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Effect of Selective Heart Rate Slowing in Heart Failure With Preserved Ejection Fraction

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Background—Heart failure with preserved ejection fraction (HFpEF) is associated with significant morbidity and mortality but is currently refractory to therapy. Despite limited evidence, heart rate reduction has been advocated, on the basis of physiological considerations, as a therapeutic strategy in HFpEF. We tested the hypothesis that heart rate reduction improves exercise capacity in HFpEF.

Methods and Results—We conducted a randomized, crossover study comparing selective heart rate reduction with the I_f blocker ivabradine at 7.5 mg twice daily versus placebo for 2 weeks each in 22 symptomatic patients with HFpEF who had objective evidence of exercise limitation (peak oxygen consumption at maximal exercise [$\dot{V}o_2$ peak] <80% predicted for age and sex). The result was compared with 22 similarly treated matched asymptomatic hypertensive volunteers. The primary end point was the change in $\dot{V}o_2$ peak. Secondary outcomes included tissue Doppler–derived E/e′ at echocardiography, plasma brain natriuretic peptide, and quality-of-life scores. Ivabradine significantly reduced peak heart rate compared with placebo in the HFpEF (107 versus 129 bpm; P<0.0001) and hypertensive (127 versus 145 bpm; P=0.003) cohorts. Ivabradine compared with placebo significantly worsened the change in $\dot{V}o_2$ peak in the HFpEF cohort (-2.1 versus 0.9 mL·kg^{-1}·min^{-1}; P=0.003) and significantly reduced submaximal exercise capacity, as determined by the oxygen uptake efficiency slope. No significant effects on the secondary end points were discernable.

Conclusion—Our observations bring into question the value of heart rate reduction with ivabradine for improving symptoms in a HFpEF population characterized by exercise limitation.

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Key Words: exercise ■ heart failure ■ heart rate

Up to half of all patients with the clinical features of heart failure have preserved left ventricular ejection fraction (HFpEF), defined as an EF ≥50%.[1–3] Mortality rates in patients with HFpEF are similar to those in patients with reduced EF (HFrEF)[1,2,4] and are due largely to cardiovascular death.[4,5] In contrast to HFrEF, there are no proven therapies for HFpEF despite the increasing prevalence and hospitalization rate.[2,3] The failure of multiple investigational therapies to influence survival or to affect symptoms in HFpEF likely reflects heterogeneous case inclusion (including geographic variation in trial recruitment), suboptimal drug administration with regard to dose, stage or endophenotype of disease, or an incomplete conception of disease pathophysiology.[6–9]

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HFpEF has been conceptualized, in part, as a disorder of diastolic function, reflecting impairments in active relaxation and intrinsic myocardial compliance.[10] More broadly, these patients have impairments in ventricular-arterial coupling and of contractile function, albeit insufficient to reduce global left ventricular EF, and abnormally low skeletal muscle O_2 extraction.[11,12]

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Given the critical contribution of diastole to ventricular filling and coronary perfusion, reduction of heart rate, with a view to prolonging diastole, especially in atrial fibrillation, has been advocated as a therapeutic strategy to mitigate symptoms in HFpEF[13] and has been endorsed by guidelines.[14] However, increased heart rate is the major physiological contributor to the rise in cardiac output necessary to meet the metabolic demands of exercise,[15] the capacity for which is substantially reduced in both HFpEF and HFrEF.[16] Mechanistic studies of patients with HFpEF subject to exercise stress have implicated chronotropic incompetence as a potential contributor to impaired cardiac output reserve and thereby likely to contribute to the exertional dyspnea and effort intolerance characteristic of the syndrome.[16–19] Accordingly, we sought to test the hypothesis that heart rate reduction improves exercise tolerance as assessed by peak oxygen consumption ($\dot{V}o_2$ peak).

We performed a placebo-controlled, crossover, clinical study to evaluate the effects of short-term selective heart rate reduction with ivabradine (2 weeks), an inhibitor of the sinoatrial pacemaker funny current (I_f) considered devoid of effects on cardiac contractility,[20] on the exercise performance of a homogeneous group of subjects with exercise-limited HFpEF. To substantiate the generalizability of the results and to inform our understanding of mechanisms responsible for exercise limitation, we performed a parallel study in a matched asymptomatic hypertensive group representing less advanced pathophysiology.

Methods

Study Design

We undertook a prospective, double-blind, placebo-controlled, randomized, crossover trial at 2 UK academic hospitals: the John Radcliffe Hospital (Oxford) and the Aberdeen Royal Infirmary. The study was designed to assess the effect of short-term administration of ivabradine on $\dot{V}o_2$ peak and other parameters of exercise performance in a well-defined cohort of patients with HFpEF and a comparator asymptomatic hypertensive group. The study was approved by the Ethics Service committees in Aberdeen and Oxford (South Central). All participants provided written informed consent to study. Detailed methods are included in the online-only Data Supplement.

Study Patients

Consensus has not been reached on the optimal method(s) with which to define HFpEF patients; however, there is broad agreement that these dynamic disturbances during exercise cannot be predicted from resting measures of diastolic function.[21] For these reasons, our inclusion criteria corresponded to those previously used,[22] with rigorous cardiopulmonary exercise testing criteria to establish that the patients were objectively limited compared with age- and sex-predicted normal values.

HFpEF was defined according to the presence of both symptoms and signs of HF and EF ≥50%, a nondilated left ventricle and relevant structural heart disease in the form of left ventricular hypertrophy, left atrial enlargement, or evidence of diastolic dysfunction on echocardiography (mitral inflow E/A ratio, e′ measured at the mitral annulus, and E/e′ ratio).[23] Eligible patients with HFpEF were at least 60 years of age with subjective exercise limitation owing to breathlessness or fatigue and objective evidence of exercise limitation as a measured $\dot{V}o_2$ peak on cardiopulmonary exercise testing of <80% predicted for age and sex, with an appropriate pattern of gas exchange.[24,25]

Screening and Intervention

Eligible participants underwent screening assessment by history taking and physical examination, quality-of-life assessment measured by the Minnesota Living With Heart Failure Questionnaire,[26] biochemical blood analysis, 12-lead ECG, transthoracic echocardiography, spirometry, and cardiopulmonary exercise testing.

We screened 65 patients for the HFpEF group and selected 34 matched asymptomatic hypertensive patients from a hypertension database over a 2-year period from December 2011 through January 2014 (Figure 1). Of these, 30 patients were found to be eligible to enter the HFpEF group, and all 34 patients were eligible for the asymptomatic hypertension group. The first 24 consecutive patients took part in the HFpEF group, of which 2 participants were excluded in the final analysis: 1 patient did not complete the study and dropped out during the second visit, and the other was excluded because of suboptimal exercise testing based on a respiratory exchange ratio of 0.81 during the second visit. Twenty-two asymptomatic hypertensive patients consented and participated in the study, and all were included in the final analysis. In line with existing trial protocols of ivabradine in HFrEF aiming for a heart rate target of 50 to 60 bpm,[27,28] eligible participants were randomly assigned through block randomization to receive either ivabradine 7.5 mg twice daily or matching placebo tablets for 2 weeks (period 1). At the end of period 1, all screening assessments were repeated; in addition, cardiovascular magnetic resonance imaging was performed in the HFpEF cohort. After a 2-week washout period, subjects were then assigned to the alternative treatment arm (placebo or ivabradine) for a further 2 weeks (period 2). At the end of this, all period 1 assessments were repeated. Participants, investigators, and outcome assessors were all blinded to treatment allocation.

Study End Points

The predefined primary end point was the change in $\dot{V}o_2$ peak. Secondary end points were changes in Doppler-derived E/e′,

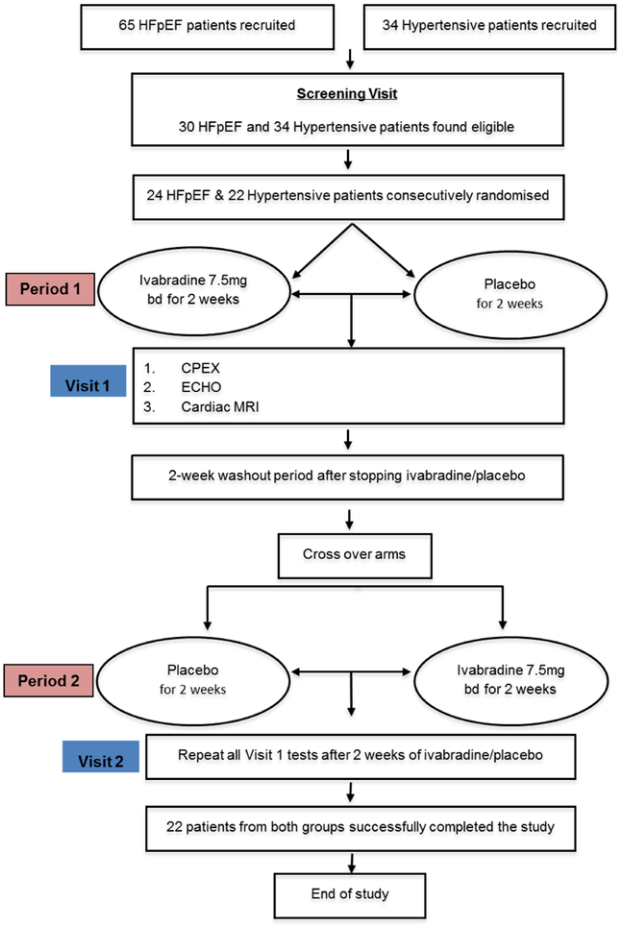

Figure 1. Flow diagram of the study. CPEX indicates cardiopulmonary exercise testing; ECHO, echocardiography; HFpEF, heart failure with preserved ejection fraction; and MRI, magnetic resonance imaging.

brain natriuretic peptide levels, and quality of life assessed by the Minnesota Living With Heart Failure Questionnaire.

Statistical Analysis

For a crossover study design, power calculation indicated that to detect a mean absolute difference in $\dot{V}o_2$ peak of 2.5 mL·kg^{-1}·min^{-1} (SD, 2.5 mL·kg^{-1}·min^{-1}), 22 patients could provide 90% power at an overall 2-sided α level of 0.05. Continuous variables are reported as mean±SD. Data sets were evaluated for normality by the Kolmogorov-Smirnov test. Comparisons between HFpEF and the asymptomatic hypertensive group were assessed by a 2-tailed Student *t* test. The comparisons between ivabradine and placebo treatments within patient groups were assessed by a 2-tailed paired Student *t* test. All statistical analyses were performed with the use of SPSS Statistics, version 19 (IBM). A value of $P \leq 0.05$ with a 2-tailed test was considered statistically significant.

Results

Baseline Clinical Characteristics

Baseline clinical characteristics of the patients are shown in Table 1. Compared with the hypertensive group, the patients with HFpEF were older (74.6 versus 66.9 years; $P=0.0001$), were more likely to be female (65% versus 23%; $P=0.014$), and had a lower proportion of hypertension (50% versus 100%; $P=0.0002$). Cardiovascular drug therapy was similar between groups, but there was a significantly greater use of calcium channel blockers in the hypertensive cohort (55% versus 5% in the HFpEF cohort; $P=0.0006$). Three HFpEF patients but no hypertensive individuals were taking β-blockers ($P=0.23$). All HFpEF patients but none in the hypertension group scored significantly on the Minnesota Living With Heart Failure Questionnaire at baseline. There were no differences in resting plasma brain natriuretic peptide. The baseline echocardiographic characteristics of HFpEF patients are shown in Table I in the online-only Data Supplement.

Response to Exercise

Cardiopulmonary exercise testing of HFpEF patients at baseline revealed a significantly lower $\dot{V}o_2$ peak (16.1 versus 27.0 mL·kg^{-1}·min^{-1} [$P<0.0001$] despite satisfactory effort indicated by a respiratory exchange ratio >1.0), anaerobic threshold (11.5 versus 20.6 mL·kg^{-1}·min^{-1}; $P<0.0001$), and maximal workload achieved (4.5 versus 7.7 metabolic equivalents; $P<0.0001$) compared with the hypertensive group but an increased ventilatory response to exercise, as indicated by a higher ratio of minute ventilation to carbon dioxide production ($\dot{V}E/\dot{V}co_2$; Table 2). Despite being asymptomatic, the hypertensive cohort had $\dot{V}o_2$ peak values that were below mean age- and sex-predicted normal values (28.0 mL·kg^{-1}·min^{-1}). HFpEF patients had marked chronotropic dysfunction with lower peak exercise heart rates (129 versus 145 bpm; $P<0.0001$).

Selective Heart Rate Lowering With Ivabradine in the HFpEF Cohort

Table 3 and Table II in the online-only Data Supplement show the comparison of the effects of ivabradine versus placebo on resting hemodynamic, cardiac imaging, and exercise parameters in the HFpEF cohort. Ivabradine reduced the mean resting heart rate by 20 bpm (77 to 57 bpm; $P<0.0001$) without any effect on blood pressure or left ventricular EF. Similarly, ivabradine treatment reduced the chronotropic response to exercise (peak heart rate, 129 versus 107 bpm; $P<0.0001$). The heart rate reduction was accompanied by reduced peak oxygen consumption in the majority of HFpEF patients (19 patients had a reduction in the $\dot{V}o_2$ peak), with a diminution in the $\dot{V}o_2$ peak from 15.9 to 14.8 mL·kg^{-1}·min^{-1} ($P=0.003$), without significantly affecting $\dot{V}E/\dot{V}co_{2\ slope}$ or the anaerobic threshold. Moreover, a paired comparison of the changes in $\dot{V}o_2$ peak resulting from the 2-week intervention blocks demonstrated a consonant lowering in the ivabradine group (−2.1 versus 0.9 mL·kg^{-1}·min^{-1}; $P=0.003$; Figure 2). Compared with placebo, ivabradine treatment induced small but significant increases in the transmitral E/A ratio (0.6 versus 0.65; $P=0.026$) and mean e′ velocity (4.5 versus 5.4 cm/s; $P=0.002$), with no effect on the E/e′ ratio, ratio of myocardial phosphocreatine to adenosine triphosphate, or symptomatic status (Minnesota Living With Heart Failure Questionnaire; Table 3).

To assess the influence of ivabradine on submaximal exercise performance in patients with HFpEF, an analysis of the relationship between oxygen consumption and ventilation, defined as the oxygen uptake efficiency slope (OUES), was also undertaken (Table II and Figure I in the online-only Data Supplement). OUES is a submaximal measure of

Table 1. Clinical and Demographic Characteristics of the HFpEF and Asymptomatic Hypertensive Cohorts at Baseline

	HFpEF (n=22)	Hypertensive (n=22)	*P* Value
Age, y	74.6±5.9	66.9±5.2	0.0001
Women, n (%)	14 (65)	5 (23)	0.014
Body mass index, kg/m^2	29.9±6.2	26.7±2.9	0.036
NYHA class I, n (%)	…	22 (100)	
NYHA class II, n (%)	22 (100)	…	
Medical history, n (%)			
Hypertension	11 (50)	22 (100)	0 0.0002
Diabetes mellitus	2 (10)	3 (14)	1.0
Dyslipidemia	9 (41)	1 (5)	0.009
Medications, n (%)			
ACE-I/ARB-II	13 (59)	15 (68)	0.75
β-Blockers	3 (14)	0	0.23
Statin	10 (46)	10 (46)	1
Calcium blockers	1 (5)	12 (55)	0.0006
Diuretics	14 (64)	8 (36)	0.13
Oral hypoglycemic agents	1 (5)	0	1
Biochemical			
Hemoglobin, g/dL	13.6±1.3	14.2±0.9	0.07
Creatinine, μmol/L	81.5±30.4	77.1±13.9	0.56
Blood glucose, mmol/L	5.5±0.9	5.5±0.9	0.84
Total cholesterol, mmol/L	4.5±0.9	4.5±0.9	0.89
BNP, pmol/L	13.4 (7.5–24.4)	16.4 (11.1–31.7)	0.10

Values are mean±SD, percentages, or median (quartiles 1–3). ACE-I indicates angiotensin-converting enzyme inhibitor; ARB-II, angiotensin-receptor antagonist II; BNP, brain natriuretic peptide; HFpEF, heart failure with preserved ejection fraction; and NYHA, New York Heart Association.

Table 2. Baseline Hemodynamics and Cardiopulmonary Exercise Testing Characteristics of HFpEF and Asymptomatic Hypertensive Cohort

	HFpEF (n=22)	Hypertensive (n=22)	*P* Value
Heart rate (rest), bpm	75±12	78±14	0.36
Heart rate (peak), bpm	127±19	159±14	< 0.0001
Systolic BP, mm Hg	148±19	147±7	0.91
Diastolic BP, mm Hg	83±6	82±12	0.82
$\dot{V}\,o_2$ peak, mL·kg^{-1}·min^{-1}	16.1 (15.0–18.2)	27.0 (22.5–31.2)	< 0.0001
Percentage of predicted $\dot{V}\,o_2$ max, %	66	96	0.009
$\dot{V}_E/\dot{V}\,co_2$	34.4±6.1	27.3±3.4	< 0.0001
Anaerobic threshold, mL·kg^{-1}·min^{-1}	11.5±2.4	20.6±4.8	< 0.0001
RER	1.08±0.08	1.17±0.06	0.0002

Values are mean±SD, percentages, or median (quartiles 1–3). BP indicates blood pressure; HFpEF, heart failure with preserved ejection fraction; RER, respiratory exchange ratio; and $\dot{V}_E/\dot{V}\,CO_2$, ratio of minute ventilation to carbon dioxide production.

cardiorespiratory reserve less sensitive to exercise duration and has strong prognostic value in HF.[29] Compared with placebo, an assessment of the OUES at 75% of the duration of exercise identified a significant reduction with ivabradine [1834 versus 1621 (mL/min O_2)/(L/min $\dot{V}_E$); (*P*=0.04)].

Selective Heart Rate Lowering With Ivabradine in the Asymptomatic Hypertensive Cohort

As with the HFpEF group, administration of ivabradine at 7.5 mg twice daily significantly reduced resting heart rate compared with placebo (from 74 to 61 bpm; *P*=0.001). Peak exercise heart rate was blunted by ivabradine use (145 versus 127 bpm; *P*=0.003). Ivabradine use was associated with a statistically nonsignificant reduction in the primary end point, $\dot{V}\,o_2$ peak (26 versus 24.5 mL·kg^{-1}·min^{-1}; *P*=0.47; Table 4 and Table III in the online-only Data Supplement). Compared with placebo, ivabradine treatment was associated with a small but significant increase in the $\dot{V}_E/\dot{V}\,co_2$ ratio (27.4 versus 29.2; *P*=0.004) but did not affect the anaerobic threshold or peak workload.

Discussion

We undertook a short term, placebo-controlled, randomized, crossover study examining the effect of selective heart rate lowering with the I_f inhibitor ivabradine on exercise capacity in a well-defined cohort of patients with symptomatic HFpEF. With individuals acting as their own controls, we found that 2 weeks of heart rate reduction with ivabradine at a dose of 7.5 mg twice daily in patients with HFpEF almost uniformly exacerbated already abnormal exercise physiology, resulting in a significant reduction in the primary end point, $\dot{V}\,o_2$peak.

Consistent with previous reports,[16–19] our cohort of HFpEF patients had poor exercise tolerance, a significantly impaired peak oxygen uptake, low $\dot{V}\,o_2$ at the anaerobic threshold, increased ventilatory response, and a reduction of the chronotropic response to exercise. Because of the broader pathogenesis of HFpEF, including prominent defects in skeletal muscle metabolism,[11,12] our patients with HFpEF were not diagnosed on the basis of resting diastolic dysfunction but rather on the basis of subjective exercise limitation with normal left ventricular EF and the absence of significant valvular disease, together with objective exercise limitation. In the Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist (TOPCAT) study, of 935 patients with HFpEF, diastolic function was normal in approximately one third of gradable participants.[30] We also have observed a poor agreement between exercise E/E′, cardiopulmonary exercise testing categorization, and current criteria based on resting diastolic function.[31] We and others have found that HFpEF is characterized by dynamic disturbances of left ventricular active relaxation during exercise.[32–34] Furthermore, plasma brain natriuretic peptide is often relatively normal at rest in HFpEF, especially in those with a high body mass index in whom brain natriuretic

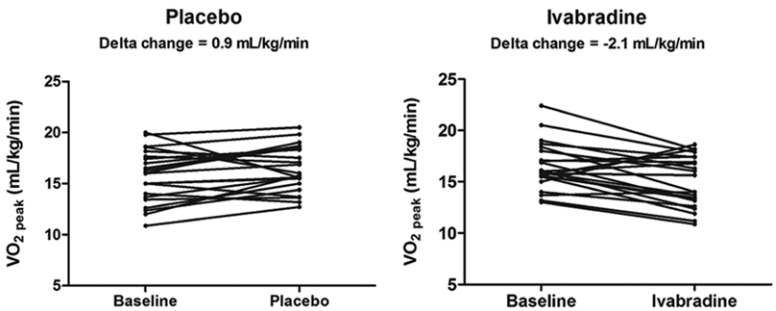

Figure 2. Effect of ivabradine on $\dot{V}\,o_2$ peak in the heart failure with preserved ejection fraction (HFpEF) cohort. Depicts the change in $\dot{V}\,o_2$ peak (mL·kg^{-1}·min^{-1}) with placebo (**left**) and ivabradine (**right**; ivabradine vs placebo, *P*=0.003) in the HFpEF cohort.

Table 3. Effect of Ivabradine Versus Placebo on Cardiac Imaging and Exercise Parameters in the HFpEF Cohort

	Placebo (n=22)	Ivabradine (n=22)	*P* Value
Change in $\dot{V}o_2$ peak during each arm of treatment, mL·kg^{-1}·min^{-1}	0.9 (–0.6 to 2.1)	–2.1 (–2.9 to 0)	0.003
$\dot{V}o_2$ peak, mL·kg^{-1}·min^{-1}	15.9 (14.9 to 18.4)	14.8 (13 to 17.4)	0.003
LVEF, %	64.4±8	66.6±4.5	0.23
e′ (mean of septal and lateral), cm/s	4.5±1.1	5.4±1.5	0.002
E/e′ ratio	10.4±2.5	10.7±2.4	0.56
MLHFQ	20.6±16.1	21.7±16.9	0.55

Values are mean±SD, percentages, or median (quartiles 1–3). HFpEF indicates heart failure with preserved ejection fraction; LVEF, left ventricular ejection fraction; and MHLFQ, Minnesota Living With Heart Failure Questionnaire.

peptide appears to be suppressed but rises dramatically on exercise (unpublished data).[31,34,35]

The choice of $\dot{V}o_2$ peak as the primary end point in this study is supported by its objective measurement of cardiac reserve, its robust correlation with survival,[36] and the difficulties in obtaining a true maximal oxygen uptake ($\dot{V}o_2$max), which relies on exercise to absolute exhaustion with plateauing of oxygen uptake despite continued exercise.[29] In common with $\dot{V}o_2$max, $\dot{V}o_2$ peak is effort dependent and does not provide insight into potential differences in submaximal exercise capacity that may be more reflective of the levels of exertion that result in symptoms in HF patients. To address this possibility, we also evaluated a measure of submaximal cardiopulmonary reserve, the OUES, the value of which has, unlike $\dot{V}o_2$, been shown to be relatively independent of exercise duration and an even more powerful predictor of prognosis than conventional measures of exercise performance.[29] We found that ivabradine treatment also significantly reduced submaximal cardiorespiratory reserve in HFpEF. Although there was a significant change in certain parameters of exercise capacity, ivabradine treatment did not discernibly alter the cardiac energetic status (ratio of phosphocreatine to adenosine triphosphate) of the HFpEF or hypertensive patients.

In contrast to the Class Ia evidence in HFrEF, limited evidence-based treatment options exist for the management of HFpEF. Current therapy includes heart rate reduction, a strategy based on physiological observations dating to the late 19th century that, primarily at higher heart rates, shortening of the diastolic filling period impairs cardiac filling and results in lower stroke volumes.[37] The findings from the present study question this widely held approach, indicating that even short-term selective heart rate lowering in the presently defined population of HFpEF patients acts to impair exercise capacity, not least as the relationship between decreasing heart rate and increasing stroke volume is asymmetrical. Moreover, the observation that despite ameliorating some measures of cardiac filling (eg, e′), heart rate reduction almost uniformly adversely affects exercise tolerance highlights the need for a broader conceptualization of HFpEF as a chronic, complex disorder of integrated cardiovascular reserve rather than a purely diastolic disease.[11,12,16,38]

Kosmala et al[13] reported increased exercise capacity in patients with HFpEF after short-term treatment with ivabradine. The reasons underlying the discrepancy with the present study are unclear but may reflect the younger population studied (mean age, 67 years), atypical of the clinical population seen with HFpEF, shorter duration, and lower dose of ivabradine (7 days of 2.5–5 mg twice daily, resulting in a reduction in resting heart rate of 10 bpm), which did not appear to affect peak heart rate response to exercise and perhaps study design (not crossover). Our patients, being older and at an age more typical of the HFpEF population, with advanced chronotropic incompetence and diminished stroke volume reserve (a largely fixed stroke volume) were more sensitive to heart rate reduction.

The present proof-of-concept study was not designed to address whether selective heart rate slowing had longer-term effects on survival or hospitalization. However, the significant and consistent reduction in multiple metabolic stress testing parameters linked to mortality in HF, including reduced $\dot{V}o_2$ peak, increased $\dot{V}E/\dot{V}co_2$,[39] low chronotropic response,[39] and reduced OUES,[29] suggests the need for caution with indiscriminate heart rate reduction in this population of patients. Harmful off-target effects beyond the inhibition of sinoatrial I_f are possible. Indeed, subgroup analyses of the Effects Of

Table 4. Effect of Ivabradine Versus Placebo on Cardiac Imaging and Exercise Parameters in the Asymptomatic Hypertensive Cohort

	Placebo (n=22)	Ivabradine (n=22)	*P* Value
Change in $\dot{V}o_2$ peak during each arm of treatment, mL·kg^{-1}·min^{-1}	1 (–1 to 4)	–1.5 (–5.3 to 1)	0.08
$\dot{V}o_2$ peak, mL·kg^{-1}·min^{-1}	26 (21 to 29)	24.5 (21.5 to 29.5)	0.47
LVEF, %	65.9±9.3	67.7±9.3	0.43
e′ (mean of septal and lateral), cm/s	7.2±1.9	8.2±2.2	0.12
E/e′ ratio	10.6±3.6	11.2±4.5	0.61
MLHFQ	0 (0 - 0.3)	0 (0 – 0)	1

Values are mean±SD, percentages, or median (quartiles–3). HFpEF indicates heart failure with preserved ejection fraction; LVEF, left ventricular ejection fraction; and MHLFQ, Minnesota Living With Heart Failure Questionnaire.

Ivabradine in Patients With Stable Coronary Artery Disease Without Heart Failure (SIGNIFY) trial using ivabradine suggested a signal for cardiovascular harm in stable coronary artery disease.[40] However, we speculate that we are observing mechanism-related drug effects and that reducing heart rate with other agents (eg, β-adrenergic blockade) may confer similar or more profound adverse effects in HFpEF as a result of their impact on heart rate and exercise-dependent ventricular lusitropy.[41]

The following represent potential limitations of our study. First, the sample size studied was small, but the treatment was not found to be beneficial in either group. Importantly, in this crossover study, we observed no evidence of a carryover or period effect; the washout period of 2 weeks (336 hours) exceeds the biological half-life of ivabradine (2 hours). Nevertheless, the study needs to be replicated in a larger clinical trial examining a well-defined homogeneous cohort powered to look at mortality and morbidity end points that may support this and point to alternative strategies to improve exercise intolerance. Second, the heart rate reduction of 20 bpm in our study group was greater than previously studied in trials using ivabradine. A beneficial effect resulting from a lesser heart rate reduction cannot be excluded.

Conclusion

The results of the present study do not support a general strategy of heart rate reduction in HFpEF and question its role in improving symptoms in these patients.

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Disclosures

None.

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CLINICAL PERSPECTIVE

Heart failure with preserved ejection fraction (HFpEF) accounts for nearly 50% of all the heart failure, with mortality figures now comparable to those in patients with heart failure with reduced ejection fraction. Despite this unmet clinical need, our limited understanding of the broad systemic pathophysiology has translated into a lack of proven therapies for HFpEF. Predicated on the hypothesis that heart rate reduction promotes diastolic filling with corresponding benefits in diastolic function in HFpEF, we investigated the influence of heart rate reduction with ivabradine in these patients in a double-blind crossover trial. Ivabradine is a particularly useful agent in this context because it acts on the I_f channels in the sinoatrial node and lowers the heart rate without substantially affecting cardiac contractility. The diagnosis of HFpEF was made with conventional echocardiographic criteria and with cardiopulmonary exercise testing to capture the dynamic impairments of physiology characteristic of HFpEF. We found heart rate reduction with ivabradine to have a largely consistently detrimental effect on peak oxygen uptake and on submaximal exercise capacity. Although a larger clinical end-point study is required, we believe that this report has implications for the widespread practice of heart rate reduction in this context.

Effect of Selective Heart Rate Slowing in Heart Failure With Preserved Ejection Fraction

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SUPPLEMENTAL MATERIAL

SUPPLEMENTAL METHODS

Resting transthoracic echocardiography was undertaken using a Philips iE33 system (Philips Medical Systems, The Netherlands) in accordance with ESC guidelines.[1] Diastolic evaluation was in accordance with joint recommendations of the European Association and American Society of Echocardiography[2] and included measurement of peak early (E) and late (A) diastolic mitral inflow velocities, the deceleration time of the early filling velocity (DT), tissue Doppler mitral annular early (e') and late (a') diastolic velocities with subsequent calculation of E/e' (e' taken as average of septal and lateral annular velocities). All measurements were averaged from three consecutive cardiac cycles and images acquired by the same experienced sonographer for each subject at every visit.

Cardiopulmonary exercise testing was undertaken using a symptom-limited erect treadmill or bicycle exercise protocol (according to patient suitability) with simultaneous respiratory gas analysis, as described.[3, 4] All exercise protocols were undertaken on the same platform once selected for an individual patient. Direct measurements of oxygen consumption (VO_2), carbon dioxide production (V_{CO2}) and minute ventilation (V_E) were made. An incremental protocol was utilised whereby speed and inclination (for treadmill exercise) or resistance and speed (for bicycle exercise) were gradually increased every minute during continual blood pressure and ECG measurement. Subjects were encouraged to exercise to exhaustion, with a corresponding adequate respiratory exchange ratio achieved as a requirement for satisfactory effort. Exercise was terminated at subject request due to fatigue or dyspnoea. Peak oxygen consumption ($VO_{2\ peak}$) was determined by averaging VO_2 measures over 30 seconds of peak exercise. The oxygen uptake efficiency slope was defined as the regression slope (a) of VO_2 against V_E plotted on a semilogarithmic scale such that $VO_2 = a \log V_E + b$.[5]

CMR at Oxford was performed on a Siemens 3T Trio MR system (Erlangen, Germany) for assessment of cardiac volumes, mass and function from SSFP short-axis stacks using Argus post-processing software (Siemens Healthcare, Erlangen, Germany) only in the HFpEF cohort. In Aberdeen, a similar protocol was performed on a 1.5 T Philips Intera and

Achieva systems (Philips Medical Systems, Best, The Netherlands). Cine images were acquired using standard Steady State Free Precession (SSFP) imaging. For ^{31}P spectroscopy, subjects were placed in the prone position, with the heart approximately centred on the middle of a ^{31}P coil. ^{31}P-MR spectroscopy was performed with 3D acquisition-weighted chemical shift imaging, using ultra-short time (UTE)-CSI. Correction factors for saturation and muscle contamination were applied. The area under each resonance is proportional to the amount of each ^{31}P nucleus species in the heart, allowing direct quantification of the relative concentrations of ATP and phosphocreatine.

Exclusion criteria for both cohorts included: LV EF < 50%; inability to perform exercise testing; inability to tolerate CMR, e.g. due to claustrophobia or inability to lie flat; contra-indications to CMR, including the presence of implantable devices, internal cardioverter-defibrillator, cranial aneurysm clip, metallic ocular foreign body or known hypersensitivity to gadolinium; the presence of other significant cardiac disease, including ischemic, valvular, pericardial disease or cardiomyopathy (hypertrophic, dilated or restrictive); asthma; second or third degree atrioventricular block; sick sinus syndrome; atrial fibrillation; significant resting bradycardia (heart rate < 60 beats/minute); objective evidence of lung disease on lung function testing; or significant renal impairment (estimated GFR < 30 mL per minute per 1.73 m^2 body surface area).

The hypertensive patient cohort were aged 60 years of age or older, with no symptoms or clinical signs of heart failure, normal LV EF with no significant valvular disease on screening echocardiography and no known cardiac or respiratory disease. Subjects were recruited prospectively from a large on-going hypertension database.

Supplemental Table 1: Baseline Echocardiographic Characteristics of the HFpEF Cohort

	HFpEF (n = 22)
LV ejection fraction (%)	64.5 ± 7.9
LV end-diastolic volume index (mL/m^2)	36.4 (30.6 – 42.2)
LA volume index (mL/m^2)	28.0 ± 12.3
LV mass index (g/m^2)	109.0 ± 25.3
E/A ratio	0.7 (0.6 – 1.1)
E wave deceleration time, ms	185 ± 67
e' (mean of septal and lateral), cm/s	5.2 ± 1.5
E/e' ratio	11.1 ± 2.4

Values are mean ± SD, percentages or median (quartiles 1 to 3). LV = left ventricular; LA = left atrial; E = peak early diastolic mitral flow velocity; A = late diastolic mitral flow velocity; e' = peak early diastolic mitral annular velocity.

Supplemental Table 2: Effect of Ivabradine versus Placebo on Resting Hemodynamic, Cardiac imaging and Exercise Parameters in the HFpEF Cohort

	Placebo (n = 22)	Ivabradine (n = 22)
Heart rate, beats/min (rest)	77 ± 13	57 ± 9
Heart rate, beats/min (exercise)	129 ± 20	107 ± 18
Systolic BP, mmHg	142 ± 25	149 ± 28
Diastolic BP, mmHg	79 ± 12	76 ± 10
LV end-diastolic volume index (mL/m^2)	30.3 (26.7 – 40.0)	29.0 (25.8 – 40.0)
LA volume index (mL/m^2)	27.0 ± 10.7	31.3 ± 12.2
LV mass index (g/m^2)	109.0 ± 29.1	102.0 ± 22.5
E/A ratio	0.60 (0.50 – 0.70)	0.65 (0.56 – 1.08)
E wave deceleration time, ms	170 ± 44	177 ± 52
V_E/V_{CO2}	36.1 ± 6.5	36.1 ± 6.1
Anaerobic Threshold (mL/kg/min)	11.5 ± 2.9	10.4 ± 2.5
RER	1.1 ± 0.1	1.1 ± 0.1
OUES	1834 ± 563	1621 ± 347
MRI LV ejection fraction (%)	74.1 ± 6.4	73.9 ± 7.2
MRI LV end-diastolic volume index (mL/m^2)	60.8 ± 11.7	64.8 ± 11.7
MRI LV end-systolic volume index (mL/m^2)	16.3 ± 6.7	17.5 ± 7.7
MRI LV mass index (g/m^2)	53.7 ± 12.3	52.1 ± 12.4
MRS PCr/ATP ratio	1.69 ± 0.41	1.68 ± 0.39

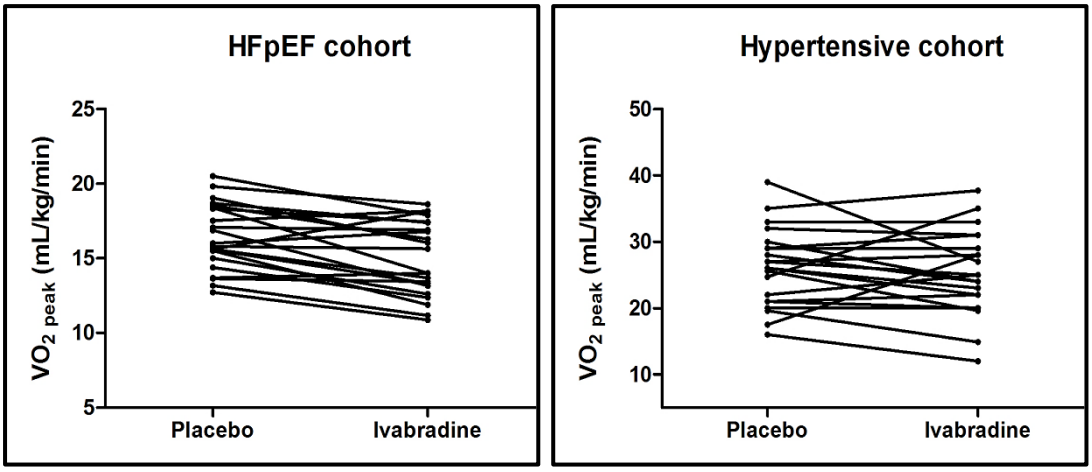
Values are mean ± SD, percentages or median (quartiles 1 to 3). BP = blood pressure; LV = left ventricular; LA = left atrial; E = peak early diastolic mitral flow velocity; A = late diastolic mitral flow velocity; V_E/V_{CO2} = minute ventilation-carbon dioxide production ratio; RER = respiratory exchange ratio; OUES = oxygen uptake efficiency slope; MRI = Magnetic Resonance Imaging;

Supplemental Table 3: Effect of Ivabradine versus Placebo on Resting Hemodynamic, Cardiac Imaging and Exercise Parameters in the Asymptomatic Hypertensive Cohort

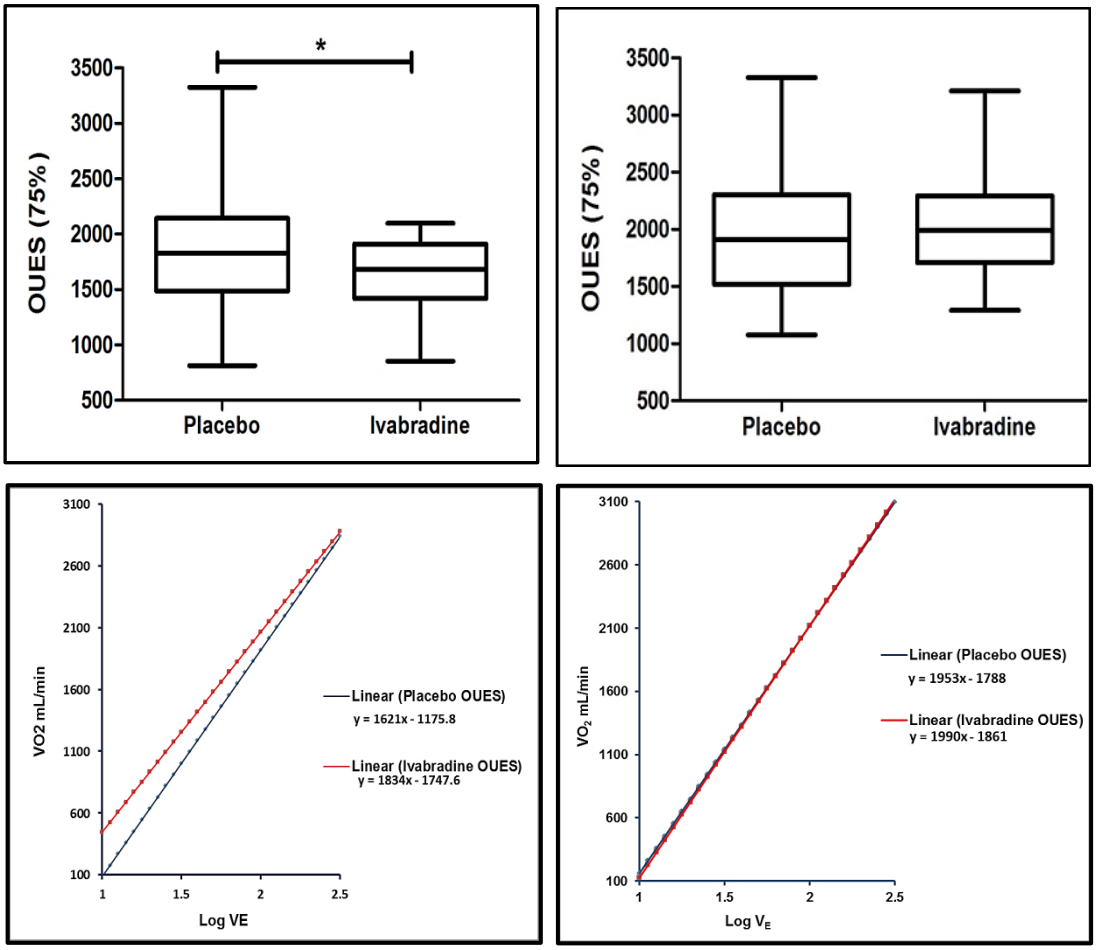
	Placebo (n = 22)	Ivabradine (n = 22)
Heart rate, beats/min (rest)	74 ± 14	61 ± 11
Heart rate, beats/min (exercise)	145 ± 21	127 ± 23
Systolic BP, mmHg	136 ± 19	144 ± 14
Diastolic BP, mmHg	83 ± 13	75 ± 13
LV end-diastolic volume index (mL/m^2)	40.9 (28.4 – 55.0)	40.6 (34.7 – 58.0)
LA volume index (mL/m^2)	34.9 ± 14.1	40 ± 12.7
LV mass index (g/m^2)	85.7 ± 26.9	89.7 ± 24.1
E/A ratio	0.84 ± 0.18	0.93 ± 0.19
E wave deceleration time, ms	248 ± 56	269 ± 72
V_E/V_{CO2}	27.4 ± 3.4	29.2 ± 3.5
Anaerobic Threshold (mL/kg/min)	19.7 ± 5.9	19.4 ± 5.6
RER	1.2 ± 0.1	1.2 ± 0
OUES	1953 ± 511	1990 ± 447
MRI LV ejection fraction (%)	65.0 ± 6.6	68.0 ± 7.4
MRI LV end-diastolic volume index (mL/m^2)	60.7 ± 20.1	61.6 ± 21.5
MRI LV end-systolic volume index (mL/m^2)	24.5 ± 8.3	22.8 ± 8.6
MRI LV mass index (g/m^2)	101.0 ± 21.2	107.0 ± 20.3
MRS PCr/ATP ratio	1.81 ± 0.84	1.49 ± 0.69

Values are mean ± SD, percentages or median (quartiles 1 to 3). BP = blood pressure; LV = left ventricular; LA = left atrial; E = peak early diastolic mitral flow velocity; A = late diastolic mitral flow velocity; V_E/V_{CO2}, minute ventilation-carbon dioxide production ratio; RER = respiratory exchange ratio; OUES = oxygen uptake efficiency slope; MRI = Magnetic Resonance Imaging;

Supplemental Figure 1: Effect of Ivabradine on Selected Parameters of Exercise Performance in HFpEF and Asymptomatic Hypertensive Cohort



The figures above depict the change in $VO_{2\ peak}$ (mL/kg/min) from Placebo to Ivabradine in the HFpEF (left) and Hypertensive (right) cohorts (comparison is made between the $VO_{2\ peak}$ values at the end of each intervention arm).



The figures above show the effect of Placebo and Ivabradine on oxygen uptake efficiency slope (OUES) in the HFpEF (left) and Hypertensive (right) cohorts.

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