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

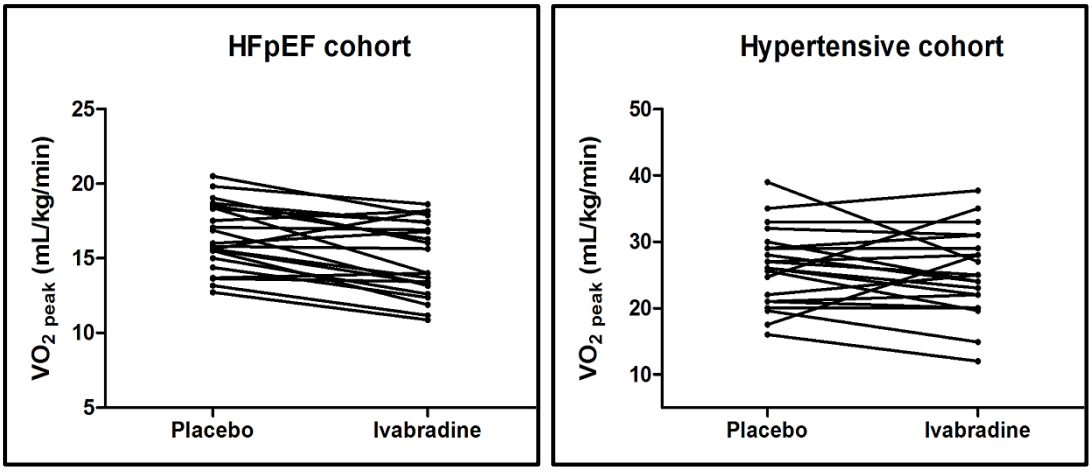
Values are mean ± SD, percentages or median (quartiles 1 to 3). BP = blood pressure; LV = left ventricular; LA = left atrial; E = peak early diastolic mitral flow velocity; A = late diastolic mitral flow velocity; V_E/V_{CO2} = minute ventilation-carbon dioxide production ratio; RER = respiratory exchange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

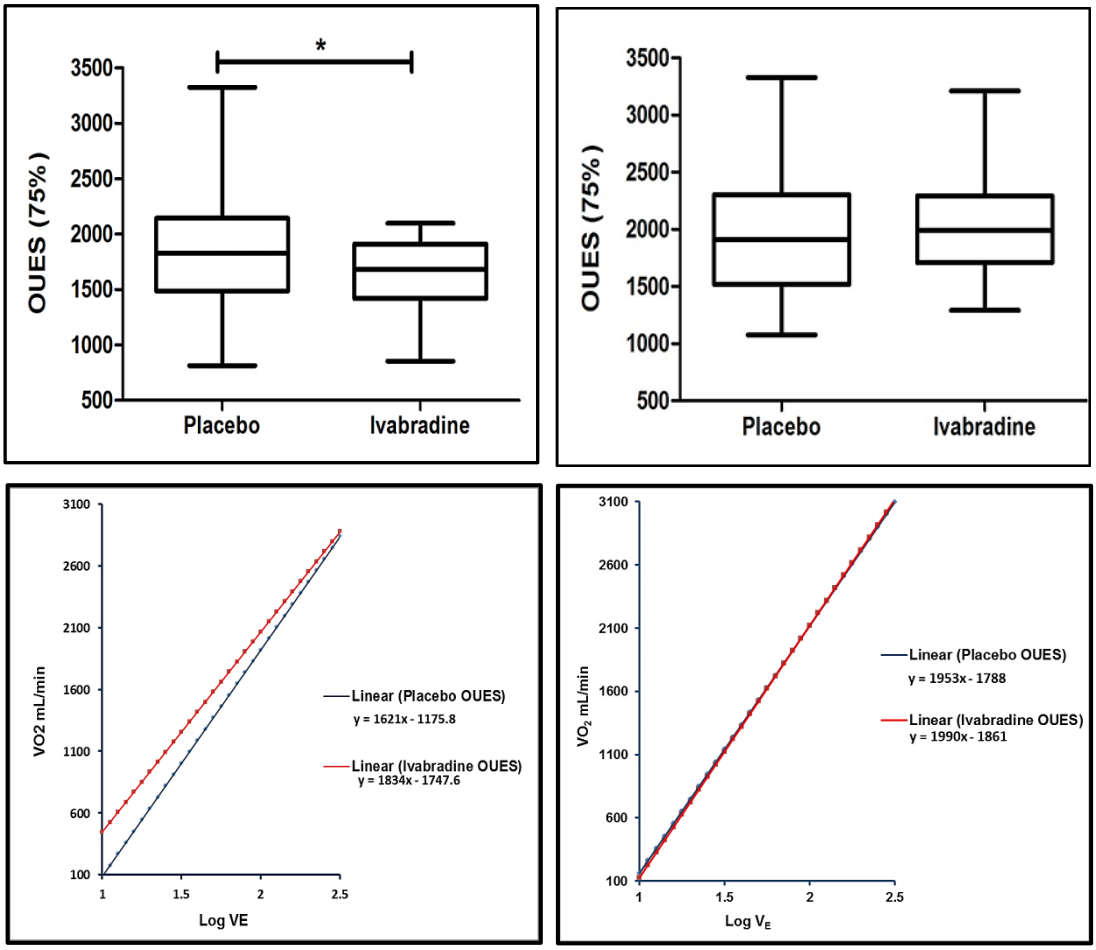
	Placebo (n = 22)	Ivabradine (n = 22)
Heart rate, beats/min (rest)	74 ± 14	61 ± 11
Heart rate, beats/min (exercise)	145 ± 21	127 ± 23
Systolic BP, mmHg	136 ± 19	144 ± 14
Diastolic BP, mmHg	83 ± 13	75 ± 13
LV end-diastolic volume index (mL/m^2)	40.9 (28.4 – 55.0)	40.6 (34.7 – 58.0)
LA volume index (mL/m^2)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