

Metoprolol Reduces Hemodynamic and Metabolic Overload in Asymptomatic Aortic Valve Stenosis Patients A Randomized Trial

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Background—Currently, no pharmacological treatment can modify the natural history of aortic valve stenosis (AS). This underlines the critical need to explore novel treatment strategies, which could postpone or prevent the need for aortic valve replacement in patients with asymptomatic AS. The objectives of this study were to investigate whether metoprolol reduce the hemodynamic and metabolic burden imposed by AS.

Methods and Results—In a double-blinded design, 40 patients with moderate-severe asymptomatic AS (aortic valve area, 0.5 ± 0.1 cm²/m²; peak gradient, 53 ± 19 mm Hg) were randomized to placebo or metoprolol treatment for 22 weeks. Patients were evaluated by echocardiography, cardiovascular magnetic resonance, and ¹¹C-acetate positron emission tomography. Compared with placebo, metoprolol (100 ± 53 mg/d) decreased heart rate; mean difference (95% confidence interval) -8 minute⁻¹ ($-13, -3$; $P=0.003$) and increased ejection time 26 ms (2, 50; $P=0.03$). Furthermore, metoprolol reduced aortic valve peak -7 mm Hg ($-13, 0$; $P=0.05$) and mean -4 mm Hg ($-7, -1$; $P=0.03$) gradients, without affecting stroke volume 3 mL/m² ($-2, 8$; $P=0.16$). Valvuloarterial impedance (ie, global afterload) and myocardial oxygen consumption were reduced by -11% and -12% ($P=0.03$ and 0.01), respectively; and decreased heart rate correlated with lower valvuloarterial impedance, myocardial oxygen consumption, and improved myocardial efficiency defined as stroke work/myocardial oxygen consumption ($r=0.63$ – 0.65 ; all $P<0.01$). There were 2 adverse cardiovascular events in the metoprolol group and none in the placebo group.

Conclusions—In patients with asymptomatic AS, metoprolol increases systolic ejection time and reduces aortic valve gradients, global afterload, and myocardial oxygen requirements. Thus, metoprolol displays favorable hemodynamic and metabolic effects and could improve outcome in patients with asymptomatic AS.

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Key Words: aortic valve stenosis ■ magnetic resonance imaging ■ metoprolol ■ oxygen consumption ■ positron-emission tomography

As life expectancy increases, the burden of aortic valve stenosis (AS) poses a growing challenge to public health.^{1,2} Unfortunately, prospective studies trying to counteract aortic valve calcification and left ventricular (LV) remodeling have been disappointing and safe handling of patients with AS is restricted to careful monitoring to ensure optimal timing of aortic valve replacement (AVR).^{3–5} These facts underline the critical need to explore novel treatment strategies in patients with asymptomatic AS, which may postpone or prevent the need for AVR.

See Editorial by Van Der Velden See Clinical Perspective

The pathophysiology of AS is characterized by a silent increase in LV afterload, stroke work, and concentric remodeling. Myocardial oxygen consumption (MVO₂) is, therefore, dramatically increased, which explains a predisposition to subendocardial ischemia.^{6–10} Thus, hemodynamic and metabolic overload plays key roles in the transition from compensated hypertrophy to failure in patients with AS.

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Risk factors in AS are similar to those of hypertension and ischemic heart disease, and β -blockers are therefore also widely used in patients with AS.¹¹ However, when prescribed to patients with AS, their negative inotropic effects may raise concern. However, retrospective studies propose that β -blocking agents may improve survival and postpone the need for AVR in both symptomatic and asymptomatic AS.^{12,13} Thus, reducing the heart rate (HR) and blood pressure by antagonizing sympathetic activation could have favorable hemodynamic effects. In addition, β -blockers reduce myocardial oxygen requirements and improve coupling between MVO₂ and stroke work (ie, myocardial efficiency).^{14,15} Thus, from a theoretical perspective, β -blocking therapy in patients with AS could, indeed, have both favorable and detrimental effects. Nevertheless, no prospective studies have yet explored the effects of β -blocking agents in patients with AS.

Therefore, we investigated the safety, hemodynamic, and metabolic effects of metoprolol in patients with asymptomatic moderate-severe AS. The primary objective of this study was to investigate whether metoprolol could improve myocardial efficiency.

Methods

This was a randomized, double-blind, placebo-controlled trial. Forty patients with asymptomatic AS were randomly assigned to receive either extended-release metoprolol or placebo (1:1) once daily for 22 weeks (Figure 1). Eligible patients were identified and recruited from outpatient clinics at 3 centers and were included between August 2013 and April 2016. The uptitration period was <6 weeks, and the target dose was set individually (50–200 mg) based on telephone interviews with home blood pressure and HR readings 2 and 4 weeks after initiation of treatment. Compliance and tolerance were evaluated by 2 additional telephone interviews (weeks 10 and 18) and 2 intermediate study visits (weeks 6 and 13). Both patients and investigators were blinded on treatment, which was ensured by an identical appearance of the medicine.

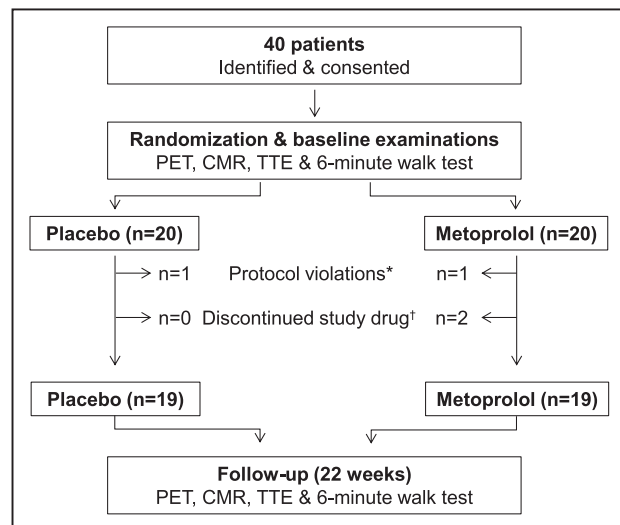


Figure 1. Consolidated Standards of Reporting Trials (CONSORT) diagram. *Patients were excluded shortly after inclusion because of protocol violations (unrecognized left ventricular ejection fraction <50% and severe aortic valve regurgitation at screening visits). †Treatment was discontinued because of fatigue (n=1) and congestion (n=1). Both patients had complete follow-up data. CMR indicates cardiovascular magnetic resonance; and PET, positron emission tomography; TTE, transthoracic echocardiography.

Major inclusion criteria were asymptomatic AS with an aortic valve area ≤ 1.2 cm² or transaortic maximal velocity ≥ 3.0 m/s and sinus rhythm with an HR ≥ 60 minute⁻¹. Major exclusion criteria were ongoing treatment with β -blockers, significant aortic valve regurgitation (vena contracta ≥ 5 mm), or ischemic heart disease evaluated by symptoms or signs of myocardial ischemia (ie, angina pectoris, abnormal electrocardiography, wall motion abnormalities). In addition, patients with a previous coronary angiography proving a $\geq 70\%$ luminal stenosis were excluded. Coronary angiography was not performed routinely before study participation. To ensure the absence of symptoms before enrollment, patients were evaluated by ergometer test when considered appropriate by the investigator (eg, patients with high valve gradients, poor global longitudinal strain values, or high NT-proBNP [N-terminal pro-B-type natriuretic peptide] levels).

All patients provided their written informed consent before enrollment, and the study was performed in accordance with the Helsinki Declaration and the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use-Good Clinical Practice guidelines. Approval was obtained from the Data Monitoring Board, the Scientific Ethics Committee in the Central Denmark Region, and the Danish Medicines Agency.

Imaging Protocol

All subjects were evaluated by echocardiography and cardiovascular magnetic resonance (CMR) on the same day followed or preceded by an ¹¹C-acetate positron emission tomography (PET) study within a median period of 2 days (interquartile range, 1–6 days).

One patient refused CMR after randomization, and therefore data were obtained from PET (stroke volume [SV] and LV mass) and echocardiography (LV ejection fraction, end-diastolic and end-systolic volumes) according to previously validated methods.^{16,17}

Transthoracic Echocardiography

Echocardiography was performed using a GE VIVID 9E system (GE Medical System, Horten, Norway) with a 2.5-MHz transducer. Images were acquired and analyzed according to previously described methods.¹⁸ Briefly, the continuity equation and time-velocity integrals from Doppler imaging were used to calculate the aortic valve area. Continuous wave Doppler imaging was used to explore the highest aortic valve peak and mean gradients. Net mean and peak gradients, that is, gradients corrected for pressure recovery, were calculated according to a previously validated method using the cross-sectional area of the ascending aorta, obtained from CMR images 1 cm distal to the sinotubular junction.¹⁹ Global longitudinal strain was assessed by 2-dimensional speckle tracking (≥ 50 frames/s) with the LV automatically divided into a 17-segment model. Pulse wave Doppler was used to evaluate mitral inflow patterns (E, A, and deceleration time).

Cardiovascular Magnetic Resonance

CMR was performed using a 1.5-Tesla Philips Achieva dStream whole body scanner (Philips Medical Systems, Best, The Netherlands) with a 32-channel coil and a scan protocol identical to previously described method.²⁰ Briefly, images were obtained during breath-hold using an ECG-triggered, temporally resolved cine scan with a balanced steady-state free precession sequence. LV volume and mass data were derived from 10 to 16 short-axis cine images. SV was measured by breath-hold through-plane phase-contrast acquisitions at the level of the LV outflow tract to avoid turbulent flow. Encoding velocities were set individually based on pulse wave Doppler imaging from echocardiography performed just before the CMR.

Image analysis was performed using Segment v1.9 R3420 (Medviso AB, Lund, Sweden).²¹

Peak systolic wall stress was evaluated using the thick-wall sphere model assuming that peak systolic wall stress occurs one third into the ejection phase.^{22,23} Systemic vascular resistance was calculated according to (systemic vascular resistance=80×mean arterial pressure/CO) and LV global afterload was estimated by valvuloarterial impedance (Z_{va}) using the formula [Z_{va}=(systolic blood pressure+net mean gradient)/SV index].^{24,25} Consequently, Z_{va} was

calculated using a hybrid approach with net mean gradients derived from echocardiography and SV index from CMR.

¹¹C-Acetate PET

Participants underwent a ¹¹C-acetate PET scan on a Siemens Biograph TruePoint TrueV 64 PET/computed tomographic scanner. After a minimum rest of 30 minutes, 400 MBq ¹¹C-acetate was injected followed by list mode PET recordings for 27 minutes. Venous blood was collected before the scan and analyzed for myocardial energy substrates (free fatty acids, glucose, 3-hydroxybutyrate, and lactate), catecholamine metabolites (metanephrine and normetanephrine), insulin, and NT-proBNP.

Reconstruction of dynamic images and attenuation correction were performed according to previously described method²⁰; and dynamic data sets were analyzed using the software package Cardiac VUer.²⁶ Image-derived arterial input function was obtained automatically and corrected for metabolites.^{26,27} The average time-activity curve of the entire LV was fitted to a 1-tissue compartment model yielding the global clearance rate (k_2) of activity from the myocardium.^{16,28} Myocardial blood flow was estimated using the global uptake rate K_1 , corrected for the incomplete extraction of ¹¹C-acetate.²⁹

Myocardial Efficiency and Oxygen Consumption

Myocardial external efficiency (MEE) was calculated as:

$$\text{MEE (\%)} = \frac{\text{Stroke work}}{\text{Total energy consumption}} \\ = \frac{\text{SV} \times \text{HR} \times (\text{MAP} + \text{net mean gradient}) \times 1.33 \times 10^{-4}}{\text{LV mass} \times \text{MVO}_2 \times 20} \times 100$$

Stroke work (J/min) was calculated as the product of SV, HR, and mean arterial blood pressure corrected for the net mean gradient. Finally, the caloric equivalent of 1 mL×mm Hg=1.33×10⁻⁴ J was applied.³⁰ Global k_2 was converted into MVO₂ (mL/min per gram) using the linear relationship (MVO₂=1.35× k_2 -9.6×10⁻³).²⁷ Subsequently, MVO₂ was multiplied by LV mass to obtain total MVO₂ (mL/min) and by the caloric equivalent of 20 (1 mL of O₂=20 J) to yield total energy consumption of the LV (J/min).³⁰

Six-Minute Walk Test and Quality of Life

Participants performed a 6-minute walk test, and they were asked to report their perceived exertion on the Borg scale. In addition, participants were asked to fill out the Minnesota Living with Heart Failure Questionnaire to evaluate quality of life (high score=low quality).

Blood Pressure and HR Measurements

HR and blood pressure were measured twice just Before echocardiography after a minimum rest of 15 minutes. For calculations of cardiac index, HR registrations during CMR were used; and for MEE estimations, average HR and mean arterial pressure obtained during PET examinations were used (5, 10, and 20 minutes after tracer injection).

Statistics

A sample size of 40 patients was estimated to provide 90% power for the primary end point (relative difference in MEE of 15%) with a 5% 2-sided significance level allowing for a 20% drop-out. Data were analyzed according to the intention-to-treat principle and by comparing the difference from baseline to follow-up values. Variables are presented as mean±SD, median (range), and mean change (95% confidence intervals).

Differences in baseline values between groups were investigated using unpaired *t* tests, Wilcoxon–Mann–Whitney tests, or the χ^2 test, as appropriate. Linear regression was used to analyze the relationships between outcome and treatment adjusted for baseline values at all times. Correlations between measurements were examined using simple linear regression and by calculating Pearson correlation

coefficients. A *P*<0.05 was considered statistically significant. All statistical analyses were performed using STATA version 13.1 software (StataCorp, TX).

Results

Study Population and Treatment

Patient characteristics are presented in Table 1. There were no statistically significant differences between groups in baseline values obtained by echocardiography, PET, and CMR for any of the parameters presented in Table 2, except for global longitudinal strain (placebo -17.3±1.5% versus metoprolol -18.9±2.2%; *P*=0.01). Two patients were excluded shortly after enrollment because of protocol violations (unrecognized LV ejection fraction <50% and severe aortic valve regurgitation at screening visits—both patients were referred to AVR). Furthermore, 2 patients discontinued their metoprolol treatment (Figure 1). The treatment dose (ie, stable dose) for the metoprolol and placebo group was 100±53 versus 126±35 mg (*P*=0.08), respectively.

Hemodynamic Effects of Metoprolol

Compared with placebo, metoprolol decreased HR by -8 minute⁻¹ (-3 to -13; *P*=0.001) and increased ejection time by 26 ms (2–50; *P*=0.03; Figure 2A and 2B). Changes in HR and in SV index correlated inversely (Figure 3A); and there was no statistically significant difference in change of cardiac index, SV, and blood pressure between the treatment groups (Table 2; Figure 4C and 4D).

Metoprolol reduced the progression of peak and mean aortic valve gradients by -7 mm Hg (-13 to 0; *P*=0.05) and -4 mm Hg (-7 to -1; *P*=0.03; Figures 2C and 4A); and changes were independent of alterations in SV index (adjusted *P*=0.02 for both). There was no correlation between changes in HR

Table 1. Characteristics

	Placebo (n=19)	Metoprolol (n=19)	<i>P</i> Value
General			
Age, y	71±5	69±5	0.33
Men, n (%)	14 (74)	10 (53)	0.31
BMI, kg/m ²	27±4	26±3	0.37
History of smoking, n (%)	6 (30)	8 (40)	0.51
Bicuspid aortic valve, n (%)	4 (21)	3 (16)	0.99
Hypertension, n (%)	12 (63)	9 (47)	0.33
Diabetes mellitus, n (%)	3 (16)	1 (5)	0.60
Medication, n (%)			
Aspirin	9 (47)	6 (32)	0.56
ACE inhibitor/ARB	8 (42)	4 (21)	0.16
Calcium antagonist	7 (37)	6 (32)	0.73
Statins	12 (63)	13 (68)	0.73
Diuretics	8 (42)	5 (26)	0.50

Values are mean±SD or n (%). ACE indicates angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; and BMI, body mass index.

Table 2. Baseline Values and Changes in Hemodynamic and Metabolic Parameters

	Placebo (n=19)			Metoprolol (n=19)			Δ (95% CI)	P Value
	Baseline	Follow-Up	Δ	Baseline	Follow-Up	Δ		
Hemodynamics								
HR, min ⁻¹	70±8	68±7	-2±5	69±8	59±10	-10±10	-8 (-13, -3)	0.001
Systolic BP, mm Hg	143±14	140±12	-3±12	141±11	136±13	-5±13	-2 (-10, 6)	0.41
Diastolic BP, mm Hg	81±9	81±7	0±7	81±8	79±8	-2±7	-2 (-6, 2)	0.28
MAP, mm Hg	102±10	101±8	-1±8	101±8	98±9	-3±8	-2 (-7, 3)	0.30
Cardiac index, L/min	3.0±0.7	2.8±0.6	-0.3±0.3	3.1±0.7	2.6±0.5	-0.5±0.5	-0.2 (-0.5, 0)	0.10
SVR, dyn×s/cm ⁵	1.5±0.3	1.7±0.5	0.2±0.4	1.5±0.4	1.7±0.4	0.2±0.3	0 (-0.2, 0.3)	0.59
Zva, mm Hg/mL per meter square	4.2±0.7	4.4±1.0	0.3±0.8	4.0±0.7	3.8±0.7	-0.3±0.8	-0.5 (-1, 0)	0.03
Wall stress, kPa	29±5	28±5	-1±4	27±5	28±5	1±5	2 (-1, 5)	0.55
Stroke work, J/min	93±22	89±25	-4±18	87±30	72±18	-14±17	-10 (-21, 1)	0.01
NT-proBNP, ng/L	127 (101 to 288)	160 (72 to 200)	-40±113	84 (59 to 278)	189 (120 to 313)	56±125	96 (18, 174)	0.002
Echocardiography								
AVA index, cm ²	0.5±0.1	0.5±0.1	0±0.1	0.5±0.1	0.5±0.1	0±0.1	0 (-0.1, 0)	0.44
Mean gradient, mm Hg	33±14	35±16	2±6	29±9	27±7	-2±4	-4 (-7, -1)	0.03
Peak gradient, mm Hg	56±23	60±29	4±11	50±15	48±12	-3±8	-7 (-13, 0)	0.05
Ejection time, ms	330±22	340±25	10±28	332±29	367±39	36±43	26 (2, 50)	0.03
GLS, %	-17.3±1.5	-15.6±1.9	1.7±1.9	-18.9±2.2	-16.2±2.2	2.7±1.5	1.0 (-0.5, 2.4)	0.92
E/e'	16.6±3.4	16.4±4.5	-0.2±3.6	15.5±6.0	14.4±6.4	-1.2±2.7	-1 (-3, 1)	0.28
E deceleration time, ms	287±77	296±61	9±60	281±58	281±59	-1±44	-10 (-45, 25)	0.44
E/A	0.8±0.2	0.8±0.2	0±0.1	0.9±0.3	0.9±0.3	0±0.3	0 (-0.1, 0.2)	0.28
Cardiovascular magnetic resonance								
Mass index, g/m ²	84±18	82±18	-2±8	83±19	78±15	-5±8	-3 (-8, 2)	0.18
EF, %	72±5	72±6	1±4	73±5	72±5	-1±6	-1 (-5, 2)	0.54
EDV index, mL/m ²	68±17	64±14	-4±10	64±16	66±14	1±12	5 (-2, 12)	0.25
ESV index, mL/m ²	20±7	18±7	-1±4	18±7	19±6	1±5	2 (-1, 5)	0.26
SV index, mL/m ²	43±8	41±9	-2±6	43±9	44±8	1±9	3 (-2, 8)	0.16
¹¹C-acetate PET								
MVO ₂ , mL/min per gram×10 ⁻³	124±54	119±45	-6±17	126±34	107±26	-20±20	-14 (-26, -2)	0.01
MBF, mL/min per gram	0.9±0.3	0.8±0.2	-0.1±0.1	0.9±0.2	0.7±0.2	-0.1±0.1	0 (-0.1, 0.1)	0.50
MEE, %	24.2±4.0	24.3±4.9	0.1±3.8	22.6±4.1	24.3±4.7	1.8±6.1	1.7 (-1.7, 5)	0.62
Other								
6-min walk test								
Distance, m	538±36	550±49	14±49	543±46	546±48	2±46	-12 (-47, 22)	0.36
Δ HR, min ⁻¹	46±13	49±14	2±11	46±14	35±12	-9±14	-11 (-20, -2)	0.003
Borg score	11±3	12±2	1±3	11±2	13±2	1±2	0 (-2, 2)	0.34
Quality of life*	4 (2 to 8)	3 (0 to 8)	-1±4	3 (1 to 6)	5 (2 to 9)	5±14	6 (-1, 12)	0.13

Values are reported as mean±SD, median (interquartile range), or mean difference (95% CI). P values are placebo vs metoprolol adjusted for baseline values. AVA indicates aortic valve area; BP, blood pressure; CI, confidence interval; EDV, end-diastolic volume; EF, ejection fraction; ESV, end-systolic volume; GLS, global longitudinal strain; HR, heart rate; MAP, mean arterial blood pressure; MBF, myocardial blood flow; MEE, myocardial external efficiency; MVO₂, myocardial oxygen consumption; NT-proBNP, N-terminal pro-B-type natriuretic peptide; PET, positron emission tomography; SV, stroke volume; SVR, systemic vascular resistance; and Zva, valvuloarterial impedance.

*Minnesota Living with Heart Failure Questionnaire (high score=low quality).

and gradients when the treatment groups were analyzed separately, whereas decreased HR correlated with reduced peak gradients when both groups were analyzed together ($r=0.34$; $P=0.04$).

Patients treated with metoprolol had 12% (ie, -0.5 mm Hg/mL per meter square) lower Zva than patients treated with placebo ($P=0.03$; Figures 2D and 4B); and reduced Zva was associated with a decreased HR ($r=0.65$; $P=0.003$; Figure 3C).

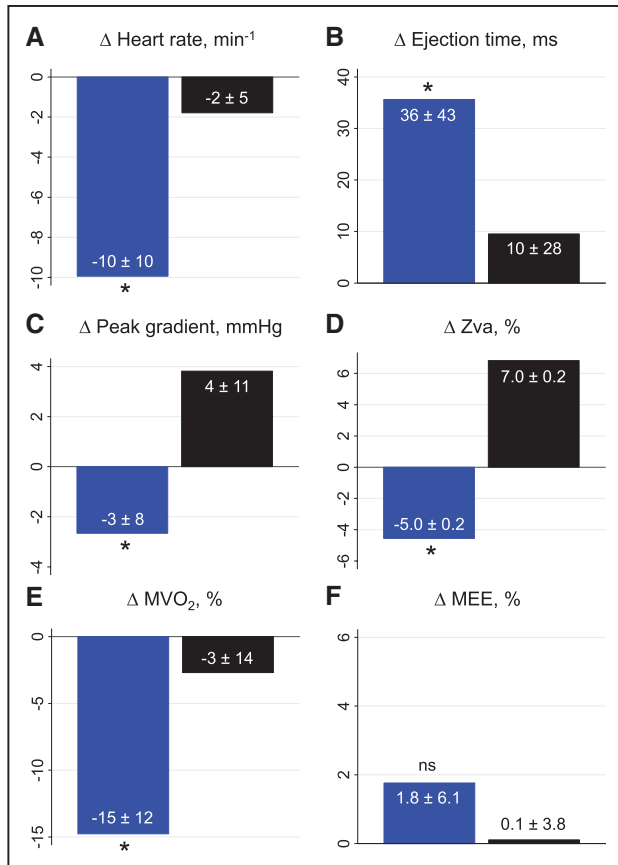


Figure 2. Changes in hemodynamic (A–F) parameters for patients treated with metoprolol (blue) and placebo (black). MEE indicates myocardial external efficiency; MVO₂, myocardial oxygen consumption; ns, nonsignificant; and Z_{va}, valvuloarterial impedance. $P < 0.05$.

There were no statistically significant differences in changes in LV ejection fraction or global longitudinal strain between treatment groups.

Effects of Metoprolol on MVO₂ and Efficiency

Compared with placebo, metoprolol reduced MVO₂ by -14 mL/min per gram ($-26, -2$; $P = 0.01$; Table 2; Figure 4E), corresponding to a relative reduction of -12% (-21 to -3 ; $P = 0.01$; Figure 2E). Changes in HR and MVO₂ correlated positively in both treatment groups (Figure 3D).

The mean absolute change in MEE was 1.7% (-1.7 to 5.0 ; $P = 0.62$; Table 2; Figures 2F and 4F) and MEE improvements correlated with reduced Z_{va} ($r = 0.64$; $P = 0.003$).

Changes in resting myocardial blood flow did not differ between treatment groups neither before nor after correction for stroke work (Table 2); and there was no correlation between changes in myocardial blood flow and HR.

Biomarkers and Substrates

NT-proBNP increased for patients treated with metoprolol compared with placebo (96 ng/L; 18 – 174 ; $P = 0.001$). NT-proBNP correlated positively with SV index and MEE ($r = 0.59$ and 0.56 ; all $P < 0.001$), whereas there was an inverse correlation with Z_{va} ($r = -0.58$; $P < 0.001$). No statistically significant differences were observed for plasma concentrations of free fatty acids, ketones, lactate, catecholamine

metabolites, glucose, and insulin between treatment groups (data not shown).

Cardiovascular Safety of Metoprolol

No serious adverse cardiovascular events were observed in the placebo group. In the metoprolol group, 1 patient developed congestion 2 to 3 weeks after enrollment and 1 patient experienced atypical chest pain shortly before study completion. There were 2 cardiovascular adverse events in the placebo group (hypertension and anemia) compared with 4 in the metoprolol group (dizziness, cold hands/feet, bradycardia, and fatigue).

All reactions ceased after a reduction in dose or discontinuation of the treatment, except for the patients who experienced congestion and atypical chest pain. Both patients were referred to AVR.

Discussion

This study is the first to investigate the effects of metoprolol in patients with asymptomatic moderate-severe AS in a randomized design. The 2 main findings were that metoprolol: (1) unloaded the LV by reducing afterload (ie, aortic valve gradients and Z_{va}); and (2) lowered myocardial oxygen requirements.

Hemodynamic Effects of β -Blocker Treatment in Asymptomatic AS

Pharmacological studies with angiotensin-converting enzyme inhibitors or statins have attempted to halt the progression of AS.^{3–5} However, results have been disappointing, and currently no medical treatment can modify the natural history of AS. Interestingly, retrospective studies have suggested that β -blockers postpone the need for AVR and improve survival in patients with AS.^{12,13} However, no prospective clinical studies have demonstrated the hemodynamic effects of β -blocker therapy in patients with AS.

In the present study, metoprolol unloaded the LV by decreasing aortic valve gradients and Z_{va}, which are both strong predictors of LV function and survival in patients with AS.^{24,25,31,32} This was caused by a decrease in HR with prolonged ejection time (Figure 5), a mechanism previously suggested as a target for intervention in patients with AS.³³ In this context, it is important to stress that the reduction in afterload represents the effect on 1 heartbeat and therefore increases proportionally to the magnitude of the reduction in HR. Most importantly, the reduction in valve gradients was independent of any change in SV.

We observed no statistically significant changes in cardiac index or blood pressure in patients who were treated with metoprolol (Table 2). This was explained by the fact that a reduction in HR was compensated by a proportional increase in SV (Figure 3A). Moreover, systemic vascular resistance remained unaltered, whereas Z_{va} was reduced. These results support the unloading effects of metoprolol to act on the valvular rather than the arterial component of afterload in patients with AS. Interestingly, these beneficial effects display striking similarities with the hemodynamic effects of β -blocker therapy in patients with hypertrophic obstructive cardiomyopathy (eg, reduced pressure gradients and flow acceleration).³⁴

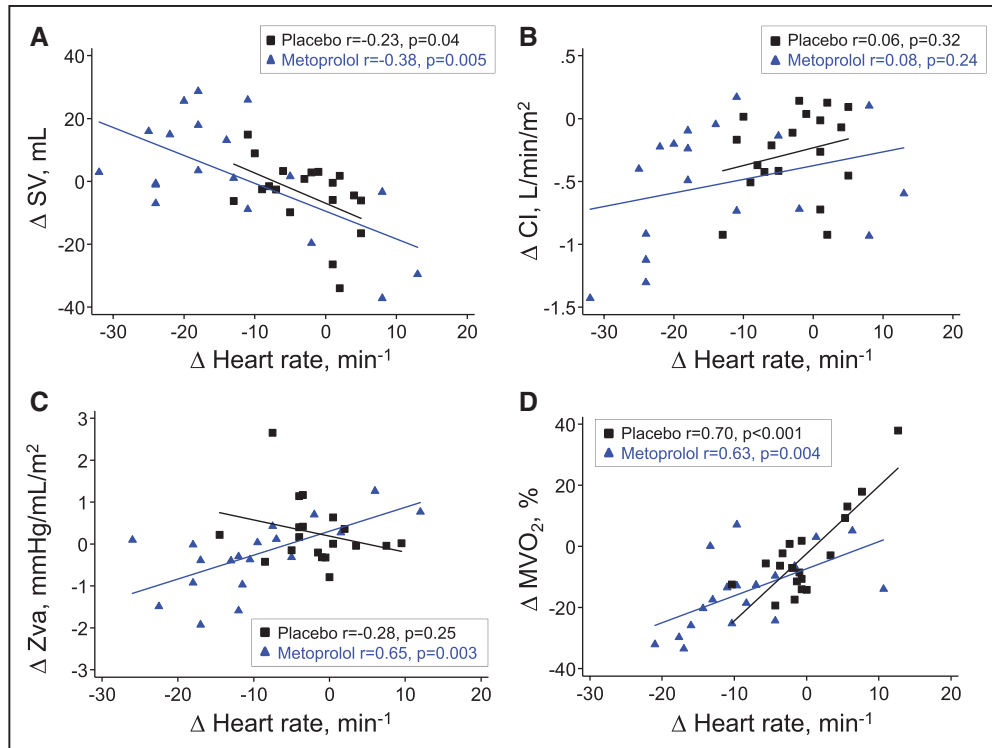


Figure 3. Correlation analysis for changes in heart rate. In patients treated with metoprolol, reduced heart rate correlated with increased stroke volume (SV; **A**). This resulted in an unaltered cardiac index (CI; **B**). Reduced heart rate decreased valvuloarterial impedance (Zva; **C**) and myocardial oxygen consumption (MVO₂; **D**). Heart rate measurements were performed during cardiovascular magnetic resonance (**A+B**), echocardiography (**C**), and positron emission tomography (**D**).

Thus, despite fundamental differences in the flow profile between AS and hypertrophic obstructive cardiomyopathy (fixed versus dynamic flow obstruction), the positive effects of β -blocker therapy seem to be translatable.

Hence, this study is the first randomized clinical trial to demonstrate a reduced LV afterload from a nonsurgical treatment strategy in patients with asymptomatic AS. These results may represent an important breakthrough in the search for a medical therapy, which can improve prognosis in a large and growing population of patients with asymptomatic AS.

Effects of Metoprolol on Cardiac Energetics

Normal myocardial function relies on a tight coupling between MVO₂ and stroke work; and uncoupling, that is, reduced myocardial efficiency, has been linked to a poor prognosis.³⁵ Similarly, the transition from compensated hypertrophy to failure in patients with AS is characterized by reduced myocardial efficiency caused by an increase in total MVO₂ (ie, MVO₂ × LV mass) and an inability to maintain stroke work.^{10,36} Thus, a combination of hemodynamic and metabolic overload contributes to the onset of heart failure in patients with AS.

β -Blockers are known to reduce MVO₂ and improve myocardial efficiency, important properties which have been linked to increased survival.^{14,15} Thus, β -blocker therapy in patients with AS may act to preserve normal myocardial efficiency and reduce AS patients' vulnerability for myocardial ischemia. However, negative inotropic effects may trigger the onset of heart failure; and despite frequently being prescribed to patients with AS, there is no evidence to support how β -blockers may affect MVO₂ and mechanoenergetic coupling.

Reduced Zva was associated with improved myocardial efficiency. This suggests that LV unloading improves coupling between mitochondrial energy production and stroke work, a finding which is supported by increasing myocardial efficiency in patients with AS who undergo AVR.³⁶ However, despite this evident relationship between afterload and myocardial efficiency, there was no overall improvement in MEE for patients treated with metoprolol (Figures 2F and 4F). This may be explained by the fact that we investigated patients with asymptomatic AS who in contrast to AS patients with heart failure may have a normal or near-normal MEE.¹⁰

Furthermore, the patients in the metoprolol group displayed a 12% reduction in MVO₂ and preserved their myocardial blood flow. Consequently, it could be argued that the oxygen extraction fraction is reduced by metoprolol therapy in patients with AS and that metoprolol carries a protective effect against myocardial ischemia.

Safety of Metoprolol in Patients With Asymptomatic AS

Patients with AS often display concomitant diseases, for example, ischemic heart disease or hypertension, which qualifies patients for β -blocker treatment.¹¹ However, evidence of the safety of such treatment and studies describing how β -blocker agents affect patients with AS are scarce.

In the current study, the total treatment period for each group was \approx 8 years (ie, 19 patients × 22 weeks), during which we registered 2 adverse cardiovascular events in the metoprolol group compared with none in the placebo group. The patient who developed atypical chest pain had a normal

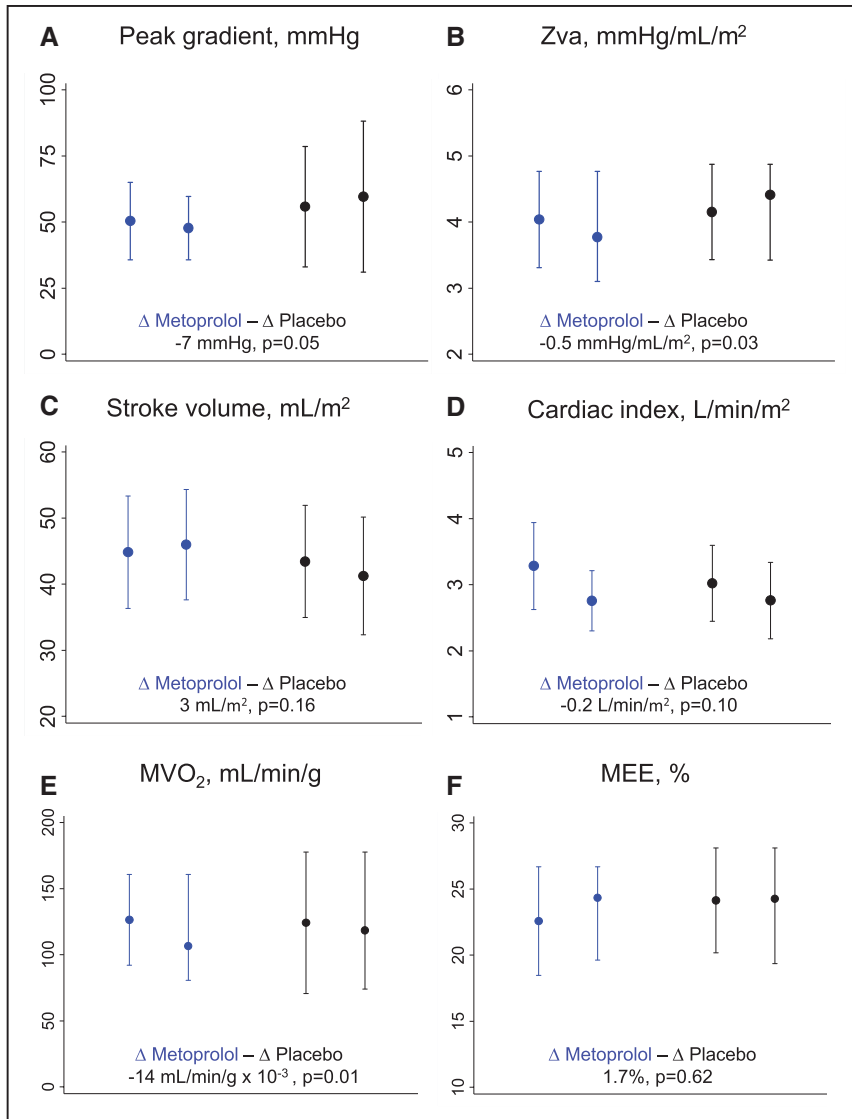


Figure 4. A–F, Baseline and follow-up data for patients treated with metoprolol (blue) and placebo (black). MEE indicates myocardial external efficiency; MVO₂, myocardial oxygen consumption; and Zva, valvuloarterial impedance.

coronary angiogram; and symptoms did not disappear after study completion (ie, after discontinued metoprolol treatment). Instead, AVR effectively relieved all symptoms supporting severe AS to be the main reason for this event. The

patient who experienced congestion had severe LV hypertrophy (LV mass index=131 g/m²), which is well-known to be associated with a poor clinical outcome in patients with AS.^{37,38} This patient also failed to register and report signs of heart failure (weight gain and dyspnea) during the initial uptitration period. Thus, a combination of an advanced stage of AS, a high metoprolol dose (150 mg), and an inappropriately late reduction of the dose/discontinuation of the treatment are likely to have caused this event.

A small increase in NT-proBNP was observed in patients who were treated with metoprolol, a finding which may raise concerns. However, this is a well-known phenomenon when initiating β -blocker treatment in patients with a normal or near-normal NT-proBNP.^{39,40}

Finally, an extensive reduction in HR (eg, >-20 minute⁻¹) appeared to inhibit the compensatory increase in SV and to reduce cardiac index (Figure 3A and 3B). This may diminish any favorable effect achieved by metoprolol and increase the risk of adverse effects. Thus, future studies investigating the effect metoprolol in patients with AS should carefully consider the magnitude of HR reduction.

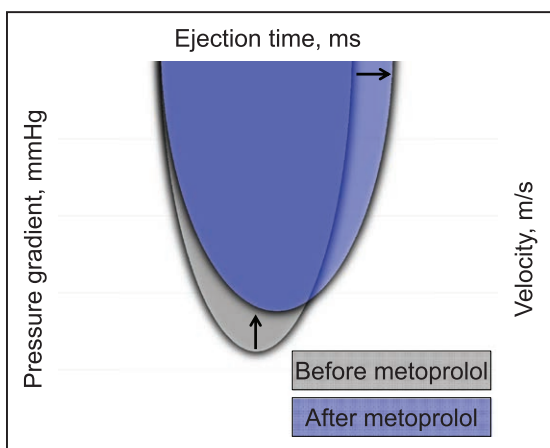


Figure 5. Metoprolol reduces heart rate and increases ejection time. Consequently, aortic valve jet velocity decreases, that is, pressure gradients are reduced.

In summary, treatment with metoprolol appeared well tolerated in patients with moderate-severe AS when using a careful up-titration strategy of the dose and appropriate monitoring. However, it is important to emphasize that the current study was not powered to investigate the safety of metoprolol treatment in patients with AS.

Limitations

It could be argued that the applicability of the results presented in this study is limited by the fact that no patients had, for example, ischemic heart disease, atrial fibrillation, or systolic heart failure. However, for these comorbidities, β -blocker therapy already has a well-documented effect; and it is likely that AS patients with any of these diseases would benefit equally or more from treatment with metoprolol.

Furthermore, the validity of the conclusions in the current study is restricted by the relatively short treatment period (ie, 22 weeks), which also prevents the authors from assessing the long-term effects of metoprolol therapy. Thus, the results from the present study need to be confirmed in prospective studies investigating the effects of metoprolol on clinical end points in a larger and more diverse population of patients with AS.

Conclusion

In patients with asymptomatic AS, metoprolol treatment increases systolic ejection time and decreases aortic valve gradients and valvuloarterial impedance, without reducing SV. Consequently, metoprolol decreases stroke work and myocardial oxygen requirement. These results may represent an important breakthrough in the search for medical treatment strategies, which can postpone or prevent the need for AVR in patients with asymptomatic AS.

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Disclosures

Dr Wiggers has been the principal or a subinvestigator in studies involving the following pharmaceutical companies: MSD, Bayer, Daiichi-Sankyo, Novartis, Novo Nordisk, Sanofi-Aventis and Pfizer. The other authors report no conflicts.

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CLINICAL PERSPECTIVE

Currently, no pharmacological treatment can modify the natural history of aortic valve stenosis (AS). β -Blockers are widely used in patients with asymptomatic AS, but the safety and hemodynamic effects of the treatment have never been studied in a randomized study. In a double-blinded design, the current report investigated the effects of metoprolol treatment in patients with asymptomatic AS. Metoprolol reduced aortic valve gradients and total left ventricular afterload (ie, valvuloarterial impedance) independently of any change in stroke volume or cardiac index. These unloading effects were further supported by a significant decrease in myocardial oxygen consumption (12%) in patients treated with metoprolol. Thus, metoprolol seems to ease the hemodynamic and metabolic burden induced by AS and could prove to postpone the need for aortic valve replacement in patients with AS.

Metoprolol Reduces Hemodynamic and Metabolic Overload in Asymptomatic Aortic Valve Stenosis Patients: A Randomized Trial

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