Effect of Aldosterone Antagonism on Myocardial Dysfunction in Hypertensive Patients With Diastolic Heart Failure

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Background—Specific treatments targeting the pathophysiology of hypertensive heart disease are lacking. As aldosterone has been implicated in the genesis of myocardial fibrosis, hypertrophy, and dysfunction, we sought to determine the effects of aldosterone antagonism on myocardial function in hypertensive patients with suspected diastolic heart failure by using sensitive quantitative echocardiographic techniques in a randomized, double-blinded, placebo-controlled study.

Methods and Results—Thirty medically treated ambulatory hypertensive patients (19 women, age 62±6 years) with exertional dyspnea, ejection fraction >50%, and diastolic dysfunction (E/A <1, E deceleration time >250ms/beat and without ischemia were randomized to spironolactone 25 mg/d or placebo for 6 months. Patients were overweight (31±5 kg/m²) with reduced treadmill exercise capacity (6.7±2.1 METS). Long-axis strain rate (SR), peak systolic strain, and cyclic variation of integrated backscatter (CVIB) were averaged from 6 walls in 3 standard apical views. Mean 24-hour ambulatory blood pressure at baseline (133±17/80±7 mm Hg) did not change in either group. Values for SR, peak systolic strain, and CVIB were similar between groups at baseline and remained unchanged with placebo. Spironolactone therapy was associated with increases in SR (baseline: −1.57±0.46 s⁻¹ versus 6-months: −1.91±0.36 s⁻¹, P<0.01), peak systolic strain (−20.3±5.0% versus −26.9±4.3%, P<0.001), and CVIB (7.4±1.7 dB versus 8.6±1.7 dB, P=0.08). Each parameter was significantly greater in the spironolactone group compared with placebo at 6 months (P=0.05, P=0.02, and P=0.02, respectively), and the increases remained significant after adjusting for baseline differences. The increase in strain was independent of changes in blood pressure with intervention. The spironolactone group also exhibited reduction in posterior wall thickness (P=0.04) and a trend to reduced left atrial area (P=0.09).

Conclusions—Aldosterone antagonism improves myocardial function in hypertensive heart disease. (Circulation. 2004; 110:558-565.)

Key Words: hypertension  ●  diastole  ●  systole  ●  myocardial contraction

Hypertensive heart disease is a common cause of heart failure (HF) in the community setting.1,2 The pathophysiology typically involves hypertrophic left ventricular (LV) remodeling in combination with variable degrees of myocardial fibrosis, both of which are associated with LV diastolic dysfunction.3,4 Hypertensive patients with abnormal LV filling patterns suggestive of diastolic dysfunction may be asymptomatic but often report exertional dyspnea. In addition, such patients are at increased risk of decompensated HF requiring hospital admission, and they also have increased total mortality rates.2

Currently, treatment of hypertensive heart disease is mainly limited to effective control of hypertension. Specific treatments targeting the pathophysiology of hypertensive heart disease are lacking and new approaches are required.5,6 Experimental studies implicate aldosterone in the genesis of myocardial fibrosis, hypertrophy, and dysfunction, and these processes may be preventable,7,8 and possibly even reversible,9 with aldosterone blockade. Indeed, improved outcomes with spironolactone in systolic heart failure have been linked to the antifibrotic effects of the drug.10 In addition, aldosterone is associated with abnormal vascular function,11 which may be related to the development of diastolic HF.12

Diastolic dysfunction is frequently accompanied by impaired LV systolic function despite a normal ejection fraction.11,14 Effective therapies for hypertensive heart disease might therefore be expected to result in improvement of both systolic and diastolic function, depending on the sensitivity and accuracy of the particular measurement techniques used. Strain rate (SR) imaging and cyclic variation (CV) of integrated backscatter (IB) are sensitive echocardiographic techniques that provide quantitative assessment of regional myocardial systolic function.15,16 These techniques are able to detect subtle myocardial dysfunction in early hypertensive...
and therefore the potential to detect changes in myocardial function that might occur in response to specific interventions. Using these techniques, we examined the effects of aldosterone antagonism on myocardial function in hypertensive patients with exertional dyspnea and abnormal LV filling who were considered to have mild isolated diastolic HF. The effect of aldosterone antagonism on arterial compliance in these patients was also assessed.

Methods

Sample Size and Randomization

This report satisfies the recommended reporting guidelines for randomized controlled trials. The primary end points were changes in long-axis strain and backscatter parameters with intervention. Sample size calculations were based on previous data from our laboratory examining hypertensive patients with impaired LV long-axis systolic function. Applying the variance seen in these patients, a significant difference (P<0.05) of 15% between groups was predicted with a sample size of 14 patients per group at a power of 80% for SR, and 95% for both peak systolic strain and CVIB. To allow for drop-outs, we randomized 30 patients to spironolactone 25 mg/d or matching placebo in a double-blinded parallel protocol for a period of 6 months. Secondary end points included changes in LV wall thickness, LV mass, indices of diastolic function, and arterial compliance. After suitable patients were selected by an investigator, block-randomization was performed by the research pharmacist who dispensed the study drugs. Investigators remained blinded to the study protocol. One patient (spironolactone group) developed gynecomastia; both patients (active group) and one female patient (placebo group) experienced mild breast pain and one patient (spironolactone group) migrated overseas and did not complete the study. All baseline investigations were therefore repeated at the end of the study; study medication was to be withheld in these patients. The study was approved by the institutional ethics committee, and was in accordance with currently accepted guidelines.

Patient Selection

To achieve the target of 30 consecutive patients with diastolic heart failure who met all selection criteria, we initially had to perform a detailed screening of 74 hypertensive subjects with suspected diastolic HF over the period from February 2002 to October 2002. These 74 ambulatory subjects were recruited from the community (a non-hospital ambulatory population in southeast Queensland) through newspaper advertisements followed by a detailed telephone interview with a cardiologist. To be eligible, patients had to have hypertension requiring antihypertensive medication and exertional dyspnea (New York Heart Association class II) but no history of angina or myocardial infarction. Patients taking angiotensin-converting enzyme inhibitors, angiotensin-receptor blockers, or spironolactone were excluded, as were patients with renal impairment (creatinine ≥0.20 mmol/dl) or hyperkalemia at baseline.

After clinical assessment by a cardiologist and screening echocardiography and echocardiography, we excluded patients with evidence of pulmonary disease, ischemic heart disease, abnormal regional or global resting LV systolic function (ejection fraction <50%), or significant (≥mild) valvular dysfunction. Exercise echocardiography was performed to exclude ischemia as a cause of the patients’ symptoms. Abnormal diastolic function, identified by impaired LV relaxation with Doppler echocardiography was required for inclusion, and resulted in the majority of the patient exclusions at this stage of selection. All of these criteria were fulfilled in 30 patients. The study was approved by the institutional ethics committee and informed written consent was obtained before enrollment from all patients.

Study Design

Patients satisfying inclusion and exclusion criteria were considered to have mild isolated diastolic HF and underwent baseline investigations including a full echo-Doppler study for analysis of cardiac dimensions, diastolic function, backscatter, and SR imaging. Automated cuff blood pressure (BP) was measured after 10 minutes of supine rest immediately before the echo, which was followed by measurement of arterial compliance. Blood was then taken for measurement of B-type natriuretic peptide (BNP), which was determined with a point-of-care system as previously described. Blood was also collected midmorning from seated patients who had been ambulant for at least 2 hours for measurement of serum aldosterone and plasma renin activity by radioimmunoassay using commercial kits. Twenty-four hour ambulatory BP monitoring was then performed.

Ambulatory BP Monitoring

This was performed on a regular work day using fully automatic machines (model TM-2420, A&D) set to take readings every 30 minutes between 0600 and 2200 hours, and every 60 minutes between 2200 and 0600 hours. Before commencing each study, BP was measured in both arms using a mercury sphygmomanometer. The 24-hour ambulatory BP cuff was always applied to the non-dominant arm except where mercury readings (systolic) on the dominant arm exceeded those on the other side by at least 10 mm Hg, in which case the dominant arm was chosen. Choice of cuff size (standard or large) was dependent on the subject’s arm circumference and was in accordance with currently accepted guidelines.

Echocardiography

A detailed 2-dimensional and Doppler echocardiogram (Vivid Five, GE Vingmed) was performed in all patients. LV M-mode measurements of wall thickness and end-diastolic and end-systolic diameters were used for calculation of fractional shortening, relative wall thickness, and LV mass, which was indexed to body surface area. LV ejection fraction was determined by a modified Simpson’s method. Left atrial area was traced in the apical 4-chamber view. Assessment of LV diastolic function included transmural and pulmonic vein pulsed-wave Doppler from the apical 4-chamber view and mitral annular velocities with tissue Doppler echocardiography. The transmirtal peak E and peak A diastolic velocities and the E wave deceleration time were recorded. All study patients had impaired LV relaxation defined by the combination of E/A ratio <1 and E wave deceleration time >250 m sec. Systolic and diastolic velocities were measured in the right upper pulmonary vein, as was the velocity of the atrial reversal wave. Systolic and early and late diastolic velocities were measured at the medial and lateral mitral annulus with pulsed-wave tissue Doppler in the apical 4-chamber view with gains minimized to allow for a clear tissue signal. Measurements were performed off-line and averaged from 3 to 5 consecutive cardiac cycles. Satisfactory measurements were obtained with all modalities.

Exercise Echocardiography

Maximal (symptom limited) treadmill exercise was performed using the Bruce protocol. The same cardiologist supervised all tests. Antihypertensive medication was not withheld before exercise. BP was obtained with a mercury sphygmomanometer at rest, at the end of each 3 minute stage, and as close to peak exercise as possible. A hypertensive response to maximum exercise was defined by maximal systolic or diastolic BP ≥210/105 mm Hg in males and ≥190/105 mm Hg in females, respectively.

Strain Rate Imaging

Three consecutive cardiac cycles of color Doppler data were digitally recorded in each of 6 LV regions (inferior septum and lateral wall, anterior and inferior walls, anterior septum and posterior wall) in 3 standard apical views. Strain and SR are sensitive measures of long-axis systolic LV function that represent dimensionless descriptions of length changes due to the deformation of tissue caused by
applied or developed force. The rate of regional myocardial deformation (SR) was derived from instantaneous differences in myocardial velocities within an 11-mm region of interest by using commercially available software (Echopac 6.1, GE Vingmed). Percent deformation of the segment (myocardial strain) was obtained by integration of the SR curve. Mean SR and peak systolic strain were calculated in each patient by averaging the results of the basal segment of each wall, and were obtainable in 336 (95%) of 354 segments.

Integrated Backscatter
Long-axis systolic LV function was also assessed by CVIB as a means of corroborating the strain rate results. Gray scale loops of 3 consecutive cardiac cycles were acquired at frame rates 80 to 120 frames/sec in 3 standard apical views, saved in raw data format and analyzed off-line (Echopac 6.1, GE Vingmed). The IB information in the 3 cycles was averaged and CVIB during systole was determined for each of the 6 basal LV segments by tracking a fixed 11×11 pixel region of interest in each frame. The magnitude of CV was determined by the difference between the minimal and maximal values of IB in a cardiac cycle. Mean CV was calculated in each patient by averaging the results of individual segments. Long axis CVIB was measurable in 340 (96%) of 354 segments.
CVIB was also obtained from the septum and posterior wall in the parasternal view to assess short-axis (radial) myocardial function. Measurements were obtained by adjusting the position of the sample volume in each frame so that it was maintained within the same region of the septum or posterior wall throughout the cardiac cycle. Short axis CVIB was measurable in 116 (98%) of 118 segments.

Arterial Compliance
Measurement of total arterial compliance was performed using the pulse pressure method. This method derives arterial compliance from measured aortic flow and peripheral resistance. Aortic flow was derived from the product of LV outflow tract area and velocity time integral obtained at echocardiography. Mean and diastolic brachial pressure (Dinamap Plus, Critikon) were used to calibrate the pressure signal derived by applanation tonometry (SPT-301 Mikro-Tip, Millar Instruments) at the radial artery, which is more feasible for tonometry than the brachial because of proximity to the surface. A transfer function, validated in an angiographic population and applied previously in a group similar to the current patient population, was then used to determine mean aortic pressure. Simultaneous gated signals from tonometry, pulsed-wave Doppler, and the ECG were acquired simultaneously using an A/D board (WaveBook 512, IOTech Inc) attached to a personal computer, and analysis was performed using a custom program written in Matlab 4.2c. Between 20 and 30 cardiac cycles were acquired; depending on data quality, 4 to 15 specific cardiac cycles were chosen from the raw data set and averaged for analysis. The analysis program determined mean values for pressure and flow and calculated mean aortic pressure using the transfer function; arterial compliance was then derived from pressure and flow data.

Statistical Analysis
Values of strain and IB were compared in the placebo and spironolactone groups at baseline and at 6 months with unpaired t testing. The changes in strain and IB values from baseline to 6 months were assessed with paired t testing. Linear regression was used to determine correlations between variables. The independent contribution of treatment to changes in strain and IB over the intervention period was assessed with multivariate linear regression analyses that adjusted for differences in baseline values of these variables. In combination with the respective t tests, these multivariate analyses represented the primary endpoints. Multivariate linear regression was also used to adjust for background medication and changes in BP, weight, and other variables over the intervention period. Continuous variables are presented as mean± SD. Data were analyzed using standard statistical software (SPSS version 9) in accordance with published methods. A probability value of <0.05 was considered significant.

Results
Patient Characteristics
The baseline characteristics for all subjects are presented in Table 1. There were no significant differences between the intervention and placebo groups with respect to any variable. The average age was 62±7 years and there were slightly more females than males. Patients were typically overweight and had high-normal average 24-hour BP while on antihypertensive therapy, which included a calcium channel blocking agent in most patients. Maximum exercise on the Bruce protocol was limited by dyspnea in all patients. Twenty-six of the 30 patients achieved >85% of maximum predicted heart rate for age. BP increased with exercise in all patients, with 14 patients (47%) demonstrating a hypertensive response. The mean resting BNP level for the group was 30±28 pg/mL at baseline.

Changes in Blood Tests, BP, and Exercise Parameters With Intervention
The mean serum levels of potassium, creatinine, aldosterone, and BNP and mean plasma renin activity levels were similar between groups at baseline. There was no significant change in serum potassium or BNP at follow-up in either group. There was a small decrease in serum creatinine in the spironolactone group from baseline to 6 months (0.80±0.15 versus 0.76±0.14 mg/dL, P=0.028), but no change with placebo. Although not reaching statistical significance, both serum aldosterone (12.6±9.1 versus 20.2±22.2 ng/dL) and plasma renin activity levels (1.7±1.6 versus 3.3±5.7 ng · mL⁻¹ · h⁻¹) tended to increase in the spironolactone group as expected. There were no significant changes in the placebo group for either serum aldosterone (16.7±11.9 versus 15.9±5.7 ng/dL) or plasma renin activity (2.5±2.5 versus 3.8±5.4 ng · mL⁻¹ · h⁻¹). Body weight decreased significantly in the spironolactone group (P<0.012) and remained unchanged with placebo. There were no significant changes in mean 24-hour ambulatory BP values (either systolic or diastolic) in either group over the intervention period. In contrast, BP measured at the time of the follow-up echocardiogram was significantly lower than that recorded at the time of the baseline echo in both the placebo (145±19/80±9 versus 137±19/74±10 mm Hg, P≤0.01 for both systolic and diastolic BP) and spironolactone groups (158±22/82±12 versus 140±14/74±11 mm Hg, P<0.001). There was no change in treadmill exercise time from baseline to follow-up in either group, and no change in the peak exercise systolic and diastolic BPs.

Changes in Strain, SR, and IB With Intervention
The Figure demonstrates mean values of long-axis SR, peak systolic strain, and CVIB for the placebo and spironolactone groups at baseline and after 6 months of intervention. Mean values at baseline were similar in the placebo and spironolactone groups for all 3 parameters. SR (P<0.01) and peak systolic strain (P<0.001) increased significantly over the intervention period with spironolactone therapy and remained
unchanged with placebo. There was a trend to improvement in CVIB in the spironolactone group ($P=0.079$). At the end of intervention, mean values of SR, strain, and CVIB were all significantly higher in the spironolactone group compared with the placebo group. The greatest increase was in peak systolic strain, with a mean change from baseline to 6 months of 6.5 ± 5.0 in the spironolactone group versus 1.4 ± 4.0 in the placebo group ($P=0.006$), representing a 32% increase in strain with spironolactone therapy. Multivariate linear regression analysis demonstrated that treatment group remained predictive of changes in SR ($P=0.011$), strain ($P=0.006$), and CVIB ($P=0.037$) after adjusting for differences in baseline values of these variables.

Assessment of CVIB in the short-axis also demonstrated an increase in LV radial function in the intervention group, with no significant changes in the placebo group. CVIB in the anterior septum increased from 5.90 ± 2.25 dB at baseline to 8.63 ± 3.68 dB after 6 months of spironolactone therapy ($P=0.038$); CVIB in the posterior wall increased from 5.15 ± 2.73 dB to 9.09 ± 4.09 dB with spironolactone ($P=0.005$). However, there was no significant difference in short-axis CVIB between the placebo and spironolactone groups at 6 months, and treatment group was not significantly related to the change in CVIB after adjusting for baseline differences in a multivariate regression.

Interobserver variability was evaluated in 10 patients randomly selected by a second observer. Mean absolute differences of the interobserver variability for SR, peak systolic strain, and CVIB were 0.10 ± 0.08 s⁻¹, 1.73 ± 1.23%, and 2.36 ± 1.50 dB, respectively.

### Relation of Changes in Strain and IB Parameters to Patient Factors, Treatment Group, and Changes in BP

There was no correlation of baseline strain and backscatter values with either average ambulatory BP or with BP measured at the time of the echocardiogram. The increases in SR, strain, and CVIB with spironolactone therapy were not related to changes in 24-hour ambulatory BP. In contrast, increases in SR ($r=0.70$, $P=0.011$), strain ($r=0.60$, $P=0.041$), and short-axis CVIB at the anterior septum ($r=0.59$, $P=0.042$) in spironolactone patients between baseline and 6 months were related to the change in systolic BP as measured at the time of the baseline and follow-up echocardiograms. As measurements of strain may be load-dependent, the independence of changes in this parameter in relation to changes in BP was assessed in a multiple linear regression model, which also included change in body weight and baseline values of the dependent variable. In these analyses, spironolactone therapy remained significantly related to changes in strain ($β=-0.69$, $P=0.003$) and strain rate ($β=-0.47$, $P=0.018$) after correcting for changes in BP, changes in weight, and baseline values. In addition, spironolactone therapy remained independently predictive of improvement in strain ($P=0.015$) and SR ($P=0.037$) in separate models adjusting for age, sex, and class of background factors.

### Table 1. Baseline Clinical and Exercise Characteristics for All Subjects

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Placebo</th>
<th>Spironolactone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female, n (%)</td>
<td>10 (66)</td>
<td>9 (60)</td>
</tr>
<tr>
<td>Age, y, mean ± SD</td>
<td>62±5</td>
<td>61±6</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>31.2±4.6</td>
<td>29.8±4.7</td>
</tr>
<tr>
<td>Mean ambulatory BP, mm Hg</td>
<td>130±16/82±8</td>
<td>135±17/80±8</td>
</tr>
<tr>
<td>Mean BP at baseline echo, mm Hg</td>
<td>145±19/80±9</td>
<td>158±22/82±12</td>
</tr>
<tr>
<td>Diabetes, n</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Hyperlipidemia, n</td>
<td>6</td>
<td>8</td>
</tr>
<tr>
<td>Current smoking, n</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Calcium channel blocker, n</td>
<td>9</td>
<td>8</td>
</tr>
<tr>
<td>Diuretic, n</td>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td>β-blocker, n</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>Exercise duration (Bruce protocol), min</td>
<td>4.4±1.7</td>
<td>5.6±2.7</td>
</tr>
<tr>
<td>Maximal workload, METS</td>
<td>6.2±1.7</td>
<td>7.1±2.3</td>
</tr>
<tr>
<td>Peak exercise systolic BP, mm Hg</td>
<td>198±26</td>
<td>199±18</td>
</tr>
<tr>
<td>Peak exercise diastolic BP, mm Hg</td>
<td>94±6</td>
<td>96±9</td>
</tr>
<tr>
<td>Peak exercise heart rate, beats/min</td>
<td>153±13</td>
<td>139±24</td>
</tr>
<tr>
<td>Serum potassium, mmol/L</td>
<td>3.9±0.3</td>
<td>4.0±0.4</td>
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<tr>
<td>Serum creatinine, mmol/L</td>
<td>0.07±0.01</td>
<td>0.07±0.01</td>
</tr>
<tr>
<td>Serum aldosterone, ng/dL</td>
<td>12.6±9.1</td>
<td>16.7±11.9</td>
</tr>
<tr>
<td>Plasma renin activity, ng·mL⁻¹·h⁻¹</td>
<td>1.7±1.6</td>
<td>2.5±2.5</td>
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<tr>
<td>B-type natriuretic peptide, pg/mL</td>
<td>29.7±27.8</td>
<td>29.3±26.8</td>
</tr>
<tr>
<td>LV ejection fraction, %</td>
<td>67±4</td>
<td>68±5</td>
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</tbody>
</table>

N=30. $P$=not significant for all variables.
antihypertensive medication. In contrast, the contribution of spironolactone therapy to changes in CVIB was not statistically significant after correcting for other variables.

Changes in Conventional Echo-Doppler Parameters With Intervention

These data are presented in Table 2. The spironolactone group exhibited a reduction in posterior wall thickness with no change in the placebo group ($P=0.79$). There was no significant change in calculated LV mass in either group, and no change in LV ejection fraction. Left atrial area was similar between the spironolactone and placebo groups at baseline ($P=0.68$) but significantly smaller in the spironolactone group at 6 months. Left atrial area indexed to height was also lower at 6 months in the spironolactone group (11.7±1.8 cm²/m² versus 13.4±2.4 cm²/m², $P=0.043$); however, the change in indexed left atrial area with intervention was not statistically significant ($P=0.084$). The decrease in left atrial area with spironolactone therapy correlated significantly with reductions in both posterior wall thickness ($r=0.58$, $P=0.031$) and LV mass ($r=0.67$, $P=0.010$), as well as with the increase in LV systolic strain ($r=0.62$, $P=0.018$).

There was no change in transmitral E velocity or E/A ratio (Table 2). The A velocity decreased significantly in the spironolactone group only and the change was independent of group differences at baseline. The E deceleration time decreased in both groups and was not related to spironolactone therapy. The pulmonary venous A reversal velocity decreased significantly in the spironolactone group and remained unchanged with placebo. There was no significant change in mitral annular systolic or early diastolic velocities as assessed by tissue Doppler imaging. The late diastolic velocity at the lateral annulus decreased with spironolactone therapy, but this reduction was not independently related to treatment group after adjusting for baseline differences and was not different to placebo at 6 months.

Change in Arterial Compliance

There was a trend for an increase in arterial compliance with spironolactone therapy (baseline: 0.82±0.40 mL/mm Hg; study-end: 0.89±0.38 mL/mm Hg; $P=0.081$), with no change in the placebo group ($P=0.87$).

Discussion

This randomized placebo-controlled study demonstrates that in an ambulatory hypertensive population with isolated LV diastolic dysfunction and reduced functional capacity due to exertional dyspnea, myocardial function can be improved over a period of 6 months with aldosterone antagonism by using a hemodynamically insignificant dose of spironolactone. Improvement of LV long-axis systolic function was confirmed by increases in strain and SR with intervention and was supported by changes of a similar magnitude in long-axis CVIB. Left ventricular radial function was also observed to increase with treatment, although these changes were not independently related to spironolactone therapy.

It has been suggested that the focus on diastolic dysfunction in patients with HF and preserved ejection fraction may be misleading. Indeed, in addition to diastolic dysfunction, abnormalities of systolic function in hypertensive patients have been clearly demonstrated in the presence of LV hypertrophy. Strain imaging and CVIB are sensitive echo techniques that in the present study provided quantitative assessment of longitudinal myocardial systolic function. We primarily examined changes in long-axis systolic function, as abnormalities in this variable occur early in myocardial disease processes and may be more susceptible to derangement than in short-axis function. Long-axis function may therefore be more sensitive to recovery of function in response to effective treatment interventions. Importantly,
these measures of long-axis LV function may be influenced by loading, although the effects of physiological variations in BP are unclear. In the present study, the observed improvement in long axis function with spironolactone therapy is unlikely to be explained by an antihypertensive effect, as there was no significant change in ambulatory BP with intervention and no significant relationship between changes in long-axis systolic function and changes in mean ambulatory systolic or diastolic BP. In addition, the increases in strain and SR with intervention were independent of changes in the BP as measured at the time of echocardiography. The results therefore suggest that the increase in long-axis function likely represents improvement in intrinsic myocardial contractile function.

Spironolactone therapy was also associated with improvement in some parameters of diastolic function. Left atrial area is regarded as a marker of chronic LV diastolic load, and tended to decrease in the spironolactone group. This reduction in left atrial size correlated with the increase in LV strain with intervention, as well as with a significant decrease in LV posterior wall thickness, suggesting a possible link between the structural and functional improvements with aldosterone inhibition. The decrease in pulmonary venous A reversal velocity observed in the spironolactone group is also consistent with a reduction in LV stiffness and/or end-diastolic pressure. Although the mechanisms underlying these changes were not addressed by this study, the results are consistent with the known antifibrotic effects of spironolactone.

There is currently no clear evidence that favors the use of specific agents to treat patients with diastolic HF. Instead, the goal of treatment for patients with hypertensive heart disease has largely been effective BP control, usually with a combination of multiple antihypertensive agents. There are relatively few clinical data evaluating the specific targeting of pathophysiological processes that lead to myocardial dysfunction in hypertensive heart disease. In an important exception, Brilla et al demonstrated in hypertensive patients with LV hypertrophy that myocardial fibrosis could be reversed with lisinopril, and that this was associated with improved diastolic function. In addition, Diez et al recently demonstrated that blockade of angiotensin type 1 receptors with losartan resulted in regression of myocardial fibrosis that was associated with diminution of LV stiffness in hypertensive patients. In the current study, we selected aldosterone antagonism with spironolactone to obtain a potentially more powerful antifibrotic agent with less antihypertensive effect. This therapy improved myocardial function in symptomatic patients with diastolic dysfunction who did not necessarily have LV hypertrophy. Thus, aldosterone blockade may have beneficial cardiac effects in selected patients with hypertensive heart disease. Large studies with clinical end points in such populations are warranted, including consideration of newer agents that may have a more favorable side effect profile.

An important further question is whether incremental improvement in LV function can be obtained in patients already taking angiotensin-converting enzyme inhibitors or angiotensin receptor blocking drugs.

Finally, significant adverse effects of aldosterone on vascular structure and function have also been proposed. In this regard, the trend for an increase in arterial compliance with spironolactone therapy in study patients is consistent with experimental evidence that aldosterone may have deleterious effects on arterial compliance. Such findings are consistent with the known antifibrotic effects of spironolactone.

### TABLE 2. Baseline and 6-Month 2-Dimensional and Doppler Echocardiographic Data

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>6 Months</th>
<th>Spironolactone</th>
<th>6 Months</th>
<th>P*</th>
<th>P†</th>
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<tbody>
<tr>
<td>LV diastolic diameter, cm</td>
<td>4.70±0.41</td>
<td>4.64±0.63</td>
<td>5.00±0.47</td>
<td>4.89±0.50</td>
<td>NS</td>
<td>NS</td>
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<tr>
<td>Septal thickness, cm</td>
<td>1.02±0.15</td>
<td>0.91±0.14</td>
<td>0.89±0.13</td>
<td>0.85±0.19</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Posterior wall thickness, cm</td>
<td>0.96±0.11</td>
<td>0.95±0.14</td>
<td>0.95±15</td>
<td>0.84±0.14</td>
<td>0.042</td>
<td>NS</td>
</tr>
<tr>
<td>LV mass/height, g/m</td>
<td>93.5±15.6</td>
<td>84.6±21.2</td>
<td>95.9±26.9</td>
<td>82.7±22.6</td>
<td>NS</td>
<td>NS</td>
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<tr>
<td>Relative wall thickness</td>
<td>0.43±0.07</td>
<td>0.41±0.09</td>
<td>0.37±0.05</td>
<td>0.35±0.07</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Left atrial area, cm²</td>
<td>22.5±4.0</td>
<td>22.5±4.1</td>
<td>21.9±3.9</td>
<td>19.5±3.6</td>
<td>0.045</td>
<td>0.090</td>
</tr>
<tr>
<td>Transmitral E velocity, cm/s</td>
<td>61±17</td>
<td>62±15</td>
<td>63±13</td>
<td>59±11</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Transmirtal A velocity, cm/s</td>
<td>74±16</td>
<td>76±20</td>
<td>81±16</td>
<td>75±15</td>
<td>NS</td>
<td>0.018</td>
</tr>
<tr>
<td>E/A ratio</td>
<td>0.83±0.10</td>
<td>0.88±0.24</td>
<td>0.79±0.12</td>
<td>0.81±0.17</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>E deceleration time, ms</td>
<td>264±10</td>
<td>242±33</td>
<td>278±23</td>
<td>254±23</td>
<td>NS</td>
<td>0.022</td>
</tr>
<tr>
<td>PV A reversal velocity, cm/s</td>
<td>32.5±7.0</td>
<td>31.9±4.0</td>
<td>31.5±5.8</td>
<td>29.2±5.0</td>
<td>NS</td>
<td>0.005</td>
</tr>
<tr>
<td>Septal Sa velocity, cm/s</td>
<td>6.9±2.0</td>
<td>6.2±1.2</td>
<td>6.1±1.4</td>
<td>6.5±1.5</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Septal Ea velocity, cm/s</td>
<td>6.7±1.3</td>
<td>6.2±1.0</td>
<td>6.3±1.5</td>
<td>6.4±1.2</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Septal Aa velocity, cm/s</td>
<td>9.6±2.2</td>
<td>9.1±1.8</td>
<td>8.9±1.6</td>
<td>8.4±1.4</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Lateral Sa velocity, cm/s</td>
<td>7.4±2.2</td>
<td>7.0±1.3</td>
<td>7.4±1.3</td>
<td>7.2±1.4</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Lateral Ea velocity, cm/s</td>
<td>7.1±1.7</td>
<td>6.9±1.1</td>
<td>7.9±1.5</td>
<td>7.9±1.2</td>
<td>0.023</td>
<td>NS</td>
</tr>
<tr>
<td>Lateral Aa velocity, cm/s</td>
<td>10.4±1.8</td>
<td>9.3±1.4</td>
<td>10.5±1.7</td>
<td>9.4±1.4</td>
<td>NS</td>
<td>0.009</td>
</tr>
</tbody>
</table>

PV indicates pulmonary venous; Sa velocity, mitral annular systolic velocity; Ea velocity, mitral annular early diastolic velocity; and Aa velocity, mitral annular late diastolic velocity.

*Placebo vs spironolactone at 6 months.
†Spironolactone at 6 months vs spironolactone at baseline.
evidence of a decreased arterial stiffness with spironolactone, and with a recent report of improvement in arterial stiffness in hypertensive patients with angiotensin receptor blockade. Furthermore, combined increases in arterial and ventricular stiffening have recently been demonstrated in patients with HF and preserved LV ejection fraction, and an important pathophysiological link has been suggested. In this context, possible beneficial effects of aldosterone blockade on vascular properties may be particularly relevant for hypertensive patients with suspected diastolic HF.

Limitations
All patients reported exertional dyspnea as a significant problem, and mean maximal exercise capacity at baseline was reduced in comparison with reference values from healthy subjects. The definition of diastolic HF remains controversial, and although many investigators support a diagnostic link has been suggested. In this context, possible clinical conditions with the potential to mimic or misdiagnose diastolic HF.

Conclusions
Aldosterone antagonism improves myocardial function in symptomatic patients with early hypertensive heart disease through mechanisms that seem to be at least partly independent of effects on BP and that may improve arterial compliance. In combination with conventional antihypertensive therapy, such an approach has the potential to provide a specific treatment for hypertensive patients with suspected diastolic HF.

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References


Effect of Aldosterone Antagonism on Myocardial Dysfunction in Hypertensive Patients With Diastolic Heart Failure
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