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Role of conduction system pacing in ablate and pace strategies for atrial fibrillation

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With the advent of conduction system pacing, the threshold for performing 'ablate and pace' procedures for atrial fibrillation has gone down markedly in many centres due to the ability to provide a simple and physiological means of pacing the ventricles. This article reviews the technical considerations for this strategy as well as the current evidence, recognized indications, and future perspectives.

Pathophysiology of atrial fibrillation and heart failure

There is a need for increasing clinical emphasis to be placed on the value of sinus rhythm as a therapy to prevent the development and/or progression of heart failure, as catheter ablation trials have consistently shown evidence of improvements in ejection fraction and reduction in mortality. However, the mechanisms underlying the entity of arrhythmia-induced cardiomyopathy remain incompletely understood.[1] Atrial fibrillation (AF) has multiple deleterious haemodynamic and adverse cellular effects on myocardial function, and particularly in those with systolic dysfunction. While sustained tachycardia induces tachycardiomyopathy in animal models, cellular mechanisms may include mitochondrial and endoplasmic reticulum dysfunction, calcium mishandling, and induction of fibrosis as central to the development of heart failure.[2-4] Second, atrial kick is lost in the setting of AF, which reduces LV preload in the absence of the final stages of diastole and atrial systole. However, the role of irregular R-R intervals is the third component of the adverse haemodynamic consequences of AF.[5-8] This 'irregulopathy' warrants further consideration and mechanistic investigation as AF, even in the setting of rate control, may exacerbate or cause heart failure.

The recent APAF-CRT trial[9] ($n = 133$) was a provocative randomized trial that demonstrated survival advantage in patients with narrow QRS that underwent atrioventricular nodal (AVN) ablation with biventricular pacing (BiV) compared with standard of care. In these patients, with an average heart rate of 101 ± 22 b.p.m. at enrolment, the potential heightened role of 'irregulopathy' is brought to the forefront, as atrial kick is absent in patients that persist in AF with AVN ablation. Mortality benefits without atrial kick and tachycardia warrants further considerations on the physiological benefit. In this context, ablate and pace therapy has re-emerged as a potential first-line therapy in those patients with AF of a long-standing and permanent nature. Appropriately so, a follow-up study is planned by Brignole and colleagues to test conduction system pacing (CSP) as the permanent form of electrical stimulation. This may indeed result in even greater differences, as biventricular pacing does not achieve physiological activation of the ventricles.

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Such emerging evidence for ablate and pace therapies to prevent and reverse LV dysfunction warrants future studies with CSP as the permanent mode of ventricular stimulation. Furthermore, the threshold to performed repeat ablation procedures on patients with refractory AF and/or long-standing to permanent AF would be anticipated to increase, if evidence suggests consistent mortality benefit with atrioventricular (AV) node ablation with physiologic pacing. In this review, we provide a summary of evidence for ablate and pace strategies with biventricular pacing and newer evidence with CSP.

Technical considerations

The AVN is located inferior and posterior to the His bundle lead and is the primary target of ablation (rather than the His bundle). With His bundle pacing (HBP), one of the main concerns is that delivery of radiofrequency adjacent to the His bundle has the potential to increase thresholds if the zone of the ablation lesions creates tissue inexcitability, and catheter manipulation in close proximity to the HBP lead may also threaten lead stability. A rise in HBP capture threshold >1 V associated with AVN ablation is observed in 2.2–15.9% of patients.[10-14] The risk of threshold rise with AVN ablation is absent when the target site is at or below the level of the ring electrode.[11] It rises exponentially when the ablation site is within 5 mm of the His lead tip,[14] which is the distance between the helix extremity and most proximal part of the distal electrode of a Medtronic (Minneapolis, MN) 3830 lead. Cryoablation was tested as an alternative to radiofrequency energy for AVN ablation in HBP patients.[14] Potential advantages are that there is no propensity for shunting of current to the pacing electrode tip, tissue adherence of the lead during application provides stability despite tachycardia, and this form of energy potentially provides greater reversibility of tissue damage if the application is interrupted in case of acute threshold rise. However, results were not superior compared with radiofrequency ablation.

Pacing output may be set at 0.5 V/0.4 ms above the capture threshold (which allows to evaluate threshold rise during application) and the device may be set to VVI 30 b.p.m. (*Figure 1*). The operator should target the AVN inferiorly and posteriorly to the HBP lead tip, at or below the level of the ring electrode (*Figure 2A*). These sites typically show presence of atrial electrograms and no (or only far-field) His potentials. Non-irrigated or irrigated catheters may be used, with a power setting starting of 30 W. A sheath can be useful to stabilize the catheter and provide better tissue contact. Application of radiofrequency of >30 s may be required before block is achieved (usually preceded by rapid junctional rhythm). If the initial applications are unsuccessful, the catheter may be moved more superiorly, eventually with lowering of the power to avoid compromising HBP thresholds. Once complete atrioventricular block is achieved, it is advisable to wait for at least 15 min to evaluate recurrence of conduction. Bonus applications may be applied if deemed necessary.

The application should be immediately interrupted if there is loss of His capture (*Figure 3*). In patients with complete left bundle branch block which is corrected by HBP, the right bundle may be targeted in case of unsuccessful applications on the AVN (mechanical complete atrioventricular block may precede radiofrequency application). This will result in HBP with a right bundle branch block pattern (*Figure 4*).

In patients undergoing HBP who are intended for AVN ablation, it is recommended to place the His lead in a more distal (ventricular) position to allow a greater safety margin when ablating the AVN. Proximal right bundle branch pacing sometimes results when the lead is placed in a distal position.[15,16] Pacing of the distal right bundle is usually fortuitous and it is unclear if it provides physiological pacing.[17,18] Left bundle branch area pacing

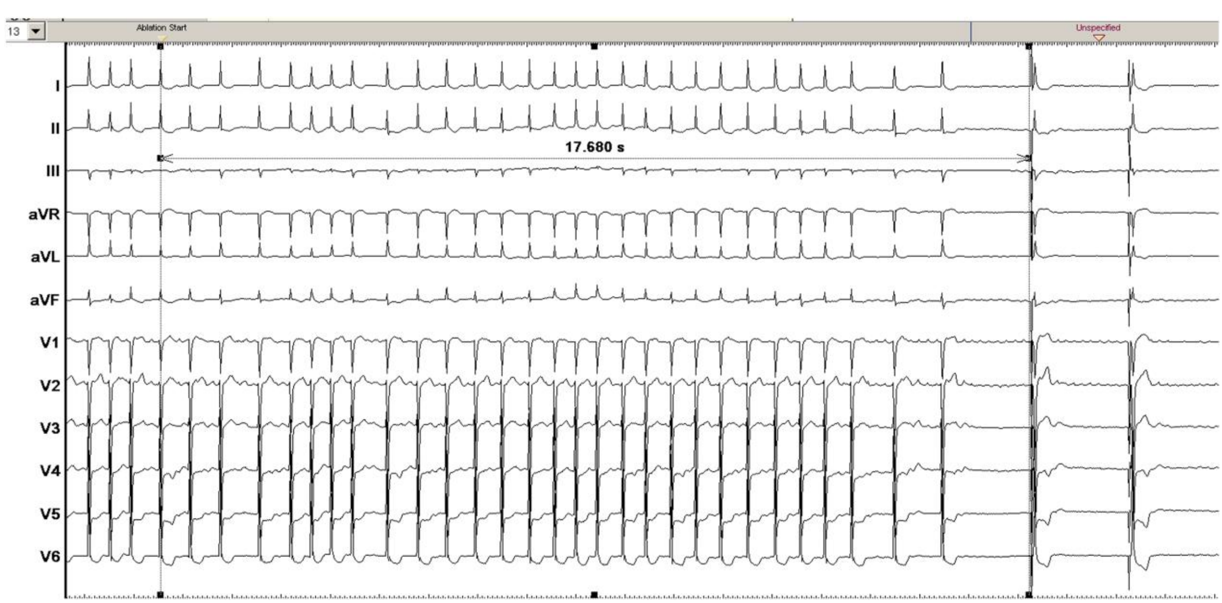

Figure 1 Atrioventricular nodal ablation in a patient with His bundle pacing, showing complete atrioventricular block and selective His bundle pacing. Sweep speed set at 13 mm/s.

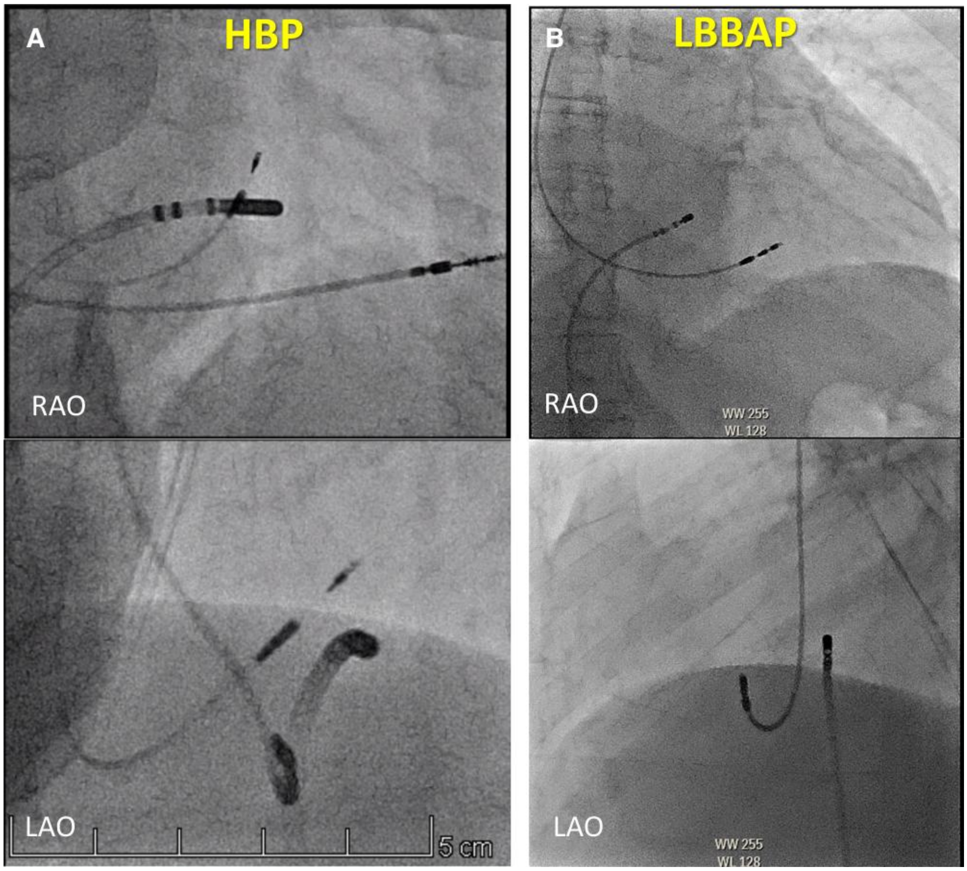

Figure 2 Ablation sites in a patient implanted with His bundle pacing (*A*) and with left bundle branch area pacing (*B*). Note that the distance to the lead tip is much greater in the latter instance. HBP = His bundle pacing; LAO = left anterior oblique; LBBAP = left bundle branch area pacing; RAO = right anterior oblique.

Figure 3 Atrioventricular node ablation in a patient with His bundle pacing, in whom there was a rise in threshold during radiofrequency application, with loss of capture by the His bundle lead and presence of backup right ventricular pacing (asterisk). The His lead was connected to the atrial port and the right ventricular lead to the ventricular port and the pacemaker was programmed in dual chamber pacing mode 30 b.p.m. with output of the His lead at 0.5 V/ 0.4 ms above threshold. Prompt cessation of radiofrequency delivery led to recovery of the His capture threshold.

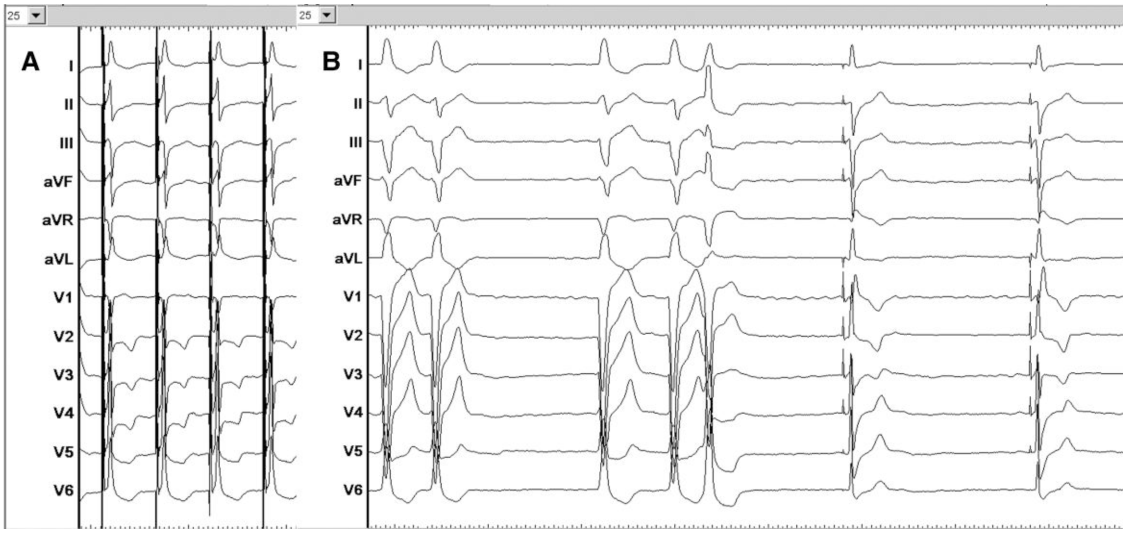

Figure 4 Atrioventricular node ablation in a patient with His bundle pacing and complete left bundle branch block. (*A*) Correction of left bundle branch block with His bundle pacing. (*B*) Complete atrioventricular block was achieved by ablating the distal right bundle branch (at a safe distance from the tip of the His lead), resulting in paced rhythm with selective His capture and right bundle branch block.

(LBBAP) provides a more practical and safer alternative to HBP in the setting of AVN ablation and is usually preferred in this setting.[19,20] As the lead is placed >1.5 cm more apical to the His region and in the left ventricular sub-endocardium, it is at a safe distance from the ablation site (*Figure 2B*), with no risk of ablating tissue adjacent to the lead tip and also has a lower risk of inadvertent lead dislodgement when manipulating the ablation catheter.

One of the primary concerns with AVN ablation and CSP is the potential for threshold rise or lead dislodgement with a solitary ventricular lead in a pacemaker-dependent patient. Due to these concerns, the 2021 European Society of Cardiology (ESC) pacing guidelines recommend placing a backup ventricular lead in patients with HBP who undergo AVN ablation, in the interest of patient safety.[21] However, this results in more hardware and greater cost. Furthermore, device programming may be more complex, especially if the HBP lead is connected to the atrial channel (with the backup ventricular lead connected to the ventricular channel).[22,23] Ablation during the same procedure as implantation has been performed via femoral or axillary access and has been shown to be safe and feasible, with same-day discharge.[24] The axillary approach may require looping of the ablation catheter below the tricuspid valve, or use of a deflectable sheath. Along with advances in technique for HBP implantation,[16] this approach to ablate and pace during the same procedure may reduce the need for a backup lead, which is not routinely recommended according to the recent Heart Rhythm Society (HRS) guidelines on physiological pacing.[25] However, many operators may wish to ablate in a more sub-acute setting once thresholds are demonstrated to be stable and wound status is evolving favourably.

A dilemma which operators sometimes face is whether to implant an atrial lead. Even though AF may be persistent, significant clinical improvement with ablate and pace strategies may result in unexpected reversion of sinus rhythm, with subsequent asynchronous ventricular pacing.

When an implantable cardioverter defibrillator is implanted, the right ventricular lead is placed in the traditional location into the apex of mid-septum, and the CSP lead can be connected to the atrial port to minimize header connections, pocket bulk, and total lead number. Dual-chamber rhythm discrimination criteria should be dis-activated in these instances.[22,26,27] In heart failure patients with reduced ejection fraction who have underlying bundle branch block which is incompletely corrected by CSP, addition of a coronary sinus lead to deliver His-optimized or left bundle branch optimized cardiac resynchronization therapy (HOT-CRT and LOT-CRT, respectively) may be considered.[28-30] In these instances, the CSP lead is connected to the atrial port, with the ventricular leads to their respective ports.

Published outcomes

Most of the data on CSP for ablate and pace are reported in non-randomized studies (see *Table 1*). A propensity-matched study in 162 patients[34] and a small randomized crossover study in 23 patients[37] compared HBP with LBBAP in patients with AVN ablation found comparable outcome between treatment modes in terms of clinical and echocardiographic outcome.[34,37]

The only study to date randomizing HBP again right ventricular apical pacing in patients with an ablate and pace indication was reported by Occhetta *et al*.[32] and included 16 patients who had both HBP as well as right ventricular pacing leads and were crossed over for 2×6 months periods of pacing. This early study did not have current tools and used stylet-driven leads without guiding catheters. Although HBP was only achieved in 4 patients (with ‘para-Hisian’ pacing in the remaining patients), the HBP periods had better New York Heart Association and 6-minute walk tests, without any difference in echocardiographic parameters.

Huang *et al*. reported results from the ALTERNATIVE-AF trial which is the only randomized study to date which

Table 1 Published studies on conduction system pacing for an 'ablate and pace' indication with clinical and/or echocardiographic follow-up

Study	Design	Inclusion criteria	*n* enrolled (final *n* with CSP)	Follow-up	Findings and comments
Deshmukh *et al.*[31]	Observational single centre	QRS ≤120 ms, LVEF < 0.40, AF scheduled for AVN ablation	18 (18 HBP)	23.4 ± 8.3 months	Improvement in LVEF, LV dimensions, NYHA class compared with baseline. Stylet-driven leads used without guiding catheter
Occhetta *et al.*[32]	Randomized, crossover single blind HBP vs. RVA, single centre	'Ablate and pace' for rapid AF	18 (16 HBP)	2 × 6 months	Better NYHA, 6MWT with HBP. No difference in LVEF, LVESV, LVEDV. Stylet-driven leads used without guiding catheter. Only 4/16 patients had HBP, all others with 'Para-Hisian' pacing
Huang *et al.*[10]	Observational, single centre	'Ablate and pace' for rapid AF	52 (42 HBP)	21.1 ± 9.3 months	Improvement in LVEF, LV dimensions, NYHA class compared with baseline. Para-Hisian pacing in 4 patients. AV node ablation with failure/rise in HBP threshold/recurrence of conduction in 8 patients
Vijayaraman *et al.*[11]	Observational, single centre	'Ablate and pace' for rapid AF	42 (40 HBP)	19 ± 14 months	Improvement in LVEF and NYHA class compared with baseline
Wang *et al.*[33]	Observational, single centre	Chronic AF with average heart rate ≤100 b.p.m., AVN ablation QRS ≤ 130 ms or RBBB, ICD indication	55 (44 HBP, 8 LBBAP)	Median 30.5 months	Improvement in LVEF, decrease in LVESV compared with baseline
Cai *et al.*[34]	Prospective (LBBAP) and retrospective (HBP), observational, single-centre propensity-matched	Persistent AF, symptomatic HF	172 (86 HBP, 86 LBBAP)	28.9 ± 11.9 months	Similar improvement in LVEF and NYHA improvement between groups, but lower thresholds, higher sensed R-wave amplitudes and fewer complications with LBBAP
Vijayaraman *et al.*[35]	Multi-centre, retrospective. CSP vs. RVP or BiV	AF with uncontrolled heart rate	223 (HBP 84, LBBAP 26)	27 ± 19 months	Significantly greater freedom of death or heart failure hospitalization with CSP compared with conventional pacing
ALTERNATIVE-AF, Huang *et al.*[36]	Randomized multi-centre, crossover. HBP + BiV in all patients	Persistent AF, NYHA II-IV, LVEF ≤0.40, QRS <120 ms	50 (50 HBP)	2 × 9 months	Greater improvement in LVEF with HBP than BiV, with similar improvement in QOL, NYHA and BNP
Ye *et al.*[37]	Single-centre randomized crossover HBP + LBBAP in all patients	Persistent AF >100 b.p.m. at rest, non-LBBB, non-NYHA IV	33 (23 with HBP + LBBP)	2 × 6 months	Similar improvement in LVEF between HBP and LBBAP. Only HBP improved TAPSE

AF, atrial fibrillation; AVN, atrioventricular node; BiV, biventricular pacing; BNP, brain natriuretic peptide; HF, heart failure; LBBB, left bundle branch block; LBBAP, left bundle branch area pacing; LBBP, left bundle branch pacing; LVEDV, left ventricular end diastolic volume; RVA, right ventricular apex; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume; NYHA, New York Heart Association; QOL, quality of life; RBBB, right bundle branch block; RVP, right ventricular pacing; TAPSE, tricuspid annulus plane systolic excursion.

compared ablate and pace strategies for AF with biventricular pacing (BiV) vs. HBP in heart failure patients with ejection fraction <40% with rate controlled persistent AF undergoing AV node ablation. In a crossover design, they assigned 50 patients to undergo both HBP and BiV, with the His bundle lead placed into the atrial port. Crossover at 9 months showed statistically significant improvement in left ventricular ejection fraction (LVEF) from baseline in both HBP and BiV, with overall superiority with HBP over BiV (~5% ejection fraction (EF) improvement). These data support clinically benefit from either pacing modality with AV node ablation, as ~95% had improvement in EF.

Guidelines and recommendations

His bundle pacing was first introduced in international guidelines as an indication for pace and ablate strategies in the 2019 ESC supra-ventricular arrhythmia guidelines, along with BiV pacing (Class I, level of evidence C).[38] The 2021 ESC pacing guidelines gave a Class IIb, level of evidence C indication for HBP, which is identical to the more recent HRS guidelines.[25] The ESC guidelines did not give any recommendations for LBBAP, as there was little published evidence regarding safety and efficacy at the time of their writing. The recent HRS guidelines[25] however include left bundle branch pacing, as a Class IIb recommendation (without mentioning the need for a backup pacing lead, which is considered optional for HBP).

Future trials and directions

Given the need for prospective and comparative trials, there are multiple studies currently registered on clinicaltrials.gov. Three randomized controlled trials are currently underway to compare biventricular pacing with CSP in Europe, China, and Canada.

Conduction system pacing versus biventricular pacing after atrioventricular node ablation in heart failure patients with symptomatic atrial fibrillation and narrow QRS (CONDUCT-AF trial) is planned in Austria and Belgium. The randomized, interventional, multi-centric study ($n = 82$) will explore whether CSP is non-inferior to BiV pacing in echocardiographic and clinical outcomes in heart failure (EF <50%) patients with symptomatic AF and narrow QRS scheduled for AV nodal ablation. In this study, LBBAP is preferred as first-line for CSP, with HBP a backup.

The LBBAP-AFHF trial (clinical efficacy of left bundle branch area pacing for patients with permanent atrial fibrillation and heart failure) is a prospective, multi-centre, randomized controlled trial planned in China that is designed to determine whether LBBAP may show superiority of improved LV function as compared with traditional biventricular pacing (BiV) in patients ($n = 60$) with permanent AF and heart failure (LVEF < 50%) who receive AVN ablation due to fast ventricular rate or require high percentage of ventricular pacing due to slow ventricular rate. The primary endpoint of this trial is the change in the LVEF at 6 months after device implantation from baseline.

The RAFT-P&A trial (resynchronization in patients with ambulatory heart failure in atrial fibrillation trial undergoing pace and atrioventricular node ablation strategy with left bundle branch area pacing compared with biventricular pacing) conducted in Canada ($n = 284$) is a prospective, randomized, double blind, control trial will randomize treated in a 1:1 allocation to AV node ablation and BiV vs. LBBAP with primary endpoint of changes in NT-proBNP and quality of life.

After completion of these trials, it is hypothesized that CSP will be comparable if not superior to BiV in the setting of AVN ablation. Future trials that include multiple arms with pulmonary vein isolation vs. AVN ablation with CSP are necessary to guide clinical practice, as the question of which strategy to prefer remains open.

A greater mechanistic understanding of which factors related to AF are most detrimental to myocardial function, on both a cellular and organ level is necessary. Lastly, the ability to predict which patients are most susceptible to arrhythmia-induced cardiomyopathy will be perhaps the greatest step forward, as not all patients with AF develop heart failure (HF). What is clear is that the armamentarium for AF management continues to widen, with the ability to maintain physiological activation of the ventricles with CSP. Physiological selection and prediction will further guide the field of pacing of the next decade.

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Data can be made available upon reasonable request.

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