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## Right Ventricular Pacing and Mechanical Dyssynchrony

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### 1. Introduction

Since the development of the first wearable cardiac pacemaker in 1957, electrical pacemaker devices have become common treatment options for a number of cardiac conditions. Dual chamber pacemakers are routinely used to treat patients with atrioventricular (AV) 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 (Birnie et al. 2006). On average, pacing reduces symptoms, and improves quality of life, exercise capacity, and survival (Gammage et al. 1991; Lamas et al. 1995; Sweeney et al. 2007). However, chronic RV pacing may be detrimental to cardiac function and lead to heart failure (HF) in some patients.

The mechanisms responsible for RV pacing-induced HF are not fully understood. However, since RV pacing induces a slower myocyte-to-myocyte propagation of the electrical activation wavefront throughout both the RV and left ventricle (LV), rather than rapid propagation through the His-Purkinje network, surface electrocardiograms exhibit a wide QRS complex and bundle branch block pattern, characteristic of electrical dyssynchrony. Locations nearest to the pacing lead are 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 LV may lead to the reduced LV function and increased incidence of HF.

### 2. 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. After transduction through the AV node, depolarization is rapidly spread throughout the LV via the bundle of His, the left and right bundle branches, and the Purkinje network. Electrical activation is nearly simultaneous within the LV, with the apex activated just a few milliseconds before the base (Sengupta et al. 2005), and the endocardium activated just a few milliseconds before the epicardium (Ashikaga et al. 2007; Sengupta et al. 2005). Repolarization, occurs in the reverse fashion, with the base repolarizing first, followed rapidly by the apex (Sengupta et al. 2005).

The LV is comprised of layered myocardial fibers arranged in a double helical pattern, 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 (Ashikaga et al. 2004; Buckberg 2002; Torrent-Guasp et al. 2004). The orientation of the myocardial fibers results in intricate three-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 (Sengupta et al. 2005). The rapid electrical transmission throughout the ventricle results in synchronous radial motion at any cross-sectional level of the long axis of the LV (Tops et al. 2007).

Rotational motion is controlled not only by the fiber orientation, but also by the relative strength of the forces generated by the contracting epicardium and endocardium. 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, and generate a clockwise rotation during systole. 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 (Buckberg et al. 2006). 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% (Buckberg 2002; Torrent-Guasp et al. 2004). Maintaining this efficient pumping mechanism may be critical to ensuring proper cardiac function.

### 3. 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. (Marwick and Schwaiger 2008) 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. (Kolb et al. 2001) Echocardiography is a relatively inexpensive and commonly used imaging technique that can be safely used in patients with cardiac devices. This chapter will focus on echocardiographic techniques used to measure many aspects of cardiac function which are affected by RV pacing.

3.1 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) (Sogaard et al. 2002b; Yu et al. 2004). This technology measures the velocity of myocardial motion along the path of incidence of the ultrasound beam. The motion of the heart during a full cardiac cycle 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 throughout the LV 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.

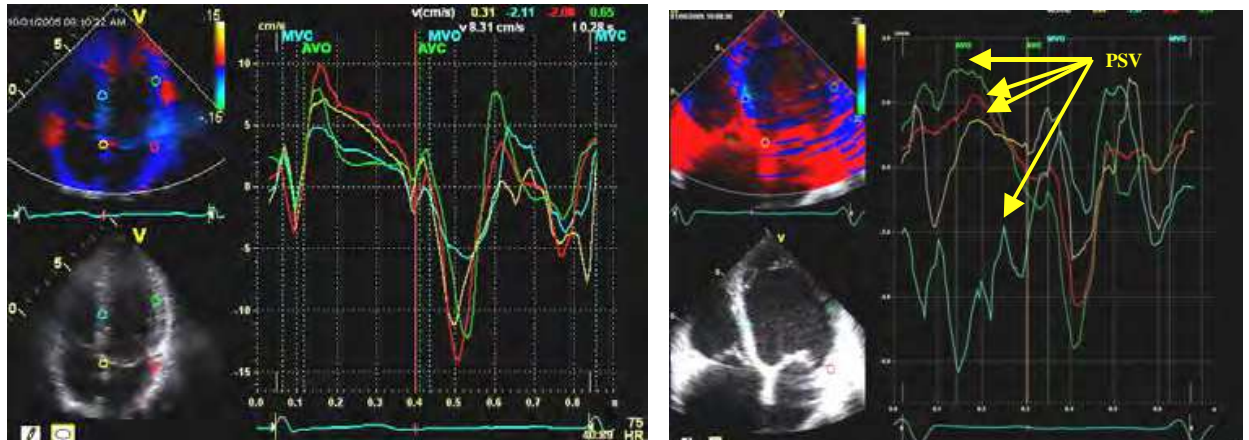


Fig. 1. Apical 4-chamber TVI images of a normal heart (left panel), and a dyssynchronous heart (right panel.) In the normal heart, the systolic velocity curves of each wall segment overlap and reach peak systolic velocity (PSV) at the same time. In the dyssynchronous heart, peak velocity occurs at different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

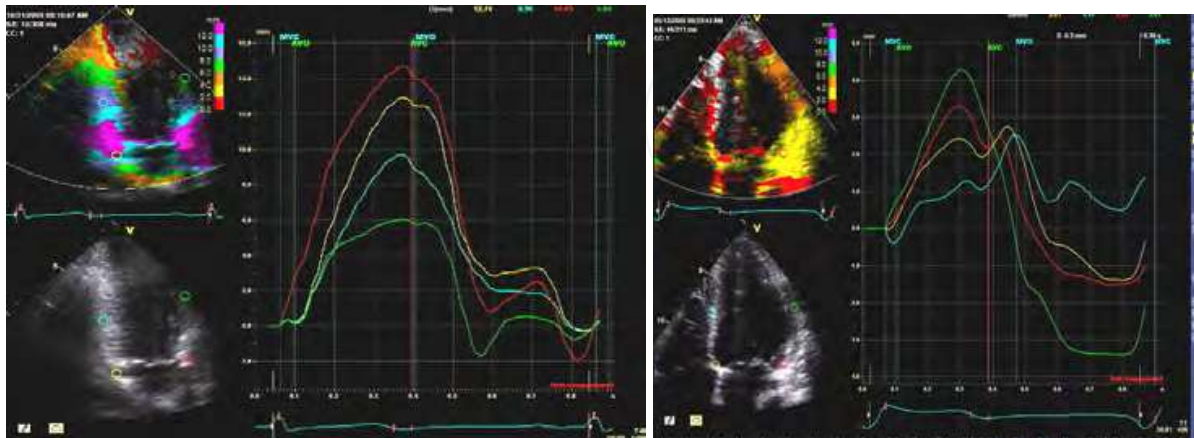


Fig. 2. Apical 4-chamber TT curves of a normal (left panel) and dyssynchronous (right panel) heart. In the normal heart, all wall segments reach peak displacement at the same time, at aortic valve closure. In the dyssynchronous heart, wall segments do not reach peak displacement at the same time, and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



The use of TVI for assessing the synchrony of the contracting myocardium is widely supported in the literature (Bax et al. 2004; Gorcsan et al. 2004; Suffoletto et al. 2006; Yu et al. 2005). 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 (Bank and Kelly 2006; Bogunovic et al. 2009).

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 HF, who may benefit from cardiac resynchronization therapy (CRT).

### 3.2 Speckle tracking echocardiography

Speckle tracking echocardiography (STE) has more recently been applied to analyze heart function (Helle-Valle et al. 2005; Suffoletto et al. 2006). 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, which is fairly 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.

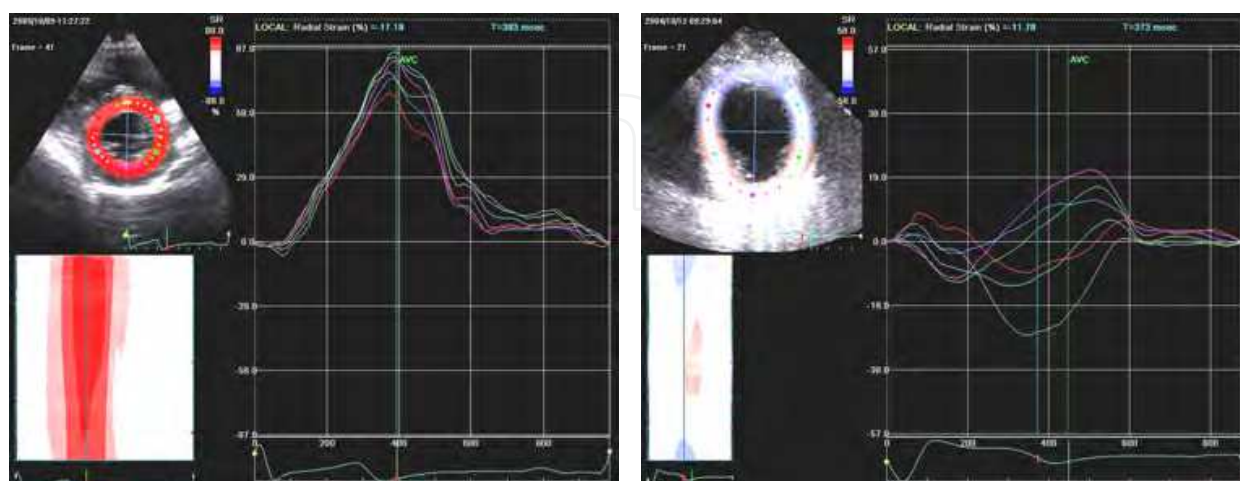


Fig. 3. STE images of radial strain in a normal (left panel) and dyssynchronous (right panel) heart. In the normal heart, strain curves overlap, while in the dyssynchronous heart strain patterns are very different for different wall segments.

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 (Borg et al. 2008; Chung et al. 2006; Delhaas et al. 2004; Dohi et al. 2008; Kanzaki et al. 2006; Suffoletto et al. 2006; Tops et al. 2007).

#### 4. 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 two-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.

##### 4.1 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 to measure longitudinal motion. A 12-segment model of the LV is commonly 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 (Sogaard et al. 2002a). A normal adult LV will shorten by 8-10 mm during systole, while the LV of HF patients may shorten 4-5 mm or less (Bank et al. 2009).

Longitudinal dyssynchrony 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) (Yu et al. 2005; Yu et al. 2006). A cut-off of 32 ms has been used to indicate clinically significant dyssynchrony (Yu et al. 2005).

Dyssynchrony can also be measured with TT in a method analogous to the Yu method (SD-TT), which may result in a more reproducible measurement (Bank et al. 2009; Kaufman et al. 2010). SD-TT may range from less than 50 ms in a normal heart to over 80 ms for a CHF patient's heart (Bank et al. 2009). Tissue displacement curves tend to be smoother than velocity curves, with fewer jagged peaks, and thus less difficulty occurs in differentiating isovolumic peaks from systolic peaks (Kaufman et al. 2010).

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 (Bank et al. 2010b; Burns et al. 2011). A pattern of paradoxical motion within a wall has been termed intramural dyssynchrony, and is depicted in Figure 4. This particular measurement of dyssynchrony appears to be a good indicator of pacing-induced LV dysfunction (Burns et al. 2011).

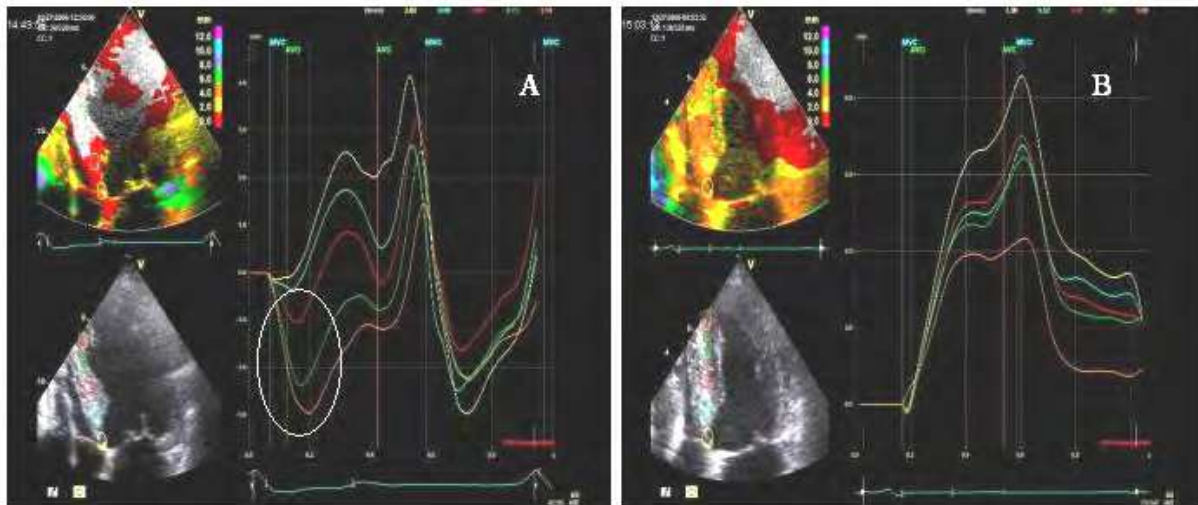


Fig. 4. Intramural dyssynchrony within the septum of a chronically RV-paced patient before (panel A; paradoxical motion is circled), and after (panel B) upgrade to CRT.

#### 4.2 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 central 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 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 (Bank et al. 2009; Kaufman et al. 2010). Mean radial strain is approximately 50% in normal, healthy subjects and 15% in CHF patients (Kaufman et al. 2010; Ng et al. 2009). 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 (Bank et al. 2009; Donal et al. 2008; Kaufman et al. 2010; Suffoletto et al. 2006). In healthy hearts, SD-RS is typically under 20 ms, while it can be over 80 ms in CHF patients (Donal et al. 2008; Kaufman et al. 2010).

#### 4.3 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 (Geleijnse and van Dalen 2009). The more recent work of Torrent-Guasp and others has led to renewed appreciation for the relationship between cardiac structure and function, and the importance of LV rotational motion on systolic and diastolic performance (Torrent-Guasp et al. 2004).

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  $-2.0^{\circ}$  to  $-4.6^{\circ}$ . Peak rotation at the apex may range from  $5.7^{\circ}$  to  $11.2^{\circ}$ . Maximum systolic torsion in normal hearts has then been found to range from  $6.1^{\circ}$  to  $14.5^{\circ}$  (Helle-Valle et al. 2005; Kanzaki et al. 2006; Nakai et al. 2006; Notomi et al. 2005; Notomi et al. 2005; Notomi et al. 2006; Takeuchi et al. 2006). An example of the rotational motion of a normal, healthy heart is presented in Figure 5 below.

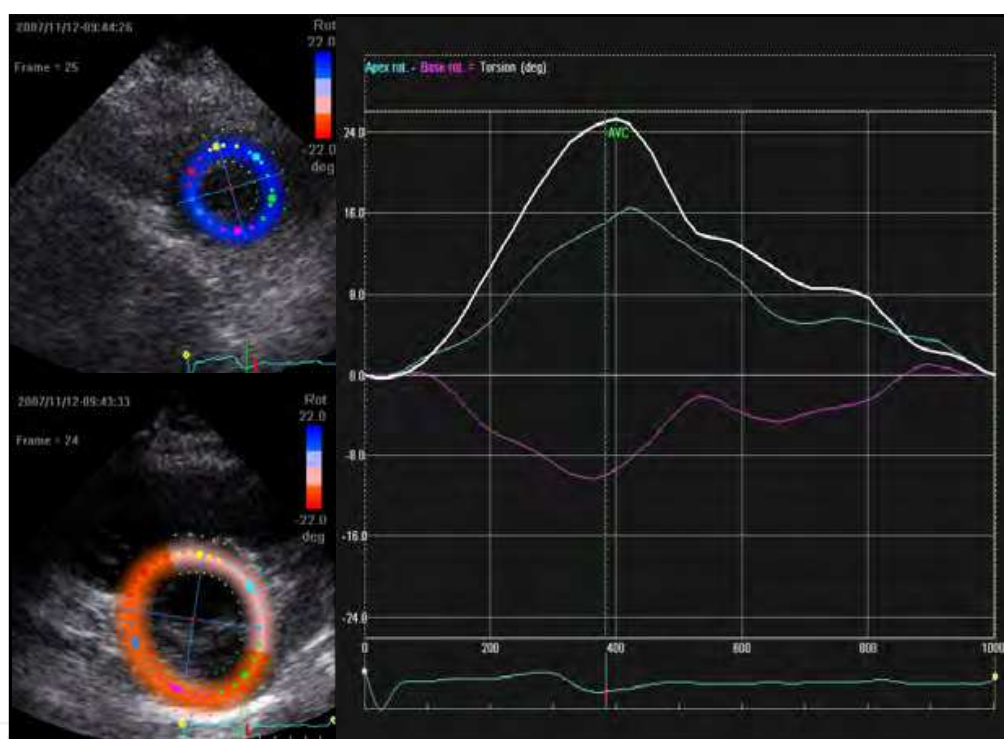


Fig. 5. Rotational motion in a normal heart. The base of the LV (pink line) rotates in a counter-clockwise direction during systole, while the apex (blue line) rotates in the opposite direction. The net difference between the rotation of the base and apex is torsion (white line).

An important consequence of systolic torsion may be the subsequent recoil of the LV during early diastole (Notomi et al. 2008; Shaw et al. 2008). Notomi et al. demonstrated in canines that untwisting coincided with relaxation of the LV, and preceded suction-aided filling (Notomi et al. 2008). The magnitude of untwisting rate also correlated with systolic torsion, relaxation time constant, and intraventricular pressure gradient. A reduced and delayed peak untwisting rate was found to occur with increasing age (Notomi et al. 2006) and in patients with dilated cardiomyopathy (Saito et al. 2009). However, in patients with isolated diastolic dysfunction, peak untwisting increased in mild cases, but was depressed in severe



cases (Park et al. 2008). 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 (Borg et al. 2008). Thus the timing and magnitude of peak diastolic untwisting rate may provide useful information about LV diastolic function.

## 5. Effects of RV pacing

In the United States, approximately 180,000 RV pacemakers are implanted each year (Birnie et al. 2006). Cases of sinus node dysfunction account for 58% of these procedures, while 31% are due to high grade AV block (due to ablation procedures, or other causes) (Birnie et al. 2006). RV pacing has been shown to improve symptoms, exercise capacity, quality of life and survival in these patients (Gammage et al. 1991; Lamas et al. 1995; Sweeney et al. 2007). However, permanent RV pacing has been associated with an increased risk of LV dysfunction, hospitalization, HF, and death (Hayes et al. 2006; Lieberman et al. 2006; O'Keefe et al. 2005; Sweeney et al. 2003; Tse and Lau 1997; Wilkoff et al. 2002). In 2002, the results of the DAVID trial revealed that RV paced patients with LV dysfunction, requiring a defibrillator, 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 (Wilkoff et al. 2002). The percentage of patients who develop pacing-induced LV dysfunction is not clear. However estimates range from 25-50% (O'Keefe et al. 2005; Thackray et al. 2003; Tops et al. 2006; Tse and Lau 1997). 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 (Zhang et al. 2008b). It has also been noted that although chronically paced subjects can exhibit reduced systolic function, similar to HF patients, their ventricles do not appear to dilate as much (Bank et al. 2010a; Burns et al. 2011). Thus RV pacing may induce a unique HF phenotype.

### 5.1 Effects of RV pacing on systolic function

Since RV pacing artificially stimulates the ventricles at a location other than the His-Purkinje 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 (Prinzen et al. 1990; Prinzen et al. 1999; Wyman et al. 1999). 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.

### 5.2 Effects of RV pacing on longitudinal systolic function

Studies of the effects of RV pacing on longitudinal mechanics have focused on measuring mechanical dyssynchrony. In a study of 26 patients with normal LV function who were acutely paced from multiple locations within the heart, our lab found that RV apical pacing

reduced LV systolic function and increased dyssynchrony (Bank et al. 2010b). As described in the animal studies above, we also found that abnormalities were most prominent near the pacing site, as demonstrated in Figure 6. Pacing from the LV free wall best preserved LV function and synchrony, while simultaneous pacing from both the RV apex and LV free wall yielded intermediate results.

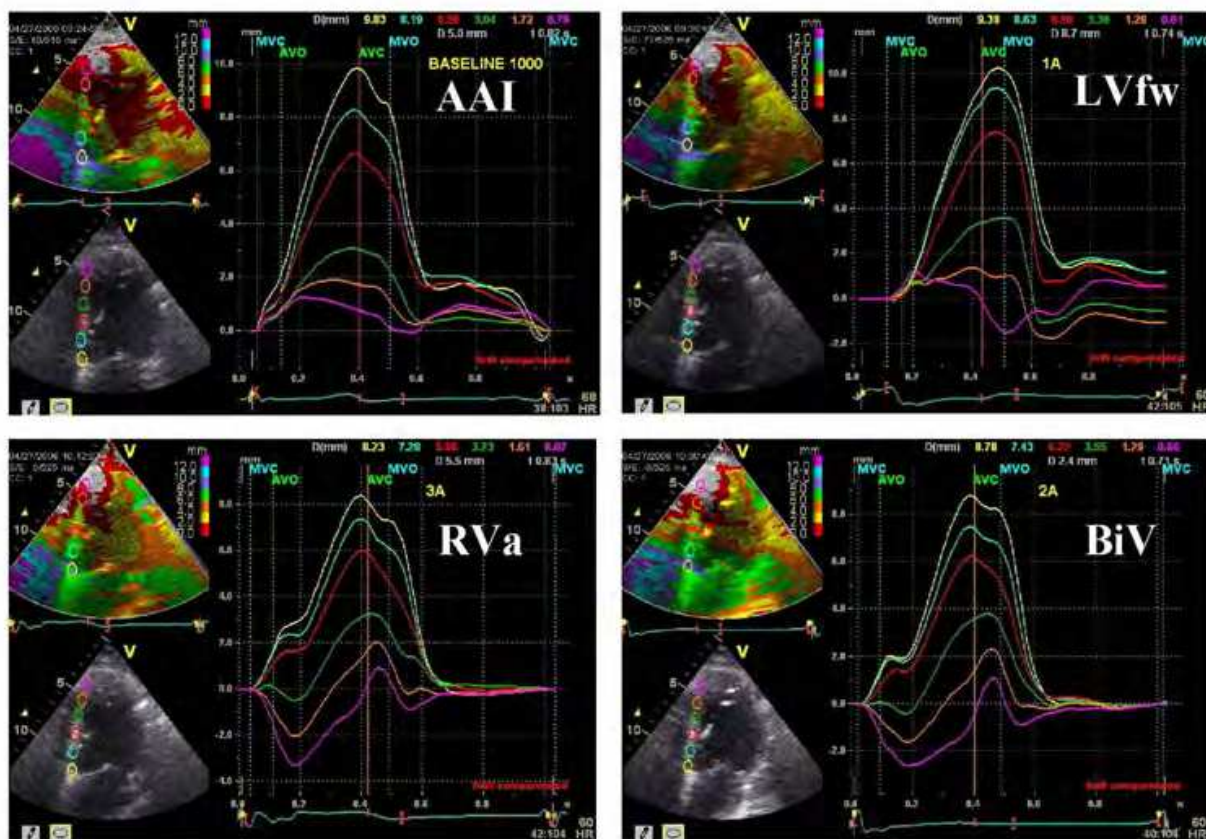


Fig. 6. Intramural TT of the septal wall from a patient with normal LV function paced from the right atrium (AAI), LV free wall (LVfw), RV apex (RVa), and both the LVfw and RVa simultaneously (BiV). Note that the apical regions on the septum are most impaired in cases where the RVa is actively paced (RVa and BiV).

Other studies have also found that paced subjects have greater systolic dyssynchrony, as quantified by SD-TVI, while paced from the RV, even when paced subjects had normal EF (Kawanishi et al. 2008; Zhang et al. 2008b). The degree of longitudinal systolic dyssynchrony was similar to that of a group of HF patients with EF of less than 35% (Zhang et al. 2008a). 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 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 (Kawanishi et al. 2008). Mechanical dyssynchrony was modestly correlated with BNP, but no correlations between dyssynchrony and EF were presented. In contrast, 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 (Ng et al. 2009). In our lab we compared patients with high degree AV block, but otherwise normal LV function prior to the initiation of RV pacing to 25 non-paced, age and gender matched controls (Burns et al. 2011). Paced subjects had been paced for at least 1 year prior to the study, and detailed echocardiographic analysis was performed. Chronically paced subjects had significantly lower EF, and greater longitudinal dyssynchrony than non-paced controls.

Acute RV pacing has been shown to increase intramural dyssynchrony in normal hearts, without an increase in between-wall dyssynchrony (Bank et al. 2010b). After chronic pacing, intramural dyssynchrony has been shown to persist, while intraventricular dyssynchrony may also become apparent (Burns et al. 2011). 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.

### **5.3 Effects of RV pacing on radial systolic 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 (Tops et al. 2007). 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. In our lab, we have found that patients with chronic RV pacemakers have reduced EF and mean peak systolic radial strain. The radial dysfunction is similar between RV paced patients, and HF patients having the same ejection fraction (Burns et al. 2011). In both our study, and that of Ng (Ng et al. 2009) radial dyssynchrony was not different between non-paced controls and RV paced subjects. It appears that radial dysfunction in this case may be reflective of the global reduction in systolic function, and may not be unique to RV pacing.

### **5.4 Effects of RV pacing on rotational systolic 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 RV pacing and biventricular pacing using MRI in 5 canine hearts (Sorger et al. 2003). 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 (Liakopoulos et al. 2006; Tomioka et al. 2006). Torsion 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.

In chronically paced humans, it has been found that both basal and apical peak rotation, and peak systolic torsion were lower than in age-matched non-paced controls (Burns et al. 2011). In addition, apical rotation was found to be in the reverse direction from normal in about 1/3 of paced patients. By comparison, HF patients who had similar EF to the chronically paced subjects, did not exhibit reversed rotational direction, and had higher peak systolic

torsion than paced subjects (Figure 7). This study suggests that pacing alters rotational function, and the alteration is not simply due to reduced systolic function.

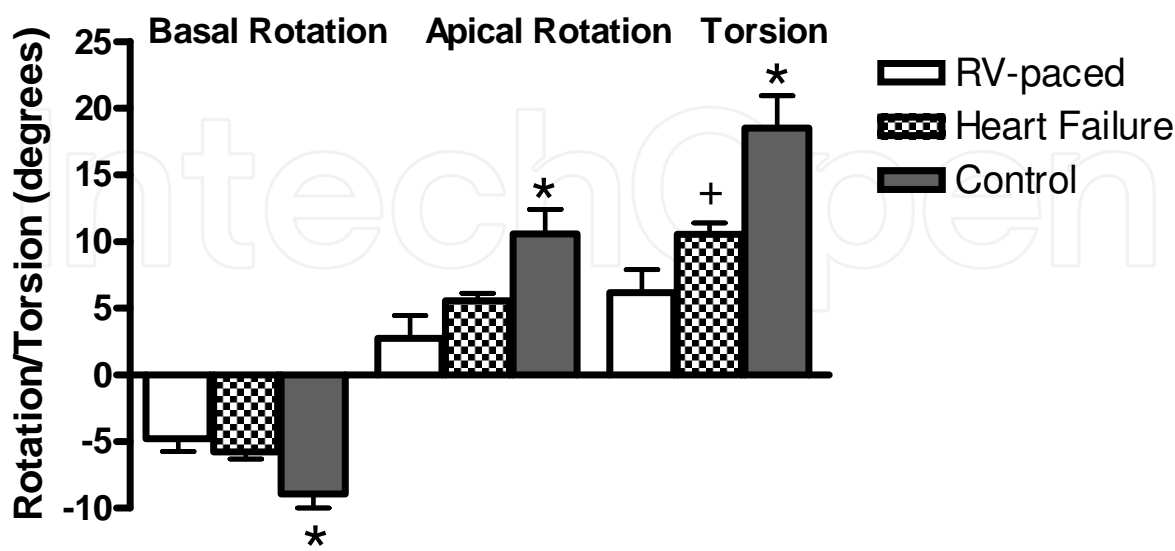


Fig. 7. Rotational function in chronically RV paced patients, heart failure patients with EF matched to the paced group, and healthy controls. \* Indicates  $p < 0.05$  when compared to RV paced and heart failure groups. + Indicates  $p < 0.05$  when compared to RV paced group.

6. Minimizing the risk of pacing-induced dyssfunction

The long-term risks associated with RV pacing have been well documented, and several treatment alternatives have been explored, including minimizing pacing frequency, alternate RV lead location, and biventricular pacing.

6.1 Reducing pacing frequency

One method of minimizing the negative affects of chronic RV pacing is to reduce the number of heart beats that are artificially paced. A sub-study from the DAVID trial revealed that outcomes in that trial were explained primarily by pacing frequency (Sharma et al. 2005). Patients paced more than 40% of the time were more likely to die or be hospitalized for HF than those paced less frequently, regardless of the pacing mode. Similarly, the primary objective of the MOST trial was to compare single chamber RV pacing to dual chamber pacing. However, in a sub-study which included 707 dual chamber patients with narrow pre-pacing QRS durations, both HF hospitalizations and incidence of atrial fibrillation increased significantly with increasing pacing frequency (Sweeney et al. 2003). Again, those paced more than 40% of the time had worse outcomes than those paced less. Finally, the SAVE PACE trial tested an algorithm specifically designed to minimize the frequency of ventricular pacing (Sweeney et al. 2007). Minimal RV pacing significantly reduced the development of atrial fibrillation. However this study included a follow-up period of only 1.7 years, so mortality and HF rates were low, and no difference was noted between the minimally-paced, and frequently-paced groups. In total, these studies



demonstrate that reducing the frequency of RV pacing is beneficial. However, in patients with high grade AV block, for example, ventricular pacing is required, and the frequency cannot be reduced. In these cases, other methods of attenuating the negative effects of RV pacing can be explored.

## 6.2 Alternate lead location

The RV apex is a readily accessible location to implant pacing leads, and has been the standard pacing site. However mounting evidence has indicated that this results in a dyssynchronous contraction pattern in the LV, and increases the risk of developing HF. As a result, many investigators have explored alternate lead locations within the RV, which may create a more physiological activation pattern and reduce the risks associated with apical RV pacing. The RV outflow tract (RVOT), the RV septum, and the His bundle have been the most commonly studied alternate pacing sites.

The most common alternate pacing site has been the RVOT. Several studies have demonstrated acute improvements in LV function and dyssynchrony, as compared to apical pacing. In a cross-over study of the acute effects of RVOT pacing, compared to apical pacing in 20 patients, Yamano and colleagues found RVOT pacing resulted in superior radial synchrony using STE, as well as better coronary blood flow dynamics (Yamano et al. 2010). Leong, et al. also showed that longitudinal LV function was better in RVOT pacing than in apical pacing in a randomized trial of 58 patients who were followed for an average of 29 months (Leong et al. 2010). Tse, et al., measured regional wall motion abnormalities in a long-term study of 24 patients with complete atrioventricular block paced from either the RV apex or RVOT for a period of 18 months (Tse et al. 2002). Changes in perfusion and dyssynchrony were not different between pacing sites after 6 months, but RVOT pacing resulted in significant reductions in perfusion defects and dyssynchrony after 18 months.

However, several studies have also failed to find any benefit from RVOT pacing. An early study of 16 patients by Victor and colleagues, in 1999, showed that pacing from the RVOT resulted in no difference in QRS duration, ejection fraction, New York Heart Association (NYHA) functional class, or exercise capacity after three months of pacing (Victor et al. 1999). Similarly, Stamber et al. performed a multi-center, randomized trial of apical RV pacing compared to RVOT pacing (Stamber et al. 2003). Patients in this trial were randomly assigned to three months of pacing from one site, followed by three months of pacing from the other site. No significant differences were found in NYHA functional class, ejection fraction or exercise capacity between the two pacing sites. Importantly, 2 recent studies have failed to demonstrate any survival (Dabrowska-Kugacka et al. 2009) or LV remodeling (Gong et al. 2009) benefit of RVOT pacing over RV apical pacing.

Pacing from the RV septum has also been investigated as a potentially superior pacing site, as compared to the RV apex. Schwaab, et al., showed in 1999 that QRS complex duration and EF were both improved acutely with pacing from the RV septum as compared to the RV apex (Schwaab et al. 1999). Only 14 patients were included in this cross-over study. In a recent pair of studies, Inoue and colleagues have used STE to demonstrate that septal pacing resulted in better longitudinal function, less longitudinal dyssynchrony, and better rotational function than apical pacing (Inoue et al. 2010; Inoue et al. 2011). Similarly, Cano, et al. showed that LV dyssynchrony was lower in a 32 patients randomly assigned to septal pacing, as compared to 28 apically paced patients (Cano et al. 2010). However, after a 1-year

follow-up, no differences were detected in quality of life scores, NYHA classification, or exercise capacity. In another study by Cho and colleagues, however, TDI measures of longitudinal dyssynchrony were not different between apically and septally paced patients (n=45 and 34, respectively) (Cho et al. 2011).

A few smaller studies have suggested that pacing at or near the His bundle may also produce less dyssynchrony and better LV function than RV apical pacing. A recent study indicated that His bundle pacing is practical, and can be achieved in approximately 85% of patients, and results in nearly normal LV activation patterns (Kronborg et al. 2011). In an acute study of LV mechanics, His bundle pacing resulted in less dyssynchrony and better LV function, as compared to acute RV apical pacing in 23 patients (Catanzariti et al. 2006). Similarly, His bundle pacing was found to reduce LV dyssynchrony using TDI, as well as preserve coronary circulation and reduce mitral regurgitation, as compared to RV apical pacing in a cross-over study of 12 patients who were paced for 3 months from each site (Zanon et al. 2008).

In summary, many studies have demonstrated benefits of pacing from sites other than the RV apex, but several studies have also contradicted these results. Alternate site pacing studies have been fairly small, with limited follow-up time. Large scale, randomized, prospective trials comparing RV pacing sites are needed to clarify the potential benefits.

### 6.3 Biventricular pacing

Another method of inducing a more synchronous contraction of the LV is to utilize biventricular pacing, or CRT. As is common in HF patients with dyssynchronous contraction, pacing both the LV and RV in a coordinated fashion may retain synchrony in patients requiring permanent pacing, and prevent LV dysfunction.

The benefits of CRT over standard dual chamber RV pacing were investigated in the HOBIPACE trial, a randomized, cross-over study of 30 patients with AV block and existing LV dysfunction (Kindermann et al. 2006). In these patients, after 3 months of treatment, CRT was found to be superior in terms of LV volumes, EF, quality of life scores, and exercise capacity. Yu and colleagues extended these findings to also include patients without LV dysfunction prior to pacing (Yu et al. 2009). Their study included 177 patients randomly assigned to either CRT or RV apical pacing. Patients receiving CRT had significantly better preserved LV volumes and EF after one year of pacing.

Long-term clinical effects of CRT, as compared to RV apical pacing, were recently examined by Brignole and coworkers (Brignole et al. 2011). In this study, 186 patients undergoing AV node ablation were randomly assigned to CRT or RV apical pacing, and followed for 20 months. Significantly more of the RV paced patients met the clinical composite endpoint of death due to HF, hospitalization due to HF, or worsening HF. This was true both in subgroups of patients meeting standard criteria for CRT ( $EF \leq 35\%$ ,  $QRS \geq 120\text{ms}$ , and NYHA class  $\geq III$ ), and in those not meeting those guidelines.

Although most studies have concluded that CRT reduces LV dysfunction in patients requiring permanent pacing, as compared to pacing from the RV apex, these studies have been relatively small and a number of unanswered questions remain. Many patients paced from the RV apex do not experience any adverse effects, but currently there is no method of

determining which patients will develop HF from RV pacing, and benefit from CRT. Thus the added expense of CRT may not be justified in many patients. Also, studies comparing CRT to dual chamber pacing from alternate lead positions have not been carried out. Further, since CRT utilizes more energy in order to pace both ventricles, battery life is shorter, so more frequent change-out procedures will be required. Similarly, the extra lead required in CRT may increase the incidence of lead-related complications, as compared to dual chamber pacing. The cost-benefit analysis for routinely implanting CRT devices rather than RV pacemakers has not been performed.

## 7. Treatment of pacing-induced heart failure patients

Several studies have indicated that patients who are paced less frequently have better-preserved LV function than those paced more frequently (Sharma et al. 2005; Sweeney et al. 2003; Sweeney et al. 2007). However, the effect of reducing the frequency of pacing in patients who have already developed LV dysfunction remains uncertain. In addition, in cases of high degree AV block, nearly 100% ventricular pacing is required. To date, the best treatment for HF that is associated with chronic RV pacing is CRT. An LV lead can be added, and the patient can be paced from both the RV and LV, thus improving the synchrony of contraction.

In most large, multi-center randomized trials of CRT, patients chronically paced from the RV have been excluded. However, a number of smaller studies have suggested that these patients may experience similar benefits to CRT. Foley et al., reported that survival and hospitalizations rates were similar between a group of 58 RV paced patients upgraded to CRT, and 336 de novo CRT patients (Foley et al. 2009). In addition, significant improvements in a composite clinical score, EF, and LV volumes were reported in both groups, and were similar between groups. Improvements in dyssynchrony have also been reported in previously RV paced CRT patients (Eldadah et al. 2006; Vatankulu et al. 2009).

Improvements in rotational function may also be important mechanisms in functional improvement following upgrade from RV pacing to CRT. As previously discussed, rotational motion is significantly impaired following chronic RV pacing, and apical rotation is reversed in about 30% of patients (Burns et al. 2011). However, it has also been shown, in de novo CRT patients, that CRT improves rotation, and corrects rotational direction (Russell et al. 2009). Although it has not been demonstrated in clinical trials, it is logical that improvements in rotational function are important to the CRT response of previously-paced RV pacing.

We studied 31 previously RV paced HF patients upgraded to CRT and compared them to 49 patients receiving CRT for HF without previous pacing (Bank et al. 2010a). Previously RV paced patients had smaller ventricles despite similar EFs prior to CRT. Following CRT, previously RV paced patients improved their EF to a significantly greater extent than non-paced patients ( $12.8 \pm 9.2\%$  vs  $7.4 \pm 7.6\%$ ). RV paced patients had much more intramural dyssynchrony within the septum before CRT, and as shown previously in this chapter in Figure 4, a much greater reduction following about 1 year of CRT (Bank et al. 2010a). In addition, improvements in intramural dyssynchrony within the septum correlated to improved EF in previously paced patients, while other measures of dyssynchrony did not. This suggests that this pattern of intramural dyssynchrony may result in reduced LV

function in chronic RV pacing, and may be readily corrected with CRT in affected patients. These patients likely developed iatrogenic HF from pacing, which was more readily corrected by improving electrical and mechanical dyssynchrony.

## 8. Summary

The increased risk of LV dysfunction associated with RV pacing has been well established. Similarly, both impaired LV systolic function and mechanical dyssynchrony have been shown to exist in groups of RV paced patients. Intramural dyssynchrony within the septum appears to be a common finding in chronically paced individuals, and may be an important mechanism in pacing-induced LV dysfunction. Similarly, rotational function appears to be more affected by RV pacing, than by other causes of heart failure. The correction of both intramural dyssynchrony and rotational dysfunction may be significant factors in the successful treatment of pacing-induced dysfunction using CRT.

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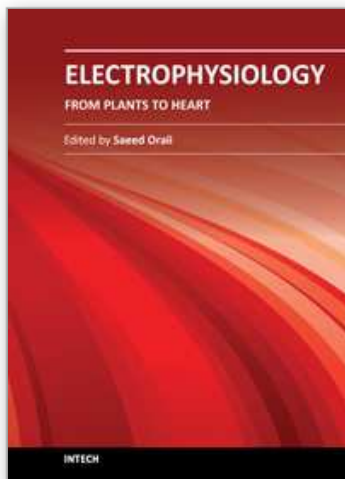
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## **Electrophysiology - From Plants to Heart**

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The outstanding evolution of recording techniques paved the way for better understanding of electrophysiological phenomena within the human organs, including the cardiovascular, ophthalmologic and neural systems. In the field of cardiac electrophysiology, the development of more and more sophisticated recording and mapping techniques made it possible to elucidate the mechanism of various cardiac arrhythmias. This has even led to the evolution of techniques to ablate and cure most complex cardiac arrhythmias. Nevertheless, there is still a long way ahead and this book can be considered a valuable addition to the current knowledge in subjects related to bioelectricity from plants to the human heart.

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