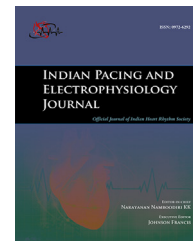


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## Ventricular pacing – Electromechanical consequences and valvular function

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### ABSTRACT

Although great strides have been made in the areas of ventricular pacing, it is still appreciated that dyssynchrony can be malignant, and that appropriately placed pacing leads may ameliorate mechanical dyssynchrony. However, the unknowns at present include:

1. The mechanisms by which ventricular pacing itself can induce dyssynchrony;
2. Whether or not various pacing locations can decrease the deleterious effects caused by ventricular pacing;
3. The impact of novel methods of pacing, such as atrioventricular septal, lead-less, and far-field surface stimulation;
4. The utility of ECG and echocardiography in predicting response to therapy and/or development of dyssynchrony in the setting of cardiac resynchronization therapy (CRT) lead placement;
5. The impact of ventricular pacing-induced dyssynchrony on valvular function, and how lead position correlates to potential improvement.

This review examines the existing literature to put these issues into context, to provide a basis for understanding how electrical, mechanical, and functional aspects of the heart can be distorted with ventricular pacing. We highlight the central role of the mitral valve and its function as it relates to pacing strategies, especially in the setting of CRT. We also provide future directions for improved pacing modalities via alternative pacing sites and speculate over mechanisms on how lead position may affect the critical function of the mitral valve and thus overall efficacy of CRT.

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**Abbreviations:** CRT, cardiac resynchronization therapy; ECG, electrocardiogram; LBBB, left bundle branch block; LV, left ventricle; MR, mitral regurgitation; RBB, right bundle branch; RV, right ventricle; TR, tricuspid regurgitation.

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## Contents

Introduction .....	20
Ventricular pacing effects on the electrical, mechanical, and structural functions of the heart .....	20
Part 1. Electrical activation of the heart, pathophysiology of pacing and why mechanical dysfunction occurs from ventricular pacing .....	20
Part 2. Electrical manifestations that correlate with dyssynchrony .....	21
Part 3. Valvular Regurgitation .....	22
Future directions .....	23
Conclusions .....	25
References .....	26

## Introduction

Cardiac pacing is an established and effective treatment for sinus node disease and atrioventricular block [1,2]. The right ventricular (RV) apex has been the standard pacing site since the development of implantable pacemaker technology because of the relative ease of access, lead stability, and the presumed safety of the right-sided circulation compared to the left (fewer fatal thromboembolic sequelae) [3]. However, several studies have shown that RV apical pacing creates electrical dyssynchrony and has detrimental effects on cardiac structure, function, and can lead to development of atrial fibrillation, valvular regurgitation and severe congestive heart failure [4–12].

Cardiac resynchronization device therapy (CRT) has shown to improve morbidity and mortality in patients with congestive heart failure [13–16], and recent trial data has expanded the indications for its use [17–24]. CRT is thought to improve atrioventricular, intraventricular and interventricular dyssynchrony through the simultaneous activation of the RV and the left ventricle (LV) [1]. The Achilles heel of CRT is the substantial number (up to 1/3) of patients that do not benefit, termed “non-responders” [25].

The utility of baseline electrocardiogram (ECG) in detecting dyssynchrony, together with multiple imaging and device based studies have attempted to identify criteria for improved patient selection, but no single validated and reliable marker has been identified [26–28]. Alternative pacing locations and the impact of novel pacing methods such as atrioventricular, leadless and far-field stimulation from the surface of the heart seem to decrease the deleterious dyssynchronous effects of pacing [29–31].

Finally, pacing-induced dyssynchrony affects valvular function as well. Tricuspid and mitral regurgitation occur or worsen if abnormal ventricular mechanic is present [32–34], and appropriately placed pacing leads can actually improve valvular function through various mechanisms [35–37].

We review the current knowledge on RV pacing and CRT, provide an overview on pacing modalities and mechanisms of dyssynchrony-induced ventricular dysfunction and valvular regurgitation, ways to improve CRT through innovation, and how this can be translated to tangible therapeutic options that are safe, effective, and mechanistically sound.

## Ventricular pacing effects on the electrical, mechanical, and structural functions of the heart

### Part 1. Electrical activation of the heart, pathophysiology of pacing and why mechanical dysfunction occurs from ventricular pacing

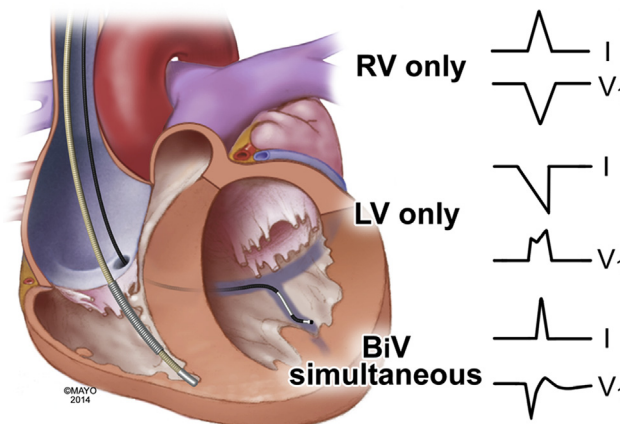
During normal sinus rhythm, electrical activation occurs through the cardiac conduction system. The depolarization wave front spreads sequentially from the atria, to the atrioventricular node, through the His-Purkinje system, resulting in almost simultaneous activation of both ventricles. The result of this is manifesting on ECG as a narrow QRS complex. In contrast, RV apical pacing causes the earliest depolarization to occur at the segment of the RV apex, followed by slow, cell-to-cell spread of the activation wavefront, with latest depolarization at the inferoposterior base of the LV [38]. This produces a wide QRS and a left superior axis on ECG.

RV pacing produces an iatrogenic form of left bundle branch block (LBBB). Native LBBB can cause hemodynamic deterioration due to ventricular dyssynchrony, mainly in patients with heart failure. However, LBBB induced by RV apical pacing seems to lead to worse outcomes when compared to native LBBB, increasing ventricular dyssynchrony [39–41]. The latest LV mechanical activation during RV apical pacing, indeed, is different from that during native LBBB, being more delayed at the baso-lateral LV wall [42].

The abnormal electrical and mechanical activation caused by RV apical pacing reduces stroke volume and causes a right-shift of the left ventricular end-systolic pressure–volume relationship. In addition to hemodynamic consequences, RV apical pacing can worsen coronary blood flow, regional myocardial fiber shortening, and any pre-existing mechanical dyssynchrony [12,43,44]. Moreover, regional patterns of ventricular activation are also altered in a complex manner [45]. Early activation of the RV apex results in vigorous RV apical shortening. Early apical shortening leads to stretching of remote ventricular regions, such as the LV free wall, and subsequent stronger contraction of these regions is needed compared to the local RV apical regions. Another important mechanical effect of RV apical pacing is abrupt posterior motion of the interventricular

septum [46]. This occurs due to earlier development of pressure in the RV compared to the LV and results in a decrease in left ventricular end diastolic volume, and consequently reduction in the cardiac output.

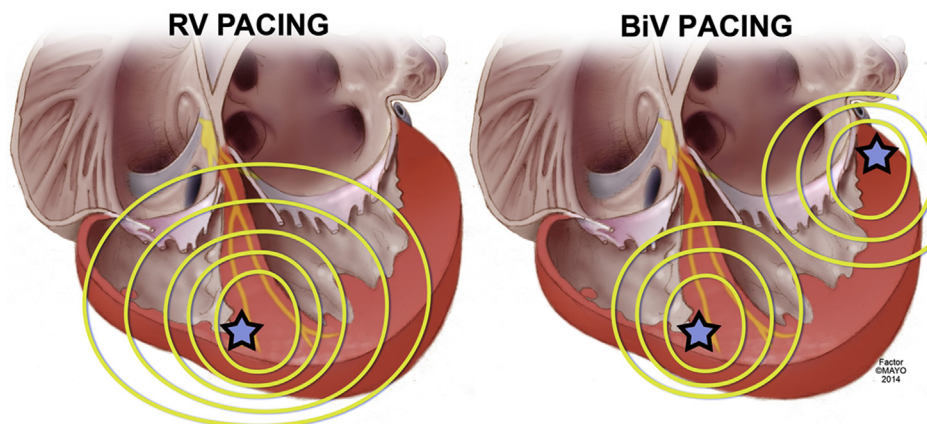
Several studies have shown superiority of CRT compared to standard RV apical pacing in terms of survival and freedom from heart failure both in patients with preserved and reduced ejection fraction [15–23]. Typically, in CRT devices three pacing leads are placed: one in the right atrium, a second one on the endocardial aspect of the RV apex, and a third lead is placed transvenously through the coronary sinus to pace the epicardial wall of the LV. During CRT pacing, the electrical activation of the myocardium occurs again through a cell-to-cell mechanism, but the simultaneous pacing from the RV and the LV leads to a decrease in the electrical delay, increases coordinated contraction between the different walls of the heart, and results in a narrower QRS complex on the surface ECG (Figs. 1 and 2). Simultaneously stimulation of the RV and LV, therefore, should restore a coordinated pumping action. Electrical resynchronization between the RV and LV should eliminate both the LBBB-induced mechanical dyssynchrony due to a preexisting cardiomyopathy and the LBBB-induced dyssynchrony caused by RV apical pacing alone [47]. However, as previously stated, RV apical pacing increases ventricular dyssynchrony compared with intrinsic LBBB. For this reason, if LV pacing alone is performed with such an atrio-ventricular delay able to ensure intrinsic activation of the heart via the right bundle branch (RBB), the fusion of these two depolarization wave fronts should be more effective than biventricular pacing [48–50]. Varma et al. [49] used electrocardiographic imaging to compare RV activation during intrinsic conduction and during pacing in patients with heart failure. Patients with normal RBB-mediated depolarization showed normal RV free wall activation, whereas they developed activation delay when RV pacing was switched on, alone or in a biventricular fashion. These data again suggest that merging of LV paced and intrinsic RBB wave fronts could be beneficial. Moreover, programmability of the inter-ventricular interval between RV and LV stimulation may further improve hemodynamics [51].



**Fig. 2 – Illustration showing RV lead located at the RV apex and LV lead inside the coronary sinus. On right-sided panel, differences in QRS duration in lead I and V1 during RV pacing alone, LV pacing alone, and simultaneous biventricular pacing.**

**Part 2. Electrical manifestations that correlate with dyssynchrony**

Baseline QRS duration is one of the most commonly used parameters in patient selection for CRT, but remains a weak criterion to predict response [52–54]. Current guidelines [1,2] suggest CRT implant in patients with heart failure and QRS duration >150 ms, or with an additional indicator of supposed good response, such as LBBB morphology, if the QRS is 120–150 ms. Right bundle branch block or aspecific intraventricular conduction delay seem to predict no positive effect or even be responsible for negative response to CRT [27]. However, several studies have shown that neither QRS duration at implant nor shortening of QRS after implant necessarily predicts clinical benefit from CRT [28,55–57]. Recently, a study from Del-Carpio Munoz et al. [58] showed that a noninvasive method of determining LV activation delay, by analyzing the time to intrinsic deflection onset on surface ECG, represents a promising alternative to QRS duration to predict CRT



**Fig. 1 – Illustration showing spread of electrical activation of the myocardium during RV apical pacing versus biventricular pacing (simultaneous RV apical and LV lateral wall pacing).**

response. Moreover, a subanalysis of MADIT-CRT trial showed a survival benefit of CRT devices in patients with LBBB compared to the group of patients assigned to defibrillators alone, independently to QRS duration [59]. On the other hand, a recent trial showed that in patients with heart failure and with QRS duration < 130 ms, CRT didn't reduce the rate of death or hospitalization and might even increase mortality, even if mechanical dyssynchrony was present [60].

Electrical dyssynchrony and mechanical dyssynchrony could be two different entities, as explained by the concept of "electromechanical dissociation." [52] Electromechanical coupling interval can significantly be different on a patient-to-patient basis, and not strictly related to the widening of the QRS complex. Electromechanical delay, defined as the time between the regional electrical depolarization and the onset of myocardial fiber contraction, or mechanical activation, is responsible for additional electromechanical dyssynchrony. The mechanical delay between early and late-activated myocardial segments exceeds the delay in electrical activation during LBBB and during pacing-induced dyssynchrony [61,62], aggravating mechanical relative to electrical dyssynchrony.

Moreover, latency from pacing stimulus to the onset of the earliest QRS further impacts on optimal delivery of CRT [63]. Latency has shown to be more prevalent during LV pacing from the epicardial veins than during RV endocardial pacing, possibly due to the longer distance from the subendocardial His-Purkinje system, interposed epicardial fat, venous tissue and slow impulse propagation in scarring and diseased myocardium [64].

It has been thought that ischemic patients have been less responsive to CRT, propagating studies to assess for amount and location of scar to CRT response [65,66]. The amount of scar and its location in the posterolateral segment of the LV appear to be a predictor of CRT non-response [67]. Delayed-enhancement magnetic resonance imaging is a useful tool to predict clinical response to CRT [68–70]. Even if studies showed that scar does not preclude myocardial capture, pacing regions of the myocardium characterized by scar tissue may not be translated into effective mechanical contraction, because both absence of sufficient viable tissue to be recruited with CRT and also because of inadequate synchronization due to scar presence [71]. Moreover, the higher percentage of CRT "non-responders" among patients with ischemic heart disease seems to be ascribed more likely to conduction abnormalities and electrical substrate issues rather than cardiomyopathy etiology itself.

Non-response to CRT appears to be associated to a myriad of electro-mechanical events. Dendy et al. [72] found anodal stimulation as an additional cause of poor response to CRT. Anodal stimulation is defined as capture at the pacing anode instead of cathode and is sometimes unrecognized perioperatively [73]. In patients with CRT, pacing from the LV tip or ring to the coil or ring of the RV lead is often used due to lower pacing thresholds. Pacing configuration of LV to RV can lead to clinically significant anodal stimulation resulting in RV capture during attempted LV pacing. If the benefit from CRT occurs through improvement in LV late depolarization, CRT with anodal stimulation essentially results in RV pacing alone, leading to persistent interventricular and intraventricular

conduction delay to the LV lateral wall. However, Lloyd et al., using left ventricular outflow tract velocity time integral as a marker of response, showed anodal pacing to markedly improve this parameter compared to cathodal pacing in 36/37 recordings [74]. Additionally, controversy exists over whether anodal pacing is beneficial or harmful. This is partially driven by the complexities in defining what an adequate response to CRT is. For example, it can be symptomatic improvement, or a marker of mechanical improvement depending on the fact that an invasive catheter based assessment such as  $dP/dt$  or an echocardiographic based assessment such as ejection fraction,  $dP/dt$ , Doppler is used. Both animal and clinical studies have demonstrated improved mechanical performance by anodal stimulation, and this is thought to be due to activation of larger volume of myocardium, increased amount of sodium available, and more rapid conduction velocity [75,76].

### Part 3. Valvular Regurgitation

The first known association of tricuspid regurgitation (TR) and device implantation was described in 1980 [77]. Since then, several case reports and observational studies have supported this association. Both new onset TR and worsening TR can occur by the mechanical effects of lead implantation or electrical dyssynchrony, which can occur early or late after device implantation [78–81]. Conversely, some small studies have suggested an improvement of TR after pacing [82]. The prevalence of TR is 25%–50% in patients with pacemaker vs no pacemaker [83,84]. The clinical presentation of TR is highly variable, from asymptomatic and incidentally detected on echocardiography, to the more severe clinical presentation of right-sided heart failure. The mechanism of TR after device implantation includes valve tethering, inadequate leaflet coaptation due to the physical presence of lead, lead adherence due to fibrosis and scar formation, lead entrapment in the subvalvular apparatus, valve perforation, valve laceration, and annular dilatation [77,85,86].

Long-term RV apical pacing is also responsible for causing mitral regurgitation (MR) due to LV dyssynchrony. A study from Alizadeh et al. shows how degree of MR can worsen during follow-up in patients with permanent apical RV pacing [32]. There are a few reported cases of acute severe MR as an immediate perioperative complication of pacemaker insertion, leading to acute hemodynamic deterioration, even in patients with preserved LV ejection fraction [87–91]. The mechanism of this includes mitral annular dilatation and abnormal leaflet coaptation perhaps due to the abnormal LV activation sequence [92,93]. It is likely that the inversion of the ventricular activation sequence with RV apical pacing is associated with a delayed reduction of both mitral annulus size and regurgitation orifice size, and this enhances MR severity [35]. Furthermore, if alteration in timing of papillary muscle contraction is corrected with a different lead location in the RV (such as the right ventricular outflow tract) or with a left-sided pacing system, degree of MR has been shown to improve [94].

Moreover, the presence of MR in patients with heart failure, before device implantation, has been showed to be an independent predictor of worsened survival [95,96]. This type of

MR, usually referred as “functional” or “secondary,” is due to dilatation of the left ventricle. Three main mechanisms are involved in secondary MR: 1) mitral annular dilatation, 2) decreased LV global systolic function, responsible for slow rise of intraventricular pressure and slow closure of mitral leaflets, 3) increased LV sphericity with subsequent displacement and malposition of the papillary muscles, leading to decreased longitudinal systolic function and increased mitral valve tethering forces (Fig. 3) [33,34]. Recently, Topilsky et al. [97] used 3D transthoracic echocardiography to show the complex interaction between mitral valve dynamics and ventricular contraction. The loss of annular contraction across the inter-commissural axis, usually responsible for early-systolic mitral competence, and the change in papillary muscle dynamics were linked to the severity of MR. Moreover, the presence of LBBB itself in patients with dilated cardiomyopathy, increasing LV isovolumic contraction and relaxation times, is responsible for worsening MR duration [98].

Cardiac resynchronization therapy, reducing electrical and mechanical dyssynchrony and leading to a final increased efficiency of LV contraction, has shown to have beneficial effects on ‘secondary’ MR [35–37,94,99–101]. Kanzaki et al. [36], utilized echocardiographic Doppler and strain images before and immediately after CRT implant, and showed a significant reduction in the coordinated timing of mechanical activation of papillary muscle insertion sites and in the severity of MR after CRT implant ( $p < 0.001$  for both comparisons). Agricola et al. [34], showed how CRT may reduce the delay in electrical activation and subsequent mechanical activity of the papillary muscle, improving contraction coordination. They stated that, with enlarged spheric ventricle, both papillary muscles are posteriorly displaced. The anterolateral papillary muscle shifts far from interventricular septum and more towards the posterior/posterolateral veins, where the left-sided CRT lead is usually implanted. In this way, the stimulation of the LV free wall can counterbalance the delay in electrical activation of the anterior papillary muscle caused by LBBB and improve muscle coordination. Matsumoto et al., [102] instead, showed an asymmetrical displacement of papillary muscles in patients with dilated cardiomyopathy, with the anterolateral papillary muscle being more posteriorly located than the posteromedial one. The restoration of the anterolateral papillary muscle position after CRT implant was one of the independent predictors of MR reduction at 6 month followup.

Moreover, thanks to a more coordinated and earlier mechanical contraction of the basal segments of the LV compared to the more apical ones, an increase in mitral annular systolic function may be achieved, leading to reduction of MR [94,99]. Earlier mitral annular contraction was hypothesized to be the responsible mechanism of a dramatic symptom improvement in a patient with RV pacing and heart failure who subsequently underwent an upgrading to a biventricular device with the LV lead being positioned in a very basal-lateral position. DeSimone et al., [103] indeed, observed an acute and significant reduction in MR and LV size dimensions with proper LV lead placement causing mitral annular pre-excitation. Ypenburg et al. [35] reported findings consistent with this by showing an acute improvement in MR after CRT, as well as during follow-up. In addition to the 43% acute improvement, the authors demonstrated a 20%

reduction of late MR 6 months after CRT. Moreover, the beneficial effects of CRT are maintained until the therapy itself is interrupted, possibly suggesting a dynamic influence on mitral valve activation kinetics. Following CRT withdrawal, acute loss of synchronization is responsible for acute MR recurrence and worsening in mitral functional parameters [94].

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## Future directions

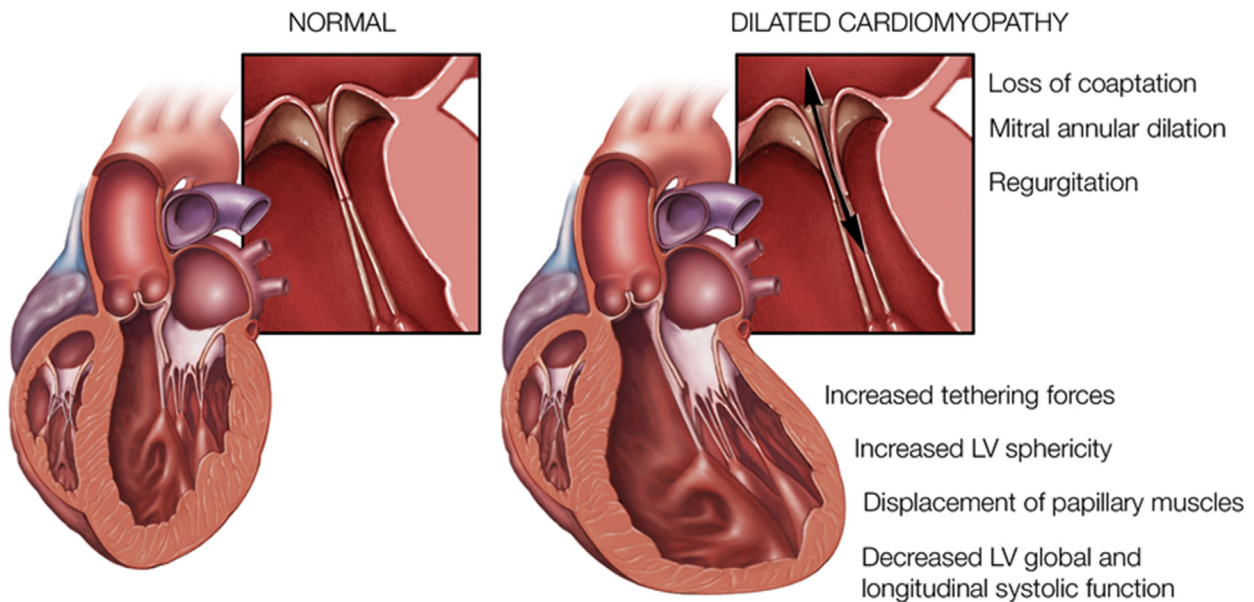
Understanding the mechanism of how mitral valve mechanics and other dyssynchrony parameters are improved with biventricular pacing will provide critical data necessary to improve number of CRT response in patients with heart failure. The location where transvenous LV leads are placed via the coronary sinus has been considered of utmost importance for CRT optimal response [104]. Meanwhile, stimulation sites alternative to RV apical pacing have been extensively studied to simulate a more physiologic electrical activation of the heart, to reduce ventricular dyssynchrony and to obtain more favorable hemodynamics. Few studies regarding non-traditional pacing sites in the right ventricle, such as the RV septum or the RV outflow tract, and His-bundle pacing have been reported in the literature (Fig. 4) [84,105–111].

The RV outflow tract has been considered primarily because placement of leads is technically easier compared to most other locations. The reason for interest in this region is that activation should result in electrical propagation from base to apex with a QRS morphology more similar to the standard QRS derived from normal cardiac conduction system, even if the duration of the QRS itself may not be significantly improved [112–115]. RV mid-septal pacing has also been used as an alternative to RV apical pacing [116]. Even if lead implantation in the inter-ventricular septum has showed to be feasible, safe, and associated with less ventricular dyssynchrony compared to standard apical pacing, no overt clinical benefits have been found [117–119]. However, both of these alternative sites still require crossing the tricuspid valve, with the potential risk of TR.

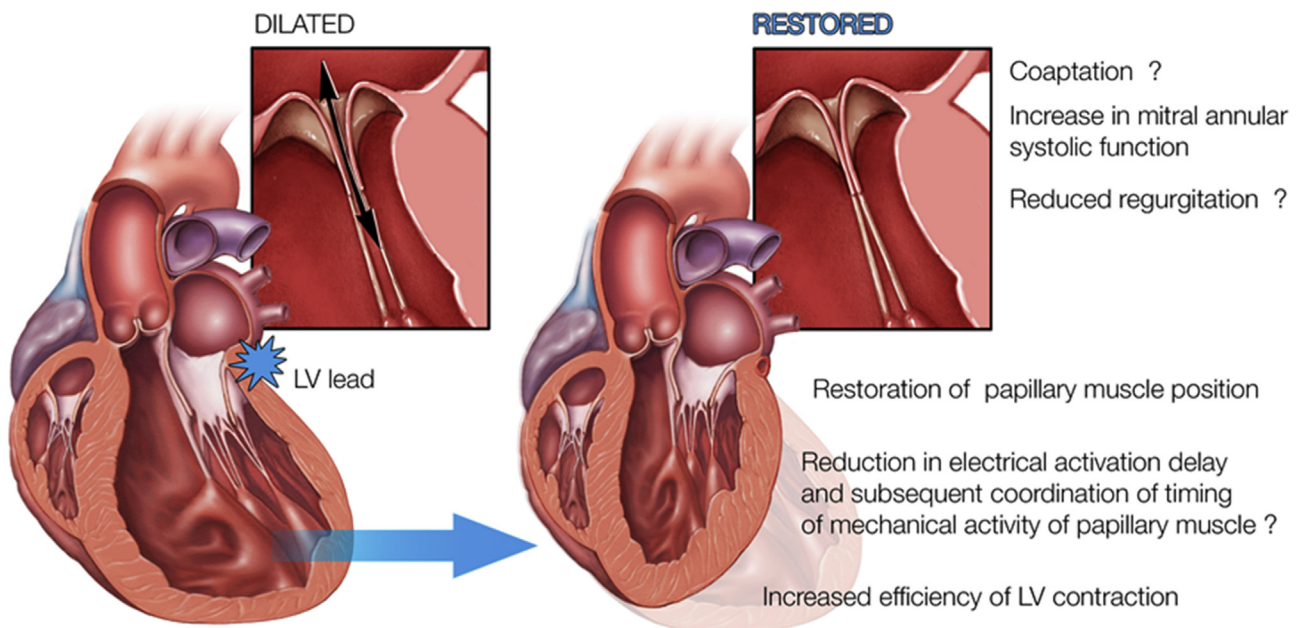
His-bundle pacing was first demonstrated in 1967 in dogs [120]. However, in this location, stable capture is difficult to obtain and higher thresholds and longer implant times are often necessary [121,122]. The issues with His-bundle pacing may be partially attenuated with parahisian pacing, in which both the His and the myocardium of the high interventricular septum are stimulated together [123]. However, parahisian pacing produces a base-to-apex activation pattern that is completely different from the true His-bundle capture, characterized by the earliest site of ventricular activation at the exit site of the right and left bundle.

More novel approaches include lead-less pacemakers such as the ‘Nanostim’ (St. Jude Medical Inc., Minneapolis, MN, USA) [124] and the ‘Micra™ Transcatheter Pacing System’ (Medtronic Inc., Minneapolis, MN, USA) which was recently implanted in man (NCT02004873, [www.clinicaltrials.gov](http://www.clinicaltrials.gov)). Other lead-less pacing systems use ultrasound-based technology and have been tested clinically for short-term use in LV pacing [31]. A comparison of lead-less RV apical pacing with

## A. Mechanisms of mitral regurgitation in patients with heart failure



## B. Beneficial effects of CRT on 'secondary' mitral regurgitation

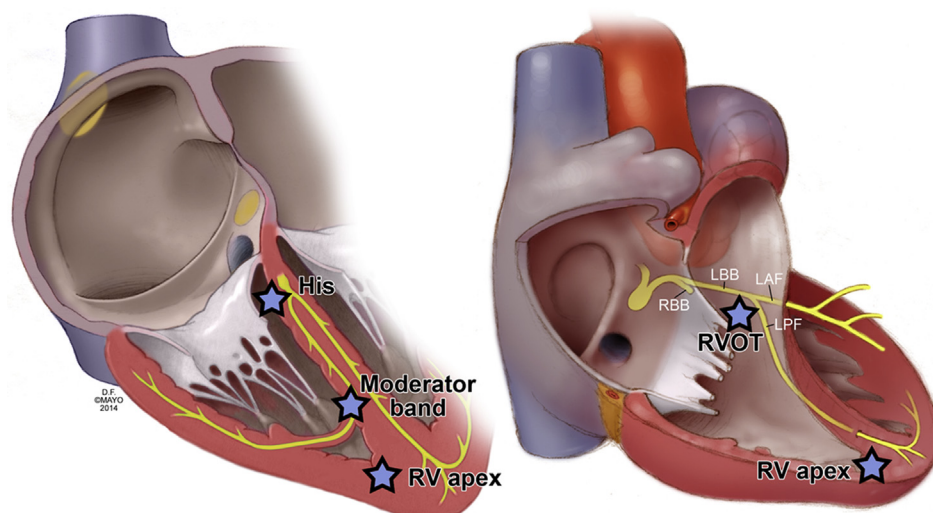


**Fig. 3 – Panel A: Mechanisms of mitral regurgitation in patients with heart failure. Panel B: Beneficial effects of CRT on 'secondary' mitral regurgitation.**

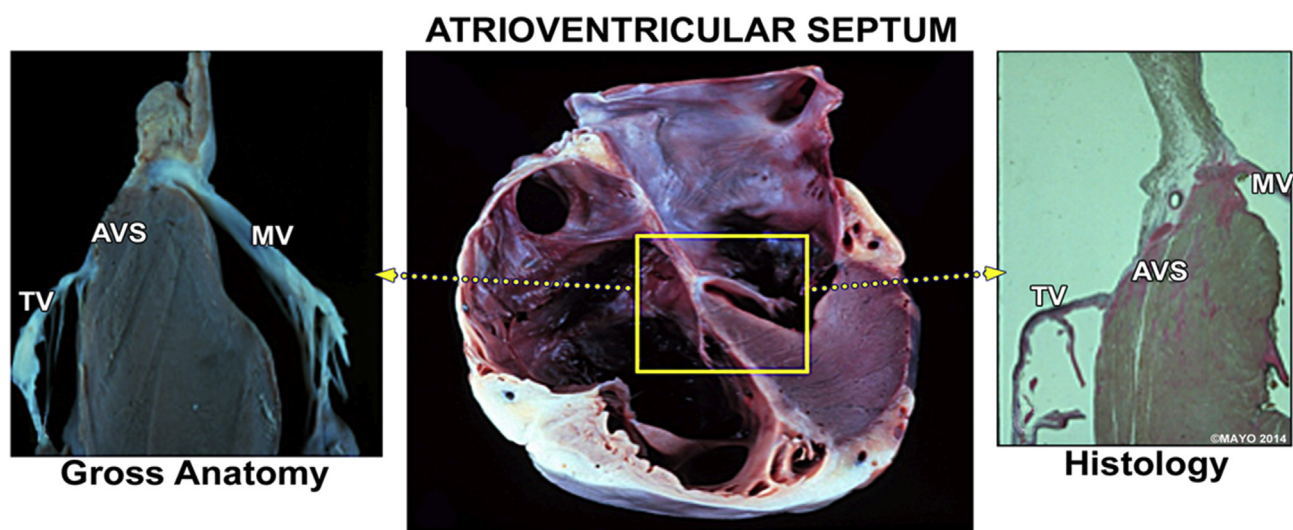
transvenous pacing may provide interesting insights into the mechanisms of both MR and TR: how much is mechanically caused by the leads vs. electrical dyssynchrony from the RV apical pacing.

Concerning the use of CRT devices, with advances in coronary sinus cannulation and dedicated LV technology, the

transvenous approach through the coronary sinus itself has become the standard technique, even if limitations such as technical challenges in finding electrically suitable sites still exist. Multisite pacing, mimicking the native conduction system activation [125], or multipoint pacing [126], using multiple electrodes on one LV lead, could optimize synchronous



**Fig. 4 – Illustration showing alternative sites for RV pacing indicated by stars. LAF = Left Anterior Fascicle; LBB = Left Bundle Branch; LPF = Left Posterior Fascicle; RBB = Right Bundle Branch; RVOT = Right Ventricular Outflow Tract.**



**Fig. 5 – Gross anatomy and histological images showing the atrio-ventricular septum region. The tricuspid valve is more apical than the mitral valve and the atrio-ventricular septum separates, at a certain location, the right atrium and the LV basal septum. AVS = Atrio-ventricular Septum; MV = Mitral Valve; TV = Tricuspid Valve.**

myocardial activation. However, the ideal CRT system would allow synchronous ventricular contraction without the need to enter the coronary sinus or cross the tricuspid valve. Based on the anatomical consideration that the tricuspid valve is more apical than the mitral valve and the atrioventricular septum separates, at a certain location, the right atrium and the LV basal septum (Fig. 5), our group recently developed a specially built intra-myocardial lead to pace the ventricular myocardium from the atrioventricular septum itself [29,127]. The intra-myocardial lead, together with this new form of synchronous pacing, could offer important advantages either in patients without heart failure who require ventricular pacing or in patients with heart failure who are candidates for resynchronization therapy. Undoubtedly, larger studies with

long-term follow-up are needed to evaluate safety, stability and durability of the novel lead and the enhanced potential benefit of the atrioventricular septum location for pacing.

## Conclusions

The field of cardiac pacing is faced with a great task to improve the utility of ventricular pacing while mitigating potential for undesired effects on heart structure and function. Further research to clarify the relationship of the critical role that the position and type of pacing leads have on proper mitral valvular function is of paramount importance. Without question, further innovative strategies will need to be

employed and will be a work in progress as more pacing data, especially with the increase in CRT use, become available in the literature.

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