DOI: 10.1161/CIRCULATIONAHA.115.017119

The Effect of Selective Heart Rate Slowing in Heart Failure with Preserved Ejection Fraction

Running title: *Pal et al.; The Effect of Heart Rate Slowing in HFpEF*

Nikhil Pal, MBBS, MRCP[1]; Nadiya Sivaswamy, MD[2]; Masliza Mahmod, MRCP, DPhil[1]; Arash Yavari, MRCP, DPhil[1]; Amelia Rudd, HND[2]; Satnam Singh MBBS, MRCP[2]; Dana K. Dawson, DM, DPhil[2]; Jane M. Francis, DCR(R)[1]; Jeremy S. Dwight, MD, FRCP[1]; Hugh Watkins, MD, PhD, FRCP, FMedSci[1]; Stefan Neubauer, MD, FRCP, FACC, FMedSci[1]; Michael Frenneaux, PhD, FRCP, FMedSci[3 *]; Houman Ashrafian, MA, DPhil, MRCP[1 *]

[1]Division of Cardiovascular Medicine, Radcliffe Department of Medicine, John Radcliffe Hospital, Oxford; [2]School of Medicine and Dentistry, University of Aberdeen, Aberdeen; [3]Norwich Medical School, University of East Anglia, Norwich, United Kingdom

*contributed equally

Address for Correspondence:
Houman Ashrafian, MA, DPhil, MRCP
Experimental Therapeutics, Radcliffe Department of Medicine
University of Oxford, John Radcliffe Hospital
Oxford, OX3 9DU, United Kingdom
Tel: 0044 1865 234 670
Fax: 0044 1865 234658
E-mail: houman.ashrafian@cardiov.ox.ac.uk

Journal Subject Term: Other heart failure

DOI: 10.1161/CIRCULATIONAHA.115.017119

Abstract

***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 randomised, 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, $VO_{2\ peak}$, <80% predicted for age and sex). The result was compared to 22 similarly treated matched asymptomatic hypertensive volunteers. The primary end point was the change in $VO_{2\ peak}$. Secondary outcomes included tissue Doppler derived E/e' at echocardiography, plasma BNP and quality of life scores. Ivabradine significantly reduced peak heart rate compared to placebo in the HFpEF (107 vs. 129 bpm, P<0.0001) and Hypertensive (127 vs. 145 bpm, P=0.003) cohorts. Ivabradine, when compared to placebo, significantly worsened the change in $VO_{2\ peak}$ in the HFpEF cohort (-2.1 vs 0.9 mL/kg/min, P=0.003) and significantly reduced submaximal exercise capacity, as determined by the oxygen uptake efficiency slope. No significant effects on the secondary endpoints were discernable.

***Conclusions*—**Our observations question the value of heart rate reduction, using ivabradine, for improving symptoms in a HFpEF population characterised by exercise limitation.

***Clinical Trial Registration Information*—**www.clinicaltrials.gov. Identifier: NCT02354573.

Key words: heart failure; heart rate; exercise

DOI: 10.1161/CIRCULATIONAHA.115.017119

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 with reduced EF (HFrEF)[1, 2, 4] and largely due to cardiovascular death.[4, 5] In contrast to HFrEF, despite the increasing prevalence and hospitalization rate,[2, 3] there are no proven therapies for HFpEF. The failure of multiple investigational therapies to influence survival or 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]

HFpEF has been conceptualised, 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 ejection fraction, and abnormally low skeletal muscle O_2 extraction.[11, 12] Given the critical contribution of diastole to ventricular filling and coronary perfusion, reduction of heart rate (HR), with a view to prolonging diastole, especially in atrial fibrillation has been advocated as a therapeutic strategy to mitigate symptoms in HFpEF[13] and endorsed by guidelines.[14] However, increased HR 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 (CO) 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 HR reduction improves exercise tolerance as assessed by peak oxygen consumption ($VO_{2\ peak}$).

DOI: 10.1161/CIRCULATIONAHA.115.017119

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. In order 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

Detailed methods are included in the Supplement.

Study Design

We undertook a prospective, double-blind, placebo-controlled, randomised crossover trial at two 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 $VO_{2\,peak}$ 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 in Oxford (South Central). All participants provided written informed consent to study.

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 to age- and gender-predicted normal values.

HFpEF was defined according to: the presence of both symptoms and signs of HF and EF ≥ 50%, a non-dilated left ventricle (LV) and relevant structural heart disease in the form of left ventricular hypertrophy (LVH), left atrial (LA) enlargement and/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 due to breathlessness or fatigue and objective evidence of exercise limitation as a measured $VO_{2\ peak}$ 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 (MLHFQ),[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 two-year period from December 2011 through January 2014 (**Figure 1**). Of these, 30 patients were found 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: one patient did not complete the study and dropped out during the second visit and the other was excluded due to sub-optimal exercise testing based on a respiratory exchange ratio of 0.81 during their second visit. 22 asymptomatic hypertensive patients consented and

participated in the study and were all included in the final analysis. In line with existing trial protocols of ivabradine in HFrEF aiming for a heart rate target of 50-60 beats per minute,[27, 28] eligible participants were randomly assigned using block randomisation 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 (CMR) 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 $VO_{2\ peak}$. Secondary end points were changes in: Doppler derived E/e', BNP (Brain natriuretic peptide) levels and quality of life assessed by the MLHFQ.

Statistical Analysis

For a crossover study design, power calculation indicated that to detect a mean absolute difference in VO_2 peak of 2.5mL/kg/min (SD of 2.5 mL/kg/min); 22 patients could provide a 90% power at an overall two sided alpha 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 two-tailed Student's t-test. The comparisons between ivabradine and placebo treatments within patient groups were assessed by two-tailed paired Student's t-test. All statistical analyses were performed with the use of SPSS Statistics, version 19 (IBM). A P value of 0.05 or less, using a two-tailed test, was considered statistically significant.

Results

Baseline Clinical Characteristics

Baseline clinical characteristics of the patients are shown in **Table 1**. In comparison to the hypertensive group, the patients with HFpEF were older (74.6 vs. 66.9 years, P=0.0001), more likely to be female (65 percent vs. 23 percent, P= 0.014) and had a lower proportion of hypertension (50 percent vs. 100 percent, 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 percent vs. 5 percent in the HFpEF cohort, P=0.0006). 3 HFpEF patients, but no hypertensive individuals, were taking beta-blockers (P=0.23). All HFpEF patients, but none in the hypertension group, scored significantly on the MLHFQ at baseline. There were no differences in resting plasma BNP. The baseline echocardiographic characteristics of HFpEF patients are shown in **supplementary Table 1**.

Response to Exercise

Cardiopulmonary exercise testing of HFpEF patients at baseline revealed a significantly lower: $VO_{2\ peak}$ (16.1 vs. 27.0 mL/kg/min, P<0.0001) (despite satisfactory effort indicated by a respiratory exchange ratio > 1.0), anaerobic threshold (11.5 vs. 20.6 mL/kg/min, P<0.0001) and maximal workload achieved (4.5 vs. 7.7 metabolic equivalents, METS, P<0.0001), compared to the hypertensive group, but an increased ventilatory response to exercise, as indicated by a higher minute ventilation-carbon dioxide production ratio (V_E/V_{CO2}) (**Table 2**). Despite being asymptomatic, the hypertensive cohort had $VO_{2\ peak}$ values that were below mean age- and gender-predicted normal values (28.0 mL/kg/min). HFpEF patients had marked chronotropic dysfunction with lower peak exercise heart rates (129 vs. 145 bpm, P<0.0001).

Selective Heart Rate Lowering with Ivabradine in HFpEF Cohort

Table 3 (and **supplementary Table 2**) shows the comparison of ivabradine versus placebo on resting haemodynamic, cardiac imaging and exercise parameters in the HFpEF cohort. Ivabradine reduced mean resting heart rate by 20 beats per minute (77 to 57, P<0.0001) without any effect on blood pressure or left ventricular ejection fraction. Similarly, ivabradine treatment reduced the chronotropic response to exercise (peak heart rate 129 vs. 107 beats/minute, 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 VO_2 peak), with a diminution in the $VO_{2\ peak}$ from 15.9 to 14.8 mL/kg/min (P=0.003), without significantly affecting $V_E/V_{CO2\ slope}$ or anaerobic threshold. Moreover, a paired comparison of the changes in VO_2 peak resulting from the 2-week intervention blocks demonstrated a consonant lowering in the ivabradine group (-2.1 vs. 0.9 ml/kg/min, P=0.003) (**Figure 2**). Compared to placebo, ivabradine treatment induced small, but significant, increases in transmitral E/A ratio (0.6 vs. 0.65, P=0.026) and mean e' velocity (4.5 vs. 5.4 cm/s, P=0.002), with no effect on the E/e' ratio, myocardial phosphocreatine to adenosine triphosphate ratios or symptomatic status (MLHFQ - **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 (**Supplement Table 2** and **Supplement Figure 1**). OUES is a submaximal measure of cardiorespiratory reserve less sensitive to exercise duration and has strong prognostic value in HF.[29] Compared to placebo, an assessment of the OUES at 75% of the duration of exercise identified a significant reduction with ivabradine (1834 vs. 1621 [mL/min O_2]/[L/min V_E], P=0.04).

Selective Heart Rate Lowering with Ivabradine in Asymptomatic Hypertensive Cohort

As with the HFpEF group, administration of ivabradine at 7.5 mg twice daily significantly reduced resting heart rate compared to placebo (from 74 to 61 beats/minute, P=0.001). Peak exercise heart rate was blunted by ivabradine use (145 vs. 127 beats/minute, P=0.003). Ivabradine use was associated with a statistically non-significant reduction in the primary end point, $VO_{2\ peak}$ (26 vs. 24.5 mL/kg/min, P=0.47) (**Table 4** and **supplementary Table 3**). Compared to placebo, ivabradine treatment was associated with a small but significant increase in the V_E/V_{CO2} ratio (27.4 vs. 29.2, P=0.004), but did not affect anaerobic threshold or peak workload.

Discussion

We undertook a short term, placebo-controlled, randomised cross-over study examining the effect of selective heart rate lowering using 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 two weeks of heart rate reduction using ivabradine at a dose of 7.5mg twice daily in patients with HFpEF almost uniformly exacerbated already abnormal exercise physiology, resulting in a significant reduction in the primary end point, $VO_{2\ peak}$.

Consistent with previous reports,[16-19] our cohort of HFpEF patients had poor exercise tolerance, a significantly impaired peak oxygen uptake, low VO_2 at anaerobic threshold, increased ventilatory response and a reduction of the chronotropic response to exercise. Cognisant of the broader pathogenesis of HFpEF, including prominent defects in skeletal muscle metabolism,[11, 12] our patients with HFpEF were not diagnosed based on resting diastolic dysfunction, but rather on the basis of subjective exercise limitation with normal LV EF and absence of significant valvular disease together with objective exercise limitation. In the

TOPCAT study, of 935 patients with HFpEF, diastolic function was normal in ~ 1/3 of gradable participants.[30] We too have observed a poor agreement between exercise E/E', cardiopulmonary exercise testing (CPEX) categorisation and current criteria based on resting diastolic function.[31] We and others have found that HFpEF is characterised by dynamic disturbances of LV active relaxation during exercise.[32-34] Furthermore, plasma BNP is often relatively normal at rest in HFpEF, especially those with a raised BMI in whom BNP appears to be suppressed, but rises dramatically on exercise (unpublished data).[31, 34, 35]

The choice of peak oxygen uptake at maximal exercise ($VO_{2\ peak}$) as the primary end point in this study is supported by its objective measurement of cardiac reserve, robust correlation with survival[36] and the difficulties in obtaining a true maximal oxygen uptake ($VO_{2\ max}$), which relies on exercise to absolute exhaustion with plateauing of oxygen uptake despite continued exercise.[29] In common with $VO_{2\ max}$, $VO_{2\ peak}$ 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 which result in symptoms in HF patients. To address this possibility, we also evaluated a measure of submaximal cardiopulmonary reserve – the OUES – whose value has, unlike VO_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 (PCr/ATP ratio) 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 asymmetric. Moreover, the observation that despite ameliorating some measures of cardiac filling (e.g. e'), heart rate reduction almost uniformly adversely impacts on exercise tolerance, highlights the need for a broader conceptualisation 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 following short-term treatment with ivabradine. The reason(s) underlying the discrepancy with the current 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 beats/minute) which did not appear to affect peak heart rate response to exercise and perhaps study design (non-crossover). Our patients, being older, 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 hospitalisation. However, the significant and consistent reduction in multiple metabolic stress testing parameters linked to mortality in HF, including reduced $VO_{2\ peak}$, raised V_E/V_{CO2}, [39] low chronotropic response[39] and reduced OUES,[29]

suggest 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 SIGNIFY 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 (e.g. □-adrenergic blockade) may confer similar or more profound adverse effects in HFpEF, due to their impact on heart rate and exercise dependant ventricular lusitropy.[41]

The following represent potential limitations of our study: i) The sample size studied was small, but the treatment was not found to be beneficial in either of the two groups. Importantly, in this crossover study, we observed no evidence of a carryover or period effects; the washout period of 2 weeks (336hrs) exceeds the biological half-life of ivabradine (2hrs). Nevertheless, the study needs to be replicated in a larger clinical trial examining a well-defined homogenous cohort powered to look at mortality and morbidity end points that may support this and point to alternative strategies to improve exercise intolerance. ii) 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.

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

Acknowledgments: Professor Houman Ashrafian acknowledges support from the BHF Centre of Research Excellence, Oxford. The research was also supported by the National Institute for Health Research (NIHR) Oxford Biomedical Research Centre Programme. This research has been funded/supported by the National Institute for Health Research Rare Diseases Translational Research Collaboration (NIHR RD-TRC). The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health.

Funding Sources: The study was funded by a project grant from the Chest Heart and Stroke Society. M. Mahmod, S Neubauer and H. Ashrafian are supported by the National Institute for Health Research (NIHR) Oxford Biomedical Research Centre based at The Oxford University Hospitals Trust at the University of Oxford. A. Yavari is supported by the UK Department of Health's National Institute for Health Research.

Conflict of Interest Disclosures: None.

References:

1. Bhatia RS, Tu JV, Lee DS, Austin PC, Fang J, Haouzi A, Gong Y, Liu PP. Outcome of heart failure with preserved ejection fraction in a population-based study. *N Engl J Med*. 2006;355:260-269.

2. Owan TE, Hodge DO, Herges RM, Jacobsen SJ, Roger VL, Redfield MM. Trends in prevalence and outcome of heart failure with preserved ejection fraction. *N Engl J Med*. 2006;355:251-259.

3. Steinberg BA, Zhao X, Heidenreich PA, Peterson ED, Bhatt DL, Cannon CP, Hernandez AF, Fonarow GC. Trends in Patients Hospitalized With Heart Failure and Preserved Left Ventricular Ejection Fraction: Prevalence, Therapies, and Outcomes. *Circulation*. 2012;126:65-75.

4. Tribouilloy C, Rusinaru D, Mahjoub H, Souliere V, Levy F, Peltier M, Slama M, Massy Z. Prognosis of heart failure with preserved ejection fraction: a 5 year prospective population-based study. *Eur Heart J*. 2008;29:339-347.

5. Zile MR, Gaasch WH, Anand IS, Haass M, Little WC, Miller AB, Lopez-Sendon J, Teerlink JR, White M, McMurray JJ, Komajda M, McKelvie R, Ptaszynska A, Hetzel SJ, Massie BM, Carson PE, Investigators IP. Mode of death in patients with heart failure and a preserved ejection fraction: results from the Irbesartan in Heart Failure With Preserved Ejection Fraction Study (I-Preserve) trial. *Circulation*. 2010;121:1393-1405.

6. Yusuf S, Pfeffer MA, Swedberg K, Granger CB, Held P, McMurray JJ, Michelson EL, Olofsson B, Ostergren J, Investigators C, Committees. Effects of candesartan in patients with chronic heart failure and preserved left-ventricular ejection fraction: the CHARM-Preserved Trial. *Lancet*. 2003;362:777-781.

7. Massie BM, Carson PE, McMurray JJ, Komajda M, McKelvie R, Zile MR, Anderson S, Donovan M, Iverson E, Staiger C, Ptaszynska A, Investigators IP. Irbesartan in patients with heart failure and preserved ejection fraction. *N Engl J Med*. 2008;359:2456-2467.

8. Pitt B, Pfeffer MA, Assmann SF, Boineau R, Anand IS, Claggett B, Clausell N, Desai AS,

Diaz R, Fleg JL, Gordeev I, Harty B, Heitner JF, Kenwood CT, Lewis EF, O'Meara E, Probstfield JL, Shaburishvili T, Shah SJ, Solomon SD, Sweitzer NK, Yang S, McKinlay SM, Investigators T. Spironolactone for heart failure with preserved ejection fraction. *N Engl J Med*. 2014;370:1383-1392.

9. Kristensen SL, Kober L, Jhund PS, Solomon SD, Kjekshus J, McKelvie RS, Zile MR, Granger CB, Wikstrand J, Komajda M, Carson PE, Pfeffer MA, Swedberg K, Wedel H, Yusuf S, McMurray JJ. International geographic variation in event rates in trials of heart failure with preserved and reduced ejection fraction. *Circulation*. 2015;131:43-53.

10. Zile MR, Baicu CF, Gaasch WH. Diastolic heart failure--abnormalities in active relaxation and passive stiffness of the left ventricle. *N Engl J Med*. 2004;350:1953-1959.

11. Haykowsky MJ, Brubaker PH, John JM, Stewart KP, Morgan TM, Kitzman DW. Determinants of Exercise Intolerance in Elderly Heart Failure Patients With Preserved Ejection Fraction. *J Am Coll Cardiol*. 2011;58:265-274.

12. Dhakal BP, Malhotra R, Murphy RM, Pappagianopoulos PP, Baggish AL, Weiner RB, Houstis NE, Eisman AS, Hough SS and Lewis GD. Mechanisms of Exercise Intolerance in Heart Failure With Preserved Ejection Fraction: The Role of Abnormal Peripheral Oxygen Extraction. *Circ Heart Fail*. 2015;8:286-294.

13. Kosmala W, Holland DJ, Rojek A, Wright L, Przewlocka-Kosmala M, Marwick TH. Effect of If-channel inhibition on hemodynamic status and exercise tolerance in heart failure with preserved ejection fraction: a randomized trial. *J Am Coll Cardiol*. 2013;62:1330-1338.

14. Hunt SA, Abraham WT, Chin MH, Feldman AM, Francis GS, Ganiats TG, Jessup M, Konstam MA, Mancini DM, Michl K, Oates JA, Rahko PS, Silver MA, Stevenson LW, Yancy CW. 2009 focused update incorporated into the ACC/AHA 2005 Guidelines for the Diagnosis and Management of Heart Failure in Adults: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines: developed in collaboration with the International Society for Heart and Lung Transplantation. *Circulation*. 2009;119:e391-479.

15. Higginbotham MB, Morris KG, Williams RS, McHale PA, Coleman RE, Cobb FR. Regulation of stroke volume during submaximal and maximal upright exercise in normal man. *Circ Res*. 1986;58:281-291.

16. Borlaug BA, Melenovsky V, Russell SD, Kessler K, Pacak K, Becker LC, Kass DA. Impaired chronotropic and vasodilator reserves limit exercise capacity in patients with heart failure and a preserved ejection fraction. *Circulation*. 2006;114:2138-2147.

17. Brubaker PH, Joo KC, Stewart KP, Fray B, Moore B, Kitzman DW. Chronotropic incompetence and its contribution to exercise intolerance in older heart failure patients. *J Cardiopulm Rehabil*. 2006;26:86-89.

18. Phan TT, Shivu GN, Abozguia K, Davies C, Nassimizadeh M, Jimenez D, Weaver R, Ahmed I, Frenneaux M. Impaired heart rate recovery and chronotropic incompetence in patients with heart failure with preserved ejection fraction. *Circ Heart Fail*. 2010;3:29-34.

19. Abudiab MM, Redfield MM, Melenovsky V, Olson TP, Kass DA, Johnson BD, Borlaug BA. Cardiac output response to exercise in relation to metabolic demand in heart failure with preserved ejection fraction. *Eur J Heart Fail*. 2013;15:776-785.

20. DiFrancesco D. The role of the funny current in pacemaker activity. *Circ Res*. 2010;106:434-446.

21. Senni M, Paulus WJ, Gavazzi A, Fraser AG, Díez J, Solomon SD, Smiseth OA, Guazzi M, Lam CSP, Maggioni AP, Tschöpe C, Metra M, Hummel SL, Edelmann F, Ambrosio G, Stewart Coats AJ, Filippatos GS, Gheorghiade M, Anker SD, Levy D, Pfeffer MA, Stough WG, Pieske BM. New strategies for heart failure with preserved ejection fraction: the importance of targeted therapies for heart failure phenotypes. *Eur Heart J*. 2014;35:2797-2815.

22. Edelmann F, Wachter R, Schmidt AG, Kraigher-Krainer E, Colantonio C, Kamke W, Duvinage A, Stahrenberg R, Durstewitz K, Loffler M, Dungen HD, Tschope C, Herrmann-Lingen C, Halle M, Hasenfuss G, Gelbrich G, Pieske B, Aldo DHFI. Effect of spironolactone on diastolic function and exercise capacity in patients with heart failure with preserved ejection fraction: the Aldo-DHF randomized controlled trial. *JAMA*. 2013;309:781-791.

23. McMurray JJ, Adamopoulos S, Anker SD, Auricchio A, Bohm M, Dickstein K, Falk V, Filippatos G, Fonseca C, Gomez-Sanchez MA, Jaarsma T, Kober L, Lip GY, Maggioni AP, Parkhomenko A, Pieske BM, Popescu BA, Ronnevik PK, Rutten FH, Schwitter J, Seferovic P, Stepinska J, Trindade PT, Voors AA, Zannad F, Zeiher A, Guidelines ESCCfP. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. *Eur Heart J*. 2012;33:1787-1847.

24. ATS/ACCP Statement on Cardiopulmonary Exercise Testing. *Am J Resp Crit Care Med*. 2003;167:211-277.

25. Edelmann F, Wachter R, Pieske B. ALdosterone inhibition in patients with heart failure with preserved ejection fraction—reply. *JAMA*. 2013;310:205-207.

26. Garin O, Ferrer M, Pont A, Rue M, Kotzeva A, Wiklund I, Van Ganse E, Alonso J. Disease-specific health-related quality of life questionnaires for heart failure: a systematic review with meta-analyses. *Qual Life Res*. 2009;18:71-85.

27. Swedberg K, Komajda M, Böhm M, Borer JS, Ford I, Dubost-Brama A, Lerebours G, Tavazzi L. Ivabradine and outcomes in chronic heart failure (SHIFT): a randomised placebo-controlled study. *Lancet*. 2010;376:875-885.

28. Fox K, Ford I, Steg PG, Tendera M, Ferrari R. Ivabradine for patients with stable coronary artery disease and left-ventricular systolic dysfunction (BEAUTIFUL): a randomised, double-blind, placebo-controlled trial. *Lancet*. 2008;372:807-816.

29. Baba R, Nagashima M, Goto M, Nagano Y, Yokota M, Tauchi N, Nishibata K. Oxygen uptake efficiency slope: a new index of cardiorespiratory functional reserve derived from the relation between oxygen uptake and minute ventilation during incremental exercise. *J Am Coll Cardiol*. 1996;28:1567-1572.

30. Shah AM, Claggett B, Sweitzer NK, Shah SJ, Anand IS, O'Meara E, Desai AS, Heitner JF, Li G, Fang J, Rouleau J, Zile MR, Markov V, Ryabov V, Reis G, Assmann SF, McKinlay SM, Pitt B, Pfeffer MA, Solomon SD. Cardiac Structure and Function and Prognosis in Heart Failure With Preserved Ejection Fraction: Findings From the Echocardiographic Study of the Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist (TOPCAT) Trial. *Circ Heart Fail*. 2014;7:740-751.

31. Mahadevan G, Dwivedi G, Jiminez D, Williams L, Frenneaux MP. How valid are the European Society of Cardiology echocardiographic diastolic criteria in diagnosing heart failure with normal ejection fraction? *Eur Heart J*. 2011;32:778-778.

32. Phan TT, Abozguia K, Nallur Shivu G, Mahadevan G, Ahmed I, Williams L, Dwivedi G, Patel K, Steendijk P, Ashrafian H, Henning A, Frenneaux M. Heart failure with preserved ejection fraction is characterized by dynamic impairment of active relaxation and contraction of the left ventricle on exercise and associated with myocardial energy deficiency. *J Am Coll Cardiol*. 2009;54:402-409.

33. Borlaug BA, Jaber WA, Ommen SR, Lam CSP, Redfield MM, Nishimura RA. Diastolic relaxation and compliance reserve during dynamic exercise in heart failure with preserved ejection fraction. *Heart*. 2011;97:964-969.

34. Borlaug BA, Nishimura RA, Sorajja P, Lam CSP, Redfield MM. Exercise Hemodynamics Enhance Diagnosis of Early Heart Failure With Preserved Ejection Fraction. *Circ Heart Fail*. 2010;3:588-595.

35. Anjan VY, Loftus TM, Burke MA, Akhter N, Fonarow GC, Gheorghiade M, Shah SJ. Prevalence, Clinical Phenotype, and Outcomes Associated With Normal B-Type Natriuretic Peptide Levels in Heart Failure With Preserved Ejection Fraction. *Am J Cardiol*. 2012;110:870-876.

36. Mancini DM, Eisen H, Kussmaul W, Mull R, Edmunds LH, Jr., Wilson JR. Value of peak exercise oxygen consumption for optimal timing of cardiac transplantation in ambulatory patients with heart failure. *Circulation*. 1991;83:778-786.

37. Nagayama T, Takimoto E, Sadayappan S, Mudd JO, Seidman JG, Robbins J, Kass DA. Control of in vivo left ventricular [correction] contraction/relaxation kinetics by myosin binding protein C: protein kinase A phosphorylation dependent and independent regulation. *Circulation*.

2007;116:2399-2408.

38. Borlaug BA. The pathophysiology of heart failure with preserved ejection fraction. *Nat Rev Cardiol*. 2014;11:507-515.

39. Robbins M, Francis G, Pashkow FJ, Snader CE, Hoercher K, Young JB, Lauer MS. Ventilatory and heart rate responses to exercise : better predictors of heart failure mortality than peak oxygen consumption. *Circulation*. 1999;100:2411-2417.

40. Fox K, Ford I, Steg PG, Tardif JC, Tendera M, Ferrari R, Investigators S. Ivabradine in stable coronary artery disease without clinical heart failure. *N Engl J Med*. 2014;371:1091-1099.

41. Cheng CP, Igarashi Y, Little WC. Mechanism of augmented rate of left ventricular filling during exercise. *Circ Res*. 1992;70:9-19.

DOI: 10.1161/CIRCULATIONAHA.115.017119

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

	HFpEF (n = 22)	Hypertensive (n = 22)	p Value
Age (years)	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 I	-	22 (100)	
NYHA II	22 (100)	–	
Past medical history, n (%)			
Hypertension	11 (50)	22 (100)	0 .0002
Diabetes	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
Beta-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 to 3). ACE = angiotensin-converting enzyme-inhibitors; ARB = angiotensin-receptor antagonist-II; BNP = brain natriuretic peptide.

DOI: 10.1161/CIRCULATIONAHA.115.017119

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, beats/min (rest)	75 ± 12	78 ± 14	0.36
Heart rate, beats/min (peak)	127 ± 19	159 ± 14	< 0.0001
Systolic BP, mmHg	148 ± 19	147 ± 7	0.91
Diastolic BP, mmHg	83 ± 6	82 ± 12	0.82
$VO_{2\ peak}$ (mL/kg/min)	16.1 (15.0 – 18.2)	27.0 (22.5 – 31.2)	< 0.0001
Percentage of predicted VO_2 max (%)	66	96	0.009
V_E/V_{CO2}	34.4 ± 6.1	27.3 ± 3.4	< 0.0001
Anaerobic Threshold (mL/kg/min)	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 to 3). BP = blood pressure; V_E/V_{CO2}, minute ventilation-carbon dioxide production ratio; RER, respiratory exchange ratio; METS = Metabolic Equivalents.

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 $VO_{2\ peak}$ (mL/kg/min) during each arm of treatment	0.9 (-0.6 – 2.1)	-2.1 (-2.9 – 0)	0.003
$VO_{2\ peak}$ (mL/kg/min)	15.9 (14.9 - 18.4)	14.8 (13 – 17.4)	0.003
LV ejection fraction (%)	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 to 3). LV = left ventricular; e' = peak early diastolic mitral annular velocity; MRI = Magnetic Resonance Imaging; MRS = Magnetic Resonance Spectroscopy, PCr/ATP ratio = Phosphocreatine-to-ATP ratio.

DOI: 10.1161/CIRCULATIONAHA.115.017119

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 $VO_{2\ peak}$ (mL/kg/min) during each arm of treatment	1 (-1 – 4)	-1.5 (-5.3 – 1)	0.08
$VO_{2\ peak}$ (mL/kg/min)	26 (21 – 29)	24.5 (21.5 – 29.5)	0.47
LV ejection fraction (%)	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 1 to 3). BP = blood pressure; LV = left ventricular; e' = peak early diastolic mitral annular velocity; MRI = Magnetic Resonance Imaging; MRS = Magnetic Resonance Spectroscopy, PCr/ATP ratio = Phosphocreatine-to-ATP ratio.

Figure Legends:

Figure 1. Flow diagram of the Study.

Figure 2. Effect of Ivabradine on $VO_{2\ peak}$ in HFpEF cohort. Depicts the change in $VO_{2\ peak}$ (mL/kg/min) with Placebo (left) and Ivabradine (right) (Ivabradine vs placebo P=0.003), in the HFpEF cohort.

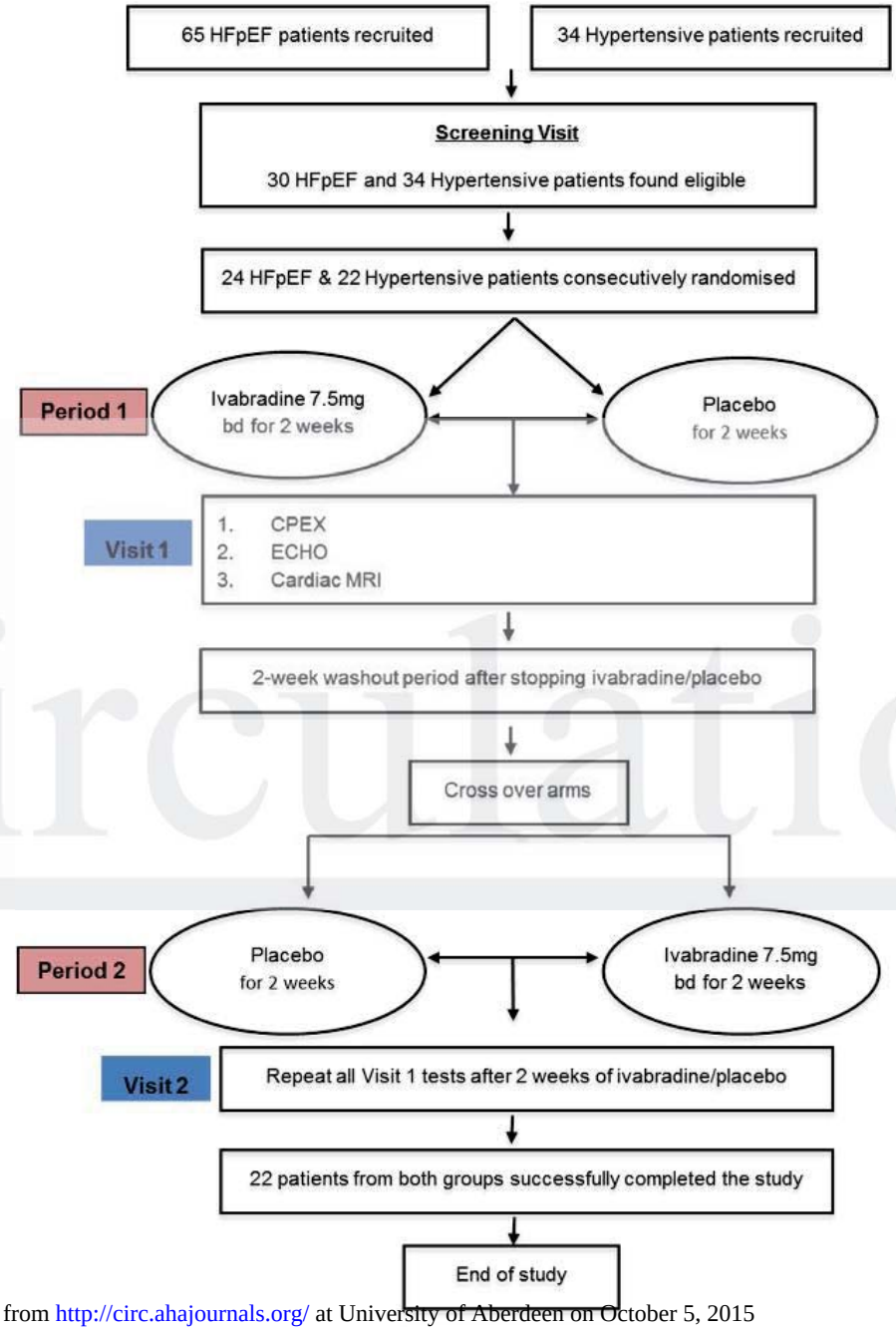
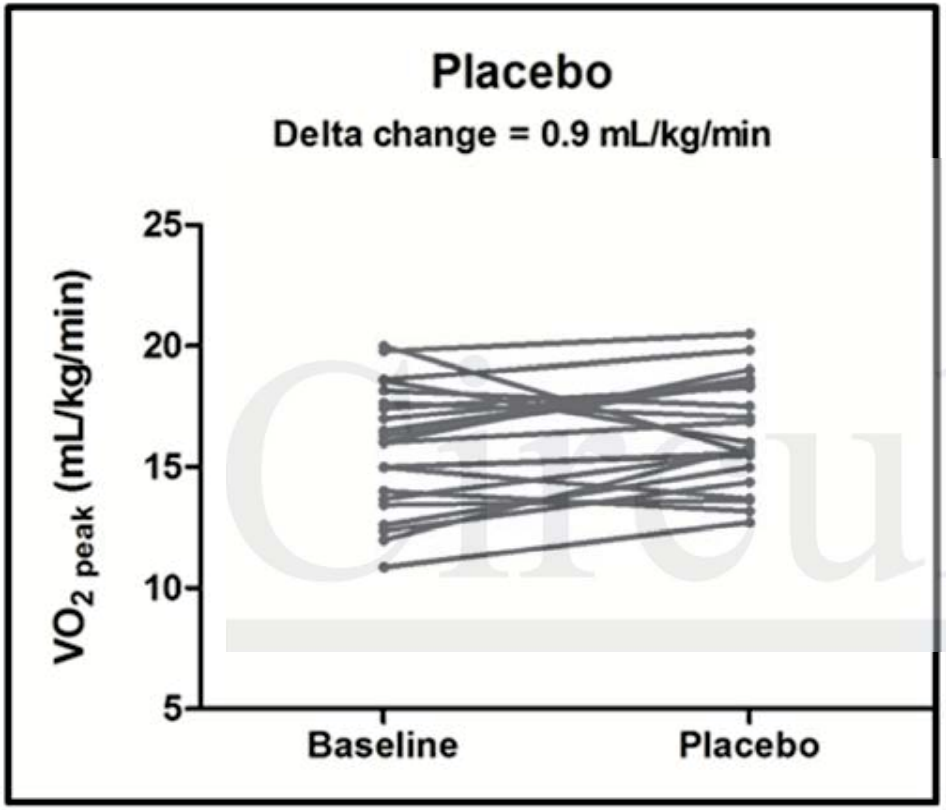


Figure 1



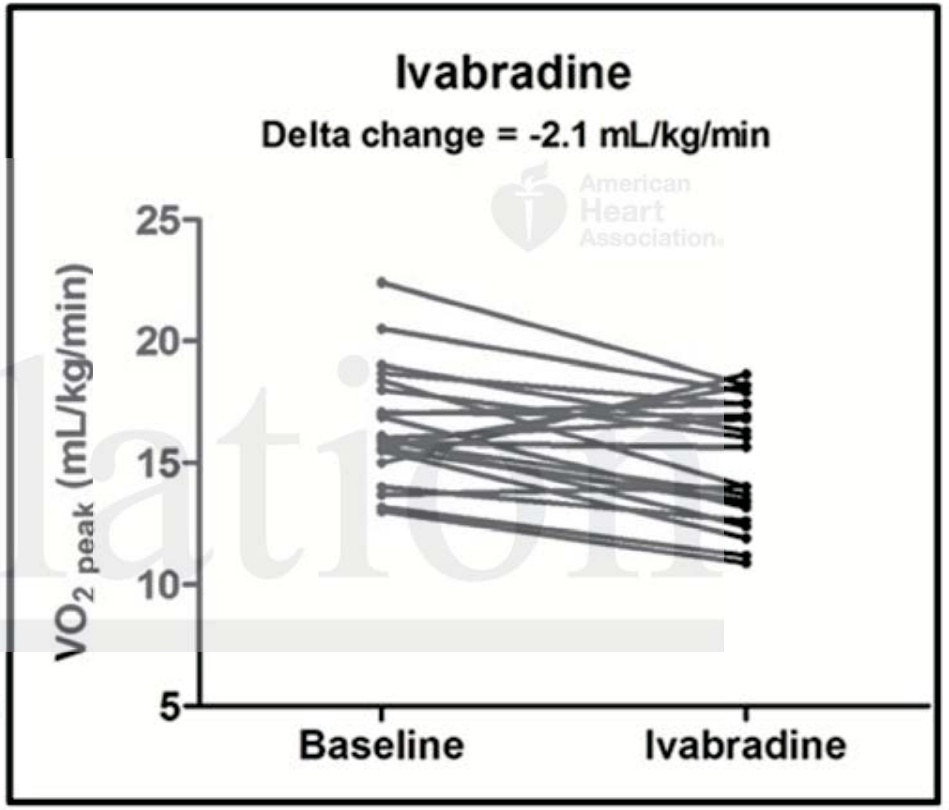


Figure 2

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

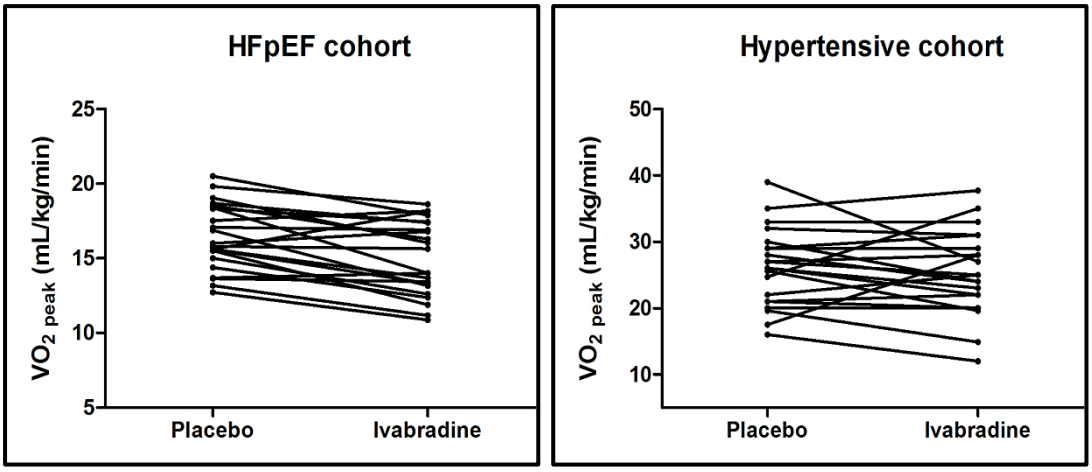
Values are mean ± SD, percentages or median (quartiles 1 to 3). BP = blood pressure; LV = left ventricular; LA = left atrial; E = peak early diastolic mitral flow velocity; A = late diastolic mitral flow velocity; V_E/V_{CO2} = minute ventilation-carbon dioxide production ratio; RER = respiratory exchange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

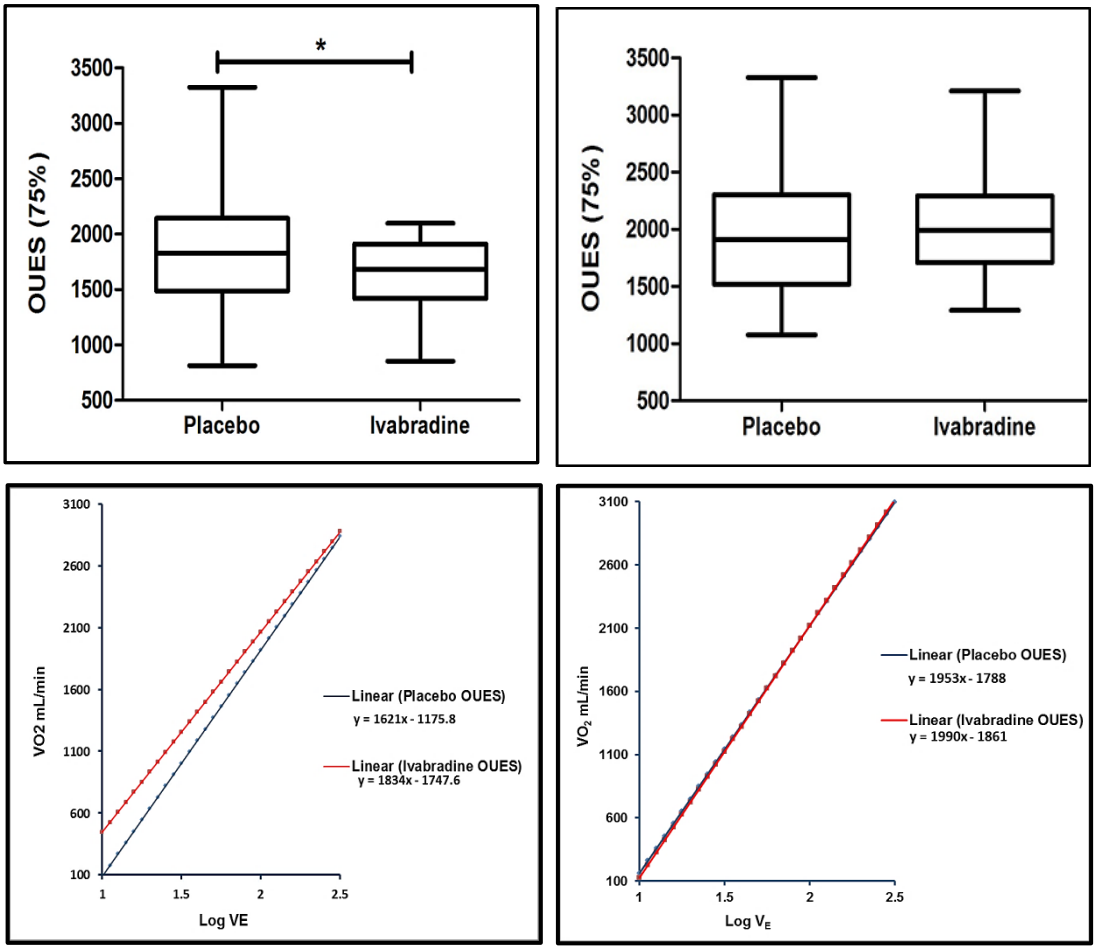
	Placebo (n = 22)	Ivabradine (n = 22)
Heart rate, beats/min (rest)	74 ± 14	61 ± 11
Heart rate, beats/min (exercise)	145 ± 21	127 ± 23
Systolic BP, mmHg	136 ± 19	144 ± 14
Diastolic BP, mmHg	83 ± 13	75 ± 13
LV end-diastolic volume index (mL/m^2)	40.9 (28.4 – 55.0)	40.6 (34.7 – 58.0)
LA volume index (mL/m^2)	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.

SUPPLEMENTAL REFRENCES

1. Evangelista A, Flachskampf F, Lancellotti P, Badano L, Aguilar R, Monaghan M, Zamorano J, Nihoyannopoulos P and European Association of E. European Association of Echocardiography recommendations for standardization of performance, digital storage and reporting of echocardiographic studies. *European journal of echocardiography : the journal of the Working Group on Echocardiography of the European Society of Cardiology*. 2008;9:438-48.

2. Nagueh SF, Appleton CP, Gillebert TC, Marino PN, Oh JK, Smiseth OA, Waggoner AD, Flachskampf FA, Pellikka PA and Evangelista A. Recommendations for the evaluation of left ventricular diastolic function by echocardiography. *Journal of the American Society of Echocardiography : official publication of the American Society of Echocardiography*. 2009;22:107-33.

3. Phan TT, Abozguia K, Nallur Shivu G, Mahadevan G, Ahmed I, Williams L, Dwivedi G, Patel K, Steendijk P, Ashrafian H, Henning A and Frenneaux M. Heart failure with preserved ejection fraction is characterized by dynamic impairment of active relaxation and contraction of the left ventricle on exercise and associated with myocardial energy deficiency. *J Am Coll Cardiol*. 2009;54:402-9.

4. Phan TT, Shivu GN, Abozguia K, Davies C, Nassimizadeh M, Jimenez D, Weaver R, Ahmed I and Frenneaux M. Impaired heart rate recovery and chronotropic incompetence in patients with heart failure with preserved ejection fraction. *Circ Heart Fail*. 2010;3:29-34.

5. Baba R, Nagashima M, Goto M, Nagano Y, Yokota M, Tauchi N and Nishibata K. Oxygen uptake efficiency slope: a new index of cardiorespiratory functional reserve derived from the relation between oxygen uptake and minute ventilation during incremental exercise. *J Am Coll Cardiol*. 1996;28:1567-72.

The Effect of Selective Heart Rate Slowing in Heart Failure with Preserved Ejection Fraction

Houman Ashrafian, Nikhil Pal, Nadiya Sivaswamy, Masliza Mahmod, Arash Yavari, Amelia Rudd, Satnam Singh, Dana K. Dawson, Jane M. Francis, Jeremy S. Dwight, Hugh Watkins, Stefan Neubauer and Michael Frenneaux

Circulation. published online September 2, 2015;
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Print ISSN: 0009-7322. Online ISSN: 1524-4539