

# Effect of $I_f$ -Channel Inhibition on Hemodynamic Status and Exercise Tolerance in Heart Failure With Preserved Ejection Fraction

## A Randomized Trial

Wojciech Kosmala, MD, PhD,\* David J. Holland, PhD,† Aleksandra Rojek, MD,\* Leah Wright, BS,‡  
Monika Przewlocka-Kosmala, MD, PhD,\* Thomas H. Marwick, MD, PhD‡

*Wrocław, Poland; and Brisbane and Hobart, Australia*

- Objectives** The aim of this study was to test the effects of treatment with ivabradine on exercise capacity and left ventricular filling in patients with heart failure with preserved ejection fraction (HFpEF).
- Background** Because symptoms of HFpEF are typically exertional, optimization of diastolic filling time by controlling heart rate may delay the onset of symptoms.
- Methods** Sixty-one patients with HFpEF were randomly assigned to ivabradine 5 mg twice daily ( $n = 30$ ) or placebo ( $n = 31$ ) for 7 days in this double-blind trial. Cardiopulmonary exercise testing with echocardiographic assessment of myocardial function and left ventricular filling were undertaken at rest and after exercise.
- Results** The ivabradine group demonstrated significant improvement between baseline and follow-up exercise capacity ( $4.2 \pm 1.8$  METs vs.  $5.7 \pm 1.9$  METs,  $p = 0.001$ ) and peak oxygen uptake ( $14.0 \pm 6.1$  ml/min/kg vs.  $17.0 \pm 3.3$  ml/min/kg,  $p = 0.001$ ), with simultaneous reduction in exercise-induced increase in the ratio of peak early diastolic mitral flow velocity to peak early diastolic mitral annular velocity ( $3.1 \pm 2.7$  vs.  $1.3 \pm 2.0$ ,  $p = 0.004$ ). Work load-corrected chronotropic response (the difference in heart rate at the same exercise time at the baseline and follow-up tests) showed a slower increase in heart rate during exercise than in the placebo-treated group. Therapy with ivabradine ( $\beta = 0.34$ ,  $p = 0.04$ ) and change with treatment in exertional increase in the ratio of peak early diastolic mitral flow velocity to peak early diastolic mitral annular velocity ( $\beta = -0.30$ ,  $p = 0.02$ ) were independent correlates of increase in exercise capacity, and therapy with ivabradine ( $\beta = 0.32$ ,  $p = 0.007$ ) was independently correlated with increase in peak oxygen uptake.
- Conclusions** In patients with HFpEF, short-term treatment with ivabradine increased exercise capacity, with a contribution from improved left ventricular filling pressure response to exercise as reflected by the ratio of peak early diastolic mitral flow velocity to peak early diastolic mitral annular velocity. Because this patient population is symptomatic on exertion, therapeutic treatments targeting abnormal exercise hemodynamic status may prove useful. (Use of Exercise and Medical Therapies to Improve Cardiac Function Among Patients With Exertional Shortness of Breath Due to Lung Congestion; [ACTRN12610001087044](https://doi.org/10.1186/1745-2975-12-1087044)) (J Am Coll Cardiol 2013;62:1330-8) © 2013 by the American College of Cardiology Foundation

Patients with heart failure with preserved ejection fraction (HFpEF) are characterized by symptoms of dyspnea and exercise intolerance, both of which contribute to reduced quality of life in this population. This is a major health care problem, accounting for almost one-half of all cases of chronic cardiac insufficiency in large-scale community studies (1,2). Current therapeutic recommendations are to effectively

control the comorbidities associated with HFpEF, especially hypertension, diabetes, coronary artery disease, and obesity (3). However, there is a clear need for the development of new strategies beyond the management of underlying etiologies.

See page 1339

From the \*Wrocław Medical University, Wrocław, Poland; †University of Queensland, Brisbane, Australia; and the ‡Menzies Research Institute Tasmania, Hobart, Australia. The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

Manuscript received March 26, 2013; revised manuscript received May 22, 2013, accepted June 13, 2013.

The latest heart failure guidelines have extended the treatment possibilities for heart failure with reduced left ventricular (LV) ejection fraction by incorporating ivabradine, a selective sinus node inward “funny” ( $I_f$ ) channel inhibitor reducing heart rate, devoid of negative inotropic

effect, which was shown to decrease mortality and morbidity in the Systolic Heart Failure Treatment With the  $I_f$  Inhibitor Ivabradine Trial (4,5). In the early stages of HFpEF, while the primary problem relates to impaired LV relaxation (rather than impaired LV compliance or increased filling pressure at rest), high heart rates during exercise may be particularly detrimental by reducing time for diastolic filling and promoting increased LV filling pressure and exercise intolerance. Therapeutic measures prolonging the LV filling phase may optimize transmitral flow, thereby reducing increased filling pressures and the resultant dyspnea. Although beta-adrenoceptor blockade has been trialed in HFpEF, these agents' negative inotropic effect is disadvantageous. Thus, the use of ivabradine in this group of patients with heart failure might represent a novel opportunity to control exertion-associated tachycardia without a deleterious impact on myocardial contractility. This application of ivabradine is consistent with the results of previous experimental studies that have demonstrated improvements of myocardial diastolic properties by  $I_f$  blockade (6-10). Accordingly, the aim of this study was to investigate the effects of treatment with ivabradine on exercise capacity and LV function, particularly the LV filling pressure response to exercise, in patients with HFpEF.

## Methods

**Study design.** The present study was designed as a prospective, blinded, parallel-group, placebo-controlled trial evaluating the potential of 7 days of therapy with ivabradine 5 mg twice daily to improve exercise tolerance and LV function, especially LV filling, with exercise in patients with HFpEF. This report follows the recommendations of the 2010 Consolidated Standards of Reporting Trials statement (11). The study adhered to the Declaration of Helsinki and was approved by the institutional ethics committees. Informed consent was obtained from all subjects before involvement in the study.

**Patient selection.** Current guidelines endorsed by the European Society of Cardiology were used to identify patients with true HFpEF from 2 large hospital-based echocardiography laboratories (University Hospital in Wroclaw, Poland, and Princess Alexandra Hospital in Brisbane, Australia) (12). In brief, patients presenting with signs or symptoms of heart failure (i.e., dyspnea, fatigue, and exercise intolerance) with normal systolic function as determined by LV ejection fraction  $\geq 50\%$  and evidence of diastolic dysfunction were deemed suitable for screening. The diagnosis of LV diastolic dysfunction was established according to the recommendations of the American Society of Echocardiography and the European Association of Echocardiography (13). To enhance the specificity of the association between diastolic abnormalities and impaired functional capacity (14,15), the key criteria essential for patient enrollment were exercise capacity  $< 80\%$  of age-predicted and sex-predicted normal ranges and a ratio of peak early diastolic mitral flow velocity (E) to peak early diastolic mitral annular velocity ( $e'$ )  $> 13$  after exercise,

reflecting an increase in LV filling pressure during exertion, both evidenced from an exercise test.

From December 2011 to December 2012, of 114 patients meeting the criteria for diastolic dysfunction, we finally recruited 61 patients of Caucasian race who met the exercise capacity and E/ $e'$  ratio criteria and were categorized in New York Heart Association functional class II or III (Fig. 1). Of the 50 patients who were not enrolled, 21 did not show significant reductions ( $< 80\%$  of normal ranges) in exercise capacity, and 38 did not show exertional E/ $e'$  ratios  $> 13$ .

Exclusion criteria were an absence of stable sinus rhythm; ischemic heart disease (excluded on the basis of the absence of significant atherosclerotic lesions on coronary angiography and no evidence of inducible ischemia during exercise testing); moderate and severe valvular heart disease; heart rate  $< 60$  beats/min; sick sinus syndrome; second-degree and third-degree atrioventricular block; severe obesity (body mass index  $> 36$  kg/m<sup>2</sup>); established or suspected pulmonary diseases (vital capacity  $< 80\%$  or forced expiratory volume in 1 second  $< 80\%$  of age-specific and sex-specific reference values); hemoglobin  $\leq 11$  g/dl; and treatment with nondihydropyridine calcium-channel blockers, class I antiarrhythmic agents, strong inhibitors of cytochrome P450 3A4, and QT interval-prolonging medications.

**Study protocol.** The baseline evaluation comprised physical examination, cardiopulmonary exercise testing, resting and immediate post-exercise echocardiography, and blood sampling for laboratory measurements, including brain natriuretic peptide (BNP).

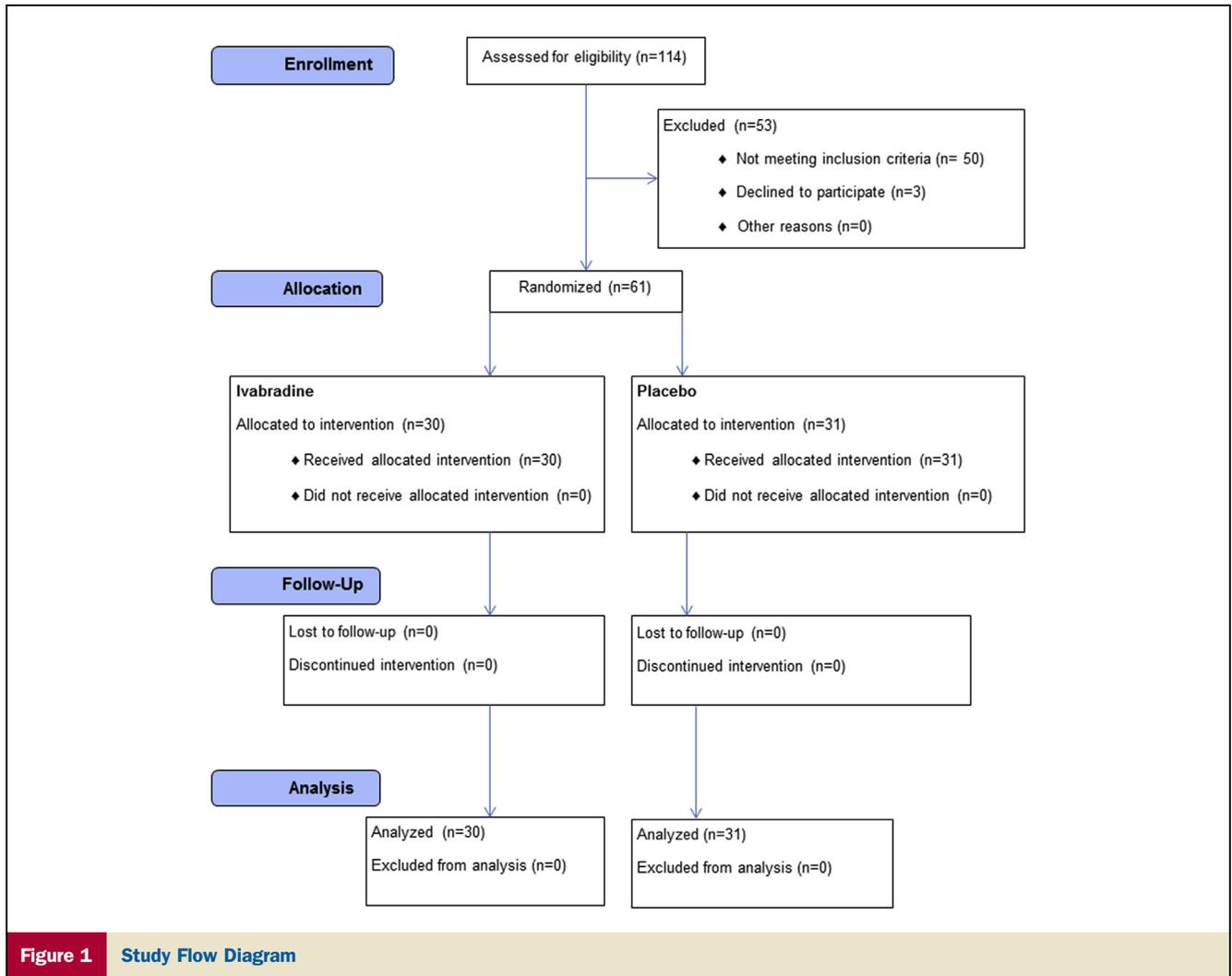
The procedure of randomization to receive either ivabradine 5 mg or placebo twice daily was performed by computerized sequence generation. The hospital pharmacies were responsible for drug randomization and dispensing, and both the investigators and patients were blinded to the treatment option. To check for the presence of bradycardia, patients were seen on the second and fourth days after the initiation of treatment. In case of a resting heart rate  $< 50$  beats/min or the occurrence of signs or symptoms related to bradycardia, the dose of ivabradine was to be reduced to 2.5 mg twice daily, or if these persisted after dose reduction, the study medication was to be withdrawn.

After 7 days, the baseline investigations were repeated.

**Echocardiography.** Echocardiographic imaging was performed using Vivid E9 and Vivid 7 equipment (GE Vingmed Ultrasound AS, Horten, Norway) with phased-array

## Abbreviations and Acronyms

<b>A</b>	= late diastolic mitral flow velocity
<b>BNP</b>	= brain natriuretic peptide
<b>CI</b>	= confidence interval
<b>E</b>	= peak early diastolic mitral flow velocity
<b><math>e'</math></b>	= peak early diastolic mitral annular velocity
<b>HFpEF</b>	= heart failure with preserved ejection fraction
<b>ICC</b>	= intraclass correlation coefficient
<b><math>I_f</math></b>	= inward "funny"
<b>LV</b>	= left ventricular
<b>MET</b>	= metabolic equivalent
<b>WCCR</b>	= work load-corrected chronotropic response
<b><math>V_{O_2}</math></b>	= oxygen uptake



2.5-MHz multifrequency transducers. All patients underwent screening echocardiography to determine their suitability for the trial by the evaluation of strict criteria for HFpEF. The same imaging protocol was used at each visit and performed by the same sonographer. Images were saved in digital format and stored on a secure server for offline analysis. The measurements of cardiac dimensions and wall thicknesses and left atrial volume (area-length method) were performed according to standard recommendations (16). LV ejection fraction was determined using a modified Simpson biplane method.

Peak E and late diastolic mitral flow velocity (A) and the deceleration time of the early diastolic flow wave were assessed from the apical 4-chamber view by pulsed-wave Doppler with the sample volume placed between the tips of the mitral leaflets. Similarly, pulsed-wave tissue Doppler was used to estimate peak early diastolic tissue velocities in the annular septum and lateral wall (septal and lateral e', respectively). Gain settings were optimized to reduce spectral broadening. The E/e' ratio, with e' being an average value from the septal and lateral aspects of the mitral annulus, was calculated to

approximate LV filling pressure, which was considered to be increased if E/e' >13 (13,14). The values of the E/e' ratio were averaged from 3 consecutive cardiac cycles.

Myocardial deformation was evaluated using a semi-automated 2-dimensional speckle-tracking technique (EchoPAC, GE Medical Systems, Milwaukee, Wisconsin) from the 3 apical views with typical temporal resolution of 60 frames/s. After initial tracing of the endocardial border and subsequent software processing, the operator confirmed adequate tissue tracking. Segments that could not be tracked were subjected to manual readjustments of the region of interest, and if this was unsuccessful, they were excluded from the analysis. The parameters (peak strain, defined as the greatest negative value on the strain curve, and peak systolic strain rate) were calculated from the entire myocardial region of interest.

**Exercise testing.** Symptom-limited exercise testing was performed on a treadmill using a modified Bruce protocol and with standard cardiopulmonary stress equipment. Ventilation, oxygen uptake (VO<sub>2</sub>), and carbon dioxide production were monitored continuously, and peak VO<sub>2</sub> was calculated as the average oxygen consumption during the last 30 s of exercise.

Echocardiographic evaluation of wall motion, myocardial deformation, and diastolic function with the assessment of E/e' ratio was undertaken before initiation and immediately after termination of the test. Transmitral flow and tissue velocities were measured after the acquisition of 2-dimensional imaging loops. In the event of fusion of early and late diastolic Doppler signals (E and A and/or e' and a') at high heart rates, images were acquired at the earliest time point when separation of the E and A waves was discernible.

To assess the progression of increment in heart rate in the context of different exercise capacity during the post-treatment exercise test, we derived the work load-corrected chronotropic response (WCCR). This was calculated from the difference in heart rate between the baseline and follow-up tests at the same exercise time. This time was defined by test completion in the test with the lower exercise time. For example, in patients with increases in exercise duration at follow-up, we used the exercise time at the baseline test, so WCCR was the maximal heart rate on the baseline test minus the intermediate heart rate on a follow-up test at the comparable time point. In patients with decreases in exercise duration at follow-up, we used the exercise time on the follow-up test, so WCCR was an intermediate heart rate on a baseline test at the time point compatible with the exercise time on a follow-up test minus the maximal heart rate on the follow-up test.

**BNP measurement.** Peripheral venous blood samples were drawn between 8 and 9 AM after a 30-min rest in the supine position. Plasma samples were frozen at -70°C until assay. BNP level was quantified using a commercially available fluorescence immunoassay (Triage BNP Test, Biosite Diagnostics, Inc., San Diego, California).

**Endpoints.** The primary endpoints were changes in exercise capacity as assessed by peak VO<sub>2</sub> and post-exercise LV filling pressure (E/e'). Secondary endpoints included alterations in myocardial deformation (2-dimensional strain and strain rate) and peak e', representing LV systolic and diastolic function, respectively, and changes in neurohormonal activation as measured by plasma BNP.

**Statistical analysis.** The initial sample size was calculated on the basis of assumption of a standard deviation of 30% of exercise capacity and a 20% effect size (assuming a similar improvement in exercise capacity as that obtained from nondihydropyridine calcium-channel blockers or beta-blockers in a recent meta-analysis of treatments for HFpEF [15]). Subsequent work showed that a 30% to 35% effect size for exercise capacity in heart failure could be achieved with ivabradine (mainly systolic heart failure) (17). On the basis of these assumptions, we planned a study of 31 patients per group to provide 80% power to show a difference in exercise tolerance at a 2-sided alpha level of 0.05.

Data are expressed as mean ± SD for normally distributed variables, as median (interquartile range) for skewed variables (BNP), and as counts and percents for categorical variables. Between-group comparisons were carried out using

unpaired 2-sided Student *t* tests for continuous variables and chi-square tests for categorical variables. Homogeneity of variances was assessed using the Levene test. Longitudinal analyses were performed using paired 2-sided Student *t* tests. BNP, which was found not to fit a normal distribution, was analyzed using the Mann-Whitney *U* test for intergroup and the Wilcoxon test for within-group comparisons. Associations between variables were studied using Pearson or Spearman correlation coefficients and stepwise multiple regression analysis. Variables were put into the stepwise models in order of descending significance in the univariate analyses. Changes in particular parameters with intervention were calculated by subtracting the baseline value from the follow-up value and were expressed in the units of their measurements. The reproducibility of measurements of E/e' ratio was evaluated in 20 randomly selected examinations and expressed using intraclass correlation and Bland-Altman (mean and 95% confidence interval [CI]) methods. All analyses were performed using standard statistical software (Statistica for Windows version 10, StatSoft Inc., Tulsa, Oklahoma). The level of statistical significance was set at a 2-sided *p* value <0.05, apart from assessment of the coprimary endpoints, for which Bonferroni correction was applied (*p* = 0.025).

## Results

**Clinical characteristics.** Patient characteristics are displayed in Table 1. The study patients had a mean age of 67 ± 8 years, were overweight, and were mostly women. A history of hypertension and/or type 2 diabetes was common. At baseline, there were no differences in resting heart rate, blood pressure, BNP level, and cardiac morphology and function, nor in cardiac functional reserve and exercise capacity, between the treatment and placebo groups

<b>Table 1 Clinical and Demographic Characteristics of the Study Population</b>			
	<b>Ivabradine (n = 30)</b>	<b>Placebo (n = 31)</b>	<b>p Value</b>
Age, yrs	66.5 ± 8.5	68.0 ± 8.7	0.49
Women	23 (77)	27 (87)	0.30
BMI, kg/m <sup>2</sup>	30.3 ± 4.0	29.1 ± 4.4	0.25
HTN	27 (90)	24 (77)	0.19
DM	12 (40)	10 (32)	0.53
LV diastolic dysfunction grade ≥ II	8 (27)	10 (32)	0.63
Hemoglobin, g/dl	13.4 ± 1.2	13.3 ± 0.9	0.70
Creatinine, mg/dl	0.99 ± 0.22	0.94 ± 0.13	0.20
<b>Pharmacological treatment</b>			
ACE inhibitors/ARBs	29 (97)	30 (97)	0.99
Beta-blockers	17 (57)	16 (52)	0.69
Calcium blockers	11 (37)	12 (39)	0.87
Thiazide diuretic agents	13 (43)	11 (35)	0.53
Loop diuretic agents	10 (33)	10 (32)	0.93
Oral hypoglycemic agents	12 (40)	9 (29)	0.37

Values are mean ± SD or n (%).  
ACE = angiotensin-converting enzyme; ARB = angiotensin II receptor blocker; BMI = body mass index; DM = diabetes mellitus; HTN = arterial hypertension; LV = left ventricular.

(Tables 2 and 3, Fig. 2). Delayed relaxation was diagnosed in 43 patients and increased filling pressure in 18 patients. There were no differences in clinical characteristics between groups allocated to ivabradine or placebo.

**Effects of intervention.** All enrollees completed the study. There were no reported adverse events or need to reduce the dose or stop the treatment with ivabradine in any participant.

**Exercise capacity.** Baseline exercise capacity (both estimated metabolic equivalents [METs] based on treadmill time and measured  $\dot{V}O_2$ ) was impaired. Figure 2 illustrates a significant increment of exercise capacity in the group treated with ivabradine, with no change in the control subjects. Consequently, the change in METs was greater in the treated patients than controls ( $1.5 \pm 1.2$  vs.  $0.4 \pm 1.2$ ,  $p = 0.001$ ), as was the change in peak  $\dot{V}O_2$  ( $3.0 \pm 3.6$  ml/kg/min vs.  $0.4 \pm 2.7$  ml/kg/min,  $p = 0.003$ ). This change was significant after correction for multiple comparisons. Likewise, changes indicating improvement in ventilation versus carbon dioxide production slope and peak oxygen pulse were seen in the ivabradine group (Table 2). All study subjects achieved peak respiratory exchange ratio values  $>1$ , satisfying the prerequisite for the validity of attained peak  $\dot{V}O_2$ .

**Echocardiography.** The treatment group showed an improvement in resting LV lusitropic function, as indicated by higher septal  $e'$  (Table 2). There was no evidence that these changes occurred in response to increased pre-load, because there was no accompanying change in resting  $E/e'$

or circulating BNP (Table 2). In post hoc analyses, this effect was shown only in patients with grade I diastolic dysfunction (E/A ratio  $0.75 \pm 0.12$  at baseline vs.  $0.94 \pm 0.26$  at follow-up,  $p = 0.01$ , and septal  $e'$   $5.2 \pm 1.1$  cm/s at baseline vs.  $6.0 \pm 1.4$  cm/s at follow-up,  $p = 0.004$ ), but not in patients with grade  $\geq$  II diastolic dysfunction (E/A ratio  $1.42 \pm 0.50$  at baseline vs.  $1.50 \pm 0.43$  at follow-up,  $p = 0.83$ , and septal  $e'$   $6.0 \pm 1.2$  cm/s at baseline vs.  $6.2 \pm 1.0$  cm/s at follow-up,  $p = 0.61$ ). Although there was no change in resting  $E/e'$  ratio, the treatment group demonstrated a reduction in exercise-induced increase in  $E/e'$  ratio, suggesting an improvement in changes in LV filling pressure induced by exertion (Table 3).

There were no changes in resting values or functional reserve for systolic function or myocardial deformation (strain, strain rate, and LV ejection fraction) (Tables 2 and 3).

**Hemodynamics.** There was a decrease in resting heart rate in the treatment group. The absence of change in the response of this parameter to exercise (Tables 2 and 3) may have reflected differences in exercise performance. WCCR (the difference in heart rate at the same exercise time on the baseline and follow-up tests) showed a slower increase in heart rate during exercise than in the placebo-treated group (Fig. 3).

There were no significant changes in other resting values or functional reserve markers at follow-up compared with baseline in the placebo group (Tables 2 and 3).

**Table 2** Resting Heart Rate, Blood Pressure, BNP, Cardiopulmonary Exercise Testing, and Myocardial Characteristics of the Study Population

	Ivabradine (n = 30)			Placebo (n = 31)			p for $\Delta$ Ivabradine vs. $\Delta$ Placebo
	Baseline	Follow-Up	p Value	Baseline	Follow-Up	p Value	
Heart rate, beats/min	72 $\pm$ 7	62 $\pm$ 8	0.001	70 $\pm$ 6	70 $\pm$ 7	0.98	0.001
Systolic BP, mm Hg	130 $\pm$ 18	130 $\pm$ 15	0.91	133 $\pm$ 17	132 $\pm$ 15	0.76	0.63
Diastolic BP, mm Hg	75 $\pm$ 8	74 $\pm$ 8	0.90	76 $\pm$ 7	76 $\pm$ 7	0.95	0.44
BNP, pg/ml	42 (18-104)	46 (21-108)	0.85	62 (28-140)	67 (36-115)	0.51	0.51
Heart rate at post-exercise E/e' recording, beats/min	96 $\pm$ 8	97 $\pm$ 10	0.49	96 $\pm$ 7	99 $\pm$ 9	0.20	0.54
Peak RER	1.07 $\pm$ 0.06	1.08 $\pm$ 0.07	0.39	1.08 $\pm$ 0.06	1.07 $\pm$ 0.06	0.51	0.33
VE/ $\dot{V}CO_2$	31.0 $\pm$ 8.3	27.7 $\pm$ 4.9	0.01	31.4 $\pm$ 6.1	30.9 $\pm$ 5.8	0.71	0.04
Peak oxygen pulse, ml/beat	9.3 $\pm$ 4.2	12.1 $\pm$ 3.5	0.004	8.1 $\pm$ 3.8	8.5 $\pm$ 3.8	0.57	0.008
LV end-diastolic diameter, mm	48 $\pm$ 6	48 $\pm$ 5	0.86	46 $\pm$ 5	47 $\pm$ 4	0.45	0.62
Septal wall, mm	12 $\pm$ 2	12 $\pm$ 2	0.55	12 $\pm$ 2	12 $\pm$ 2	0.77	0.80
Posterior wall, mm	10 $\pm$ 2	10 $\pm$ 1	0.97	10 $\pm$ 2	10 $\pm$ 2	0.97	0.54
LV mass index, g/m <sup>2</sup>	115 $\pm$ 33	118 $\pm$ 36	0.95	113 $\pm$ 32	115 $\pm$ 35	0.73	0.72
LA volume, ml/m <sup>2</sup>	37.2 $\pm$ 9.0	34.9 $\pm$ 8.7	0.19	36.3 $\pm$ 9.3	35.5 $\pm$ 8.6	0.73	0.43
LV ejection fraction, %	67 $\pm$ 7	68 $\pm$ 6	0.87	69 $\pm$ 6	68 $\pm$ 5	0.98	0.43
Strain, %	19.8 $\pm$ 3.0	20.7 $\pm$ 3.8	0.17	20.8 $\pm$ 3.7	21.0 $\pm$ 2.6	0.94	0.29
Strain rate, 1/s	1.12 $\pm$ 0.17	1.13 $\pm$ 0.24	0.99	1.20 $\pm$ 0.17	1.21 $\pm$ 0.21	0.99	0.95
E/A ratio	0.91 $\pm$ 0.38	1.07 $\pm$ 0.38	0.002	1.02 $\pm$ 0.57	1.01 $\pm$ 0.55	0.99	0.004
E-wave deceleration time, ms	232 $\pm$ 54	226 $\pm$ 43	0.74	236 $\pm$ 60	232 $\pm$ 52	0.89	0.65
E/e'	13.5 $\pm$ 3.2	14.2 $\pm$ 3.0	0.40	14.3 $\pm$ 3.1	14.3 $\pm$ 3.3	0.99	0.23
Septal velocity (e'), cm/s	5.4 $\pm$ 1.1	6.1 $\pm$ 1.3	0.007	5.4 $\pm$ 1.2	5.4 $\pm$ 1.2	0.86	0.01
Lateral velocity (e'), cm/s	7.6 $\pm$ 1.7	8.1 $\pm$ 1.8	0.18	7.2 $\pm$ 1.7	7.0 $\pm$ 2.0	0.55	0.16

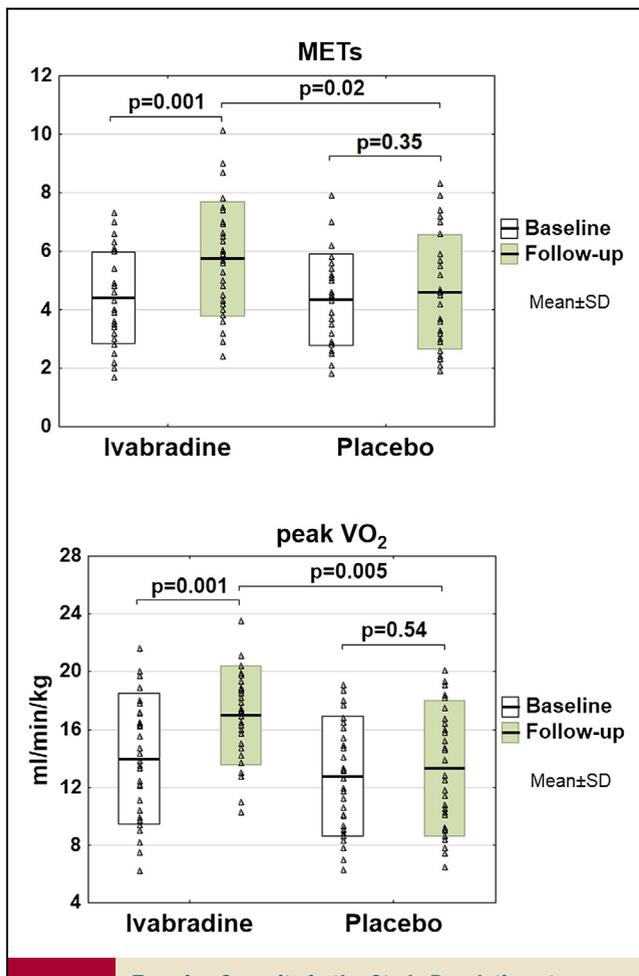
Values are mean  $\pm$  SD or median (interquartile range).

A = late diastolic mitral flow velocity; BNP = brain natriuretic peptide; BP = blood pressure;  $\Delta$  = change during follow-up (follow-up value minus baseline value); E = peak early diastolic mitral flow velocity; e' = peak early diastolic mitral annular velocity; LA = left atrial; LV = left ventricular; RER = respiratory exchange ratio; VE/ $\dot{V}CO_2$  = ventilation versus carbon dioxide production slope.

**Table 3 Myocardial and Hemodynamic Reserve (Exercise Increment) at Baseline and After Treatment in the Study Population**

Exercise Increment*	Ivabradine (n = 30)			Placebo (n = 31)			p for Δ Ivabradine vs. Δ Placebo
	Baseline	Follow-Up	p Value	Baseline	Follow-Up	p Value	
E/A ratio	0.30 ± 0.37	0.31 ± 0.29	0.99	0.33 ± 0.35	0.21 ± 0.29	0.07	0.06
E-wave deceleration time, ms	-56 ± 39	-44 ± 32	0.40	-55 ± 39	-55 ± 37	0.99	0.26
E/e'	3.1 ± 2.7	1.3 ± 2.0	0.004	3.5 ± 3.0	2.8 ± 1.9	0.31	0.11
Septal velocity (e'), cm/s	1.1 ± 0.9	1.8 ± 1.1	0.03	1.0 ± 0.8	1.4 ± 1.2	0.18	0.59
Lateral velocity (e'), cm/s	1.2 ± 1.1	2.0 ± 1.6	0.18	1.1 ± 1.4	1.8 ± 1.4	0.24	0.96
Strain, %	1.8 ± 2.0	1.6 ± 1.5	0.96	1.7 ± 1.1	1.6 ± 1.3	0.98	0.85
Strain rate, (1/s)	0.18 ± 0.17	0.22 ± 0.11	0.85	0.21 ± 0.19	0.19 ± 0.15	0.98	0.43
LV ejection fraction, %	6 ± 5	5 ± 5	0.80	7 ± 5	7 ± 5	0.98	0.66
Heart rate, beats/min	46 ± 16	52 ± 17	0.21	49 ± 20	49 ± 17	0.98	0.27
Systolic BP, mm Hg	34 ± 19	37 ± 15	0.89	32 ± 18	35 ± 19	0.90	0.98
Diastolic BP, mm Hg	-1 ± 11	-1 ± 12	0.95	-1 ± 10	-1 ± 9	0.97	0.90

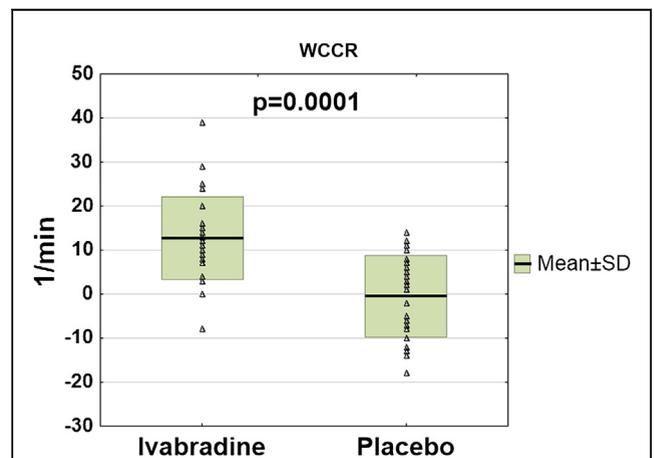
Values are mean ± SD. \*Increase from rest to exercise (exercise value minus resting value). Abbreviations as in Table 2.



**Figure 2 Exercise Capacity in the Study Population at Baseline and Follow-Up**

There were no differences in baseline metabolic equivalents (METs) or peak oxygen uptake (Vo<sub>2</sub>) between the ivabradine and placebo groups, but follow-up METs (p = 0.02) and peak Vo<sub>2</sub> (p = 0.005) were greater with ivabradine. This reflected significant increments of both METs (p = 0.001) and peak Vo<sub>2</sub> (p = 0.001) with ivabradine therapy but none with placebo.

**Diastolic dysfunction and heart rate subanalyses.** The effect of heart rate slowing may be different in patients with grade I and grade II diastolic dysfunction, on the basis of potential benefits of prolonging LV filling in the former and heart rate dependence of cardiac output in the latter. However, no differences between these subgroups of patients were found in baseline or follow-up BNP, METs, peak Vo<sub>2</sub>, and exercise increment of E/e' ratio (Online Table 1). Similarly, subdivision according to resting heart rate subgroups of >70 and ≤70 beats/min, as well as with normal and reduced chronotropic response to exercise (a failure to achieve 80% of the maximum age-predicted peak heart rate) were similar (Online Tables 2 and 3). Likewise, there were no differences in exercise and hemodynamic responses to treatment or placebo in groups below and at or above the median stroke volume (Online Table 4).



**Figure 3 Work Load-Corrected Chronotropic Response**

Work load-corrected chronotropic response (WCCR) is based on the difference in heart rate between the baseline and follow-up tests at the same exercise time. The figure shows that at the same work load, the heart rates of most ivabradine-treated patients were 10 beats/min less than those of placebo-treated patients.

**Determinants of improvements in exercise capacity and response of E/e' ratio to exercise.** The independent correlates of changes in exercise capacity and diastolic physiology were assessed by modeling combinations of covariates. These included resting and maximal exercise heart rate and blood pressure, body mass index, LV mass index, baseline METs (for  $\Delta$ METs), background treatment with beta-blockers, and, for  $\Delta$ METs and  $\Delta$  peak  $V_{O_2}$ , change with treatment in exertional increases in LV ejection fraction and strain. Therapy with ivabradine was independently associated with improvement in exercise capacity, as indicated by increases in METs and peak  $V_{O_2}$  (Table 4). Other independent associations were WCCR, change with treatment in exertional increase in E/e' ratio, age, and baseline peak  $V_{O_2}$  (for  $\Delta$  peak  $V_{O_2}$ ). Improvement of LV filling pressure estimated by E/e' ratio was independently associated with ivabradine treatment ( $\beta = -0.24$ ), as well as the baseline value of exertional increase in E/e' ratio (Table 4). The use of beta-blockers was not a significant correlate, either univariate or multivariate, of changes in exercise capacity and LV filling pressure.

**Reproducibility.** The level of agreement in measurements of E/e' ratio between both centers participating in this trial was high, as suggested by the intraclass correlation coefficients (ICCs) and mean differences: ICC = 0.93 ( $p < 0.001$ ) and  $-0.4$  (95% CI:  $-1.5$  to  $0.7$ ) at rest and ICC = 0.92 ( $p < 0.001$ ) and  $0.2$  (95% CI:  $1.0$  to  $0.6$ ) at exercise. Intra-observer and interobserver variability of E/e' ratio were as follows: at the Polish center, ICC = 0.96 ( $p < 0.001$ ) and  $0.5$  (95% CI:  $0.0$  to  $1.0$ ) and ICC = 0.96 ( $p < 0.001$ ) and  $-0.2$  (95% CI:  $-0.6$  to  $0.2$ ) at rest and ICC = 0.94 ( $p < 0.001$ ) and  $-0.3$  (95% CI:  $-1.0$  to  $0.3$ ) and ICC = 0.97 ( $p < 0.001$ ) and  $0.7$  (95% CI:  $0.2$  to  $1.2$ ) during exercise; at the Australian center, ICC = 0.99 ( $p < 0.001$ ) and  $0.0$  (95% CI:  $-0.3$  to  $0.3$ ) and ICC = 0.93 ( $p < 0.001$ ) and  $0.3$  (95% CI:  $-0.4$  to  $1.0$ ) at rest and ICC = 0.97 ( $p < 0.001$ ) and  $0.0$  (95% CI:  $-0.3$  to  $0.3$ ) and ICC = 0.98 ( $p < 0.001$ ) and  $-0.1$  (95% CI:  $-0.7$  to  $0.4$ ) during exercise.

**Discussion**

This randomized, placebo-controlled study demonstrated that short-term treatment with ivabradine improves exercise

capacity in patients with HFpEF. This coincided with a reduction of the exercise-induced increase in LV filling pressure (E/e' ratio). These findings in carefully selected patients with reduced exercise capacity, exercise-induced diastolic dysfunction, and low resting BNP levels support further investigations of ivabradine in larger and longer duration clinical trials in patients with HFpEF.

**Diastolic evaluation.** Exertional dyspnea is a nonspecific symptom, and concern is often expressed over the frequency of diastolic dysfunction leading to the overdiagnosis of HFpEF. The present study was performed in a carefully selected group of symptomatic, functionally impaired patients with HFpEF after the exclusion of other plausible causes of shortness of breath, such as lung disease or anemia. The lack of specificity of diastolic abnormalities as the reason for exercise intolerance is a limitation of previous investigations in HFpEF. We sought to avoid this in this study by performing the evaluation during exercise, which allowed us to relate symptomatic status to exercise changes in hemodynamic status.

Delayed relaxation represents the early process associated with diastolic dysfunction, which is followed by LV stiffening, both exerting deleterious effects on diastolic filling (18,19). Importantly, significant slowing of LV relaxation may result in elevation of both early and, to a lesser extent, late diastolic pressure, regardless of coexisting abnormalities of myocardial compliance (19). Despite near normal LV filling pressure values at rest in some patients, elevation of LV filling pressure on exertion is associated with exertional dyspnea (20-22). Patients with increments of E/e' ratio with exercise were selected to make the group more specific for cardiac dyspnea (15,23-25).

A number of mechanisms may explain the favorable effect of ivabradine in HFpEF. In patients with delayed relaxation, lengthening of diastolic filling time may permit more complete LV filling. Patients with HFpEF have inappropriate tachycardia during exercise, with higher heart rates at constant work loads than in subjects with normal LV filling (20,26), on the basis of impaired stroke volume reserve and reliance on increasing heart rate to augment cardiac output. Interestingly, patients with increased LV filling pressure or the absence of resting tachycardia were no less likely to respond to ivabradine (Online Tables 1 and 2).

**Table 4 Multivariate Predictors of Improvements in Exercise Capacity and Response of E/e' Ratio to Exercise in the Study Population**

	$\Delta$ METs ( $R^2 = 0.40$ )			$\Delta$ Peak $V_{O_2}$ ( $R^2 = 0.58$ )			$\Delta$ Exl E/e' ( $R^2 = 0.62$ )		
	$\beta$	SE	p Value	$\beta$	SE	p Value	$\beta$	SE	p Value
WCCR	0.42	0.14	0.005	0.15	0.11	0.20			
Change in exercise increment of E/e'	-0.30	0.13	0.02						
Ivabradine therapy	0.34	0.16	0.04	0.32	0.11	0.007	-0.24	0.08	0.006
Age	-0.20	0.13	0.14	-0.35	0.11	0.003			
Peak $V_{O_2}$ at baseline				-0.68	0.11	0.001			
Exl E/e' at baseline							-0.81	0.09	0.001
LVMI							0.12	0.08	0.18

Exl = increase from rest to exercise (exercise value minus resting value); LVMI = left ventricular mass index; MET = metabolic equivalent;  $V_{O_2}$  = oxygen uptake; WCCR = work load-corrected chronotropic response; other abbreviations as in Table 2.

As demonstrated in animal models, the mechanisms behind the favorable effect of ivabradine on LV diastolic function are not confined to a simple lengthening of diastolic filling time. Other benefits include acceleration of myocardial relaxation by enhancing the phosphorylation of phospholamban and subsequent stimulation of sarcoplasmic reticulum  $\text{Ca}^{2+}$  adenosine triphosphatase, increase in myocardial compliance by reducing the expression of the titin N2B isoform and myocardial collagen content, and improvement of arterial stiffness and endothelial function (6,8,27). Clearly, some of these mechanisms require a longer treatment duration to be effective.

As evidenced in our analysis, the improvement of exercise capacity with ivabradine was associated with a slower increase in heart rate during exercise (as expressed by WCCR). This may have been paralleled by a slower exertional increase in LV filling pressure with delayed onset of dyspnea and exercise termination. Indeed, some patients might have developed similar levels of LV filling pressures as in the pre-treatment period but at a later stage of exercise. Unfortunately, noninvasive estimation of LV filling pressure during exercise (in contrast to post-exercise measurements in our protocol) using the E/e' ratio is difficult because of the fusion of the E and A waves of the mitral inflow and annular e' and a' waves at high heart rates. These considerations may explain the lack of post-treatment reduction in exercise-induced increase in E/e' ratio between treatment and control.

We did not demonstrate significant differences in beneficial effect of ivabradine on exercise tolerance between patients with grade I and grade  $\geq$ II diastolic dysfunction, but this finding needs to be verified in larger patient populations.

**Heart rate control and heart failure.** Although the heart failure guidelines mention a possible use of heart rate-slowing drugs (especially beta-blockers) for alleviating heart failure symptoms in patients with HFpEF (3,4), the role of therapeutic bradycardia in this population is controversial. Previous studies showed inconsistent results concerning effects of beta-blockade on LV diastolic function and exercise tolerance in patients with HFpEF (28-33). Notably, heart rate control attained with beta-receptor antagonists is accompanied by the negative inotropic and lusitropic effects of this class of drugs. Apart from this, beta-blockade may directly increase cardiomyocytes stiffness (34). Compared with atenolol, ivabradine lacks a negative lusitropic effect at similar levels of heart rate reduction (10) and provides similar decreases in myocardial oxygen demand without detrimentally affecting LV contractility (35,36). Finally, traditional beta-blockade may contribute to increased central systolic loading, despite lowering brachial blood pressure (37). This effect may be detrimental to central hemodynamic status in HFpEF, especially on exertion, and substitution of this drug class with ivabradine may be particularly useful. Indeed, apart from the beneficial changes during exercise, ivabradine therapy was associated with a positive lusitropic

effect at rest in patients with HFpEF with grade I diastolic dysfunction, as indicated by higher septal e' and mitral E/A ratio. This finding is in line with prior experimental studies (6,7,9,10).

**Study limitations.** First, BNP was ineffective in tracking clinical and hemodynamic improvements in this study. This reflects challenges in applying BNP in this population, especially in the context of their mean body mass index of 30  $\text{kg}/\text{m}^2$  (38). Additionally, we measured this marker only at rest, not during exercise, when the favorable effect of ivabradine on LV filling pressure was observed.

Second, the improvement in exercise capacity after a short duration of treatment represents the acute effect of therapy on hemodynamic status. Long-term treatment may permit patients with HFpEF to engage in greater levels of physical activity, further improving functional capacity.

Third, we studied the effects of ivabradine on maximal exercise performance and cannot extrapolate our data to the effects of the drug on submaximal exercise hemodynamic status.

Fourth, we did not evaluate the effect of ivabradine on arterial function, especially in the context of its potential impact on exercise tolerance.

Fifth, there is a dose-response effect of ivabradine on heart rate reduction (39). In this study, we examined the effects of a fixed dose of ivabradine (5 mg), which is effective for rate reduction, but we did not titrate the drug to reach specific heart rate thresholds.

Finally, the limited sample size precluded testing interactions with treatment groups in the multivariate regression model.

## Conclusions

Ivabradine therapy is an effective therapy to increase exercise tolerance in patients with HFpEF. This beneficial effect is potentially mediated by the improved LV filling pressure response to exercise. Because patients with HFpEF are often symptomatic only on exertion, treatments targeting abnormal exercise hemodynamic status may prove useful.

---

**Reprint requests and correspondence:** Dr. Thomas H. Marwick, Menzies Research Institute Tasmania, 17 Liverpool Street, Hobart, T7000, Australia. E-mail: tom.marwick@utas.edu.au.

---

## REFERENCES

1. 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;355:251-9.
2. Bhatia RS, Tu JV, Lee DS, et al. Outcome of heart failure with preserved ejection fraction in a population-based study. *N Engl J Med* 2006;355:260-9.
3. Hunt SA, Abraham WT, Chin MH, et al. 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. *J Am Coll Cardiol* 2009;53:e1-90.

4. McMurray JJ, Adamopoulos S, Anker SD, et al., for the ESC Committee for Practice Guidelines. 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;33:1787-847.
5. Swedberg K, Komajda M, Böhm M, et al. Ivabradine and outcomes in chronic heart failure (SHIFT): a randomised placebo-controlled study. *Lancet* 2010;376:875-85.
6. Reil JC, Hohl M, Reil GH, et al. Heart-rate reduction by  $I_f$ -inhibition improves vascular stiffness and left ventricular systolic and diastolic function in a mouse model of heart failure with preserved ejection fraction. *Eur Heart J* 2012 Jul 24 [E-pub ahead of print]; <http://dx.doi.org/10.1093/eurheartj/ehs218>.
7. Fang Y, Debonne M, Vercauteren M, et al. Heart-rate reduction induced by the  $I_f$  current inhibitor ivabradine improves diastolic function and attenuates cardiac tissue hypoxia. *J Cardiovasc Pharmacol* 2012;59:260-7.
8. Busseuil D, Shi Y, Mecteau M, et al. Heart-rate reduction by ivabradine reduces diastolic dysfunction and cardiac fibrosis. *Cardiology* 2010;117:234-42.
9. Becher PM, Lindner D, Miteva K, et al. Role of heart-rate reduction in the prevention of experimental heart failure: comparison between  $I_f$ -channel blockade and  $\beta$ -receptor blockade. *Hypertension* 2012;59:949-57.
10. Colin P, Ghaleh B, Hittinger L, et al. Differential effects of heart-rate reduction and  $\beta$ -blockade on left ventricular relaxation during exercise. *Am J Physiol Heart Circ Physiol* 2002;282:H672-9.
11. Schulz KF, Altman DG, Moher D, for the CONSORT Group. CONSORT 2010 statement: updated guidelines for reporting parallel group randomized trials. *PLoS Med* 2010;7:e1000251.
12. Paulus WJ, Tschope C, Sanderson JE, et al. How to diagnose diastolic heart failure: a consensus statement on the diagnosis of heart failure with normal left ventricular ejection fraction by the Heart Failure and Echocardiography Associations of the European Society of Cardiology. *Eur Heart J* 2007;28:2539-50.
13. Nagueh SF, Appleton CP, Gillebert TC, et al. Recommendations for the evaluation of left ventricular diastolic function by echocardiography. *J Am Soc Echocardiogr* 2009;22:107-33.
14. Burgess MI, Jenkins C, Sharman JE, Marwick TH. Diastolic stress echocardiography: hemodynamic validation and clinical significance of estimation of ventricular filling pressure with exercise. *J Am Coll Cardiol* 2006;47:1891-900.
15. Holland DJ, Kumbhani DJ, Ahmed SH, Marwick TH. Effects of treatment on exercise tolerance, cardiac function and mortality in heart failure with preserved ejection fraction; a meta-analysis. *J Am Coll Cardiol* 2011;57:1676-86.
16. Lang RM, Bierig M, Devereux RB, et al. Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. *J Am Soc Echocardiogr* 2005;18:1440-63.
17. Volterrani M, Cice G, Caminiti G, et al. Effect of carvedilol, ivabradine or their combination on exercise capacity in patients with heart failure (the CARVIVA HF trial). *Int J Cardiol* 2011;151:218-24.
18. Kawaguchi M, Hay I, Fetec B, Kass DA. Combined ventricular systolic and arterial stiffening in patients with heart failure and preserved ejection fraction: implications for systolic and diastolic reserve limitations. *Circulation* 2003;107:714-20.
19. 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;350:1953-9.
20. Kitzman DW, Higginbotham MB, Cobb FR, Sheikh KH, Sullivan MJ. Exercise intolerance in patients with heart failure and preserved left ventricular systolic function: failure of the Frank-Starling mechanism. *J Am Coll Cardiol* 1991;17:1065-72.
21. Borlaug BA, Nishimura RA, Sorajja P, Lam CS, Redfield MM. Exercise hemodynamics enhance diagnosis of early heart failure with preserved ejection fraction. *Circ Heart Fail* 2010;3:588-95.
22. Maeder MT, Thompson BR, Brunner-La Rocca H-P, Kaye DM. Hemodynamic basis of exercise limitation in patients with heart failure and normal ejection fraction. *J Am Coll Cardiol* 2010;56:855-63.
23. Holland DJ, Prasad SB, Marwick TH. Contribution of exercise echocardiography to the diagnosis of heart failure with preserved ejection fraction (HFpEF). *Heart* 2010;96:1024-8.
24. Ha J-W, Oh JK, Pellikka PA, et al. Diastolic stress echocardiography: a novel noninvasive diagnostic test for diastolic dysfunction using supine bicycle exercise Doppler echocardiography. *J Am Soc Echocardiogr* 2005;18:63-8.
25. Holland DJ, Prasad SB, Marwick TH. Prognostic implications of left ventricular filling pressure with exercise. *Circ Cardiovasc Imaging* 2010;3:149-56.
26. Borlaug BA, Olson TP, Lam CSP, et al. Global cardiovascular reserve dysfunction in heart failure with preserved ejection fraction. *J Am Coll Cardiol* 2010;56:845-54.
27. Maczewski M, Mackiewicz U. Effect of metoprolol and ivabradine on left ventricular remodelling and  $Ca^{2+}$  handling in the post-infarction rat heart. *Cardiovasc Res* 2008;79:42-51.
28. Flather MD, Shibata MC, Coats AJ, et al. Randomized trial to determine the effect of nebivolol on mortality and cardiovascular hospital admission in elderly patients with heart failure (SENIORS). *Eur Heart J* 2005;26:215-25.
29. van Veldhuisen DJ, Cohen-Solal A, Böhm M, et al. Beta-blockade with nebivolol in elderly heart failure patients with impaired and preserved left ventricular ejection fraction: data from SENIORS (Study of Effects of Nebivolol Intervention on Outcomes and Rehospitalization in Seniors With Heart Failure). *J Am Coll Cardiol* 2009;53:2150-8.
30. Ghio S, Magrini G, Serio A, et al. Effects of nebivolol in elderly heart failure patients with or without systolic left ventricular dysfunction: results of the SENIORS echocardiographic substudy. *Eur Heart J* 2006;27:562-8.
31. Bergstrom A, Andersson B, Edner M, Nylander E, Persson H, Dahlstrom U. Effect of carvedilol on diastolic function in patients with diastolic heart failure and preserved systolic function. Results of the Swedish Doppler-Echocardiographic Study (SWEDIC). *Eur J Heart Fail* 2004;6:453-61.
32. Nodari S, Metra M, Cas LD. Beta-blocker treatment of patients with diastolic heart failure and arterial hypertension. A prospective, randomized, comparison of the long-term effects of atenolol vs. nebivolol. *Eur J Heart Fail* 2003;5:621-7.
33. Conraads VM, Metra M, Kamp O, et al. Effects of the long-term administration of nebivolol on the clinical symptoms, exercise capacity, and left ventricular function of patients with diastolic dysfunction: results of the ELANDD study. *Eur J Heart Fail* 2012;14:219-25.
34. Hamdani N, Paulus WJ, van Heerebeek L, et al. Distinct myocardial effects of beta-blocker therapy in heart failure with normal and reduced left ventricular ejection fraction. *Eur Heart J* 2009;30:1863-72.
35. Colin P, Ghaleh B, Monnet X, et al. Contributions of heart-rate and contractility to myocardial oxygen balance during exercise. *Am J Physiol Heart Circ Physiol* 2003;284:H676-82.
36. Joannides R, Moore N, Iacob M, et al. Comparative effects of ivabradine, a selective heart-rate-lowering agent, and propranolol on systemic and cardiac haemodynamics at rest and during exercise. *Br J Clin Pharmacol* 2006;61:127-37.
37. Protogerou A, Stergiou G, Vlachopoulos C, Blacher J, Achimastos A. The effect of antihypertensive drugs on central blood pressure beyond peripheral blood pressure. Part II: evidence for specific class-effects of antihypertensive drugs on pressure amplification. *Curr Pharm Des* 2009;15:272-89.
38. Mehra MR, Uber PA, Park MH, et al. Obesity and suppressed B-type natriuretic peptide levels in heart failure. *J Am Coll Cardiol* 2004;43:1590-5.
39. Borer JS, Fox K, Jaillon P, Lerebours G, for the Ivabradine Investigators Group. Antianginal and antiischemic effects of ivabradine, an  $I_f$  inhibitor, in stable angina: a randomized, double-blind, multicentered, placebo-controlled trial. *Circulation* 2003;107:817-23.

**Key Words:** diastolic function ■ heart failure with preserved ejection fraction ■ ivabradine.

**APPENDIX**

For supplementary tables, please see the online version of this article.