Preventing ventricular dysfunction in pacemaker patients without advanced heart failure: rationale and design of the PREVENT-HF study

Eduardo de Teresa1, Juan José Gómez-Doblas1, Gervasio Lamas2, Javier Alzueta1, Ignacio Fernández-Lozano3, Erik Cobo4, Xavier Navarro5, Francisco Navarro-López6, and Martin Stockburger7*

1Hospital Clínico Virgen de la Victoria, Campus Universitario Teatinos, 29010 Málaga, Spain; 2Mount Sinai Medical Center, 4300 Alton Rd, Miami Beach, FL 33140, USA; 3Hospital Puerta de Hierro, C/ San Martín de Porres, 4. 28035 Madrid, Spain; 4Universidad Politécnica de Catalunya, C/ Pau Gargallo, 5, 08028 Barcelona, Spain; 5Medtronic Ibérica, S.A., C/ Maria de Portugal, 11, 28050 Madrid, Spain; 6Hospital Clinic i Provincial de Barcelona, Universidad de Barcelona, Villarroel 170, 08036 Barcelona, Spain; and 7Charité—Universitätsmedizin Berlin, Campus Virchow-Klinikum, Medizinische Klinik M.S.

Kardiologie, Augustenburger Platz 1, D-13353 Berlin, Germany

Aims Right ventricular (RV) pacing has been shown to cause heart failure symptoms in patients with and without previous systolic left ventricular (LV) dysfunction. The aim here was to evaluate the preventive effect of biventricular pacing vs. RV apical pacing in patients with indication for permanent ventricular pacing.

Methods PREVENT-HF is an ongoing multicentre randomized controlled pilot study designed to assess whether biventricular pacing is superior to RV pacing in patients receiving a bradycardia pacemaker for standard indications. Patients with Class I or IIa indication according to ACC/AHA guidelines for cardiac pacing judged likely to require high (>80%) ventricular pacing are randomized to receive either RV or biventricular stimulation. Patients are ineligible if younger than 18 years, have Class III or IV heart failure, or experienced a recent myocardial infarction or cardiac surgery. Echocardiographic parameters of LV function are assessed at baseline, 6 months, and 12 months. The primary endpoint is change in LV end diastolic volume. Secondary outcomes include LV ejection fraction, mortality, morbidity, and mitral regurgitation. In subsets of patients, NT-pro-BNP and oxygen uptake are analysed.

Centres in Spain (five), Italy (four), and Germany (seven) will enrol 100 patients.

Conclusion PREVENT-HF will contribute to better define the role of chronic biventricular pacing for advanced atrioventricular block.

KEYWORDS
Heart failure; Cardiac resynchronization; Right ventricular pacing; Biventricular pacing

Introduction

The mechanical efficiency of the cardiac systole depends upon many factors, one of them being the synchronous contraction of the different parts of the left ventricle. Synchronous intraventricular and interventricular contraction is a consequence of normal electrical activation through the different parts of the infrahisian system.1,2 The classic example of dysynchrony is the patient with left bundle branch block (LBBB). There is ample literature documenting an associated dysynchronous contraction, even in patients with an otherwise normal heart.3,4 In the 1980’s the first reports appeared, suggesting that left ventricular (LV) or biventricular pacing improved ejection fraction and cardiac output in patients with LBBB.5,6 Now there is convincing evidence from several randomized controlled multicentre trials that biventricular pacing improves symptoms and prognosis when severe systolic dysfunction accompanies symptomatic heart failure in the presence of delayed ventricular activation.7–9

Mortality in patients with atrioventricular block is high despite pacemaker therapy and approaches 60% within 10 years.10 This may in part be due to advanced and progressive structural heart disease which is more common in patients with atrioventricular conduction disturbance than in other populations. Recent appreciation that the LBBB produced by right ventricular (RV) apical pacing is physiologically indistinguishable from native LBBB has led to speculation that progressive LV dysfunction due to RV apical pacing may account for at least some of the excess mortality of paced patients with AV block. Indeed, there is growing evidence from secondary and non-prespecified analyses,11,12 as well as from haemodynamic studies13 pointing at
potentially detrimental effects of RV apical pacing in patients with impaired systolic function. It has been recognized that patients with impaired systolic function are at particular risk when they are inadvertently exposed to RV apical pacing. The dual chamber vs. VVI implantable defibrillator trial (DAVID) compared dual-chamber and single-chamber defibrillators in patients with severely depressed systolic LV function and found a higher incidence of the combined primary endpoint (heart failure hospitalization or death) in the dual-chamber defibrillator group. This could be demonstrated to be an effect of unintended but serendipitous RV pacing occurring in the dual-chamber patients. The data suggesting that there is also risk for patients with overall normal systolic function when ventricular-paced are somewhat less compelling. For example, a post hoc subgroup analysis from the Mode Selection Trial identified percentage of RV pacing as a major determinant of hospitalization for heart failure in patients with narrow QRS and nearly normal LV systolic function. Another post hoc analysis identified paced-beat QRS duration, a rough measure of LV activation synchrony, as a predictor of the late development of heart failure. There are physiological studies suggesting that even with a normal LV function, biventricular pacing is superior to RV apical pacing. During acute invasive measurements of LV haemodynamics in patients with slightly reduced LV ejection fraction and chronic AF after AV nodal ablation RV pacing was found to be consistently inferior to LV-based pacing. Dysynchronous LV activation during acute pacing has already been described in small studies almost 30 years ago in mongrel dogs and in humans. Right ventricular pacing, however, does not appear to produce the same degree of dysynchrony in all patients. The mechanical consequences of dysynchronous paced ventricular activation may be of greater importance in individuals with severely depressed LV function, but even in the presence of a normal global LV function, RV pacing appears to cause signs of heart failure over time.

Long-term RV apical pacing results in a high incidence of myocardial perfusion defects that increase with the duration of pacing. These myocardial perfusion abnormalities are associated with wall motion abnormalities and impaired global LV function. Regional abnormalities of the myocardial adrenergic innervation have also been documented as a consequence of RV apical pacing. Impaired and heterogeneous adrenergic innervation may promote arrhythmias and has been found to be predictive for cardiac death. The published information on whether adverse effects of conventional RV pacing are prevented by the biventricular pacing configuration is still very limited at this point of time. One multicentre trial found a small but significant advantage in the 6 min walking distance after 6 months in patients with biventricular pacing when compared with those with RV pacing after AV nodal ablation. Another small single-centre study included upgrades and first pacemaker implants and found a significant advantage of biventricular over RV pacing in patients with severely depressed LV function and AV block. Owing to the inclusion of first implants and biventricular upgrades of an existing system, the treatment effect in this trial consists of a combination of resynchronization of actually desynchronized ventricles and prevention of asynchrony.

Reliable data on the purely preventive effectiveness of primary biventricular pacing for AV block in terms of LV remodelling or clinical outcome are still lacking to date. Indeed, the present clinical trials literature supports biventricular pacing as superior to RV apical pacing in patients with a prolonged QRS that have symptomatic HF and severely reduced systolic LV function. Whether there are physiological, functional, neuroendocrine, or clinical benefits to biventricular pacing in patients without severe systolic dysfunction and heart failure who undergo routine pacemaker implantation, however, is unknown. These are the questions that PREVENT-HF seeks to address.

Changes in LV volumes and LV ejection fraction have been shown to be among the most powerful predictors of survival in patients with chronic heart failure and also in those without advanced cardiac disease. Many of the beneficial effects of angiotensin-converting enzyme (ACE) inhibitors and beta-blockers in heart failure appear to be related to the ability of these agents to inhibit or reverse cardiac remodelling, and studies on LV remodelling using ACE-inhibitors preceded the definitive clinical trials showing a beneficial impact of these drugs on hard endpoints, such as mortality. Accordingly, based on the experience with ACE-inhibitors, the PREVENT-HF trial uses LV volumes and ejection fraction as the surrogate endpoint to assess the effect of RV pacing on patients with atrioventricular block and absent overt heart failure and to assess the hypothesis of attenuation of these effects with biventricular pacing.

Methods

Objectives

The primary objective of PREVENT-HF is to determine whether using biventricular pacing in patients with atrioventricular block will result in a significant difference in LV end diastolic volume after 1 year when compared with conventional RV apical pacing. Secondary objectives of the trial include the following:

- changes in LV end systolic volume and LV ejection fraction;
- a combined endpoint of cardiac mortality, development of symptomatic heart failure (according to the diagnosis guidelines of the European Society of Cardiology), and hospitalization due to cardiovascular causes;
- new development or worsening of mitral regurgitation.

Study design

PREVENT-HF is an ongoing multicentre randomized controlled pilot study designed to assess whether biventricular pacing is superior to RV pacing in patients receiving a bradycardia pacing system for standard indications. Patients are randomized to receive either a conventional dual-chamber pacemaker with the ventricular lead in the RV apex or a dual-chamber biventricular pacemaker with leads at the RV apex and the left ventricle. Leads are placed using techniques that are standard across performance sites.

Study implementation

The PREVENT-HF study is being conducted in Spain (five centres), Italy (four centres), and Germany (seven centres). Written approval for the protocol and informed consent forms were initially obtained from the local Ethics Committees at each study site. Following informed consent, patients are randomly assigned via an internet connection to receive a standard Medtronic dual-chamber pacemaker (DDDR, e.g. Kappa 700) or a biventricular dual-chamber Medtronic pacemaker.
pacemaker (InSync 8040 or InSync III 8042). Randomization is stratified according to the presence or absence of AF. In the absence of AF, the assignment will be carried out by balancing the two groups in each centre, whereas in the less common case of AF, the randomization is not stratified by site. In case of a coexisting indication for an implantable cardioverter-defibrillator (ICD), patients randomized to the conventional pacing group receive a standard dual-chamber Medtronic device (e.g. GEM III DR, Marquis DR) and those randomized to the biventricular group are implanted with a biventricular Medtronic ICD (InSync ICD, InSync Marquis, or InSync III Marquis). In the presence of permanent AF, a single-chamber VVIR pacemaker or a single-chamber ICD (e.g. Kappa SR or GEM III VR, Marquis VR) is implanted in patients randomized to the RV pacing group and a triple-chamber pacemaker or ICD (InSync 8040 or InSync III 8042, InSync ICD, InSync Marquis or InSync III Marquis) with plugged atrial port in patients randomized to biventricular pacing.

Adverse events are classified to be severe, moderate, or mild according to European regulations (EN-540 and ISO 14155 standards). The steering committee is charged with the task of reviewing all adverse events. Patient data from the follow-up visits and adverse events are assessed by the local investigators and transferred via an encoded internet connection to the central server. Central and on-site data monitoring is carried out by the central study organization to ensure adherence to the research plan, good clinical practice, and applicable rules and regulations.

At present, 88 of the planned 100 patients have been enrolled in the study.

Eligibility

Patients ≥18 years of age are eligible for this trial if they meet Class I and/or Class IIa implantation criteria for pacemaker stimulation according to the guidelines of the American College of Cardiology (ACC)/American Heart Association (AHA) and if they have an expected need for ventricular pacing of at least 80%. Exclusion criteria include advanced heart failure (New York Heart Class III or IV) prior to the development of a pacing indication, a myocardial infarction or cardiac surgery during the preceding 3 months, future need for revascularization within 3 months, hypertrophic cardiomyopathy, constrictive pericarditis, aortic stenosis, bad echo window, a previously implanted pacemaker or defibrillator (i.e. upgrades are not admitted), pregnancy, life expectancy <1 year, or lacking signed informed consent.

Randomization and implantation

Only experienced implanting sites and site principal investigators were invited to participate in the study. Standard techniques including fluoroscopy and coronary sinus venography were used in all patients as needed. Lateral (comprising strictly lateral, antero-lateral, and postero-lateral) positions for the transvenous LV lead are required by the study protocol. In case that acceptable positioning of the LV lead is not possible, the implantation will be carried out using a conventional pacing system, although the patient will be classified at the end of the study as being part of the biventricular pacing group. The patient is blinded to treatment assignment. The investigators are encouraged to perform an optimization procedure prior to hospital discharge. The optimization method is left to the site investigator’s discretion. All patients receive appropriate medical therapy, including ACE-inhibitors and beta-blockers (installed after implant) for those with an ejection fraction below 40%, spironolactone and diuretics in case of development of overt heart failure (New York Heart Class III and IV), digoxin only in patients with persisting symptoms despite the medication mentioned above, and oral anticoagulants in case of paroxysmal or permanent AF and systemic or pulmonary thromboembolism.

Follow-up

Follow-up consists of a baseline visit, the implantation, a pre-hospital discharge visit, and visits at 6 and 12 months, respectively. The target time for the pre-discharge visit is 24–48 h after implant, and the schedule for the 6 month visit ranges from day 165 to day 195 and for the 12 month visit from day 345 to day 375 after implant. At each visit, an appropriate clinical evaluation with assessment of adverse experiences, hospitalizations, and the concomitant medication is performed. A 12-lead ECG is recorded at each visit, and a chest X-ray is scheduled to be performed after implant and at 12 months. The device interrogation is saved to diskette at the beginning and the end of each visit, and the respective files are transmitted to the central server via internet. The echocardiographic recordings are recommended to be performed always by the same examiner on the same echocardiography device. Video tapes are provided by the central study organization and are labelled by numbers. The tapes are sent to the echocardiography core laboratory (Malaga, Spain) and are read by the Director of the Echo Core Lab (J.J. Gomez-Doblas). The echo examiner is blinded as to the point of time of the recording and assignment of treatment, although the presence of an LV lead may be adumbrated by visible artefacts.

In subsets of patients, in addition, cardiopulmonary exercise testing (before hospital discharge, at 6 and 12 months) and NT-proBNP measurements (at enrolment, before hospital discharge, at 6 and 12 months) are analysed. From cardiopulmonary exercise testing, peak oxygen uptake, oxygen uptake at the anaerobic threshold, ventilatory efficiency (VE/VO₂ slope), and total exercise time are utilized for analysis.

Sample size computation

The primary study endpoint is the change in LV end diastolic volume between the treatment groups after 1 year. Under the assumption of a standard deviation of the primary endpoint of 30 mL (from the control group from the SOLVD echo substudy), and a bilateral α = 0.05, an 80% power in detecting a difference of 18 mL can be achieved by analysis of 88 individuals (44 per treatment group). Primary endpoint will be compared between the two groups, taking into account the baseline LV value by an analysis of covariance. Primary and secondary endpoints will be compared between the two groups with student’s t-test or χ² test as appropriate. The principal analysis will be carried out according to the assigned group (intention to treat analysis), carrying over the last valid results in the cases that were not completed, although an analysis per protocol will also be performed. Pre-specified subgroup analyses will be performed according to the presence or absence of AF, the extent of ventricular pacing, the presence of a pre-existing LBBB, and the initial LV ejection fraction.
Study organization
University-based and sponsor-based scientists with methodological and clinical expertise compose the steering committee and are responsible for the study design, organization, conduction, and analysis at the highest quality. The steering committee is also responsible for drafting and approval of the publication(s) reporting primary and secondary study results.

Conclusion
In light of increasing concern about detrimental effects of chronic RV pacing and the absence of definitive clinical data, PREVENT-HF has been designed to better define the role of chronic biventricular pacing in patients with advanced atrioventricular block. The change of LV volumes is the primary study endpoint, and LV enlargement is taken as an early and meaningful sign of incipient heart failure and a well-known surrogate of adverse long-term clinical outcome. PREVENT-HF will be the first randomized controlled multicentre trial to comparing conventional RV with biventricular pacing in patients with atrioventricular block simply needing bradycardia support.

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Conflict of interest: E.D.T. is chairing the Steering Committee of the PREVENT-HF trial, supported by Medtronic. J.J.G-D. is on the Steering Committee of the PREVENT-HF trial, supported by Medtronic. G.L. consults for Medtronic. X.N. is an employee of the Steering Committee of the PREVENT-HF trial, supported by Medtronic. J.J.G-D. is on the Steering Committee and a well-known surrogate of adverse long-term clinical outcome. PREVENT-HF will be the first randomized controlled multicentre trial to comparing conventional RV with biventricular pacing in patients with atrioventricular block simply needing bradycardia support.

Appendix: PREVENT-HF investigators and clinical centres
Spain
A. Barrera, Hospital. Clínico U. Virgen de la Victoria, Málaga; I. Fernandez Lozano, Hospital Puerta de Hierro, Madrid; L. Mont, Hospital Clinic i Provincial, Barcelona; J.G. Martinez, Hospital General, Alicante; J. Fernández de la Concha, Hospital Infanta Cristina, Badajoz.

Italy
A. Curnis, Ospedale Civile, Brescia; M.V. Pizzalis, Azienda Ospedaliera Policlinico, Bari; R. Ometo, Ospedale San Bortolo, Vicenza; D. Spaziani, H. Legnano; Legnano.

Germany
M. Stockburger, Charité, Campus Virchow-Klinikum, Berlin; T. Lawo, Berufsgenossenschaftliche Kliniken Bergmannsheil, Bochum; M. Desaga, Klinikum Dachau; H. Nägele, St. Adolf-Stift, Reinbek; S. Spencer, Charité, Campus Benjamin Franklin, Berlin; M. Winterhalter, Unfallklinikum Daslau, Göttingen; U. Wiegand, Universitätsklinikum Schleswig-Holstein, Campus Lübeck, Lübeck.

Central Laboratories
Echocardiography Core Center, J.J. Gomez-Doblas, Hospital Clinico Universitario, Málaga, Spain.

Steering committee

Database electronic management
RDES, S.L. and S.L. Demiurgo.

Clinical monitors
M.P. López, C. Koenig, and A. Denaro.

Statistical adviser
E. Cobo, Universidad Politécnica, Barcelona.

Study management
M.P. López.

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