

## Beta-Blocker Use Is Associated With Impaired Left Atrial Function in Hypertension

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**Background**—Impaired left atrial (LA) mechanical function is present in hypertension and likely contributes to various complications, including atrial arrhythmias, stroke, and heart failure. Various antihypertensive drug classes exert differential effects on central hemodynamics and left ventricular function. However, little is known about their effects on LA function.

**Methods and Results**—We studied 212 subjects with hypertension and without heart failure or atrial fibrillation. LA strain was measured from cine steady-state free-precession cardiac MRI images using feature-tracking algorithms. In multivariable models adjusted for age, sex, race, body mass index, blood pressure, diabetes mellitus, LA volume, left ventricular mass, and left ventricular ejection fraction, beta-blocker use was associated with a lower total longitudinal strain (standardized  $\beta = -0.21$ ;  $P = 0.008$ ), and lower LA expansion index (standardized  $\beta = -0.30$ ;  $P < 0.001$ ), indicating impaired LA reservoir function. Beta-blocker use was also associated with a lower positive strain (standardized  $\beta = -0.19$ ;  $P = 0.012$ ) and early diastolic strain rate (standardized  $\beta = 0.15$ ;  $P = 0.039$ ), indicating impaired LA conduit function. Finally, beta-blocker use was associated with a lower (less negative) late-diastolic strain (standardized  $\beta = 0.15$ ;  $P = 0.049$ ), strain rate (standardized  $\beta = 0.18$ ;  $P = 0.019$ ), and a lower active LA emptying fraction (standardized  $\beta = -0.27$ ;  $P < 0.001$ ), indicating impaired booster pump function. Use of other antihypertensive agents was not associated with LA function.

**Conclusions**—Beta-blocker use is significantly associated with impaired LA function in hypertension. This association could underlie the increased risk of atrial fibrillation and stroke seen with the use of beta-blockers (as opposed to other antihypertensive agents) demonstrated in recent trials. (*J Am Heart Assoc.* 2017;6:e005163. DOI: 10.1161/JAHA.116.005163.)

**Key Words:** angiotensin-converting enzyme inhibitors •  $\beta$ -adrenergic antagonists • hypertension • left atrium • magnetic resonance imaging

An increase in left atrial (LA) size in patients with hypertension has long been known to be associated with worse cardiovascular morbidity and mortality.<sup>1,2</sup> Over the last decade, however, the prognostic importance of

phasic LA function, independent of LA size, has been recognized.<sup>3</sup> Compensatory changes in dynamic LA function are seen early in the course of hypertension, even before left ventricular hypertrophy (LVH) develops. Early in response to the impaired left ventricular (LV) relaxation in hypertension, the conduit function of the LA decreases, whereas its booster function increases.<sup>4</sup> However, with progression of hypertensive heart disease, booster function also declines and is associated with progression to heart failure<sup>5,6</sup> and a poor prognosis.<sup>7</sup>

Various classes of antihypertensive medications exert differential effects on LV function and central hemodynamics. Available trials, including the Losartan Intervention For Endpoint reduction (LIFE) and the Anglo Scandinavian Cardiac Outcomes Trial (ASCOT) [as well as the Conduit Artery Function Evaluation (CAFE) substudy of ASCOT] have shown that, among patients with hypertension, atenolol, when compared to angiotensin receptor blockers (ARBs) and calcium-channel blockers, is associated with lower LV mass regression,<sup>8</sup> greater central systolic pulse pressure relative to brachial pressures (ie, lower pulse pressure amplification),<sup>9</sup> and a higher risk of

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An accompanying Video S1 is available at <http://jaha.ahajournals.org/content/6/2/e005163/DC1/embed/inline-supplementary-material-1.mov>

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stroke<sup>10</sup> and atrial fibrillation (AF).<sup>11</sup> Unfortunately, little is known about the effects of various antihypertensive agents on LA function. In particular, an unfavorable effect of beta-blockers on LA function is a plausible mechanism for the increased risk of AF and stroke associated with beta-blocker use, compared to angiotensin receptor blockade.<sup>11</sup> However, no data are available regarding the association between the use of beta-blockers (or other antihypertensive drugs) and LA function.

In this study we aimed to assess whether the use of beta-blockers, when compared to other antihypertensive agents, is associated with impaired LA function, as assessed by MRI-based measurements of atrial deformation and phasic volumes.

## Methods

### Study Population

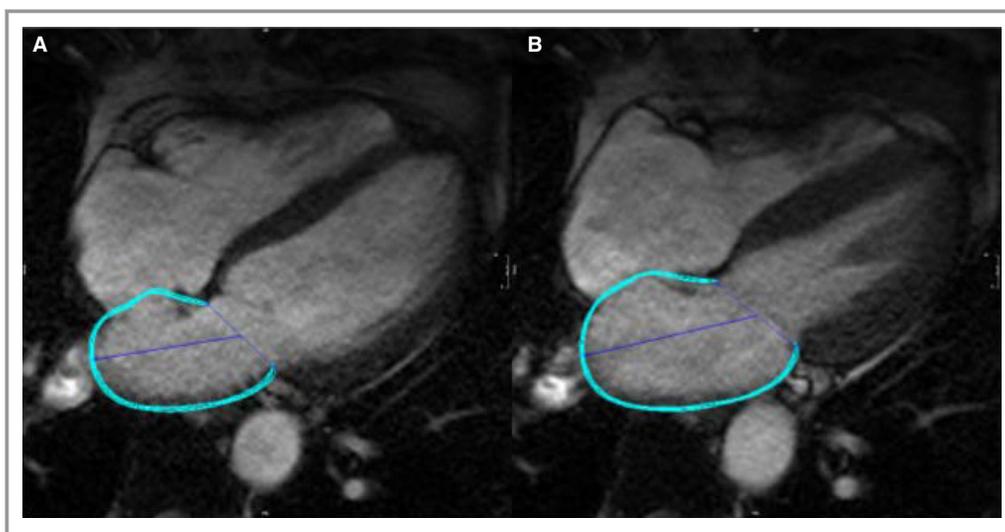
We enrolled a convenience clinical sample of 212 subjects with history of hypertension at the Corporal Michael J. Crescenz VA Medical Center. The protocol was approved by the Philadelphia VA Medical Center Institutional Review Board, and written informed consent was obtained from all participants. Key exclusion criteria were as follows: (1) claustrophobia; (2) presence of metallic objects or implanted medical devices within the body; (3) AF at the time of enrollment; (4) conditions that would make the study measurements less accurate or unreliable (ie, arrhythmia affecting cardiac gating, inability to perform an adequate breath hold for cardiac MRI acquisitions); (5) heart failure with preserved or reduced ejection fraction (EF); and (6) a left ventricular EF <50%.

### Cine Imaging

Participants underwent a cardiac MRI examination to assess LV structure and function, using a 1.5-Tesla (T) whole-body MRI scanner (Avanto or Espree, Siemens, Malvern, PA) equipped with a phased-array cardiac coil. LV volumes and EF were determined using balanced steady-state free-precession (SSFP) cine imaging. Typical parameters were as follows: TR=30.6 milliseconds; TE=1.3 milliseconds; phases=30; slice thickness=8 mm; matrix size=192×192; and parallel image (IPAT) factor=2. LV short-axis stack cine images were manually traced at end-diastole and end-systole using CMR42 software (Circle CVI, Calgary, AB, Canada). LV mass (LVM) was computed as the difference between epicardial and endocardial volumes, multiplied by myocardial density. LVM was normalized for body height in meters raised to the allometric power of 1.7.<sup>12</sup>

### Left Atrial Longitudinal Strain and Volumetric Analysis

All image analyses were performed using cvi42 image analysis software (Circle Cardiovascular Imaging Inc, Calgary, AB, Canada), blinded to the clinical characteristics of the study subjects. Feature-tracking techniques for the measurement of LA phasic strain have previously been described.<sup>13,14</sup> LA endocardial borders were manually traced in apical 2- and 4-chamber views using LV end-diastole as the point of reference. An automated tracking algorithm was applied, and the tracking of all atrial segments was confirmed. Manual



**Figure 1.** Representative example of atrial tissue tracking using cine SSFP-MRI images. A, The diastolic left atrial phase, in which reference points are prescribed. B, The tracking of atrial tissue, shown at a different phase of the cardiac cycle (see Video S1). The blue line represents the atrial wall contour. MRI indicates magnetic resonance imaging; SSFP, steady-state free-precession.

adjustments were performed as needed to optimize wall tracking. An example of atrial wall tracking is shown in Figure 1 and in Video S1.

Values of segmental deformation were exported and further processed using custom software programmed in Python (Python Software Foundation, Wilmington, DE). We recomputed strain (deformation) and strain rate relative to the diastatic LA length (rather than end-diastolic length), because diastasis represents the length for LA tissue at the end of atrial diastole (reference phase). As shown in Figure 2, strain and strain rate were calculated in the reservoir (total longitudinal strain), conduit (positive longitudinal strain and early-diastolic strain rate), and booster (negative longitudinal strain and late-diastolic strain rate) phases.<sup>14</sup> Maximum ( $LA_{MAX}$ ), minimum ( $LA_{MIN}$ ), and diastatic ( $LA_{DIAS}$ ) LA volumes were also measured. LA expansion index, passive LA emptying fraction (LAEF), and active LAEF were calculated as volumetric measures of reservoir, conduit, and booster phases, respectively. LA expansion index was calculated as  $(LA_{MAX}-LA_{MIN})/LA_{MIN}$ , passive LAEF as  $(LA_{MAX}-LA_{DIAS})/LA_{MAX}$ , and active LAEF as  $(LA_{DIAS}-LA_{MIN})/LA_{MAX}$ .

## Measurement of Central Blood Pressure

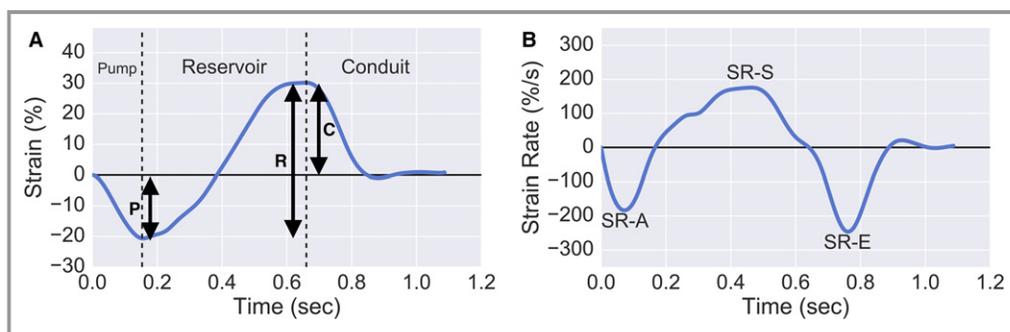
Arterial tonometry of the common carotid artery was performed using a SphygmoCor EM3 device (AtCor Medical, Sydney, Australia), equipped with a high-fidelity Millar Applantation tonometer (SPT-301; Millar Instruments, Houston, TX). Tonometry was performed at the carotid artery in the supine position immediately after the MRI. The carotid waveform was calibrated with brachial diastolic and mean blood pressures (which do not vary substantially along the arterial tree) and were used as a direct surrogate of the central pressure waveform. This approach does not require the use of a generalized transfer function.

## Statistical Methods

Continuous variables are presented as mean $\pm$ SD. Categorical variables are presented as frequencies and percentages. Various general characteristics and parameters of LA function were compared between subjects who were receiving beta-blockers versus those who were not. For continuous variables, we used nonpaired t tests or Wilcoxon signed-rank tests as appropriate. For categorical variables, we used chi-squared tests. Multivariable linear regression was then performed to determine the relationship between beta-blocker use (expressed as a binary variable) and various measures of LA function. This relationship was assessed after adjustment for potential confounders, including age, sex, race, body mass index, systolic blood pressure, diastolic blood pressure, diabetes mellitus, LA volume, LV mass, and LV EF. For easier comparisons of the magnitude of the relationships of different predictors, we present standardized regression coefficients ( $\beta$ ). All probability values are 2-tailed. Statistical significance was defined as a 2-tailed  $P<0.05$ . All statistical analyses were performed using SPSS software (SPSS v24 for Mac; IBM SPSS version 24, Chicago, IL).

## Results

Baseline characteristics of study participants are presented in Table 1. The average age was  $63\pm 10$  years; the majority of subjects were males (94%), with similar proportions of white and black participants. There was a moderate prevalence of other cardiovascular risk factors, including diabetes mellitus, hyperlipidemia, and smoking. Mean systolic and diastolic blood pressures were  $147\pm 19$  and  $84\pm 12$  mm Hg. The majority of participants were receiving more than 1 antihypertensive agent at the time of enrolment. There were no significant differences in most



**Figure 2.** Representative Plots of Strain (A), and Strain rate (B), along with measures of reservoir, conduit and booster pump function derived from strain and strain rate measurements. A, left atrial strain curve, where total (reservoir, R), positive (conduit, C) and negative (booster pump, P) strain are demonstrated. B, left atrial strain rate curve, where early diastolic (SR-E), late-diastolic (SR-A) and systolic (SR-S) strain rate can be demonstrated. SR-E and SR-A represent left atrial conduit and booster pump function, respectively. Note that atrial diastasis was used as the reference length for all strain/strain rate measurements.

**Table 1.** Baseline Characteristics of Study Participants

Characteristics	Beta-blocker Use (n=106)	No Beta-blocker Use (n=106)	P Value
Age, y	63±9	62±10	0.41
Male sex	102 (96)	97 (91)	0.15
Race			
White	49 (46)	51 (48)	0.49
Black	49 (46)	52 (49)	0.49
Body mass index, kg/m <sup>2</sup>	31±7	31±7	0.87
Systolic blood pressure, mm Hg	148±19	145±18	0.26
Diastolic blood pressure, mm Hg	84±14	84±11	0.46
Mean blood pressure, mm Hg	117±17	114±14	0.16
Pulse pressure, mm Hg	63.8 (13.6)	62.1 (14.4)	0.39
Current smoker	19 (18)	33 (31)	0.025
Diabetes mellitus	47 (44.3)	53 (50)	0.41
Hemoglobin A1C, %	6.5±1.3	6.4±1.6	0.61
eGFR, mL/(min·1.73 m <sup>2</sup> )	85±29	86±30	0.80
Coronary artery disease	18 (17)	45 (42.5)	<0.001
ACE inhibitor use	62 (59)	54 (51)	0.27
ARB use	13 (12)	10 (9)	0.51
Calcium-channel blocker use	36 (34)	39 (37)	0.67
Thiazide use	32 (30.2)	38 (36.2)	0.36
Spirolactone use	6 (5.7)	2 (1.9)	0.28
Specific beta-blocker used			
Metoprolol	55 (51.9)	—	—
Carvedilol	28 (26.4)	—	—
Atenolol	13 (12.3)	—	—
Labetalol	4 (3.8)	—	—
Propranolol	4 (3.8)	—	—
Other	2 (1.9)	—	—
LVEF, %	60±8	62±8	0.035
LVM, g	154±41	151±38	0.54
LVM index, g/m <sup>1.7</sup>	58±14	58±14	0.89
Left atrial volume index, mL/m <sup>2</sup>	33±14	34±22	0.58
E to septal e' ratio	11±6	11±8	0.65
Resting heart rate, beats/min	61.9±11.1	65.2±11.9	0.053
Carotid augmentation index*	13.6±15.2	11.2±16.7	0.12
Carotid pulse pressure*	62.9±23.5	56.6±22.1	0.065
Carotid-to-brachial pressure amplification*	1.08±0.23	1.18±0.28	0.008

Values are mean±SD or counts (percentages). ACE indicates angiotensin-converting enzyme; ARB, angiotensin receptor blocker; eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction; LVM, left ventricular mass.

\*Data available in 176 subjects (89 who used beta-blockers and 87 who did not use beta-blockers).

general characteristics between subjects who were receiving beta-blockers and those who were not, except for a slightly lower prevalence of smoking, a slightly lower LV EF, and a

significantly greater prevalence of coronary artery disease among beta-blocker users. Central hemodynamic data (available in 176 subjects: 89 who used beta-blockers and

87 who did not) are also presented in Table 1. In contrast to brachial pulse pressure, central pulse pressure tended to be greater in beta-blocker users (62.9 mm Hg vs 56.6 mm Hg;  $P=0.065$ ). Central-to-brachial pulse pressure amplification was significantly lower in beta-blocker users (1.08 vs 1.18,  $P=0.008$ ).

### Correlation of Left Atrial Parameters With Antihypertensive Medications

Table 2 shows values of LA deformation measures and volumes among subjects who were receiving beta-blockers versus those who were not. Total longitudinal strain and LA expansion index were significantly lower in subjects receiving beta-blockers (total longitudinal strain 24% vs 28%,  $P=0.005$ ; LA expansion index 1.10 vs 1.35,  $P<0.001$ , Figure 3). Similarly, negative longitudinal strain ( $-13\%$  vs  $-15\%$ ,  $P=0.008$ ), late-diastolic strain rate ( $-140\%/s$  vs  $-163\%/s$ ,  $P=0.008$ ), and active LAEF (37% vs 42%,  $P=0.001$ ) were lower in subjects receiving beta-blockers. Less negative values of late-diastolic strain and strain rate, present in subjects receiving beta-blockers, indicate worse LA booster pump function. Subjects receiving beta-blockers also demonstrated lower values of negative early-diastolic strain rate ( $-83\%/s$  vs  $-99\%/s$ ,  $P=0.022$ ), indicating impaired conduit function.

**Table 2.** Left Atrial Parameters Among Subjects Receiving Beta-blockers and Subjects Not Receiving Beta-blockers

Left Atrial Parameters	Beta-blocker Use	No Beta-blocker Use	P Value
<b>Reservoir function</b>			
Total longitudinal strain, %	24±10	28±11	0.005
LA expansion index	1.10±0.41	1.35±0.43	<0.001
<b>Conduit function</b>			
Positive longitudinal strain, %	11±7	13±8	0.06
Early-diastolic strain rate, %/s*	-83±49	-99±54	0.022
Passive LA ejection fraction, %	22±8	23±9	0.13
<b>Booster pump function</b>			
Negative longitudinal strain, %*	-13±6	-15±6	0.008
Late-diastolic strain rate, %/s*	-140±62	-163±66	0.008
Active LA emptying fraction, %	37±10	42±10	0.001

LA indicates left atrium.

\*Less negative value of diastolic strain and strain rate indicates worse LA function.

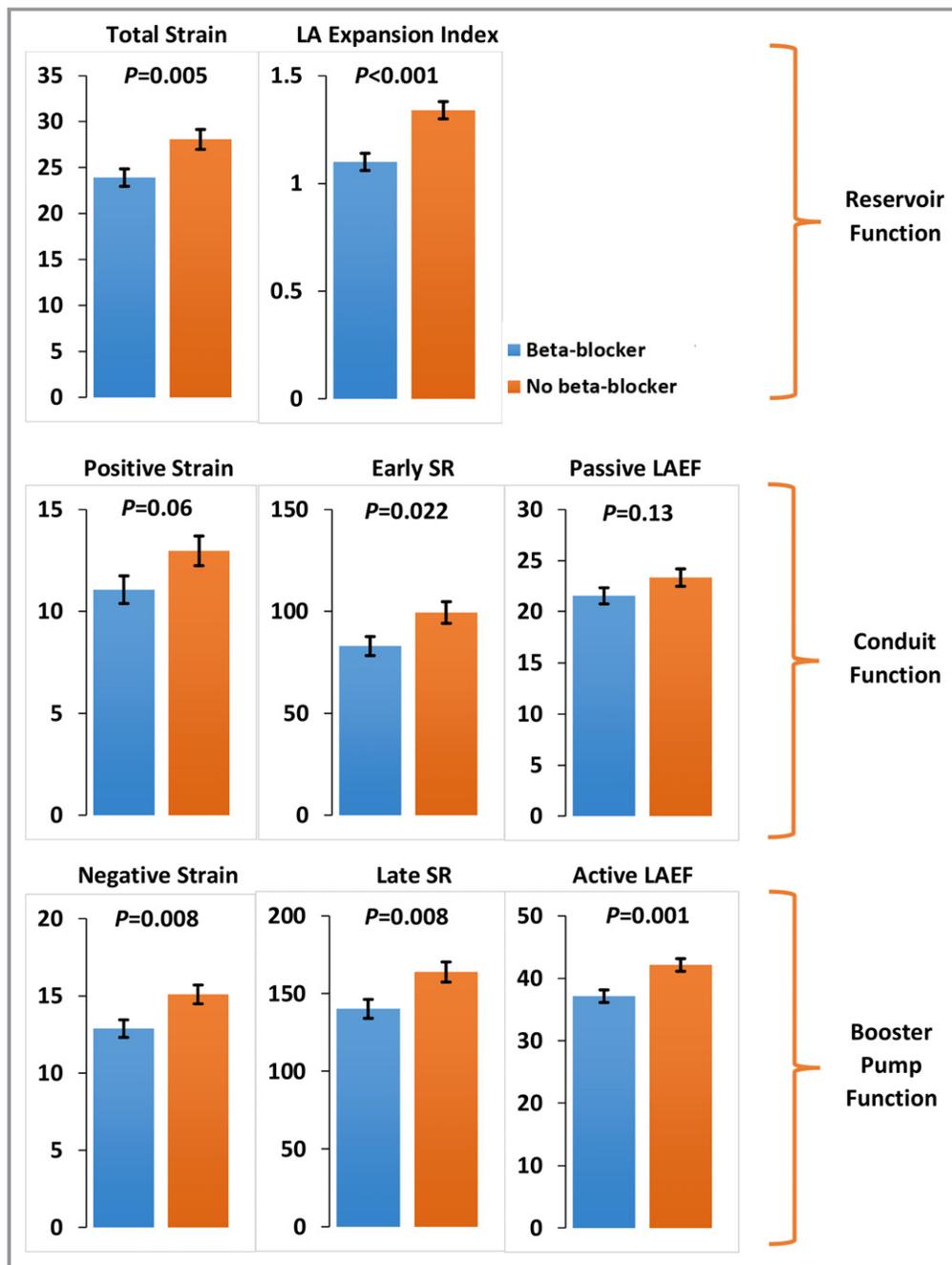
Table 3 shows the results of multivariable models in which the relationship between beta-blocker use and LA function is analyzed. In models that adjusted for adjusted for age, sex, and race (Model 1, Table 3), beta-blocker use was consistently associated with measures of impaired reservoir and booster pump function, including lower total longitudinal strain, LA expansion index, negative longitudinal strain, late-diastolic strain rate, and active LAEF. In addition, beta-blocker use was associated with a lower (less negative) early-diastolic strain rate (standardized  $\beta=0.14$ ;  $P=0.036$ ) in these adjusted models.

In multivariable models that adjusted for age, sex, race, body mass index, blood pressure, the presence of diabetes mellitus, and use of other antihypertensive agents (Model 2, Table 3), beta-blocker use was associated with lower total longitudinal strain (standardized  $\beta=-0.21$ ;  $P=0.005$ ), and lower LA expansion index (standardized  $\beta=-0.27$ ;  $P<0.0001$ ), indicating impaired LA reservoir function. Beta-blocker use was also associated with a lower positive strain (standardized  $\beta=-0.16$ ;  $P=0.024$ ) and lower (ie, less negative) early-diastolic strain rate (standardized  $\beta=0.17$ ;  $P=0.016$ ), indicating impaired LA conduit function. Finally, beta-blocker use was associated with a lower (less negative) late-diastolic strain (standardized  $\beta=0.16$ ;  $P=0.028$ ) and strain rate (standardized  $\beta=0.16$ ;  $P=0.041$ ), and lower active LAEF (standardized  $\beta=-0.26$ ;  $P=0.001$ ), indicating impaired booster pump function. Angiotensin-converting enzyme inhibitor, angiotensin receptor blocker, calcium-channel blocker, thiazide, and spironolactone use were not associated with LA function (not shown).

With further multivariable adjustment for LV mass, LA volume, and LV EF (Model 3, Table 3), the association of beta-blockers with impaired LA reservoir and booster pump function persisted. There was also a significant association between beta-blocker use and a lower positive longitudinal strain (standardized  $\beta=-0.19$ ;  $P=0.012$ ) and early-diastolic strain rate (standardized  $\beta=-0.15$ ;  $P=0.039$ ), which are measures of LA conduit function.

### Sensitivity Analyses

Given the significant differences in the prevalence of coronary artery disease between subjects who were taking beta-blockers and those who were not, we performed sensitivity analyses in which subjects with a history of coronary artery disease were excluded (Table 4). As in the overall study population, in these sensitivity analyses, beta-blocker use was significantly associated with LA function. The numeric value of the point estimates for standardized coefficients in these analyses were, in general, similar to or greater than the estimates in the overall population.



**Figure 3.** Bar graphs comparing various left atrial parameters in participants on beta-blockers to participants not on beta-blockers. LA indicates left atrium; LAEF, left atrial emptying fraction; SR, strain rate. Absolute values for early-diastolic strain rate, negative longitudinal strain, and late-diastolic strain rate are presented for the ease of direct comparison between the groups. Error bars represent standard errors of the mean.

Given the significant differences in pulse pressure amplification between subjects who were receiving beta-blockers and those who were not, we performed sensitivity analyses regarding the association of beta-blocker use with LA function among subjects with available carotid tonometry data (Table 5). In this table Models 2 and 3 (multivariable models) include adjustment for pulse pressure amplification. It can be

observed that in models that adjusted for various confounders (including measures of LV structure and function and central-to-brachial pulse pressure amplification, Model 3), beta-blocker use remained predictive of LA function, suggesting that the observed relationship between beta-blocker use and parameters of LA function is, at least in part, independent of the effect of beta-blockers on central pressures.

**Table 3.** Unadjusted and Adjusted Standardized Regression Coefficients for the Association of Left Atrial Measures With Beta-blocker Use

Left Atrial Parameters	Model 1 Estimated Standardized $\beta$ Coefficient (P Value)	Model 2 Estimated Standardized $\beta$ Coefficient (P Value)	Model 3 Estimated Standardized $\beta$ Coefficient (P Value)
<b>Reservoir function</b>			
Total longitudinal strain	-0.18 (0.009)	-0.21 (0.005)	-0.21 (0.006)
LA expansion index	-0.26 (<0.001)	-0.27 (<0.001)	-0.30 (<0.001)
<b>Conduit function</b>			
Positive longitudinal strain	-0.11 (0.094)	-0.16 (0.024)	-0.19 (0.012)
Early-diastolic strain rate*	0.14 (0.036)	0.17 (0.016)	0.15 (0.039)
Passive LA ejection fraction	-0.08 (0.235)	-0.10 (0.140)	-0.08 (0.26)
<b>Booster pump function</b>			
Negative longitudinal strain*	0.18 (0.010)	0.16 (0.028)	0.15 (0.049)
Late-diastolic strain rate*	0.18 (0.009)	0.16 (0.041)	0.18 (0.019)
Active LA emptying fraction	-0.23 (0.001)	-0.26 (0.001)	-0.27 (<0.001)

Model 1: adjusted for age, sex, and race. Model 2: adjusted for variables in Model 1 plus body mass index, systolic and diastolic blood pressure, presence of diabetes mellitus, coronary artery disease, use of angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, calcium-channel blockers, spironolactone, and diuretics. Model 3: adjusted for variables in Model 2 plus LA volume, left ventricular mass, and left ventricular ejection fraction. LA indicates left atrium.

\*Positive coefficients in diastolic strain and strain rate indicate "less negative values" and therefore worse left atrial function.

## Discussion

We demonstrate for the first time that among hypertensive subjects without heart failure and AF, beta-blocker use is significantly associated with impaired LA reservoir, conduit, and booster pump function. This association may underlie the increased risk of atrial arrhythmia and stroke that has been observed with the use of these agents in patients with hypertension.<sup>11</sup>

## Left Atrial Remodeling in Hypertension

Structural and functional remodeling of the LA is seen early in the course of hypertension. In a cross-sectional study using 2-dimensional echocardiographic volumes and spectral Doppler, Eshoo et al<sup>4</sup> found that reservoir and conduit LA functions were decreased, whereas booster function was increased, among participants with untreated mild hypertension compared to healthy volunteers. In that study LA volumes

**Table 4.** Sensitivity Analyses Showing Unadjusted and Adjusted Standardized Regression Coefficients for the Association of Left Atrial Measures With Beta-blocker Use, After Excluding Subjects With CAD (n<sub>included</sub>=146)

Left Atrial Parameters	Model 1 Estimated Standardized $\beta$ Coefficient (P Value)	Model 2 Estimated Standardized $\beta$ Coefficient (P Value)	Model 3 Estimated Standardized $\beta$ Coefficient (P Value)
<b>Reservoir function</b>			
Total longitudinal strain	-0.22 (0.007)	-0.28 (0.002)	-0.29 (0.002)
LA expansion index	-0.27 (0.001)	-0.34 (<0.001)	-0.32 (<0.001)
<b>Conduit function</b>			
Positive longitudinal strain	-0.14 (0.078)	-0.21 (0.02)	-0.27 (0.003)
Early-diastolic strain rate*	0.21 (0.005)	0.26 (0.002)	0.25 (0.004)
Passive LA ejection fraction	-0.08 (0.28)	-0.10 (0.205)	-0.09 (0.28)
<b>Booster pump function</b>			
Negative longitudinal strain*	0.21 (0.010)	0.23 (0.01)	0.19 (0.036)
Late-diastolic strain rate*	0.23 (0.006)	0.24 (0.008)	0.26 (0.004)
Active LA emptying fraction	-0.23 (0.001)	-0.29 (0.002)	-0.28 (<0.001)

Model 1: adjusted for age, sex, and race. Model 2: adjusted for variables in Model 1 plus body mass index, systolic and diastolic blood pressure, presence of diabetes mellitus, use of angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, calcium-channel blockers, spironolactone, and diuretics. Model 3: adjusted for variables in Model 2 plus left atrial volume, left ventricular mass, and left ventricular ejection fraction. LA indicates left atrium.

\*Positive coefficients in diastolic strain and strain rate indicate "less negative values" and therefore worse left atrial function.

**Table 5.** Sensitivity Analyses Showing Unadjusted and Adjusted Standardized Regression Coefficients for the Association of Measures of Left Atrial Measures With Beta-blocker Use, Among Subjects With Available Carotid Tonometry Data (n Included=176)

Left Atrial Parameters	Model 1 Estimated Standardized $\beta$ Coefficient (P Value)	Model 2 Estimated Standardized $\beta$ Coefficient (P Value)	Model 3 Estimated Standardized $\beta$ Coefficient (P Value)
<b>Reservoir function</b>			
Total longitudinal strain	−0.15 (0.052)	−0.19 (0.022)	−0.20 (0.017)
LA expansion index	−0.23 (0.003)	−0.25 (0.003)	−0.24 (0.004)
<b>Conduit function</b>			
Positive longitudinal strain	−0.12 (0.092)	−0.15 (0.062)	−0.18 (0.028)
Early-diastolic strain rate*	0.18 (0.012)	0.20 (0.01)	0.19 (0.02)
Passive LA ejection fraction	−0.12 (0.09)	−0.10 (0.18)	−0.07 (0.36)
<b>Booster pump function</b>			
Negative longitudinal strain*	0.11 (0.162)	0.15 (0.073)	0.19 (0.036)
Late-diastolic strain rate*	0.13 (0.10)	0.17 (0.055)	0.19 (0.029)
Active LA emptying fraction	−0.17 (0.03)	−0.20 (0.022)	−0.15 (0.093)

Model 1: adjusted for age, sex, and race. Model 2: adjusted for variables in Model 1 plus central-to-brachial pulse pressure amplification, body mass index, systolic and diastolic blood pressure, presence of diabetes mellitus, coronary artery disease, use of angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, calcium-channel blockers, spironolactone, and diuretics. Model 3: adjusted for variables in Model 2 plus LA volume, left ventricular mass, and left ventricular ejection fraction. LA indicates left atrium.

\*Positive coefficients in diastolic strain and strain rate indicate “less negative values” and therefore worse LA function.

were increased in association with the degree of LVH, indicating the presence of structural remodeling. As hypertensive heart disease progresses, booster and booster reserve function (an index of the degree of booster function increase with exercise) also decrease.<sup>5,6</sup> Structural and functional remodeling of LA have been associated with an increased risk of cardiovascular morbidity and mortality in population-based studies.<sup>1,3</sup> In the Dallas Heart Study, LAEF (an indicator of LA reservoir function) predicted mortality even after adjustment for LA volume index, suggesting the prognostic importance of functional remodeling independent of LA structure.<sup>15</sup> In a cohort study of participants with chronic hypertension, Kaminski et al showed that a decrease in active LAEF (an indicator of LA booster pump function) was independently associated with all-cause mortality and major adverse cardiac events.<sup>7</sup>

### Beta-blockers, Hypertension, and Left Atrial Parameters

To the best of our knowledge, no prior study has examined the relationship between the use of specific antihypertensive agents and measures of LA mechanical function. We used cardiac MRI-based LA volume measurements, along with feature tracking–based assessment of phasic atrial wall longitudinal deformation.<sup>14</sup> We utilized these modalities to measure LA volumes, LA strain, and strain rate during various phases. We found that, in contrast to other antihypertensive agents (such as calcium-channel blockers, angiotensin-

converting enzyme [ACE] inhibitors, and ARBs), beta-blocker use was consistently associated with impaired reservoir, conduit, and booster pump LA function.

Beta-blocker use has been associated with an increased risk of cardiovascular morbidity and mortality.<sup>16,17</sup> Furthermore, an atenolol-based strategy, when compared to a losartan-based strategy, was associated with a higher risk of AF and stroke<sup>10,11</sup> in the Losartan Intervention for Endpoint Reduction in Hypertension (LIFE) trial. In this randomized trial participants in the atenolol-based group also showed less regression of LA and LV structural remodeling.<sup>8,18</sup> Although we found depressed LA phasic function (a marker of LA functional remodeling) in participants using beta-blockers, there was no difference in LV mass and LA volumes (a marker of structural remodeling). This might be because, unlike LIFE trial participants, nearly two-thirds of the participants who used beta-blockers in our study were also receiving an ACE inhibitor or ARB. Interestingly, in a cohort study by Kaminski et al, a significantly higher proportion of participants with depressed active LAEF were taking beta-blockers compared to those with higher LAEF (71% vs 57%,  $P=0.04$ ). However, this association was not explored further in this study. In our comprehensive evaluation of LA function with use of volumetric and strain-based parameters, we found that beta-blocker use was associated with depressed LA function in all 3 domains (reservoir, conduit, and booster), and this association was consistently demonstrated with various measures of LA function in each domain.

Potential mechanisms linking beta-blocker use with atrial dysfunction may include any of the following factors, alone or in combination: (1) direct negative inotropic effects of beta-blockers on the LA myocardium<sup>19</sup>; (2) LA dysfunction secondary to negative inotropic or lusitropic effects of beta-blockers on the LV<sup>20,21</sup>; and (3) worsening LA-LV-aortic coupling due to the effects of beta-blockers on central hemodynamics. Although we observed a slightly decreased LVEF in participants using beta-blockers ( $60\pm 8\%$  vs  $62\pm 8\%$ ,  $P<0.035$ ), the association between LA function and beta-blocker use persisted after adjustment for LVEF. Previous studies indicate that central pulsatile hemodynamics is associated with LA remodeling and dysfunction in hypertension.<sup>22,23</sup> In the CAFE study,<sup>9</sup> a prospective substudy of ASCOT, the use of atenolol-based regimens was associated with higher central systolic and pulse pressure despite similar reduction in peripheral blood pressure when compared to amlodipine-based regimens. In the LIFE trial,<sup>24</sup> higher pulse pressure was observed in the atenolol-based group when compared to the losartan-based group, and this independently predicted increased risk of cardiovascular morbidity and mortality in these participants. We found that hypertensive subjects who were receiving beta-blockers demonstrated a lower pulse pressure amplification, indicating greater central pulse pressure for any given level of brachial pulse pressure. Interestingly, in our sensitivity analyses examining the relationship between beta-blocker use and LA function among subjects with available central pressure data (Table 4), beta-blocker use remained predictive of measures of LA function after adjustment for various confounders, including carotid-to-brachial pulse pressure amplification. This indicates that the effects of beta-blockers on LA function are, at least in part, independent on their effects on central pulse pressure.

## Strengths and Limitations

To the best of our knowledge, this is the first study to evaluate the relationship between the use of different antihypertensive agents and phasic LA function. An additional strength of our study is the use of cardiac MRI, which provides superior quantitative data about volumes and chamber function. Furthermore, we used novel tissue-tracking algorithms to assess tissue strain (deformation), a more direct measure of myocardial function. The high consistency of our results with various functional LA indices, and with multiple adjustments for potential confounders, adds confidence to our results. However, these results should be interpreted in the context of the study limitations. Although the observed relationships with beta-blocker use were highly consistent and statistically significant, the magnitude of the association in multivariable analyses was modest to moderate. However, this may be due to the multiple potential factors (other than beta-blocker use)

that can have an impact on LA function. Residual confounding cannot be excluded, and our study does not firmly establish a cause-effect relationship because of its cross-sectional nature. Many patients were receiving combination therapy with various agents and various doses; it is possible that concomitant therapy may have confounded the association between beta-blocker use and LA function. However, this is unlikely given that there was no evidence of an association between other classes of antihypertensives and LA function parameters in the sample. In addition, we adjusted for concomitant drug class. More detailed modeling of the potential confounding effects of specific drugs in each class and at different dosages was not possible due to the moderate sample size. Another limitation is that we did not account for the duration of hypertension or of drug therapy with various agents. Interestingly, because beta-blockers were historically a first-line medication, beta-blocker use could reflect a longer duration of hypertension, which in turn would reflect greater negative effects of hypertension on LA function. However, we note that adjustment for other structural factors (including LV mass, end-diastolic volume, and EF) did not attenuate the observed associations. Furthermore, we utilized a convenience sample to recruit our study participants at our VA Medical Center, which limits the generalizability of the findings. Our study population was therefore composed predominantly of males. Although we included sex as a covariate in multivariable regression models, further validation of our observations in samples that include a larger number of women should be performed. Finally, there was a significant difference in the prevalence of coronary artery disease between the 2 groups. Although we performed sensitivity analyses to address these differences, residual confounding cannot be fully excluded.

## Conclusions

In summary, in this cross-sectional analysis of participants with chronic hypertension, we found a significant association of beta-blocker use with impaired reservoir, conduit, and booster pump LA function when compared to other antihypertensive agents. This association could underlie the increased risk of AF and stroke seen with the use of beta-blockers (as opposed to other antihypertensive agents) in recent trials.

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