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Research Article

Association of beta-blocker use with increased aortic wave reflection

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Abstract

Studies have found less cardiovascular risk reduction in patients treated with beta-blockers (BBs) compared with other agents. We compared the severity of aortic atherosclerosis, arterial stiffness, and wave reflection in patients treated and not treated with BBs. Seventy-two patients, 37 treated with BBs and 35 not treated, referred for transesophageal echocardiography were studied. Augmentation index (AI), heart-rate-corrected AI (AI-75), aortic systolic (SBP) and diastolic blood pressure, pulse wave velocity (PWV), and aortic intima-media thickness (MAIMT) were measured. There were no differences in MAIMT (2.8 ± 1.6 mm vs. 2.4 ± 1.2 mm, $P = .20$) and PWV (8.9 ± 2.0 m/s vs. 8.5 ± 2.6 m/s, $P = .46$) between the BB and non-BB groups. The BB group had higher AI (28.7 ±11.9% vs. 22.3 ± 14.1%, $P = .04$), AI-75 (27.7 ± 10.7% vs. 20.1± 11.0%, $P = .005$), aortic SBP (140 ± 21 mm Hg vs. 125 ± 21 mm Hg, $P = .01$), and aortic pulse pressure (62 ± 20 mm Hg vs. 47 ± 19 mm Hg, $P = .01$) than the non-BB group despite similar brachial blood pressure. BB use was associated with increased aortic wave reflection despite similar degree of aortic atherosclerosis. © 2008 American Society of Hypertension. All rights reserved.

Keywords: Beta-blockers; atherosclerosis; arterial stiffness; augmentation index.

Introduction

Beta-blockers (BBs) have long been recommended as first-line treatment for hypertension. Recently, their benefits with regard to cardiovascular risk reduction have come into question. Large meta-analyses have found BBs inferior to other medications in reducing stroke and mortality.[1,2] The reason for these findings is unknown. BBs are known to portend deleterious effects on glucose and lipid metabolism.[3,4] Specifically, these agents worsen insulin resistance and increase triglycerides in a dose-dependent manner.

In addition, although BBs lower blood pressure (BP) to similar degrees as other drug classes, they have been found to be less effective in regressing left ventricular (LV) hypertrophy.[5,6] This latter observation has led to speculation that BBs cause deleterious effects on arterial stiffness. Studies of BB effects on arterial stiffness have shown variable results.[7–15] Accordingly, the objective of this study was to compare arterial stiffness and wave reflection indices in patients who were on treatment with and without BBs.

Methods

The study protocol was approved by the State University of New York Downstate Institutional Review Board. We prospectively studied 72 patients over 18 years of age who were referred for transesophageal echocardiography (TEE) and had applanation tonometry within 24 hours. Indications for TEE examination included cerebrovascular accident in 30%, atrial fibrillation in 30%, assessment of valvular heart disease in 28%, and 12% for other miscellaneous indications. Clinical data including past medical history, smoking status, family history, and medications were obtained from patient interview and chart review. For study purposes patients were categorized into those taking BBs and those not taking BBs at the time of the study. The duration of BB therapy was not evaluated. Patients were excluded if they had inadequate radial, brachial, or carotid pulses for applanation tonometry, if they reported or had documented noncompliance with medications, had atrial fibrillation, or had inadequate TEE measurements. Risk factors evaluated in this study included age, hypercholestrolemia, diabetes mellitus, hypertension, body mass index, family history of cor-

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onary artery disease, previous stroke, and smoking status. Smokers were defined as patients consuming at least one cigarette daily. Hypercholesterolemia, hypertension, and diabetes mellitus were defined as self-reported, documented diagnosis, or treatment with medications.

Measurement of Aortic Intima-Medial Thickness

Using a standardized clinical approach, TEE was performed using a Phillips SONOS 5500 equipped with a 4.0- to 7.0-MHz multi-plane TEE probe (Phillips, Andover, MA). The probe was advanced to distal esophagus and rotated posteriorly and slowly withdrawn to scan descending thoracic aorta. For every patient, gain and instrument settings were optimized for imaging the aortic wall. The entire study was recorded on standard super VHS videotape for subsequent off-line analysis and interpretation. The maximal aortic intima-media thickness (MAIMT) was defined as the distance in millimeters between the leading edge of the lumen-intima echo and the leading edge of the media-adventia echo on cross-sectional images of descending aorta. Three MAIMT measurements taken of the descending aortic wall at the maximum dimension visualized were averaged. Aortic atherosclerosis was also quantified to an ordinal grading scale of intima-media complex.[16] Grade I was defined as a smooth and continuous intimal surface, with an intima-medial thickness <1.0 mm. Grade II was simple atherosclerotic plaque with increased echo density of the intima extending <3.0 mm into the aortic lumen. Grade III was atherosclerotic plaque extending ≥3.0 mm and <5.0 mm into the aortic lumen, and grade IV was atherosclerotic plaque ≥5.0 mm. Two experienced observers who had no knowledge of the hemodynamic data interpreted the TEE recordings independently. The intra-observer and inter-observer coefficient of variation between measurements of MAIMT were 5.1% and 4.7%, respectively, with the MAIMT range from 1.1 to 6.9 mm.

Measurement of Arterial Stiffness

Arterial stiffness and arterial wave reflection was evaluated by measuring augmentation index (AI) and pulse wave velocity (PWV) by applanation tonometry, using SphygmoCor applanation tonometer, software version 8.0 (AtCor Medical, New South Wales, Australia). The central aortic pressure waveform, aortic systolic blood pressure (SBP), aortic diastolic blood pressure (DBP), aortic pulse pressure (PP), and AI were derived from the radial artery waveform by means of a validated generalized transfer function.[17] AI was defined as the proportional increase in systolic pressure due to the reflected wave and was expressed as a percentage of the PP. AI was also heart-rate-adjusted to a heart rate of 75 beats/min.[18] Sequential recordings of arterial pressure waveform at the carotid and radial arteries measured the carotid-to-radial PWV. Distances from the supra-sternal notch to the carotid sampling site (distance A) and from the supra-sternal notch to the radial artery (distance B) were measured. PWV distance was calculated as distance B minus distance A. PWV was calculated as the ratio of the distance in meters to the transit time in seconds.

Statistics

All values were expressed as mean ± standard deviation. Univariate associations between study variables were analyzed using the Spearman correlation coefficients. Continuous data were compared using the Student *t* test. The Fisher exact test was used to compare dichotomous variables. Stepwise linear regression analysis was used to assess the association of independent predictors of aortic wave reflection defined by heart-rate-corrected AI (AI-75). All statistical analyses were achieved using the Statistical Package for Social Sciences 15.0 software (SPSS Inc., Chicago, IL). A P value <.05 was considered to be statistically significant.

Results

The population studied was predominantly middle-aged, African-American, female, and overweight. Of the 72 patients, 37 were taking BBs, and 35 were not taking BBs. The mean age for BB group was similar to the non-BB group (59 ± 14 vs. 62 ± 14 years) (P = .47). There were 73% females in the BB group and 63% females in the non-BB group (P = .36). Specific BBs included: labetalol in 43%, metoprolol 41%, atenolol 11%, and carvedilol in 5% of patients. The BB group had a lower proportion of African-Americans (76% vs. 100%, P = .002) and was more likely to be on statin drugs (54% vs. 26%, P = .02). Other baseline characteristics were similar between the groups (Table 1).

On the basis of grading system described by Rohani et al,[16] the majority of patients had grade II (n = 50) and grade III (n = 16) aortic atherosclerosis. Six patients had grade IV lesions, and none had grade I lesions. Among the 37 patients taking BBs, 62.2%, 24.3%, and 13.5% had grade II, III, and grade IV lesions, respectively, while in the non-BB group, 77.1%, 20%, and 2.9% had grade II, III, and grade IV lesions, respectively. There was no significant difference in the distribution of the atherosclerotic grades between BB and non-BB groups (P = .20).

There were no significant differences in mean MAIMT (2.8 ± 1.6 mm vs. 2.4 ± 1.2 mm, P = .20), PWV (8.9 ± 2.0 m/s vs. 8.5± 2.6 m/s, P = .46), brachial SBP (146 ± 25 mm Hg vs. 144 ± 22 mm Hg, P = .64), brachial DBP (72 ± 15 mm Hg vs. 77 ± 15 mm Hg, P = .13), brachial PP (75 ± 15 mm Hg vs. 66 ± 23 mm Hg, P = .07), and aortic DBP (78 ± 12 mm Hg vs. 77 ± 16 mm Hg, P = .81) between the BB and non-BB groups. As shown in Table 2 and in the Figure, the BB group had significantly higher AI (28.7 ± 11.9% vs. 22.3 ± 14.1%, P = .04), AI-75 (27.7 ± 10.7% vs. 20.1 ± 11.0%, P = .005), aortic SBP (140 ± 21 mm Hg