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STATE-OF-THE-ART REVIEW

Advances and Future Directions in Cardiac Pacemakers

Part 2 of a 2-Part Series

Malini Madhavan, MBBS, Siva K. Mulpuru, MD, Christopher J. McLeod, MBChB, PhD, Yong-Mei Cha, MD, Paul A. Friedman, MD

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ABSTRACT

In the second part of this 2-part series on pacemakers, we present recent advances in pacemakers and preview future developments. Cardiac resynchronization therapy (CRT) is a potent treatment for heart failure in the setting of ventricular dyssynchrony. Successful CRT using coronary venous pacing depends on appropriate patient selection, lead implantation, and device programming. Despite optimization of these factors, nonresponse to CRT may occur in one-third of patients, which has led to a search for alternative techniques such as multisite pacing, His bundle pacing, and endocardial left ventricular pacing. A paradigm shift in pacemaker technology has been the development of leadless pacemaker devices, and on the horizon is the development of batteryless devices. Remote monitoring has ushered in an era of greater safety and the ability to respond to device malfunction in a timely fashion, improving outcomes.
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In the first part of this series (1), we explored the state-of-the-art in the basics of pacing physiology, pacing modes and indications, periprocedural management, complications, basic troubleshooting, perioperative management, and cardiac magnetic resonance imaging of patients with pacemakers. In this second part, we examine recent advances and future directions (**Central Illustration**), including resynchronization for heart failure (HF), His bundle pacing, remote monitoring (RM), and leadless and batteryless devices.

CARDIAC RESYNCHRONIZATION

Although cardiac pacing had been used historically to effectively treat bradycardia (delayed or absent activation of the *entire* ventricle), cardiac resynchronization therapy (CRT) introduced the concept of pacing to treat a delayed *segment* of the ventricle. When segments of the left ventricle (LV) contract with marked delay (most commonly of the free wall due to left bundle branch block [LBBB]), they fail to meaningfully contribute to stroke volume and cardiac output. This is termed *dyssynchrony* (**Figure 1**). Cardiac resynchronization improves ventricular function by pacing to improve electrical (and consequently mechanical) coordination and thus pump efficiency. It is accomplished by near simultaneous pacing of the right ventricle (RV) and LV, most commonly using an epicardial lead in the coronary sinus to restore interventricular and intraventricular synchrony. This, in turn, improves LV contractility, stroke volume, and ejection fraction (EF). CRT has been shown to reverse adverse cellular remodeling, improve ventricular function, lower levels of HF biomarkers (e.g., B-type natriuretic peptide), reduce HF hospitalization, and lower mortality (2–4). However, CRT is not uniformly effective, and careful patient selection, lead positioning, and device programming are necessary to maximize its benefits. Here, we provide an overview of best practices to optimize CRT and future directions.

OPTIMIZING CRT TO MAXIMIZE CLINICAL RESPONSE AND VENTRICULAR REMODELING. The CRT response refers to the modification of the natural history of HF progression (**Figure 2**). Defining CRT response is complex, and numerous endpoints have been used, including New York Heart Association (NYHA) functional class and echocardiographic changes. The success of cardiac resynchronization is dependent on: 1) selection of appropriate patients; 2) maximal LV resynchronization to correct the delayed activation imposed by a conduction abnormality (i.e., pacing the correct location); and 3) continuous delivery of biventricular (BiV) pacing with every cardiac cycle to deliver the maximal "dose" of therapy. Techniques to ensure optimal CRT are discussed later and are summarized in **Figure 3**.

Patient selection. The selection of patients who are most likely to benefit from CRT relies heavily on the severity of HF symptoms and on electrocardiographic

criteria indicative of ventricular dyssynchrony. A summary of the results of selected large, randomized, clinical trials of CRT stratified by key patient characteristics is presented in **Figure 4A** (5). The guidelines for implantation of a CRT device from the American Heart Association (6) are summarized in **Figure 4B**, and are discussed later.

Electrocardiographic criteria. A wide QRS complex is a marker of electrical dyssynchrony and, in the presence of an LBBB pattern, is the most powerful predictor of CRT response. All of the randomized controlled trials (RCTs) that have shown improvement in HF symptoms and survival using patients enrolled in CRT with a minimal QRS duration of 120 to 150 ms (3,4,7). The wider the QRS complex, the greater the likelihood of response. There is interplay between the *type* of bundle branch block and the QRS *duration,* likely because a sufficiently wide right bundle branch block (RBBB) (>150 ms) reflects delay in both bundles, so that delay of the LV lateral wall activation is present, and CRT is thus effective. However, the presence of bifascicular block (RBBB with left anterior fascicular block) was not predictive of CRT response in the MADIT-CRT (Multicenter Automatic Defibrillator Implantation Trial With Cardiac Resynchronization Therapy) (8). Current guidelines require the presence of LBBB if the QRS complex is relatively narrow (120 to 149 ms) for a Class I indication for CRT (6). CRT is not indicated when the QRS complex is <120 ms, as it may potentially cause harm (6,9). Women are more likely to benefit from CRT than men, particularly when the QRS duration is <150 ms (10). When patients with depressed ventricular

ABBREVIATIONS AND ACRONYMS

CRT = cardiac resynchronization therapy

EF = ejection fraction

HF = heart failure

LBBB = left bundle branch block

LV = left ventricle/ventricular

RBBB = right bundle branch block

RI = remote interrogation

RM = remote monitoring

RV = right ventricle/ventricular

TTM = transtelephonic monitoring

CENTRAL ILLUSTRATION **Future Directions in Cardiac Pacing: The Need for Advances in Cardiac Pacing and Emerging Techniques**

CARDIAC PACEMAKERS: RECENT ADVANCES AND FUTURE DIRECTIONS

Improve cardiac resynchronization and cardiac efficiency

Goal: Increase the number of pacing sites:

Cardiac resynchronization therapy with multipoint/multisite pacing allows simultaneous pacing of multiple sites at the same time

Goal: Recruit His-Purkinje conduction

His-bundle pacing recruits the His-Purkinje system to mimic normal cardiac activation

Reduce hardware to reduce lead failure, valve injury, device infection

Goal: Eliminate pacemaker leads

Introduction of single-component leadless pacemakers

Goal: Eliminate leads from left ventricle endocardial pacing

Introduction of multicomponent leadless pacemaker for left ventricular endocardial pacing

Eliminate batteries and other hardware

Goal: Eliminate need for battery replacement

In development: Batteryless pacemakers that harvest the mechanical energy of cardiac contraction to power the pacemaker

Goal: Eliminate need for hardware

In development: Biological pacemakers that are gene- or cell-based

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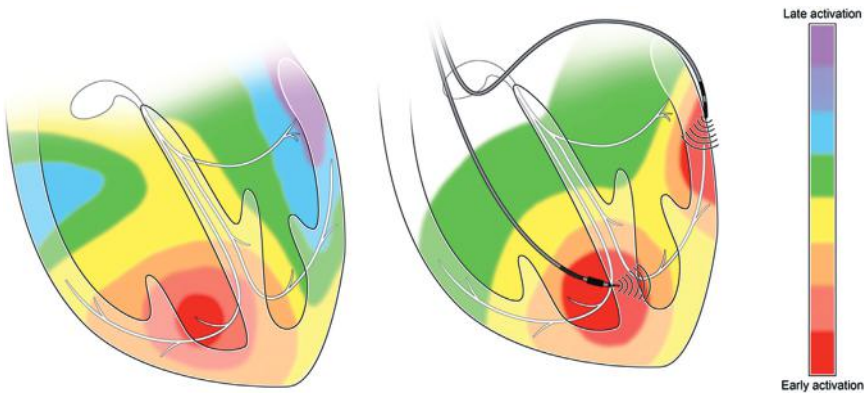
Several strategies have been developed and are emerging to enhance device therapy. Pump efficiency is addressed with multisite left ventricle pacing and, potentially, His-Purkinje recruitment. Hardware reduction and simplification include leadless pacemakers (single component and multicomponent), and future advances may eliminate the need for batteries, which deplete over time.

FIGURE 1 CRT for the Treatment of Heart Failure

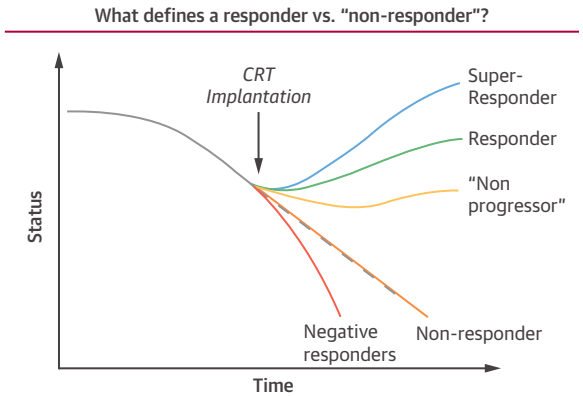


Left bundle branch block causes delayed electrical and mechanical activation of the LV, which in turn results in atrioventricular, interventricular, and intraventricular dyssynchrony, consequently reducing LV pump function. This results in adverse LV remodeling over time. CRT, by pacing the right and left ventricles near-simultaneously, aims to correct mechanical dyssynchrony, improve LV function, and over time, cause reverse remodeling. CRT = cardiac resynchronization therapy; LV = left ventricle/ventricular.

function and a pacemaker manifest an LBBB that is caused by frequent RV pacing, upgrading to a CRT system often improves ventricular function.

An intrinsic LBBB or a mechanical dyssynchrony induced by a high percentage of RV apical pacing are the main substrates for resynchronization. In a meta-analysis of RCTs, the benefit of CRT was limited to those patients with LBBB (11). Patients with RBBB and a nonspecific intraventricular conduction delay with a QRS complex >150 ms may still be considered for CRT, although the strength of the indication is smaller and the likelihood of nonresponse is greater (6). Certain subgroups of patients with non-LBBB QRS morphologies, such as those with echocardiographic dyssynchrony, may have better outcomes after CRT (12).

FIGURE 2 Response to CRT

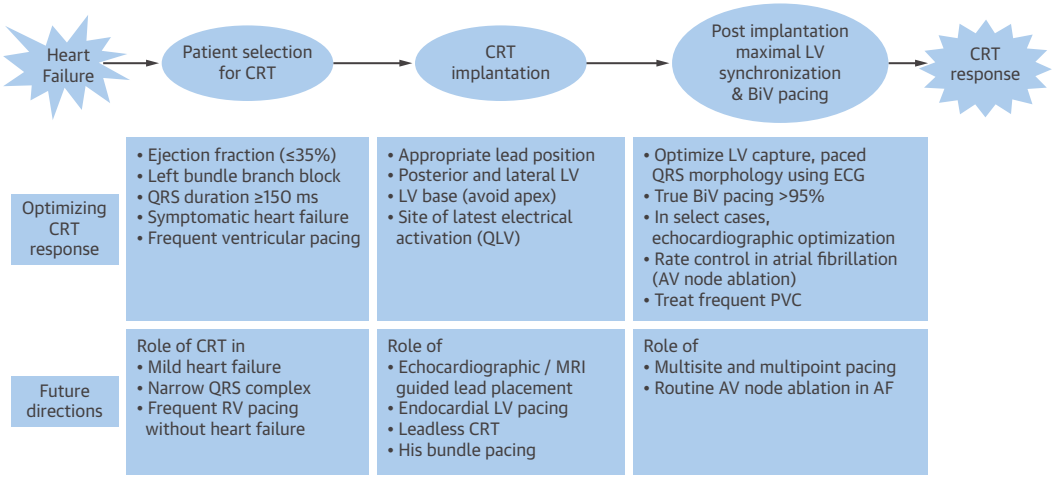


Response to CRT is determined by a host of parameters, including patient symptoms, objective measurements of functional capacity, and cardiac function. Those who demonstrate improvement in these parameters are termed *responders*, with *super-responders* referring to a subgroup with near normalization of LV function. Patients who demonstrate stabilization of LV function without experiencing the progressive decline that is expected with heart failure are termed *nonprogressors*. A small proportion of patients may experience a rapid decline in LV function following CRT (negative responders). Reproduced with permission from Steffel et al. (74). Abbreviations as in **Figure 1**.

Severity of HF. Initial RCTs predominantly enrolled patients with EF ≤35% and NYHA functional class III or ambulatory class IV (no hospital admissions within 1 month) HF (7). Subsequent trials included patients with EF ≤30% to 40% and asymptomatic or mild HF (NYHA functional classes I and II) (4,13). However, the majority of trial participants had symptomatic HF (NYHA functional class II to IV); hence, the evidence supporting CRT for these patients is much stronger (6). Clinical scenarios that warrant special consideration are discussed later.

Atrial fibrillation. Experience in randomized trials of CRT in patients with atrial fibrillation (AF) and with symptomatic HF, QRS complex ≥120 ms, and no other indication for pacing is limited. The MUSTIC (Multisite Stimulation in Cardiomyopathies) trial reported improvement in functional status in patients with both sinus rhythm and AF (14). A meta-analysis of observational studies reported a greater mortality risk and a higher rate of CRT nonresponse in AF compared with sinus rhythm (15). Current guidelines recommend CRT implantation in patients with AF, HF,

FIGURE 3 **Techniques to Optimize CRT and Future Directions**



Optimizing response to CRT implantation requires careful attention to patient selection and lead implantation. Following implantation, close follow-up to ensure optimal LV lead capture, and BiV pacing are essential. AF = atrial fibrillation; AV = atrioventricular; BiV = biventricular; MRI = magnetic resonance imaging; PVC = premature ventricular contraction; RV = right ventricle/ventricular; other abbreviations as in Figure 1.

LVEF ≤35%, and QRS complex ≥120 ms (6). However, it is critical to control the ventricular response in AF to provide >99% BiV pacing (6).

CRT in patients who require pacing for bradycardia. RV apical pacing induces electrical and mechanical dyssynchrony, and has been associated with an increased risk of HF, particularly when pacing is frequent (>40%) and LV systolic function is depressed (16). In patients with atrioventricular (AV) block who require pacing, EF ≤50%, and NYHA functional class I to III HF, BiV pacing (with a defibrillator, if indicated) reduces the combined endpoint of mortality, intravenous therapy for HF, or reduction in LV end-systolic volume compared with RV-only pacing (17). BiV pacing can reasonably be considered in patients who are anticipated to require a high percentage of ventricular pacing and have EF ≤50% with mild HF symptoms (17).

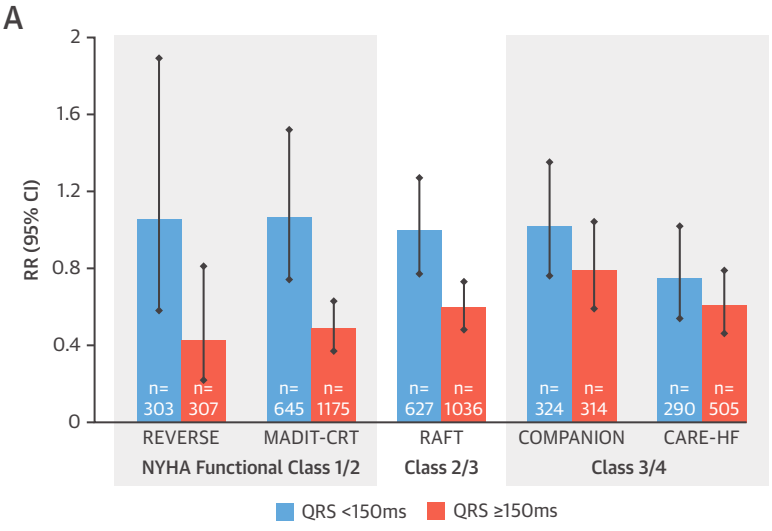
Measurement of mechanical dyssynchrony for patient selection. Only patients with a QRS complex ≥120 ms were enrolled in initial CRT studies. Because many patients with EF <35% and symptomatic HF have a narrow QRS complex, to identify potential resynchronization candidates, several studies used echocardiography to identify mechanical dyssynchrony by assessing the time difference between activation of the LV septum and lateral wall with M-mode, tissue Doppler, speckle tracking, or other modalities (18). Three multicenter trials failed to show substantial improvement in CRT response with dyssynchrony assessment by these means, and 1 found increased mortality in patients with a QRS complex <130 ms and echocardiographic dyssynchrony (3,19,20). Whether these study findings reflect limitations of the specific echocardiographic assessments used or whether the strategy of using a mechanical measurement to select an electrical therapy is doomed to failure is unclear. At present, there is no role for routine echocardiographic assessment of dyssynchrony in patient selection for CRT.

Lead position. Positioning of the LV lead at the site of latest activation to maximize resynchronization seems intuitive. The effect of the location of the LV lead for assessing CRT response has been extensively studied. Broadly, 3 metrics have been used to characterize the LV lead position to determine its effect on CRT response: anatomic LV lead position, LV local electrogram timing, and mechanical delay or scar assessment at the LV lead site.

Anatomic LV lead position. The ideal site for LV pacing is the subject of debate. However, it is clear that the closer the LV and RV electrodes are placed, the lower the potential for resynchronization. As a general rule of thumb, maximizing the distance between the RV and LV electrodes in the horizontal plane in the lateral view (or left anterior oblique [LAO] view) is associated with a better CRT response (21). Apical positions are unattractive, in part because they necessarily result in

FIGURE 4 Effect of CRT in Randomized Clinical Trials and Indications for CRT for Patients in Sinus Rhythm

A



B

LVEF ≤35%, QRS Duration ≥120 ms and Sinus Rhythm

QRS morphology	QRS duration (ms)	NYHA functional class	Level of recommendation
LBBB	≥150	II, III, ambulatory IV	Class I
	120-149	II, III, ambulatory IV	Class IIa
	≥150	I + LVEF ≤30% + ischemic heart disease	Class IIb
Non-LBBB	≥150	III, ambulatory IV	Class IIa
	120-149	III, ambulatory IV	Class IIb
	≥150	II	Class IIb
	120-149	I, II	Class III (no CRT)
Significant (>40%) ventricular pacing	Any QRS	I, II, III, ambulatory IV	Class IIa

(A) Effect of CRT on composite clinical outcomes in large randomized clinical trials. The effect of CRT on composite clinical outcomes in selected large randomized trials is stratified by patient characteristics, including NYHA functional class and QRS duration. Patients with severely prolonged QRS duration (>150 ms) were more likely to have improved outcomes compared with those with QRS duration <150 ms. The New York Heart Association (NYHA) functional class was less predictive of clinical improvement. Adapted from Sipahi et al. (5). **(B)** Indications for CRT for patients in sinus rhythm: guidelines from the American Heart Association/American College of Cardiology. Severity of heart failure symptoms, ejection fraction, cardiac rhythm, QRS morphology, and QRS duration are considered when selecting patients for CRT. CARE-HF = Cardiac Resynchronization-Heart Failure; CI = confidence interval; COMPANION = Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure; LBBB = left bundle branch block; LVEF = left ventricular ejection fraction; MADIT-CRT = Multicenter Automatic Defibrillator Implantation Trial-Cardiac Resynchronization Therapy; NYHA = New York Heart Association; RAFT = Resynchronization-Defibrillation for Ambulatory Heart Failure Trial; REVERSE = Resynchronization Reverses Remodeling in Systolic Left Ventricular Dysfunction; RR = relative risk.

less separation between the RV and LV leads, and in part due to potentially nonphysiological ventricular activation. This is supported by a randomized clinical trial showing worse outcomes with apical pacing sites (22). Posterior and lateral positions are generally preferred (23). However, compelling differences in outcomes with different lead positions in large studies have been inconsistently found, perhaps due to the

presence of a large target region in patients with LBBB or due to patient-specific variations in the ideal site of pacing.

LV local electrogram timing. The site of latest electrical activation can be identified using the timing of the local LV electrogram recorded during lead implantation. As an LV lead is moved within a coronary sinus tributary, the greater the time interval between the start of the surface QRS complex and the local electrogram (the QLV interval), the larger the local delay. Longer QLV intervals result in a more favorable acute hemodynamic response to CRT, long-term reverse LV remodeling, and improved quality of life (24). A QLV interval >50% of the QRS width was associated with fewer HF hospitalizations and death in 1 small study (25). Larger studies are examining the feasibility of testing multiple coronary vein tributaries. Although data regarding the feasibility of consistent lead implantation at the site of latest activation and the long-term clinical outcome using the QLV interval are lacking, this approach appears promising.

Mechanical delay or scar assessment to identify the LV lead site. In contrast to the inability of imaging-based indexes of delayed activation to *select patients* for CRT (see earlier discussion), these techniques appear promising when used to *select attractive LV pacing sites*. Optimal LV pacing sites are those with the latest mechanical activation, and undesirable sites are those with scarring, which may limit the amount of LV myocardium captured by the pacing pulse. Use of echocardiographic speckle tracking and tissue Doppler imaging improved CRT response in small studies (26,27). With speckle tracking, the ultrasound backscatter "fingerprint" is used to track the motion of specific myocardial segments. The randomized controlled TARGET (Targeted Left Ventricular Lead Placement to Guide Cardiac Resynchronization Therapy) study found a reduction in death and HF hospitalization in patients with LV lead placement at the site of latest activation identified using speckle tracking (28). The STARTER (Speckle Tracking Assisted Resynchronization Therapy for Electrode Region) RCT reported that patients with QRS width 120 to 149 ms and non-LBBB morphology, a group at high risk of nonresponse, were most likely to benefit from echocardiography-guided lead placement (27). Cardiac magnetic resonance imaging may be useful as well; BiV pacing from sites of late gadolinium enhancement (e.g., scar) increases mortality (29). The concept of avoiding scar for lead placement was further supported by the TARGET trial, in which echocardiogram speckle tracking was used to avoid lead implantation at sites of scarring (28).

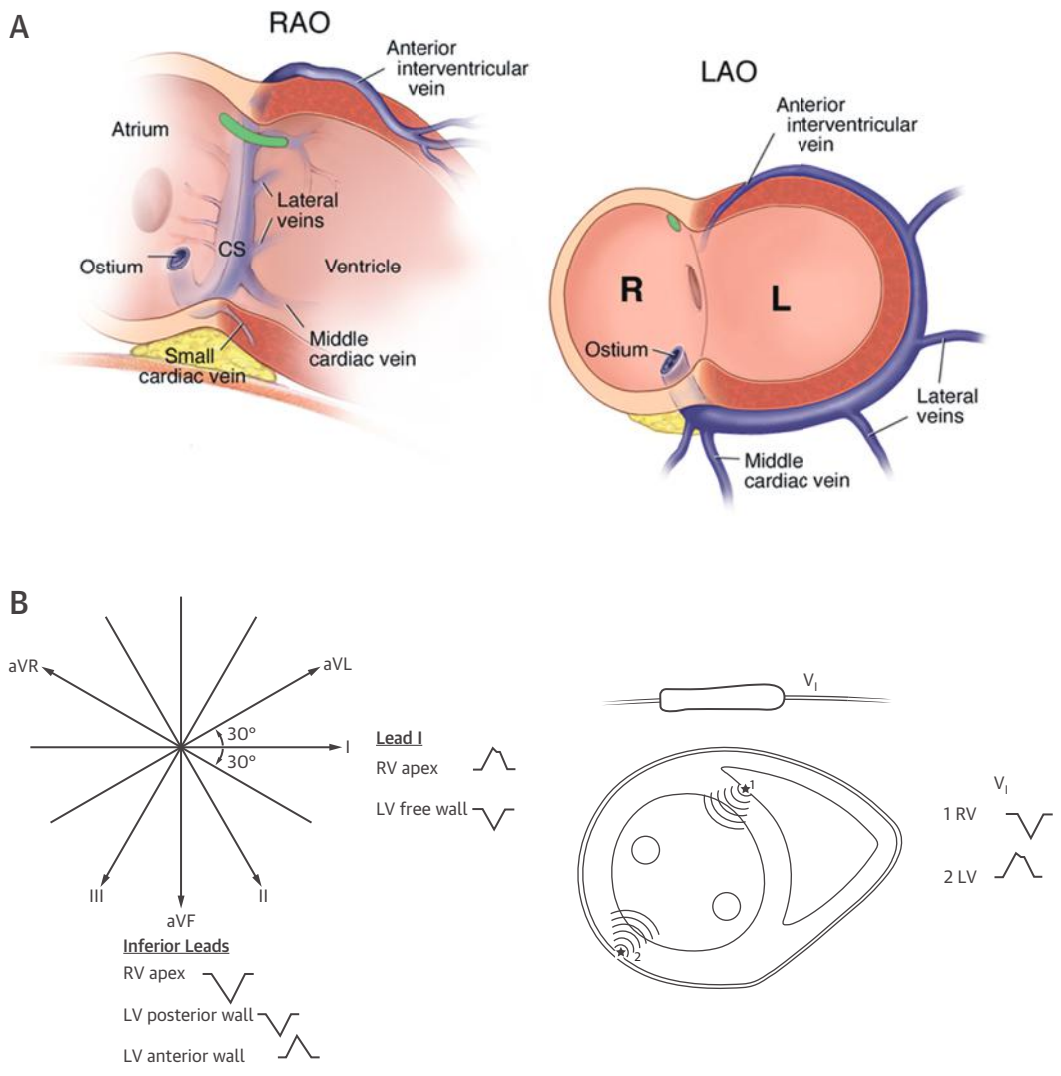
Computational models. Computational models of electromechanical cardiac function have shown promise in improving patient selection, lead localization, and device optimization for optimal CRT, and are the subject of ongoing research (30).

Multisite pacing. Because dyssynchrony is the underlying substrate for CRT, it has been proposed that pacing from more than 1 LV site may improve resynchronization and outcomes. *Multisite* pacing using 2 or more LV leads and *multipoint* pacing using 1 LV multipolar lead have shown promise in improving CRT response. The use of 2 epicardial coronary venous leads compared with 1 improves acute hemodynamic response, EF, LV end-systolic volume, and symptoms of HF in small, randomized trials (31). The implantation of 2 LV leads has been shown to be feasible and safe in the short term, but has a high long-term failure rate due to the inability to chronically capture using a Y adaptor to pace simultaneously from 2 leads, and due to rapid battery depletion (31,32). Studies of the effectiveness of multilead, multisite pacing have had mixed results (33).

Multipoint pacing through a single quadripolar lead has emerged as a feasible and safe option for providing CRT. Quadripolar leads offer the advantage of multiple programmable pacing vectors, hence minimizing the chance of lead abandonment due to a high pacing threshold or phrenic nerve capture. In a national database of quadripolar lead implantation, the risk of lead deactivation and replacement was lower with quadripolar than with bipolar leads (34). In addition, emerging evidence from small cohorts shows hemodynamic advantages to multipoint pacing using a quadripolar lead, with acute improvement in LV systolic function (35). The ability to choose a pacing vector with the best hemodynamic response and the ability to capture a large region of LV myocardium by pacing from widely spaced electrodes are potential explanations for the observed improvement. In a nationwide study of over 18,000 recipients of a quadripolar lead, mortality was noted to be lower compared with patients receiving CRT with a bipolar lead (34). Ongoing RCTs are comparing the efficacy of quadripolar versus bipolar leads.

Endocardial LV pacing. Although all CRT has been delivered via epicardial electrodes, epicardial LV pacing introduces multiple mechanisms of nonresponse, including unsuitable coronary venous anatomy, lead dislodgement, phrenic nerve capture, and nonphysiological epicardial-to-endocardial activation. Endocardial LV pacing may allow for pacing from any noninfarcted LV site; it results in a narrower QRS complex and improved acute hemodynamic

FIGURE 5 Radiographic Lead Position of Coronary Venous Lead and Paced QRS Morphology: Electroanatomic Correlation



(A) Anatomy of the coronary veins in the LAO and RAO views. Tributaries of the CS are best assessed using angiography in the LAO and RAO views during lead placement. The LAO view helps distinguish between lead placement in the lateral wall (preferred) and the septum. The RAO view helps assess whether the lead is anterior versus posterior and basal (preferred) versus apical. **(B)** Correlation between paced QRS morphology and CS lead position. The QRS morphology during coronary venous pacing can be used to confirm capture and assess satisfactory lead positioning and the contribution of LV activation to the overall biventricular paced morphology. Electrocardiographic vectors in the limb leads and the precordial leads as they correlate with coronary venous tributaries are presented here. Pacing from the lateral LV wall results in a predominantly negative vector in leads I and aVL. The inferior limb leads II, III, and aVF distinguish anterior from posterior LV pacing, with a predominantly positive vector resulting from pacing anteriorly and a negative vector resulting from posterior pacing. Precordial lead V_1 is placed anteriorly and rightward on the chest. Hence, pacing the LV, the posteriorly placed ventricle, results in a predominantly positive vector (i.e., right bundle branch morphology). The exception is pacing the anterior interventricular vein, which will produce a negative vector in V_1 (i.e., left bundle branch morphology). **(C to F)** Twelve-lead ECG and chest x-ray in the posteroanterior and lateral views showing correlation between lead position and paced QRS morphology in the **(C)** anterior interventricular vein, **(D)** anterolateral vein, **(E)** posterolateral vein, and **(F)** middle cardiac vein. **Arrows** in **C to F** point to the tip of the coronary sinus lead. CS = coronary sinus; LAO = left anterior oblique; RAO = right anterior oblique.

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FIGURE 5 **Continued**

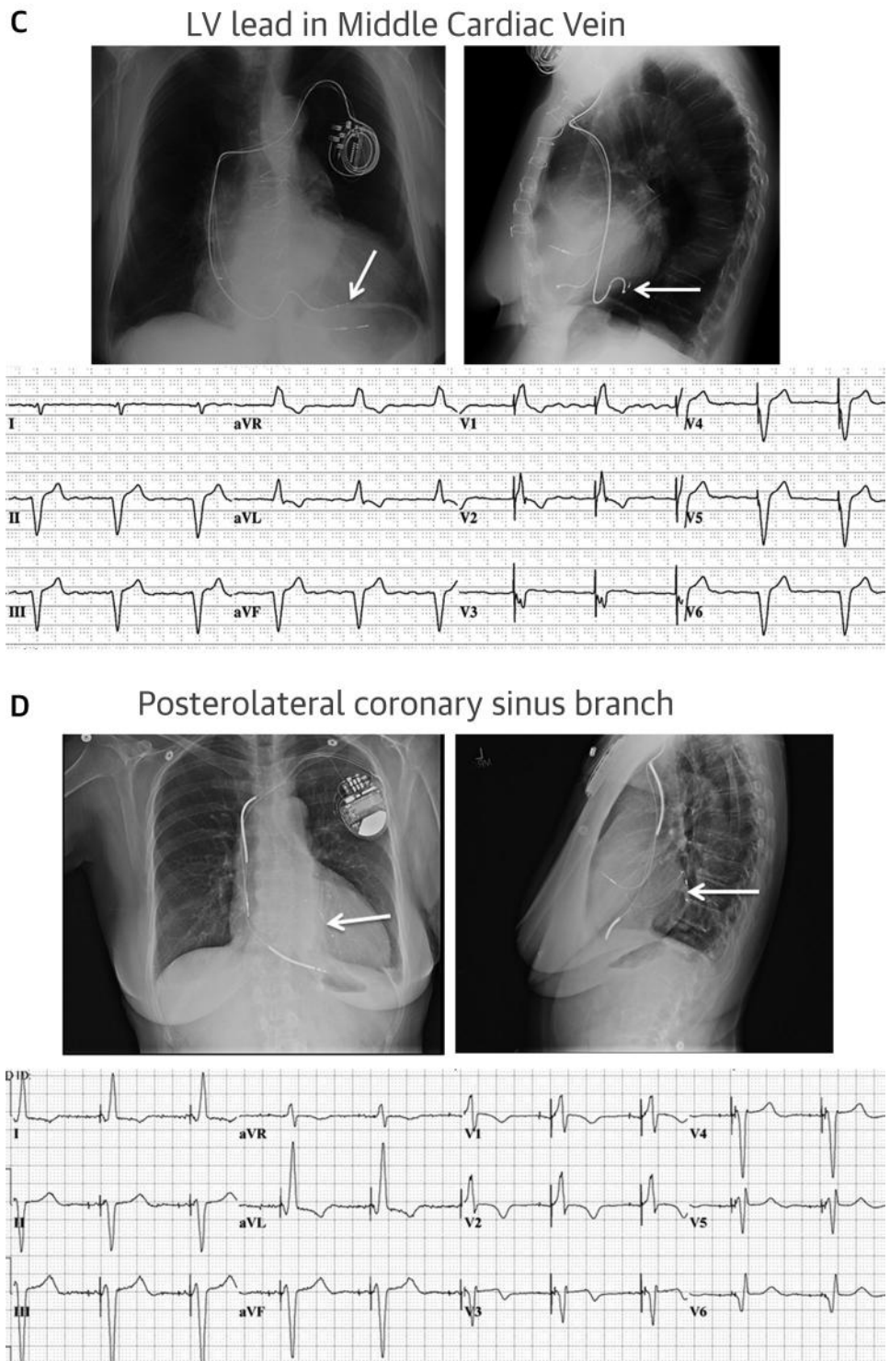

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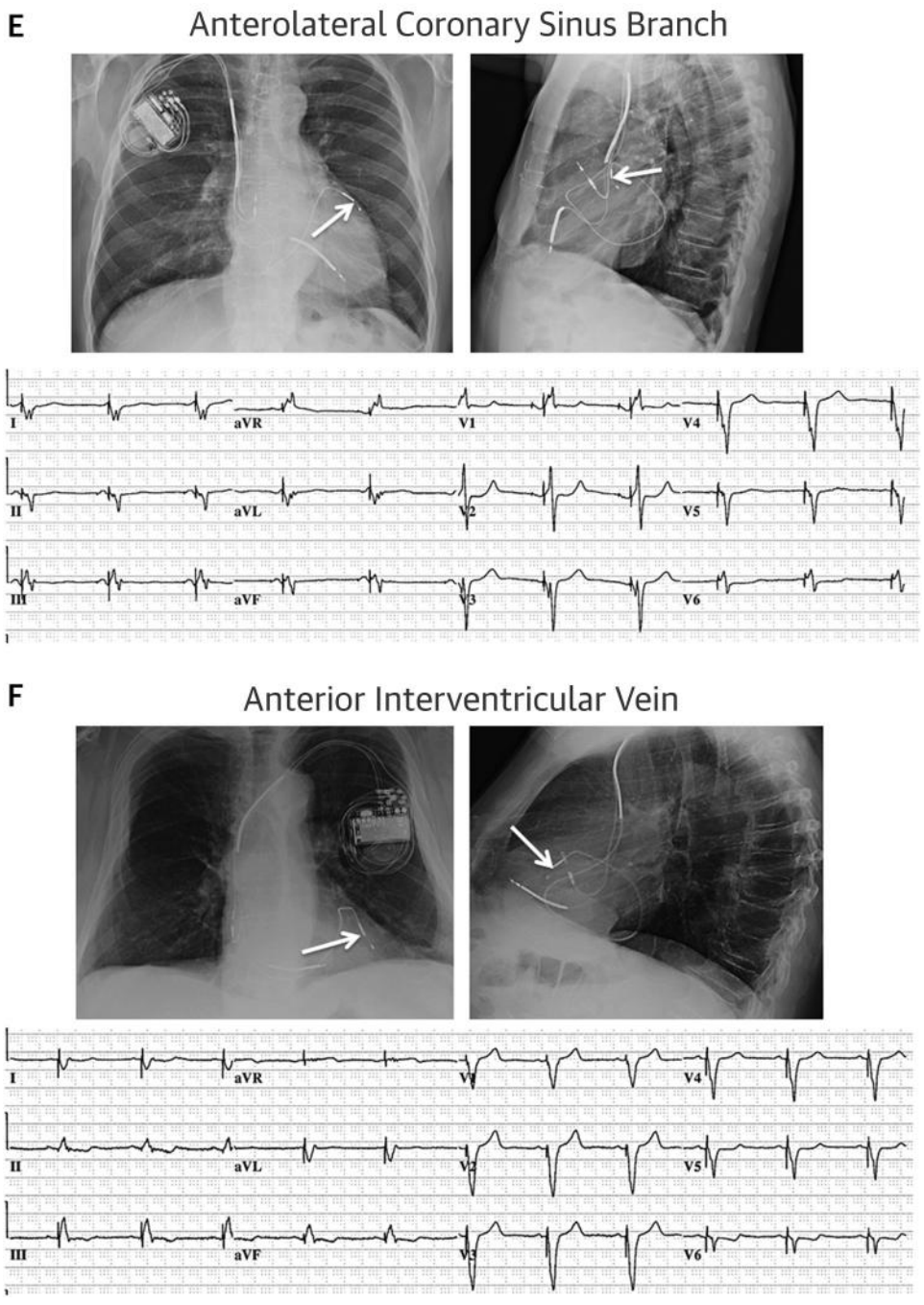
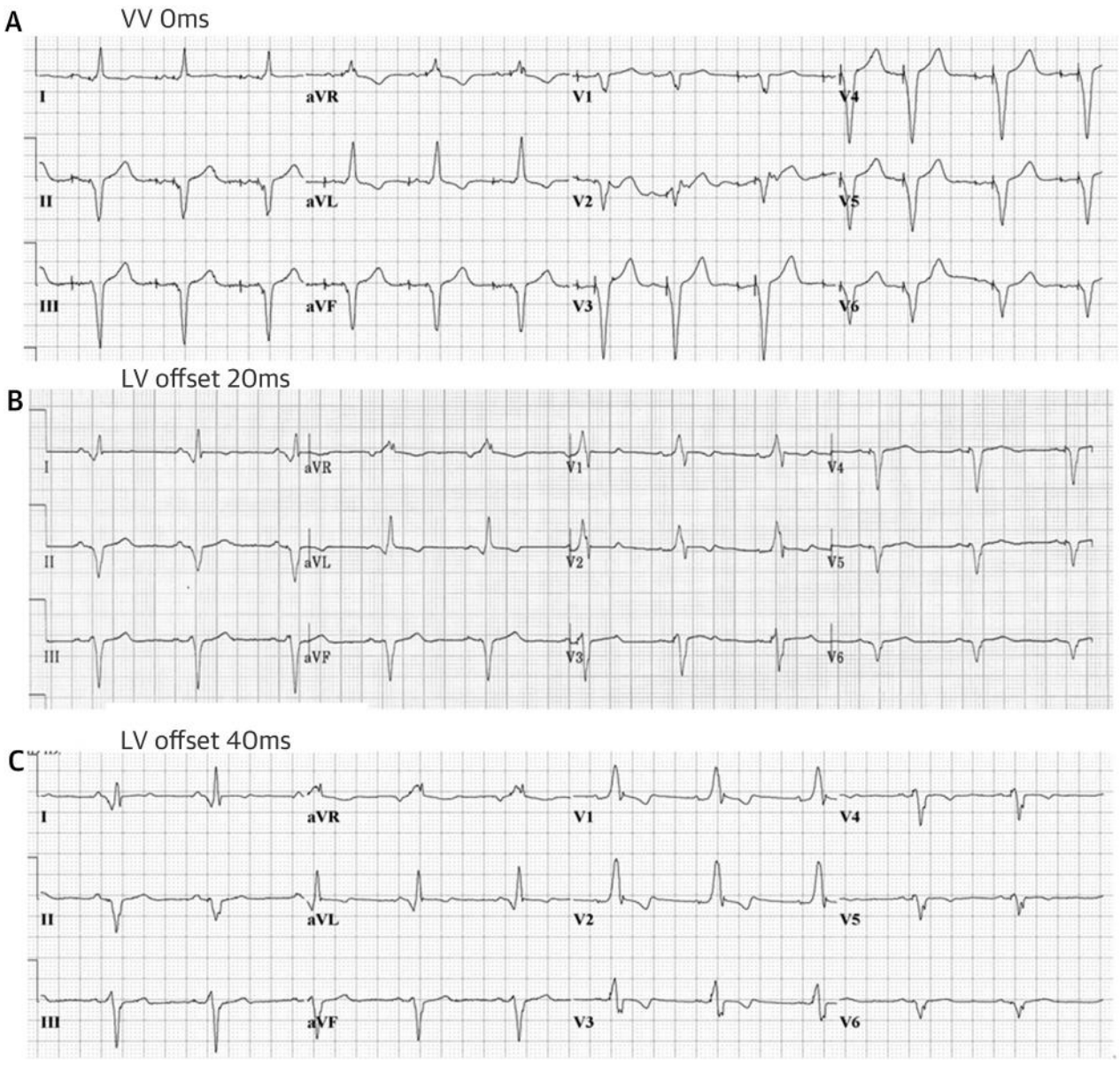
FIGURE 5 Continued



function compared with epicardial pacing (36). Endocardial pacing may be preferred due to greater flexibility in selecting the site of lead implantation, absence of phrenic nerve stimulation, and more physiological LV activation. Endocardial LV pacing using conventional pacing leads placed transapically, or through the interatrial or interventricular septum, has been described in small case series (37,38). Despite the attractive resynchronization potential, this technique is marred by a prohibitive risk of systemic thromboembolism and mitral valve regurgitation. Leadless LV electrodes under development have shown promise in reducing these complications (as discussed later).

FIGURE 6 **Optimization of the VV Interval Using Electrocardiography**

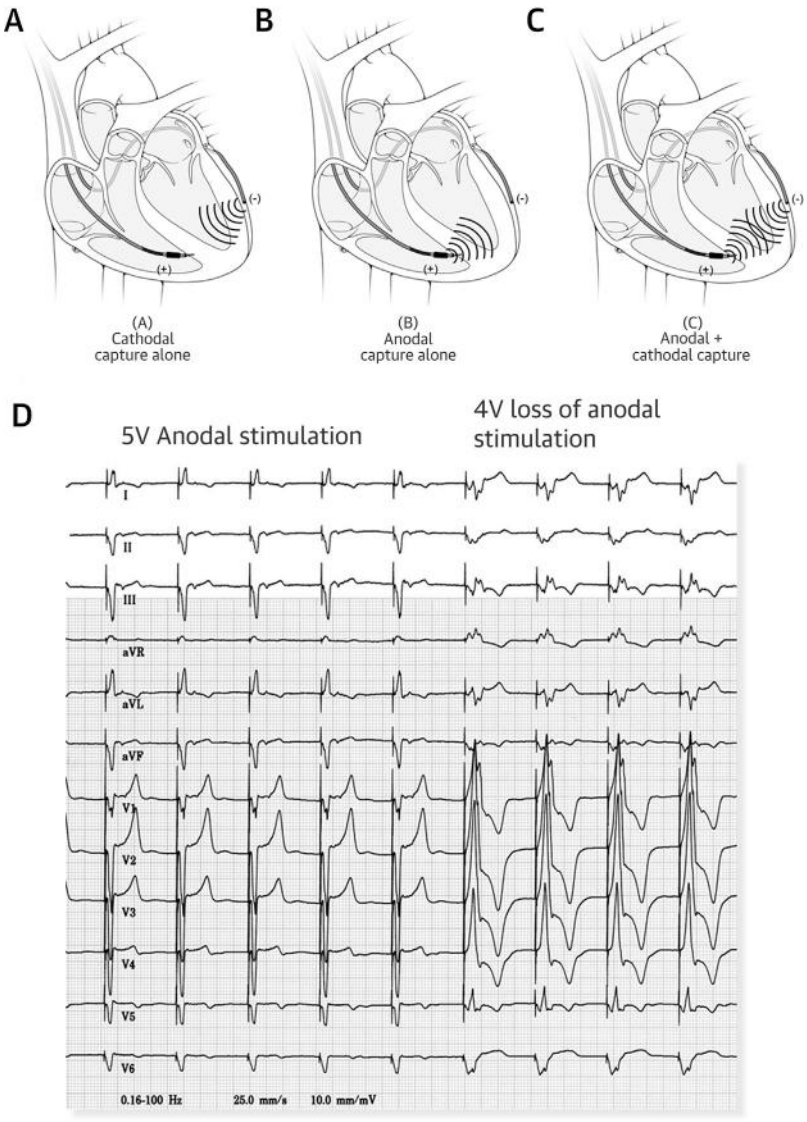


(A) Simultaneous pacing of the LV and RV (LV offset 0 ms) results in a negative vector in lead V_1 and an R-wave in lead I due to activation of the majority of the LV by pacing from the RV. Serial electrocardiograms are obtained with increasing pre-excitation of the LV lead in **(B)** (LV offset 20 ms) and **(C)** (LV offset 40 ms). When the LV is paced prior to the RV, the QRS morphology reflects progressively greater contribution from LV pacing with resultant positive vector in V_1 and negative vector in lead I. Abbreviations as in Figures 1 and 3.

POST-IMPLANTATION MANAGEMENT. CRT nonresponse, the absence of improvement in LV systolic function and HF symptoms, is present in 30% of recipients (39). Early recognition of nonresponse and its causes permits interventions to improve outcomes. A multidisciplinary approach to CRT optimization has been shown to identify a cause in 74% of nonresponders, leading to changes in device settings or therapy (40). Common causes for nonresponse include suboptimal lead position, lack of baseline dyssynchrony, LV lead malfunction, inadequate device settings, loss of BiV pacing, and arrhythmias (40).

Successful CRT requires ongoing assessment of the efficacy of BiV pacing following implantation.

FIGURE 7 Anodal Stimulation in a BiV Device

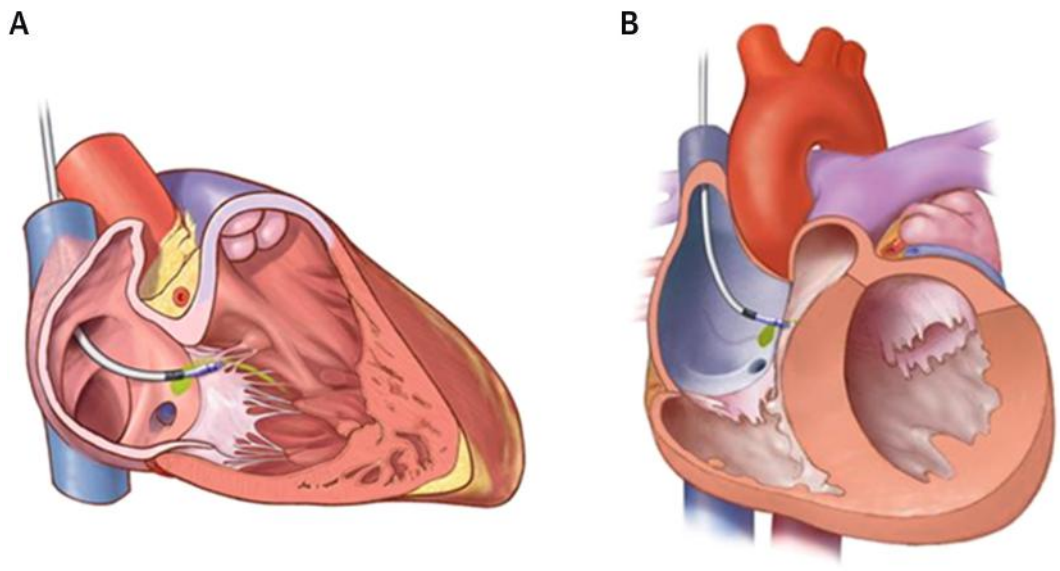


Anodal stimulation may occur when LV pacing is configured with the LV electrode as cathode and the RV ring or coil (in a defibrillator) as anode. **(A)** Capture typically occurs at the LV electrode only (cathodal-only capture) producing LV paced morphology. **(B)** If capture occurs at the anode alone, the QRS morphology resembles RV pacing and leads to loss of resynchronization. Anodal stimulation is more likely to occur at high pacing output. **(C)** Capture at both the cathode and anode may rarely occur, resulting in a narrow QRS complex with maintenance of cardiac resynchronization. **(D)** Electrocardiogram during pacing from the LV tip electrode (cathode) to the RV coil (anode) with reducing pacing output. **(Left)** Pacing at output of 5 V produces a QRS complex resembling RV pacing consistent with anodal only stimulation. **(Right)** As the pacing output is reduced to 4 V, there is a change in QRS to LV pacing morphology. This represents loss of anodal stimulation with capture at the cathode as the pacing output is reduced. Abbreviations as in Figures 1 and 3.

Follow-up visits assess: 1) HF symptoms; 2) LV lead capture threshold; 3) percentage BiV pacing; 4) device settings; and 5) presence of arrhythmias. When appropriate, further investigation may include an electrocardiogram (ECG), echocardiogram, oxygen consumption treadmill test, 6-min walk, and Holter monitor. CRT response is improved by ensuring: 1) effective LV capture; 2) a high percentage of BiV pacing; and, uncommonly, 3) optimization of AV and VV intervals; or 4) LV lead repositioning.

Assessing LV capture: importance of the 12-lead ECG. Poor LV lead performance due to dislodgement,

FIGURE 8 His Bundle Pacing



(A) Right anterior oblique and **(B)** left anterior oblique views of the heart showing placement of the lead on the proximal conduction system.

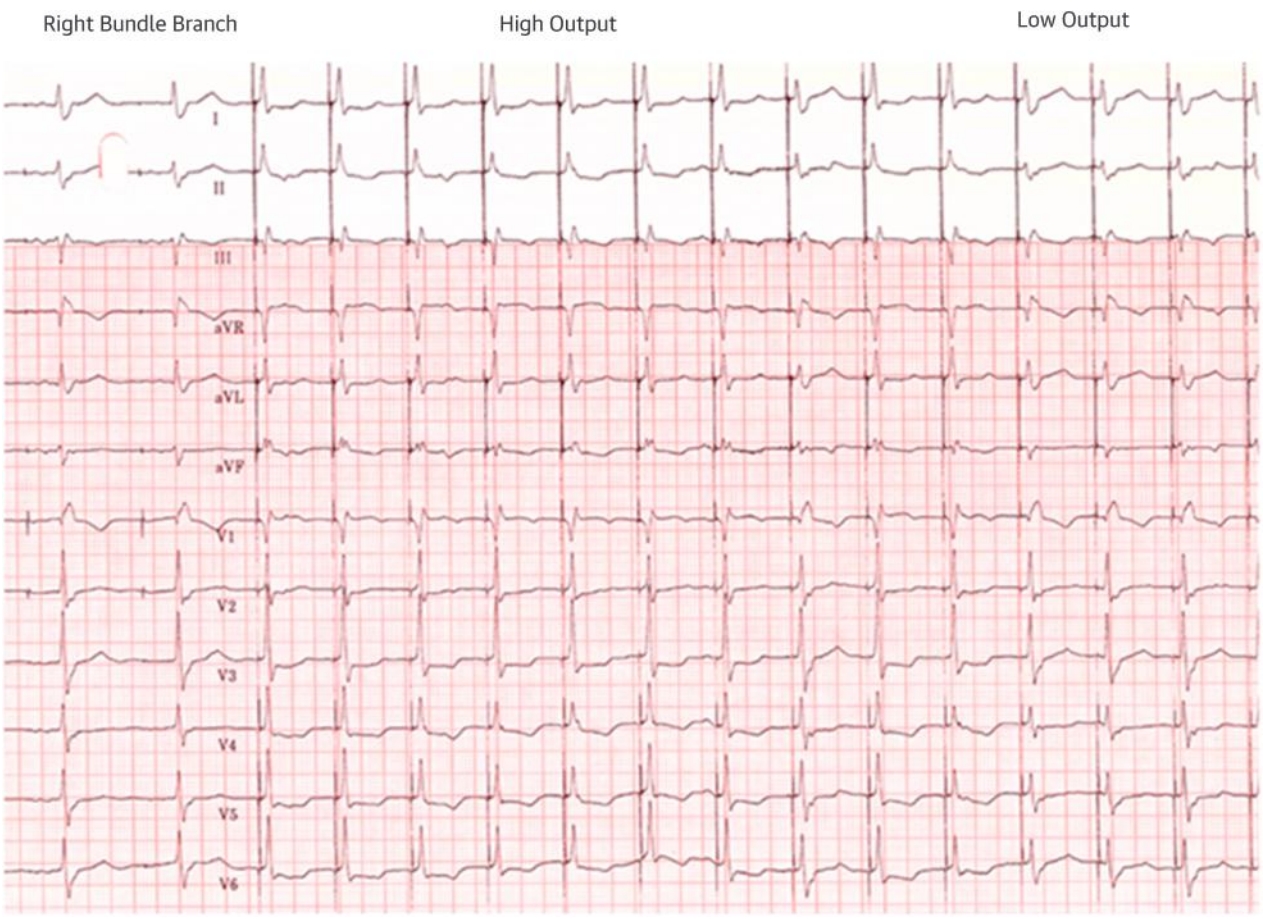
high capture thresholds, phrenic nerve capture, or structural lead dysfunction may affect CRT. A 12-lead ECG facilitates assessment of LV lead performance and its contribution to overall ventricular activation. The QRS morphology during LV and BiV pacing is determined by lead position, capture latency, and the presence of anodal capture. **Figure 5** shows the correlation between radiographic lead position and 12-lead QRS morphology during BiV pacing. Capture of the LV free wall is associated with a dominant R-wave in V_1 and a QS complex in lead I, which indicate a wave front propagating away from the LV toward the RV. The absence of these features can indicate: 1) loss of LV capture; 2) LV lead dislodgement; 3) LV capture latency or conduction delay, resulting in the majority of the LV being activated by an RV lead-initiated wave front; 4) fusion between CRT and intrinsic complexes; or 5) anodal capture.

The LV lead capture threshold is tested independently (RV lead output programmed off) with a real-time ECG to record the paced QRS morphology and to identify loss of capture. Conceptually, if an LV lead is placed in a zone of slow electrical conduction, during synchronous BiV pacing, very little LV myocardium is stimulated by the wave front initiated by the LV electrode, and little resynchronization is present. Pre-exciting the tissue at the LV electrode (by pacing the LV ahead of the RV, also known as LV offset) to give the slowly propagating wave front a "head start" results in its greater contribution to LV activation (Online Video 1). Serial ECGs performed with varying VV intervals can be used to identify the LV offset interval that produces a dominant R-wave in V_1 and QS complex in lead I (**Figure 6**). In an observational study, increasing R-wave amplitudes in V_1 and a change in axis from left to right with CRT was associated with favorable LV remodeling (41). Although there are no systematic studies of the value of ECG optimization, this is a widely available, inexpensive, and simple tool that the authors frequently use.

Anodal stimulation is an often under-recognized cause for a lack of CRT response (42). During pacing, electrons exit the cathode and return via the anode, with capture desired at the cathode. CRT devices allow multiple programmable pacing configurations. If pacing occurs between an LV electrode (cathode) and RV ring electrode (anode), and myocardial stimulation occurs only at the RV anode, effective CRT is not delivered (**Figure 7**). Anodal-only capture is corrected by adjusting the pacing output or configuration.

Percentage BiV pacing: ensuring continuous CRT. The percentage of QRS complexes that are resynchronized (i.e., the CRT "dose") correlates with HF outcome and mortality. Hayes et al. (43) reported optimal improvement in survival with >98.4% BiV pacing; a goal of >95% is commonly used. In a large national registry, 40% and 11% of patients had <98%

FIGURE 9 ECG Demonstrating Effects of His Bundle Pacing



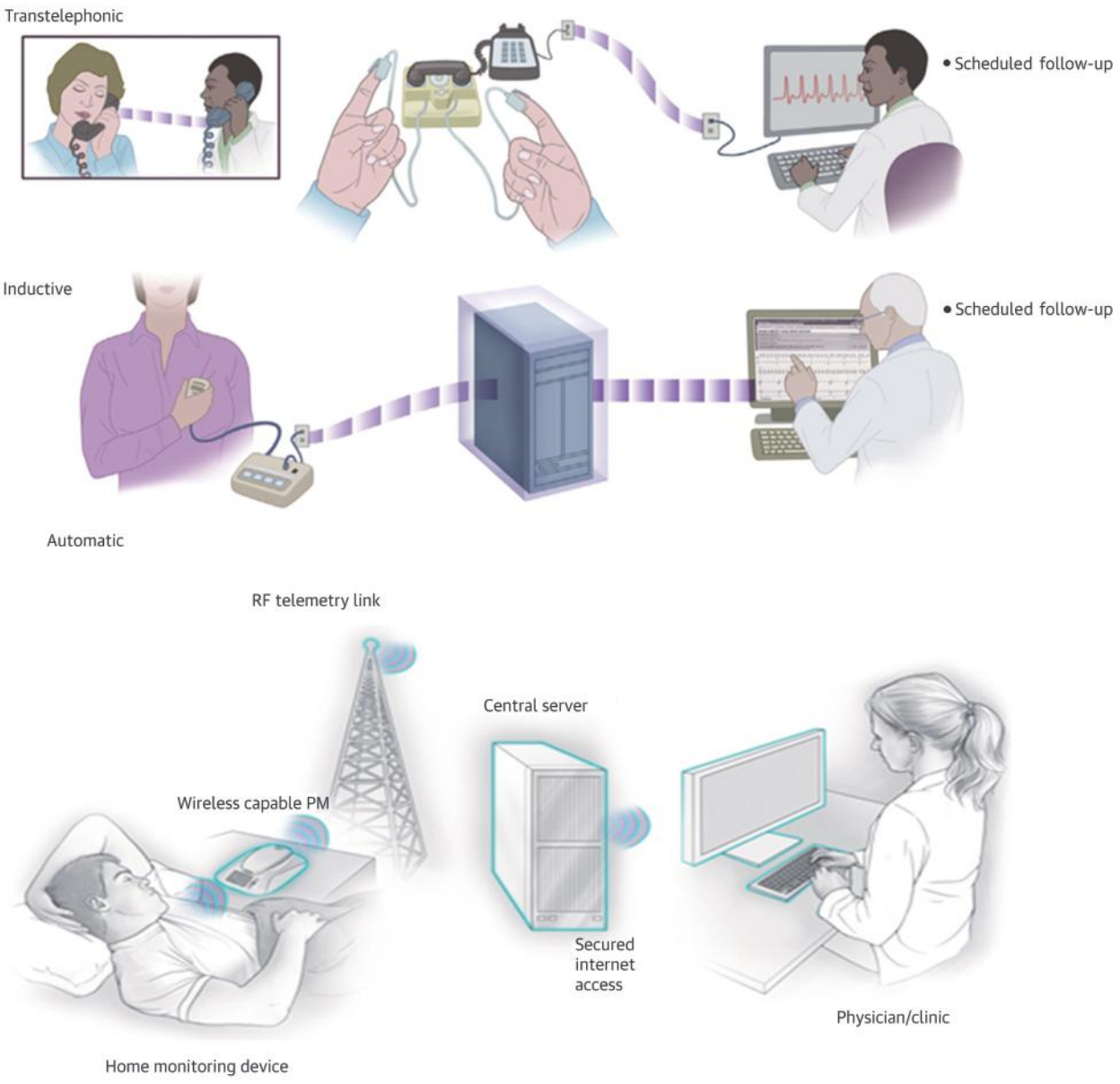
(Left) Atrial pacing is seen with native RBBB configuration. When high output pacing (VVI mode) is performed **(middle)**, the QRS normalizes in duration representing recruitment of the right and left ventricular conduction system. **(Right)** When the output is reduced, RBBB morphology is reproducible with loss of the recruitment of the left-sided conduction system. ECG = electrocardiogram; RBBB = right bundle branch block.

and <90% BiV pacing, respectively (44). Among patients with <98% pacing, atrial arrhythmias, premature ventricular contractions (PVCs), and inappropriately programmed AV intervals account for 30%, 17%, and 35% of pacing loss, respectively (44). Device interrogation provides the percentage of BiV pacing, as well as clues to the reason for its loss. CRT devices have the capability to provide "trigger" pacing from the LV lead in response to a sensed event on the RV lead. This leads to fusion or pseudofusion between the intrinsic beat and LV pacing. Triggered LV pacing does not afford the same hemodynamic benefits of "true" BiV pacing, and hence should be minimized. Although some device manufacturers provide data regarding frequency of triggered LV pacing, Holter monitoring may be required to detect fused QRS morphologies in others.

Frequent PVCs interfere with CRT and may independently worsen HF due to dyssynchrony. Treatment with beta-blockers or membrane-active antiarrhythmic drugs, and in select patients, catheter ablation of PVCs may improve CRT response (45).

Intrinsically conducted AF results in fusion and pseudofusion between LV pacing and native conduction, leading to loss of BiV pacing. Ablation of the AV node restores BiV pacing and improves CRT response (46). Routine AV node ablation in CRT recipients with permanent AF is controversial, as the benefits of response are weighed against the risks associated with pacemaker dependency. Hence, in patients with permanent AF, an initial strategy of pharmacological rate control with rapid escalation to AV node ablation if >99% BiV pacing is not achieved is reasonable. The role of antiarrhythmic drug

FIGURE 10 Evolution of Techniques for Monitoring of Pacemakers: Transtelephonic, Inductive, and Remote Wandless Monitoring

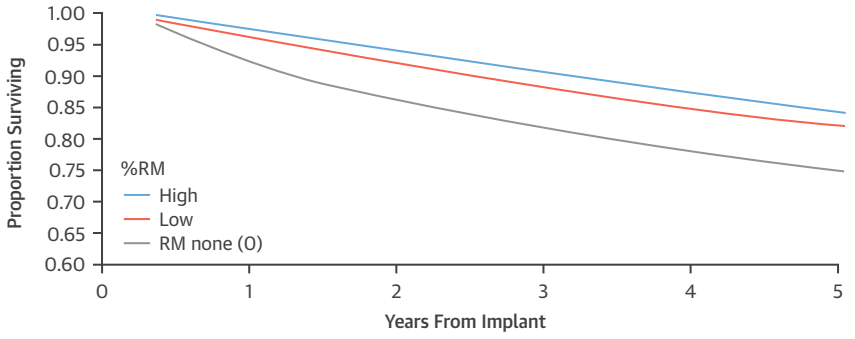


Although transtelephonic and inductive monitoring provide intermittent monitoring, radiofrequency wandless monitoring can provide device- and patient-related information more continuously. Modified from Slotwiner et al. (75). PM = pacemaker; RF = radiofrequency.

therapy and catheter ablation to restore sinus rhythm in paroxysmal AF in improving CRT response needs further investigation.

Optimizing device programming: programming AV and VV intervals. A number of studies have optimized device AV and VV intervals to determine whether CRT response may be improved. ECG-based, echocardiographic, and intracardiac electrogram-based AV and VV interval optimization have all been tested. Although in selected cases such a strategy is used, trials of routine optimization using echocardiography and device-based AA and VV interval optimization have been universally disappointing. Optimization is not routinely performed.

FIGURE 11 RM Use Is Associated With Better Patient Survival



No. at Risk

High	67,920	66,096	60,519	29,812	7,726	533
Low	59,786	57,221	52,473	30,715	10,236	1,042
RM	141,765	129,137	115,230	62,720	18,032	1,735

Cox survival

High %RM vs RM none; HR: 2.10 (2.04-2.16) P<0.001
Low %RM vs RM none; HR: 1.58 (1.54-1.62) P<0.001
High %RM vs low %RM; HR: 1.32 (1.27-1.36) P<0.001

In 269,471 patients with pacemakers and implantable cardioverter-defibrillators remotely monitored with the Merlin network, survival improved with greater use of RM. RM was not used in 53% of this cohort (RM None). Among those using RM at least once, high and low RM use was defined using a cutpoint of 75%. Patient survival was noted to improve in a graded fashion as the percentage of RM use increased. Adapted with permission from Varma et al. (55). HR = hazard ratio; RM = remote monitoring.

PARA-HISIAN PACING. As noted earlier, chronic RV apical pacing is associated with an increased risk of death, HF hospitalization, and persistent AF. BiV pacing is superior to RV pacing in patients with reduced EF (16). However, procedural complexity, complications, increased lead burden, CRT nonresponse, and long-term costs of device replacement have led to interest in selective pacing of the proximal conduction system to mimic the natural activation of the ventricles (**Figure 8**). His-bundle capture enables rapid activation of the ventricles by engaging the highly branching Purkinje network. On the ECG, selective capture of the His bundle results in a QRS complex similar to normal conduction (**Figure 9**). There is an isoelectric interval from the pacing stimulus to the QRS complex that is often equal to the HV interval. The restoration of a narrow QRS complex by His pacing represents an intact His-Purkinje system or the capability of overcoming impaired conduction within the His-Purkinje system by pacing current (**Figure 6**). Para-Hisian pacing can be achieved using a small-caliber pacing lead (Select Secure Model 3830, Medtronic, Minneapolis, Minnesota) delivered through specially designed sheaths (C 315 HIS) to map the AV septal region (**Figure 8**). Unipolar pacing aids selective capture of myocardial tissue at the lead tip, and is successful in 84% of patients (47,48). In patients with a wide complex, unstable escape rhythms, and diffuse infra-Hisian disease, it may not be feasible to map and place a pacing lead that results in a narrow QRS complex. Select Secure leads placed in the ventricle have a cumulative survival probability of 97.2% at 78 months, although data on long-term performance is lacking. Reliable selection of patients who are likely to have recruitment of the left-sided conduction system is challenging. His bundle pacing in patients with AV block results in higher rates of His-Purkinje system recruitment when the block is at the AV nodal level (93% to 98%) compared with when it is at the infranodal level (52% to 76%) (47). With His-bundle pacing, sensed R waves are often smaller than with pacing at other sites due to the paucity of ventricular myocardium near the membranous septum. The pacing thresholds are often higher when compared with traditional sites, resulting in shorter battery life. There are limited data regarding extraction of leads placed on the membranous septum. Technical aspects of His-bundle pacing are discussed elsewhere (49). Although promising as a superior alternative to RV apical pacing, larger studies involving longer follow-up are required before widespread adoption.

REMOTE MONITORING OF PACEMAKERS AND DIAGNOSTICS

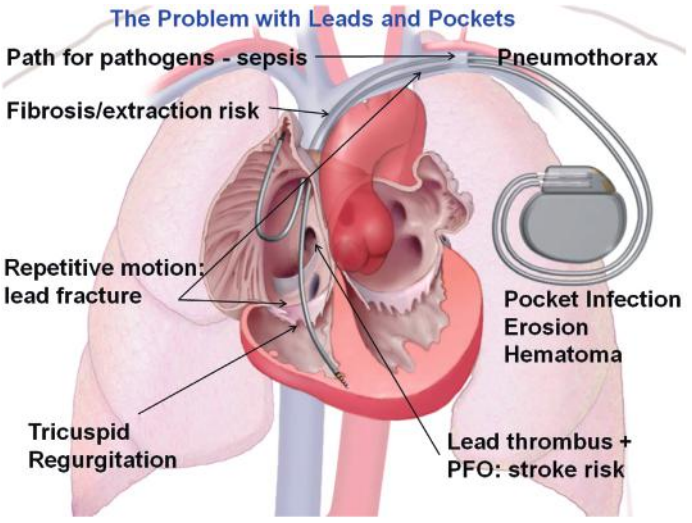
Worldwide, 7 million people live with a cardiovascular implantable electronic device to treat bradycardias, tachyarrhythmias, or HF and require effective monitoring for long-term care. RM and remote interrogation (RI) refer to acquisition of system or patient information from a cardiovascular implantable electronic device and transmitting it to a clinic distant from the patient to enhance care. When properly implemented, they can substantially reduce clinic burden and care delay, and can improve patient outcomes. Specifically, RI is routine and scheduled, requires coordination between the patient and clinic, and mirrors an office checkup; RM is automatic data transmission that typically requires no action by the patient that is triggered by clinical and device function alerts.

RM TECHNOLOGY. Transtelephonic monitoring. Transtelephonic monitoring (TTM) has been in use since approximately 1970, and requires a patient to make contact with skin electrodes (such as bracelets) that record a single-lead ECG and transmit it through an analog phone to the clinic (**Figure 10**). By observing the ECG and pacemaker magnet behavior, device status and battery function can be deduced. Due to the complexity for patients and clinic, and the marked superiority of RI and RM, new pacemakers do not use TTM, although many patients with legacy devices continue to use it.

Inductive transmission. RI typically uses inductive transmission. A patient holds a transmitter's inductive wand over the pacemaker to perform a full interrogation. The transmitter, in turn, connects via a landline or cellular connection to a server, which delivers a full device interrogation to the clinic that is often identical to the report created by an in-office visit. This includes: 1) battery status; 2) lead integrity; 3) lead sensing and pacing (threshold) function; 4) activity sensor statistics; 5) pacing frequency; and 6) stored arrhythmic events.

Radiofrequency RM. A wandless transmitter with radiofrequency capabilities automatically connects to the implanted pacemaker, with no action required on the patient's part, as long as he or she is within range. Typically, the transmitter is placed on or near a nightstand to enable daily communication in the event of alerts (e.g., device or rhythm abnormalities). Episodically, full transmissions that include all of the information available with RI are performed. Patients also can manually force a transmission by pushing a button on the transmitter.

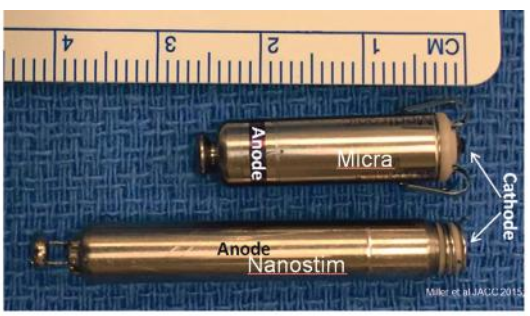
FIGURE 12 Mechanisms of Complications in Pacemaker With Extravascular Pockets and Transvenous Leads



Limitations of traditional transvenous pacemakers include increased risk of infection, thromboembolism, and lead failure, among others. PFO = patent foramen ovale.

In contrast to RI and TTM, RM checks patient and device status on a daily basis (as opposed to every 3 months), is fully automatic, and can verify transmissions and generate alerts when they are absent. Evidence suggests that this form of monitoring detects abnormalities sooner and may improve survival; new pacemakers either include this capability or will do so in the near future (50).

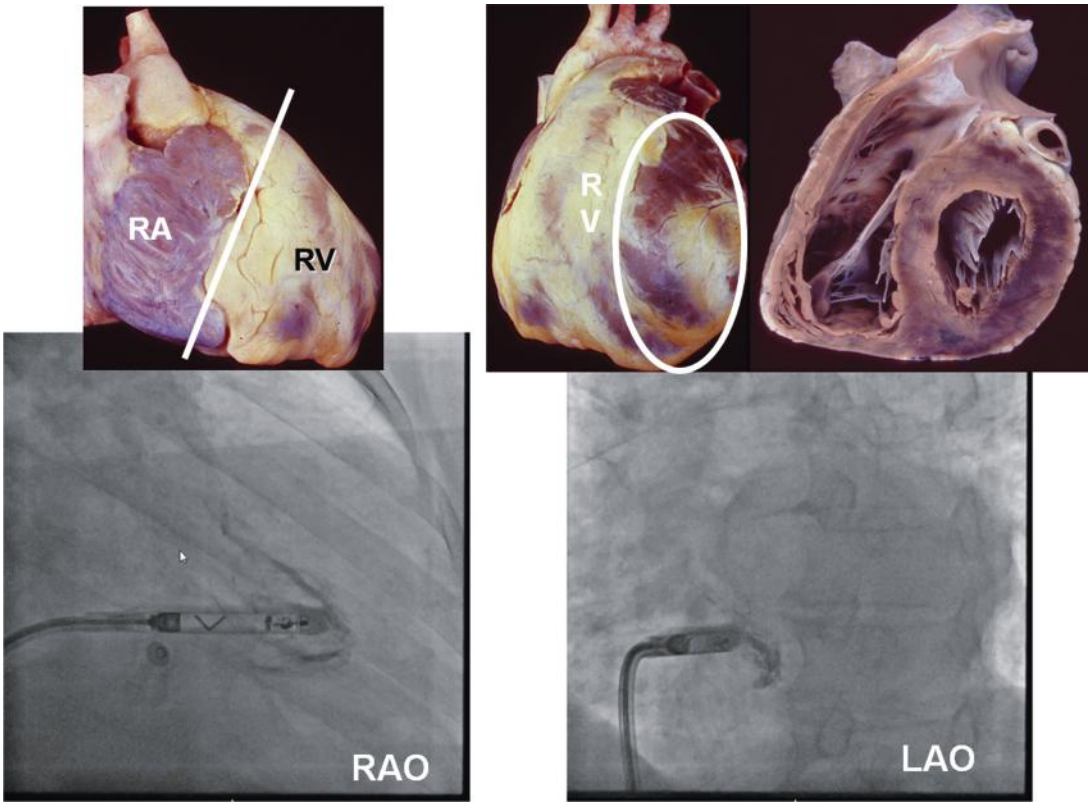
FIGURE 13 Single-Component Leadless Pacemakers



Device	Size	Means of Fixation	Patients	Successful Implantation	Major Complications	Perforation or Effusion	Device Dislodgement	Adequate Pacing Measures at 6 Mo
	cm^3		no.	%	%	%	%	%
Nanostim	1.0	Helical wire screw	526	95.8	6.5	1.5	1.1	90.0
Micra	0.8	Tines	725	99.2	4.0	1.6	0	98.3

The MICRA (Medtronic, Minneapolis, Minnesota) and Nanostim (St. Jude Medical, St. Paul, Minnesota) leadless pacemakers are compared. Reprinted with permission from Miller et al. (61) and Link et al. (76).

FIGURE 14 Leadless Pacemaker Implantation

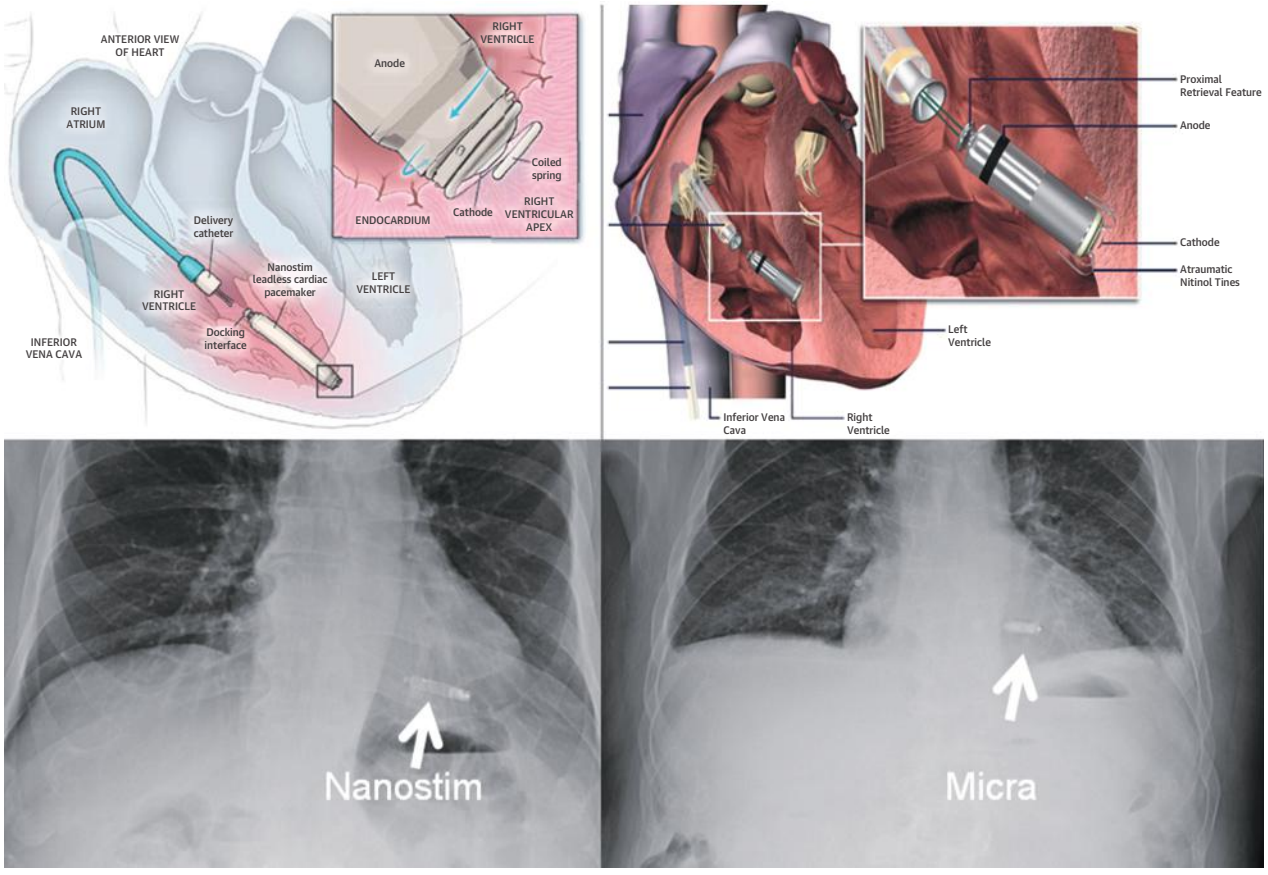


(Left panels) (Top) Anatomic specimen in the RAO view, corresponding to the cine image below. The **angled vertical line** separates the RA from the RV. **(Bottom)** A delivery catheter has entered the RA, crossed the tricuspid valve, and positioned the leadless pacemaker at the RV apical septum. Contrast medium injection highlights the pacemaker's position and RV trabeculations. **(Right panels) (Top)** Anatomic specimen in the LAO view, with a **circle** around the LV and RV indicating the crescent-shaped RV. The **top right** specimen is cut to show the internal RV. **(Bottom)** Corresponding cine image showing the septal pacemaker position. RA = right atrium; other abbreviations as in Figures 3 and 5.

MONITORING OF DEVICE AND LEAD FUNCTION. RM effectively detects system malfunction with less delay than clinic visits with TTM (51). In a randomized study comparing RM versus in-person clinic visits augmented by TTM, the remote arm had a shorter mean time to first diagnosis of clinically actionable events (5.7 months vs. 7.7 months). Events included significant pacing threshold increases or loss of capture, changes in lead impedance, and generator battery depletion to replacement indicators (51). Furthermore, a randomized trial of long-term RM versus in-clinic follow-up of pacemaker recipients showed that the RM group had a similar rate of death and hospitalization for device-related or cardiovascular adverse events, demonstrating its safety (52).

DETECTION OF SUPRAVENTRICULAR ARRHYTHMIA AND STROKE PREVENTION. Detection of asymptomatic AF using RM permits timely therapy, including the introduction of anticoagulation therapy to prevent stroke in at-risk individuals (53). Remotely monitored patients are also less likely to be hospitalized for atrial arrhythmias (52). In patients without clinical AF, subclinical atrial arrhythmias lasting 6 min or longer are associated with a significantly increased risk of ischemic stroke or embolism (54). Ongoing trials will determine the effect of therapy for these brief, asymptomatic events. Unrelated to stroke, atrial tachyarrhythmia detection permits medical therapy and rate control interventions, potentially accounting for the reduction in inappropriate shocks with RM and improving HF.

FIGURE 15 Leadless Pacemaker Fixation Mechanism and Radiographic Appearance



(Left) Nanostim active fixation leadless pacemaker. **(Right)** Micra passive fixation transcatheter pacing system. **Top panels** adapted from Reddy et al. (62) and Reynolds et al. (63).

DETECTION OF VENTRICULAR TACHYARRHYTHMIA. The benefit of detection of ventricular arrhythmia by RM has been demonstrated in multiple implantable cardioverter-defibrillator (ICD) studies and registries; its role in patients with pacemakers is less clear. A meta-analysis comparing RM to in-clinic visits demonstrated a nonsignificant trend toward reduced cardiovascular mortality, a similar overall shock rate, a significantly reduced inappropriate shock rate, and shorter time to the detection of atrial and ventricular arrhythmias with RM (50).

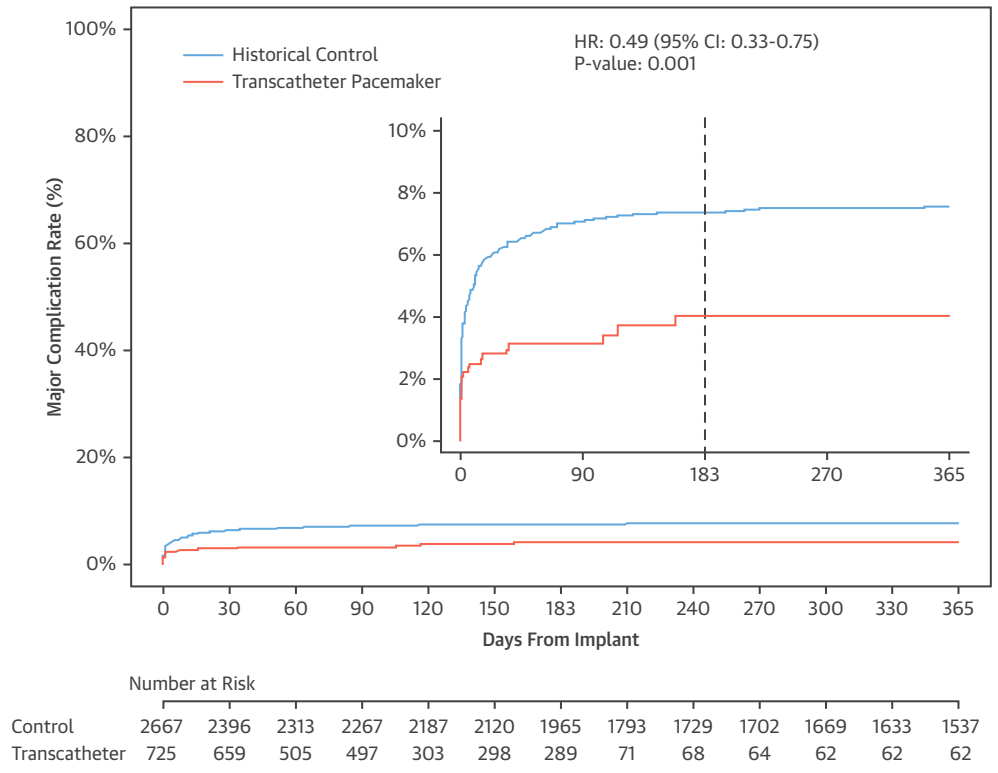
RM AND SURVIVAL. RM permits analytics on large patient numbers. In the ALTITUDE registry and Merlin network, the use of RM was associated with a lower mortality in recipients of pacemakers, ICDs, and CRT (**Figure 11**) (55,56). The improved survival may have resulted from early recognition and management of arrhythmia and HF. However, a meta-analysis of RM trials found no difference in survival compared with in-office visits (indicating safety), with a potential survival benefit limited to systems using daily transmission verification (radiofrequency systems) (50).

HF MONITORING. Current ICDs and CRT devices can monitor for HF using thoracic impedance as a surrogate for pulmonary congestion. This is sometimes used in combination with other parameters, such as heart rate variability, patient activity level, rapid ventricular rate during AF, and low CRT pacing, to detect possible worsening of HF. Although these programs can provide early warning of worsening HF, their use has not been shown to improve HF clinical outcomes and survival (57,58).

LEADLESS PACING

Cardiac pacemakers are extremely effective for treating symptomatic bradycardia. However, the same system paradigm has been in use for the past

FIGURE 16 Complications With Transcatheter Leadless Pacemakers Versus Historical Transvenous Control Subjects

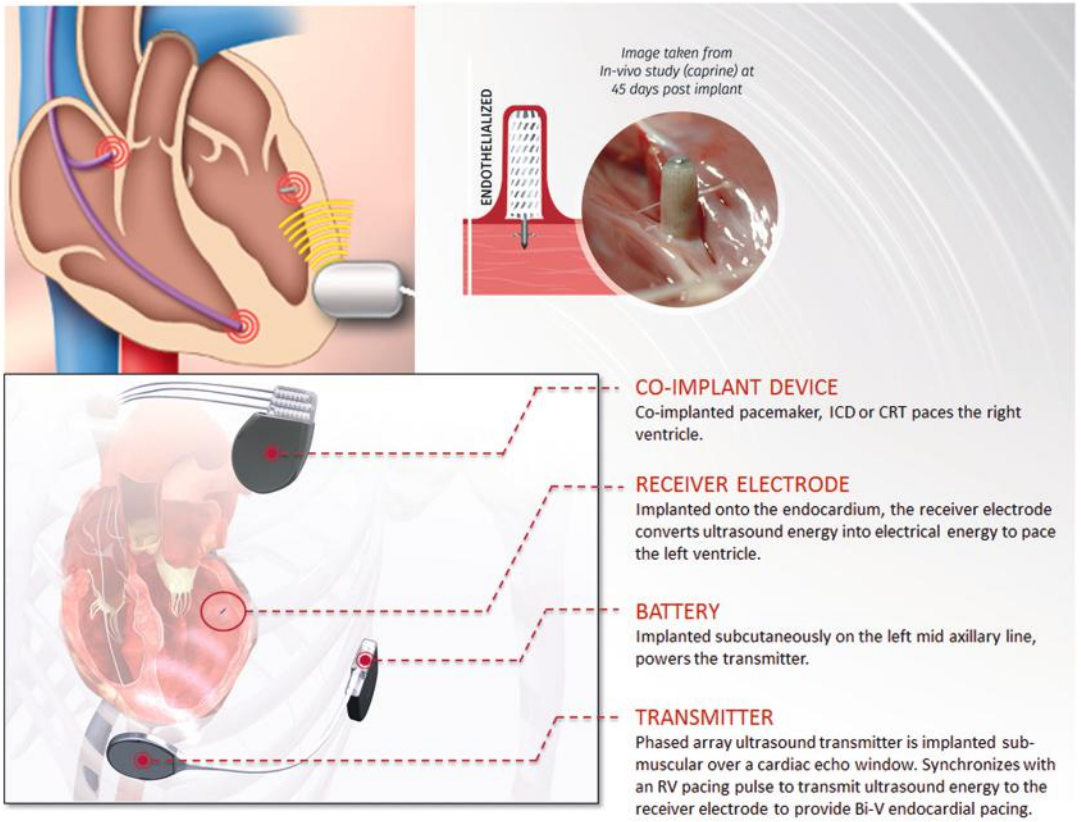


In this Micra TPS (Medtronic, Minneapolis, Minnesota) study post hoc analysis, the 725 study patients were compared with 2,667 patients who received transvenous pacemakers in previous studies as a historical control cohort. Leadless study patients were older and had more comorbidities than control subjects. At 6-month follow-up, patients with leadless pacemakers had significantly fewer major complications than control patients (HR: 0.49; $p < 0.001$), with study patients experiencing fewer hospitalizations, system revisions, and dislodgments. Reprinted with permission from Reynolds et al. (63). Abbreviations as in Figure 4.

50 years, namely, an implanted extravascular pulse generator connected to a lead that traverses the vasculature to make contact with the endocardium. Although reliable and effective, complications are almost universally caused by the lead, which is a polyurethane- or silicone-encapsulated conductor that is subject to repetitive mechanical motion with each cardiac cycle and with shoulder girdle motion, exposing its constituent materials to mechanical stress and fracture (**Figure 12**) (59). Because pulse generator pockets are extravascular, they may serve as a nidus for bacterial growth by providing a surface for bacterial biofilm elaboration; the lead then serves as a conduit for bacterial entry to the blood pool. Moreover, leads are inherently thrombogenic, eliciting fibrotic reactions that make removal technically challenging, with a risk of venous perforation, valve disruption, hemothorax, and death. Lead thrombogenicity also introduces a risk of stroke in the setting of venosystemic shunts. Last, by crossing the tricuspid valve, a lead can impinge on leaflet motion, promote clinically significant tricuspid regurgitation, and impair the response to cardiac resynchronization (60). Given the effectiveness of pacemakers and the host of potential lead-related complications, a leadless pacemaker was developed.

Leadless pacemakers have been developed using 2 distinct strategies: single-component and multicomponent systems (61). With single-component systems, the entire pacemaker (battery, electronics, stimulating electrodes, and sensors) is compressed into a small capsule that is delivered into the heart using a deflectable sheath. Advantages of this strategy include greater energy efficiency, system simplicity, and ease of implantation. Limitations, however, include retrieval of intracardiac systems years later after battery depletion, and uncertain thrombus and infection risk. With a multicomponent system, a small "seed" is placed within a cardiac chamber to act as an energy transducer. A second, extrathoracic

FIGURE 17 Multicomponent Leadless Pacing System



The battery/transmitter unit detects the pacing stimulus from the coimplant, and an ultrasound pulse is sent to the receiver electrode, which converts the ultrasound energy to a pacing pulse. ICD = implantable cardioverter-defibrillator; other abbreviations as in Figures 1 and 3.

component beams energy (ultrasound or radio waves) to the seed, and the seed then converts the energy to a pacing pulse.

SINGLE-COMPONENT LEADLESS PACING. In single-component leadless pacemakers, the pulse generator and sensing and pacing electrodes are all entirely self-contained in a capsule designed for intraventricular placement, eliminating the need for pockets and leads. There are currently 2 devices that have been widely tested in humans: the Nanostim leadless cardiac pacemaker (LCP) (St. Jude Medical, St. Paul, Minnesota), and the MICRA transcatheter pacing system (TPS) (Medtronic), both of which can deliver single-chamber rate-responsive ventricular pacing (Figure 13) (62,63). The systems are placed via an 18- (LCP) or 24-F (TPS) sheath inserted in a femoral vein, and are delivered to the RV apical septum (Figure 14). The systems differ with regard to fixation mechanism. The LCP uses an active fixation helix, with rotation of the entire device via a delivery catheter handle control knob at the time of implantation, whereas the TPS has integrated electrically inert nitinol tines that are used solely for fixation (Figure 15). In the initial trial experience for both systems, successful implantation occurred in over 95% of cases, with major complications in 4% to 6.5% of cases, perforation or effusion in 1.5% to 1.6% of cases, and adequate pacing measures at 6 months in 90% to 98.3%. (62,63). The TPS is physically smaller than the LCP (0.8 cm^3 vs. 1.0 cm^3), but has a larger diameter (24-F vs. 18-F introducer sheath) and a smaller battery, with shorter anticipated longevity at nominal settings (9.6 years vs. 14.7 years) (61). The TPS uses autocapture technology to algorithmically use the lower energy pacing pulses to extend longevity, and uses radio-frequency telemetry, which may permit daily alerts and passive follow-up for true RM. The LCP uses conductive telemetry, which saves battery charge, but requires placement of patches on the skin for

pacemaker communication. Direct comparisons between systems have not been performed.

Ideal management of leadless pacemakers after battery depletion is not known. Little data exists regarding removal of chronically implanted systems. Both available pacemakers have a posterior docking button designed to facilitate late device retrieval (Online Videos 2A, 2B, and 2C, Online Figure 1). In the TPS experience, 7 of 9 attempts at percutaneous retrieval were successful, including all attempts within 6 months of implantation (64). Specifically designed removal tools have been developed for the LCP. Fourteen of 15 removal attempts were successful in a recent report; 4 of 4 acute removals (<6 weeks) and 10 of 11 chronic removals (implant duration 88 to 1,188 days) (65). The 1 failed removal was because of inaccessibility of the proximal hub due to its position under the tricuspid valve. Given that leadless pacemakers are one-fiftieth the volume of the typical RV, device deactivation and insertion of a replacement may be a viable strategy for battery depletion for those patients who outlive their pacemaker's battery.

Both leadless pacemaker systems have been compared with cohorts of transvenous pacemaker recipients, although direct, prospective randomized comparisons are lacking (**Figure 16** describes the MICRA study) (63,66). In these analyses, the leadless pacemaker was associated with fewer short- and intermediate-term complications. This was driven largely by reductions in or the absence of lead complications, infections, and pocket complications. Across all leadless devices, infections appear rare, perhaps due to the lack of an extravascular pocket with direct connection to the bloodstream (63,66).

The major limitation of current-generation leadless pacemakers is their ability to only perform single-chamber ventricular pacing. Thus, for most patients with sinus node dysfunction, or sinus rhythm and AV block, dual-chamber transvenous devices are preferred. Similarly, patients in need of cardiac resynchronization are not candidates for single-component leadless pacemakers. Patients with inferior vena cava filters and mechanical tricuspid valves are not candidates. Although chronic device embolization has not been reported, it remains a potential concern. The accuracy of rate-responsive features, given that sensors are intracardiac, is not well understood. And last, as noted earlier, optimal management at the time of battery depletion is not known. Nonetheless, given the lack of a surgical wound, absence of post-implant arm restrictions, and reduced rate of complications, leadless pacemakers represent a paradigm shift that will likely be clinically transformative. Dual-chamber systems are currently under active development; design challenges include device-device communication and fixation in the thin-walled right atrium.

MULTICOMPONENT LEADLESS PACING. The WiSE-CRT system (EBR Systems, Sunnyvale, California) uses a multicomponent strategy to provide leadless cardiac resynchronization. A tiny (9.1 mm × 2.7 mm, 0.05 cm^3) receiver electrode composed of polyester-covered titanium is implanted endocardially in the LV. A subcutaneous pulse generator is placed in the left lateral thorax and generates ultrasound pulses, which are converted to electrical pacing stimuli by the endocardial seed (**Figure 17**). All patients in the WiSE-CRT study had a traditional pacemaker or defibrillator; the subcutaneous WiSE-CRT pulse generator detected the RV pacing pulse from the standard system, which triggered endocardial LV pacing. In the initial trial, patients with failed coronary sinus lead placement, nonresponse to CRT, or need for an upgrade to CRT were enrolled. Data from small studies demonstrated significant QRS narrowing, absolute EF improvements of 5%, and improvements in composite clinical scores at 6 months (67). The initial WiSE-CRT study was stopped for safety reasons: 3 patients (18%) developed pericardial effusions associated with seed delivery (68). Following delivery system redesign, early data from 14 patients demonstrated no implant-related adverse events (69). Leadless endocardial LV pacing holds promise in that it may be more physiological, afford greater opportunities for LV pacing site selection, lead to a greater CRT response with lower risk of proarrhythmia, eliminate phrenic nerve stimulation, and mitigate against the risks of mitral regurgitation and lead-related thrombus. However, the technology is early in its development, and there are many unknowns. Challenges may include identification of acoustic windows in a subset of patients, energy inefficiency and early battery depletion, theoretical hazards of chronic sonification of cardiac tissues, and uncertain susceptibility to environmental interference. Other mechanisms for 2-stage leadless pacing are under early exploration. Pre-clinical experiments have been performed using magnetic induction rather than ultrasound to drive an endocardial seed (70). Other multicomponent leadless systems including the integration of a subcutaneous ICD with a leadless pacemaker are under development, allowing for antibradycardia pacing and antitachycardia pacing in conjunction with a subcutaneous ICD (61).

BATTERYLESS PACING. Battery depletion and pulse generator exchanges represent sources of

complications for transvenous systems and uncertainty in leadless systems. Cardiac and pulmonary motion provide an inexhaustible source of energy during the life of a patient. Piezoelectric nanowires have been deployed on flexible devices to generate voltages as large as 1 to 2 V and currents up to 100 nA, sufficient to power the microelectronics of a pacemaker (71). Motion harvesting pacemakers remain in the realm of research, although devices have been built and tested in animal models.

Biological pacemakers modify nonpacemaker myocytes to provide automaticity using gene therapy technologies, or add pacemaker syncytia to the heart through adult or embryonic stem cell therapies (72,73). Biological pacemakers are in the early stages of development, and current challenges include difficulty ensuring long-term engraftment and potential for proarrhythmia.

CONCLUSIONS

Pacemakers have evolved from simple devices that prevent catastrophic bradycardia to complex, highly programmable systems. Cardiac resynchronization is established for the treatment of HF, but patient selection, optimization of response, management of nonresponders, and multisite LV pacing remain areas of active investigation. His-bundle pacing and leadless pacing offer fundamental shifts in approach and potentially improved clinical outcomes. On the horizon may be batteryless pacemakers that transform mechanical motion into usable electrical energy.

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KEY WORDS His bundle pacing, leadless pacing, remote monitoring, resynchronization

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