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β-Blocker treatment of patients with diastolic heart failure and arterial hypertension. A prospective, randomized, comparison of the long-term effects of atenolol vs. nebivolol

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Abstract

We compared the effects of 6 months administration of atenolol or nebivolol on resting and exercise hemodynamic parameters and maximal exercise capacity, in 26 patients with hypertension and left ventricular (LV) diastolic dysfunction (ejection fraction >50%, end-diastolic diameter <60 mm and increased pulmonary wedge pressure at rest and/or at peak exercise). Both atenolol and nebivolol administration was associated with a significant decrease in the resting and peak exercise heart rate and blood pressure and in LV mass, with an increase in the E/A ratio. This latter effect was greater with nebivolol. Nebivolol was associated with an increase in the peak V_{O_2}, V_{O_2} at the anaerobic threshold and with a decrease in the VE/V_{CO_2} ratio. With regards to the hemodynamic parameters, compared to patients on atenolol, those on nebivolol showed a lower reduction in the cardiac index, a greater increase in the stroke volume index and a decline in the mean pulmonary artery pressure and pulmonary wedge pressure, both at rest and peak exercise. Thus, although the two β-blockers have a similar antihypertensive action, nebivolol administration was associated with a greater hemodynamic improvement, compared to atenolol.

Keywords: β-Blockers; Diastolic function; Heart failure

1. Introduction

Predominant left ventricular (LV) diastolic dysfunction is the cause of heart failure in more than one third of patients and its prevalence increases among the elderly, females, and patients with hypertension and/or coronary artery disease [1,2]. Even in the absence of a clinical history of heart failure, impaired LV early diastolic relaxation, detected by pulsed Doppler echocardiography, is predictive of an higher incidence of major cardiovascular events both in the general population [3] and in hypertensive patients [4], with a relation independent of age, gender, LV mass and ambulatory blood pressure [4]. Thus, an improvement in LV diastolic function is an important goal of both the treatment of heart failure and the prevention of cardiovascular events. Treatment of LV diastolic dysfunction remains, however, empirical [5–7]. β-Blockers have many potentially useful effects. They reduce the heart rate and myocardial ischemia and cause regression of myocardial hypertrophy in patients with hypertension. However, no study to date has specifically assessed the effects of their long-term administration in patients with diastolic heart failure.

Nebivolol is a β-blocker with associated vasodilator activity mediated through increased nitric oxide (NO) release [8–12]. This mechanism has many potentially beneficial effects for the treatment of the patients with hypertension and diastolic heart failure. First, peripheral vasodilatation may contribute to the antihypertensive effect of this agent [13]. Second, increased NO release in the vessels of the skeletal muscle may increase their dilatatory capacity and thus allow better muscle perfusion during exercise. Lastly, NO is one of the most powerful endogenous lusitropic agents [14]. Its increased release shifts the LV pressure–volume curve downward and to the right and augments the LV pre-load reserve with, hence, a greater stroke volume [15–17]. Moreover, patients with LV hypertrophy seem to be particularly

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sensitive to the beneficial effects of NO on diastolic function [18]. Studies in patients with LV systolic dysfunction have shown a greater improvement in the parameters of diastolic function, associated with an increase in exercise capacity, with nebivolol administration, compared with the traditional β-blockers [19–22]. The aim of our study was, therefore, to compare the effects of the long-term administration of either atenolol or nebivolol on hemodynamic parameters, assessed both at rest and during maximal exercise, and the exercise capacity of a group of patients with hypertension and diastolic heart failure.

2. Methods

2.1. Patients

We studied 30 patients with mild arterial hypertension and chronic heart failure due to LV diastolic dysfunction. Entry criteria included New York Heart Association (NYHA) class II or III symptoms of heart failure for $\geqslant$6 months, a peak V_{O_2} $\leqslant$25 ml/kg/min by cardiopulmonary exercise testing, evidence of normal LV systolic function, defined by an ejection fraction $\geqslant$0.50 and an end-diastolic diameter $<$32 mm/m^2 by 2D echocardiography, and of diastolic dysfunction, defined by a mitral valve Doppler flow velocity pattern with peak E wave less than peak A wave velocity (E/A$<$1.0) and/or by a pulmonary wedge pressure $>$12 mmHg at rest and/or$>$20 mmHg at peak exercise [23–25]. Patients were excluded if they had evidence of myocardial ischemia at stress myocardial perfusion scintigraphy or of coronary artery disease at coronary angiography; primary valve disease or congenital heart disease; resting systolic blood pressure $>$200 mmHg or diastolic blood pressure $>$100 mmHg; atrial fibrillation; concomitant diseases that might adversely influence prognosis or impair exercise capacity (e.g. malignancy, musculoskeletal diseases); contraindications to β-blocker therapy, (e.g. asthma, advanced heart block or bradyarrhythmias); and concomitant treatment with other β-blockers. Four patients were not reassessed after β-blocker therapy (refusal to undergo the second hemodynamic study in 3 patients and β-blockade intolerance for bronchial wheezing in one) and were therefore excluded from the study.

The investigation conformed to the principles outlined in the Declaration of Helsinki and the protocol was approved by the local ethics committee. Written informed consent was obtained from all study patients.

2.2. Protocol

A prospective, parallel design was used with 1:1 randomization to either atenolol or nebivolol using a permuted block design. Each patient underwent maximal cardiopulmonary exercise testing with hemodynamic monitoring, resting 2D echocardiogram, Doppler measurements of mitral valve flow velocities and clinical symptom assessment at baseline, before the initiation of β-blocker therapy, and after 6 months of treatment with atenolol or nebivolol.

Atenolol and nebivolol were started at the doses of 50 and 2.5 mg once a day, respectively, with an up-titration after 2 weeks to the doses of 100 mg daily for atenolol and 5 mg daily for nebivolol. Titration could be increased to higher doses when needed, to achieve a better control of blood pressure. Dose titration was deferred, interrupted or stepped back in the case of an increase in heart failure symptoms, dizziness, hypotension (systolic blood pressure $\leqslant$80 mmHg), bradycardia (resting heart rate $\leqslant$60 b/min) or other untoward effects possibly related to β-blockade. Concomitant treatment was maintained constant throughout the study.

2.3. Procedures

At least 1 h before performance of the maximal cardiopulmonary exercise test, a triple lumen Swan–Ganz catheter was inserted percutaneously through the right internal jugular vein and positioned in the pulmonary artery to obtain hemodynamic measurements. Cardiac output was measured using the thermodilution method. Resting hemodynamic data were obtained both in the supine position, after an equilibration period of at least 15 min. Bicycle exercise testing was then performed in the sitting position with simultaneous expiratory gas exchange and hemodynamic monitoring, starting at a workload of 20 W with increments of 20 W every 2 min up to limiting dyspnea or fatigue according to a protocol previously described in detail [26]. All patients had performed at least two preliminary cardiopulmonary exercise tests in order to be familiar with the procedure and to ensure stability of the results, defined as a $\leqslant$1 ml/kg/min change in peak V_{O_2} between two consecutive tests. The slope of the relation between minute ventilation and carbon dioxide production (VE/V_{CO_2} slope) [27] and the half-time of the V_{O_2} recovery after exercise [28] were also calculated.

Echocardiographic studies were performed at rest, with the patient in the left lateral position, using commercially available instruments with a mechanical transducer of 2.5 MHz, by two experienced echocardiographers who were blinded to the clinical data and ongoing therapy. Two-dimensional guided M-mode measurements of the left atrial and LV internal dimensions, and septum and posterior wall thickness were made at the LV minor axis at the level of the chordae tendinae just beyond the mitral leaflet tips, as recommended by the American Society of Echocardiography [29]. LV mass was calculated using the Penn convention [30] according to the equation: LV mass = 1.04 ((LV end-diastolic diameter + posterior wall thick-

ness + interventricular septum thickness)^3 − (LV end-diastolic diameter)^3) − 13.6 g, and normalized for body surface area. The transmitral flow velocity was measured using pulsed-wave Doppler with the sample volume positioned between the mitral leaflet tips during diastole. The E wave and A wave peak velocities and the ratio of the E wave to the A wave peak velocities (E/A ratio) were measured on three separate beats and then averaged [31].

2.4. Statistical analysis

Since, in patients with chronic diastolic heart failure, the LV filling pressure may be normal at rest and increase only during exercise [25,32], the primary objective of our study was to compare the effects of nebivolol and atenolol on the pulmonary wedge pressure assessed at peak exercise. The secondary objectives were to compare the effects of the two β-blockers on the other hemodynamic parameters, assessed at rest and peak exercise, and on the maximal exercise tolerance. Based on the changes in exercise hemodynamic variables observed in earlier studies [33,34] and assuming a dropout rate of 20%, we calculated that the enrollment of 30 patients would have provided 95% power to detect an absolute difference of 5 mmHg in the change from baseline of the peak exercise PWP between the atenolol and the nebivolol treatment groups ($\alpha = 0.05$).

Results are expressed as mean ± S.D. Baseline data were compared using Student's *t* test for continuous variables and by χ^2 test for categorical variables. Changes from baseline were compared between the atenolol and the nebivolol treatment group by two-way analysis of variance (ANOVA) and, within each treatment group, by Student's *t* test for paired samples. In all analyses, a value of $P < 0.05$ in a two-tailed distribution was considered statistically significant.

3. Results

3.1. Baseline characteristics

The studied patients had mild hypertension (systolic blood pressure, 149 ± 21 mmHg; diastolic blood pressure, 92 ± 7 mmHg), symptoms of heart failure (NYHA functional class, 2.42 ± 0.50) and an impairment in functional capacity (peak V_{O_2}, 18.0 ± 4.8 ml/kg/min) with a normal LV systolic function (LV ejection fraction, 56 ± 7%; LV end-diastolic diameter index, 28 ± 2 mm/m^2) and signs of LV diastolic dysfunction (mitral E/A ratio, 0.82 ± 0.12; mean pulmonary wedge pressure, 14 ± 5 mmHg at rest and 24 ± 4 mmHg at peak exercise). The patients randomized to atenolol and nebivolol were similar with respect to all pretreatment characteristics. Their mean age was 65 ± 9 and 62 ± 13 years, respectively. There were 8 males in the atenolol group and 7 in the nebivolol treatment group. With regards to concomitant therapy, oral furosemide was administered to all but one patient treated with atenolol (mean dose, 26 ± 16 mg daily), and to all patients on nebivolol (29 ± 10 mg daily). An angiotensin converting enzyme inhibitor or, when not tolerated, an angiotensin II antagonist, was administered to 11 patients on atenolol and 12 on nebivolol. Lastly, 7 patients on atenolol and 8 patients on nebivolol were on amlodipine (10 mg daily). Following completion of the up-titration period, all patients randomized to atenolol received the dose of 100 mg daily while the final dose of nebivolol was of 5 mg daily in all but one patient who received 10 mg daily.

3.2. Effects on functional capacity, echocardiographic and Doppler parameters

Compared with baseline, both the β-blockers improved clinical symptoms, assessed by NYHA class. Only nebivolol was associated with a significant improvement from baseline in exercise capacity, assessed by peak V_{O_2}, V_{O_2} at the anaerobic threshold, and the VE/V_{CO_2} slope (Table 1). Peak V_{O_2} and V_{O_2} at the anaerobic threshold increased by 1.2 ± 1.6 ml/k/min and 1.6 ± 2.1 ml/k/min, respectively, (both $P <$ 0.01 vs. baseline) in the patients treated with nebivolol while no significant change (0.1 ± 2.3 ml/k/min and 0.1 ± 1.5 ml/k/min) was observed in those on atenolol. Similarly, the VE/V_{CO_2} slope decreased by 2.3 ± 1.3 ($P < 0.05$) in the patients who received nebivolol but not in those on atenolol. However, these differences did not reach statistical significance with between-group ANOVA.

The LV ejection fraction and end-diastolic diameter did not change from baseline with either atenolol or nebivolol. Both the β-blockers were associated with a significant decrease from baseline in the LV end-diastolic septal wall thickness and the LV mass index with an improvement in the transmitral flow E/A ratio. Nebivolol administration was also associated with a decrease from baseline in the LV end-diastolic posterior wall thickness. No significant difference in the magnitude of these changes was found between the two β-blockers, except for the E/A ratio, which increased to a greater extent in the nebivolol group (Table 1).

3.3. Effects on the hemodynamic parameters

Hemodynamic data obtained at rest, in the supine position, and at peak exercise are shown in Tables 2 and 3. Compared with baseline, both agents significantly decreased heart rate and blood pressure. The reduction in heart rate also caused a decrease in the cardiac index which was of greater magnitude after atenolol, compared to nebivolol administration. Nebivolol, was also associ-

Table 1
Effect on clinical status, exercise capacity and echo-Doppler parameters

	Atenolol ($n=13$)		Nebivolol ($n=13$)		P (ANOVA)
	Baseline	6 months	Baseline	6 months	
NYHA class	2.38±0.51	2.08±0.64*	2.46±0.52	2.08±0.49*	NS
Cardiopulmonary exercise testing					
Exercise duration (s)	623±203	568±218	619±213	658±232	NS
Peak V_{O_2} (ml/kg/min)	18.4±4.5	18.5±5.4	17.6±5.4	18.8±5.1*	NS
V_{O_2} at anaerobic threshold (ml/kg/min)	13.8±3.6	13.9±4.2	11.2±2.8	12.8±2.7*	NS
Minute ventilation vs. V_{CO_2} slope	35.8±7.5	37.1±8.0	34.9±6.4	32.6±7.3*	NS
Post-exercise V_{O_2} recovery half-time (s)	129±52	135±57	115±31	107±33	NS
Two-dimensional echocardiography and Doppler exams					
LV ejection fraction (%)	57±6	57±8	57±7	57±10	NS
LV end-diastolic diameter index (cm/m^2)	2.81±0.24	2.78±0.20	2.77±0.24	2.75±0.20	NS
End-diastolic septal wall thickness (cm)	1.23±0.06	1.20±0.08*	1.17±0.14	1.08±0.12**	NS
End-diastolic posterior wall thickness (cm)	1.16±0.09	1.14±0.10	1.11±0.12	1.05±0.16*	NS
LV mass index (g/m^2)	158±24	149±19**	144±16	129±18***	NS
E/A ratio	0.84±0.12	0.89±0.15*	0.79±0.13	0.91±0.11***	0.004

V_{O_2}, oxygen consumption; V_{CO_2}, carbon dioxide production; LV, left ventricular. *$P<0.05$, **$P<0.01$, ***$P<0.001$ for differences between pre- and post-treatment values (within each group). P (ANOVA) denotes significance of differences in the magnitude of change in the atenolol group vs. the magnitude of change in the nebivolol group.

ated with a significant increase from baseline in the stroke volume index and a decline in mean pulmonary artery pressure and pulmonary wedge pressure, both at rest and peak exercise, and with a decrease in the peak exercise systemic vascular resistance. In contrast, atenolol administration was only associated with an increase from baseline in the peak exercise stroke volume index, with no change in the other parameters. The changes from baseline in the cardiac index, systemic vascular resistance, mean pulmonary artery pressure and pulmonary wedge pressure were significantly different, both at rest and peak exercise, between the atenolol and the nebivolol treated group (Tables 2 and 3). At peak exercise, the changes in the stroke volume index and stroke work index were also significantly different between the two patient groups (Table 3). Percentage change from baseline in the main hemodynamic parameters is shown in Fig. 1.

4. Discussion

4.1. Major findings

Our data show that long-term therapy with β-blockers in patients with arterial hypertension and diastolic heart failure is associated with a significant improvement in many parameters of LV function with, however, meaningful differences between the different agents. In particular, nebivolol administration was associated with a greater improvement in the E/A ratio, a greater decline in pulmonary wedge pressure and mean pulmonary artery pressure and a smaller reduction in cardiac index,

Table 2
Hemodynamic data at rest

	Atenolol ($n=13$)		Nebivolol ($n=13$)		P (ANOVA)
	Baseline	6 months	Baseline	6 months	
Heart rate (bpm)	82±11	65±9***	76±11	65±8***	NS
Systolic blood pressure (mmHg)	151±19	139±17**	147±23	132±16**	NS
Diastolic blood pressure (mmHg)	91±7	83±9***	92±6	82±7***	NS
Cardiac index (l/min/m^2)	3.62±0.51	2.98±0.46***	3.46±0.45	3.20±0.48**	0.01
Stroke volume index (ml/m^2)	45±7	46±7	46±8	49±7*	NS
Stroke work index (g m/m^2)	59±9	55±6	59±11	58±9	NS
Systemic vascular resistance (dyn s/cm^5)	1405±239	1523±352	1366±228	1334±243	0.05
Mean right atrial pressure (mmHg)	3.0±2.0	2.2±2.0	3.5±2.6	2.5±2.5	NS
Mean pulmonary artery pressure (mmHg)	19±6	18±6	21±5	17±6**	0.03
Pulmonary wedge pressure (mmHg)	14±5	13±5	15±4	12±5**	0.03
Pulmonary vascular resistance (dyn s/cm^5)	71±27	74±35	70±30	69±30	NS

*$P<0.05$, **$P<0.01$, ***$P<0.001$ for differences between pre- and post-treatment values (within each group). P (ANOVA) denotes significance of differences in the magnitude of change in the atenolol group vs. the magnitude of change in the nebivolol group.

Table 3
Hemodynamic responses at peak exercise

	Atenolol ($n=13$)		Nebivolol ($n=13$)		P (ANOVA)
	Baseline	12 months	Baseline	12 months	
Heart rate (bpm)	142±11	122±14***	144±22	123±17***	NS
Systolic blood pressure (mmHg)	209±19	175±16***	197±30	167±13***	NS
Diastolic blood pressure (mmHg)	106±6	95±7**	101±14	88±10**	NS
Cardiac index (l/min/m^2)	5.85±1.22	5.31±1.26**	5.84±1.83	5.79±1.80	0.005
Stroke volume index (ml/b/m^2)	41±8	44±11*	42±15	48±15***	0.05
Stroke work index (g m/m^2)	65±15	59±15**	62±24	62±21	0.05
Systemic vascular resistance (dyn s/cm^5)	1057±240	1037±289	1001±274	886±274*	0.07
Mean right atrial pressure (mmHg)	6.9±2.7	5.3±2.7*	8.0±3.7	6.5±3.6*	NS
Mean pulmonary artery pressure (mmHg)	31±4	29±3	31±4	24±6***	0.01
Pulmonary wedge pressure (mmHg)	24±5	23±3	24±4	19±6**	0.03
Pulmonary vascular resistance (dyn s/cm^5)	49±15	51±27	60±29	45±23	NS

*$P<0.05$, **$P<0.01$, ***$P<0.001$ for differences between pre- and post-treatment values (within each group). P (ANOVA) denotes significance of differences in the magnitude of change in the atenolol group vs. the magnitude of change in the nebivolol group. Values reflect data in patients with paired measurements.

both at rest and at peak exercise, and with a decline in systemic vascular resistance and an increase in the stroke volume index and stroke work index at peak exercise. Lastly, only the patients on nebivolol showed an increase from baseline in the peak V_{O_2}, V_{O_2} at the anaerobic threshold, and a decrease in the VE/V_{CO_2} slope.

4.2. Mechanisms of the different effects of atenolol and nebivolol

Four possible mechanisms may account for the differences observed between the nebivolol and atenolol treatment groups: the chronotropic response to exercise, the regression of LV hypertrophy and the effects on peripheral resistance and on LV diastolic function.

The chronotropic response to exercise is known to be an accurate measure of the cardiac response to adrenergic drive. Previous studies in patients with LV systolic dysfunction, have related the differences in the effects on maximal exercise capacity between different β-blockers to the magnitude of their negative chronotropic effects and hence to their degree of antiadrenergic activity [34,35]. However, this mechanism may not be applied to our results. In fact, the magnitude of the reduction in heart rate was similar between the atenolol and the nebivolol group, both at rest and during exercise, consistent with their similar, selective, action on β_1 adrenergic receptors. Other studies have shown a lower negative chronotropic activity of nebivolol, compared to atenolol, in normal subjects [36].

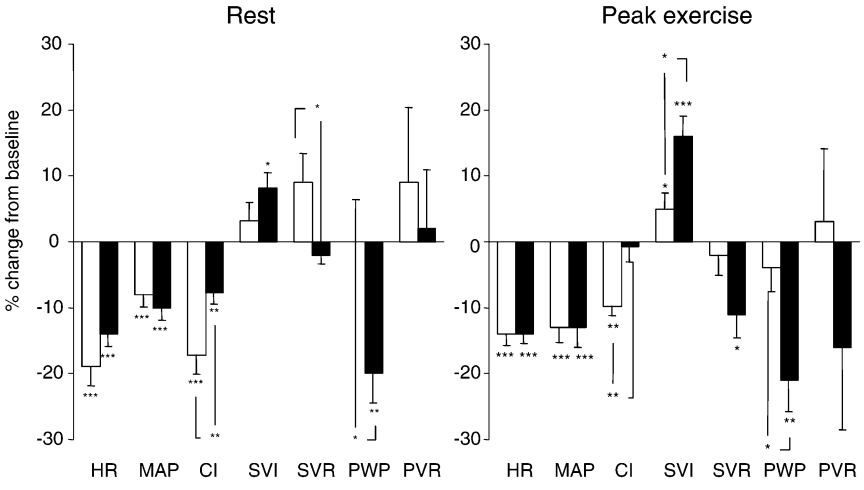

Fig. 1. Percentage changes from baseline (mean±S.E.M.) in hemodynamic variables at rest and during peak exercise after treatment with atenolol (white bars) or nebivolol (black bars) for 6 months. Symbols immediately above or below the columns designate significance of differences from baseline, whereas symbols between the columns designate significance of differences between groups. *$P<0.05$, **$P<0.01$, ***$P<0.0001$. HR denotes heart rate, MAP mean arterial pressure, CI cardiac index, SVI stroke volume index, SVR systemic vascular resistance, PWP pulmonary wedge pressure and PVR pulmonary vascular resistance.

With regards to the effects of the two β-blockers on LV hypertrophy, both atenolol and nebivolol administration was associated with a decrease in LV septal wall thickness and LV mass, with a concomitant improvement in the E/A ratio. These results are consistent with previous studies [37–40]. Compared to atenolol, nebivolol administration was associated with a more significant decrease in the end-diastolic septal wall thickness and LV mass index and with a decrease in the LV end-diastolic posterior wall thickness. Although the magnitude of these changes was not significant by ANOVA, it is consistent with the greater improvement in the E/A ratio and in the LV filling pressures after nebivolol, compared to atenolol administration.

The differences observed between the two β-blockers may also be ascribed to the peripheral vasodilatatory action and the increase in NO release associated with nebivolol administration [8–11]. Our results are similar to those previously obtained in comparative studies between traditional β-blockers and β-blockers with associated vasodilating activity [41–43]. Differently from these studies, we directly assessed both the resting and peak exercise ventricular filling pressures and maximal exercise capacity and specifically studied patients with symptoms of chronic heart failure caused by LV diastolic dysfunction.

The hemodynamic improvement and the increase in exercise tolerance after nebivolol, may be explained by its peculiar effects on NO release. NO release may cause both vasodilatation and perfusion of the exercising skeletal muscle and a greater improvement in LV diastolic function [12–14]. The improvement in early diastolic relaxation, likely associated with NO release, may explain the decline in LV filling pressure, with better LV filling and hence a greater stroke volume, both at rest and during exercise. As the impairment in LV diastolic filling and pre-load recruitment is the primary mechanism of exercise intolerance in patients with diastolic heart failure [32], this increase in LV NO release may explain the increase from baseline in the exercise capacity observed in the patients treated with nebivolol.

In conclusion, our study demonstrates that the chronic administration of nebivolol is associated with a greater hemodynamic improvement, both at rest and during exercise, when compared to atenolol administration, in the patients with arterial hypertension and diastolic heart failure. These differences are likely related to a greater improvement in LV diastolic function related to the ancillary properties of nebivolol.

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References

[1] Vasan RS, Benjamin EJ, Levy D. Prevalence, clinical features and prognosis of diastolic heart failure: an epidemiologic perspective. J Am Coll Cardiol 1995;26:1565–74.
[2] Banerjee P, Banerjee T, Khand A, Clark AL, Cleland JG. Diastolic heart failure: neglected or misdiagnosed? J Am Coll Cardiol 2002;39:138–41.
[3] Bella JN, Palmieri V, Roman MJ, et al. Mitral ratio of peak early to late diastolic filling velocity as a predictor of mortality in middle-aged and elderly adults. The Strong Heart Study. Circulation 2002;105:1928–33.
[4] Schillaci G, Pasqualini L, Verdecchia P, et al. Prognostic significance of left ventricular diastolic dysfunction in essential hypertension. J Am Coll Cardiol 2002;39:2005–11.
[5] Vasan RS, Benjamin EJ, Levy D. Congestive heart failure with normal left ventricular systolic function. Clinical approaches to the diagnosis and treatment of diastolic heart failure. Arch Intern Med 1996;156:146–57.
[6] Cleland JG. ACE inhibitors for ‘diastolic’ heart failure? Reasons not to jump to premature conclusions about the efficacy of ACE inhibitors among older patients with heart failure. Eur J Heart Fail 2001;3:637–9.
[7] Zile MR, Brutsaert DL. New concepts in diastolic dysfunction and diastolic heart failure: part II. Causal mechanisms and treatment. Circulation 2002;105:1503–8.
[8] Bowman AJ, Chen CP, Ford GA. Nitric oxide mediated venodilator effects of nebivolol. Br J Clin Pharmacol 1994;38:199–204.
[9] Cockcroft JR, Chowienczyk PJ, Brett SE, et al. Nebivolol vasodilates human forearm vasculature: evidence for an *L*-arginine/NO-dependent mechanism. J Pharmacol Exp Ther 1995;274:1067–71.
[10] Parenti A, Filippi S, Amerini S, Granger HJ, Fazzini A, Ledda F. Inositol phosphate metabolism and nitric-oxide synthase activity in endothelial cells are involved in the vasorelaxant activity of nebivolol. J Pharmacol Exp Ther 2000;292:698–703.
[11] Altwegg LA, d’Uscio LV, Barandier C, Cosentino F, Yang Z, Luscher TF. Nebivolol induces NO-mediated relaxations of rat small mesenteric but not of large elastic arteries. J Cardiovasc Pharmacol 2000;36:316–20.
[12] Tzemos N, Lim PO, MacDonald TM. Nebivolol reverses endothelial dysfunction in essential hypertension: a randomized, double-blind, crossover study. Circulation 2001;104:511–4.
[13] Taddei S, Virdis A, Ghiadoni L, Sudano I, Salvetti A. Effects of antihypertensive drugs on endothelial dysfunction: clinical implications. Drugs 2002;62:265–84.
[14] Paulus WJ, Shah AM. NO and cardiac diastolic function. Cardiovasc Res 1999;43:595–606.
[15] Paulus WJ, Vantrimpont PJ, Shah AM. Acute effects of nitric oxide on left ventricular relaxation and diastolic distensibility in humans. Circulation 1994;89:2070–8.
[16] Prendergast BD, Sagach VF, Shah AM. Basal release of nitric oxide augments the Frank–Starling response in the isolated heart. Circulation 1997;96:1320–9.
[17] Heymes C, Vanderheyden M, Bronzwaer JG, Shah AM, Paulus WJ. Endomyocardial nitric oxide synthase and left ventricular preload reserve in dilated cardiomyopathy. Circulation 1999;99:3009–16.
[18] Matter CM, Mandinov L, Kaufmann PA, Vassalli G, Jiang Z, Hess OM. Effects of NO donors on LV diastolic function in patients with severe pressure-overload hypertrophy. Circulation 1999;99:2396–401.

[19] Van de Water A, Van Neuten J, Xhonneux R, et al. Pharmacological and hemodynamic profile of nebivolol, a chemically novel, potent, and selective beta1-adrenergic antagonist. J Cardiovasc Pharmacol 1988;11:552–63.
[20] Brune S, Schmidt T, Tebbe U, Kreuzer H. Hemodynamic effects of nebivolol at rest and on exertion in patients with heart failure. Angiology 1990;41:696–701.
[21] Wisenbaugh T, Katz I, Davis J, et al. Long term (3 month) effects of a new beta blocker (nebivolol) on cardiac performance in dilated cardiomyopathy. J Am Coll Cardiol 1993;21:1094–100.
[22] Rousseau MF, Chapelle F, Van Eyll C, et al. Medium-term effects of beta-blockade on left ventricular mechanics: a double-blind, placebo-controlled comparison of nebivolol and atenolol in patients with ischemic left ventricular dysfunction. J Cardiac Fail 1996;2:15–23.
[23] European Study Group on Diastolic Heart Failure. How to diagnose diastolic heart failure. Eur Heart J 1998;19:990–1003.
[24] Vasan RS, Levy D. Defining diastolic heart failure: a call for standardized diagnostic criteria. Circulation 2000;101:2118–21.
[25] Zile MR, Brutsaert DL. New concepts in diastolic dysfunction and diastolic heart failure: part I. Diagnosis, prognosis, and measurement of diastolic function. Circulation 2002;105:1387–93.
[26] Metra M, Faggiano P, D'Aloia A, et al. Use of cardiopulmonary exercise testing with hemodynamic monitoring in the prognostic assessment of ambulatory patients with chronic heart failure. J Am Coll Cardiol 1999;33:943–50.
[27] Metra M, Dei Cas L, Panina G, Visioli O. Exercise hyperventilation chronic heart failure, and its relation to functional capacity and hemodynamics. Am J Cardiol 1992;70:622–8.
[28] Cohen-Solal A, Laperche T, Morvan D, Geneves M, Caviezel B, Gourgon R. Prolonged kinetics of recovery of oxygen consumption after maximal graded exercise in patients with chronic heart failure. Analysis with gas exchange measurements and NMR spectroscopy. Circulation 1995;91:2924–32.
[29] Sahn DJ, DeMaria A, Kisslo J, Weyman A. The Committee on M-mode standardization of the American Society of Echocardiography. Recommendations regarding quantitation in M-mode echocardiography: results of a survey of echocardiographic measurements. Circulation 1978;8:1072–83.
[30] Devereux RB, Alonso DR, Lutas EM, et al. Echocardiographic assessment of left ventricular hypertrophy: comparison to necropsy findings. Am J Cardiol 1986;57:450–8.
[31] Oh JK, Appleton CP, Hatle LK. The noninvasive assessment of left ventricular diastolic function with two-dimensional and Doppler echocardiography. J Am Soc Echocardiogr 1997;10:246–70.
[32] 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.
[33] Metra M, Nardi M, Giubbini R, Dei Cas L. Effects of short- and long-term carvedilol administration on rest and exercise hemodynamic variables, exercise capacity and clinical conditions in patients with idiopathic dilated cardiomyopathy. J Am Coll Cardiol 1994;24:1678–87.
[34] Metra M, Giubbini R, Nodari S, Boldi E, Modena MG, Dei Cas L. Differential effects of β-blockers in patients with heart failure. A prospective, double-blind comparison of the long-term effects of metoprolol versus carvedilol. Circulation 2000;102:546–51.
[35] Metra M, Nodari S, D'Aloia A, et al. Effects of neurohumoral antagonism on symptoms and quality of life in heart failure. Eur Heart J 1998;19(suppl. B):B25–B35.
[36] Van Bortel LM, de Hoon JN, Kool MJ, Wijnen JA, Vertommen CI, Van Nueten LG. Pharmacological properties of nebivolol in man. Eur J Clin Pharmacol 1997;51:379–84.
[37] Schobel HP, Langenfeld M, Gatzka C, Schmieder RE. Treatment and post-treatment effects of alpha- versus beta-receptor blockers on left ventricular structure and function in essential hypertension. Am Heart J 1996;132:1004–9.
[38] Schmieder RE, Martus P, Klingbeil A. Reversal of left ventricular hypertrophy in essential hypertension: meta-analysis of randomized double-blind studies. JAMA 1996;275:1507–13.
[39] Liu GS, Wang LY, Nueten LV, Ooms LA, Borgers M, Janssen PA. The effect of nebivolol on left ventricular hypertrophy in hypertension. Cardiovasc Drugs Ther 1999;13:549–51.
[40] Thurmann PA, Kenedi P, Schmidt A, Harder S, Reitbrock N. Influence of the angiotensin II antagonist valsartan on left ventricular hypertrophy in patients with essential hypertension. Circulation 1998;98:2037–42.
[41] Lund-Johansen P. Central haemodynamic effects of beta blockers in hypertension. A comparison between atenolol, metoprolol, timolol, penbutolol, alprenolol pindolol and bunitrolol. Eur Heart J 1983;4(Suppl. D):1–12.
[42] Lund-Johansen P. Exercise and antihypertensive therapy. Am J Cardiol 1987;59:98A–107A.
[43] Lund-Johansen P, Omvik P. Acute and chronic hemodynamic effects of drugs with different actions on adrenergic receptors: a comparison between alpha blockers and different types of beta blockers with and without vasodilating effect. Cardiovasc Drugs Ther 1991;5:605–15.