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TRIAL DESIGN

The PhysioVP-AF study, a randomized controlled trial to assess the clinical benefit of physiological ventricular pacing vs. managed ventricular pacing for persistent atrial fibrillation prevention in patients with prolonged atrioventricular conduction: design and rationale

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Aims

In patients with prolonged atrioventricular (AV) conduction and pacemaker (PM) indication due to sinus node disease (SND) or intermittent AV-block who do not need continuous ventricular pacing (VP), it may be difficult to determine which strategy to adopt. Currently, the standard of care is to minimize unnecessary VP by specific VP avoidance (VPA) algorithms. The superiority of this strategy over standard DDD or DDD rate-responsive (DDD/DDDR) in improving clinical outcomes is controversial, probably owing to the prolongation of the atrialventricular conduction (PR interval) caused by the algorithms. Conduction system pacing (CSP) may offer the most physiological-VP approach, providing appropriate AV conduction and preventing pacing-induced dyssynchrony.

Methods and results

PhysioVP-AF is a prospective, controlled, randomized, single-blind trial designed to determine whether atrial-synchronized conduction system pacing (DDD-CSP) is superior to standard DDD-VPA pacing in terms of 3-year reduction of persistent-AF occurrence. Cardiovascular hospitalization, quality-of-life, and safety will be evaluated. Patients with indication for permanent DDD pacing for SND or intermittent AV-block and prolonged AV conduction (PR interval > 180 ms) will be randomized (1:1 ratio) to DDD-VPA (VPA-algorithms ON, septal/apex position) or to DDD-CSP (His bundle or left bundle

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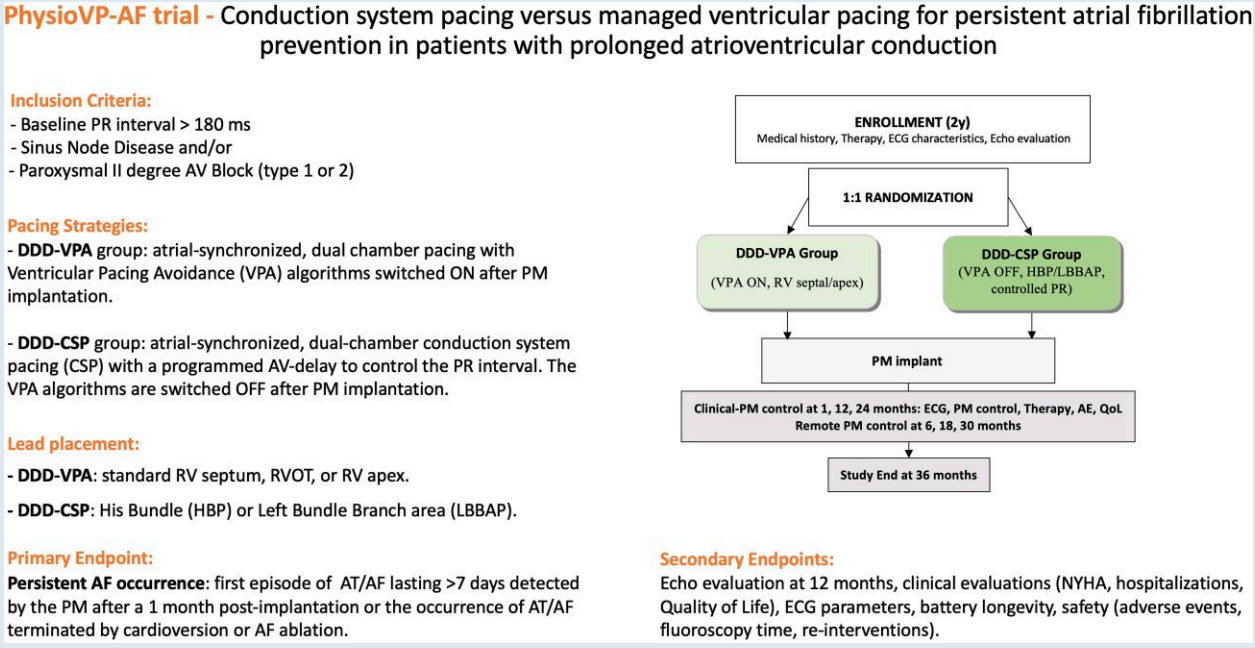
branch area pacing, AV-delay setting to control PR interval, VPA-algorithms OFF). Approximately 400 patients will be randomized in 24 months in 13 Italian centres.

Conclusion The PhysioVP-AF study will provide an essential contribution to patient management with prolonged AV conduction and PM indication for sinus nodal disease or paroxysmal 2nd-degree AV-block by determining whether CSP combined with a controlled PR interval is superior to standard management that minimizes unnecessary VP in terms of reducing clinical outcomes.

Graphical Abstract



Keywords His bundle pacing • Left bundle branch area pacing • Managed ventricular pacing • Atrial fibrillation • Ventricular pacing avoidance

What's new

- The effects of providing an appropriate atrioventricular (AV) conduction and preventing pacing-induced dyssynchrony by conduction system pacing (CSP) in terms of reducing clinical outcomes.
- The strategy of pacing to adopt in patients with prolonged AV conduction who do not need continuous ventricular pacing (sinus node disease or intermittent AV-block).
- A comparison between CSP and standard right ventricular pacing by a large multicentre randomized trial in terms of clinical outcomes, safety, and feasibility.

Introduction

In patients without atrioventricular (AV) block, unnecessary right ventricular (RV) pacing has been shown to be detrimental, causing cardiac dyssynchrony and increasing the risk of developing permanent atrial fibrillation (AF).[1,2] A linearly increasing relationship between the cumulative percentage of RV apical pacing (CumVP%) and AF risk has been demonstrated.[2] Recent studies have shown that RV apical pacing adversely impacts left atrial structure and function and may trigger new-onset atrial arrhythmias.[3,4] Therefore, algorithms to minimize ventricular pacing have been made available in the DDD/DDDR pacing modes. However, recent studies and a meta-analysis[1,5] have not convincingly confirmed that atrial pacing, or RV pacing minimization, is superior to the standard DDD/DDDR pacing mode in improving clinical outcomes in pacemaker (PM) patients. Indeed, there is growing evidence that a prolonged PR interval is associated with a higher risk of AF and poor prognosis.[6,7] Progression to persistent AF (PeAF) is prevented by minimizing RV pacing in patients with a normal PR interval and by implementing standard dual-chamber pacing in patients with a long PR interval.[8] The current standard of care in patients with sinus node disease (SND) or paroxysmal 2nd-degree AV-block on dual-chamber pacing is to programme the PM with a long AV-delay or with specific algorithms to minimize unnecessary ventricular pacing.[9] However, many patients with these conduction disorders who require PM implantation also show a concomitant prolongation of AV conduction. This AV management further increases the PR interval, owing to the intra-/inter-atrial conduction delay caused by standard atrial pacing and concomitant drug use. Physiological RV pacing is achieved by delivering a pacing stimulus to a cardiac conduction structure such as the His bundle (HBP) or left bundle branch area of the His-Purkinje system (LBBAP).[10,11] Conduction system pacing (CSP) activates the heart through the native His-Purkinje system, replicating the physiological cardiac activation sequence and avoiding pacing-induced dyssynchrony. We hypothesize that preserving AV synchrony by setting an AV-delay that controls the PR interval (onset 'p'-wave to onset QRS not exceeding 180 ms) during CSP (DDD-CSP) can reduce the risk of

PeAF occurrence in comparison with a pacing mode that minimizes RV pacing by conventional dual-chamber PMs, including algorithms to avoid unnecessary RV pacing (DDD-VPA). The PhysioVP-AF randomized controlled trial will evaluate the occurrence of PeAF during DDD-CSP or DDD-VPA pacing in patients with prolonged AV conduction and PM indication due to SND or paroxysmal 2nd-degree AV-block. The effect on myocardial systolic and diastolic function parameters and clinical status [hospitalization, quality-of-life (QoL)] of the two different pacing modes will also be assessed.

Study design and current status

PhysioVP-AF is an independent, prospective, single-blind controlled trial and is expected to enrol up to 400 patients in 13 Italian centres with proven experience in CSP. Patients with standard Class I or II indications for permanent DDD pacing[9] who meet the inclusion criteria (*Table 1*) are eligible for the study. After approval of the study protocol by the respective institutional review boards, the participating centres can start to enrol patients who have given their written informed consent. The first enrolment took place in Rovigo in July 2022, and the study (including follow-up and data analysis) is expected to last 5 years. To date (December 2022), 25 patients have been enrolled. An 'Electronic Data Capture' platform based on the 'Research Electronic Data Capture' facilities (REDCap[12] by Vanderbilt University and 'REDCap Consortium') will be used for data collection by the various participating centres and for data quality monitoring. PhysioVP-AF is registered on the ClinicalTrials.gov website: NTC05367037.

Primary study end-point

The main objective is to compare the impact on 3-year freedom from PeAF occurrences of physiological pacing (CSP associated to a controlled PR interval) with that of standard DDD pacing with ventricular pacing avoidance (VPA) algorithms. PeAF occurrence is defined as the first episode of AF, atrial flutter, or atrial tachycardia lasting >7 days (AT/AF) detected by the PM after a 1-month post-implantation lead-stabilization period. One day of AF is defined as a device-detected daily AT/AF burden of ≥23 h, in accordance with the clinical definition in the Americal College of Cardiology (ACC)/European Society of Cardiology (ESC) guidelines.[13] This definition also includes the occurrence of AT/AF episodes that are terminated by electrical or chemical cardioversion, whatever its duration, or AF ablation.

Secondary study end-points

(1) Variation in haemodynamic performance (baseline vs. 12th-month control); this is ascertained by means of echocardiographic evaluations of LV remodelling and the evaluation of systolic function, diastolic function, left atrial volume, and mitral regurgitation.
(2) Clinical evaluations: Variation in New York Heart Association (NYHA) class and QoL, as assessed by means of the Minnesota Living with Heart Failure Questionnaire. Access to healthcare facilities owing to cardiovascular diseases. Hospitalizations for heart failure (HF).
(3) ECG parameters (at baseline and every 6 months thereafter): Verification of atrial rhythm, p-wave duration, PR interval, both spontaneous and during forced atrial pacing, and spontaneous and paced QRS duration.
(4) Estimated battery longevity.
(5) Safety: Rate of all procedure-related adverse events and evaluation of potentially harmful factors, such as procedure and fluoroscopy times, and the rate of re-interventions for lead revision, replacement, or infection.

Patient selection and enrolment

Investigators will screen their consecutive patients for eligibility on the basis of age, PM indication,[9] and cardiovascular medical history.

Table 1 Inclusion and exclusion criteria

Inclusion criteria	Baseline PR interval > 180 ms
	Sinus node disease
	Paroxysmal type 1st- or 2nd-degree AV-block
Exclusion criteria	Less than 18 years of age
	Indication to implantable cardioverter defibrillator or cardiac resynchronization therapy
	Severe grade mitral or aortic regurgitation/stenosis
	Atrial fibrillation ablation
	Cardiac surgery <3 months before PM implantation
	History of long-standing persistent AF
	Permanent 3rd-degree AV-block
	Participation in another clinical trial in the past 3 months
	Pregnancy or intention to be pregnant 3 years
	Life expectancy of <3 years

AF, atrial fibrillation; AV, atrioventricular; PM, pacemaker; PR, XXX.

Subsequently, patients with Class I or II indications for dual-chamber pacing (SND and paroxysmal 2nd-degree AV-block), ECG-documented baseline PR interval >180 ms, and who have given their written informed consent will be invited to participate in the study.

During the screening visit, demographic data, cardiovascular history, including cardiac surgery, previous cardiovascular drug therapy, risk factors and comorbidity, and echocardiographic and electrocardiographic data will be collected. Before PM implantation, the enrolled patients will be assigned in a 1:1 ratio by means of centre-stratified randomization to one of the two pacing mode groups: DDD-VPA or DDD-CSP.

The echocardiographic examination will evaluate: LV remodelling and systolic function [LV end-systolic volume and left ventricular ejection fraction (LVEF)]; diastolic function [E to A mitral wave amplitude ratio and E-wave deceleration time, pulsed-wave tissue Doppler early diastolic septal mitral annular velocity (e′) and E/e′ ratio; Time from onset E-wave to end A-wave, normalized for RR interval]; left atrial volume; valvular heart disease.

Device requirements and implantation procedure

All currently available PMs with RV pacing avoidance (VPA) algorithms are suitable for both pacing modes. According to the assignment group, the VPA algorithm will be switched OFF (DDD-CSP group) or ON (DDD-VPA group).

Among the available strategies for minimizing ventricular pacing, the true 'single-camber atrial pacing (AAI) <-> DDD mode-switching' algorithms are recommended. Current PMs with atrial leads are highly reliable in detecting atrial high-rate events (primary study end-point) such as AF, atrial flutter, and atrial tachyarrhythmia.[14] All the devices (declaration of European Union Compliance (CE)-marked pacing systems and their accessories) will be used in accordance with their regulatory-approved indications.

In the DDD-CSP group, a pacing lead is to be delivered by means of a specifically designed introducer, in order to pace the cardiac conduction structure, and tested by means of a continuously recorded 12-lead ECG. Both HBP and LBBAP are considered CSP techniques. Briefly, in HBP, the paced QRS morphology may either be identical to that seen during the intrinsic rhythm (selective HBP) or show complete or partial correction of the underlying bundle branch block. In left LBBAP, the target site is distal to the His bundle left-side conduction

system, and is reached by screwing the lead deep inside the interventricular septum close to the LBB area. LBBAP is confirmed by the following criteria[11]: (i) right bundle branch conduction delay in ECG leads V1 and V2; (ii) recording of LBB potential (only in 50–80% of patients with non-LBBB); (iii) fast LV peak activation time of approximately 80 ms (as measured in lead V5 or V6 from the onset of the artefact of pacing to peak R-wave-V_6RWPT); (iv) inter-peak interval between the R-wave peak in lead V6 and the R-wave peak in lead V1 > 33 ms.[15]

In any case, the capture of conduction tissue is confirmed on 12-lead ECG by a transition of paced QRS morphology (from non-selective to either selective or myocardial) with differential voltage output or programmed stimulation.[16]

The adoption of HBP or LBBAP will be left to the physician's discretion, as per routine clinical practice.

In the DDD-VPA group, the RV standard leads are implanted in the RV myocardium (septum or apex). In both groups, the atrial leads are implanted in the right atrial appendage.

PM programming will be implemented according to the treatment group:

DDD-VPA group: Atrial-synchronized, dual-chamber pacing, with 'AAI<-> DDD mode-switching' algorithms switched ON after PM implantation.

DDD-CSP group: Atrial-synchronized, dual-chamber pacing with a programmed AV-delay to control the PR interval, so that the interval between the onset of the 'p'-wave and the onset of the QRS on 12-lead ECG must not exceed 180 ms. The VPA algorithms are switched OFF after PM implantation.

In both pacing groups, the value of the basic pacing rate and the activation of the rate-response function is left to the investigators' discretion, as per routine clinical practice, according to clinical needs/PM indication.

Follow-up characteristics

Figure 1 summarizes the study procedures.

The study will include the following:

(1) A pre-discharge examination including PM control (i.e. standard lead measurements: lead sensing/capture threshold and impedance) and a 12-lead ECG (stored in eCRF for further evaluation by the study's Core Lab). Data on prescribed cardiovascular drug therapy and any post-procedural complications will be recorded and stored. A post-PM lead-stabilization blanking period of one month is scheduled. Consequently, cardioversion will be scheduled for patients who develop AT/AF to restore sinus rhythm, and they will continue the study.
(2) A 1-month examination with PM check and 12-lead ECG to evaluate correct CSP capture in the DDD-CSP group.
(3) Follow-up examination every 6 months:
    (a) in-office at 12, 24, and 36 months (PM examination, 12-lead ECG, and concomitant medical therapy assessment),
    (b) remotely at 6, 18, and 24 months (PM examination only).
(4) Patients will undergo echocardiographic re-evaluation during the 12-month follow-up examination.

The PM examination will include: time of PeAF occurrence; AF/AT burden; atrial and ventricular pacing burden; lead sensing/capture threshold and impedance; battery status.

The 12-lead ECG evaluation will include: atrial rhythm; correct CSP capture (only in the DDD-CSP group); spontaneous and paced p-wave duration; spontaneous PR interval; spontaneous QRS duration; paced QRS duration.

Medication changes are allowed and will be documented during the study visits.

Patients in whom the CSP procedure fails will be transferred to the DDD-VPA arm by turning-ON the VPA algorithm to minimize RV pacing. Similarly, patients randomized to the DDD-VPA group who develop permanent AV-block will continue in the DDD-only mode. These events will be recorded in the eCRF and, in the intention-to-treat (ITT) analysis, the patient will still be considered as randomized.

After successful implantation, in patients needing reintervention, this procedure will be performed according to standard clinical practice, and information will be collected.

In the case of revision or replacement, the leads will be placed according to the arm assignment while safeguarding the patient's primary interest. In both study arms, any adverse event will be recorded.

Sample size and statistical considerations

The study aims to demonstrate that DDD-CSP is superior to managed ventricular pacing over 36 months of follow-up. From our analysis of the scientific literature,[4,8,17] we can hypothesize that the proportions of subjects free from PeAF occurrence throughout the 36 months of follow-up will be 72% in the physiological ventricular pacing group and 57% in the managed ventricular pacing group.

A two-sided log-rank test with an overall sample size of 400 subjects (200 in the VPA and 200 in the CSP groups) achieves 90.0% power to detect a hazard ratio of 1.71 at a 0.05 significance level when the proportion of PeAF-free subjects is 0.72 in the CSP group and 0.57 in the VPA group. The study will last 5 years, with subject accrual in the first 2 years. The accrual pattern is hypothesized to be uniform, and the drop-out rate in both groups will be 0.10/year (27% total). The power was estimated by means of PASS v.11 (NCSS Inc., Kaysville, UT, USA).

All variables will be analysed descriptively by means of the appropriate statistical methods: for categorical variables, we will use frequency tables; for continuous variables, sample statistics [e.g. average, median, standard deviation (SD), minimum and maximum value, 25th and 75th quartile, as appropriate]. The baseline covariates may be compared for 'like-to-like' in the two groups of subjects by means of appropriate statistical tests for discrete and continuous variables. All statistical tests will be 2-tailed and have a significance level of 5% unless otherwise specified. All primary and secondary analyses will be performed in the modified ITT population, including all randomized subjects who have undergone one of the study pacing procedures. Subsequently, the data will be treated according to the per-protocol analysis, considering any cross-over between pacing modes or failure/replacement types. Subjects who are randomized but who withdraw consent before undergoing one of the study procedures can be replaced, though they will not lose their unique identification code. Subjects who leave the observation without presenting the end-point will be considered censored, participating in the risk during the observation period. Regarding those who do not turn up for clinical evaluations, every possible effort will be made to ascertain a possible outcome of interest so that they can be assessed with regard to the study end-points. No formal ad-interim analyses are planned with a view either to terminating the study early or to declare effectiveness or futility.

The raw cumulative proportion of subjects free from PeAF occurrence throughout follow-up in the two treatment groups will be described by means of the Kaplan–Meier method and tested for difference by means of the log-rank test. Cox's proportional hazard multivariate regression will test the likely presence of risk factors for the primary efficacy end-point. The covariates will be: the type of pacing assigned, age, and gender; additional risk factors for PeAF occurrence (including obesity, sleep apnoea, coronary artery disease, diabetes, NYHA class, hypertension, previous history of AF, LVEF, atrial function, and size) will be significantly associated in univariate analysis. All the variables included in the final model will be tested for the assumption of proportionality of risks by means of the usual graphic method.

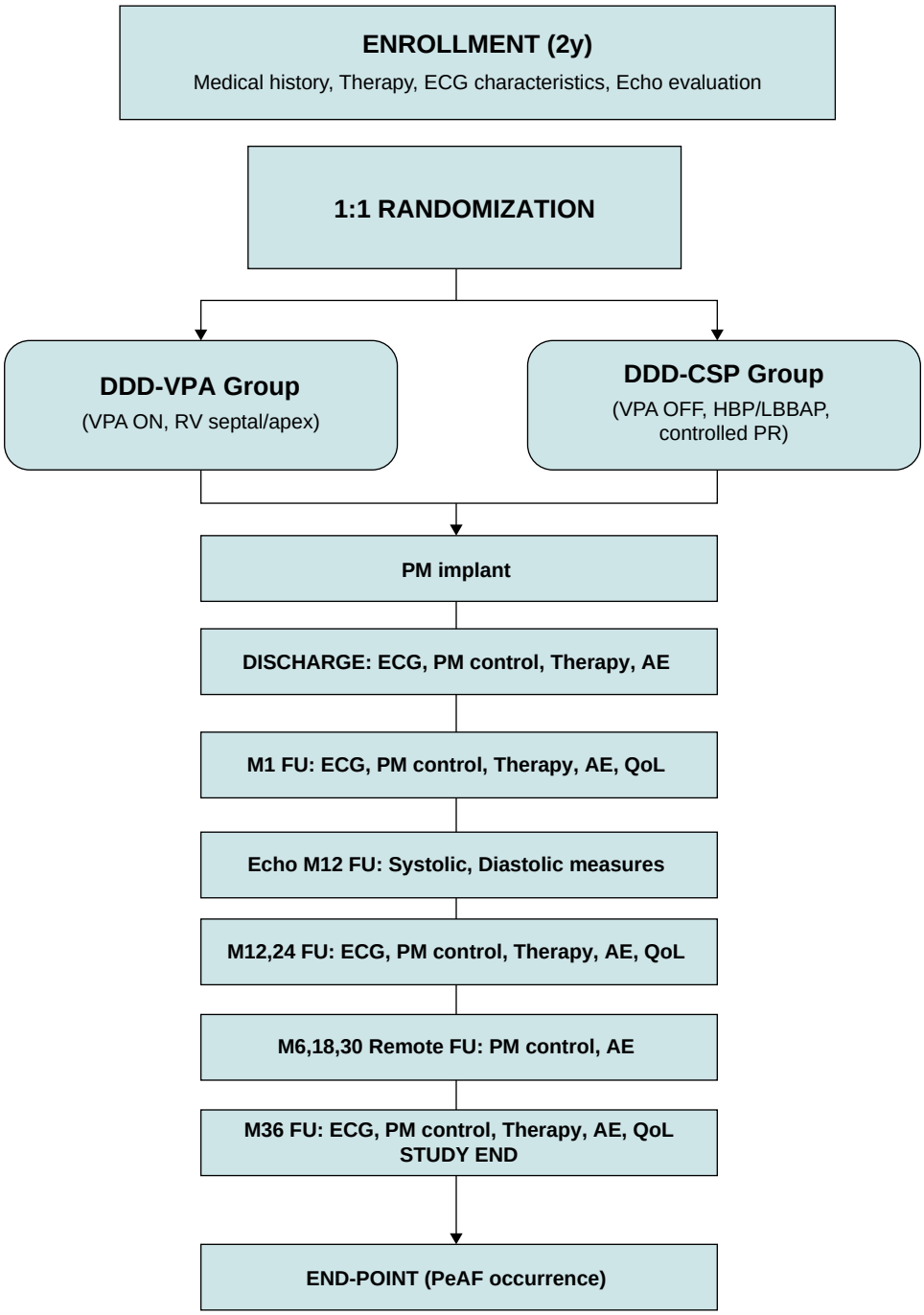


Figure 1 PhysioVP-AF study flowchart. AE, adverse event; DDD-VPA, dual-chamber pacing with algorithms for right ventricular pacing avoidance; DDD-CSP, dual-chamber conduction system pacing; FU, follow up; HBP, His bundle pacing; LBBAP, left bundle branch area pacing; M1, 1-month control; RV, right ventricular; PeAF, persistent atrial fibrillation; QoL, quality-of-life evaluation.

The Wald method will select a significant subset of variables in forwarding stepwise.

All continuous secondary end-points will be summarized in terms of the number of non-missing data, mean ± SD, median, and range. As appropriate, a paired *t*-test, a *t*-test, or an equivalent non-parametric test will be used for comparisons within the groups or between groups, respectively. All categorical secondary end-points will be tabulated in terms of occurrence and proportion. Finally, a Chi-square or Fisher's exact test, as appropriate, will be used to compare the groups.

Study organization

The PhysioVP-AF trial has been designed by an independent steering committee composed of the authors of the present paper.

A selected subgroup of investigators (CoreLab of the study) will check each ECG of each patient at the baseline, on discharge, and during in-office visits in order to verify the appropriate performance of the pacing system.

The study is promoted by QUOVADIS, a non-profit association, and is supported by an Investigator Sponsored Research grant from Boston Scientific International S.A.

Discussion

Dual-chamber pacing implies a trade-off between the paced restoration of a reasonable heart rate and undesired pacing-induced cardiac dyssynchrony. However, it is sometimes difficult to decide when pacing is required and when it is more appropriate to avoid pacing. This is particularly true for patients with intermittent atrialventricular block (AVB) and those with prolonged PR intervals. In these patients, re-establishing a favourable AV sequence by means of VP with the best possible trans-mitral LV filling may be offset by pacing-induced LV impairment; in contrast, preserving prolonged intrinsic AV conduction may prevent pacing-related dyssynchrony but may, in turn, produce undesirably fused trans-mitral filling. This randomized study aims to determine the optimal dual-chamber pacing strategy in patients with prolonged AV conduction (PR > 180 ms) and a PM indication due to SND or paroxysmal 2nd-degree AV-block.

The SAVE PACe trial was the first landmark study of a RV pacing minimization algorithm and showed the advantage of avoiding ventricular pacing in patients with SND, who displayed a lower rate of development of PeAF.[1] However, subsequent studies in both SND and AV-block patients, including the DANPACE,[6] PreFER MVP,[7] and MINERVA[18] trials, did not support the results of the SAVE PACe trial.

The ANSWER[19] trial suggested that using an aggressive strategy of ventricular pacing reduction in a general dual-chamber PM population (equally distributed between SND and AV-block populations) was effective and safe. However, it yielded only marginal benefits regarding clinical outcomes in terms of reducing cardiac mortality and HF hospitalization rates, regardless of the pacing indication. It is conceivable that the inclusion of different patient populations, especially patients with AV-block, was responsible for this difference.

For patients with 1:1 AV conduction and QRS abnormalities such as bifascicular block, bundle branch block, prolonged PR interval, and unexplained syncope, and those in whom intermittent or impending high-degree AVB is probable, an empirical PM may be considered. In intermittent bradycardia, pacing may be required only for short periods. In this situation, the benefits of preventing bradycardia and pauses must be weighed against the detrimental effects of permanent pacing, particularly that of pacing-induced HF. Specific algorithms that prevent unnecessary RV pacing play a critical role in this patient group.[9] Significantly, in these patients, using these algorithms together with atrial pacing may induce a very long PR interval, which may affect ventricular filling and atrial emptying; on the other hand, the percentage of VP has been seen to increase over time, reflecting progressive AV conduction disease.[19]

Evidence suggests that a long PR interval is associated with increased AF risk and poor prognosis.[6–8] Indeed, the PREFER MVP trial found a higher incidence of PeAF in managed ventricular pacing vs. DDD pacing in patients with PR interval ≥230 ms.[7] Similarly, the DANPACE trial documented a higher AF incidence in AAI vs. DDD pacing in patients with PR interval > 180 ms.[6] In a sub-analysis of MINERVA study, the progression to PeAF was prevented by minimizing RV pacing in patients with a normal PR (<180 ms) and by standard dual-chamber pacing in those with a long PR (>180 ms).[8]

In the main analysis of ANSWER study,[19] about 25% of patients who received a PM for SND presented a concomitant baseline prolonged PR interval of >230 ms,[18] which significantly increased over time. In the PRECISE study,[20] half of the patients with pure SND developed long PR intervals (>350 ms) in the year following PM implantation, owing to drug use (amiodarone).

The current ESC guidelines[9] support AV management by means of DDD pacemakers with algorithms that promote intrinsic AV conduction, but suggest avoiding AV-delay programming >230 ms.

Managed ventricular pacing is not the optimal solution, however, as clinical equipoise is imposed by the competing goals of optimizing AV synchrony while maintaining normal ventricular activation, particularly in patients with long PR intervals and narrow QRS intervals.

More recent data have suggested that RV pacing burden >20% might be associated with a higher risk of clinical worsening/pacing-induced cardiomyopathy.[9]

Other techniques for preventing pacing-induced LV dysfunction should be explored along with pacing prevention algorithms. Permanent CSP, such as HBP or LBBAP, may provide a promising solution. His-bundle pacing is a feasible method for delivering permanent pacing. It produces physiological ventricular activation via the His-Purkinje system and may offer an alternative to RV pacing for bradycardia prevention.[16] Although it has many limitations, such as a longer learning curve, higher capture thresholds, a higher rate of lead revision, and the potential to distal conduction block, it may be suitable for the non-dependent PM patients included in our study. A new method of physiologic pacing (LBBAP) has been introduced in recent years. This is a feasible primary pacing technique for all-comers, regardless of the pacing indication. In the MELOS study,[21] the overall success rate of LBBAP lead implantation was 92.4% in procedures for bradyarrhythmia prevention; failures were more likely to occur in patients with HF, an enlarged left ventricle, and broad baseline QRS. When LBBAP is adopted in routine clinical practice, it does not provide homogeneous capture types ranging from LBBP to LB fascicular pacing (LBFP) and left ventricular septal pacing (LVSP), as a result of differences in pacing locations, implantation technique and baseline substrate.[21] In the MELOS study, the predominant type of LBBAP was LBFP (69.5%), diagnosed according to the LBB potential-QRS onset interval when conduction system capture criteria were present. This finding is indicative of distal fascicular/arborization capture rather than the capture of the pre-divisional LBB trunk.

Interestingly, because of the more distal pacing site, LBFP seems to offer faster LV activation than LBBP, as suggested by shorter paced V_6RWPT and shorter paced QRS duration, resulting in physiological LV activation. In the same study, LVSP, which constituted 21.5% of cases, was considered a successful mode of LBBAP, as QRS morphology and duration were similar to those achieved with LBBP and LVSP. Haemodynamic and electrocardiographic studies of LVSP point to favourable activation/contraction of the ventricles.[22] Consequently, LBBAP is feasible in a high percentage of patients and is able to bypass conduction blocks in the distal His bundle or proximal left bundle. Moreover, low and stable pacing parameters make it a promising alternative pacing strategy to standard RV.

Conclusions

The PhysioVP-AF study will yield important information regarding the management of patients with accepted indications for dual-chamber PM implantation. Indeed, it is aimed at determining whether CSP combined with a controlled PR interval is superior to standard managed ventricular pacing in terms of reducing PeAF occurrence and cardiovascular hospitalizations.

This study will be the first to ascertain whether real dual-chamber physiologic pacing can reduce the incidence of important clinical endpoints in patients who have a PM indication but do not need continuous RV pacing, such as those with SND or paroxysmal 2nd-degree AV-block and baseline prolonged AV conduction.

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Conflict of interest: G.D.: fee for lectures and proctorship for conduction system pacing by Biotronik Italia; G.K., Le.M.: fee for proctorship for conduction system pacing by Biotronik and Medtronic Italia; M.Z.: received speaker's fees from Abbott Medical, Biotronik, and Boston Scientific; F.N.: fees for statistical and methodological consulting from Abbott Medical. All other authors have no conflicts to declare.

Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

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