

Cardiac Resynchronization Therapy

A Review

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IMPORTANCE Heart failure (HF) affects more than 64 million individuals worldwide, and acute HF is associated with 1-year mortality rates of 23.6% in North America and Europe. Cardiac dyssynchrony from conduction system disease may cause HF progression, particularly in patients with left ventricular (LV) systolic dysfunction.

OBSERVATIONS Electrical dyssynchrony in HF most commonly presents as left bundle-branch block and affects 20% to 30% of patients with reduced LV ejection fraction (LVEF). Cardiac resynchronization therapy, which includes biventricular pacing and conduction system pacing, restores synchronous ventricular contraction and is recommended for patients with symptomatic HF despite optimal medical therapy, LVEF of 35% or less, and left bundle-branch block. Delayed referral for device therapy in this population is associated with worse clinical outcomes. Resynchronization should also be considered for patients requiring chronic ventricular pacing, typically due to symptomatic bradycardia because right ventricular pacing for atrioventricular block may result in ventricular dyssynchrony and increased risk of LV systolic dysfunction. Biventricular pacing uses 2 leads to stimulate the right ventricle and LV simultaneously; conduction system pacing uses a single lead to stimulate the His bundle or left bundle branch. An individual patient-level meta-analysis of 5 randomized clinical trials (N = 3872) reported biventricular pacing was associated with lower all-cause mortality compared with medical therapy or implantable cardioverter-defibrillator over a median follow-up of 23.7 months (13.7% vs 20.8%; hazard ratio, 0.66 [95% CI, 0.57-0.77]). A meta-analysis of 7 small randomized clinical trials, including 408 patients with HF and LVEF of 40% or less, reported that compared with biventricular pacing, conduction system pacing was associated with improvement in LVEF (mean difference, 2.06%; $P = .03$). An observational study of 1778 patients with LVEF of 35% or less undergoing cardiac resynchronization therapy reported conduction system pacing was associated with lower rates of HF hospitalization (12% vs 19%; hazard ratio, 0.67 [95% CI, 0.52-0.86]). A trial of 249 patients without HF undergoing permanent pacing for atrioventricular block-related bradycardia reported lower rates of pacing-induced cardiomyopathy, defined as a decrease in LVEF of at least 10% to less than 50% after conduction system pacing vs right ventricular pacing (6% vs 15%; $P = .01$).

CONCLUSIONS AND RELEVANCE Cardiac dyssynchrony due to conduction system disease occurs in 20% to 30% of patients with HF and systolic dysfunction. Cardiac resynchronization therapy restores synchronous ventricular activation in patients with HF, reduced LVEF, and left bundle-branch block, or in those requiring chronic ventricular pacing, and may improve LV function, decrease HF hospitalizations, and reduce mortality.

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More than 64 million people worldwide have heart failure (HF),¹ and the lifetime risk of developing HF is approximately 1 in 4 persons.² In the US, HF affects 6.7 million adults and accounts for more than 1.2 million hospital admissions and 425 000 deaths annually.³ One-year mortality rates are 23.6% for acute HF and 6.4% for chronic HF across North America and Europe.¹

Cardiac dyssynchrony contributes to the development and progression of HF through conduction abnormalities that disrupt coordinated cardiac contraction, particularly left bundle-branch block (LBBB).⁴ Dyssynchrony may also occur in patients with normal ejection fraction (EF) undergoing chronic right ventricular (RV) pacing for symptomatic bradycardia, which can lead to pacing-induced cardiomyopathy.⁵ Cardiac resynchronization therapy was developed to restore coordinated ventricular activation in patients with HF with reduced ejection fraction (HFrEF) and QRS duration of 130 ms or longer.⁶ Biventricular pacing, the standard resynchronization technique for more than 2 decades, combines an RV lead and a left ventricular (LV) lead positioned in a lateral or posterolateral coronary sinus branch overlying the epicardial surface.⁷ Conduction system pacing is a more recent pacing strategy in which a single septal lead directly stimulates the His bundle or left bundle branch (Table 1).⁸ This Review provides evidence on resynchronization therapy using conduction system pacing compared with biventricular pacing, discusses strategies to mitigate HF progression in patients with conduction abnormalities, and addresses pacing-induced cardiomyopathy, typically defined as a 10% or greater decrease in LV ejection fraction (LVEF) to less than 50% at any time after pacemaker implant (Box).

Methods

A PubMed literature review was performed to identify English-language studies on cardiac physiologic pacing, using the terms *cardiac resynchronization therapy*, *biventricular pacing*, *conduction*

system pacing, *heart failure*, and *electrical dyssynchrony*, published between January 1, 2000, and March 11, 2026. Studies were selected based on rigor of study design, patient population with HF and cardiac dyssynchrony, reporting of major adverse cardiovascular events or arrhythmia-related clinical outcomes, and relevance to clinical practice. Current HF management and cardiac pacing guidelines were also reviewed. The search yielded 538 articles, of which 99 were included, comprising 19 randomized clinical trials (RCTs), 8 systematic reviews with meta-analysis, 8 narrative reviews, 53 observational studies, 5 expert consensus statements, and 6 guidelines.

Pathophysiology of Cardiac Dyssynchrony

The heart's electrical impulse is initiated at the sinoatrial node, which triggers atrial depolarization and enables ventricular filling. The impulse then propagates through the atrioventricular (AV) node, down the His bundle, and into the right and left bundle branches and Purkinje fibers, resulting in synchronous ventricular activation (Figure 1).⁹ In physiologic conditions, the cardiac conduction system ensures coordinated interatrial, AV, and inter- and intraventricular activation, resulting in synchronous contraction, optimal stroke volume, adequate heart rate, and cardiac output. Dyssynchrony arises from abnormal timing of myocardial activation within or between the heart's chambers, including delays between the atria and ventricles, between the ventricles, or within the LV (Table 2).¹⁰ Conduction system disease causes electrical dyssynchrony, and mechanical dyssynchrony results from uncoordinated myocardial contraction due to heterogeneous timing of regional myocardial activation.¹¹

LBBB

LBBB causes electrical dyssynchrony (QRS duration ≥120 ms) and is present in approximately 1% of the general population.¹² Although isolated LBBB without HF may remain asymptomatic for

Table 1. Definitions of Terminology and Techniques Used in Physiologic Pacing

Technique	Description
Cardiac physiologic pacing	Any pacing method designed to maintain or restore synchronized ventricular contraction aimed at prevention or mitigation of HF; techniques include either biventricular pacing or conduction system pacing for cardiac resynchronization therapy in patients with reduced EF or conduction system pacing for bradycardia
Cardiac resynchronization therapy	Pacing to restore ventricular synchrony in patients with HF, reduced EF, and conduction delay, typically seen as QRS widening of ≥130 ms with bundle-branch block morphology
Biventricular pacing	Cardiac resynchronization therapy that directly stimulates the myocardium, using leads positioned in the RV endocardium and in a distal branch of the coronary sinus or surgically placed on the epicardium to pace the LV
Cardiac resynchronization therapy upgrade	A change in patient's pacing device from standard RV pacing to physiologic pacing, most often to mitigate deterioration in systolic function from chronic pacing in symptomatic bradycardia
Conduction system pacing	Pacing techniques designed to engage the heart's native conduction system at the level of the His bundle or the left bundle branch
His bundle pacing	Direct conduction system pacing with capture of the His bundle engaging the native conduction system; a lead is placed near the membranous septum at the level of the His bundle
LBBP	Direct conduction system pacing capturing any portion of the left bundle branch and fascicular network; a pacing lead is positioned through the interventricular septum toward the LV subendocardium to engage the left conduction system
LV septal pacing	Pacing confined to the left septal subendocardial myocardium without capture of the left bundle branch
LBBAP	Pacing techniques comprising both LBBP and LV septal pacing
Hybrid pacing modalities	Conduction system pacing through hybrid pacing stimulation of the His bundle to engage the native conduction system, with adjunctive LV myocardial pacing via the coronary sinus or epicardial lead (His-optimized cardiac resynchronization therapy) or of the left bundle branch fascicular network with adjunctive LV myocardial pacing via the coronary sinus or epicardial lead (LBBP-optimized cardiac resynchronization therapy)

Abbreviations: EF, ejection fraction; HF, heart failure; LBBAP, left bundle-branch area pacing; LBBP, left bundle-branch pacing; LV, left ventricle; RV, right ventricle.

Box. Frequently Asked Questions About Resynchronization Therapy in Heart Failure

Which mechanisms of cardiac dyssynchrony contribute to heart failure progression?

Cardiac dyssynchrony most commonly arises from conduction system impairment, particularly left bundle-branch block, which delays activation in the LV, resulting in adverse cardiac remodeling and progressive decline in LV systolic function. Cardiac dyssynchrony can also arise from chronic right ventricular pacing that is used for symptomatic bradycardia.

Which patients should be referred to an electrophysiologist for evaluation for cardiac resynchronization therapy?

Patients with symptomatic heart failure and reduced LV ejection fraction despite guideline-directed medical therapy, particularly those with left bundle-branch block and a widened QRS complex (≥ 130 ms), should be referred to an electrophysiologist for consideration of cardiac resynchronization therapy to reduce morbidity and mortality. Patients with symptomatic bradycardia requiring chronic ventricular pacing for symptomatic atrioventricular block, regardless of LV ejection fraction, should also be referred for consideration of cardiac resynchronization therapy to preserve systolic function.

What are the differences between biventricular pacing and conduction system pacing?

Biventricular pacing uses 1 right atrial lead and 2 transvenous leads to stimulate the right and left ventricles simultaneously through myocardial cell-to-cell activation. Conduction system pacing uses a single lead implanted in either the His bundle or left bundle branch in the intraventricular septum to directly stimulate the heart's native conduction system.

Abbreviation: LV, left ventricle.

years.¹³ LBBB at baseline in a longitudinal cohort of 4541 adults 65 years or older with structurally normal hearts was associated with a higher cumulative risk of incident HF compared with those without LBBB (48% vs 12.2%; hazard ratio [HR], 4.98 [95% CI, 2.18-11.39]) over a median follow-up of 14.6 years.¹⁴ In a cohort of 1418 ambulatory patients with chronic HF, LBBB was present in 34% at study enrollment and developed in an additional 10.9% of patients at 1 year.¹⁵ According to the 2018 American College of Cardiology/American Heart Association/Heart Rhythm Society Guideline on the Evaluation and Management of Patients With Bradycardia and Cardiac Conduction Delay, asymptomatic patients with isolated LBBB and preserved 1:1 AV conduction (each P wave is conducted to the ventricles) do not require permanent pacing.¹⁶ However, all patients with newly diagnosed LBBB should undergo transthoracic echocardiography to evaluate LVEF and assess for structural heart disease, such as ischemic and nonischemic cardiomyopathy, left-sided valvular disease, and infiltrative myocardial disease.^{12,17}

For patients with HF, conduction block most commonly involves the left bundle branch, resulting in delayed ventricular activation and dyssynchrony (wide QRS complex) (Table 2), adverse remodeling characterized by progressive LV dilation, and decreasing cardiac function.¹⁸ LBBB typically causes early septal contraction and delayed LV lateral wall activation,¹⁹ which impairs mitral valve closure, disrupts papillary muscle function, increases myocardial workload, and may lead to cardiomyopathy with decline in EF.²⁰

Right Bundle-Branch Block

In contrast to LBBB, isolated right bundle-branch block in patients with HF is not typically associated with progressive decline in LVEF and has not demonstrated clear benefit from cardiac resynchronization therapy.²¹ Concomitant right bundle-branch block with cardiomyopathy, reduced EF, and a wide QRS complex has been reported in 5% to 13% of patients enrolled in major cardiac resynchronization therapy trials.²²

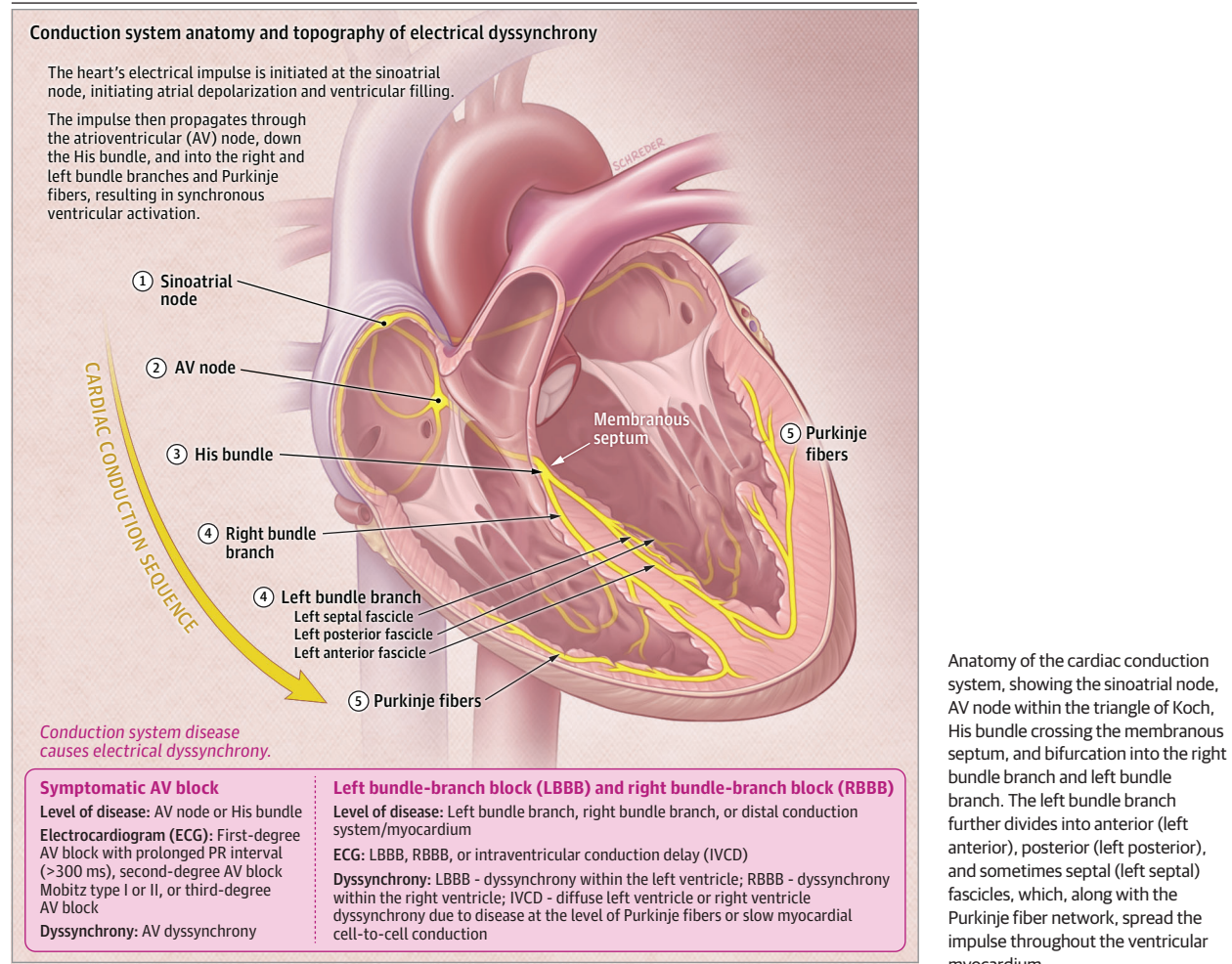
Symptomatic AV Block

First-degree AV block is typically asymptomatic, except when the PR interval is extremely prolonged (>300 ms) and associated with diastolic mitral regurgitation.^{23,24} Second-degree AV block (Mobitz I or II) may cause symptoms (eg, dizziness, palpitations, dyspnea, syncope), especially with persistent bradycardia. Patients with third-degree AV block are typically symptomatic due to complete AV dyssynchrony and bradycardia.²⁵ Ventricular pacing for AV block has traditionally been achieved by placing a lead in the RV apex to deliver electrical impulses to the RV myocardium, resulting in slow myocardial cell-to-cell conduction (Figure 2).²⁶ This pattern of nonphysiologic ventricular activation may lead to pacing-induced cardiomyopathy, defined as a decline in LVEF of at least 10 percentage points to below 50%, with reported incidence ranging from 5.9% to 39% in observational cohorts.²⁷ Higher rates of RV pacing, particularly when comprising at least 20% to 40% of total ventricular beats, may lead to systolic dysfunction and adverse cardiovascular events.²⁸ In a trial of 2010 patients with sinus node dysfunction randomized to undergo dual-chamber vs ventricular pacing, a higher percentage of RV pacing among patients receiving dual-chamber pacemakers was associated with increased rates of HF hospitalization (HR, 2.99 [95% CI, 1.15-7.75] for $>40\%$ paced ventricular beats).²⁹

Epidemiology and Risk Factors for Cardiac Dyssynchrony in HF

Although electrical dyssynchrony can occur in patients with HF who have normal or mildly reduced LV systolic function, it is predominantly observed with EF of 40% or less and affects approximately 20% to 30% of patients with HFrEF.^{30,31} Similarly, mechanical dyssynchrony may occur across HF phenotypes, affecting approximately 10% to 30% of patients with narrow QRS and 50% to 70% of those with widened QRS and LBBB.^{32,33} Cardiac dyssynchrony from HF and conduction system disease share a common underlying pathophysiology, with overlapping risk factors such as older age, hypertension, coronary artery disease, obesity, valvular disease (particularly mitral regurgitation and aortic valve disease), acute myocardial infarction, and infiltrative cardiomyopathies, including cardiac amyloidosis and cardiac sarcoidosis.^{34,35} Age-related degenerative fibrosis and myocardial scarring can replace normal conduction tissue, impairing cardiac impulse propagation, and infarction or chronic hypoperfusion can cause ischemic injury to the conduction system.³⁶ Among infiltrative cardiomyopathies, cardiac sarcoidosis is associated with HF in approximately 15% to 25% of patients, with advanced AV block reported in approximately 23% to 30% of biopsy-proven cases and bundle-branch block observed in 12% to 61% in case series.^{37,38} HF commonly coexists with conduction disease in patients with transthyretin cardiac amyloidosis,

Figure 1. Illustration of Conduction System Anatomy and Topography of Electrical Dyssynchrony



of whom 40% to 50% have a wide QRS complex (≥ 120 ms) and approximately 10% develop AV block-related bradycardia requiring permanent pacing.³⁹

Lamin A/C (LMNA) genetic variants account for approximately 5% to 8% of familial cases of dilated cardiomyopathy and 1.5% to 3% of all cases of dilated cardiomyopathy.⁴⁰ *LMNA*-associated cardiomyopathy is characterized by progressive cardiac conduction disease, ventricular arrhythmias, and systolic dysfunction, with AV block reported in 60% to 90% of genetic variant carriers. Additionally, channelopathies are primary electrical disorders caused by pathogenic variants in cardiac ion channel genes, such as long QT syndrome type 3 due to variants in *SCN5A*, which may exhibit phenotypic cardiomyopathy overlap with progressive conduction disease and a decline in EF.⁴¹

Clinical Presentation

Patients with cardiac dyssynchrony exhibit a range of electrical abnormalities and varying frequency and severity of HF-associated symptoms.¹⁶ AV block and intra-Hisian block can cause slow ventricular rates, leading to symptomatic bradycardia with nonspecific fatigue, dizziness, lightheadedness, syncope, or even confusional

states due to cerebral hypoperfusion (Table 2). LBBB is often asymptomatic until ventricular dyssynchrony leads to HF symptoms (fatigue, worsening dyspnea, and peripheral edema).⁴²

Assessment of Patients at Risk for Cardiac Dyssynchrony

Clinicians initially assessing patients with HF and suspected bradycardia and/or underlying conduction system disease should obtain a comprehensive medical and family history and perform a medication review. Physical examination should assess for elevated jugular venous pressure, crackles on lung auscultation, and peripheral edema. Laboratory testing should include hemoglobin, creatinine, and natriuretic peptides, which increase with myocardial wall stress and volume overload.^{23,43} A 12-lead electrocardiogram (ECG) should be performed to evaluate cardiac rhythm, AV conduction, and QRS morphology, and identify candidates for cardiac resynchronization therapy. An echocardiogram should be obtained to evaluate for structural heart disease, including ventricular dilation and mitral or aortic valve disease, and to determine EF.⁴⁴ In selected patients, particularly those with ischemic cardiomyopathy, cardiac magnetic resonance imaging may be useful for assessment of ventricular func-

Table 2. Electrocardiogram (ECG) Findings and Conduction Abnormalities in Candidates for Physiologic Pacing Across Heart Failure (HF) Phenotypes

LVEF category	ECG findings	Underlying conduction abnormalities	Clinical presentation	Pacing strategies
HFrEF ≤40%	LBBB with QRS ≥130 ms	LBBB	Congestive HF symptoms, decline in EF	Resynchronization (biventricular or conduction system pacing)
	Non-LBBB with QRS ≥150 ms	RBBB or nonspecific intraventricular conduction delay	Congestive HF symptoms, decline in EF	Biventricular or conduction system pacing
	LBBB and RBBB	Alternating bundle-branch block	Alternating bundle-branch block	Biventricular or conduction system pacing
	AV block, prolonged PR interval (>300 ms), ^a Mobitz I or II, complete heart block	AV nodal or intra-Hisian disease	Intermittent to persistent bradycardia	Conduction system pacing (preferred) or biventricular pacing
	AF with slow ventricular response	AV nodal or intra-Hisian block in AF	Bradycardia-related symptoms	Conduction system pacing (preferred) or biventricular pacing
	AF with rapid ventricular response	Iatrogenic complete AV block	AF refractory to rate control	AV node ablation and physiologic pacing (biventricular or conduction system pacing)
HFmrEF 41%-49%	LBBB with QRS ≥150 ms	LBBB	Congestive HF symptoms, decline in EF	Biventricular or conduction system pacing
	AV block, prolonged PR interval	AV node or intra-Hisian block in sinus rhythm	Bradycardia-related symptoms	Conduction system pacing preferred (LBBP)
	AF with slow ventricular response	AV node or intra-Hisian block in AF	Bradycardia-related symptoms	Conduction system pacing preferred (LBBP)
	AF with rapid ventricular response	Iatrogenic complete AV block	AF refractory to rate control	AV node ablation and conduction system pacing
Normal range ≥50% ^b	AV block, prolonged PR interval	AV node or intra-Hisian block in sinus rhythm	Bradycardia-related symptoms	Conduction system pacing preferred over RV pacing
	AF, QRS ≥150 ms, slow heart rate	AV node or intra-Hisian block in AF	Bradycardia-related symptoms	Conduction system pacing preferred (LBBP)
	AF with rapid ventricular response	Iatrogenic complete AV block	AF refractory to rate control	AV node ablation and conduction system pacing

Abbreviations: AF, atrial fibrillation; AV, atrioventricular; EF, ejection fraction; HFmrEF, heart failure with mildly reduced ejection fraction; HFrEF, heart failure with reduced ejection fraction; LBBB, left bundle-branch block; LBBP, left bundle-branch pacing; LVEF, left ventricular ejection fraction; RBBB, right bundle-branch block; RV, right ventricle.

^a Excessive AV delay (PR interval >300 ms) causes atrial relaxation before ventricular contraction, leading to diastolic mitral regurgitation and worse outcomes, regardless of LVEF.

^b Patients with normal LVEF requiring frequent ventricular pacing are at increased risk of pacing-induced cardiomyopathy with RV pacing; conduction system pacing is preferred to maintain systolic function.

tion and myocardial scar.⁴⁵ Patients with symptomatic HF despite optimized guideline-directed medical therapy, LVEF of 50% or less, and either a prolonged QRS duration (≥130 ms) or an indication for permanent pacemaker expected to require at least 20% to 40% of ventricular pacing should receive an expedited referral to an electrophysiologist.²³ Compared with resynchronization therapy implant at 3 to 9 months from the achievement of optimized medical therapy for HF at maximum tolerated doses, earlier implant (<3 months) was associated with a 9% lower risk of cardiovascular death (adjusted HR, 0.91 [95% CI, 0.83-1.00]; *P* = .05).⁴⁶

Cardiac Resynchronization Therapy

Cardiac resynchronization therapy was developed to treat ventricular dyssynchrony in symptomatic patients with HF and either LBBB or iatrogenic dyssynchrony from chronic RV pacing.

Biventricular Pacing

The standard technique used since the early 2000s is biventricular pacing (Table 1), achieved through transvenous implant of a cardiac resynchronization therapy device with or without defibrillator capability.⁴⁷ The biventricular pacing device is placed in a prepectoral pocket and connected to 2 or 3 transvenous leads positioned within the heart. In most cases, a right atrial lead is included to detect intrinsic atrial activity, deliver pacing as needed, and maintain AV synchrony. However, for patients with permanent atrial fibrilla-

tion (AF), only ventricular leads are implanted.⁴⁸ Biventricular pacing corrects dyssynchrony by delivering direct myocardial stimulation in 2 sites: the RV and the lateral LV wall via an epicardial lead placed in a distal branch of the coronary sinus (Figure 2). Although biventricular pacing improves ventricular synchrony compared with isolated RV pacing, it relies on slow myocardial cell-to-cell activation that does not follow the normal His-Purkinje activation pattern. In a study of 526 patients with EF of 35% or less who underwent biventricular pacing, 44.9% were deemed responders (defined as EF change of 5%-20%), 17.9% as super-responders (EF change >20%), and 37.3% as nonresponders (EF change ≤4%).⁴⁹

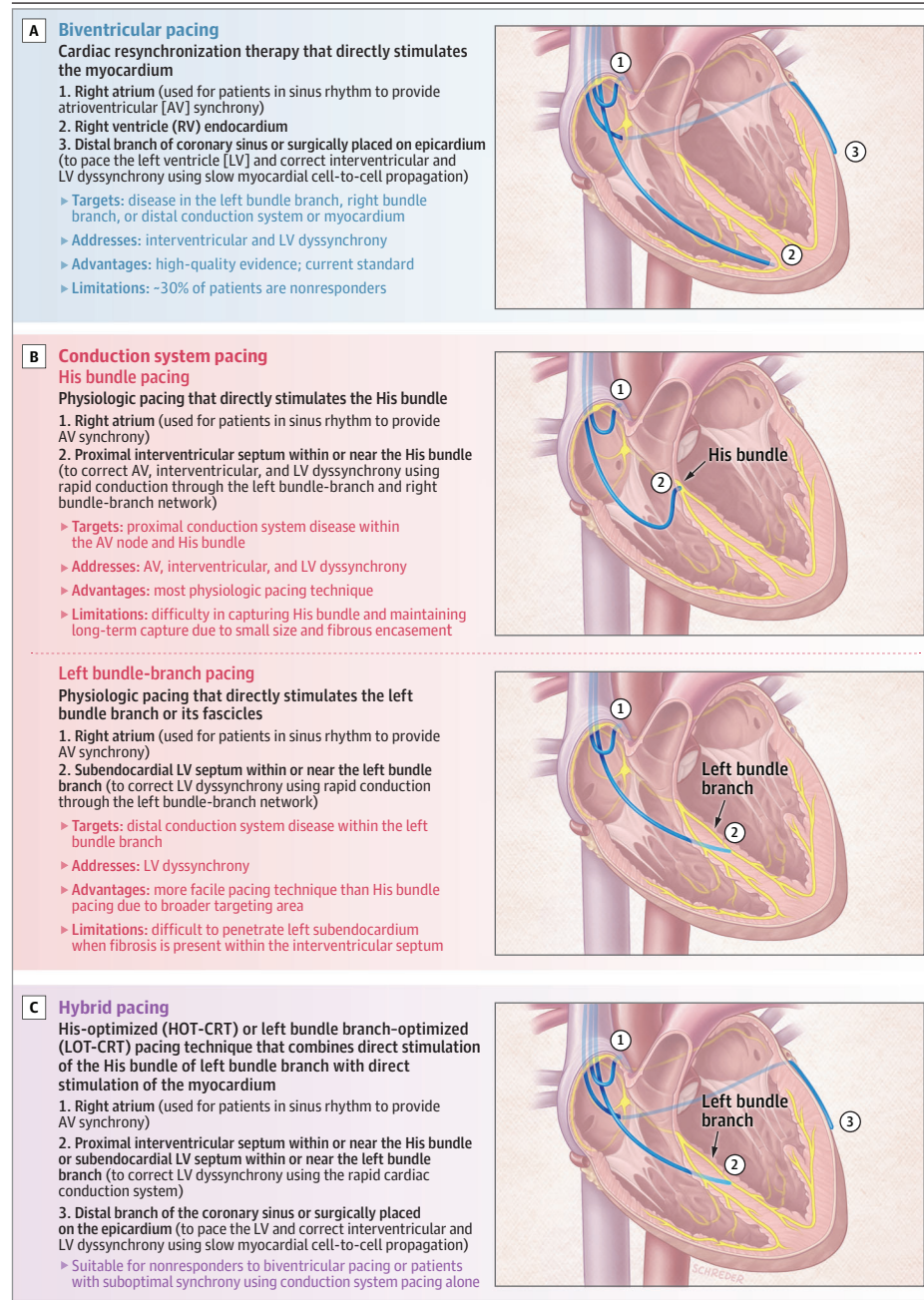
Conduction System Pacing

Conduction system pacing has increasingly been adopted as an alternative strategy to cardiac resynchronization therapy since 2017 (Table 1, Figure 2).⁵⁰ In contrast to the 2 ventricular leads used in biventricular pacing, conduction system pacing uses a single ventricular septal lead positioned to capture the His bundle or left bundle branch, thereby reestablishing rapid His-Purkinje conduction (Table 1, Figure 2).⁵¹⁻⁵³

Hybrid Pacing

Hybrid pacing combines lead placement techniques from both biventricular pacing and conduction system pacing, while avoiding deleterious stimulation at the RV apex.⁵⁴ This strategy may benefit patients in whom single-lead conduction system pacing is insufficient to achieve ventricular synchrony because the complementary LV

Figure 2. Illustrations of Cardiac Physiologic Pacing Techniques



epicardial lead can provide early activation of the left lateral wall to enhance resynchronization.⁵⁵ Hybrid pacing includes His bundle–⁵⁶ and left bundle branch–optimized⁵⁷ resynchronization therapy (Figure 2).

Cardiac Resynchronization Therapy for HFrEF

HFrEF is defined by an LVEF of 40% or less and is managed with guideline-directed medical therapy aimed at reducing mortality, hospitalizations, and symptoms.^{58,59} Despite optimization of guideline-directed medical therapy, one-third of patients with HFrEF and elec-

trical dyssynchrony experience persistent HF-related symptoms and progressive systolic dysfunction. Cardiac resynchronization therapy promotes coordinated synchronous contraction that pharmacologic treatment cannot achieve.⁶⁰

Clinical benefit from cardiac resynchronization therapy is observed mainly in 2 dyssynchrony patterns among patients with HF: (1) LBBB meeting the Strauss criteria, defined as a QRS duration of 130 ms or longer in women or 140 ms or longer in men, a predominantly negative deflection (QS or rS) in ECG leads V1 and V2, and a broad mid-QRS notched or slurred complex in at least 2 contiguous lateral leads (I, aVL, V5, or V6)⁶¹; and (2) bundle-branch blocks other than complete LBBB, such as nonspecific intraventricular conduction

Table 3. Randomized Clinical Trials Comparing Conduction System Pacing With Biventricular Pacing in Heart Failure

Trial	Sample size, No.	No. (%)		Baseline QRS, mean (SD), ms	No. (%)		LVEF, mean (SD), %		Paced QRS duration, mean (SD), ms		LVEF at last follow-up, mean (SD), %		All-cause death, No. (%)	
		Female	Ischemic		LBBB	AF	Follow-up, mo	Conduction system pacing	Biventricular pacing	Conduction system pacing	Biventricular pacing	Conduction system pacing	Biventricular pacing	
His-SYNC, ^{65,66} 2019	40	15 (38)	26 (65) ^a	168 (18)	25 (62)	13 (33)	28 (23 to 34) ^b	12	125 (22)	164 (25)	35 (31 to 45) ^b	32 (31 to 40) ^b	1 (6)	1 (4)
His-Alternative, ⁶⁷ 2021	50	18 (36)	11 (22)	167 (15)	50 (100)	0	30 (6)	6	131 (20)	134 (15)	46 (9)	43 (7)	0	0
LBBP-RESYNC, ⁶⁸ 2022	40	20 (50)	0	175 (14)	40 (100)	0	30 (6)	6	131 (12)	137 (13)	49 (13)	46 (9)	0	0
HOT-CRT, ⁶⁹ 2023	100	31 (31)	39 (39)	165 (27)	62 (62)	34 (34)	31 (9)	6	137 (20)	141 (19)	43 (10)	39 (10)	2 (4)	2 (4)
CONSYST-CRT, ⁷⁰ 2025	134	36 (27)	46 (34)	175 (22)	75 (56)	27 (20)	28 (7)	12	126 (17)	131 (13)	18 (10) ^c	17 (11) ^c	1 (1.5)	3 (4.5)
CSP-SYNC, ⁷¹ 2025	62	18 (29)	20 (32)	174 (18)	62 (100)	0	29 (6)	12	-33 (-40 to -26) ^d	-32 (-39 to -25) ^d	14 (11 to 17) ^d	8 (6 to 11) ^d	1 (3)	0
PhysioSync-HF, ⁷² 2026	179 ^e	86 (50)	22 (13)	180 (170 to 200) ^b	165 (95)	12 (7)	26 (22 to 31) ^b	12	122 (25)	126 (21)	35 (12)	39 (12)	11 (12.6)	4 (4.7)
HeartSync-LBBP, ⁷³ 2026	200	64 (32)	35 (17)	168 (18)	200 (100)	0	28 (4)	36	121 (18)	137 (16)	47 (11)	41 (9)	2 (2)	5 (5)

Abbreviations: AF, atrial fibrillation; LBBB, left bundle-branch block; LVEF, left ventricular ejection fraction.

^a Patients with coronary artery disease at baseline.^b Median (IQR).^c Study reported change in LVEF.^d Study reported mean difference in LVEF from baseline at 6 months with 95% CI.^e A total of 179 participants were randomized; 6 did not undergo the index procedure for resynchronization (primary analysis, n = 173).

delay or right bundle-branch block, for which clinical benefit is mainly observed at a QRS duration of 150 ms or longer (Table 2).^{23,62}

Several RCTs have demonstrated reductions in morbidity and mortality with biventricular pacing (eTable 1 in the [Supplement](#)). The Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy (MADIT-CRT) study randomized 1820 patients with EF of 30% or less and QRS of 130 ms or longer to undergo biventricular pacing with defibrillator capability or to an implantable cardioverter-defibrillator. The trial was terminated early due to superiority of biventricular pacing, which reduced mortality or HF hospitalization compared with implantable cardioverter-defibrillator (17% vs 25%; HR, 0.66; $P = .001$).³⁰ The Cardiac Resynchronization – Heart Failure (CARE-HF) trial reported lower rates of all-cause death (n = 813; 20% vs 30%; HR, 0.64 [95% CI, 0.48-0.85]) and HF hospitalization (18% vs 33%; HR, 0.48 [95% CI, 0.36-0.64]) with biventricular pacing vs medical therapy.⁶³ In an individual patient-level meta-analysis of 5 RCTs that included 3872 patients with symptomatic HF, biventricular pacing was associated with lower all-cause mortality compared with medical therapy or implantable defibrillator (13.7% vs 20.8%; HR, 0.66 [95% CI, 0.57-0.77]) over a median follow-up of 23.7 months.⁶⁴ Fewer RCTs have compared biventricular pacing with conduction system pacing for resynchronization (Table 3).⁶⁵⁻⁷³

Conduction System Pacing for HFrEF and Comparison With Biventricular Pacing

Conduction system pacing of the His-Purkinje system has been evaluated as an alternative to biventricular pacing in patients with HFrEF (Table 1, Figure 2).⁸ For those with LVEF of 35% or less, sinus rhythm, LBBB, QRS of 150 ms or longer, and New York Heart Association functional class II to IV, the 2023 Heart Rhythm Society Guideline on Cardiac Physiologic Pacing for the Avoidance and Mitigation of Heart Failure proposes conduction system pacing as a reasonable alternative strategy to biventricular pacing.¹²

RCTs comparing conduction system pacing and biventricular pacing in HFrEF are summarized in Table 3.⁶⁵⁻⁷³ A meta-analysis and systematic review of 7 RCTs (408 patients with LVEF $\leq 40\%$) found that conduction system pacing was associated with greater reduction in QRS duration (mean difference, -13.34 ms [95% CI, -24.32 to -2.36]; $P = .02$) and LVEF improvement (mean difference, 2.06% [95% CI, 0.16%-3.97%]; $P = .03$) compared with biventricular pacing.⁷⁴ A meta-analysis of 4 RCTs and 17 observational studies, including 4327 patients with HFrEF and dysynchrony requiring cardiac resynchronization therapy, reported that conduction system pacing (n = 1960) was associated with lower all-cause mortality (10% vs 13%; odds ratio, 0.68 [95% CI, 0.56-0.83]) and reduced HF hospitalization (11% vs 20%; odds ratio, 0.52 [95% CI, 0.44-0.63]) than biventricular pacing. Overall complications (6% vs 8%) and lead revision rates (4% vs 5%) were similar between groups.⁷⁵

However, two 2026 RCTs enrolling patients with HF, LVEF of 35% or less, and LBBB have reported opposing treatment

effects with resynchronization strategies.^{72,73} A trial conducted at 6 centers in China (N = 200) reported lower rates of death or HF hospitalization over a median follow-up of 3 years among patients randomized to undergo conduction system pacing vs biventricular pacing (8% vs 28%; HR, 0.26 [95% CI, 0.12-0.57]).⁷³ In contrast, a noninferiority trial of 179 patients in Brazil reported that conduction system pacing was inferior to biventricular pacing for the primary composite outcome of all-cause death, HF hospitalization, urgent HF visits, and change in LVEF at 12 months (17.2% vs 9.3%; HR, 2.35 [95% CI, 0.99-5.61]).⁷² However, the Kaplan-Meier curves separated within 30 days, suggesting that early clinical events possibly related to procedural complications contributed to the observed difference.⁷² RCTs designed to account for variations in baseline characteristics and follow-up duration are ongoing to evaluate all-cause mortality or HF hospitalization in patients undergoing cardiac resynchronization with conduction system pacing (eTable 2 in the Supplement).^{76,77}

In an observational study of 1778 patients with LVEF of 35% or less undergoing cardiac resynchronization therapy for either HF with LBBB or chronic ventricular pacing for AV block-related bradycardia, left bundle-branch area pacing (LBBAP) was not associated with lower rates of mortality (12% vs 17%; HR, 0.88 [95% CI, 0.68-1.14]; $P = .30$), but was associated with lower rates of HF hospitalization (12% vs 19%; HR, 0.67 [95% CI, 0.52-0.86]; $P = .002$), new-onset AF (2.8% vs 6.6%; HR, 0.34 [95% CI, 0.16-0.73]; $P = .008$), and sustained ventricular tachycardia and ventricular fibrillation (4.2% vs 9.3%; HR, 0.46 [95% CI, 0.29-0.74]; $P < .001$) compared with biventricular pacing over a mean (SD) follow-up of 33 (16) months.^{78,79} In a registry-based observational study of 696 patients with HF at 14 European centers, with 87% followed up prospectively, successful lead placement was achieved in 82% of LBBAP implants, with a nonfatal complication rate of 8.3% (3.7% acute septal perforation into the LV, 1.5% septal lead dislodgment).⁸⁰ Conduction system pacing is estimated to reduce 12-month direct medical costs by \$7090 (95% CI, \$5779-\$8648) compared with biventricular pacing, largely driven by lower device costs, and may represent a strategy to expand access to resynchronization therapy.⁷²

HF With Mildly Reduced EF

HF with mildly reduced EF is defined as an EF of 41% to 49%.³⁵ Cardiac resynchronization therapy may be considered in this population when patients with marked delay in LV activation (LBBB with QRS ≥ 150 ms) (Table 2) have another indication for pacing, such as symptomatic bradycardia or requiring chronic ventricular pacing.⁵³ In these settings, physiological pacing with either biventricular pacing or conduction system pacing (Table 1) is increasingly preferred over RV pacing to prevent further dyssynchrony and decline in EF.⁸¹ In an RCT of 691 patients with AV block requiring permanent pacing and a mean baseline EF of 40%, the primary outcome (time to death; unplanned outpatient, emergency department, or inpatient visits requiring intravenous therapy due to HF symptoms; or a $\geq 15\%$ increase in LV end-systolic volume index) was improved with biventricular pacing compared with RV pacing (53.3% vs 64.3%; HR, 0.74 [95% credible interval, 0.60-0.90]).⁸²

In an observational study of 1004 symptomatic patients with HF with mildly reduced EF and either an LBBB or symptomatic bradycardia with anticipated frequent ventricular pacing, conduction system pacing was associated with lower rates of all-cause mortal-

ity or HF hospitalization (22% vs 34%; HR, 0.64; $P = .03$), lower incidence of new-onset AF (5% vs 12%; $P < .001$), and fewer episodes of sustained ventricular tachycardia and ventricular fibrillation (1% vs 5%; $P < .001$) compared with biventricular pacing.⁸³ The 2023 Heart Rhythm Society Guideline on Cardiac Physiologic Pacing for the Avoidance and Mitigation of Heart Failure recommends conduction system pacing or biventricular pacing (2a/2b recommendations for both treatments) (Figure 2) for patients with an indication for permanent pacing and LVEF of 36% to 50%.¹² Current guidelines suggest conduction system pacing for conditions in which pacing more than 40% of ventricular beats is expected (such as chronic AV block or AF with slow ventricular response) (Table 2) to preserve EF, improve bradycardia-related symptoms, and reduce the risk of cardiomyopathy.^{12,23} Additionally, conduction system pacing might help preserve ventricular function in patients with HF who have LVEF of 41% to 49% and are in sinus rhythm, have LBBB, QRS of 150 ms or longer, and New York Heart Association functional class II to IV.¹²

Patients With Normal EF

Pacing guidelines recommend against biventricular pacing as an initial ventricular pacing strategy for bradycardia in patients with normal EF (LVEF $\geq 50\%$), regardless of HF symptoms.^{12,84} Patients without HF and a persistent resting heart rate below 60 beats per minute may present with symptoms attributable to low cardiac output, including fatigue, lightheadedness, dizziness, presyncope, syncope, or exercise intolerance. Clinicians should review medications, and rate-slowing drugs, such as β -blockers, should be discontinued if possible.⁸⁵ If pacing is needed for patients with sinus node dysfunction and intact AV conduction, atrial-based pacing is recommended. For patients with AV block, dual-chamber pacing is indicated to maintain synchrony (Table 2).¹⁶ A trial of 108 patients with AV block and normal EF reported no difference in the composite outcome of cardiovascular mortality, HF onset, or HF hospitalization with biventricular pacing vs RV pacing (30% vs 31%; HR, 0.78; $P = .65$).⁸⁶ Similarly, a trial of 1810 patients requiring frequent ventricular pacing (mean baseline LVEF, 55%; QRS duration, 118 ms) reported no significant difference in time to death or HF hospitalization in those randomized to undergo biventricular pacing vs RV pacing (38.4% vs 40%; HR, 0.88 [95% CI, 0.76-1.02]; $P = .09$) over nearly 6 years of follow-up.⁸⁷

Although existing evidence has not demonstrated superiority of biventricular pacing over RV pacing in preventing pacing-induced cardiomyopathy in patients with normal EF and AV block, conduction system pacing may better preserve systolic function than RV pacing.⁵³ A trial of 249 patients without HF requiring permanent pacing for AV block-related symptomatic bradycardia reported conduction system pacing reduced pacing-induced cardiomyopathy compared with RV pacing (6% vs 15%; $P = .01$).⁸⁸ In a multicenter registry of 860 patients with symptomatic bradycardia (mean LVEF, 59%), conduction system pacing was associated with lower rates of HF hospitalization, pacemaker upgrade to cardiac resynchronization therapy, or all-cause mortality compared with RV pacing (13% vs 30%; $P < .001$).⁸⁹ Among those requiring more than 20% ventricular pacing, HF hospitalization was also lower (5% vs 21%; $P = .03$).⁸⁹ A meta-analysis of 6 observational studies, including 1577 patients with symptomatic bradycardia without HF, reported that conduction system pacing was associated with lower

rates of new-onset AF compared with RV pacing (9% vs 27%; HR, 0.32; $P < .001$).⁹⁰ In a retrospective comparative analysis of US Medicare beneficiaries with normal LVEF receiving pacing for symptomatic bradycardia, compared with RV pacing ($n = 16\,989$), conduction system pacing ($n = 6197$) was associated with lower adjusted 30-day mortality (1.1% vs 1.5%; $P = .02$) and reduced 6-month mortality risk (HR, 0.66; $P < .001$). Rates of reintervention for device revision or lead replacement were similar between groups (2.9% vs 3.0%; HR, 0.95; $P = .63$).⁹¹

Pacing-Induced Cardiomyopathy

Pacing-induced cardiomyopathy is typically defined as a 10% or greater decrease in LVEF to less than 50% at any time after pacemaker implant, although LV systolic deterioration can occur outside this range.²⁷ When pacing-induced cardiomyopathy is identified early in EF decline, ventricular function is often reversible with physiologic pacing.^{89,92} A trial of 360 patients with RV pacing-induced cardiomyopathy reported lower all-cause mortality or HF hospitalization among those randomized to undergo biventricular pacing combined with defibrillator capability compared with defibrillator therapy alone (10% vs 32%; HR, 0.27; $P < .001$) (Table 1).⁹³ An observational study of 48 patients with pacing-induced cardiomyopathy who received a device upgrade to conduction system pacing reported a greater mean EF improvement (12.8% vs 6.9%; $P < .001$) and QRS narrowing (-57 ms vs -35 ms; $P < .001$) compared with biventricular pacing (Figure 2).⁹⁴

Adverse Events of Cardiac Resynchronization Therapy Implant

Procedure-related adverse events after cardiac resynchronization therapy implant occurred in 5.6% to 8.1% of patients across observational and randomized studies.⁹⁵ The most common adverse events were lead-related complications, including lead dislodgment or fracture, reported in both registries (3.5% of 12 266 procedures) and RCTs (6.5% of 4465 patients); followed by pocket hematoma (2.5% vs 2.0%); device-related infection (1.0% vs 1.5%); and pneumothorax (0.6% vs 1.3%).⁹⁵ In a cohort study of all Danish patients who underwent cardiac-implantable electronic device procedures from May 2010 to April 2011, the in-hospital mortality rate was 0.1%, and the 6-month cumulative incidence of complications managed conservatively or requiring reintervention was 9.6% with biventricular pacing alone vs 17.7% with biventricular pacing plus a defibrillator.⁹⁶ Compared with dual-chamber pacemaker, biven-

tricular pacing may also result in higher energy consumption and shorter device longevity, requiring more frequent generator replacements, with additional associated procedural risks, such as device infection.⁹⁷ Safety data for conduction system pacing are predominantly observational. In a multicenter retrospective study of patients at 10 centers who required conduction system pacing lead extraction (224 His bundle pacing and 117 LBBAP leads) over a mean (SD) follow-up of 22 (26) months, the most common causes were lead dislodgment or increasing energy needs to maintain effective cardiac stimulation (68%) and infection (19%). Lead extraction was successful in all patients, and the success rate of interventricular septal lead reimplant was 95%.⁹⁸

Practical Considerations

Patients with conduction system abnormalities on ECG (Table 2) and HF with a decline in EF should be evaluated by electrophysiologists, ideally within 3 months. Guidelines suggest that patients should undergo echocardiography within 3 to 12 months after cardiac resynchronization therapy implant to assess ventricular function.¹² Guidelines also recommend continuous wireless transmission of data from patients with HF after cardiac resynchronization therapy for early detection of arrhythmias and confirmation of pacing adequacy.^{12,23} During annual in-person visits, a 12-lead ECG should be obtained to determine if paced QRS duration and morphology remain consistent with prior tracings (eFigure in the Supplement).⁹⁹

Limitations

This review has limitations. First, the quality of included studies was not systematically assessed. Second, some relevant articles may have been missed. Third, evidence about conduction system pacing applicability is primarily based on small trials and observational studies with limited follow-up.

Conclusions

Cardiac dyssynchrony due to conduction system disease occurs in 20% to 30% of patients with HF and systolic dysfunction. Cardiac resynchronization therapy restores synchronous ventricular activation in patients with HF, reduced LVEF, and LBBB, or in those requiring chronic ventricular pacing, and may improve LV function, decrease HF hospitalizations, and reduce mortality.

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Submissions: We encourage authors to submit papers for consideration as a Review. Please contact Kristin Walter, MD, at kristin.walter@jamanetwork.org.

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