REVIEW ARTICLE

Physiologic Pacing in Heart Failure

Mihail G. Chelu, M.D., Ph.D.,[1-3] Jeanne E. Poole, M.D.,[4] and Kenneth A. Ellenbogen, M.D.[5]

SUMMARY

Cardiac physiologic pacing, also known as cardiac resynchronization therapy, is indicated in patients with heart failure, reduced left ventricular ejection fraction (LVEF) of 50% or less, and either a high (or anticipated high) ventricular pacing burden or a wide QRS complex. Traditionally, physiologic pacing has been achieved with biventricular pacing with a right ventricular lead and a coronary sinus branch lead. Randomized trials involving more than 10,000 patients with heart failure have shown clinical, exercise, and quality-of-life benefits associated with biventricular pacing, as well as improved LVEF and reduced mitral regurgitation and ventricular volumes. These benefits are greatest in patients with left bundle-branch block and a QRS duration of 150 msec or longer. Recent studies support targeting the His bundle or left bundle branch as an alternative cardiac physiologic pacing strategy. Ongoing randomized trials are expected to more clearly define the comparative efficacy and safety of conduction system pacing as compared with biventricular pacing.

Cardiac resynchronization therapy (CRT), now referred to as cardiac physiologic pacing in society guidelines, is a cornerstone therapy for the management of heart failure with reduced ejection fraction and concomitant conduction system disease.[1] Between 80,000 and 120,000 patients receive implanted CRT devices each year in the United States. Traditionally, CRT was accomplished with biventricular pacing, which uses pacing leads in the right ventricle and the coronary sinus (Fig. 1). A variety of leads that can be implanted in the coronary sinus are currently available, including quadripolar leads (leads with 4 electrodes and 14 pacing configurations) that give greater flexibility in choosing pacing vectors (direction and magnitude of the pacing electrical impulse) and allow for multisite pacing.

There has been tremendous progress in physiologic pacing with the addition of conduction system pacing at the level of the His bundle[2] and left bundle branch[3] (Fig. 1). These latest developments are anticipated to fundamentally change our approach to the management of heart failure and concomitant conduction system disease.

Given the conceptual developments in the field, ongoing major clinical trials, publications of new guidelines, and increasing numbers of patients with a CRT device, all clinicians should have a basic understanding of the framework behind CRT (an essential treatment in the management of heart failure), the differences between biventricular pacing and conduction system pacing, the data supporting each therapy, the electrocardiographic characteristics, the management of devices, and the future of CRT. We also suggest that the nomenclature for CRT be replaced by cardiac physiologic pacing with a coronary sinus lead or cardiac physiologic pacing with a conduction system lead to be more descriptive.

Author affiliations are listed at the end of the article. Kenneth A. Ellenbogen may be contacted at kenneth.ellenbogen@vcuhealth.org or at the Division of Cardiology and Cardiac Electrophysiology, Virginia Commonwealth University School of Medicine, P.O. Box 980053, Richmond, VA 23298.

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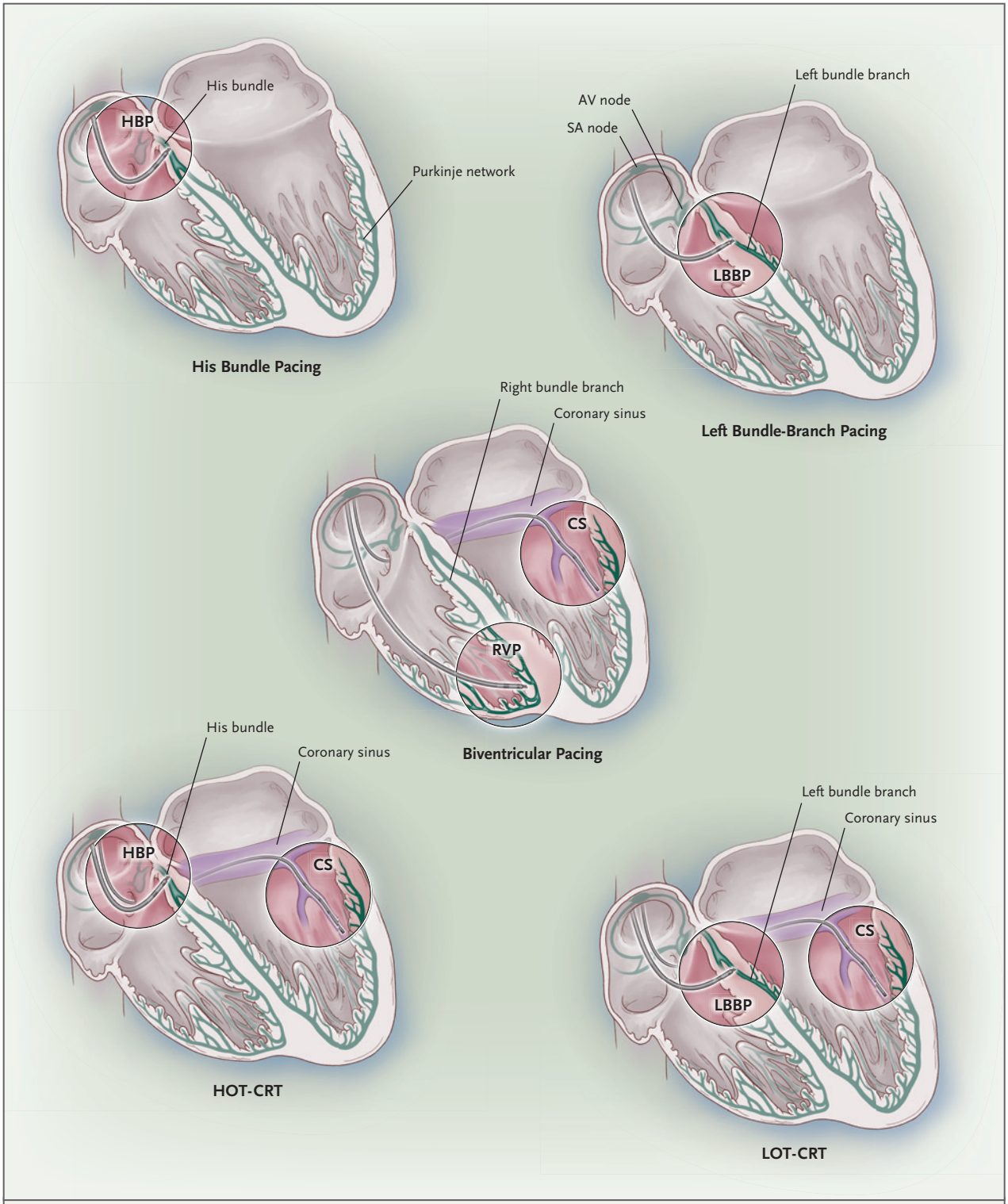


Figure 1. Lead Configurations.

Shown are the lead configurations for His bundle pacing (HBP), left bundle-branch pacing (LBBP), biventricular pacing, His bundle-branch–optimized cardiac resynchronization therapy (HOT-CRT), and left bundle-branch–optimized cardiac resynchronization therapy (LOT-CRT). AV denotes atrioventricular, CS coronary sinus, RVP right ventricular pacing, and SA sinoatrial node.

BIVENTRICULAR PACING FOR CARDIAC PHYSIOLOGIC PACING

The physiologic functions of the human conduction system ensure that mechanical contractions of the heart maintain atrioventricular, intraventricular, and interventricular synchrony. When activation of the right and left ventricles is dyssynchronous, with left bundle-branch block or pacing of the right ventricular myocardium, left ventricular function may decrease. This decrease in function is more likely to occur in patients who already have reduced left ventricular systolic function.[4,5] For the past 20 years, the primary approach to overcoming left ventricular dyssynchrony in patients with heart failure with reduced ejection fraction has been biventricular pacing, with a lead introduced through the coronary sinus into a lateral or posterolateral coronary sinus venous branch to capture the epicardium (Fig. 1). Alternatively, when placement of the left ventricular lead through the coronary sinus is not possible, a lead may be placed directly on the left ventricular epicardium during an open or thoracoscopic surgical procedure. Biventricular pacing achieves its salutary effect by synchronizing the activation of the right ventricular endocardium with that of the left ventricular epicardium by means of a pacing or implantable cardioverter–defibrillator (ICD) lead placed in the right ventricle, which results in reverse ventricular remodeling. Activation proceeds from cell to cell in the myocardium without directly engaging the conduction system, resulting in a fusion of the electrical wavefronts from stimulation of the right ventricle and left ventricle. Challenges to successful biventricular pacing include a lack of appropriate target vessels in the coronary sinus in which to place leads, lead dislodgement, lateral myocardial scarring, and differential benefit relative to both QRS morphologic features and QRS duration. Device algorithms have been developed to optimize pacing by fusing intrinsic conduction down the right bundle branch with pacing from the coronary sinus lead.

BIVENTRICULAR PACING IN HEART FAILURE

Biventricular pacing has been tested in many randomized clinical trials — which have together involved more than 10,000 patients with heart failure — and has been shown to improve clinical outcomes (Table 1). Early trials showed that biventricular pacing improved left ventricular ejection fraction (LVEF), reduced mitral regurgitation, reduced left ventricular volumes, and improved quality of life.[7-10,12,24-26]

Following these encouraging results, several large randomized trials were conducted to evaluate the end points of death and hospitalization. The first two of these trials, the COMPANION (Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure) and CARE-HF (Cardiac Resynchronization — Heart Failure) trials,[13,14] focused on patients with advanced heart failure (New York Heart Association [NYHA] class III or IV). Both trials required a minimum QRS duration of at least 120 msec and an LVEF of 35% or less. In the COMPANION trial, a total of 1520 patients were assigned to receive a biventricular pacemaker, a biventricular pacemaker plus an ICD, or no implanted device (control group).[13] All the patients were to be treated with the best available medical therapy for heart failure. Patients in the biventricular pacemaker group and those in the biventricular pacemaker plus ICD group had a significant benefit with respect to the incidence of death from any cause or hospitalization for any cause (the composite primary end point) as compared with the control group. A significant reduction in death from any cause was confined to patients with a biventricular pacemaker and ICD, as compared with the control group. The greatest benefit was observed among patients with a QRS duration of at least 150 msec.

In the CARE-HF trial, a total of 813 patients with a QRS duration of at least 120 msec were assigned to receive a biventricular pacemaker or the best available medical therapy.[14] The incidence of death from any cause or hospitalization for a major cardiovascular event (the composite primary end point) was substantially lower among the patients who received a biventricular pacemaker than among those in the control group. Long-term follow-up showed that biventricular pacing was associated with a significant reduction in sudden cardiac death.[27] Similar to the findings in the COMPANION trial, the results of the CARE-HF trial showed that the patients who had the widest QRS duration (≥160 msec) had the best outcomes.

The question of the benefit of biventricular pacing in cases of less severe heart failure (predominantly NYHA class II) was tested in MADIT-CRT

Table 1. Trials of Cardiac Physiologic Pacing with Biventricular Pacing.*

Trial	Type or Comparison	NYHA Class	LVEF	SR or AF	QRS	LBBB or IVCD	Primary End Point	Primary End-Point Results
			%		*msec*	%		
Early trials								
MUSTIC-SR (48 patients)[6]	Single-blind, crossover CRT on or off	III	≤35	SR	>150	87	6MWT, peak VO_2, LVEF, NYHA class, QOL, MR	Improved peak VO_2, LVEF, NYHA class, QOL, MR
MUSTIC AF (43 patients)[7]†	Single-blind crossover CRT on or off	III	≤35	AF	≥200	NA	6MWT, peak VO_2, QOL	Improved 6MWT, QOL
MIRACLE (453 patients)[8]	CRT vs. medical care	III, IV	≤35	SR	≥130	NA	6-mo QOL, NYHA class, 6MWT	Improved QOL, NYHA class, 6MWT
PATH-CHF (41 patients)[9]	Single-blind, crossover CRT on or off	III, IV	≤35	SR	>120	97	VO_2, QOL, 6MWT, LVEF, NYHA class	Trend toward an improvement in all primary and secondary end points with BIVP
MIRACLE ICD (369 patients)[10]	Double-blind, parallel controlled, ICD vs. CRT CRT on or off	III, IV	≤35	SR	≥130	94	6-mo QOL, NYHA class, 6MWT	Improved QOL, NYHA class, 6MWT
CONTAK CD (490 patients)[11]	ICD vs. CRT CRT on or off	II–IV	≤35	SR	≥120	46	At 6 mo, death from any cause, hospitalization for HF, and VT or VF requiring device intervention	Decreased HF progression; improved peak VO_2, NYHA class, QOL, LV volumes
MIRACLE ICD II (186 patients)[12]	ICD vs. CRT, double blind, parallel-controlled CRT on or off	II	≤35	SR	≥130	83.4	VO_2, NYHA class, QOL, 6MWT, LV volumes, and LVEF at 6 mo; composite clinical response	No change in exercise capacity; improved LV volumes, LVEF, and composite clinical responses
Large RCTs								
COMPANION (1520 patients)[13]	Three groups: ICD with CRT, CRT without ICD, or optimal medical therapy	III, IV	≤35	SR	≥120	86	Death from any cause or hospitalization for any cause	Both CRT and ICD with CRT better than optimal medical therapy alone
CARE-HF (813 patients)[14]	CRT vs. optimal medical therapy	III, IV	≤35	SR	≥120	95	Death from any cause or unplanned cardiovascular hospitalization	CRT better than optimal medical therapy
MADIT-CRT (1820 patients)[15]	ICD with CRT vs. ICD alone	I, II	≤30	SR	≥130	70.5	Death from any cause or HF events	CRT better than optimal medical therapy
RAFT (1798 patients)[16]	ICD with BIVP vs. ICD alone	II, III	≤30	SR or AF	≥120	72	Death from any cause or hospitalization for HF	CRT did not reduce mortality but did reduce HF events

REVERSE (610 patients)[17]	CRT with ICD if LVEF ≤35% CRT alone if LVEF ≥36% and ≤40% CRT on or off over 12 mo	I, II	≤40	SR	≥120	60.5	HF clinical score composite	Clinical composite score better with CRT (with or without ICD)
RCTs in HF, QRS ≤120 to 130 msec								
NARROW-CRT (120 patients)[18]‡	CRT and ICD vs. DDD and ICD	II, III	≤35	SR	<120	NA	HF clinical composite response	CRT associated with better HF clinical composite response
LESSER-EARTH (85 patients)[19]†	CRT or ICD CRT on or off	None§	≤35	SR	<120	NA	Submaximal exercise duration with VO_2, QOL, reverse LV remodeling	CRT did not improve exercise capacity, symptoms, QOL or reverse LV remodeling
EchoCRT (809 patients)[20]†‡	CRT or ICD CRT on or off	III, IV	≤35	SR	≤130	NA	Death from any cause or HF hospitalization	CRT did not decrease mortality or HF hospitalization
RethinQ (172 patients)[21]	CRT or ICD CRT on or off	III	≤35	SR	≤130	NA	VO_2, at 6 mo	CRT did not improve VO_2
ESTEEM-CRT (68 patients)[22]	CRT or ICD CRT on or off	III	≤35	SR	≤130	NA	Hemodynamics (LV dP–dt[max]) at the time of implantation and chronic exercise performance, echo-determined reverse remodeling	CRT did not improve hemodynamics at the time of implantation, long-term exercise performance, or reverse remodeling
RCT of HF prevention, substantial RV pacing								
BLOCK HF (691 patients)[23]	Pacemaker indicated for AV block Double-blind randomization to BIVP or RVP If LVEF ≤35%, patients randomly assigned to ICD with BIVP or without BIVP ¶	I–III	≤50	SR or AF	NA	NA	Death from any cause, HF-related urgent care, or ≥15% increase in LVESI	BIVP reduced mortality and morbidity, improved clinical outcomes, QOL, HF symptoms

* 6MWT denotes 6-minute walk test, AF atrial fibrillation, AV atrioventricular, BIVP biventricular pacing, CRT cardiac resynchronization therapy, HF heart failure, ICD implantable cardioverter–defibrillator, IVCD intraventricular conduction delay, LBBB left bundle-branch block, LV dP–dt(max) left ventricular maximal pressure rise, LVEF left ventricular ejection fraction, LVESI left ventricular end-systolic index, MR mitral regurgitation, NA not applicable, NYHA New York Heart Association, QOL quality of life, RVP right ventricular pacing, SR sinus rhythm, VF ventricular fibrillation, VO_2 maximum volume of oxygen, and VT ventricular tachycardia.
† The trial was terminated early for futility.
‡ Echocardiographic evidence of cardiac dyssynchrony was required.
§ Patients had symptoms of heart failure.
¶ ICD is indicated in CRT NYHA class IV.

(Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy) and RAFT (Resynchronization–Defibrillation for Ambulatory Heart Failure Trial), which enrolled 1820 and 1798 patients, respectively.[15,16] An important distinction of these trials from earlier trials is that all patients received an ICD on the basis of guideline indications (ischemic or nonischemic heart failure and LVEF ≤35%) and were randomly assigned to receive biventricular pacing in combination with an ICD or an ICD alone. Both trials showed significant reductions in their primary composite outcomes of death and heart failure as well as reductions in death from any cause alone. Greater benefit was observed among patients with QRS durations of 150 msec or longer and QRS morphologic features of left bundle-branch block. In a post hoc analysis of the MADIT-CRT trial, a benefit of CRT was not observed among patients who had morphologic features of non–left bundle-branch block.[1,28]

Results of the REVERSE (Resynchronization Reverses Remodeling in Systolic Left Ventricular Dysfunction) trial also support these findings.[17] This trial was designed as a crossover study and enrolled 610 patients with moderate heart failure, all of whom had received an implanted biventricular pacemaker (LVEF, ≥36 to ≤40%) or a biventricular pacemaker plus ICD (LVEF, ≤35%). The patients were randomly assigned to biventricular pacing either in the on or off mode for 12 months. Biventricular pacing was associated with a significant improvement in the primary heart-failure composite outcome, which scored patients' condition as improved, unchanged, or worsened. A post hoc analysis showed that the benefit increased as a continuum of the QRS duration with negligible benefit for patients with QRS durations of 130 msec or less.[29] Subsequently, four randomized trials confirmed the lack of benefit in patients with a borderline narrow QRS duration.[18-22]

A consistent observation is that nonresponse to biventricular pacing will be observed in approximately one third of patients with heart failure and concurrent conduction-system disease. Response is generally measured by evidence of reverse cardiac remodeling with a reduction in left ventricular end-systolic volume along with improvements in functional status, LVEF, and 6-minute walk distance. In the large randomized trials of biventricular pacing, reductions in the primary end point–driven outcomes of heart-failure events and hospitalizations were observed consistently. Extrapolation of these findings to an individual patient may be reasonable if heart-failure symptoms stabilize, even without a change in left ventricular end-diastolic volume or LVEF. Patients who do not have a response may include those with morphologic features of non–left bundle-branch block, a QRS duration of up to 120 to 130 msec, absence of an adequate target coronary-sinus branch in the lateral left ventricular wall, high pacing thresholds with subsequent loss of pacing capture, end-stage heart failure, and competing rhythms (e.g., frequent premature ventricular beats or conducted atrial fibrillation) that prevent ideal biventricular pacing (≥95% paced beats). In general, patients with nonischemic heart failure have higher rates of biventricular pacing response than patients with ischemic heart failure. In addition, a number of studies have shown that women have a response to biventricular pacing at shorter QRS durations than men, as do persons with shorter body height; these observations are reflected in the most recent guidelines.[1,30]

BIVENTRICULAR PACING IN EXPECTED SUBSTANTIAL RIGHT VENTRICULAR PACING

Among patients with a LVEF of 50% or less who receive right ventricular pacing, a decline in left ventricular function may develop, an effect known as pacing-induced cardiomyopathy.[1,4,5] This group includes patients in whom spontaneous atrioventricular block develops, those with induced atrioventricular block from atrioventricular node ablation for atrial fibrillation with rapid heart rates, and those with anticipated frequent right ventricular pacing. For patients with atrioventricular block, the largest randomized trial conducted was the Block HF Trial (Table 1).[23] In this trial, 691 patients with an LVEF of 50% or less with a pacing indication were randomly assigned to receive right ventricular–only pacing or biventricular pacing. Patients who additionally had an indication for an ICD were randomly assigned to receive an ICD with biventricular pacing or an ICD with right ventricular–only pacing. Biventricular pacing, regardless of whether an ICD was implanted, was associated with a significantly lower risk of death from any cause or urgent hospital visit for heart failure or an increase of 15% or more in the left ventricular end-systolic volume index (the composite primary outcome).[23]

Current guidelines stress appropriate pacemaker programming to avoid unnecessary pacing and pacemaker-induced cardiomyopathy.[1]

CONDUCTION SYSTEM PACING IN HEART FAILURE

ANATOMY OF THE CONDUCTION SYSTEM

The cardiac conduction system begins with the sinoatrial node located at the junction of the superior vena cava and the right atrium. Conduction proceeds to the atrioventricular node, the bundle of His, the right and left bundle branches, and the Purkinje network (Fig. 1).[31,32] The His bundle is a strand of specialized myocardium that provides electrical conduction between the atria and ventricles. It has an average length of 2.6 mm, average width of 3.7 mm, and average thickness of 1.4 mm; it penetrates the membranous septum, where it is completely encased by the central fibrous body.[31,32] The size and location of the His bundle has serious clinical implications for His bundle pacing because it is a small and difficult area to target. Owing to the surrounding fibrous tissue, pacing thresholds can be elevated and increase over time, resulting in loss of capture. In addition, thresholds can change owing to lead microdislodgement. In contrast, the left bundle branch is a wider diffuse subendocardial structure of up to 14 mm in width; it is located in close proximity to the interventricular myocardium, and it branches into an anterior fascicle and posterior fascicle and often a septal fascicle. Hence, there is a larger target zone for lead implantation and a lower risk of losing capture at the left bundle branch than at the His bundle.

CONDUCTION SYSTEM PACING

His bundle pacing is the most physiologic pacing mode, because it preserves the natural activation of the left and right ventricles (Fig. 1).[2] It is indicated in patients with atrioventricular nodal and intra-Hisian conduction system disease that is associated with symptomatic bradycardia (Fig. 2).[33] His bundle pacing can also

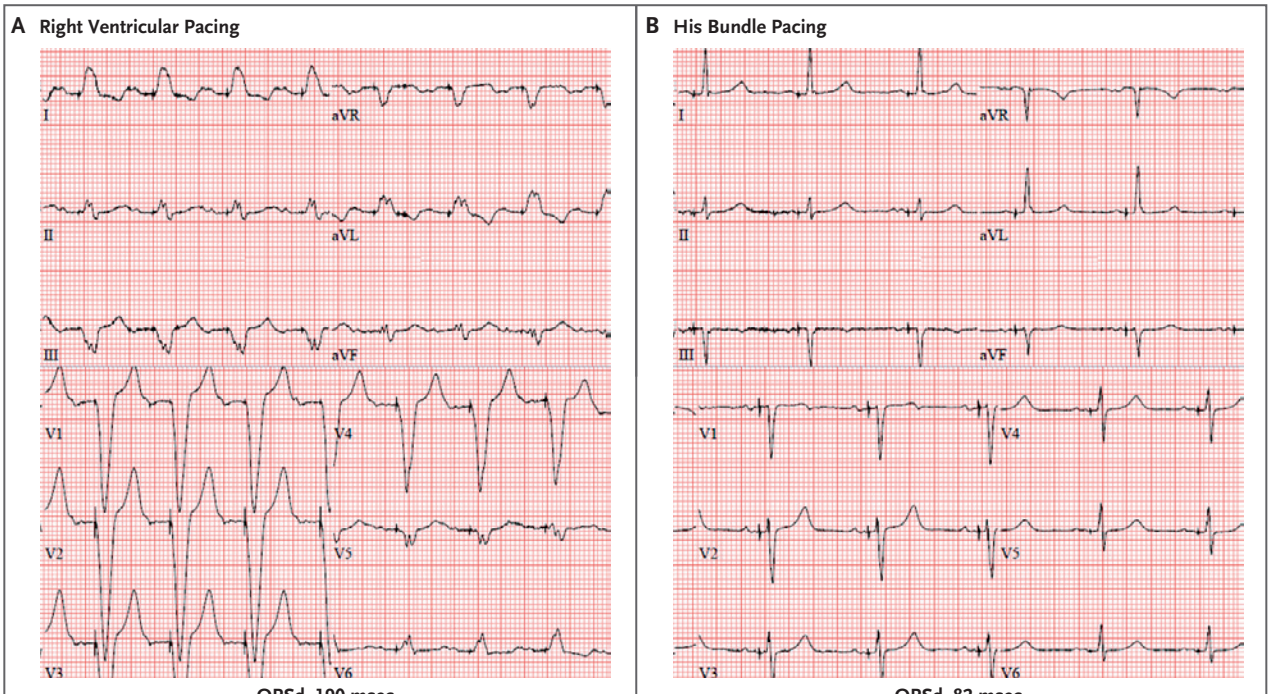


Figure 2. His Bundle Pacing Shown on Electrocardiogram (ECG).

Panel A shows an ECG of right ventricular pacing with a paced QRS duration (QRSd) of 190 msec. In this patient, who had complete heart block at baseline and a left ventricular ejection fraction (LVEF) of 60 to 65%, pacing-induced cardiomyopathy developed, leading to a LVEF of 35 to 40% with 100% right ventricular pacing. Panel B shows an ECG of His bundle pacing with a paced QRSd of 82 msec. Upgrading the patient's pacemaker to a His bundle pacemaker improved the LVEF to a range of 60 to 65%.

correct left bundle-branch block in the subgroup of patients who have disease in the His–Purkinje fibers that become the left bundle branch.[34,35]

Left bundle-branch pacing requires the implantation of a pacing lead through the interventricular septum to the left ventricular subendocardial left bundle branch or its fascicles (Fig. 1).[3] This procedure has rapidly become the dominant conduction system pacing approach owing to its higher success rate and lower and more stable pacing thresholds than those obtained with His bundle pacing, and because it provides correction of left bundle-branch block due to disease below the level of the His bundle (Fig. 3).[29] The Multicentre European Left Bundle Branch Area Pacing Outcomes Study (MELOS) showed high success rates of 92.4% and 82.2% for left bundle-branch pacing among early European adopters when it was performed in patients with bradycardia and heart failure, respectively.[36] Implantation of a left bundle-branch lead appears to be a safe procedure. Although MELOS reported the highest percentage of complications among all trials of conduction system pacing (8.3%), nearly half (3.7%) were due to acute perforation though the septum and into the left ventricle, which can be recognized easily. The pacing lead can be withdrawn and repositioned and does not appear to be associated with adverse clinical events in the long term. Left bundle-branch pacing uncommonly results in capture of the conduction system alone, but it most often results in capture of the conduction system and the local ventricular myocardium (nonselective left bundle-branch pacing). Left bundle-branch pacing may capture either the left bundle trunk or one of the fascicles; which of these is captured will be reflected in characteristic QRS morphologic features.

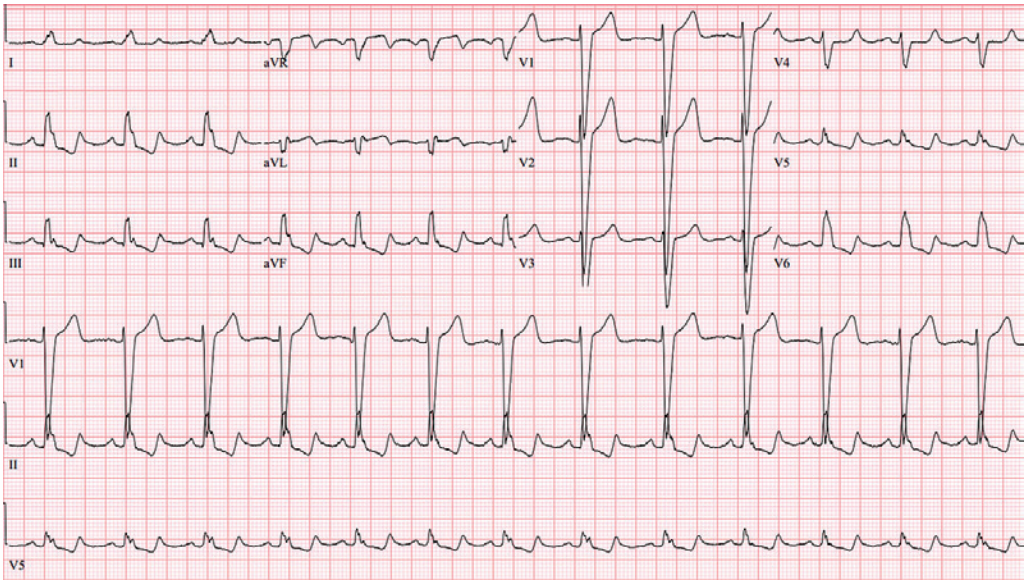
The role of conduction system pacing at the level of the His bundle or left bundle branch has been examined in several small randomized clinical trials involving patients with heart failure and reduced ejection fraction (LVEF, <35 to 40%) and clinical scenarios in which left ventricular synchrony is desired, including left bundle-branch block,[35,37-40]atrial fibrillation with atrioventricular node ablation,[41] and a prolonged PR interval[42] (Table 2).

In one trial, His bundle pacing was found to narrow the QRS duration in the majority of patients with ischemic heart disease but only in about two thirds of the patients with nonischemic cardiomyopathy (21 of 29), whereas the quality of life, NYHA class, 6-minute walk distance, and LVEF were improved from baseline to the same degree with biventricular pacing and with His bundle pacing.[37]

Similarly, in the His-SYNC (His Bundle Pacing versus Coronary Sinus Pacing for Cardiac Resynchronization Therapy) trial, biventricular pacing and His bundle pacing shortened the QRS duration and improved the LVEF at 6 months as compared with the baseline.[35] In addition, there was no significant between-group difference in cardiovascular hospitalization or death at 12 months. Of note, the crossover from His bundle pacing to biventricular pacing was high (48%) owing to strict requirements for QRS duration narrowing with His bundle pacing and a requirement for acceptable pacing thresholds.

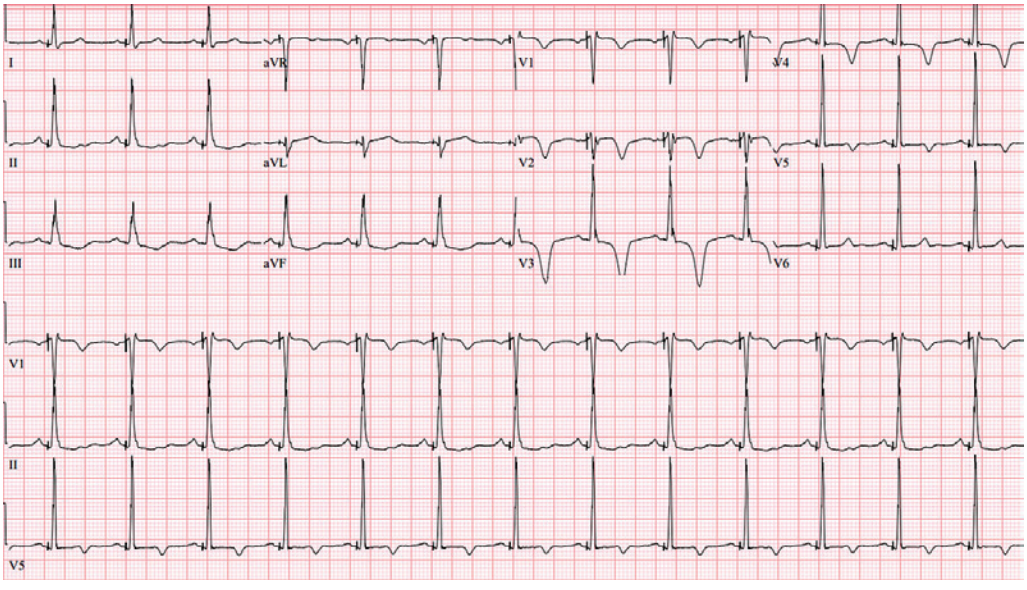
In the His-Alternative (His Pacing Versus Biventricular Pacing in Symptomatic HF Patients with Left Bundle Branch Block) trial, His bundle pacing corrected left bundle-branch block in 72% of the patients.[38] There was crossover from His bundle pacing to biventricular pacing in 28% of the patients. No significant differences in LVEF improvement were observed between the two treatment groups at 6 months in the intention-to-treat analysis, but there was greater improvement in LVEF and end-systolic volume at 6 months in the His bundle pacing group than in the biventricular pacing group in the per-protocol analysis. In the ALTERNATIVE-AF (His Bundle Pacing and Bi-Ventricular Pacing in Heart Failure with Atrial Fibrillation) trial, His bundle pacing was found to modestly improve LVEF as compared with biventricular pacing among patients who had symptomatic heart failure with reduced ejection fraction (LVEF, ≤40%), persistent atrial fibrillation, and atrioventricular node ablation.[41] The HOPE-HF (His Optimized Pacing Evaluated for Heart Failure) trial showed that His bundle pacing provided no benefit with regard to peak oxygen uptake and did not adversely affect ventricular function at 6 months among patients with heart failure with reduced ejection fraction (LVEF, ≤40%).[42] Patients in this trial had a

A LBBB-Induced Cardiomyopathy



QRSd, 138 msec

B Left Bundle-Branch Pacing



QRSd, 86 msec

Figure 3. Left Bundle-Branch Pacing Shown on ECG.

Panel A shows baseline ECG findings in a patient with left bundle-branch block (LBBB)–induced cardiomyopathy (QRSd, 138 msec) with an LVEF of 30 to 35%. Panel B shows an ECG from the same patient with left bundle-branch pacing and a paced QRSd of 86 msec. With left bundle-branch pacing, the LVEF improved to 50 to 54%. Right bundle-branch morphologic features in lead V_1 indicate either left bundle-branch pacing or left ventricular septal pacing. Additional pacing maneuvers are performed to distinguish between left bundle-branch pacing and left ventricular septal pacing. In this case, left bundle-branch pacing was confirmed.

Table 2. Trials and Studies of Conduction System Pacing for Cardiac Physiologic Pacing.*

Trial	Type or Comparison	NYHA Class	LVEF	SR or AF	QRS	LBBB	Primary End Points	Primary End-Point Results
			%		*msec*	%		
Early Trials								
Lustgarten et al. (29 patients)[37]	Randomized crossover, BIVP vs. HisBP at 6 mo with crossover and 12-mo follow-up	II, III	<40	SR	138–186	96	QOL, NYHA class, 6MWT, LVEF	No differences between HisBP and BIVP
His-SYNC (41 patients)[35]	Single-blinded crossover, His CRT vs. BIV CRT	II–IV	≤35	SR	>120	70	LVEF, LVESV, NYHA class, QOL at 6 and 12 mo	High crossover rate, no differences
His-Alternative (50 patients)[38]	Single-blinded crossover, His CRT vs. BIV CRT	II–IV	≤35	SR	>130 (women), >140 (men)	100	QRS, NYHA class, 6MWT, LVEF, LVESV, success of implanting a His bundle lead at 6 mo	No differences based on intention-to-treat analysis
LBBP-RESYNC (40 patients)[39]	Nonischemic cardiomyopathy and LBBB, LBBP-CRT vs. BIV-CRT, single-blinded	II–IV	≤40	SR	≥140	100	6-mo LVEF, LVESV, NT-pro BNP, NYHA class, 6MWT, QRS duration	Improved LVEF in LBBP-CRT
LEVEL-AT (70 patients)[40]	Single-blinded, randomized, BIV-CRT vs. CSP	NA	≤35	SR	>130 (LBBB), ≥150 (non-LBBB)	97	LV activation time, LVESV, HF hospitalization at 6 mo	No differences
ALTERNATIVE-AF (50 patients)[41]	Randomized, crossover, persistent AF after AVNA to HisBP vs. BIVP	II–IV	≤40	AF	≤120 or RBBB	NA	LVEF, LVEDD, NYHA class, BNP, QOL at 9 mo	Improved LVEF with HisBP
HOPE-HF (167 patients)[42]	Randomized, crossover at 6 mo, HisBP vs. no pacing, PR ≥200ms	I–IV	≤40	SR	≤140 or RBBB		Peak VO_2, QOL, LVEF	No differences in peak VO_2 or LVEF; improvement of QOL with HisBP
Observational Studies								
Vijayaraman et al. (477 patients)[44]	Observational two-center study, BIVP vs. CSP, mean follow-up of 27 mo	II–IV	≤35	SR	≥120	52	Death from any cause or unplanned CV hospitalization	Greater reduction in HF hospitalization with CSP in all patients and patients with LBBP, better LVEF and narrower QRS duration with CSP
Diaz et al. (371 patients)[43]	Observational multicenter study, BIVP vs. LBBAP, mean follow-up of 11.3 mo	II–IV	≤35–40	SR	≥120	91	HF hospitalization and death from any cause; NYHA class, ECG	Higher LVEF and fewer HF hospitalizations with CSP
Vijayaraman et al., I-CLAS (1778 patients)[48]	Observational 15-center, international study; BIVP vs. LBBAP, mean follow-up of 36 mo	II–IV	≤35	SR	≥120	61	Death from any cause or HF hospitalization	Greater reduction in composite of death from any cause and HF hospitalization with LBBAP in all patients and patients with LBBB, greater LVEF improvement and narrower QRS duration with LBBAP

Herweg et al., I-CLAS (1414 patients)[45]	Propensity-matched, observational, 15-center, international study, BIVP vs. LBBAP, mean follow-up of 32 mo	II–IV	≤35	SR	≥120	61	VT or VF, new-onset AF	Lower incidence of sustained VT or VF and new-onset AF with LBBAP than with BVP
Zhu et al. (259 patients)[49]	Observational two-center study, BIVP vs. LBBP and LVSP, mean follow-up of 28.8 mo	I–IV	<50	SR	>130 with LBBB, ≥150 with no LBBB and LVEF ≤35% or advanced AVB and LVEF <50%	63	Death from any cause or HF hospitalization or ECG measures of LV remodeling	Greater reduction in primary end-point events with LBBP than with BIVP or LVSP; death from any cause higher with LVSP than with BIVP
Vijayaraman et al., I-CLAS (1004 patients)[47]	Observational 16-center international study, BIVP vs. CSP (HisBP and LBBAP), mean follow-up of 49 mo	II–IV	36–50	SR	>120 with LBBB or expected RVP >40%	33	Death from any cause or HF hospitalization	Greater reduction in composite of death from any cause and HF hospitalization with CSP
Ongoing Trials								
LEAP (470 patients) NCT04595487	LVSP vs. RVP	NA	>40	SR, AF	2nd or 3rd AVB or atrial arrhythmia with slow VR; expected VP >20%	NA	Combined death, hospitalization for HF, and decline in LVEF by >10%	Enrolling; 12-mo follow-up
OptimPacing (683 patients) NCT04624763	LBBP vs. RVP	I–III	>35	SR, AF	2nd or 3rd AV block or persistent or permanent AF with VR <50 bpm	NA	Combined death, hospitalization for HF, and PICM	Enrolling; 36-mo follow-up
LEFT HF (1280 patients) NCT05015660	LBBP vs. RVP	NA	>35	SR	High-degree AVB and anticipated RVP >90%	NA	Combined CV death, HF events, and increase in LVESV by 15%	Enrolling; 36-mo follow-up
PROTECT-HF (2600 patients) NCT05815745	HisBP or LBBP vs. RVP	NA	>35	SR, AF	Any AVB or infrahisian block with pacing indication, or AF with slow ventricular rate, or planned AV node ablation	NA	Combined mortality and incidence of HF events	Enrolling; 78-mo follow-up
Left vs. Left RCT (2136 patients) NCT05650658	HisBP or LBBP vs. BIVP	NA	≤50	SR, AF	QRSd ≥130 or anticipated RVP >40%, or upgrade to CRT due to RVP >40%	NA	Combined death and HF hospitalization	Enrolling; 66-mo follow-up

* AVB denotes atrioventricular block, AVNA atrioventricular nodal ablation, BNP brain natriuretic peptide, CSP conduction system pacing, HisBP His bundle pacing, LBBAP left bundle-branch area pacing, LBBP left bundle-branch pacing, LVEDD left ventricular end-diastolic dimension, LVESV left ventricular end-systolic volume, LVSP left ventricular septal pacing, QRSd QRS duration, RBBB right bundle-branch block, and RVP right ventricular pacing.

prolonged PR interval (>200 msec) and a relatively narrow QRS or right bundle-branch block. The majority of the patients with His bundle pacing had a substantially improved quality of life and fewer symptoms.

In the LBBP-RESYNC (Left Bundle Branch Pacing Versus Biventricular Pacing for Cardiac Resynchronization Therapy) trial, which included 40 patients, left bundle-branch pacing resulted in greater LVEF improvement and reductions in left ventricular end-systolic volume and NT-proBNP but it led to changes in NYHA functional class, 6-minute walk distance, QRS duration, and rates of response to CRT at 6 months that were similar to those seen with biventricular pacing.[39] The LEVEL-AT (Left Ventricular Activation Time Shortening with Conduction System Pacing vs. Biventricular Resynchronization Therapy) trial, which included 70 patients, did not show a significant difference in left ventricular activation time, a marker of left ventricular resynchronization at 45 days.[40] In addition, no difference in the QRS duration, LVEF, left ventricular end-systolic volume index, NYHA functional class, or the combine end point of death from any cause or hospitalization for heart failure at 6 months was observed with conduction system pacing and biventricular pacing. Although these small randomized clinical trials were not powered for death and hospitalization for heart failure, data from retrospective comparative studies suggest that His bundle pacing or left bundle-branch pacing may be superior to biventricular pacing with regard to these outcomes (Table 2).

Results of I-CLAS (the International Collaborative LBBAP Study), the largest retrospective case–control study, showed that in patients with a LVEF of up to 35% and those with a LVEF of 36 to 50%, left bundle-branch pacing led to a lower incidence of death and hospitalization for heart failure (the composite end point) than biventricular pacing.[47,48] In addition, His bundle pacing or left bundle-branch pacing was associated with less new-onset atrial fibrillation and ventricular arrhythmia, even in patients with no history of ventricular arrhythmia who had not previously received antiarrhythmic therapy.[45] Similar benefits in the composite of death from any cause and hospitalization for heart failure were reported in two additional retrospective studies, although the results were driven by hospitalization for heart failure as reported in I-CLAS.[43,49] However, a meta-analysis of 4 randomized trials and 17 observational studies was sufficiently powered to suggest a significant reduction in death from any cause with conduction system pacing as compared with biventricular pacing.[46]

Left bundle-branch pacing offers a technically simpler and more reliable alternative to His bundle pacing; however, it presents its own set of technical challenges. One notable issue is the potential for capturing only the myocardium adjacent to the left bundle branch without engaging the left bundle branch itself, a scenario defined as left ventricular septal pacing. Emerging evidence indicates that left bundle-branch pacing is associated with clinical outcomes that are superior to both left ventricular septal pacing and biventricular pacing.[50] Notably, outcomes between left ventricular septal pacing and biventricular pacing were similar, suggesting that although left ventricular septal pacing may not confer the same benefits as left bundle-branch pacing, it performs similarly to biventricular pacing.[50] Another challenge is confirmation of left bundle-branch capture, which requires the use of 12-lead electrocardiograms during unipolar pacing and pacing maneuvers. Future research will be focused on visualization of the conduction system with preprocedural imaging.

Despite the lack of large randomized clinical trials, the recent Heart Rhythm Society–Asia Pacific Heart Rhythm Society–Latin America Heart Rhythm Society pacing guidelines for the avoidance and mitigation of heart failure support conduction system pacing as an alternative to traditional biventricular pacing when effective CRT cannot be achieved.[1] Multiple moderate-to-large randomized clinical trials that are sufficiently powered to determine whether conduction system pacing is superior to current standard pacing strategies are ongoing. These trials will test conduction system pacing for all major clinically significant outcomes (Table 2).

CLINICAL CONSIDERATIONS FOR THE TREATMENT OF PATIENTS WITH PHYSIOLOGIC-PACING DEVICES

HEART-FAILURE AND ELECTROPHYSIOLOGY CLINICS

A multidisciplinary approach to cardiac physiologic pacing, which involves collaborative efforts in combined heart-failure and electrophysiology clinics, promotes guideline-directed medical therapy

KEY POINTS

PHYSIOLOGIC PACING IN HEART FAILURE

- Cardiac physiologic pacing can be achieved with biventricular pacing with a right ventricular lead and coronary sinus lead or conduction system pacing by way of the His bundle or left bundle branch. It is indicated in patients with heart failure, left ventricular ejection fraction (LVEF) of 50% or less, and high or anticipated high ventricular pacing burden and left ventricular resynchronization in patients with a wide QRS complex.
- Randomized trials of biventricular pacing in more than 10,000 patients with heart failure have shown improved LVEF, reduced mitral regurgitation and left ventricular volumes, enhanced quality of life and exercise capacity, fewer hospitalizations for heart failure, and improved survival. The greatest benefit is seen in patients who have a left bundle-branch block with a QRS duration of 150 msec or longer, whereas biventricular pacing may be of negligible benefit when the QRS duration is 130 msec or less.
- Retrospective studies suggest that conduction system pacing may offer benefits equal to or greater than biventricular pacing. Ongoing randomized trials will clarify the relative efficacy and safety of cardiac physiologic pacing as compared with biventricular pacing.

and the selection of appropriate physiologic pacing strategies. This integrated-care model has been associated with improved patient outcomes, including enhanced quality of care, increased patient engagement, improved medication safety, reduced hospitalization rates, and decreased mortality.[1,51]

MAGNETIC RESONANCE IMAGING (MRI)

MRI conditionality (manufacturer-defined conditions under which a pacing device is safe in the setting of an MRI) is important, given the frequent use of MRI scanning in multiple clinical situations. Some leads and pacing systems used for conduction system pacing are labeled as MRI conditional. Ongoing clinical trials are expected to provide sufficient safety data that will lead to the MRI-conditional labeling of multiple leads and pacing systems.

LEAD EXTRACTION

Experience with lead extraction is growing. Leads used for conduction system pacing can either be lumenless (not stylet driven because there is no inner lumen) or stylet driven. In one study, the success of lead extractions for lumenless leads was reported to be 100%, although there were retained distal fragments in 1% of the patients.[52] It is reassuring that minor complications occurred in only 2.1% of the patients. Extraction of ICD or pacemaker leads becomes more difficult the longer the leads are implanted. Given the relatively recent emergence of conduction system pacing leads, dwell time is short, with a mean (±SD) of 22±26 months.[52] There are limited data on extraction of stylet-driven leads implanted in either the His or left bundle-branch positions.

FUTURE DIRECTIONS

Physiologic pacing is a dynamic field with ongoing developments on multiple fronts. The role of biventricular pacing is well established for the treatment of patients with abnormal cardiac function and conduction system disease and is supported by multiple large randomized trials with clinically relevant end points, including mortality. The body of evidence is rapidly increasing for conduction system pacing, with special emphasis on left bundle-branch pacing. Ongoing randomized clinical trials will establish the relative efficacy and safety of conduction system pacing as compared with biventricular pacing. If the two pacing strategies are equivalent, other factors may play a role in making the appropriate choice.

His bundle pacing and left bundle-branch pacing involve a simpler system and shorter procedural times for implantation than biventricular pacing, with potential downstream favorable consequences that include reduced cost, lower radiation dose, lower contrast dose, and increased battery life. Reduced costs may further be derived from less-expensive generators and fewer or less-expensive leads. CRT ICD or pacemaker generators (intended for use with biventricular pacing) are much more expensive than an ICD alone or pacemakers without CRT capability — the type of generators used for conduction system pacing. Also, pacing leads are less expensive than the coronary-sinus left ventricular leads used in biventricular pacing systems. In addition, because the His bundle pacing or left bundle-branch pacing lead provides the dual functions

of pacing and cardiac resynchronization, only one lead, rather than the two needed for biventricular pacing, is needed. Furthermore, conduction system pacing will probably replace traditional right-ventricular pacing for indications of symptomatic sinus-node dysfunction and atrioventricular block.

However, there remain a number of additional questions that may be resolved in the next 5 to 10 years as the results of large randomized trials become available. Will His bundle pacing be completely replaced with left bundle-branch pacing? Will conduction system pacing improve cardiac dyssynchrony in patients with a right bundle-branch block or nonspecific intraventricular conduction delay — two patient populations in whom there has been a lack of benefit shown with biventricular pacing? Will conduction system pacing be the go-to approach for patients with heart failure and left bundle-branch block, with biventricular pacing as the backup approach? Some patients may benefit from simultaneous conduction system pacing with either a His or left bundle-branch pacing lead and a simultaneously activated left ventricular pacing with a coronary sinus lead, referred to as His bundle–optimized CRT and left bundle-branch–optimized CRT, respectively (Fig. 2).[53,54] As the field advances, it would benefit from improvements in leads, delivery tools, devices, and device-selection algorithms.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

AUTHOR INFORMATION

[1] Section of Cardiology, Department of Medicine, Baylor College of Medicine, Houston; [2] Cardiovascular Research Institute, Baylor College of Medicine, Houston; [3] Texas Heart Institute at Baylor College of Medicine, Houston; [4] Division of Cardiology, University of Washington, Seattle; [5] Division of Cardiology and Cardiac Electrophysiology, Virginia Commonwealth University School of Medicine, Richmond.

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