Cardiac Remodeling in Patients With Primary and Secondary Aldosteronism

A Tissue Doppler Study

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Susanna Sciomer, MD; Silvia Rosi, MD; Gian Paolo Rossi, MD

Background—Primary aldosteronism (PA) causes excess left ventricular (LV) hypertrophy and diastolic dysfunction; whether this occurs also in secondary aldosteronism (SA) without hypertension is unknown. We investigated the cardiac modifications in patients with preserved LV ejection fraction who had PA or SA.

Methods and Results—We measured several Doppler echocardiography–derived variables, including tissue Doppler imaging (TDI) parameters and strain rate analysis, in 262 patients with PA, 117 with SA because of liver cirrhosis, and in 61 control healthy subjects. SA and PA patients showed markedly elevated aldosterone levels (67 versus 39 ng/dL, respectively; normal values <15 ng/dL) but contrasting values of plasma renin activity (15.00 versus 0.56 ng/mL/h; P<0.001). Compared with PA, SA patients showed higher heart rate, and lower blood pressure and vascular resistance values. Both PA and SA showed increased LV diameters, LV volumes, stroke volume, stroke work, and septal peak systolic tissue velocity, and had more LV hypertrophy (61% and 39%, respectively) and diastolic dysfunction (35% and 36%, respectively) than healthy subjects. Peak systolic septal strain (20% versus 23%; P=0.001) and midwall fractional shortening (15.9% versus 16.7%; P=0.001) were lower in PA than in SA patients.

Conclusions—Primary and secondary hyperaldosteronism correlate with LV enlargement and high prevalence of LV hypertrophy and diastolic dysfunction; a subclinical systolic dysfunction is evident only in PA. In SA, the high rate of LV hypertrophy, in spite of low peripheral resistances and low-to-normal blood pressure, could be accounted for the high renin and aldosterone values, and the work overload associated with a hyperdynamic circulatory state. (Circ Cardiovasc Imaging. 2016;9:e004815. DOI: 10.1161/CIRCIMAGING.116.004815.)

Key Words: aldosterone◼ cirrhosis◼ diastolic dysfunction echocardiography◼ echocardiography◼ hypertrophy◼ left ventricular systolic function◼ strain rate imaging

Primary aldosteronism (PA) is a common curable cause of high blood pressure (BP) characterized by undetectable renin and angiotensin II, and an excess rate of metabolic syndrome,1 cardiovascular damage,2,3 and events.4,5 Secondary aldosteronism (SA) is a common feature of conditions characterized by effective circulating volume, causing cardiovascular underfilling as heart failure, nephrotic syndrome, and liver cirrhosis.6 The latter also features low systemic vascular resistance owing to splanchic vasodilatation, which might suggest that in liver cirrhosis patients, the left ventricle (LV) does not need to undergo remodeling to cope with the low afterload. Although PA and SA share the hyperaldosteronism, from the pathophysiological standpoint, these conditions are antithetical in that in PA, the aldosterone secretion is inappropriate for the prevailing systemic vascular resistance and volume status, whereas in SA, it reflects a physiological response to reduced intravascular volume/sodium status. An independent association of high levels of plasma aldosterone or renin with increased LV mass (LVM)2,3,7 and development of LV hypertrophy (LVMH)2,3,8 has been reported. Whether hyperaldosteronism in the setting of low-to-normal BP, as found in conditions characterized by underfilling,6 also causes morpho-functional changes of the LV is unknown.

See Editorial by Parker and Aurigemma
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The long axis–oriented fibers in the luminal part of the myocardium are more susceptible to changes in cardiomyocyte function than the midwall radial-oriented fibers. Hence, tissue Doppler imaging (TDI) technique in the long-axis plane allows accurate detection even of subtle changes of systolic and diastolic function. Moreover, because TDI-derived indexes (early diastolic peak velocity of mitral annulus [sep tal E′], early and late diastolic strain rate [SR] parameters [SRe and SRA], and their ratio [SR el/a]) are held to be less...
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load-dependent than mitral inflow velocity parameters. TDI can allow a more accurate detection of diastolic dysfunction (DD) than transmitral Doppler velocity parameters. We therefore hypothesized that hyperaldosteronism, either primary aldosteronism (PA) or secondary aldosteronism (SA), induces subtle early changes of LV geometry and systolic/diastolic function that can be noninvasively detected by TDI. To test this hypothesis, we enrolled prospectively a large cohort of referred patients with hyperaldosteronism because of PA or of SA (liver cirrhosis), who had preserved LV ejection fraction but contrasting levels of BP and plasma renin activity.

Methods

We recruited consecutive white PA patients referred to the Hypertension Clinic, Department of Medicine–DIMED (Center of Excellence of European Society of Hypertension) of the University of Padova and to the Department of Internal Medicine and Cardiology of the University La Sapienza of Rome, and patients with cirrhosis (SA) referred to the Unit of Hepatic Emergencies and Liver Transplantation Department of Surgery of the University of Padova between 1992 and 2015.

The study was approved by an institutional review committee, and the subjects gave informed consent. All patients underwent a standard transthoracic Doppler echocardiography and TDI evaluation, which was performed by the same 2 operators (Dr Cesari and Sciomer) with the same protocol. Inclusion criteria comprised the availability of complete demographic, biochemical, and hormonal data. Exclusion criteria entailed history of heart disease and diabetes mellitus and, in the SA group, also arterial hypertension because we aimed at assessing the effect of SA without the confounding effect of high BP.

With regard to ongoing medical treatment, in the PA patients, the echocardiogram was performed during treatment with calcium channel blockers and doxazosin; in SA patients, β-blockers, whenever prescribed, were stopped 48 hours before echocardiography. Hence, at the time of evaluation, no SA patients were on β-blockers (Table 1).

PA was diagnosed following guidelines as detailed; the diagnosis of aldosterone-producing adenoma was done according to the 4 corners criteria and that of bilateral adrenal hyperplasia was based on lack of aldosterone excess lateralization at adrenal vein sampling. The diagnosis of liver cirrhosis was based on clinical, biochemical, imaging, and endoscopic findings. Obesity was defined as body mass index (BMI) ≥30 kg/m². Coronary heart disease was excluded in all participants on the basis of absence of symptoms, family history, normal standard 12-lead ECG, and wall motion on 2D-echocardiographic examination. Sixty-one age-matched healthy volunteers of both sex, without known cardiovascular, renal, or hepatic disorders, were selected as controls.

Echocardiography Parameters Analysis

Echocardiograms were performed using a General Electrics Vivid 7 ultrasound machine (General Electric Medical Systems, Horten, Norway) with a 2.5 MHz transducer and an Aplio CV Toshiba with a 3 MHz transducer. Measurements were performed according to the American Society of Echocardiography guidelines. LV end-diastolic and end-systolic diameters and wall thickness were assessed by M-mode.

For PA patients, the assessment was performed blindly to the diagnosis, which was made thereafter when the biochemical test results became available. The healthy subjects (HS) and the SA patients were assessed by one expert sonographer (Dr Cesari) not blinded to the diagnosis between 2012 and 2015. LV ejection fraction and fractional shortening were measured by biplane 2D mode using the Simpson’s method. As at a given contractile state, ejection fraction increases as LV geometry becomes more concentric, midwall fractional shortening was also calculated to assess underlying systolic dysfunction in the setting of concentric hypertrophy. The LVM was estimated by Devereux’s formula and normalized by body surface area and also by height (in meters) to the 2.7 power. LVH was defined as LVM/height ≥68 g/m² for men and ≥64 g/m² for women following current recommendations. LV geometry was also examined by the recently

Table 1. Clinical and Biochemical Features of Patients With PA and SA, and Healthy Subjects

<table>
<thead>
<tr>
<th>Variable</th>
<th>HS (n=61)</th>
<th>P (HS vs PA)</th>
<th>PA (n=262)</th>
<th>P (PA vs SA)</th>
<th>SA (n=117)</th>
<th>P (HS vs SA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>53±11</td>
<td>0.02</td>
<td>51±12</td>
<td>&lt;0.001</td>
<td>59±12</td>
<td>0.002</td>
</tr>
<tr>
<td>Sex M/F, %</td>
<td>46/54</td>
<td>0.09</td>
<td>57/43</td>
<td>=0.006</td>
<td>72/28</td>
<td>0.001</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>71±14</td>
<td>&lt;0.001</td>
<td>79±16</td>
<td>=0.12</td>
<td>76±14</td>
<td>=0.04</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>25±3</td>
<td>0.001</td>
<td>27±4</td>
<td>=0.06</td>
<td>26±3</td>
<td>=0.09</td>
</tr>
<tr>
<td>Obesity, %</td>
<td>5</td>
<td>0.007</td>
<td>21</td>
<td>=0.35</td>
<td>11</td>
<td>=0.62</td>
</tr>
<tr>
<td>Systolic BP, mmHg</td>
<td>127±9</td>
<td>&lt;0.001</td>
<td>159±20</td>
<td>&lt;0.001</td>
<td>125±17</td>
<td>=0.68</td>
</tr>
<tr>
<td>Diastolic BP, mmHg</td>
<td>81±7</td>
<td>&lt;0.001</td>
<td>97±12</td>
<td>&lt;0.001</td>
<td>77±11</td>
<td>=0.02</td>
</tr>
<tr>
<td>HR, b/min</td>
<td>68±10</td>
<td>0.23</td>
<td>66±9</td>
<td>&lt;0.001</td>
<td>73±12</td>
<td>=0.007</td>
</tr>
<tr>
<td>Pulse pressure, mmHg</td>
<td>46±8</td>
<td>&lt;0.001</td>
<td>62±17</td>
<td>&lt;0.001</td>
<td>49±12</td>
<td>=0.23</td>
</tr>
<tr>
<td>DM, %</td>
<td>0</td>
<td>...</td>
<td>0</td>
<td>...</td>
<td>0</td>
<td>...</td>
</tr>
<tr>
<td>Alpha-blockers, %</td>
<td>0</td>
<td>...</td>
<td>42</td>
<td>...</td>
<td>0</td>
<td>...</td>
</tr>
<tr>
<td>CCBs, %</td>
<td>0</td>
<td>...</td>
<td>73</td>
<td>...</td>
<td>0</td>
<td>...</td>
</tr>
<tr>
<td>Beta-blockers, %</td>
<td>0</td>
<td>...</td>
<td>20</td>
<td>...</td>
<td>0</td>
<td>...</td>
</tr>
<tr>
<td>MR antagonist, %</td>
<td>0</td>
<td>...</td>
<td>13</td>
<td>...</td>
<td>48</td>
<td>...</td>
</tr>
<tr>
<td>Aldosterone, ng/dL</td>
<td>NA</td>
<td>...</td>
<td>39 (25–253)</td>
<td>&lt;0.001</td>
<td>67 (15–255)</td>
<td>...</td>
</tr>
<tr>
<td>PRA, ng/mL/h</td>
<td>NA</td>
<td>...</td>
<td>0.55 (0.48–0.63)</td>
<td>&lt;0.001</td>
<td>15 (12–19)</td>
<td>...</td>
</tr>
</tbody>
</table>

The data are reported as mean±SD or median (and 25th and 75th percentiles) as appropriate. B/min indicates beats per minute; BMI, body mass index; BP, blood pressure; CCBs, calcium antagonists treatment; DM, diabetes mellitus; HR, heart rate; MR, mineralocorticoid receptor; NA, not available; PA, primary aldosteronism; PRA, plasma renin activity; and SA, secondary aldosteronism.
proposed 4-tiered classification of LVH based on concentricity (defined as a relative wall thickness ≤0.42) and LV end diastolic volume (classified as increased when LV end diastolic volume/body surface area >274 mL/m² in men and 61 mL/m² in woman). The theoretical (predicted) value of LVM, which estimates the LVM expected for cardiac workload, height (used as surrogate for genetically programmed lean body mass for a given height), and sex, was also calculated using an indicator variable for sex, height, and stroke work (SW), as a measure of cardiac workload. Predicted LVM was \[ \text{LVM} = 55.3 + 6.64 \times \text{height} \times 0.0014 + 0.64 \times \text{SV} \times 0.0018 \times \text{sex} \] (where sex was coded as male=1 and female=2). The observed LVM divided by the predicted LVM, expressed as a percentage (observed LVM/predicted LVM×100), was considered categorized as inappropriate when in excess >35% from the predicted value referenced to the 97.5th percentiles of the distribution in normotensive, taken as a normal range in the reference adult white population. We calculated mean arterial pressure as diastolic BP+1/3 of pulse pressure and stroke volume (SV) as indexes of LV volume load. Cardiac output (CO) was calculated as product of SV and heart rate; Cardiac index (CI) as CO adjusted by the body surface area; systemic vascular resistance as product of mean arterial pressure and 80/CI; SV-pulse pressure ratio (SV/PP) as an index of arterial compliance (AC); SW as product of systolic BP (pressure load) and SV (volume load) and converted into grams per beat by multiplying for the conversion factor 0.0014. Starting in 1992, we used the Doppler transmitial flow parameters for the evaluation of DD: after introduction of the TDI technology, we also used the TDI-derived indexes. Pulsed Doppler recordings at the level of the mitral valve tips were obtained from an apical 4-chamber view to measure early (E) and late (A) diastolic filling velocities, their ratio (E/A ratio), and early wave deceleration time. To assess TDI parameters, echocardiograms were stored digitally and analyzed off-line. The TDI program was set to pulse-wave Doppler mode; filters were set to exclude high-frequency signals. Gains were minimized to allow a clear tissue signal with minimal background noise. The TDI of the diastolic velocities was obtained from the apical 4-chamber view. The recorded wall was positioned in the center of the sector. A 1.5-mm sample volume was placed at the septal corner of the mitral valve annulus; utmost care was taken to minimize the angle between the Doppler beam and the longitudinal motion of the septal mitral valve annulus. All Doppler parameters were recorded at a horizontal speed of 100 mm/s. Average values obtained during at least 3 consecutive cardiac cycles were taken into consideration. Early diastolic peak velocity of septal mitral annulus (septal E') was obtained, and E/E' ratio, reflecting the LV filling pressure, was derived. Given the different time points at which E/A and septal E' were introduced in our protocol and considering that mitral E/A ratio cannot be reliably applied to identify DD in volume-depleted patients (as cirrhotic patients with ascites), we used mitral E/A ratio and deceleration time in 188 PA patients and in 61 HS to identify abnormal LV relaxation, defined as E/A<1 and deceleration time >240 ms. Since 2008, TDI indexes were also used to identify and grade DD according to guidelines. Analysis of all SR parameters was performed offline (VC 6.4%, ICC r=0.84); and 0.12±0.44 for SR/eA (VC 8.8%, ICC r=0.63). Bland–Altman plots were used to verify the reproducibility of measurements and exclude systematic biases.

### Statistical Analysis

Data are expressed as mean±SD (or SEM) or median and range, as appropriate. All echocardiographic and hemodynamic parameters showed a normal distribution, which was formally verified by Kolmogorov–Smirnov test. One-way analysis of variance followed by Bonferroni’s post hoc test was used to compare quantitative variables across patients and controls. Categorical variables were investigated by Chi-square analysis. To identify determinants of LVM, a logistic regression analysis, including age, sex, BMI, systolic BP, diastolic BP, plasma renin activity, and aldosterone levels, was performed separately in PA and SA patients. The statistical analysis was performed with SPSS 23 for Mac (SPSS Italy Inc, Bologna, Italy), and significance was set at P<0.05.

### Results

Between 1992 and 2015, we recruited a total of 440 patients, of which 262 had PA and 117 SA because of liver cirrhosis (57% alcoholic) and 61 were healthy control subjects. Their clinical and biochemical data are reported in Table 1. The TDI indexes were available in 51 PA patients, in 81 SA patients, and in all 61 HS. The PA patients showed high systolic and diastolic BP, pulse pressure and systemic vascular resistance, and reduced AC, besides the expected high aldosterone/renin ratio. On average, the SA patients were slightly older, mostly men, and with higher heart rate than the PA patients. In spite of high levels of renin and aldosterone, they showed normal BP values, increased AC, and reduced peripheral vascular resistance (Tables 1 and 2). The rate of treatment with mineralocorticoid receptor antagonists at the time of echocardiography examination was 13% in PA and 48% in SA patients (<0.0001).

### LV Geometry

Compared with HS, both PA and SA showed increased LV systolic and diastolic dimensions, volumes, wall thickness, and LVM. In addition, the PA patients showed significantly higher LV systolic and diastolic dimensions and wall thickness than SA patients (Table 2). Both PA and SA patients showed a marked increase in the rate of LVH (64% in PA and 39% in SA; Table 2); concentric LVH was found in 78% of PA and in 80% of SA. The rate of inappropriate LVM was 30% in PA and 41% in SA, respectively. Using the 4-tiered classification of LVH, the PA patients showed a tendency to dilatation, compared with the SA patients (Figure). Thus, notwithstanding low-to-normal BP, the SA patients exhibited increased LVM, mostly entailing concentric geometry, which was disproportionally increased for sex and cardiac workload. At stepwise logistic regression analysis, the major determinants of LVM in the PA group were sex, BMI, and systolic BP (F=34.40; P<0.001); in the SA group, they entailed age, BMI, and aldosterone levels (F=6.61; P=0.001).

### LV Systolic Function and Hemodynamic Parameters

Peripheral vascular resistances were significantly increased in PA and decreased in cirrhotic patients (SA; Table 2); AC showed opposite changes.
SV, SW, CO, CI, and septal $S'$ were higher in both PA and SA than in HS. SV and SW were also higher in PA than in SA because of the increased BP and plasma volumes in the former$^{24}$; CO, CI, ejection fraction, septal SRs, and septal $S'$ did not differ between PA and SA (Table 3). At variance, midwall fractional shortening, fractional shortening, and septal strain were slightly reduced in PA compared with both HS and SA patients, thus indicating a subclinical systolic dysfunction. This reduction remained significant after exclusion of PA patients on $\beta$-blockers.

**LV Diastolic Function**

Patients with hyperaldosteronism showed a reduction of $E'/E$ and septal $S'$, and an increase of $E'/E'$ compared with HS; PA patients also showed a slight reduction of the septal SR $e/a$ ratio but no differences of deceleration time (Table 4). Abnormal LV relaxation was found in 19% of PA and in 10% of HS. The prevalence of DD, as defined by current guidelines, was similar in PA (35%) and SA (36%) patients and 3-fold higher than in HS (12%). In most of the PA (79%) and SA (73%), the DD was mild (grade I); in the rest, it was moderate (21% and 27% in PA and SA, respectively).

**Discussion**

Based on evidence that hyperaldosteronism$^4$ and hyperreninism$^{25,26}$ are both directly and independently associated with an excess rate of CV events,$^{4,5}$ we sought to determine whether these hormones could have an additive detrimental effect on the heart. To this end, we used as models two clinical conditions that share the hyperaldosteronism, but have contrasting phenotypic and pathophysiological features: PA, which shows high peripheral vascular resistance, elevated BP values, reduced AC, and low-to-undetectable plasma renin activity, and SA caused by liver cirrhosis, which features low-to-normal BP values, reduced peripheral vascular resistance, high AC, and increased CO and CI due to the compensatory increase of HR.

We could recruit the largest cohort ever reported of consecutive PA patients studied with echocardiography, besides a relatively large cohort of well-characterized patients with a conclusive diagnosis of SA caused by liver cirrhosis. Of note, the findings observed in these groups perfectly matched the hemodynamic expected features for these two conditions.

**Prevalence of LVH**

Both PA and SA patients showed a high prevalence of LVH, mainly of the concentric type. The rate of LVM inappropriately high for workload and sex was higher in SA than in PA patients. According to the recent 4-tiered classification of LVH, the PA patients showed a slight tendency toward more LV dilatation, compared with SA. These findings, which confirm and extend previous reports,$^{2,3}$ were anticipated in the PA group owing to the elevated systemic vascular resistance and BP. Instead, they were unexpected in the SA patients with liver cirrhosis, inasmuch as these patients show low afterload, reduced peripheral vascular resistance, high AC and, consequently, low-to-normal BP values. Hence, we would like to contend that in these SA patients, the excess LVH originated from the cardiac work overload secondary to the hyperdynamic circulatory state$^{27}$ and from the increased levels of renin and aldosterone.$^{3,4,8}$

**Changes of LV Systolic Function**

Another main finding of this study regards systolic function: both PA and SA patients showed an enhanced cardiac work, as evidenced by increased SV, peak systolic tissue velocity of the mitral annulus, and SW, which can be accounted for by the Frank–Starling mechanism owing to the increase of LV volume.$^{22}$ Compared with HS and SA patients, PA patients showed a reduction of midwall fractional shortening.

### Table 2. Left Ventricular Geometry Indexes, Systemic Resistance, and Arterial Compliance in Patients With PA and SA, and Healthy Subjects

<table>
<thead>
<tr>
<th>Variable</th>
<th>HS (n=61)</th>
<th>P (HS vs PA)</th>
<th>PA (n=262)</th>
<th>P (PA vs SA)</th>
<th>SA (n=117)</th>
<th>P (HS vs SA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVEDD, mm</td>
<td>46±3</td>
<td>&lt;0.001</td>
<td>49±5</td>
<td>=0.009</td>
<td>48±4</td>
<td>=0.002</td>
</tr>
<tr>
<td>LVESD, mm</td>
<td>27±3</td>
<td>&lt;0.001</td>
<td>30±4</td>
<td>=0.005</td>
<td>29±3</td>
<td>=0.002</td>
</tr>
<tr>
<td>LVED, mm</td>
<td>10.4±1.3</td>
<td>&lt;0.001</td>
<td>11.9±2.0</td>
<td>&lt;0.001</td>
<td>10.9±1.5</td>
<td>=0.07</td>
</tr>
<tr>
<td>PWd, mm</td>
<td>10.3±1.2</td>
<td>&lt;0.001</td>
<td>11.4±1.9</td>
<td>&lt;0.001</td>
<td>10.7±1.3</td>
<td>=0.15</td>
</tr>
<tr>
<td>LVED volume, mL</td>
<td>97±16</td>
<td>&lt;0.001</td>
<td>116±29</td>
<td>=0.007</td>
<td>108±20</td>
<td>=0.004</td>
</tr>
<tr>
<td>LVES volume, mL</td>
<td>28±7</td>
<td>&lt;0.001</td>
<td>37±14</td>
<td>=0.004</td>
<td>33±10</td>
<td>=0.01</td>
</tr>
<tr>
<td>LVMass, g</td>
<td>168±39</td>
<td>&lt;0.001</td>
<td>224±69</td>
<td>&lt;0.001</td>
<td>193±45</td>
<td>=0.01</td>
</tr>
<tr>
<td>LVM/height, g/m$^2$</td>
<td>41±8</td>
<td>&lt;0.001*</td>
<td>53±14</td>
<td>&lt;0.001*</td>
<td>46±10</td>
<td>=0.05*</td>
</tr>
<tr>
<td>LVH, %</td>
<td>20</td>
<td>&lt;0.001</td>
<td>64</td>
<td>&lt;0.001</td>
<td>39</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>SVR, dyne/cm$^2$-m$^{-4}$</td>
<td>3059 (2921–3236)</td>
<td>0.01</td>
<td>3401 (3192–3611)</td>
<td>&lt;0.001</td>
<td>2770 (2623–2917)</td>
<td>0.02</td>
</tr>
<tr>
<td>AC, mL/mmHg</td>
<td>1.56±0.41</td>
<td>0.01</td>
<td>1.34±0.47</td>
<td>&lt;0.001</td>
<td>1.70±0.86</td>
<td>0.13</td>
</tr>
</tbody>
</table>

The data are reported as mean±SEM or median (and 25th and 75th percentiles) as appropriate. AC indicates arterial compliance; BP, blood pressure; HS, healthy subject; IVSd, interventricular septum thickness at diastole; LVEDD, left ventricular end-diastolic diameter; LVEDV, left ventricular end-diastolic volume; LVESD, left ventricular end-systolic diameter; LVESD, left ventricular end-systolic volume; LVH, left ventricular hypertrophy; LVM, left ventricular mass; PA, primary aldosteronism; PWd, posterior wall thickness in diastole; SA, secondary aldosteronism; and SVR, systemic resistance index.

*After adjustment for sex, age, weight, and mean BP, calculated as diastolic+1/3 pulse pressure.
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and septal strain that, however, remained close to the normal range, indicating a subclinical systolic dysfunction. The lack of concomitant reduction of septal SRs and septal $S'$ could be explained by the Frank–Starling mechanism via increased LV volume.

Because a subtle systolic impairment of both longitudinal and circumferential midwall systolic function has been reported in hypertensive patients studied by 2D speckle tracking echocardiography$^{29,30}$ and TDI,$^{31-34}$ it would seem that concurrence of hypertension can be more important than aldosteronism per se in inducing early systolic dysfunction. This contention was also supported by the observation that when antihypertensive treatment was optimized, this impairment was ameliorated.$^{33}$

A correlation between circumferential midwall systolic dysfunction and inappropriate LVM has been reported in PA and essential hypertensive patients.$^{20}$ In our SA patients, who were assessed after withholding $\beta$-blockers to avoid a potential confounding effect of this treatment on TDI indexes, no evidence for such LV systolic impairment could be found notwithstanding the high prevalence of inappropriate LVM (41%) and the high levels of renin and aldosterone. From the clinical standpoint, these findings support the following views: (1) subclinical LV systolic dysfunction develops only if BP is elevated; (2) hyper-reninism and hyperaldosteronism are not sufficient by themselves to cause LV systolic dysfunction, even when inappropriate LVM coexists; (3) the concurrence of hyper-reninism and hyperaldosteronism with high BP exerts a detrimental synergic effect, resulting in LV systolic dysfunction.$^{31}$

**Diastolic Function**

A harmful action of high aldosterone and renin on the heart is also supported by our findings concerning DD: both PA and SA patients showed a high (35% and 36%, respectively) rate of DD compared with healthy controls, who exhibited a prevalence similar to that found in a large survey of healthy normotensive subjects.$^{32}$ In the SA patients, such prevalence was lower than that (42%) found in a large cohort of patients with stage 2 to 3 arterial hypertension$^{32}$ and in cirrhotic patients (58%).$^{35}$ Intriguingly, it was also much lower than that (80%)
found in patients with cirrhosis and increased renin by Ruiz-Del-Arbol et al, who, however, also reported a much lower (11%) prevalence of DD and normal renin in the cirrhotic patients.36 Hence, altogether, previous and the present findings support the contention of a direct effect of high renin in the development of LVH and related DD. The fact that in the absence of hypertension, hyper-reninism and hyperaldosteronism are insufficient by themselves to cause LV systolic dysfunction, while they were associated with a high rate of DD, presumably independent of BP, lends support to the view that cardiac fibrosis can be the link because both hormones were associated with collagen deposition in the heart.37,38 Finally, it is worth highlighting that we found a pseudo normalization pattern of the transmitral Doppler flow velocity E/A ratio in both PA and SA patients, which unambiguously indicates that these parameters are inadequate for assessing DD. Therefore, we support the use of TDI to evaluate diastolic function in these patients, in line with current guidelines.11

Limitations and strengths are to be acknowledged in this study. Potential limitations are related to the lack of total blinding of the sonographers to patient’s diagnosis and the cross-sectional design of our study. The blinding was in fact only limited to the PA group, and we cannot totally rule out a bias in the assessment of the LV remodeling, although in our view this was unlikely. We could not assess also the potential impact on the systolic/diastolic LV parameters and of LVH in the different etiologies of duration of hypertension, a variable notoriously difficult to measure with accuracy. Moreover, this design did not allow us to determine the prognostic relevance of the aforementioned changes of LV indexes for which aim prospective outcome studies are eagerly needed. Further limitations might entail the comparison of groups with respect to a large number of echo variables, which might have inflated type I error. For this reason, results giving modest P values (eg, P>0.01) should be interpreted with caution. In addition, the relatively smaller number of patients in which TDI parameters were available (51 PA patients and 81 SA patients) might have introduced a type II error in the group comparison of these variables. Finally, the possibility that treatment with calcium antagonists treatment, which were commonly prescribed to PA patients at the time of hormone and echocardiographic assessment, could have blunted, albeit only slightly, the systolic function and, therefore, the differences between PA and SA patients. Finally, more SA than PA patients (48% versus 13%, respectively) received mineralocorticoid receptor antagonists, which might also have introduced a bias. However, clinically, it was obviously unfeasible to match the use of these drugs between SA and PA patients; yet, if any, these agents should have maximized differences of LV systolic and diastolic dimensions, wall thickness, LVM, concentric LVH, and rate of inappropriate LVM between PA and SA groups, which was obviously not the case. This observation further emphasizes the role of the hormonal and hemodynamic derangement in causing LV remodeling in SA patients.

Strengths of this study to be underscored include its prospective design, use of state-of-the-art echo-Doppler techniques with use of a validated protocol during the entire length of the study, the centralized readings by a single observer, and the performance of the echocardiograms not by technicians but by (only) 2 experienced cardiologists, one of which assessed all the HS and the SA patients as well the vast majority of those with PA.

Conclusions

In summary, hyperaldosteronism implies prominent changes of LV remodeling and function, which occur through different mechanisms in PA and SA. Patients with PA exhibited increased LVM, a high prevalence of LVH (64%), inappropriate LVM in 30% of cases, a subclinical systolic dysfunction, and a high prevalence of DD (35%). Patients with SA because of liver cirrhosis also showed increased LVM, which was often inappropriate (41%), a high prevalence of LVH (39%), no evidence of subclinical systolic dysfunction, and high prevalence of DD (36%). In these latter patients, these changes likely occur as a consequence of the work overload caused by a hyperdynamic circulatory state and the hyperreninism with ensuing hyperaldosteronism. Of note, the differences between PA and SA patients remained significant after adjustment for BMI, which was higher in PA than in SA patients, and after exclusion of overweight–obese patients, indicating that they are not simply because of the adiposity associated with PA.39 From the clinical standpoint, the high prevalence of LVH suggests the importance of assessing the LV remodeling for risk stratification purposes in liver cirrhosis patients, owing to the fact that LVH (both nondilated and dilated) predicts an increased cardiovascular risk in normotensive patients with SA.40,41 Further research is eagerly needed to collect follow-up outcome data in these patients to support this contention.

Sources of Funding

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Table 4. Left Ventricular Diastolic Function in Patients With PA and SA, and Healthy Subjects

<table>
<thead>
<tr>
<th>Variable</th>
<th>HS (n=61)</th>
<th>P (HS vs PA)</th>
<th>PA (n=188)</th>
<th>P (PA vs SA)</th>
<th>SA (n=81)</th>
<th>P (HS vs SA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>E/A</td>
<td>1.35±0.42</td>
<td>&lt;0.001</td>
<td>1.04±0.32</td>
<td>0.07</td>
<td>1.13±0.39</td>
<td>0.001</td>
</tr>
<tr>
<td>DT, ms</td>
<td>224±47</td>
<td>0.72</td>
<td>227±50</td>
<td>0.36</td>
<td>233±55</td>
<td>0.30</td>
</tr>
<tr>
<td>Septal E’, cm/s</td>
<td>10.3±2.5</td>
<td>&lt;0.001</td>
<td>8.5±2.1</td>
<td>0.89</td>
<td>8.6±2.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>E/E’</td>
<td>7.9±1.9</td>
<td>&lt;0.001</td>
<td>9.9±2.5</td>
<td>0.25</td>
<td>10.4±3.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Septal SR e’a</td>
<td>1.7±1.1</td>
<td>0.03</td>
<td>1.4±0.6</td>
<td>0.45</td>
<td>1.5±0.6</td>
<td>0.09</td>
</tr>
</tbody>
</table>

The data are reported as means±SD. DT indicates early wave deceleration time; E/A, early and late diastolic velocity ratio; E/E’, early diastolic transmitral and myocardial velocity on TDI; PA, primary aldosteronism; SA, secondary aldosteronism; Septal E’, early diastolic myocardial velocity on TDI; Septal SR e’a, early and late diastolic TDI velocities ratio; and TDI, tissue Doppler imaging.
Cardiac Modifications in Hyperaldosteronism

Disclosures

None.

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CLINICAL PERSPECTIVE

This study showed that hyperaldosteronism, both primary and secondary to liver cirrhosis, is associated with increased left ventricular (LV) diameters, LV volumes, stroke volume, and stroke work, as well as with high prevalence of LV hypertrophy and diastolic dysfunction. Subclinical LV systolic dysfunction was evident in primary aldosteronism, but not in secondary aldosteronism, and was presumably secondary to high blood pressure. The high prevalence of LV hypertrophy despite low blood pressure values in secondary aldosteronism likely derives from the increased cardiac work related to the hyperdynamic circulatory state and the high levels of aldosterone and plasma renin activity. From a clinical standpoint, this study underscores the importance of assessing for LV remodeling for risk stratification purposes not only in primary aldosteronism, but also in normotensive patients with secondary aldosteronism because of liver cirrhosis, owing to the fact that LV hypertrophy (both nondilated and dilated) predicts an increased risk of cardiovascular events. Moreover, these data suggest that in hyperaldosteronism the subclinical systolic dysfunction is likely related to high blood pressure values although it can be enhanced by high levels of aldosterone and plasma renin activity.
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