LV function prior to the initiation of pacing, and will have been paced for > 1 year, with > 90% of their heartbeats RV-paced. This chapter will report the observed differences between these groups in ejection fraction (EF), and various LV longitudinal and radial mechanical dyssynchrony indices derived from TDI and STE techniques. Alterations to septal wall motion due to RV pacing, particularly discordant motion of the distal septum will be emphasized. This paper has been submitted to *The Journal of Cardiac Failure*.

Functional and structural differences between HF patients either with chronic RV pacing, or without previous pacing, will be investigated in chapter five. Chronically paced (>1 year of RV pacing with >90% of heartbeats RV paced) and non-paced groups will be matched for gender, age, and EF. Differences in LV structure,

longitudinal and radial motion, and dyssynchrony will be discussed. However, this chapter will focus primarily on differences in rotational motion and torsion, or twisting, of the LV between the two groups of HF patients. This paper has been submitted to *The American Journal of Cardiology*.

The sixth chapter of this dissertation briefly summarizes the cumulative findings of the three manuscripts presented in the previous chapters. This chapter focuses on the clinical implications of these findings, and suggests potential areas for future research.

CHAPTER 2. REVIEW OF LITERATURE

Cardiac Structure and Function

The pumping action of the heart is normally initiated by the spontaneous depolarization of myocardial cells in the sinoatrial (SA) node. This electrical activity first triggers the contraction of the left and right atria, forcing blood into the ventricles. The atria are electrically isolated from the ventricles, except for conduction through the atrioventricular (AV) node. The AV node delays the propagation of the activation wave front, to allow for complete ventricular filling, before transmitting the impulse to the ventricles via the bundle of His, the left and right bundle branches, and the Purkinje network. (19) The electrical activation is rapidly spread throughout the left ventricle (LV) by this specialized conduction system. Electrical activation is nearly simultaneous within the LV, with the apex activated just a few milliseconds before the base (20), and the endocardium activated just a few milliseconds before the epicardium (20, 21). Repolarization, however, occurs in the reverse fashion, with the base repolarizing first, followed rapidly by the apex (20).

A double helical myocardial fiber orientation is found in the LV, with counter-directional fiber layers meeting at the apex. When viewed from the apex, fibers are arranged in a counter clockwise direction in the epicardium and a clockwise direction in the endocardium (22-24). In addition, the fibers at the base of the heart are oriented in a more transverse, or circumferential manner than the more longitudinal configuration of the apical fibers. The orientation of the myocardial fibers results in a

intricate 3-dimensional motion during contraction and relaxation. This motion can be described as the summation of motion in three planes: 1) longitudinal shortening or lengthening in the long-axis plane extending from apex to base, 2) radial thickening or thinning in the short axis plane, and 3) rotation about the long axis, as viewed from short-axis projections of motion. Similar to electrical activation, longitudinal systolic shortening begins in the apex and rapidly progresses to the base (20). The rapid electrical transmission throughout the ventricle results in synchronous radial motion at any cross-sectional level of the long axis of the LV (13).

Rotational motion is controlled not only by the fiber orientation, but the relative strength of the forces generated by the contracting epicardium and endocardium is also a critical factor. At the apex of the LV, the epicardium produces greater force during contraction than the endocardium because it contains a greater mass, and also has the mechanical advantage of being located farther from the center of rotation (i.e., it has a longer lever arm). This creates a counter clockwise rotation at the apex. Conversely, the endocardium exhibits greater strain than the epicardium at the base of the LV. The endocardial fibers then determine the rotational direction, so rotation of the base occurs in the clockwise direction. The difference in rotation at the base and apex creates a twisting motion, defined as torsion. As epicardial fibers relax, twisted fibers recoil rapidly with continued active contraction of the endocardial layers. This creates suction during the isovolumic relaxation period, and enhances early diastolic filling (25). Thus, rotational motion is an important link between systolic and diastolic function.

The 3-dimensional motion created by the contraction of the helically structured myocardium generates efficient pumping action with minimal fiber shortening. It is estimated that, as a result of these mechanics, the heart can generate an ejection fraction (EF) of 50% or more with a fiber shortening of only 15% (22, 23). Maintaining this efficient pumping mechanism may be critical to ensuring proper cardiac function.

Methods of quantifying LV function

The motion of the heart can be quantified in a number of ways. Invasive methods such as placing sonomicrometer crystals in the myocardium enable accurate tracking of motion during the cardiac cycle. Not only does the invasive nature of this type of test limit its utility, but also the procedure of implanting crystals may alter subsequent cardiac motion. Magnetic resonance imaging (MRI) is a common non-invasive alternative to measure cardiac structure and motion. While spatial resolution is excellent, temporal resolution of the beating heart is more limited. (26) The procedure is relatively costly, restricting clinical and research use. In addition, the electromagnetic field used in this procedure can interfere with the electronics of the pacing device, and generate heat within the leads, potentially damaging the myocardium. (27) Echocardiography is a relatively inexpensive and commonly used imaging technique that can be safely used in patients with cardiac devices. For this

reason, the following discussion will focus on echocardiographic techniques, which can be used to measure many aspects of cardiac function.

Standard 2-Dimensional Echocardiography

Reflections created by the introduction of ultrasonic waves carefully focused at cardiac structures can be measured using piezoelectric crystals. When a series of such reflections are measured, or an array of crystals is used, a reconstruction of the anatomical features of the heart can be generated (28). These images can be created rapidly, so that cardiac motion can be captured and quantified.

Systolic function of the LV is most commonly assessed by the calculation of EF using Simpson's biplane method (28, 29). In this method, the LV is modeled as a series of stacked disks, and the volume of the LV is estimated to be the sum of the volume of all the disks. The dimensions of the disk are assumed to be oblong in shape, with the major and minor axes determined from orthogonal long-axis planes of the LV (the apical 4-chamber and apical 2-chamber views are generally used). EF can be calculated by determining LV volumes at both the end of diastole and the end of systole. The EF is then calculated using Equation 1 below:

$$EF = \frac{EDV - ESV}{EDV} \times 100\%$$

Equation 1: Ejection fraction (EF), as a percentage, can be calculated from end-diastolic volume (EDV) and end-systolic volume (ESV).

Due to the wavelength of the ultrasound beam, reflections off of small particles, such as red blood cells, can be detected. Furthermore, the Doppler frequency shift between the incident beam and the reflection can be used to determine the speed of the red blood cells relative to the transducer (28). The ultrasound beam can be focused to measure blood flow through valves in the heart, for example. Blood flow through the mitral valve is often used to assess diastolic function. During diastole, two peaks in transmitral flow are typically observed. The early peak (E) is due to passive filling caused by the low intraventricular pressures that occur following systole. The later peak (A) is created by atrial contraction forcing blood into the ventricle. The ratio of the peak velocities on the E and A waves (E/A ratio) is one common measurement used to assess LV diastolic function.

Tissue Doppler Imaging

Projections of the three-dimensional motion onto the longitudinal plane of the LV, parallel to the long axis, have been studied extensively using tissue Doppler imaging (TDI) (30, 31). This technology measures the velocity of myocardial motion along the path of incidence of the ultrasound beam. If the reflections from high velocity red blood cells are filtered out, the result is a signal containing the velocities of myocardial tissue in relation to the transducer. Regions of interest are placed on small segments of myocardium, and curves describing the motion of the selected regions throughout the cardiac cycle are generated. The motion of the heart is commonly displayed as either the velocity (tissue velocity imaging; TVI) or displacement (tissue tracking; TT) of the region of interest with respect to the

transducer. In normal hearts, velocity or displacement curves from different regions of interest have the same general shape, so that peaks and troughs occur nearly simultaneously. Because of this, TDI is commonly used to assess dyssynchrony within the LV. Examples of TVI and TT curves for a normal and dyssynchronous heart are shown in Figures 1 and 2.

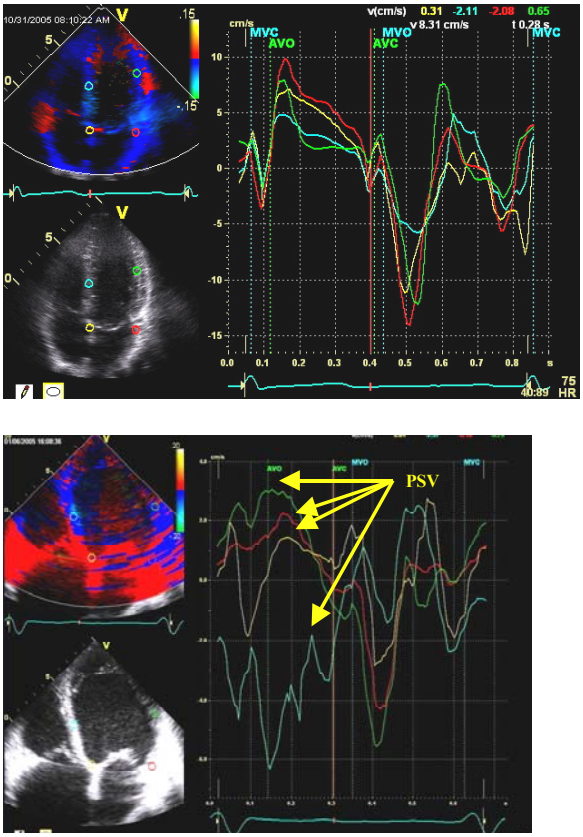
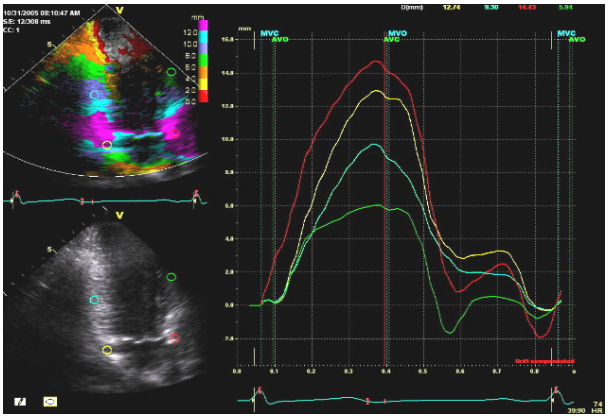


Figure 1: Apical 4-chamber TVI images of a normal heart (left panel), and a dyssynchronous heart (right panel.) In the normal heart, the velocity curves of each wall segment overlap and reach peak values (PSV) at the same time. In the dyssynchronous heart, PSV occurs at different times for each wall segment.



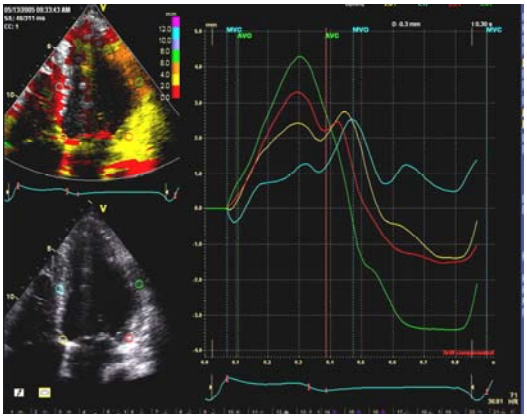


Figure 2: Apical 4-chamber tissue tracking curves of a normal (left panel) and dyssynchronous (right panel) heart. In the normal heart, all wall segments reach peak displacement at the same time, at aortic valve closure. In the dyssynchronous heart, wall segments do not reach peak displacement at the same time, and may reach a peak after aortic valve closure.

The use of TVI for assessing the synchrony of the contracting myocardium is widely supported in literature (32-35). However, it is sometimes difficult to identify which systolic velocity is the peak velocity, due to multiple or jagged peaks in the velocity curves. Displacement curves can be derived from TVI data by integration of the velocity profiles over time to produce TT curves. The displacement curves generated in this manner are often smoother, with less noise, than velocity curves. The identification of times to peak wall displacement may be less variable with this technique (36).

In both TVI and TT modes, active contraction cannot be differentiated from passive motion (such as that due to tethering with the adjacent myocardium or translational movement of the heart). Measurements are also limited to one dimension, along the line of incidence of the ultrasonic beam, which, in some images, may not coincide with the long axis of the heart. In spite of these limitations, TDI techniques are commonly used to assess dyssynchrony, particularly in patients with heart failure (HF), who may benefit from cardiac resynchronization therapy (CRT).

Speckle Tracking Echocardiography

Speckle tracking echocardiography (STE) has recently been applied to analyze heart function (32, 37). STE is based on the identification and tracking of stable speckle patterns in the two-dimensional ultrasound image, which are assumed to correspond to fixed points within the myocardial tissue. The relative motion of these speckles represents the strain of the myocardium, and is relatively independent of ultrasound angle of incidence. To perform the analysis, the endocardial border is manually traced at a single time point during the cardiac cycle, and the thickness of the region of interest is set to encompass the entire myocardium. Speckles within the region of interest are then tracked throughout the cardiac cycle. The region of interest is divided into segments, and the average motion of the speckles within each segment is displayed. Motion is most commonly displayed as strain, but strain rate, displacement, velocity and rotation can also be derived from STE data. Examples of normal and dyssynchronous radial strain patterns are presented in Figure 3.

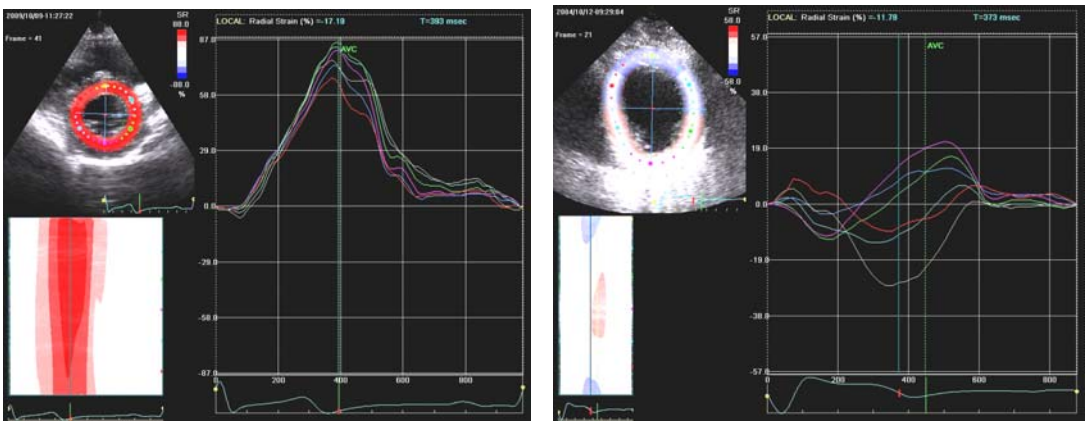


Figure 3: STE images of radial strain in a normal (left panel) and dyssynchronous (right panel) heart. In the normal heart, strain curves overlap, while in the dyssyncronous heart strain patterns are very different for different wall segments.

STE can be applied to both long axis and short axis images of the heart. Long axis motion analysis with STE has not been widely used, since TDI analysis of longitudinal function has a longer history of use, and may be more reliable (38). But STE has been frequently used to assess radial function using short axis images of the LV. The magnitude of radial systolic function can be expressed as the average strain of all wall segments in an image, and dyssynchrony in the radial plane can be expressed by describing the heterogeneity of the curves from multiple segments. Using the same short axis images, rotational motion around a central point in the LV can be measured with STE. Both radial and rotational motion measurements, derived from STE, have recently been used in a variety of settings to assess cardiac function (13, 32, 39-43).

Normal LV Mechanics

As the helically arranged myocardial fibers contract, the walls of the LV shorten longitudinally, thicken radially, and rotate about the long axis. Although this coordinated motion is complicated, it can be simplified using 2-dimensional echocardiographic projections. The magnitude of motion and timing between different wall segments can be measured with TDI and STE so that longitudinal, radial and rotational motion can be assessed.

Longitudinal Motion

Motion of the LV parallel to the long axis of the LV is referred to as longitudinal motion. When the ultrasound transducer is placed at the LV apex, the longitudinal motion of the LV can be approximated as the motion either towards or away from the transducer. For this reason, TDI is well-suited, and commonly used, to measure longitudinal motion. A 12 segment model of the LV is used, in which regions of interest are placed in the basal and mid-ventricle areas of the lateral, anterior, anteroseptal, septal, inferior and posterior walls. Global LV systolic function in the longitudinal plane can be assessed using TT. The average displacement of all 12 segments (global systolic contraction score; GSCS) that occurs between the closing of the mitral valve (the end of the previous beat) and the closing of the aortic valve (the end of systole) can be used to assess the magnitude of useful systolic longitudinal shortening (44). A normal adult LV will shorten by 8-10 mm during systole, while the LV of CHF patients may shorten 4-5 mm or less (45). Intra-

observer and inter-observer reproducibility of this measurement has been demonstrated to have a coefficients of variation of 5.4% and 7.2% respectively (46).

Longitudinal dyssynchony is typically measured with TDI, using the same 12-segment model. In either TVI or TT mode, the curves describing the motion of the regions of interest move in unison in the normal heart. Several methods of quantifying deviations from synchronous movement have been proposed. The most common method was proposed by Yu, et al. and involves calculating the standard deviation of the times to peak systolic velocity among the 12 regions of interest (SD-TVI) (35, 47). A cut-off of 32 ms has been proposed to indicate clinically significant dyssynchrony (35). The reliability and reproducibility of this method have recently been questioned, however. In a recent large study of CRT, SD-TVI had intra-observer coefficient of variation of 11.4%, but inter-observer coefficient of variation of 33.7% (48).

Dyssynchrony can be also be measured with TT in a method analogous to the Yu method (SD-TT), which may result in a more reproducible measurement (45, 49). SD-TT may range from less than 50 ms in a normal heart to over 80 ms for a CHF patient's heart (45). Tissue displacement curves tend to be smoother than velocity curves, with fewer jagged peaks, and less difficulty in differentiating isovolumic peaks from systolic peaks. Coefficients of variation for intra-observer and inter-observer reproducibility of this measurement have been reported to be 12.1% and 14.3% (49).

Radial Motion

Not only does the LV shorten and lengthen longitudinally, but it also moves in a perpendicular direction; either towards or away from an imaginary line representing the long axis. Most of this radial motion is not parallel to the angle of incidence of the ultrasound beam, so cannot be accurately assessed with TDI. Instead, STE can be used to measure the relative position of speckles within the myocardium during the cardiac cycle. When nearby speckles move closer to one another, the wall thickness is being reduced, and negative radial strain is measured. Positive radial strain corresponds to speckles moving farther apart as the myocardial wall thickens.

Global LV function has been assessed using STE by computing the mean radial strain in six myocardial segments comprising the short axis image of the LV at the papillary muscle level (45, 49). Mean radial strain is approximately 50% in normal, healthy subjects and 15% in CHF patients (49, 50). Coefficients of variation for this measurement have been reported to be 7.6% for intra-observer reproducibility and 13.5% for inter-observer reproducibility (50).

The standard deviation of the time to peak radial strain among the six myocardial segments (SD-RS) can also be used as a measure of LV radial dyssynchrony (32, 45, 49, 51). In healthy hearts, SD-RS is typically under 20 ms, while it can be over 80 ms in CHF patients (49, 51). Intra-observer and inter-observer reproducibility has

been reported to have coefficients of variation of 13.9% and 17.6%, respectively (49, 51).

Rotational Motion

During contraction, the LV also rotates about its long axis as the myocardial fibers longitudinally shorten and radially thicken. The helical structure of the fibers, and the twisting motion generated by the contraction of these fibers was described as early as the 1600's by Leonardo DaVinci (52). The more recent work of Torrent-Guasp and others has lead to renewed appreciation for the relationship between cardiac structure and function, and the importance of LV rotational motion on systolic and diastolic performance (23).

Tagged magnetic resonance imaging (MRI) is considered the gold standard for rotational motion measurement. However, this technique is costly, and is potentially dangerous in patients with implanted devices, limiting its clinical application. Alternatively, STE can be used to assess both regional and global rotation in the LV. STE methods have been validated against tagged MRI measurements with good agreement ($r = 0.85$ to 0.93) (37, 53).

The intra-observer reproducibility of STE rotation and torsion measurements was recently assessed in canines (54). These investigators found all measurements to be repeatable and reproducible, with coefficients of variability of <20% for within-day and between-day measurements. For peak systolic torsion, the coefficients of

variability were 16.4% for within-day measurements, and 6.8% for between-day measurements. These values are similar to those reported for TDI measures (48). Peak systolic torsion, dyssynchronous rotation of the apex and base, and the magnitude and time of peak untwisting velocity have been demonstrated to be useful measures of LV performance (39, 55-57).

When viewed from the apex in the short axis plane, the base of the normal heart rotates primarily counter-clockwise during systole, while the apex rotates primarily in a clockwise direction. Peak rotation in both planes occurs at, or just before aortic valve closure. Peak rotation at the base has been reported to range from -2.0º to -4.6º. Peak rotation at the apex may range from 5.7º to 11.2º. Maximum systolic torsion in normal hearts has then been found to range from 6.1º to 14.5º (37, 42, 53, 58-61).

An important consequence of systolic torsion may the subsequent recoil of the LV during early diastole (62, 63). Notomi et al. demonstrated in canines that untwisting coincided with relaxation of the LV, and preceded suction-aided filling (62). The magnitude of untwisting rate also correlated with systolic torsion, relaxation time constant, and intraventricular pressure gradient. The maximal early diastolic torsion rate has been reported to be 57º/s to 69º/s (42, 53, 58, 60, 61). A reduced and delayed peak untwisting rate was found to occur with increasing age (56) and in patients with dilated cardiomyopathy (64). However, in patients with isolated diastolic dysfunction, peak untwisting increased in mild cases, but was depressed in severe cases (65). Diastolic dysfunction in these patients did not effect the time at which

peak untwist rate occurs within the cardiac cycle. In patients with chronic mitral regurgitation, however, peak untwisting was both reduced in magnitude and delayed (40). Thus the timing and magnitude of peak diastolic untwisting rate may provide useful information about LV diastolic function.

Effects of RV Pacing

Dual chamber pacemakers are routinely used to treat patients with atrioventricular node dysfunction or bundle branch block by electrically stimulating the right ventricle (RV). In the United States, 180,000 patients per year receive RV pacemakers (15). On average, pacing reduces symptoms, and improves quality of life, exercise capacity, and survival (16-18). However, data indicates that chronic RV pacing may be detrimental to cardiac function.

Risks Associated with RV Pacing

Permanent RV pacing has been associated with an increased risk of LV dysfunction, hospitalization, heart failure, and death (1, 6, 7, 10-12). In 2002, the results of the DAVID trial revealed that RV-paced patients who were actively paced in DDDR-70 mode had a 60% greater risk for hospitalization or death than patients who received minimal back-up pacing in VVI-40 mode (1). Approximately 30-50% (6-9) of RV-paced patients exhibit pacing-induced LV dysfunction. Zhang and colleagues reported that, of 79 patients who were paced from the RV more than 90% of the time, 25% developed systolic HF within the 8-year follow-up period (2). A better

understanding of the mechanisms of pacing-induced LV dysfunction, and a method of identifying patients most susceptible to pacing-induced complications, may improve treatment of patients requiring ventricular pacing.

Effects of RV Pacing on Systolic Function

Since RV pacing artificially stimulates the ventricles at a location other than the His-Purkinjie system, the action potential is propagated more slowly through myocytes rather than through the specialized conduction system. Electrical activation then becomes heterogeneous, with early activation near the pacing site, and delayed activation at distant locations. The resultant LV mechanical contraction becomes dyssynchronous. Studies by Prinzen and Wyman in acutely paced dogs, demonstrated that pacing results in heterogeneous electrical activation, strain and perfusion of the LV (3-5). Specifically, pacing results in low systolic strain near the pacing site, and pre-stretch and increased systolic strain in the LV wall farthest from the pacing site. Dyssynchronous mechanical activation, along with reduced systolic function, has also been reported in chronically paced humans, as discussed in more detail later in this chapter.

Effects of RV Pacing on Diastolic Function

While most studies of RV pacing focus on systolic function, a few studies have suggested that diastolic function may also be compromised (14, 66). Diastolic function was more impaired in subjects with RV apical pacing than in subjects with systolic HF, in the study of Zhang, and colleagues (14). In this study, qualitative

assessment of mitral inflow patterns revealed fewer normal inflow patterns and more restrictive patterns in paced subjects, while diastolic dyssynchrony (defined by the authors as the standard deviation among 12 myocardial segments of times to peak negative velocity during early filling) was higher in the paced subjects. Similarly, a study of diastolic function by Kolettis found that acute pacing from the RV apex impaired the maximum rate of LV pressure fall (-dp/dt(max)) compared to atrial pacing with native AV conduction(66). Pacing from the RV outflow track (RVOT), rather than the RV apex, did not result in impaired diastolic function in this study. This evidence indicates that pacing site may impact diastolic function.

Effects of RV Pacing on Longitudinal Function

Studies of the effects of RV pacing on longitudinal mechanics have been limited to measuring mechanical dyssynchrony. Paced subjects have been found to exhibit greater systolic dyssynchrony, as quantified by SD-TVI, while paced from the RV, even when paced subjects had normal EF (2, 67). The degree of longitudinal systolic dyssynchrony was similar to that of a group of HF patients with EF of less than 35% (14). Thus, chronic pacing-induced dyssynchrony may put an unusual and excessive stress on the left ventricle, leading to remodeling and eventual heart failure.

In a recent study of 34 high degree AV block patients, paced for an average of 7 years, longitudinal dyssynchrony was increased as compared to non-paced control subjects. Plasma levels of B-type natriuretic peptide (BNP; a marker of abnormal ventricular wall stretch) were also increased, and EF was reduced (67). Mechanical

dyssynchrony was modestly correlated with BNP, but no correlations between dyssynchrony and EF were presented. In contrast, however, Ng and colleagues recently reported no difference in SD-TVI between non-paced controls and RV-paced subjects, however other measurements of dyssynchrony were not reported (50).

Recently, TT has also been used to investigate the coordinated motion within a particular wall of the LV, rather than the more typical method of assessing motion between several different walls. (68) A pattern of paradoxical motion within a wall has been termed intramural dyssynchrony. Acute RV pacing has been shown to increase intramural dyssynchrony in normal hearts, without an increase in between-wall dyssynchrony . (68) Thus, intramural dyssynchrony may be an important mechanism in pacing-induced LV dysfunction. However, it remains unclear if mechanical dyssynchrony is the primary cause of LV dysfunction in RV-paced patients, what percentage of RV-paced patients with mechanical dyssynchrony will develop LV dysfunction, and which patients might be at greatest risk for developing pacing-induced LV dysfunction.

Effects of RV Pacing on Radial Function

Radial function and dyssynchrony have also been investigated in RV paced patients. Tops, et al. observed that peak radial strain, and the time to reach peak radial strain in 6 short-axis segments became heterogeneous after long-term RV pacing (13). These investigators found that radial strain was most reduced and peaked earliest in septal

and anteroseptal regions, and increased in magnitude and delayed in lateral and posterior regions. However, mean radial strain and SD-RS were not different between non-paced controls and RV-paced subjects in a study by Ng (50). These two studies suggest that pacing may result in regional dysfunction, but that the net effect on the entire LV may be minimal due to compensatory mechanisms in other regions.

Effects of RV Pacing on Rotational Function

The effects of various pacing modalities on LV torsion have been evaluated in animal models. Sorger et al. compared acute right atrial pacing to right ventricular pacing and biventricular pacing using MRI in 5 canine hearts (69). Peak systolic torsion was 11.1 ± 3.5º during right atrial pacing, 6.1 ± 1.7º during RV pacing and 6.1 ± 0.7º during biventricular pacing. These authors concluded that torsion was highly sensitive to the site of excitation. Torsion has also been assessed qualitatively using sonomicrometric images in porcine hearts (70, 71). Torsional motion was normal in right atrial and high septal RV pacing, however this motion was disrupted by pacing from other RV sites. These studies suggest that torsion is a sensitive indicator of alterations in the normal LV activation sequence due to non-physiologic pacing sites. The effects of permanent RV pacing and pacing site, on torsion and untwisting mechanics have not yet been investigated in humans.

Alternate Site Pacing

In order to induce a more physiological activation sequence and reduce the risk of developing HF, alternate lead positions, such as the RV septum or RVOT, have been proposed. Although the RV apex has been considered the most practical lead position, more recent reports indicate that the ease and success of lead placement was similar between the apex and alternate sites in the RV (72, 73). Alternate-site pacing would be clinically practical if it proves to be effective.

Studies comparing pacing from alternate sites to the RV apex have yielded inconsistent results. Several studies have demonstrated improved hemodynamic and clinical outcomes with alternate site (RV septum or RVOT) pacing (11, 74-76), and several studies have shown no differences (73, 77-79). For example, Tse, et al, found no difference in perfusion or wall motion abnormalities after 6 months of pacing from either the RV apex or alternate sites (76). In the same study, though, alternate site pacing was found to result in significantly fewer wall motion abnormalities than apical pacing after 18 months. This suggests that some LV functional differences associated with various pacing sites may not become apparent acutely, but may develop over time.

However, in another study with a follow-up of 18 months, changes in EF, BNP levels, and exercise capacity were not different between septal and apical pacing (73). Furthermore, Ng et al. found that septal pacing resulted in greater impairment of EF and circumferential strain than apical pacing (50). The relationship between

circumferential strain and rotation suggests that rotation and torsion may also have been different between septal and apical pacing in these subjects.

These inconsistent results may partly be due to differences in follow-up time, pacing site definition and outcome variables assessed. It remains unclear whether alternate site pacing may help to alleviate the risks of LV dysfunction and HF associated with RV pacing.

Summary

The increased risk of LV dysfunction associated with RV pacing has been well established. Similarly, both impaired LV function and mechanical dyssynchrony have been shown to exist in groups of RV paced patients. However, it is not clear if those patients with the greatest degree of mechanical dyssynchrony also have the greatest LV dysfunction. In addition, LV torsion appears to be sensitive measures of global LV systolic and diastolic function. The effects of RV pacing on measures of LV torsion may reveal important mechanisms for pacing-induced LV dysfunction, but these have not been investigated. Thus, this dissertation will focus on the acute and chronic effects of RV pacing on LV function, mechanical dyssynchrony and LV torsion in hearts with normal LV systolic function prior to pacing.

CHAPTER 3. THE EFFECTS OF ACUTE VENTRICULAR PACING MODALITIES ON TORSION AND STRAIN IN NORMAL HEARTS

The effects of acute ventricular pacing modalities on torsion and strain in normal hearts

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Short Title: Torsion and strain in normal and paced hearts

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Synopsis:

Background: The purpose of this study was to use speckle tracking echocardiography (STE) to describe the impact of different pacing configurations on left ventricle (LV) strain and dyssynchrony in healthy subjects.

Methods: Echocardiograms were performed in 10 subjects with normal LV function during acute atrial pacing (RA), right ventricular apical pacing (RVa), LV free wall pacing (LVfw), and pacing from both ventricular sites (BiV). Longitudinal, radial, circumferential and rotational motion at the LV base, mid-wall and apex were measured using STE.

Results: Acute pacing from the LVfw resulted in LV strain patterns most similar to RA pacing. This was particularly evident in the longitudinal plane of motion, but similar trends were seen in the radial and circumferential planes (ANOVA $p>0.05$ for all). Dyssynchrony varied with pacing configuration only in the longitudinal plane and was lowest in LVfw pacing and greatest in RVa pacing ($p>0.05$ for pair wise comparisons). In contrast, apical rotation was reduced in LVfw and BiV pacing ($p>0.05$ for both), but not RVa pacing.

Conclusion: Acute pacing from the LVfw best preserves LV strain and synchrony. However, rotation of the LV apex was more reduced in LVfw and BiV pacing than in RVa pacing.

Background

Although patients with bradycardia due to AV node dysfunction or bundle branch block are routinely treated by pacing the right ventricular apex (RVa), this treatment has been associated with left ventricular (LV) mechanical dyssynchrony, systolic dysfunction, heart failure, and reduced survival.(1, 6, 9, 12) Recent investigations have explored the possible benefits of pacing from alternate sites in the RV,(11) LV, (5, 68, 80) and from both ventricles. (68, 80-82)

Studies that have assessed LV mechanics have largely ignored circumferential and rotational motion of the LV and deformation of the LV apex. As the myocardium of the LV contracts during systole, the helically structured myocardial fibers shorten, resulting in a complicated three-dimensional motion of the LV. Previous studies have suggested that mechanical dysfunction in one plane of motion might be compensated for by enhanced motion in another plane.(83) In addition, motion at the LV apex may be especially susceptible to dysfunction during RVa pacing, since animal studies have demonstrated that motion nearest the pacing site is significantly reduced.(4) Finally, rotational motion and torsion have been proposed as sensitive indicators of LV function that are altered with ventricular pacing.(69) The acute effects of different pacing configurations on these parameters have not been well characterized.

Recent advances in speckle tracking echocardiography (STE) have enabled the quantification of the longitudinal, radial, circumferential and rotational motion of the

LV. In addition, motion at the apex, which is often difficult to assess with other methods, such as tissue Doppler imaging (TDI), can be readily measured. STE measurements have been validated against tagged MRI with good agreement. (37, 53) Thus, the purpose of this study was to use STE to examine the longitudinal, radial, circumferential and rotational motion in healthy, normal subjects paced from the RV apex (RVa), LV free wall (LVfw) and both ventricular sites simultaneously (BiV).

Methods

Study Population

This study included a subset of subjects from a larger study investigating the effects of pacing site on LV mechanics and dyssynchrony.(68)(OPTIMA) Of the 26 subjects in the larger study, complete echocardiographic image sets for measuring myocardial strain at the base, mid-ventricle and apex were collected in 10 subjects. The present study includes all of these subjects with complete image sets. Inclusion criteria for the larger study are reported elsewhere.(68) In brief, patients 18 years of age or older, with normal LV size and function, normal valve function, and normal electrical activity, who were already scheduled for electrophysiology study (usually for paroxysmal atrial fibrillation or other supraventricular arrhythmias) were invited to participate. The study was approved by an Institutional Review Board, and all patients provided written informed consent.

Pacing Protocol

Pacing leads were placed in the right atrial appendage, endocardial RVa and mid LVfw locations. BiV pacing was completed by simultaneously pacing the RVa and LVfw. Pacing configurations were studied in random order, in each patient. The echocardiographer acquiring the images was blinded to the pacing condition. The heart rate during pacing was maintained at 10 bpm greater than the measured intrinsic heart rate with an AV delay of 20 ms. A fixed, short AV delay was chosen to eliminate variations in systolic performance due to fusion of intrinsic and paced waveforms. Echocardiographic and electrophysiological data were recorded after 5 minutes of continuous pacing at each site. No subjects were in atrial fibrillation during the pacing protocol.

Echocardiographic Examination

Echocardiographic examinations were performed by a trained sonographer using a GE Vivid 7 Ultrasound system (GE Healthcare, Milwaukee, Wisconsin). Digital gray-scale two-dimensional cine loops were collected from the LV apical 2-, and 4-chamber views, apical long axis view, and parasternal long and short axis views at the base, mid-ventricle and apex. Average frame rate of the video images used for STE was 64 ± 17 frames per second, which was sufficient for accurate tracking in all images. Pulsed Doppler echocardiography was used to measure blood flow velocities across the aortic, mitral, and pulmonic valves over three consecutive beats. The onset and termination of flow was used to determine the times at which valves opened and closed, using the QRS complex as a reference. Digital images and cine loops,

triggered to QRS complex, were stored and analyzed off-line using GE EchoPac 7.0.0 by a single observer.

LV Function

The ejection fraction (EF) of the LV during atrial pacing was measured from two-dimensional, grey-scale apical 2-, and 4-chamber views by using the biplane Simpson's method. The velocity-time integral (VTI) was calculated from the pulsed Doppler flow image with the sample volume placed in the LV outflow tract (LVOT), and was used as a surrogate for stroke volume during ventricular pacing conditions. The VTI of the flow through the mitral valve was used as a secondary indicator of global LV function. In addition, myocardial performance index (MPI) was calculated from the isovolumic contraction time (IVC), isovolumic relaxation time (IVR), and ejection period (MPI = (IVC+IVR)/ejection period).

Speckle Tracking Echocardiography

Longitudinal strain was measured with STE using the apical 4-chamber and 2-chamber views. The endocardial border was manually traced at one time point (end-systole), and the thickness of the region of interest was adjusted to encompass the myocardium. Software automatically located stable acoustical markers in the LV, and tracked their motion from frame to frame. The myocardium of the LV was automatically divided into 6 wall segments in each view corresponding to basal, mid-ventricle, and apical segments of the septal and lateral walls (4-chamber view) and the inferior and anterior walls (2-chamber view). Regional longitudinal motion at

each level of the LV (base, mid-ventricle and apex) was defined as the average strain of the septal, lateral, inferior and anterior walls at that level. Global longitudinal motion was quantified as the average strain of all 12 segments.

Radial, circumferential and rotational function was assessed with STE using parasternal short axis images of the LV base, mid-ventricle, and apex in a similar fashion to that described for longitudinal assessment. The myocardium was divided into six segments corresponding to anterior, lateral, posterior, inferior, septal, and anteroseptal regions. The mean strain from the six automatically assigned segments at each level was calculated as a measure of regional radial function. The mean strain of all segments from all 3 levels was defined as the global radial strain in the LV. Similarly, regional rotation was defined as the average rotation within each level of the LV. Global torsion was defined as the difference in regional rotation between the apex and base of the LV at each time point in the cardiac cycle.

Intraventricular mechanical dyssynchrony was calculated as the standard deviation (SD) of time from mitral valve closure of the previous beat to peak motion (strain or rotation) in all LV segments. Thus, longitudinal dyssynchrony was the SD of the 12 segments from the apical 4-chamber and 2-chamber views. Radial and circumferential dyssynchrony was the SD of the time to peak strain of 18 segments from parasternal short axis views of the base, mid-LV, and apex. Rotational dyssynchrony was the standard deviation of the time to peak rotation of the same 18 short axis segments.

Data Analysis

Data were interpolated to allow for comparisons of motion at isochronal points during the cardiac cycle. In addition, time points were expressed as percentages of the cardiac cycle for each patient, to allow for comparisons between images and patients with differing heart rates.

Results are presented as mean ± SD. Repeated measures, single factor analysis of variance (ANOVA) was used to compare multiple pacing conditions. Post hoc pair-wise comparisons were performed using the Tukey test for multiple comparisons. Statistical analyses were performed using GraphPad Prism version 4.00 (GraphPad Software, San Diego, CA). A p-value of <0.05 was considered significant.

Results

Mean age of the study subjects was 53 ±9 years, and 2 (20%) were female. Subjects had body mass index of 30.4 ± 4.0 kg/m2, systolic blood pressure of 140 ± 19 mmHg and diastolic blood pressure of 78 ± 11 mmHg. Ejection fraction in the study group was 51 ± 7%, with volumes of 103 ± 20 mL and 51 ±10 mL at end-diastole and end-systole, respectively. Without pacing, the QRS duration was 80 ± 14 ms.

Results of standard 2-dimensional echocardiographic analyses during the 4 pacing configurations are presented in Table 1. All ventricular pacing configurations resulted in reduced LVOT VTI and ejection time as compared to atrial pacing. LVfw pacing resulted in greater LVOT VTI than either RVa or BiV pacing. Mitral VTI was similar between atrial and LVfw pacing, but was reduced in RVa and BiV pacing.

Ejection time was also significantly greater, and MPI was lower (an indication of improved function) during LVfw pacing than during RVa pacing. BiV pacing resulted in an intermediate ejection period and MPI, not significantly different from either of the other single ventricular pacing site.

Regional and global strains and rotations are presented in Table 2. Global longitudinal strain was significantly greater in LVfw pacing than in either other ventricular pacing configuration, and was not different than atrial pacing. The effects of pacing on longitudinal deformation were primarily due to differences in apical and mid-ventricular strain, while pacing did not significantly influence strain at the basal level. Global radial strain was also different among the pacing configurations, with reduced radial function in all ventricular pacing configurations except LVfw pacing. Global circumferential strain was mildly influenced by pacing configuration. While no pair-wise comparisons between configurations revealed significant differences, there was a trend for LVfw pacing to result in the highest global circumferential strain of the ventricular pacing configurations.

In contrast to strain measurements, rotation and torsion measurements were more altered by LVfw and BiV pacing than by RVa pacing. Apical rotation, in particular was only different than atrial pacing in LVfw and BiV pacing. Torsion was only significantly lower than atrial pacing during BiV pacing.

Dyssynchrony values measured in each plane of motion, during each pacing configuration, are presented in Figure 1. Pacing configuration significantly influenced only longitudinal dyssynchrony. Of the ventricular pacing sites, LVfw pacing resulted in significantly lower longitudinal dyssynchrony than ventricular pacing in either of the other configurations. In addition, BiV pacing resulted in less dyssynchrony than RVa pacing. Although not statistically significant, dyssynchrony in the radial and circumferential planes also followed this pattern, with LVfw pacing resulting in the least dyssynchrony and RVa pacing resulting in the greatest.

Discussion

This study was a sub-analysis of a larger study performed by our group, in which TDI was used to assess longitudinal and mid-LV radial function and dyssynchrony in the LV during various pacing configurations.(68) In both studies we found that global LV function, assessed by LVOT TVI, mitral VTI and MPI was most impaired by RVa pacing and best preserved during LVfw pacing. In the previous study, TDI analysis revealed that global longitudinal function, mid-ventricular radial function, and longitudinal dyssynchrony were best preserved during LVfw pacing. In the current study, we have used STE to provide a more thorough evaluation of the pacing-induced mechanics in multiple planes of motion, and at multiple levels within the LV. We found that longitudinal strain, particularly at the apex and mid-ventricle were most impaired during RVa pacing, and most preserved during LVfw pacing, with similar but less dramatic impairments of radial and circumferential strain during each pacing configuration. Rotational motion was also most impaired at the apex of

the LV, but, unlike motion in other planes, rotational motion was most impaired during LVfw and BiV pacing.

Magnetic resonance imaging and STE have been previously used to measure longitudinal strain, radial strain, and rotation in healthy human hearts, with good agreement between methods.(37, 84) Our results during atrial pacing are in agreement with the previous studies using STE regarding the magnitude of peak longitudinal (83, 85-89), radial (86-88, 90), circumferential (83, 89), and rotational (83, 88, 91, 92)motion in normal hearts.

Adverse effects of RV apical pacing have been previously identified, including increased longitudinal and radial dyssynchrony (8, 13, 14), reduced EF (6-9), and increased risk of developing heart failure (1, 6, 7, 10-12). Numerous studies have evaluated the possible benefits of alternate site or multi-site pacing. In animals, LV pacing has been shown to result in greater LV stroke volume, stroke work and maximal rates of pressure rise and fall (4, 93). Similarly, studies including humans with normal systolic function, mildly decreased function, and HF have demonstrated that LV pacing results in preserved LV systolic function and reduced mitral regurgitation compared to RVa pacing (94, 95)((96, 97). Our findings are in agreement with these, and also demonstrate the benefits of LV pacing over RVa pacing in hearts with normal function. Our findings extend this body of work by suggesting that the functional benefits of LV pacing are primarily due to the

preservation of longitudinal strain at the apex and mid-ventricle, while circumferential and radial motion, as well as motion at the base are less affected.

An unexpected finding of this study is that LVfw and BiV pacing resulted in reduced rotational function compared to atrial pacing, while RVa pacing was not found to significantly alter rotation or torsion. Previous studies have demonstrated a reduction of about 3-6° in LV torsion with RVa pacing.(98, 99) Although not statistically significant, our subjects exhibited a similar difference between atrial and RVa pacing ($15.3 \pm 9.2°$ vs $11.6 \pm 8.4°$). Our small sample size may have contributed to our inability to detect differences in the amount of torsion produced in these pacing conditions. Furthermore, although BiV pacing has been shown to improve torsion in heart failure populations(57), the effects of this pacing modality on torsion in healthy human hearts have not been studied to our knowledge. In healthy canine hearts, however, BiV pacing was found to reduce torsion when compared to atrial pacing in the same animals(69). RVa pacing in these canines reduced torsion to the same extent as BiV pacing. To our knowledge, the effects of LV pacing alone on torsion have not been investigated in either animals or humans, thus our finding of reduced rotational motion with LVfw pacing, as compared to to RVa pacing, warrants further investigation.

Cardiac deformation in the longitudinal, radial and circumferential planes of motion, and rotational motion have rarely been incorporated into one study. However, subjects with asymptomatic diastolic dysfunction were found to exhibit reduced

longitudinal strain compared to healthy control subjects, while circumferential strain was slightly higher and radial strain was not different.(83) It was suggested that the increased circumferential strain may be a compensatory mechanism, responsible for maintaining global LV function. We also found that longitudinal strain was most affected by various pacing configurations. However, we did not find a compensatory increase in either radial or circumferential strain. We did find that rotational motion was best preserved in RVa pacing, when longitudinal strain was most dramatically impaired. Thus preserved rotational motion may have aided in maintaining LV pump function. The long-term implications of the alterations to longitudinal and rotational motion that occur during these pacing configurations remain uncertain.

The limitation of our small sample size was balanced by the carefully controlled experimental conditions and the use of a repeated measures study design, which substantially reduces variability since subjects serve as their own controls. In order to avoid fusion of native conduction with the paced ventricular beat, the AV delay during ventricular pacing during this study was set to 20 ms. As a result, it is likely that some difference between atrial pacing and the 3 ventricular pacing configurations was due to the loss of the atrial kick, rather than the changes in electrical activation. However, the AV delay was constant during each ventricular pacing protocol, so comparisons between those 3 configurations should be valid. Our study only included 1 RV pacing site, the RVa. Other possible RV pacing sites such as the septum or outflow tract were not evaluated and might produce different results.

In conclusion, LV mechanics are acutely affected by ventricular pacing configuration. Global LV pump function, as measured by LVOT VTI was most impaired during RVa pacing, best preserved during LVfw pacing, and intermediate during BiV pacing. Strain and dyssynchrony measurements mirrored the differences in LVOT VTI. This was more evident in longitudinal measurements than radial or circumferential measurements. In addition, differences in strain were most evident when measured at the apex and mid-ventricle, rather than at the base of the LV. Rotational motion was altered differently than strain. Apical rotation was most impaired during BiV and LVfw pacing, as compared to RVa pacing. The long-term consequences of these pacing configurations, and the resulting mechanics, remain to be determined. However, this study suggests that LVfw and BiV pacing may better preserve global LV function, in spite of reduced rotational function, in patients with normal LV function who require ventricular pacing.

Figure Legends

Table 1: Echocardiographic analysis of left ventricular (LV) function.

Data are presented as mean ± standard deviation. Repeated measures, single factor ANOVA is between all pacing configurations. * Indicates $p<0.05$ compared with baseline. + Indicates $p<0.05$ compared with RVA pacing. # Indicates $p<0.05$ compared with BiV pacing. LVOT = LV outflow tract, VTI = velocity time integral, MV=mitral valve, E=Early inflow velocity, A=Late/active inflow velocity, IVC = isovolumic contraction time, IVR = isovolumic relaxation time, MPI = myocardial performance index.

Table 2: Echocardiographic analysis of left ventricular (LV) mechanics.

Data are presented as mean ± standard deviation. Repeated measures, single factor ANOVA is between all pacing configurations. * Indicates $p<0.05$ compared with baseline. + Indicates $p<0.05$ compared with RVA pacing. # Indicates $p<0.05$ compared with BiV pacing.

Figure 1: Echocardiographic analysis of left ventricular (LV) dyssynchrony.

Data are presented as mean ± standard deviation. Bracket indicates repeated measures, single factor ANOVA p-value between all pacing configurations. * Indicates $p<0.05$ compared with baseline. + Indicates $p<0.05$ compared with RVA pacing. # Indicates $p<0.05$ compared with BiV pacing.

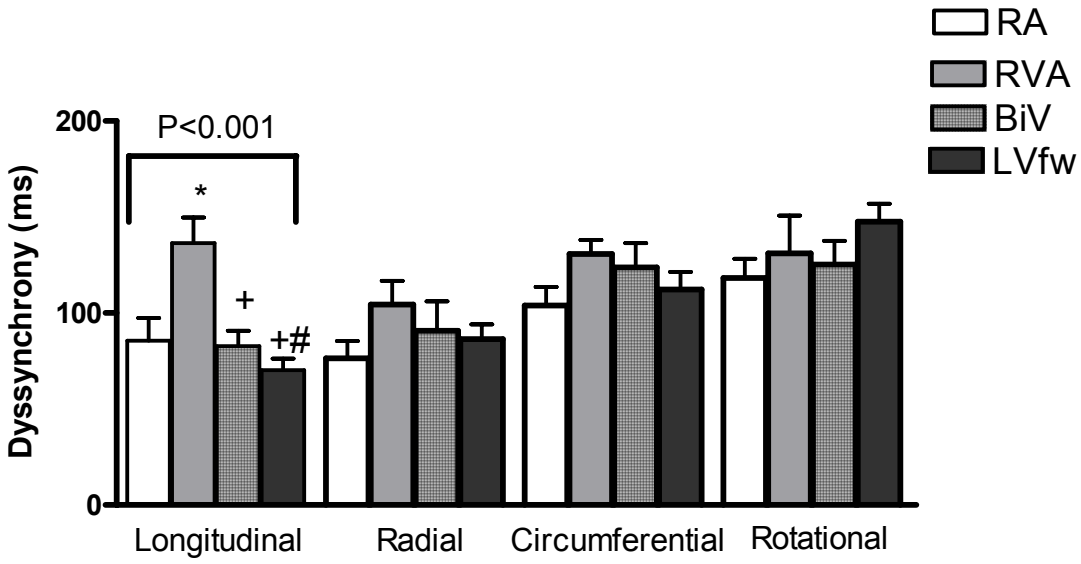
Table 1: Echocardiographic analysis of left ventricular (LV) function.

Variable	RA	RVa	BiV	LVfw	ANOVA P-value
LV Function					
LVOT VTI	22.1±5.	216.3±3.2*	16.0±3.6*	18.9±4.1*+#	**<0.001**
MV E Velocity (cm/s)	0.76±0.13	0.70±0.13	0.72±0.11	0.78±0.13	0.055
MV A Velocity (cm/s)	0.58±0.17	0.22± 0.13	0.27±0.22	0.40± 0.39	0.067
MV E/A Ratio	1.48±0.75	2.60±0.83	2.65±1.04	2.44±1.43	0.092
MV VTI	20.4±2.6	17.3±3.2*	17.7±2.3*	18.8±2.0	**0.001**
Cardiac Cycle Timing					
Heart Rate (bpm)	66±8	66±8	66±8	67±8	0.508
IVC Time (ms)	46±16	64±24	60±33	51±17	0.201
Ejection Period (ms)	320±35	271±24*	278±31*	289±35*+	**<0.001**
IVR Time (ms)	89±42	106±30	99±38	91±29	0.296
Filling Period (ms)	469±68	480±76	484±74	483±75	0.690
MPI	0.43±0.17	0.62±0.10*	0.58±0.20*	0.50±0.16+	**<0.001**

Table 2: Echocardiographic analysis of left ventricular (LV) mechanics.

Variable	RA	RVa	BiV	LVfw	ANOVA P-value
Longitudinal Strain					
Apical (%)	-16.1 ± 2.1	-8.9 ± 4.0*	-12.3 ± 3.8	-14.9 ± 6.3+	**<0.001**
Mid-LV (%)	-12.4 ± 2.2	-8.6 ± 4.0*	-9.7 ± 3.2*	-12.3 ± 3.9+#	**<0.001**
Basal (%)	-13.0 ± 3.4	-10.4 ± 5.3	-9.8 ± 4.3	-10.5 ± 3.9	0.148
Global (%)	-13.5 ± 1.9	-8.8 ± 3.1*	-10.2 ± 2.4*	-12.3 ± 4.0+#	**<0.001**
Radial Strain					
Apical (%)	38.5 ± 8.0	25.4 ± 12.0*	30.5 ± 15.1	37.5 ± 16.0+	**0.013**
Mid-LV (%)	42.4 ± 18.7	31.8 ± 15.5	38.6 ± 15.8	39.3 ± 14.3	0.244
Basal (%)	40.5 ± 16.0	28.8 ± 15.3	24.6 ± 16.4*	26.2 ± 15.8	**0.032**
Global (%)	37.7 ± 11.3	25.3 ± 10.0*	27.9 ± 11.0*	35.7 ± 12.5	**0.003**
Circumferential Strain					
Apical (%)	-24.2 ± 12.0	-20.6 ± 10.0	-19.3 ± 9.4	-25.9 ± 9.9	0.070
Mid-LV (%)	-16.2 ± 4.7	-18.2 ± 9.3	-15.1 ± 7.4	-17.1 ± 5.5	0.682
Basal (%)	-12.7 ± 4.5	-9.5 ± 4.1	-9.0 ± 4.1	-11.2 ± 4.8	0.094
Global (%)	-17.2 ± 5.1	-15.8 ± 5.7	-14.3 ± 4.7	-17.5 ± 3.0	**0.049**
Rotation					
Apical (°)	10.9 ± 7.4	7.5 ± 7.8	4.5 ± 5.6*	5.9 ± 5.8*	**0.008**
Mid-LV (°)	1.2 ± 4.7	3.8 ± 4.8	2.5 ± 5.6	1.5 ± 4.7	0.630
Basal (°)	-6.4 ± 3.0	-3.8 ± 3.6	-5.4 ± 3.0	-4.9 ± 3.2	0.304
Torsion (°)	15.3 ± 9.2	11.6 ± 8.4	9.3 ± 4.7*	10.0 ± 4.3	**0.038**

Figure 1: Echocardiographic analysis of left ventricular (LV) dyssynchrony.



CHAPTER 4. LEFT VENTRICULAR FUNCTION AND MECHANICAL DYSSYNCHRONY AFTER CHRONIC PACING OF THE RIGHT VENTRICLE

Left Ventricular Function and Mechanical Dyssynchrony after Chronic Pacing of the Right Ventricle

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Short Title: Effects of Chronic RV Pacing

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Synopsis

Background: Although right ventricular (RV) pacing is standard treatment for high degree atrioventricular block, it may create mechanical dyssynchrony, and lead to heart failure. The purpose of this study was to describe the relationship between systolic function and synchrony in chronically paced patients.

Methods: Consecutive patients with normal pre-pacing systolic function, and third degree atrioventricular block were eligible to participate in this study. Echocardiograms were performed after 4.0±2.1 years of pacing in 29 patients, as well as in 33 age-matched non-paced control subjects with normal LV function. Longitudinal and radial function were quantified as the mean peak systolic longitudinal displacement and radial strain. Dyssynchrony was calculated as the standard deviation of times to peak longitudinal displacement or radial strain. Abnormal motion within the septal and lateral walls was investigated using an intramural dyssynchrony index.

Results: The ejection fraction (EF) of the RV paced patients was lower than non-paced controls (43±8% vs. 57±5%, $p<0.0001$). Both longitudinal and radial function was reduced in the paced group. Paced patients had significantly more longitudinal, radial and septal intramural dyssynchrony (IM-S) than non-paced controls ($p<0.01$ for all). Higher EF in the paced patients was associated with lower IM-S ($r=0.43$, $p=0.02$), but not other measures.

Key words: RV pacing, mechanical dyssynchrony, left ventricular mechanics

Introduction

Dual chamber pacemakers are routinely used to treat patients with atrioventricular node dysfunction or bundle branch block by stimulating the right ventricle (RV). In the United States, 180,000 patients per year receive RV pacemakers.(15) On average, pacing reduces symptoms, and improves quality of life, exercise capacity, and survival.(16-18) However, data indicate that chronic RV pacing may be detrimental to cardiac function. The DAVID trial demonstrated that heart failure patients who were actively paced from the RV had a 60% greater risk of hospitalization or death due to heart failure (HF) than patients receiving only back-up pacing.(1) Furthermore, Zhang et al found that one-quarter of RV pacemaker-dependant patients (over 90% of beats paced), without HF prior to implant, developed HF within 8 years of implant.(2)

The mechanisms responsible for the increased risk of developing HF as a result of RV pacing remain unclear. However, it has been suggested that chronic pacing-induced mechanical dyssynchrony may impair cardiac function in these patients.(8, 76) Animal models have demonstrated that RV pacing results in heterogenous activations times within the left ventricle (LV), with early and reduced deformation near the pacing site, and delayed and increased deformation in opposing regions.(3, 4) Studies in humans have confirmed that RV pacing results in increased mechanical dyssynchrony in the longitudinal and radial planes(13, 14) Some patients, however, do not develop HF as a result of chronic RV pacing. It is uncertain

if this is due to a lack of pacing-induced dyssynchrony in these patients, or if other factors act to preserve LV function in these patients.

The purpose of this study was to compare LV systolic function and mechanical dyssynchrony, in patients from a single clinical center who have been chronically paced from the RV, with non-paced subjects of similar age. We hypothesized that RV paced patients would exhibit reduced systolic function and greater dyssynchrony than non-paced controls and that patients with more impaired systolic function would have greater mechanical dyssynchrony.

Methods

Study Population

Records from the St. Paul Heart Clinic (St. Paul, MN) were screened to identify all patients who had undergone dual chamber pacemaker implantation for third degree heart block between the dates of January 1, 2001 and December 31, 2006. Only patients with a clinical assessment of normal cardiac function prior to pacing, who were paced from the RV >90% of the time, and who had not been subsequently upgraded to cardiac resynchronization therapy (CRT) were included in the study. Each of the 83 patients meeting study criteria was contacted, and invited to participate. A total of 29 patients participated in the study, completed the study protocol and were included in the final analysis. Pacemaker patients were required to make one clinical visit, which included an echocardiographic examination with Tissue Doppler Imaging (TDI).

Thirty-three non-paced patients of similar age, who had undergone clinical ultrasound examination and were found to have normal cardiac function, as judged by a clinician not involved in this study, served as a control group. The study protocol was approved by a central Institutional Review Board, and informed consent was received from all patients before the study visit was conducted.

Echocardiographic Examination

Echocardiographic examinations were performed by a trained sonographer using GE Vivid 7 Ultrasound equipment (GE Vingmed Ultrasound, Milwaukee, WI). Digital gray-scale two-dimensional cine loops were collected from the LV apical 2-, and 4-chamber, apical long axis, parasternal long axis and mid-ventricular short axis views. Pulsed Doppler echocardiography was used to measure blood flow velocities across the aortic, mitral, and pulmonic valves over three consecutive beats. The onset and termination of flow was used to determine the times at which valves opened and closed, using the QRS complex as a reference. These values were used to calculate the myocardial performance index [MPI; (isovolumic contraction time + isovolumic relaxation time)/ejection time]. Finally, TDI images of the apical 2-, and 4-chamber views, and long axis views were recorded. Digital images and cine loops, triggered to QRS complex, were stored and analyzed off-line by a single observer using GE Echopac 7.0.0 (GE Vingmed Ultrasound, Milwaukee, WI).

LV Function Assessment

Ejection fraction (EF) was the primary indicator of LV systolic function. EF was measured from two-dimensional, grey-scale apical 2-, and 4-chamber views by using the biplane Simpson's method. Secondary measures of LV systolic function were derived from TDI and speckle tracking echocardiography (STE) methodologies. A global systolic contraction score (GSCS) was derived from TDI images of the apical 2-, and 4-chamber, and long axis views. Basal and mid-ventricle regions of interest (8mm high, by 8mm wide) were placed on opposing walls in each of the three views, and tissue displacement profiles were generated. For each region of interest, the longitudinal displacement occurring between the end of diastole (defined as the time of mitral valve closing from the previous beat), and the end of systole (defined as the time of aortic valve closing) was measured. The average displacement of all 12 regions of interest was defined as GSCS, and was used as an indicator of longitudinal systolic function.(31)

Radial systolic function was assessed with STE using two-dimensional images of the mid ventricle in the short axis plane. To perform this analysis, the endocardial border was manually traced at one time point (end systole), and the region of interest thickness was adjusted to encompass the entire myocardium. Stable acoustical patterns within the region of interest were automatically identified, and their locations were traced throughout the cardiac cycle. The myocardium was divided into 6 segments corresponding to anterior, lateral, posterior, inferior, septal,

and anteroseptal regions. The mean radial strain (M-RS) from the 6 automatically assigned segments was calculated.

Dyssynchrony Measurements

Longitudinal mechanical dyssynchrony was assessed using the same 12 tissue displacement curves generated to measure GSCS. Within the LV, longitudinal dyssynchrony was defined as the standard deviation, among the 12 curves, of the time from the end of the previous beat to the peak systolic displacement. (47, 100)

Visual inspection of the recorded images suggested that abnormal longitudinal septal motion may result from RV pacing. In order to better quantify this motion, and to determine its effect on LV function, a new index of dyssynchrony was used. Intramural dyssynchrony (within a wall of the LV) was defined as abnormal longitudinal motion away from the apex during early systole. This type of dyssynchrony was measured using TDI by placing 8 equally spaced regions of interest along a given wall, extending from base to apex. Intramural dyssynchrony for a given wall was defined as a count of the number of myocardial segments initially moving away from the ultrasound transducer after mitral valve closure. Dyssynchrony within the LV septal wall (IM-S), and lateral wall (IM-L) was assessed from apical 4-chamber views, as shown in figure 1.

Radial mechanical dyssynchrony was measured using STE and was quantified as the standard deviation, among the 6 LV segments, of the times from the end of the previous beat to the peak radial strain. (32, 45)

Reproducibility of dyssynchrony measurements by our lab has been previously reported. (45, 101) Intraclass correlation coefficients for intra-observer and inter-observer variability in SD-TT measurements were 0.88 and 0.90, respectively. (45) For SD-RS measurement, these coefficients were 0.97 and 0.96. (45) And for IM-S, they were 0.95 and 0.88.(101)

Statistics

Continuous variables were compared using unpaired Student's t-tests when appropriate. Abnormal EF was defined as less than 45%. For all other measurements, abnormal values were defined as the mean value for the non-paced control group, plus or minus one standard deviation. Frequency data was compared using Fisher's exact test. Associations between LV function (EF) and demographic and echocardiographic variables were investigated using Pearson correlations. Results are presented as mean ± standard deviation or as number (%). Statistical analyses were performed using GraphPad Prism version 4.00 (GraphPad Software, San Diego, CA). A p-value of <0.05 was considered significant.

Results

Patient Characteristics

Demographic information describing the 29 paced and 33 control subjects is presented in Table 1. The groups were relatively well-matched for age and gender composition. The study group was paced for 5.6±2.7 years. The right atrium was paced for 40±34% of the heartbeats, and the right ventricle was paced for 99±2% of the beats. The RV lead had been implanted in the RV apex in 15 patients (52%), and in the RV septum in 14 (48%).

Echocardiographic Findings

All patients and control subjects had adequate two-dimensional, pulsed Doppler and TDI echocardiographic images for analysis. Speckle tracking was possible in 24 of the 29 patients (83%) and 28 of the 33 control subjects (85%).

The results of the echocardiographic measurements are presented in Table 2. When compared to the control group, RV paced patients had increased heart rates, reduced systolic ejection time and diastolic filling time, and longer isovolumic contraction periods. As a result, MPI was significantly greater (indicating reduced function) in paced patients than in controls (0.69±0.25 vs. 0.48±0.14, $p<0.0001$).

<u>Systolic Function</u>

Pre-implant EF of the study group was 55±7%, similar to the EF of the control group (57±4%, $p=0.2128$). After chronic pacing, the EF of the RV-paced

patients was significantly lower than that of the control group (41±7%, $p<0.0001$). A total of 22 (76%) of the RV-paced patients had an EF below the defined abnormal value of 45%, while, by definition, no control patients had abnormal EF ($p<0.0001$, RV-paced vs. controls). LV volume was greater in the RV-paced group than in controls at both end diastole and end systole ($p<0.0001$ for both). In addition, both longitudinal and radial systolic function, as measured by GSCS and M-RS, respectively, was lower in the RV-paced group than in the controls ($p<0.01$ for both comparisons).

Mechanical Dyssynchrony

Longitudinal mechanical dyssynchrony was significantly higher in the paced patients and a higher percentage of RV-paced patients had abnormal SD-TT values than controls (69% vs. 12%, $p<0.0001$). In addition, intramural dyssynchrony within the septal wall was greater in paced patients than controls (IM-S=2.4±1.8 vs. 0.5±1.2; $p<0.0001$). As exemplified in Figure 1, the regions of interest most often demonstrating abnormal longitudinal motion were apical segments. The most distal 3 segments accounted for 60% of the abnormal segments. There was no difference in intramural dyssynchrony within the lateral wall between groups. Abnormal IM-S was found in 20 (69%) of the paced patients, but only 5 (15%) of the controls ($p<0.0001$), and co-existed with abnormal SD-TT values in 11 paced patients and 1 control subject.

Radial dyssynchrony was also greater in paced patients than in controls. Abnormal SD-RS was found in 34% of the RV-paced patients and 12% of the controls (p=0.0656). Isolated radial dyssynchrony was found to exist in 2 control patients, but no RV-paced patients. Radial dyssynchrony coexisted with longitudinal dyssynchrony in 5 RV-paced patients and 1 control patient. Longitudinal, intramural and radial dyssynchrony occurred together in 5 RV-paced patients, but in no control subjects.

Predictors of Systolic Function

Results of linear regression analysis are presented in Table 3 and Figure 3. Within the group of paced patients, a higher EF was associated with a higher GSCS (slope=0.086±0.038, r=0.401, p=0.0310) and lower IM-S (slope=-0.104±0.042, r=0.428, p=0.0205). No other variables investigated, including SD-TT, SD-RS, age and duration of pacing, were associated with EF. In addition, no differences in EF or dyssynchrony measures were found between patients paced from the RV apex and from the RV septum.

Discussion

Long term clinical complications associated with RV pacing, including increased risk of hospitalization, heart failure, and death, have been well-documented. (1, 7, 10, 12) In the current study, we also sought to investigate the long-term impact of RV pacing, including effects on LV function and dyssynchrony in both longitudinal and radial planes of motion. Our findings provide evidence that

mechanical dyssynchrony is associated with reduced LV function, and that this is a common condition in RV-paced patients, even when LV function was normal prior to pacing.

Studies in animals and humans with normal ejection fractions have demonstrated that acute RV pacing reduces LV function and increases LV dyssynchrony. (4, 5, 14) Zhang et al. reported that, in 57 patients with normal LV function, acute pacing from the RV apex resulted in decreased EF and increased longitudinal mechanical dyssynchrony. (14) Kawanishi and colleagues described similar findings in chronically paced patients, as compared to non-paced control subjects (67), suggesting that acute pacing-induced changes in LV function are maintained in chronic pacing. Tops et al. also demonstrated that chronic RV pacing increases radial dyssynchrony using STE. (13) In the current study, we also observed that chronic RV-pacing had a negative impact on both LV function, remodeling and both longitudinal and radial mechanical dyssynchrony in patients with normal LV function prior to pacemaker implantation.

We also found that RV paced patients had significantly longer isovolumic contraction times, which is likely a consequence of slower pressure development during a dyssynchronous LV contraction. Longer isovolumic contraction limits the time available for adequate systolic ejection and diastolic filling. Heart rates were also slightly higher in paced patients, further shortening ejection and filling times. This may be an important mechanism in reducing LV function in RV paced patients.

An index of longitudinal dyssynchrony within a wall of the LV, which we termed intramural dyssynchrony, was also presented here. This index represents the amount of myocardium within a given wall that, during early systole, moves away from the ultrasound transducer placed at the apex. This type of paradoxical motion was seen to occur frequently within the septum of RV-paced patients, and, in some cases, it occurred independently of significant intraventricular longitudinal dyssynchrony measured by other means. The myocardial segments most frequently displaying this paradoxical motion were located near the apex, nearest the RV lead. This observation is consistent with the findings of Prinzen who showed reduced strain and perfusion near the pacing site. (3, 4) Furthermore, among the paced patients, greater intramural dyssynchrony within the septal wall, but not other measures of dyssynchrony, was associated with reduced systolic function. This suggests that septal wall motion abnormalities may be a more important contributor to impaired LV function than more global measures of mechanical dyssynchrony in chronically paced patients.

Although, average LV systolic function declined after permanent RV pacing, there was significant heterogeneity in responses. This may be due to genetic or anatomical variation, lead location, or differences in cardiac health history. Further study is warranted to identify which patients are most likely to be adversely affected by RV-pacing, and which pacing sites might produce a more synchronous LV contraction.

Study Limitations

In this observational study, echocardiograms from patients undergoing chronic RV pacing were compared to a group of non-paced subjects of similar age. Echocardiograms with TDI, taken before implant, were not available for the paced patients, thus limiting conclusions that differences are entirely due to pacing effects.

Although 83 RV paced patients met the study criteria, only 29 agreed to participate. The small sample may not accurately reflect the characteristics of the larger group of RV-paced patients. In particular, the patients agreeing to participate may have been healthier, with greater mobility, and so more likely to make the clinical visit required. It is also possible that eliminating those patients who were upgraded to CRT, for example, created a bias towards improved LV function in the RV-paced group.

Summary

Echocardiographic analysis of chronically RV-paced patients showed reduced LV systolic function, along with significant longitudinal, radial, and intramural systolic dyssynchrony, as compared to non-paced subjects. Intramural dyssynchrony was modestly associated with EF, suggesting that uncoordinated motion within the LV septum may be an important factor in pacing-induced LV functional impairment.

Table and Figure Legends

Table 1. Clinical characteristics of control and paced subjects. Data are presented as mean ± standard deviation. ACE = angiotensin-converting enzyme inhibitors, ARB = angiotensin II receptor blockers, BMI = body mass index, DBP = diastolic blood pressure, SBP = systolic blood pressure.

Table 2. Echocardiogram analysis of control and paced subjects. Data are presented as mean ± standard deviation. EF = left ventricular ejection fraction, GSCS = global systolic contraction score, MPI = myocardial performance index, M-RS = mean radial strain, SD-RS = standard deviation of time to peak radial strain, SD-TT = standard deviation of time to peak systolic motion by tissue tracking, IM-L = intramural dyssynchrony within the lateral wall, IM-S = intramural dyssynchrony within the septum.

Table 3. Predictors of left ventricular ejection fraction (%) in RV-paced patients, by univariate linear regression. Slope is expressed as best fit slope ± standard error of slope. Abbreviations are the same as in table 2.

Figure 1: Intramural dyssynchrony measurement. Examples of tissue Doppler tracings of a control subject (septal wall shown in panel A, lateral wall in panel B), and a RV-paced subject (septal wall shown in panel C, lateral wall in panel D) are shown. The septal wall of the paced patient shows intramural dyssynchrony (noted in yellow circle), while other traces show no dyssynchrony by this method.

Figure 2: Regression analysis plot. Individual data points, regression line, and 95% confidence band demonstrate the significant association (p=0.0205) between LV ejection fraction and intramural dyssynchrony within the septal wall (Panel A).

However, no association is found between LV ejection fraction and either longitudinal (Panel B), or radial (Panel C) measures of dyssynchrony.

Table 1. Clinical characteristics of control and paced subjects.

	Control (n = 33)	RV paced (n = 29)	
Subject Characteristics			P-value
Male, n (%)	15 (45%)	17 (59%)	0.322
Age (years)	75 ± 9	75 ± 13	0.305
Weight (kg)	75.2 ± 11.3	75.2 ± 11.3	0.699
SBP (mmHg)	125 ± 18	117 ± 19	0.946
DBP (mmHg)	71 ± 13	68 ± 11	0.770
Duration Paced (yr)	NA	5.6 ± 2.7	NA
Medical History			
Atrial Fibrillation, n (%)	7 (21%)	5 (17%)	0.762
Coronary Artery Disease, n (%)	5 (15%)	4 (14%)	0.999
Myocardial Infarction, n (%)	0 (0%)	2 (7%)	0.215
Diabetes, n (%)	0 (0%)	6 (21%)	0.008
Cancer, n (%)	2 (6%)	3 (10%)	0.658
Medications			
Anti-Arrhythmia, n (%)	3 (9%)	0 (0%)	0.241
Anti-Coagulant, n (%)	6 (18%)	7 (24%)	0.756
Aspirin, n (%)	6 (18%)	13 (45%)	0.030
ACE/ARB, n (%)	8 (24%)	12 (41%)	0.181
Diuretic, n (%)	3 (9%)	12 (41%)	0.006
Statin, n (%)	8 (24%)	0 (0%)	0.005

Table 2. Echocardiogram analysis of control and paced subjects.

Variable	Control (n = 33)	RV paced (n = 29)	P-value
LV Systolic Function			
EF (%)	57.2 ± 4.2	41.3 ± 7.4	<0.001
LV EDV (mL)	72.0 ± 20.1	100.8 ± 27.6	<0.001
LV ESV (mL)	31.1 ± 9.7	60.0 ± 22.0	<0.001
MPI	0.48 ± 0.14	0.69 ± 0.25	<0.001
GSCS (mm)	7.7 ± 1.5	6.3 ± 1.7	<0.001
M-RS (%)	41.3 ± 20.4	24.5 ± 13.3	0.002
Dyssynchrony			
SD-TT (ms)	30.3 ± 16.7	65.5 ± 34.1	<0.001
SD-RS (ms)	38.3 ± 42.1	77.6 ± 60.3	0.008
IM-S (# walls)	0.5 ± 1.2	2.4 ± 1.8	<0.001
IM-L (# walls)	1.3 ± 2.2	1.3 ± 2.1	0.995

Table 3. Predictors of left ventricular ejection fraction (%) in RV-paced patients, by univariate linear regression.

Variable	Slope	R	P-value
MPI	0.004 ± 0.007	0.114	0.551
GSCS (mm)	0.086 ± 0.038	0.401	0.031
M-RS (%)	0.451 ± 0.352	0.265	0.213
SD-TT (ms)	-0.196 ± 0.892	0.045	0.828
SD-RS (ms)	1.168 ± 1.601	0.155	0.474
IM-S (# walls)	-0.104 ± 0.042	0.428	0.021
IM-L (# walls)	0.030 ± 0.056	0.105	0.591
Age (years)	-0.097 ± 0.350	0.054	0.783
Duration of pacing (years)	0.114 ± 0.066	0.315	0.097

Figure 1: Intramural dyssynchrony measurement.

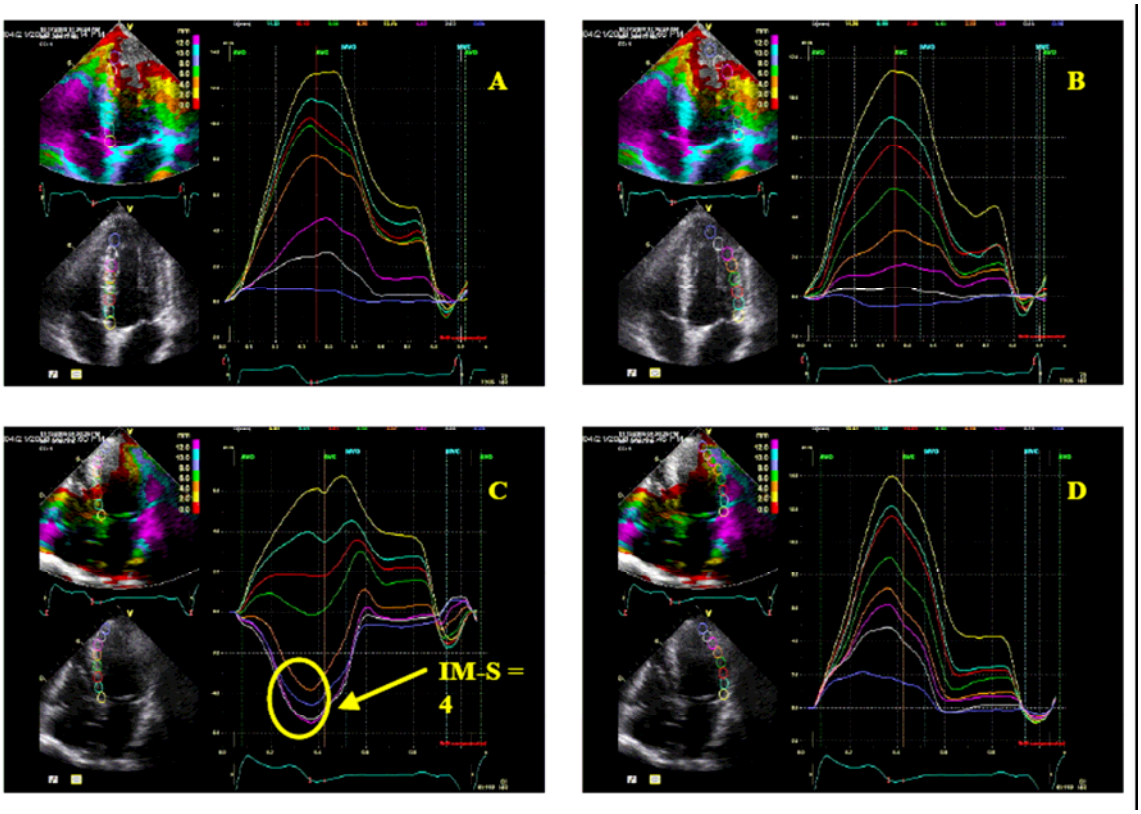
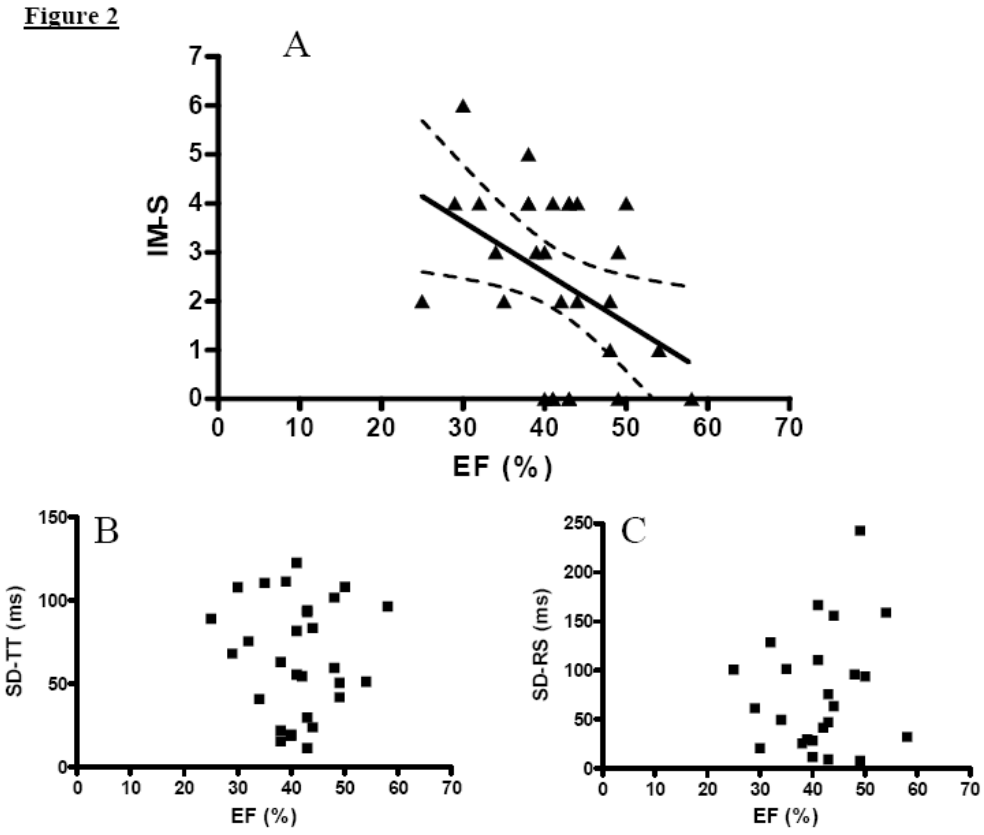


Figure 2: Regression analysis plot.



CHAPTER 5. TORSION AND DYSSYNCHRONY DIFFERENCES BETWEEN CHRONICALLY PACED AND NON-PACED HEART FAILURE PATIENTS

Torsion and Dyssynchrony Differences Between Chronically Paced and Non-paced Heart Failure Patients

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Short Title: Torsion in Chronic RV Pacing

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Synopsis

Background: Chronic right ventricular (RV) pacing may lead to left ventricular (LV) dyssynchrony, reduced function, remodeling, and heart failure (HF). Cardiac mechanics in pacing-induced HF may be different than in HF from other causes, potentially affecting treatment.

Methods and Results: Echocardiograms were performed after chronic RV pacing in 20 patients with complete heart block but otherwise normal cardiac function prior to pacing (RVP group), and in 29 non-paced patients with different HF etiologies but similar ejection fractions (HF group). Longitudinal dyssynchrony within the LV and intramural dyssynchrony within the septum and lateral walls were measured using tissue displacement imaging. Speckle tracking echocardiography was used to measure radial and rotational motion. LV volumes were smaller in RVP than HF, but longitudinal and radial dyssynchrony were similar. Dyssynchrony within the septum was greater, systolic torsion was lower, untwisting was delayed, and apical rotation was more frequently reversed in RVP patients compared to HF.

Conclusion: Intraventricular dyssynchrony was similar between RPP and HF patients with similar ejection fraction. However, RVP patients had smaller ventricles, greater dyssynchrony within the septum, lower torsion, altered apical rotation, and delayed untwisting. Torsion and septal wall dyssynchrony may be useful parameters of LV dysfunction in paced patients.

Key Words: **Speckle tracking, tissue Doppler echocardiography, rotation.**

Background

Although patients with AV node dysfunction or bundle branch block require permanent ventricular pacing, this treatment has been associated with an increased risk of left ventricle (LV) dysfunction, hospitalization, heart failure (HF), and death (1, 6, 7, 10-12). Approximately 30-50% (6-9) of RV-paced patients exhibit pacing-induced LV dysfunction.

Artificial pacing of the right ventricle (RV) alters the physiological conduction of cardiac action potentials, slowing ventricular activation, similar to that occurring in bundle branch block. Studies in animals and humans have shown that pacing results in heterogeneous electrical activation, strain and perfusion of the LV (3-6). Compared to normal, healthy subjects, longitudinal and radial mechanical dyssynchrony have been demonstrated in both RV-paced patients (8, 13, 14), and in non-paced HF (34, 102). Similarly, altered LV rotational motion has been reported in both RV-paced subjects (69) and in non-paced subjects with HF (57). We have demonstrated that patients with RP pacing-induced HF and ejection fractions (EF) <35% have smaller LV volumes, greater intramural dyssynchrony within the septum, and respond better to cardiac resynchronization therapy (CRT) than other HF patients (101). In this study, we extend these findings by including rotational measurements, and by assessing patients with less severe HF.

Methods

Study Population

St. Paul Heart Clinic (St. Paul, MN) patients were retrospectively identified for inclusion in this study. RV paced patients who had undergone an echocardiogram between January 1, 2006 and December 31, 2008, and who had been paced a minimum of 1 year prior to the echocardiogram, were identified. Patients who had normal systolic function prior to pacing, were paced >90% of the time, and whose echocardiogram included all required images for analysis were included in this study (RVP group). In all, 20 patients met the study criteria, and were included in the final analysis.

In addition, 29 non-paced heart failure patients, who had undergone clinical ultrasound examination, and were found, by a cardiologist blinded to the status of the RVP group, to have mild to moderately reduced systolic function served as a control group (HF group). Patients included in the study were matched to the RVP group for age and LV ejection fraction (EF). A central Institutional Review Board approved this study protocol. Informed consent was not required of participants since the study was retrospective in nature.

Echocardiographic Examination

Echocardiographic examinations were performed by a trained sonographer using GE Vivid 7 Ultrasound equipment (GE Healthcare). Digital gray-scale two-dimensional

cine loops were collected from the LV apical 2-, and 4-chamber, apical long axis, parasternal long axis, and the basal, apical and mid-ventricle short axis views. Pulsed Doppler echocardiography was used to measure blood flow velocities across the aortic, mitral, and pulmonic valves over three consecutive beats. The onset and termination of flow was used to determine the times at which valves opened and closed, using the QRS complex as a reference. Tissue Doppler imaging (TDI) images of the apical views were recorded. Digital images and cine loops, triggered to QRS complex, were stored and analyzed off-line using GE Echopac 7.0.0 by a single observer.

LV Function

EF was the primary indicator of LV systolic function, and was measured from two-dimensional, grey-scale apical 2-, and 4-chamber views by using the biplane Simpson's method. Diastolic function was assessed by measuring peak early (E) and late (A) transmitral flow velocities, and taking their ratio (E/A), by measuring the E velocity deceleration time (MDT), and by taking the ratio of early transmitral flow velocity to early mitral annular tissue velocity (E/e′). Early mitral annular velocity was taken to be the average of tissue velocity of the basal septal and basal lateral regions of interest, measured using TDI.

Longitudinal Motion Assessment

A global systolic contraction score (GSCS) was derived from TDI images of the three apical views. Basal and mid-ventricle regions of interest, 8mm by 8mm in

dimension, were placed on opposing walls in each of the three views, and tissue displacement profiles were generated. For each region of interest, the longitudinal displacement occurring between the time of mitral valve closing from the previous beat and the time of aortic valve closing was measured. The average displacement off all 12 regions of interest was defined as GSCS, and was used as an indicator of longitudinal systolic function (31). Within the LV, systolic longitudinal dysynchrony was defined as the standard deviation of the time to peak systolic displacement among the 12 curves (SD-TT) (47, 100).

In order to better quantify abnormal septal wall motion frequently observed in RV paced patients, an additional index of dyssynchrony within a wall of the LV (intramural dyssynchrony) was used. This type of dyssynchrony was measured with TDI displacement imaging by placing 8 equally spaced regions of interest along one wall, extending from base to apex. Intramural dyssynchrony for a given wall was defined as a count of the number of walls paradoxically moving away from the ultrasound transducer during early systole (101). Dyssynchrony within the LV septal wall (IM-S), and lateral wall (IM-L) was assessed from apical 4-chamber views.

Radial Motion Assessment

Radial systolic function was assessed with speckle tracking echocardiography (STE) using mid-ventricular LV short axis images. The endocardial border was manually traced using one frame at end systole, and the region of interest thickness was manually adjusted to span the thickness of the myocardium. Stable acoustical

patterns within the region of interest were identified, and automatically traced throughout the cardiac cycle. The myocardium was divided into six segments corresponding to anterior, lateral, posterior, inferior, septal, and anteroseptal regions. The mean radial strain (M-RS) from the six automatically assigned segments was calculated as a measure of global radial function. The standard deviation of the times between mitral valve closing and the peak radial strain of each segment (SD-RS) was computed to quantify radial mechanical dyssynchrony.

Rotational Motion Assessment

Rotational motion was also measured with STE using two-dimensional images of the LV base and apex, as depicted in Figure 1. Basal and apical regions of interest were identified as described above. For analysis, rotation-time data was exported to a custom spreadsheet (Microsoft Excel 2000). Global rotations were defined as the average segmental rotations of 6 basal and 6 apical segments. Peak systolic basal rotation (BR) and apical rotation (AR) were identified, and the times from mitral valve closure to peak rotations were measured. Rotational dyssynchrony (ΔR) was defined as the time difference between BR and AR. LV torsion was defined as the difference between BR and AR at each time point. Peak systolic torsion (TOR) was defined as the largest torsion measurement at any time point.

Diastolic untwisting mechanics were also investigated. Torsion rate curves throughout the cardiac cycle were derived by differentiation of the torsion curves. The peak untwisting rate (UT) during early diastole was identified. The time

between peak torsion and peak untwisting rate was defined as the untwisting delay (dUT).

Statistics

Results are presented as mean ± standard deviation or as number (%). Continuous variables were compared using unpaired student's t-tests, with Welch's correction for unequal variance when appropriate. Frequency data was compared using Fisher's exact test. Associations with EF, torsion, peak untwisting rate and other demographic and echocardiographic variables were investigated using univariate linear regression. Statistical analyses were performed using GraphPad Prism version 4.00 (GraphPad Software, San Diego, CA). A p-value of <0.05 was considered significant.

Results

A total of 49 subjects were studied, including 29 in the HF group, and 20 RVP patients. Demographic data describing these groups is presented in Table 1, and was similar between the groups. In the RVP group, 11 patients (55%) had RV leads located in the mid-septum, and 9 patients (45%) had leads located in the RV apex.

Standard 2-dimensional and TDI echocardiographic analysis was performed in all subjects. Image quality was adequate to perform STE analysis at the mid-ventricle, for radial strain measurements, in 46 (94%) of the subjects. Basal rotation could be measured in 46 (94%) subjects. Apical rotation could be measured in 47 (96%)

subjects. A total of 44 (90%) subjects had rotation data at both the basal and apical level.

Results of echocardiographic analyses of LV function and longitudinal and radial mechanics are presented in Table 2. By design, the EF was similar between the RVP (42.5±4.6%) and HF groups (42.8±3.3%, p=0.7717). Both LV end diastolic and end systolic volumes were lower in RVP than in HF. Most parameters of diastolic function were similar between groups, however mitral inflow A velocity was greater in RVP (0.85±0.27cm/s) than in HF (0.71±0.20cm/s, p=0.0292).

Longitudinal systolic function, quantified as GSCS, was not different between groups. SD-TT was also similar in the HF and RVP groups. IM-S was greater in the RVP group (IM-S=1.9±1.7) than in the HF group (0.9±1.7, p=0.0450). However, IM-L was not different between groups. Radial systolic function and dyssynchrony were also not different between groups.

Comparisons of rotational motion measurements between groups are presented in Table 3. LV torsion was significantly lower in the RVP group (6.2±7.3º) than in the HF (10.6±4.2º, p=0.0312) group. The LV base typically rotated in a clockwise direction, when viewed from the apex. By convention, this direction was defined as negative rotation. There was no difference in BR between the RVP and HF groups. The apex of the LV typically rotated in the counter-clockwise, or positive direction. Although the differences in AR failed to reach statistical significance, RVP patients

tended to have lower AR than HF patients (2.7±7.5º vs. 5.6±2.8º, p=0.1309). Rotational directions at the apex or base were reversed in several patients. Basal rotation was reversed in 1 patient in each group. Apical rotation was reversed in 7 (35%) RVP subjects, but in no HF patients (0%, p=0.0010). Differences in timing of rotational motion also were not statistically significant, but RVP patients tended to have greater ΔR (145±123ms) than HF patients (91±89ms, p=0.0978).

Untwisting mechanics were also different between groups. Peak untwisting velocity was similar in RVP patients and HF patients, however, it occurred later in the RVP group (dUT=188±141 ms vs. 102±73 ms, p=0.0280).

Discussion

The purpose of this study was to investigate the differences in LV mechanics between patients with HF associated with RV pacing, and those with HF from other causes. We found significant differences in LV size, intramural dyssynchrony within the septal wall, rotational function and untwisting mechanics.

We have described elsewhere increased intramural dyssynchrony within the septum in acutely-paced healthy subjects with normal LV function (68), and in chronically paced subjects with HF (101). In patients receiving CRT, those previously paced from the RV have less LV remodeling and greater intramural dyssynchrony within the septum, as compared with HF patients not previously paced (101). In the current

study involving patients with less severe HF, we also found that RVP patients have greater intramural dyssynchrony and smaller LV volumes than other HF patients. This demonstrates that these differences in dyssynchrony and remodeling are present earlier in the time course of HF development, before patients reach the standard EF criteria for CRT (≤35%).

Rotational motion of the LV occurs because of differences in the relative forces generated by double helical myocardial fiber orientation. When viewed from the apex, fibers are arranged in a counter clockwise rotation in the epicardium and a clockwise rotation in the endocardium (22-24). At the apex of the healthy, normal LV, the epicardium produces greater force during contraction than the endocardium, creating a counter clockwise rotation. Conversely, the endocardium creates greater rotational force at the base, so rotation of the base occurs in the clockwise direction. Abnormalities that effect fiber orientation, or the timing of mechanical activation between either epicardium and endocardium or the apex and the base, may result in altered rotational function. We found that RVP patients exhibit impaired rotational function compared to non-paced HF patients with similar EF, suggesting that anatomical and/or electrical factors are altered differently in these patient groups.

Several investigators have previously reported rotational function in healthy, normal subjects Maximal systolic torsion in normal hearts has then been found to range from 13º to 16º (57, 65, 92, 103). In the current study, both RVP and HF patients with similar EF had much lower torsion than the value reported in normal subjects.

However, torsion was more severely depressed in RVP subjects than other HF patients. The greater reduction of torsion in RVP was accompanied by trends for lower apical rotation and greater rotational dyssynchrony between the apex and base in those patients. The functional abnormalities described in the RVP patients were most prominent in the distal septum and the apex, the areas nearest the pacing lead. This observation in humans is consistent with previous studies in canines, which have shown that pacing results in reductions in strain and myofiber work near the pacing site (3, 4).

Differences in torsion between RVP patients, and patients with other causes of HF may result in different responses to treatments such as CRT. Rotational motion in HF patients receiving CRT was previously described by Sade, et al. (57). These investigators found that dilated cardiomyopathy patients who responded favorably to CRT (LV end-systolic volume reduced by >10%) had lower pre-CRT torsion than patients who did not improve. In addition, reversed apical rotation was found in 13% of these patients and reversed basal rotation in 14% of patients. These abnormal rotational directions were corrected with CRT in nearly all patients. We found that RVP patients exhibit greater rotational impairment, and more frequent reversal of rotational direction, than other HF patients. The normalization of rotational motion may be an important mechanism for improvement in LV function after CRT in patients with pacing-induced LV dysfunction.

As epicardial fibers relax, the twisted fibers recoil with continued active contraction of the endocardial layers. This creates suction during the isovolumic relaxation period, and enhances early diastolic filling (25, 62). Thus, untwisting motion may be a useful indicator of diastolic function, and several investigators have demonstrated that diastolic dysfunction results in reduced and delayed peak untwisting rate (40, 56, 64, 65). While we found little difference in traditional echocardiographic parameters of diastolic function between RVP and HF patients, we did find that RVP resulted in significantly delayed peak untwisting rate, suggesting that diastolic function may be more impaired in paced patients with reduced EF than in non-paced patients with similar EF.

Several limitations should be considered when drawing conclusions from this study. In this observational study, a relatively small percentage of the patients implanted with RV pacers during the period of interest met the study criteria. It is not certain that the group in the final analysis represented the larger population of RVP patients. In addition, the effects of RV pacemakers lead location were not investigated in this study. Additional studies may address the possibility that other RV lead sites may produce a more physiological activation pattern. Finally, the number of paced patients with reversed rotational direction was fairly small, preventing the investigation of the correlation between this variable and measures of LV function. A larger study is warranted to address this question.

In conclusion, patients paced from the RV remodel to a lesser extent and have greater intramural dyssnchrony within the septum than non-paced HF patients with similar, mild impairment of LV systolic function. In addition, RV-paced patients have reduced LV torsion, greater apex-to-base rotational dyssynchrony, and delayed untwisting. These differences suggest that pacing produces a distinct functional and structural HF phenotype.

Tables and Figure Captions

Table 1: Demographic data describing the HF group and the RVP group. Data are presented as mean ± standard deviation or as number (percentage). BMI= Body mass index, SBP= Systolic blood pressure, DBP= Diastolic blood pressure, ACE= Angiotensin-converting enzyme inhibitor, ARB= Angiotensin II receptor blocker.

Table 2: Echocardiographic analysis of left ventricular (LV) size, function and dyssynchrony. Data are presented as mean ± standard deviation. EF=Ejection fraction, EDV=End-diastolic volume, ESV=End-systolic volume, GSCS=Global systolic contraction score, M-RS=Mean radial strain, MV=mitral valve, E=Early inflow velocity, A=Late/active inflow velocity, E'=Peak tissue velocity of mitral annulus during early filling, SD=Standard deviation, TT=Time to peak tissue displacement, RS=Time to peak radial strain, IM-S=Intramural dyssynchrony within the septal wall, IM-L=intramural dyssynchrony within the lateral wall.

Table 3: Rotational and torsion measurements by speckle tracking echocardiography. Data are presented as mean ± standard deviation.

Figure 1: STE images of apical (top image, blue trace) and basal (top image, red trace) LV rotations, torsion (top image, white trace) and untwisting rate (lower image, white trace) in a paced subject. BR=peak basal rotation, AR=peak apical rotation, TOR=peak torsion, ΔR=rotational dyssynchrony (time between peak apical and basal

rotations), UT=peak untwisting rate, dUT=untwisting delay (time between peak torsion and peak untwisting rate).

Table 1: Demographic data describing the HF group and the RVP group.

	HF (n = 29)	RVP (n = 20)	
Subject Characteristics			P-value
Female, n (%)	15 (52%)	10 (50%)	0.999
Age (years)	69 ± 14	71 ± 16	0.273
BMI (kg/m^2)	28.6 ± 5.0	27.9 ± 4.3	0.590
SBP (mmHg)	128 ± 22	125 ± 18	0.579
DBP (mmHg)	76 ± 13	73 ± 8	0.303
Duration Paced (yr)	NA	4.0 ± 2.4	NA
Medical History			
Atrial Fibrillation, n (%)	3 (10%)	5 (17%)	0.245
Coronary Artery Disease, n (%)	17 (59%)	4 (14%)	0.009
Myocardial Infarction, n (%)	6 (21%)	2 (7%)	0.445
Diabetes, n (%)	9 (31%)	6 (21%)	0.999
Medications			
Anti-Arrhythmia, n (%)	5 (17%)	0 (0%)	0.070
Anti-Coagulant, n (%)	3 (10%)	3 (15%)	0.677
Aspirin, n (%)	23 (79%)	9 (45%)	0.017
ACE/ARB, n (%)	25 (86%)	8 (40%)	0.002
Diuretic, n (%)	13 (49%)	7 (35%)	0.563
Statin, n (%)	19 (66%)	8 (40%)	0.090

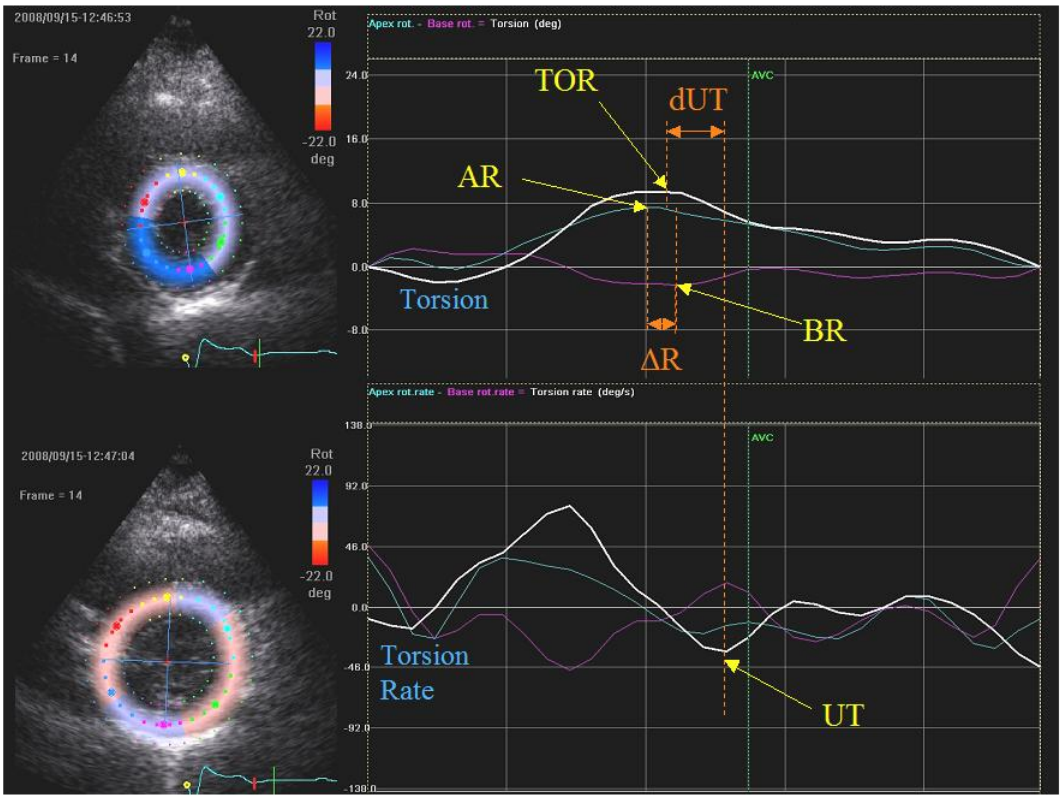
Table 2: Echocardiographic analysis of left ventricular (LV) size, function and dyssynchrony.

Variable	HF (n = 29)	RVP(n = 20)	P-value
LV Size and Systolic Function			
EF (%)	42.8 ± 3.3	42.5 ± 4.6	0.772
LV EDV (ml)	112.1 ± 22.8	93.6 ± 25.1	0.010
LV ESV (ml)	63.9 ± 14.6	54.3 ± 17.0	0.039
GSCS (mm)	5.6 ± 1.3	6.1 ± 1.6	0.208
M-RS (%)	25.5 ± 12.2	29.7 ± 15.8	0.315
LV Diastolic Function			
MV E Velocity (cm/s)	0.75 ± 0.21	0.76 ± 0.21	0.883
MV A Velocity (cm/s)	0.71 ± 0.20	0.85 ± 0.27	0.029
MV E/A Ratio	1.24 ± 0.72	1.16 ± 1.23	0.795
MV Deceleration Time (ms)	220 ± 84	231 ± 53	0.639
E/E'	19.6 ± 10.6	19.0 ± 8.7	0.641
Dyssynchrony			
SD-TT (ms)	60.7 ± 27.7	54.4 ± 32.9	0.473
SD-RS (ms)	60.7 ± 50.7	57.3 ± 45.3	0.817
IM-S (#)	0.9 ± 1.8	1.9 ± 1.7	0.045
IM-L (#)	1.2 ± 2.0	1.0 ± 2.0	0.659

Table 3: Rotational and torsion measurements by speckle tracking echocardiography.

Variable	HF (n = 29)	RVP(n = 20)	P-value
Basal Rotation (°)	-5.8±2.7	-4.8±4.3	0.374
Apical Rotation (°)	5.6±2.8	2.7±7.5	0.131
Torsion (°)	10.6±4.2	6.2±7.3	0.031
Untwist Rate (°/s)	73±55	70±61	0.845
Rotational Dyssynchrony (ms)	91±89	145±123	0.098
Untwisting Delay (ms)	102±73	188±141	0.028

Figure 1: STE images of apical (top image, blue trace) and basal (top image, red trace) LV rotations, torsion (top image, white trace) and untwisting rate (lower image, white trace) in a paced subject.



CHAPTER 6. CONCLUSION

Overview of Research Implications

The use of artificial cardiac pacemakers has become widespread since the development of the first wearable version in 1957. Pacemaker and lead designs of today offer a wide variety of options intended to better mimic the activation patterns of normal, healthy hearts. Ventricular pacing impulses, in cases of AV conduction abnormalities, have traditionally been delivered by a lead placed in the RV apex. While improving symptoms of conduction disease, mounting evidence indicates that long-term pacing of this type is detrimental to cardiac function in a significant proportion of patients.

Lead delivery systems have evolved which allow greater flexibility in the choice of ventricular lead location. In addition, multiple ventricular leads can now be implanted in an attempt to produce a more synchronous and physiologic contraction pattern. The 3-dimensional cardiac mechanics imposed by these various pacing modalities have previously been difficult to ascertain. More recent advancements in echocardiography, including TDI and STE, now enable researchers and physicians to make detailed measurements of heart motion. A deeper understanding of the mechanical consequences of acute and chronic pacing may improve the treatment of patients needing ventricular pacing. The previous three chapters of this thesis describe novel findings that further the understanding of the mechanical consequences of RV pacing.

Summary of Chapter Three Results

Chapter three described in detail the effects of different possible ventricular pacing configurations on LV motion. Global LV pump function was most impaired during RV apical pacing, best preserved during LV free wall pacing, and intermediate when both of these ventricular sites were paced simultaneously. Strain and dyssynchrony measurements mirrored the differences in pump function. This was more evident in longitudinal measurements and when measured at the apex and mid-ventricle. Rotational motion was altered differently than strain, however, and was most impaired when the LV was paced, either alone or in combination with the RV. This may indicate that rotational and longitudinal motion compensate for one another. However, this study suggests that LV free wall and biventricular pacing may better preserve global LV function, in spite of reduced rotational function, in patients with normal LV function who require ventricular pacing. The long-term consequences associated with these pacing-induced mechanics remain to be determined.

Summary of Chapter Four Results

In chapter four of this thesis, chronically RV-paced patients were compared to age-matched, non-paced control subjects. Echocardiographic analysis showed reduced LV systolic function, along with significant longitudinal, radial, and intramural (within the septal wall, as opposed to between-walls) systolic dyssynchrony, in paced subjects as compared to the non-paced group. Intramural dyssynchrony was modestly associated with EF, suggesting that uncoordinated motion within the septum may be an important factor in pacing-induced LV functional impairment.

In addition, no differences were seen between patients paced from the apex of the RV, and those paced from the septum. While the number of subjects was small, the lack of any indication of improvement with septal pacing is in agreement with a number of larger studies that have failed to identify differences between these pacing sites. Other studies, however, have described significant differences in apical and septal RV pacing. Thus the benefit of pacing from the septum, rather than the apex of the RV, remains open to further study.

Summary of Chapter Five Results

Chapter five compared the structural and mechanical differences between age, gender and EF-matched HF patients that were either RV paced or did not have pacemakers. Patients paced from the RV had smaller LV volumes and greater intramural dyssynchrony within the septum than non-paced HF patients. In addition, RV-paced patients had reduced LV torsion, greater apex-to-base rotational dyssynchrony, and delayed untwisting. These differences suggest that pacing produces a distinct functional and structural HF phenotype, and that previous RV pacing might be a factor impacting the treatment of patients with HF. In particular, the criteria used to determine the appropriateness of CRT might be different for RV-paced and non-paced HF patients.

The results of chapters three and five may appear to conflict with respect to the impact of RV pacing on LV rotation and torsion. In chapter three it was reported that

acute RV apical pacing maintained normal rotational motion, while in chapter five, chronically RV-paced patients exhibited greater rotational dysfunction than EF-matched subjects. Together these findings may be interpreted to suggest that rotational motion is maintained in acute pacing as a compensatory mechanism, but this compensation is not sustained in chronic pacing. While rotational motion is important to normal cardiac function, the significance of altered rotational motion in paced patients requires further clarification before these measurements are useful in clinical practice.

Clinical Significance of Presented Research

It was noted in chapter four that some chronically RV-paced patients had developed LV mechanical dyssynchrony and suffered from reduced LV function, while others maintained normal function. So in treating these patients it is important to perform regular examinations to detect and treat LV dysfunction. It was found in chapter four that the duration of pacing was not a significant predictor of LV dysfunction. So annual follow-up, including echocardiography exams with TDI or STE, are important in identifying and treating patients with pacing-induced dysfunction. Since all patients included in the study described in chapter four had been paced for at least 1 year, it is possible that much of the LV dysfunction described in that chapter began within the first year of pacing. Therefore more frequent follow-up during the first year or two of pacing might be beneficial.

The results of chapters four and five regarding intramural dyssynchrony may be useful in identifying pacing-induced LV dysfunction. Intramural dyssynchrony appears to be more sensitive to pacing-induced dysfunction that more common echocardiographic measurements of LV function and dyssynchrony. The measurement of intramural dyssynchrony is a relatively simple, and has been utilized at the St. Paul Heart Clinic to identify paced patients who might benefit from the placement of an additional LV lead to establish biventricular pacing and improve mechanical synchrony. In particular, echocardiograms, with TDI, should be performed in RV-paced patients before generator replacement. Since these patients will require surgery for a battery change-out, implanting a biventricular pacemaker at this time may be convenient and cost-effective.

Suggestions for Future Research

Since ventricular pacing is currently the only treatment alternative for patients with AV conduction dysfunction, it is important that future research continues, in order to reduce the adverse long-term consequences of this therapy. While a significant proportion of RV-paced subjects develop LV dysfunction, many do not. The identification of those patients at greatest risk for pacing-induced complications would be an important step in reducing the incidence of HF in this population. Investigations into alternate lead locations, including the RVOT, the septum, the bundle of His, and multiple ventricular sites (i.e. biventricular pacing) also offer the promise of reducing pacing-induced dysfunction in patients who require ventricular pacing. Furthermore, continued advances in imaging technologies, such as three-

dimensional echocardiography, may improve our ability to detect abnormal motion of the heart and simplify the clinical application of these findings.

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