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The Restoration of Chronotropic Competence in Heart Failure Patients with Normal Ejection Fraction (RESET) Study: Rationale and Design

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Abstract

Background—Heart failure with preserved ejection fraction (HFpEF) is the predominant form of HF among the elderly and in women. However, there are few if any evidence-based therapeutic options for HFpEF. The chief complaint of HFpEF is reduced tolerance to physical exertion. Recent data revealed that one potential mechanism of exertional intolerance in HFpEF patients is inadequate chronotropic response. Although there is considerable evidence demonstrating the benefits of rate-adaptive pacing (RAP) provided from implantable cardiac devices in patients with an impaired chronotropic response, the effect of RAP in HFpEF is unknown.

Methods and Results—The RESET study is a prospective, multi-center, double-blind, randomized with stratification, study assessing the effect of RAP on peak VO₂ and quality of life. RAP therapy will be evaluated in a cross-over paired fashion for each patient within each study stratum. Study strata are based on patient beta-blocker usage at time of enrollment. The study is powered to assess the impact of pacing independently in both strata.

Conclusions—The RESET study seeks to evaluate the potential benefit of RAP in patients with symptomatic mild to moderate HFpEF and chronotropic impairment. Study enrollment began in July 2008.

Keywords

Heart failure; heart rate; diastole; ejection fraction

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Conflicts of interest: Drs. Kass and Kitzman have received honoraria as consultants from Boston Scientific CRM. Dr. Alvarez is an employee of Boston Scientific CRM.

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Introduction

Congestive heart failure (HF) is a major cause of morbidity and mortality and represents the leading discharge diagnosis among older individuals in the United States 1-2. Epidemiological data suggest that nearly 50% of HF patients exhibit a left ventricular ejection fraction in the normal range (HF with a preserved EF; HFpEF) 3-7. This disorder has a high prevalence, morbidity, and is associated with substantial economic burden 8-13. However, despite the importance of HFpEF, the pathophysiology and treatment of this disorder remains poorly understood and ill-defined. Deficiencies in this understanding and a paucity of clinical trials have led to the subsequent lack of evidence based guidelines for the management of HFpEF.

A primary manifestation of all forms of HF is exercise intolerance and a reduced functional capacity 14-15. Exertional capacity is closely related to the ability of the left ventricle (LV) to augment cardiac output (CO) upon demand. Reduced CO reserve can be due to depressed systolic function, excessive arterial loading, insufficient chamber filling, and/or an inadequate heart rate (HR) response. In dilated HF with reduced EF (HFrEF), the primary culprit is thought to be systolic dysfunction, though elevated afterload and HR incompetence also may play a role 16-18. LV chamber filling is typically too high at rest and reserve is therefore limited. The situation with HFpEF is somewhat different. Systolic function is generally considered normal at rest, but there exists little to no data regarding contractile reserve during exertion. Preload (filling volume) is normal or even reduced at rest 19-20, and cannot be recruited during exertion due to structural and diastolic abnormalities 21.

Recently, Borlaug et al 22 provided novel insight into potential mechanisms of exertional intolerance in HFpEF patients. In a study that compared HFpEF patients to a controls matched for age, sex, ethnicity, hypertension, and left ventricular hypertrophy (LVH) - but without HF - the investigators found that CO reserve was indeed markedly depressed in HFpEF and that this correlated with exertional capacity. However, rather than being due to contractile or preload deficiencies, the major limitation was inadequate arterial vasodilation and chronotropic response 22. Heart rate increased nearly half as much in HFpEF patients as in the non-HF controls, and this best predicted the limited CO reserve as well as net exercise performance. Intriguingly, increases in end-diastolic volumes during exercise were identical between the two cohorts. Furthermore, the depression of HR reserve was similarly observed in those subjects treated and not-treated with beta-blockade.

The observation of a HR impairment by Borlaug et al. is supported by another recent investigation which examined a well-defined group of HFpEF patients in comparison to a group of patients with HFrEF and a group of healthy, age-matched normal subjects 23. Although all subject groups gave similar effort, as evidenced by respiratory exchange ratio in the expired gas analyses, chronotropic incompetence (CI) was present in 19.6% of HFpEF, 26.0% of HFrEF, and only 7% of healthy subjects 23. Further, HR impairment was related to the reduction in peak VO_2 . Peak exercise capacity was reduced by an additional 15% in HF patients who exhibited CI compared to those who had normal HR response to exercise. The authors concluded that CI was likely a key contributor to the severe exercise intolerance observed in many older HF patients.

Chronotropic incompetence was demonstrated in HF patients with a depressed EF by the laboratory of Colucci in the late 1980's, where a strong correlation between exercise capacity and HR response was observed 16. These data were obtained at a time when beta-blockade was not standard therapy for low EF heart failure. In this sense, the recent evidence in HFpEF patients of a similar correlation between HR response and exercise capacity is less surprising. Rate modulation or rate-adaptive pacing (RAP) via an implanted cardiac pacemaker can benefit

patients with impaired chronotropic responses²⁴⁻²⁶. However, whether or not RAP employed in HFpEF patients with chronotropic insufficiency would prove beneficial is unknown. Indeed, the concept confronts conventional wisdom that maintaining slow heart rates is essential for these patients to have adequate diastolic filling, and to avoid possible myocardial ischemia.

The striking chronotropic incompetence demonstrated by Borlaug et al., and supporting evidence that it can play an important role in limiting exertional reserve, were the impetus for the RESET trial. The RESET study seeks to quantify the benefit of RAP in patients with symptomatic HF, a normal or preserved EF and an impaired chronotropic response.

Methods

Study Population

Study inclusion and exclusion criteria are listed in the Table. Inclusion criteria were designed to enroll patients exhibiting HF signs and symptoms with additional evidence of HF supported by prior hospitalization or intervention for decompensation or congestion, or elevated natriuretic peptide. Additionally, patients must have a documented preserved left ventricular ejection fraction (LVEF, $\geq 50\%$). Exclusion criteria were designed to rule out patients with substantive confounding medical conditions, or an inability to meaningfully participate in the trial.

Study Objectives and Design

The RESET trial is a prospective, multi-center, double-blind, randomized with stratification, study assessing the effect of Atrial pace – Atrial sense – Inhibits pacing in response to sensed event – Rate modulation (AAIR) pacing on functional capacity and quality of life measures. AAIR pacing therapy will be evaluated acutely (1 mo. post implant) in a cross-over paired fashion for each patient within each study stratum (see below), and chronic efficacy and safety will be assessed after 6 and 12 months (Figure 1).

Stratified randomization is employed based on patient beta-blocker usage at time of enrollment with pacing order randomization within study arm following stratification. The study is powered to assess the impact of AAIR pacing independently in both strata. Enrollments into study strata will continue until the strata implant target is met. The effect of pacing therapy on study endpoints will be evaluated in each patient within each stratum in a randomized fashion, that is, with and without pacing therapy. Study patients and study center personnel responsible for primary endpoint data collection are blinded to the pacing randomization assignment.

Implant Eligibility

Once enrolled, a patient will undergo screening to determine eligibility for pacemaker implant (see Figure). Implant eligibility criteria are as follows:

1. Confirmed LVEF $\geq 50\%$ by echocardiogram post enrollment;
2. Completion of valid maximal symptom-limited exercise (CPX) test ($\text{RER} \geq 1.05$);
3. Exercise intolerant defined as a peak $\text{VO}_2 \leq$ age and gender-adjusted value; and
4. CI defined using the percent of age-predicted HR reserve (%HRR) achieved during maximal exercise and standard formulae²⁷.

The thresholds for defining the presence of CI in each patient stratum are as follows: A percent increase in HRR that is $\leq 80\%$ of age-predicted for patients in the non-beta-blocker group, and $\leq 62\%$ in those treated with beta-blockers. Only patients meeting the implant eligibility criteria will be implanted with a pacemaker device.

Device Description and Rate-Adaptive Pacing Background

Pacing therapy will be provided by market-approved Boston Scientific pacemakers including the INSIGNIA[®] Plus (models 1297, 1298 and 1194) and Ultra (models 1290, 1291 and 1190), and ALTRUA[™] (models 40 and 60) stimulators.

The primary types of rate-adaptive pacing (RAP) sensors used in current pacemakers are an accelerometer (XL) and minute ventilation (MV). The XL measures vibrations inside the pulse generator at frequencies that correlate with physical activity of the patient and generates an electronic signal that is proportional to the magnitude of motion. MV, the product of respiratory frequency and tidal volume, can be derived via measurement of transthoracic electrical impedance and used to modulate HR by responding to impedance changes. The XL provides a relatively rapid response at the beginning of activity, but may not provide sufficient response at upper limits of activity^{28, 29}. XL or activity based-sensors may also be deceived by certain types of motion not truly indicative of patient activity and may not respond adequately to forms of activity that do not lead to significant motion of the pectoral region³⁰⁻³². MV provides a more physiologic response to exercise, particularly at the upper limits of activity^{29, 33} and a more appropriate HR response during forms of activity where motion in the pectoral region is limited³⁴.

For the RESET study, the Boston Scientific MV blended sensor combining both the XL and MV will supply RAP. This blending principle allows the MV sensor to drive the sensor-indicated rate after exercise is initiated and has been shown to restore chronotropic competence²⁶. Sensor optimization with RAP is important³⁵, therefore implanted patients will perform a hall walk to optimize sensor settings prior to undergoing the 1 mo. exercise test evaluation.

Study Endpoints

The primary study endpoint is change in functional capacity (peak VO₂) at 1 mo. post implant and will be quantified by direct measures of ventilation and gas exchange during maximal cardiopulmonary exercise (CPX). All implanted patients, within each study stratum, will perform one paired set of CPX tests at 1 mo. post implant in randomized order with respect to pacing therapy separated by no less than twenty-four, but no more than seventy-two hours. In other words both active and passive pacing therapy will be evaluated in a randomized, paired cross-over fashion in all patients for each stratum. A non-randomized (i.e., active pacing therapy in all patients in both strata) CPX test will be conducted at 6 mos. post implant. All CPX tests (1 and 6 mos. post implant) will be validated against defined criteria to substantiate maximal effort (respiratory exchange ratio ≥ 1.05) and will be reviewed by an independent laboratory.

Quality of life (QoL) is the secondary endpoint and will be assessed at 1, 6, and 12 mos. post implant via the Minnesota Living with Heart Failure Questionnaire and the Medical Outcomes Study Short-Form 36-Item Health Survey.

Sample Size

An enrollment ceiling of 400 patients has been set to achieve seventy-six implants (thirty-eight patients per stratum). Sample size calculations were based on the test of the primary endpoint (peak VO₂ at 1 mo. post implant) anticipating a 2.0 ml·kg⁻¹·min⁻¹ change with therapy (80% power, type I error 5%, standard deviation 4.0 ml·kg⁻¹·min⁻¹, 30% attrition) within each study stratum.

Data Analysis

Descriptive statistics used to describe patient groups will include means/medians, standard deviations, and two-sided 95% confidence intervals. Comparisons of patient groups will

employ chi-squared or exact permutation tests for categorical variables and general linear models for continuous variables. All tests will be 2-sided and performed at the $\alpha = 0.05$ level, unless otherwise noted.

The primary endpoint comparison of the randomized groups will be made separately for each stratum using 1-sided paired t-tests, comparing the pair-wise changes in peak VO_2 1 month post implant. The long-term influence of rate-adaptive pacing will be assessed using two separate paired t-tests for each stratum: (1) comparing 1 month peak VO_2 without RAP to 6 month peak VO_2 with RAP, and (2) comparing 1 month peak VO_2 with RAP to 6 month peak VO_2 with RAP. The potential confounding effect of beta-blockade will be monitored using a general linear model assessing the influence of RAP and beta-blockade on peak VO_2 . Additionally, the potential relationship between the amount of RAP and peak VO_2 will be analyzed by standard correlation analysis.

The secondary endpoint comparison will be made separately for each stratum using 1-sided paired t-tests, comparing the pair-wise changes in QoL before RAP at 1 month to QoL after RAP at 6 months. The potential confounding effect of beta-blockade will be monitored using a general linear model assessing the influence of RAP and beta-blockade on QoL.

Study Organization

This study is sponsored by Boston Scientific CRM (St. Paul, MN) and is conducted in accordance with all laws and regulations governing medical research. Institutional Review Board approval is required before center participation in the study. An independent CPX laboratory has been established to validate and evaluate primary endpoint data. The trial is overseen by a Clinical Advisory and Steering Committee (CASC) comprised of key investigators who collaborated with the Sponsor in the development of the study protocol and provided guidance on study logistics. The CASC, along with Sponsor representation, will function as the publication committee for the trial. All patient adverse events will be prospectively captured during the course of the study. A Data Safety Monitoring Committee (DSMC), independent of the CASC and Sponsor, will be responsible for the review and monitoring of study safety data at regular intervals.

Status of the Study

The first patient was enrolled, and subsequently implanted, in July of 2008. The study is projected to conclude all patient implants in July of 2010 and complete patient follow-up visits in August of 2011. Up to 30 centers are anticipated to participate in the trial. Study registration can be found at ClinicalTrials.gov (NCT00670111).

Discussion

Exercise Intolerance and HFpEF

A primary pathophysiologic focus in patients with HFpEF has been on diastolic dysfunction, reflected by delay in isovolumic relaxation, altered filling patterns (typically reduced early filling, and more rapid deceleration of early filling), and increased diastolic stiffness 36-39. Based on this notion, cardiac reserve is limited principally by the inability of the heart to fill adequately during diastole, and thus a decline in CO due to reduced SV. However, evidence for this mechanism particularly under conditions of physiologic stress such as exercise remains very scant. In one study from Kitzman et al 14, a small group of subjects were studied using invasive right heart catheterization and volumetric measurements, and those with HFpEF displayed a limited increase in end-diastolic volume (EDV), but rise in end-diastolic pressure (EDP), versus the normal controls. However, some of these individuals had restrictive heart disease (e.g. amyloidosis), where diastolic abnormalities are marked. In contrast, studies in

HFpEF patients show a substantial number have mild or moderate diastolic dysfunction, but this is also common in subjects with hypertension and LVH – yet no HF, and does not in of itself predict symptoms. In the recent I-PRESERVE study of >4000 patients with HFpEF, the incidence of more severe diastolic dysfunction was uncommon 40. In the study by Borlaug et al. 22, HFpEF patients showed a similar rise in EDV to their control counterparts, despite marked disparities in exercise capacity.

The lack of a necessary and sufficient role of limited diastolic filling in the exertional reserve limitations of HFpEF renders the question of what alternative mechanisms may exist quite relevant. Among these are depressed contractile reserve, as suggested by Liu et al. 41, reduced central and peripheral vasodilator capacity 42, 43, and/or an abnormal HR response upon exertion 16. A role of the latter two factors was demonstrated by Borlaug *et al.* 22, whereas in this study contractile reserve, measured at the low level of exercise achieved, was similar between HFpEF and controls. Importantly, the reference group had a similar age and co-morbidities 22. This data, and the work of others 23, supports the notion that impairment of the HR response during exercise likely has a considerable impact on exertional capacity.

Chronotropic Incompetence and Heart Failure

Chronotropic incompetence (CI) is defined as an attenuated exercise HR response, commonly perceived as inability to achieve a predetermined percentage of predicted maximal HR, and is diagnosed through various types of exercise stress tests 44. More refined methods for determination of CI utilizing an individuals age, resting HR, peak functional capacity, and the physiologic relationship between HR and oxygen consumption, termed the metabolic-chronotropic relation or MCR, have been proposed and confirmed 26, 27. The application of these techniques to HF patients has shown CI as an important predictor of cardiovascular related death and all-cause mortality 45. The presence of CI within the HF population is well recognized, although the reported prevalence varies considerably (25-70%) 45-49. This likely reflects different criteria used to determine CI as well as differences between patient study groups (i.e., clinical and medication status). Whether CI represents a protective or maladaptive response to severe HF remains unclear, but it appears to be linked to HF severity 16 and has been shown to occur with similar prevalence among HFrEF and HFpEF patients 23.

The benefits of beta-adrenoceptor antagonists (beta-blockers) on HF outcomes have advanced their use as part of the regimen for HF management. Many HFpEF patients are treated with beta-blockers given the presence of co-morbidities (i.e., hypertension, atrial fibrillations, coronary artery disease) and despite the lack of evidenced-based recommendations, guideline groups suggest that beta-blockers be used as a management tool in HFpEF 50, 51. However, a number of features of this approach should be revisited in the context of the RESET study.

First, beta-blockade does not improve but can actually delay relaxation 52, 53. Second, studies have shown no direct impact on diastolic compliance in patients with LVH 54, and there are no prolonged treatment data indicating chronic benefits. Beta-blockers have been studied in hypertension trials, and consistently performed poorly in ameliorating hypertrophy or survival compared with agents in other drug classes 55-57. The impact of beta-blockade on effective vascular loading is also detrimental, increasing the pulsatile load imposed on the heart, and potentially adversely influencing ventricular-arterial coupling 58. This is important since HFpEF patients display ventricular-arterial stiffening 19, 59, and adverse interaction of these systems may play a role in limiting cardiac reserve. Finally, the common use of beta-blockers confounds the determination of CI by attenuating the exercise-induced increase in HR and may be an iatrogenic contributor to limited exercise capacity, but also makes identification of underlying HR regulation abnormalities more difficult. Nonetheless, the occurrence of CI appears to be an intrinsic component of HF progression and occurs irrespective of beta-blockade 16, 48, 49. Jorde and colleagues 48 reported equal prevalence of CI among HF patients

receiving and not receiving beta-blocker therapy. Further, in subjects with CI, VO_2 was associated with CI with those subjects demonstrating the most impaired functional capacity having the highest CI (72%) prevalence. The relationship between VO_2 and CI remained after adjusting for age, gender, ischemic etiology, and beta-blockade⁴⁸. A recent retrospective study addressed the issue of CI and the effect of beta-blocker usage as a predictor of death in patients with a normal electrocardiogram, presumably a surrogate of normal EF. Through careful statistical analyses, CI was assessed with appropriate attention given to the negative chronotropic effect of beta-blockade. The authors identified a suitable chronotropic response cut-off value for the determination of CI among study patients taking beta-blockers. Using this more stringent criterion, it was concluded that CI is present and independently predictive of death even among those patients taking beta-blockers⁶⁰. Further, using this criterion the percentage of CI among beta-blocker recipients (22%) is comparable to previous reports of CI among HF patients⁴⁵⁻⁴⁷.

Pacing, Heart Failure, and HFpEF

Rate-adaptive pacing (RAP) has been demonstrated to improve aerobic capacity and maximum workload in patients with inadequate chronotropic responses^{25, 61} and improvements are most pronounced in patients with CI²⁴⁻²⁶. Despite the importance of HR response on the augmentation of CO, the impact of rate on functional performance and life quality in HF patients has received only limited attention^{62, 63}. A study of pacemaker recipients with structural heart disease and an inappropriate exercise HR response found that rate response pacing improved VO_2 in patients with low ($\leq 45\%$) and preserved ($\geq 55\%$) EF⁴⁸. Interestingly, in patients with a preserved EF, improvement in VO_2 was observed across a wider range of pacing rates (up to 86% of predicted maximal HR), whereas low EF patients experienced a plateau or reduction in VO_2 at rates $\sim 10\%$ lower⁴⁸. The benefit of RAP, in conjunction with CRT, on exercise performance was addressed by Tse et al.⁶³. Patients were assessed with CRT alone and CRT with RAP in a randomized fashion. Peak VO_2 , exercise time and METs were positively correlated with percent changes in HR during exercise among all study patients. Additionally, CRT with RAP was found to have an incremental benefit on peak exercise time, HR, and METs in HF patients with reduced EF who demonstrated the most severe CI. Importantly, the improvement in HR response with RAP was associated with a 20% increase in peak VO_2 in the majority of these patients (82%)⁶³. These data suggest that CI is one mechanism for impaired exercise capacity in patients with severe HF and that appropriately selected patients may benefit from RAP therapy.

Several studies have examined acute incremental atrial pacing responses in patients with HFpEF. The most recent by Westermann et al.⁶⁴ suggested that increasing HR in HFpEF might be detrimental. In particular, this study reported a rate-dependent decline in SV in HFpEF patients that was opposite to a rise in SV (and EDV) observed in the controls. The latter resulted in a marked rise in CO with faster heart rates in the normals, making the lack of such changes in HFpEF subjects seem abnormal. However, as discussed in the companion editorial⁶⁵, the majority of prior studies have established that the normal response to pure HR increase is a graded decline in SV coupled to reduced preload volumes (reduced filling time), so that CO remains fairly unaltered⁴¹⁻⁶⁶. This has been demonstrated using x-ray contrast or nuclear ventriculography, echocardiography, and volume catheter measurements⁴¹⁻⁶⁷⁻⁷². Furthermore, pacing at rest does not mimic the reserve mechanisms invoked by exercise, including neurohumoral activation, arterial dilation, and veno-constriction.

Nevertheless, the data from Westerman et al. highlights the potential for a decrement to left ventricular filling and SV that could diminish pacing-induced increases in CO during exercise. Whether or not this potentially adverse effect will occur during physiologic, rate responsive atrial pacing during upright aerobic exercise in HFpEF patients with CI is unknown. Thus,

there is true equipoise with regard to this proposed therapy. This equipoise and the importance of understanding whether CI is a fundamental mechanism contributing to exercise intolerance in HFpEF patients, provide compelling rationale for RESET.

Vasodilator Reserve

Another feature of HFpEF patients is increased arterial vascular loading due to higher systemic resistance and arterial stiffening (reduced compliance). This is typical in the elderly 73-74 and also common in HFpEF patients and individuals with similar co-morbidities but without HF symptoms¹⁹. The net rise in ventricular afterload (often indexed by effective arterial elastance, Ea, that reflects both mean and pulsatile load) is accompanied by greater ventricular end-systolic stiffening (Ees) 75, and together this contributes to marked blood pressure lability including hypertension during stress, and an increased sensitivity to diuretics 76-77. In an analysis of the Olmsted County, Minnesota population, Redfield et al. 78 showed that women develop both higher Ea and Ees than did men as a function of age, and this has been observed in HFpEF subjects as well. In the HFpEF study of Borlaug et al ²², CO was limited both by HR and less peripheral vasodilation, and the latter also correlated with reduced exercise capacity in HFpEF subjects. Insufficient peripheral arterial dilation particularly in the exercising muscle bed is an important feature of HFpEF and attributed to endothelial dysfunction and abnormalities of neurohormonal and muscular control. Similar defects may well exist in patients with HFpEF.

The RESET trial does not directly address this vascular abnormality, and so it is worth considering the potential impact of raising HR without changes in systemic arterial tone. Ea is directly dependent on systemic resistance and HR, and net effective ventricular afterload will rise if HR increases. This is related to the rise in CO in the absence of a primary change in peripheral impedance. Indeed in the study of Borlaug et al ²², Ea change with exercise was similar for both HFpEF and control groups– but in one case this was due lower systemic resistance and enhanced HR, and CO, while in the other there was higher resistance but and less HR and CO increase. In RESET, We are predicting that the HR response is a primary defect, so by enhancing HR and CO, Ea will rise some, but the heart will adequately meet this load, and the flow improvement will dominate. We further speculate that the greater CO may stimulate flow-dependent peripheral vasodilation that could offset the Ea rise. Vascular properties of individuals with similar co-morbidities – some with HF symptoms, and others without – are very similar ²⁰, so this hypothesis seems reasonable.

Conclusion

HFpEF is the predominant form of HF among the elderly and in women and represents a large part of the overall morbidity and mortality burden of HF. Evidence-based therapy options for this patient population are minimal. Although there is substantial evidence supporting the benefits of RAP in patients with an impaired chronotropic response, the effect of RAP in a patient population with symptomatic HF and CI has not been clearly established, and true equipoise exists regarding potential benefit versus risk. Thus, the RESET study seeks to evaluate the potential benefit of RAP in patients with symptomatic mild to moderate HF, a normal or preserved EF and CI.

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Figure.

RESET Study schema. Patients satisfying the inclusion and exclusion criteria are stratified according to beta-blocker usage then progress to the screening visit for implant eligibility testing. Pacing therapy will be evaluated within each stratum in all implanted patients during the one month visits A and B in a randomized fashion. Upon completion of the one month visits, pacing therapy will be active in all patients in each stratum for the duration of the study. βB + or -, with or without beta-blocker; CPX, cardiopulmonary exercise test; CI, chronotropic incompetence; EF, left ventricular ejection fraction; QoL, quality of life; R, within strata randomized cross-over; mo. = 1, 6, 12 month patient follow-up visits respectively; RAP, rate-adaptive pacing; EoS, end of study.

Table

Inclusion and Exclusion Criteria

Inclusion Criteria	Exclusion Criteria
<ul style="list-style-type: none"> • Age ≥ 18, or of legal age to give informed consent • Willing and capable of providing informed consent, undergoing a device implant and participating in all study testing • Life expectancy > one year • Exhibit signs and symptoms of HF with NYHA Class II or III limitations • Have had at least one of the following within previous 24 months: <ul style="list-style-type: none"> – Prior hospitalization for decompensated HF – Acute treatment for pulmonary congestion/volume overload that resolved with a loop diuretic or hemofiltration – Chronic treatment with a loop diuretic – A BNP level > 125 ng/l • LVEF $\geq 50\%$ within previous 12 months • Stable medical therapy for at least 60 days as defined by: <ul style="list-style-type: none"> – No addition or removal of ACE, ARB, βB, CCB – No dosage increase or decrease of ACE, ARB, βB, or CCB > 100% • Sinus rhythm at consent 	<ul style="list-style-type: none"> • Women who are pregnant or plan to become pregnant • A contraindication for a pacemaker system • Enrollment in any concurrent study • Neuromuscular, orthopedic or other non-cardiac condition preventing exercise testing • HCM with obstruction or restriction or infiltrative CM • Hypercontractile disorder (LVEF > 90%) • Currently implanted pacing/ICD lead(s) or pulse generator • Indication for a pacemaker per AHA/ACC guidelines • MI or unstable angina, or undergone PTCA or CABG 60 days prior, or requires PTCA or CABG at time of consent • Valve disease > than moderate or prior valve repair or replacement • Pulmonary disease defined by any one of the following: <ul style="list-style-type: none"> – FVC or FEV₁ < 60% of predicted values – Use of two or more pulmonary inhalers – Use of supplemental oxygen – Chronic oral steroid use for pulmonary disease • Cor pulmonale (PASP > 60 mmHg) • Documented AF / AFI 90 days prior to consent • Uncontrolled diabetes or hospitalization 60 days prior for hyperosmotic state or diabetic ketoacidosis • Uncontrolled hypertension (SBP > 160 or DBP > 95 mmHg) • Any of the following 60 days prior to consent: <ul style="list-style-type: none"> – A serum creatinine level > 3 mg/dl – Any liver function test > than 2.5 times the ULN – A hemoglobin value < 10.5 g/dl

HF, heart failure; NYHA, New York Heart Association HF Classification; LVEF, left ventricular ejection fraction; BNP, brain natriuretic peptide; ACE, angiotensin converting enzyme inhibitors; ARB, angiotensin receptor blockers; β B, beta-blockers; CCB, calcium channel blockers; HCM, hypertrophic cardiomyopathy; MI, myocardial infarction; PTCA, percutaneous transluminal coronary angiography; CABG, coronary artery bypass grafting; FVC, forced vital capacity; FEV₁, forced expiratory volume in one second; PAP, pulmonary arterial pressure; AF, atrial fibrillation; AFI, atrial flutter; SBP / DBP, systolic and diastolic blood pressure, respectively; ULN, upper limit of normal.