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Conduction System Pacing for Heart Failure

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Background

Biventricular pacing (BIVP) traditionally delivers cardiac resynchronization therapy (CRT) by using pacing leads in the right ventricle and the coronary sinus.

Cardiac resynchronization therapy is the heart failure (HF) therapy "that simultaneously improves cardiac function and functional capacity, reduces hospitalization, and prolongs survival"[1] in patients with HF with a reduced ejection fraction and a wide QRS complex.[2-16] Solid randomized clinical trial (RCT) efficacy and safety data in more than 8,500 patients with biventricular devices[17,18] have established CRT as the standard therapy in this category of patients. Approximately 20% to 40% of patients, however, do not respond to CRT via BIVP depending on the measure used.[17] Up to 7% of biventricular pacemaker implants are furthermore unsuccessful as a result of difficulties encountered while implanting the left ventricular coronary sinus lead.[9]

For patients with a left ventricular ejection fraction of 36% to 50%, the BLOCK HF trial showed the superiority of BIVP to right ventricular pacing[9] for a composite outcome of all-cause mortality, hospitalization as a result of HF, and an increase of more than 15% in the left ventricular end-systolic volume index. Because of higher costs, BIVP is not used often as a first-line therapy over right ventricular pacing outside of the United States.

Recent Developments

Because of the limitations of BIVP, conduction system pacing (CSP) at the level of His bundle[19] or the left bundle branch[20] has emerged as an alternative physiologic pacing treatment that preserves or restores left ventricular electrical and mechanical synchrony. Left bundle branch area pacing has become the dominant approach because of its higher success rate, lower and more stable pacing thresholds, and its correction of the left bundle branch block below the level of the His bundle compared with His bundle pacing.[21]

There are only 7 randomized clinical trials comparing His bundle pacing and left bundle branch area pacing with BIVP.[21] All of the trials are small, of short duration, and were not powered for major clinical end points such as HF hospitalizations and death. His bundle pacing and left bundle branch area pacing are at least equal or superior to BIVP in terms of surrogate parameters for electrical and mechanical synchrony.

There are substantially more data from large registries and retrospective comparative studies suggesting that His bundle pacing and left bundle branch area pacing may be superior to BIVP in terms of hard outcomes and possibly safety. An analysis of the safety of left bundle branch area pacing from the Multicentre European Left Bundle Branch

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Area Pacing Outcomes Study (MELOS) demonstrated higher success rates among early European adopters of left bundle branch area pacing when the procedure was performed for bradycardia (92.4%) and HF (82.2%).[22] This study reported the highest complication rate (8.3%), though a notable majority of the complications were clinically insignificant septal perforations.

The largest retrospective case-control study, I-CLAS, suggested that left bundle branch area pacing outperformed BIVP and was associated with reduction in time to death and HF hospitalizations.[21] Similar results were reported by 2 additional retrospective studies.[23,24] Left bundle branch area pacing was also associated with a lower time to onset of both new-onset atrial fibrillation and ventricular arrhythmias, even in those patients with no history of ventricular arrhythmias who were naive to antiarrhythmic therapy.[25] A meta-analysis of 4 randomized and 17 observational studies showed CSP was associated with a significant reduction in all-cause mortality and HF hospitalizations compared with BIVP for CRT.[26]

Future Directions

Despite the lack of large RCTs on these therapies, His bundle pacing and left bundle branch area pacing have been included in the most recent pacing guidelines for the avoidance and mitigation of HF as Class of Recommendation grades 2a and 2b, with similar indications to BIVP.[22] Current Heart Rhythm Society, Asia Pacific Heart Rhythm Society, and Latin American Heart Rhythm Society guidelines recommend CSP as an alternative to traditional BIVP when effective CRT cannot be achieved (Class of Recommendation 2a).[22] There are, however, multiple ongoing moderate to large RCTs that will fill gaps in clinical knowledge (Table I).

Physiologic pacing for HF with a left ventricular ejection fraction of less than 50% remains a dynamic field with multiple ongoing RCTs that will determine the relative benefits and safety of different pacing modalities. There is also an acute need to develop sheaths, leads, devices, and algorithms to improve and optimize the success rate of CSP.

Abbreviations

BIVP, biventricular pacing
CRT, cardiac resynchronization therapy
CSP, conduction system pacing
HF, heart failure
RCT, randomized clinical trial

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TABLE I. Major Clinical Trials, by Left Ventricular Ejection Fraction Subpopulation, Comparing BVP, His Bundle Pacing, and Left Bundle Branch Area Pacing for CRT and Their Primary End Points

<table>
<tr><th>Left ventricular ejection fraction ≤35%</th><th>Left ventricular ejection fraction 36%-49%</th><th>Left ventricular ejection fraction ≥50%</th></tr>
<tr><td>CSP-SYNC [NCT05155865]
(CSP vs BIVP) (N = 60)
End points: left ventricular ejection fraction, left ventricular volume, New York Heart Association classification, 6-minute walk test, quality of life</td><td colspan="2">His-PACE [NCT04672408]
(His bundle pacing vs right ventricular pacing) (N = 50)
End point: left ventricular ejection fraction</td></tr>
<tr><td>HIS-alt_2 [NCT04409119]
(CSP vs BIVP) (N = 125)
End points: left ventricular end-systolic volume, QRS duration</td><td colspan="2">HIS-PrEF [NCT04529577]
(His bundle pacing vs right ventricular pacing) (N = 40)
End point: left ventricular ejection fraction</td></tr>
<tr><td>HIS-CRT [NCT05265520]
(His bundle pacing vs BIVP) (N = 120)
End point: left ventricular ejection fraction</td><td colspan="2">LEAP [NCT04595487]
(Left ventricular septal pacing vs right ventricular pacing) (N = 470)
End points: death, HF hospitalizations, left ventricular ejection fraction decrease by 10%</td></tr>
<tr><td>His-SYNC [NCT02700425]
(His bundle pacing vs BIVP) (N = 41)
End point: QRS duration</td><td colspan="2">LEFT HF [NCT05015660]
(Left bundle branch area pacing vs right ventricular pacing) (N = 1,280)
End points: cardiovascular death, HF events</td></tr>
<tr><td>LeCaRT [NCT05365568]
(Left bundle branch area pacing vs BIVP) (N = 170)
End points: composite death, HF hospitalizations, worsening HF, implant failure, cardiac implantable electrical device re-intervention</td><td colspan="2">OptimPacing [NCT04624763]
(Left bundle branch area pacing vs right ventricular pacing) (N = 683)
End points: death, HF hospitalizations, pacemaker-induced cardiomyopathy</td></tr>
<tr><td>LIT-HF [NCT05572957]
(CSP vs guideline-directed medical therapy) (N = 50)
End point: left ventricular ejection fraction</td><td colspan="2">PROTECT-HF [NCT05815745]
(His bundle pacing vs right ventricular pacing) (N = 2,600)
End points: cardiovascular death, HF events</td></tr>
<tr><td>Left-Bundle CRT [NCT05434962]
(Left bundle branch area pacing vs BIVP) (N = 176)
End point: CRT response</td><td colspan="2">REINVENT-CRT [NCT05652218]
(Left bundle branch area pacing vs BIVP) (N = 20)
End point: myocardial perfusion imaging</td></tr>
<tr><td>PhysioSync-HF [NCT05572736]
(CSP vs BIVP) (N = 304)
End points: death, HF hospitalizations, left ventricular ejection fraction</td><td></td><td></td></tr>
<tr><td colspan="2">CONSYST-CRT [NCT05187611]
(CSP vs BIVP) (N = 130)
End points: composite death, cardiac transplant, HF hospitalizations, and left ventricular ejection fraction</td><td>LBB Pacing Versus Conventional Pacing in Atrioventricular Block [NCT05722379]
(Left bundle branch area pacing vs right ventricular pacing) (N = 27)
End point: global work efficiency</td></tr>
<tr><td colspan="2">HIPPOS [NCT05491655]
(His bundle pacing vs backup right ventricular pacing) (N = 34)
End point: left ventricular ejection fraction</td><td>RHYSPAVB [NCT05214365]
(His bundle pacing vs right ventricular pacing) (N = 200)
End point: pacemaker-induced cardiomyopathy</td></tr>
<tr><td colspan="2">LBBAP-AFHF [NCT05549544]
(Left bundle branch area pacing vs BIVP) (N = 60)
End point: left ventricular ejection fraction</td><td>Vanguard [NCT05015660]
(Left bundle branch area pacing vs right ventricular pacing) (N = 100)
End points: death, HF events, left ventricular end-systolic volume, changes in lead parameters, quality of life; and safety</td></tr>
<tr><td colspan="2">LBB Pacing in Patients with Cardiac Dysfunction and AV Block [NCT05553626]
(Left bundle branch area pacing vs BIVP) (N = 160)
End point: left ventricular ejection fraction</td><td></td></tr>
<tr><td colspan="2">Left vs Left [NCT05650658]
(CSP vs BIVP) (N = 2,136)
End points: death, HF hospitalizations, quality of life</td><td></td></tr>
</table>

BIVP, biventricular pacing; CRT, cardiac resynchronization therapy; CSP, conduction system pacing; HF, heart failure.

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