Long-term Control of Arterial Hypertension and Regression of Left Ventricular Hypertrophy With Treatment of Primary Aldosteronism

Gian Paolo Rossi, Maurizio Cesari, Cesare Cuspidi, Giuseppe Maiolino, Maria Verena Cicala, Valeria Bisogni, Franco Mantero, Achille C. Pessina

Abstract—Primary aldosteronism (PA), a common cause of high blood pressure (BP), induces left ventricular (LV) hypertrophy and an excess rate of cardiovascular events. Whether its treatment provides long-term cure of hypertension and regression of cardiovascular damage remains uncertain. To the aim of assessing the effect of treatment of PA on BP and LV changes, we prospectively recruited 323 patients in a long-term follow-up study entailing serial echocardiography evaluations. Of them, 180 had PA and were assigned to either adrenalectomy (n=110) or medical therapy (n=70) on the basis of the adrenal vein sampling. The remaining 143 were consecutive optimally treated primary hypertensive patients. At baseline, the PA patients had more inappropriate LV mass than PH patients (27.1% versus 16.2%; P=0.020), despite similar BP values. At a median follow-up of 36 months (range, 6–225), BP was lowered (P<0.0001 versus baseline) to similar values in adrenalectomized (135±15/83±9 mmHg), medically treated PA (133±11/83±7 mmHg), and PH (139±15/86±9 mmHg) patients. To this end, the adrenalectomized patients required significantly less drugs than the other groups. In PA patients, the LV mass index and the rate of LV hypertrophy fell through LV inward remodeling to the level of optimally treated PH patients, indicating that the LV work markedly decreased. Findings were similar when long-term (≥5 and ≥10 years) data were examined. Thus, an early diagnosis and a specific treatment of PA warrant normalization of BP and reversal of detrimental LV changes at long term. (Hypertension. 2013;62:00-00. ) • Online Data Supplement

Key Words: adrenalectomy ■ LVH ■ mineralocorticoid receptor antagonists ■ outcome ■ primary aldosteronism ■ remodeling

Primary aldosteronism (PA) is a common curable cause of high blood pressure (BP).1 PA is of peculiar interest because the excess aldosterone secretion is held to be autonomous from angiotensin II, which allows elucidating the cardiovascular effects of excess aldosterone without the confounding effects of excess angiotensin II. Moreover, the excess of aldosterone is cured with adrenalectomy in practically all patients,2 causation between aldosterone excess and the cardiovascular changes could be inferred. However, whether surgery or pharmacological blockade of the mineralocorticoid receptor (MR) warrant cure of high BP and regression of cardiovascular damage, and of cardiac remodeling, at long term remains unclear because limited data exist.3 4

The adaption of the left ventricle (LV) to the increased afterload of patients with high BP involves development of hypertrophy (LVH), which predicts cardiovascular events and death,3 and when regressed improved prognosis.6 In the complex interplay of hemodynamic, genetic, and endocrine-paracrine factors that underlie development of LVH aldosterone plays a pivotal role.7 8 In the setting of a high sodium intake, this major effector of the system causes LVH, transcription of collagen type I and III genes,9 and promotes fibroblasts proliferation, oxidative stress, and inflammation,10 in part, by potentiating the effects of angiotensin II on AT-1 receptors.11 12–14 These actions, alongside the effects of the steroid on pre- and after-load, are held to cause inflammation and fibrosis, which contribute to worsening prognosis of patients with hyperaldosteronism.11 12,16 and can explain the survival benefit conferred by MR antagonists to optimally treated patients with LV systolic dysfunction.17 18

Compared with BP-matched primary (essential) hypertensive patients, those with PA have an excess LVH and a LV mass inappropriately high for the degree of LV workload and BP elevation.2–4,9,19–28 Cardiac fibrosis with ensuing altered LV diastolic dysfunction can lead to left atrium dilatation and increased risk of atrial fibrillation (AF)2,8,29, whether these changes regress with specific treatment for PA remains uncertain.3 4,19,20,26 We, therefore, set out to prospectively investigate the long-term effects of correction of hyperaldosteronism on BP, LV mass, and cardiovascular events in a large cohort of patients with PA.
Methods

Patients
We recruited consecutive white patients with high BP referred to the Hypertension Center of the Clinica Medica 4 and to the Endocrinology Unit of the University of Padua between 1992 and 2012. Inclusion criteria comprised the availability of complete demographic, biochemical, hormonal data, and of a high-quality echocardiographic Doppler assessment at baseline.

PA was diagnosed following guidelines\(^\text{30}\) as described.\(^\text{31}\) Aldosterone-producing adenoma was diagnosed by the 4 corners criteria (Table S1 in the online-only Data Supplement).\(^\text{1}\)

Demographically similar primary (essential) hypertension (PH) patients were also consecutively recruited at the same units and at the Department of Clinical Medicine and Prevention of the University of Milan.

Phenotypic Assessment
BP was measured at each follow-up visit according to guidelines,\(^\text{32}\) with a mercury sphygmomanometer. Plasma renin activity and aldosterone concentration were measured using commercial kits after 1 hour in the supine position and again 45 minutes after administration of 50 mg captopril PO. Serum levels and 24-hour urinary excretion of Na\(^+\) and K\(^+\) were measured with standardized procedures. All biochemical measurements were performed in an ISO 9001 certified laboratory; normal values and within- and inter-assay coefficient of variation have been reported.\(^\text{1,33}\)

Echocardiography
M-mode and 2D echocardiography (Megas, Esaote Biomedica, Italy and Vivid 7 Pro, General Electric) were performed in all patients with a 3.5-MHz transducer by a cardiologist blind to the cause of hypertension and ongoing medical therapy. All measurements were performed on the average of ≥3 cardiac cycles according to the American Society of Echocardiography guidelines. For all details on the measurements please see the online-only Data Supplement.

The theoretical (predicted) value of LV mass, which provides an estimate of LV mass expected for cardiac workload, height\(^2,7\) (used as surrogate for genetically programmed lean body mass for that height), and sex\(^\text{34,35}\) was calculated using an indicator variable for sex, height\(^2\), and stroke work, as a measure of cardiac workload.

Follow-Up Study
All patients underwent follow-up entailing echocardiography and a comprehensive collection of clinical and demographical data, biochemical values, ongoing medical treatment, and incident cardiovascular events (Figure S1). Data were gathered with a predefined form by a physician blind to the echocardiographic features of the patients initially 3 to 6 months after the baseline examination and yearly thereafter. The last available follow-up was considered for long-term assessment for the patients who had >1 follow-up visit. To gather insight on the short- and long-term effects, data obtained within and after 1-year follow-up were also analyzed.

Statistical Analysis
The data are expressed as mean±SD (or SEM, or median and range), as appropriate. Statistical significance was defined as \(P<0.05\). SPSS 20.00 for Mac (SPSS Italy Inc, Bologna, Italy) was used for all analyses. For all details please see the online-only Data Supplement.

Results

Baseline Characteristics
The flow-chart of the study is shown in Figure S1. Twenty-three patients (7%) were excluded because of lack of high-quality echocardiographic data. Hence, 323 patients were investigated: of them, 180 had PA and 143 had PH (Table 1).

No patient was on MR antagonists at baseline. All the PA patients had low plasma renin activity and raised plasma aldosterone concentration and thus a marked elevation of the aldosterone renin ratio, as expected by definition.\(^\text{3}\) They did not differ for serum Na\(^+\) and 24-hour Na\(^+\) excretion (not shown) and were well matched to the patients with PH for sex, age, BMI, and known duration of arterial hypertension. However, they showed slightly higher systolic and diastolic BP values, and greater need for antihypertensive drugs than the patients with PH.

The majority (61%; n=110) of the PA cases had an aldosterone-producing adenoma that was treated with adrenalectomy; the rest (39%; n=70) had nonlateralized aldosterone excess at adrenal vein sampling. Therefore, they were allocated to receiving a MR antagonist alone or in combination with other agents as needed to achieve BP control. The baseline and follow-up BP values and biochemical data of the PA divided into surgically and medically treated groups are shown in Table 2. The medically and the surgically treated patients with PA showed similar values of serum K\(^+\), plasma renin activity, plasma aldosterone concentration, and aldosterone renin ratio which all differed from those of patients with PH.

![Figure 1](image-url)
Table 1. Baseline Demographic, Clinical, and Biochemical Features of the Patients With PA and PH

<table>
<thead>
<tr>
<th>Variable</th>
<th>Patients With PA (n=180)</th>
<th>Patients With PH (n=143)</th>
<th>P Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>51.1±12.0</td>
<td>52.4±14.0</td>
<td>ns</td>
</tr>
<tr>
<td>Sex, M/F, %</td>
<td>57/43</td>
<td>57/43</td>
<td>ns</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>26.5±4.0</td>
<td>26.9±4.3</td>
<td>ns</td>
</tr>
<tr>
<td>Duration of high BP, mo</td>
<td>81±8</td>
<td>69±12</td>
<td>ns</td>
</tr>
<tr>
<td>Systolic BP, mm Hg</td>
<td>164±20</td>
<td>159±23</td>
<td>0.024</td>
</tr>
<tr>
<td>Diastolic BP, mm Hg</td>
<td>100±12</td>
<td>94±14</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Antihypertensive treatment, no. of drugs</td>
<td>2.55±1.41</td>
<td>2.21±1.43</td>
<td>0.033</td>
</tr>
<tr>
<td>Serum K⁺, mmol/L</td>
<td>3.29±0.57</td>
<td>4.02±0.50</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>PRA, ng/mL per h</td>
<td>0.53 (0.10–1.10)</td>
<td>1.75 (0.2–5.79)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>PAC, ng/dL</td>
<td>37.4 (15.0–252.0)</td>
<td>13.8 (5.3–16.1)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>ARR, ng/dL per ng/mL per h</td>
<td>137 (27.4–3813)</td>
<td>17 (2.5–20.7)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Atrial fi brillation, % history or current</td>
<td>6.5</td>
<td>0.9</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Data are reported as mean±SD or median (and interquartile range) as appropriate. ARR indicates aldosterone:renin ratio; BP, blood pressure; ns, not significant; PA, primary aldosteronism; PAC, plasma aldosterone concentration; PH, primary hypertension; and PRA, plasma renin activity.

Baseline Echocardiography Variables

Table 3 shows the baseline echocardiographic parameters of the surgically and medically treated PA, and of the PH patients. The interventricular septum (P<0.05) and the LV posterior wall (P<0.001) thickness were higher in patients with PA than in PH, which translated into a higher left ventricular mass index (51.8±0.9 g/m² versus 50.0±0.9; P=0.027). When the left ventricular mass index was adjusted for BP at baseline, the left ventricular mass index remained higher in the PA. Accordingly, although the rate of patients with LVH did not differ significantly across groups, that of inappropriate LV mass was higher in the patients with PA.

Table 2. Changes of Clinical and Biochemical Features in Adrenalectomized and Medically Treated Patients Before and After Follow-Up

<table>
<thead>
<tr>
<th>Variable</th>
<th>Surgically Treated PA (n=110)</th>
<th>Medically Treated PA (n=70)</th>
<th>PH (n=143)</th>
<th>P Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body mass index, kg/m²</td>
<td>25.9±3.9</td>
<td>26.2±4.0</td>
<td>27.5±4.0</td>
<td>ns</td>
</tr>
<tr>
<td>Systolic BP, mm Hg</td>
<td>164±20</td>
<td>137±15</td>
<td>165±21</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Diastolic BP, mm Hg</td>
<td>100±12</td>
<td>83±9</td>
<td>101±12</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Antihypertensive treatment, no. of drugs</td>
<td>2.70±1.43</td>
<td>1.76±1.37‡</td>
<td>2.33±1.40†</td>
<td>0.015</td>
</tr>
<tr>
<td>Serum K⁺, mmol/L</td>
<td>3.19±0.56 ¶</td>
<td>4.12±0.44</td>
<td>3.33±0.51¶</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>PRA, ng/mL per h</td>
<td>0.40¶ (0.2–0.7)</td>
<td>1.60 (0.8–3.15)</td>
<td>0.47¶ (0.2–0.95)</td>
<td>2.00 (1.2–3.12)</td>
</tr>
<tr>
<td>PAC, ng/dL</td>
<td>35.1¶ (23.7–56.1)</td>
<td>8.8 (4.2–15.2)</td>
<td>28.0¶ (18.3–49.5)</td>
<td>17.4* (18.3–49.5)</td>
</tr>
<tr>
<td>ARR, ng/dL per ng/mL per h</td>
<td>216¶ (30–228)</td>
<td>8 (1–15)</td>
<td>212¶ (30–281)</td>
<td>16 (4–38)</td>
</tr>
</tbody>
</table>

Data are reported as mean±SD or median (and interquartile range) as appropriate. ARR indicates aldosterone:renin ratio; BP, blood pressure; ns, not significant; PA, primary aldosteronism; PAC, plasma aldosterone concentration; PH, primary hypertension; and PRA, plasma renin activity.

*P<0.05 vs surgically treated PA.
†P<0.0001 vs surgically treated PA.
‡P<0.05 vs medically treated PA.
§P<0.01 vs medically treated PA.
||P<0.05 vs PH.
¶P<0.0001 vs PH.
than in the PH (27.1% versus 16.2%; \(P=0.020\); Table 4), even more so (44.4% versus 24.0%; \(P=0.005\)) when only patients with LVH at baseline were considered. Thus, the LV mass was disproportionally increased for sex and for cardiac workload in the patients with PA.

### Cardiovascular Events at Baseline

At baseline, the patients with PA had a 7.2-fold higher prevalence of history or current AF than the patients with PH (6.5% versus 0.9%; \(\chi^2=10.9\); \(P=0.001\); Figure 1). Two patients had history of stroke and I of hospital admission for acute decompensated heart failure in the PA group, whereas no other major cardiovascular events, including myocardial infarction, were seen in any groups.

### Clinical Data at Follow-Up

Table 2 shows the follow-up data (median length, 36 months; range, 6–225 months). Both the adrenalectomized and the medically treated patients with PA exhibited a marked decrease of BP, which on average did not differ significantly from that in the PH (27.1% versus 16.2%; \(P=0.020\); Table 4), even more so (44.4% versus 24.0%; \(P=0.005\)) when only patients with LVH at baseline were considered. Thus, the LV mass was disproportionally increased for sex and for cardiac workload in the patients with PA.

### Table 3. Echocardiography and Doppler Variables in Surgically and Medically Treated Patients at Baseline and Follow-Up

<table>
<thead>
<tr>
<th>Variable</th>
<th>Surgically Treated PA (n=110)</th>
<th>P Values (2-Tail)</th>
<th>Medically Treated PA (n=70)</th>
<th>P Values (2-Tail)</th>
<th>PH (n=143)</th>
<th>P Values (2-Tail)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LAD, mm</td>
<td>Baseline</td>
<td>38.7±4.3</td>
<td>0.099</td>
<td>Baseline</td>
<td>37.8±4.1</td>
<td>0.020</td>
</tr>
<tr>
<td></td>
<td>Follow-Up</td>
<td>38.0±4.3</td>
<td></td>
<td>Follow-Up</td>
<td>37.1±3.6</td>
<td>0.03</td>
</tr>
<tr>
<td>Aortic dimension, mm</td>
<td></td>
<td>33.8±3.9</td>
<td>0.002</td>
<td></td>
<td>34.6±3.9</td>
<td>0.005</td>
</tr>
<tr>
<td></td>
<td></td>
<td>34.8±4.0</td>
<td></td>
<td></td>
<td>35.0±3.9</td>
<td>0.005</td>
</tr>
<tr>
<td>LAD/AoD</td>
<td></td>
<td>1.13±0.13</td>
<td>0.097</td>
<td></td>
<td>1.13±0.12</td>
<td>0.097</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1.10±0.13</td>
<td></td>
<td></td>
<td>1.10±0.13</td>
<td>0.097</td>
</tr>
<tr>
<td>LV mass index, mL/m²</td>
<td></td>
<td>62±13</td>
<td>&lt;0.0001</td>
<td></td>
<td>72±11</td>
<td>0.18</td>
</tr>
<tr>
<td>LV stroke work, g/m/beat</td>
<td></td>
<td>189±48</td>
<td>&lt;0.0001</td>
<td></td>
<td>187±51</td>
<td>0.18</td>
</tr>
<tr>
<td>LV Ejection fraction, %</td>
<td></td>
<td>68±6</td>
<td>ns</td>
<td></td>
<td>68±6</td>
<td>0.032</td>
</tr>
<tr>
<td>DT/E wave (s²/cm⁻10⁻³)</td>
<td></td>
<td>3.20±1.02</td>
<td>0.008</td>
<td></td>
<td>3.34±1.02</td>
<td>0.008</td>
</tr>
<tr>
<td>DT/E wave, mitral E wave deceleration time/E wave duration</td>
<td></td>
<td>ns</td>
<td>0.95</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LVMI, g/m²</td>
<td></td>
<td>41.7±1.3</td>
<td>ns</td>
<td></td>
<td>42.0±1.4</td>
<td>0.059</td>
</tr>
</tbody>
</table>

Data are reported as mean±SD or median (and interquartile range) as appropriate. ACLF indicates atrial contribution to left ventricular filling; AoD, aortic root diameter; DT/E wave, mitral E wave deceleration time/E wave duration; E/A, early/late diastolic LV filling wave ratio; E/E’, peak early diastolic mitral inflow/annular velocity ratio; NSd, end-diastolic interventricular septum thickness; LAD, left atrial dimension; LVEDD, LV end-diastolic dimension; LVESD, LV end-systolic dimension; LVMI, left ventricular mass index; ns, not significant; PA, primary aldosteronism; PH, primary hypertension; PWd, end-diastolic LV posterior wall thickness; and RWT, relative wall thickness.

*\(P<0.01\) vs surgically treated PA.
†\(P<0.0001\) vs surgically treated PA.
‡\(P<0.05\) vs medically treated PA.
§\(P<0.05\) vs PH.
||\(P<0.001\) vs PH.
¶\(P<0.0001\) vs PH.

than in the PH (27.1% versus 16.2%; \(P=0.020\); Table 4), even more so (44.4% versus 24.0%; \(P=0.005\)) when only patients with LVH at baseline were considered. Thus, the LV mass was disproportionally increased for sex and for cardiac workload in the patients with PA.

### Table 4. Prevalence of LVH and Inappropriate LVH in the 3 Groups

<table>
<thead>
<tr>
<th>Variable</th>
<th>Surgically Treated PA (n=110)</th>
<th>P Values (2-Tail)</th>
<th>Medically Treated PA (n=70)</th>
<th>P Values (2-Tail)</th>
<th>PH (n=143)</th>
<th>P Values (2-Tail)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVH, %</td>
<td>Baseline</td>
<td>61.3</td>
<td>0.03</td>
<td>Baseline</td>
<td>48.6</td>
<td>0.03</td>
</tr>
<tr>
<td></td>
<td>Follow-Up</td>
<td>45.5</td>
<td></td>
<td>Follow-Up</td>
<td>35.7</td>
<td>0.009</td>
</tr>
<tr>
<td>Inappropriate LVH, %</td>
<td>31.8</td>
<td>49.5</td>
<td>0.009</td>
<td>20.0</td>
<td>50.8</td>
<td>0.0002</td>
</tr>
</tbody>
</table>

At baseline, the prevalence of LVH did not differ significantly across groups, whereas that of inappropriate LVH was higher in surgically treated PA than in PH (\(P=0.004\)); at the last available follow-up, the prevalence of LVH did not differ significantly across groups, whereas that of inappropriate LVH was significantly higher in both surgically and medically treated PA than in PH (\(P=0.0001\)). LVH indicates left ventricular hypertrophy; PA, primary aldosteronism; and PH, primary hypertension.
achieved in the patients with PH. In the adrenalectomized patients, this fall of BP was accomplished, despite a tapering of the number and doses of antihypertensive drugs (Table 2; Figure S2); by contrast, a reinforcement of treatment was necessary in the medically treated patients with PA and PH.

Of note, in the adrenalectomy group HT was long-term cured in 45.2%, as defined by normotension with no antihypertensive drugs; an additional 32% of the patients required only 1 drug to achieve BP control. By contrast, cure of HT was not seen in any of the medically treated patients with PA and PH, whose need for antihypertensive treatment increased over time (Figure 2).

Serum K⁺ increased in both the adrenalectomized and the medically treated patients with PA, but not in the patients with PH. The aldosterone renin ratio normalized not only in the adrenalectomized but also in the medically treated patients, likely because of the increase of renin and the decrease of aldosterone induced by treatment with renin-angiotensin system antagonists. The follow-up data observed within 1 year after baseline evaluation and at long-term, for example, at ≥5 and ≥10 years follow-up, did not differ significantly.

**Echocardiographic Data at Follow-Up**

Table 3 shows the echocardiographic parameters at follow-up. The left atrium and aortic root to left atrium ratio diameter did not change significantly in any groups, although the aortic root diameter slightly increased in the surgically treated PA group. In both the surgically and the medically treated patients with PA, but not in the patients with PH, LV end-diastolic diameter and LVMI index decreased. Thus, the overall prevalence of LVH fell in both PA groups (Table 4), indicating the unchanged septum and posterior wall thickness because of inward LV remodeling.

Although the rate of LVH fell in both the PA groups that of inappropriate LV mass unexpectedly increased in all groups, albeit this reached statistical significance only in the medically treated patients with PA and in the PH (Table 4), indicating that the LV mass remained disproportionally increased for sex and for cardiac workload in spite of the regression of LVH.

Overall there were no differences between the changes observed within 1 year after baseline evaluation and at long-term follow-up (eg, at ≥5 and ≥10 years).

**Cardiovascular Events at Follow-Up**

Exhaustive information on cardiovascular events at follow-up was available for 148 (82%) and 111 (78%) patients with PA and PH, respectively. With exception of 1 fatal stroke in the PH group and 1 death for acute leukemia in the surgically treated PA group, there were no other major cardiovascular events in any groups. The incidence of AF, albeit low, remained the only common cardiovascular event in the entire population; although a trend toward regression to sinus rhythm was noted in the patients with PA, there were no differences between PA and PH groups (P=NS). The small number of patients available for long-term follow-up and of incident AF are obvious limitations of this analysis. However, considering the time from known onset of high BP to the last available follow-up the AF-free survival was lower in the PA than in the PH group in a highly significant (P=0.008) way (Figure 3).

**Discussion**

Compelling evidences have led to challenge the long-standing views that PA is a rare and benign form of hypertension, because it was found to involve 11.2% of referred hypertensive patients, and to carry a rate of cardiovascular events in excess of that expected from the high BP. Whether targeted treatment of PA could provide long-term cure of high BP and regression of the adverse cardiovascular changes remained, however, uncertain. To answer these questions, 2 decades ago we started prospectively submitting consecutive patients, who were diagnosed with PA by state-of-the-art criteria, to long-term follow-up with collection of clinical and echocardiography data (Figure S1). They were selected for surgery or medical treatment on the basis of the adrenal vein sampling following the guidelines, and the diagnosis of aldosterone-producing adenoma was confirmed retrospectively by the 4 corners criteria (Table S1). The long-term effects of treatment on BP control, LV changes, and incidence of cardiovascular events, including AF, could, therefore, be accurately assessed in the largest cohort of patients with PA submitted to long-term echocardiographic follow-up to date. The results obtained provided solid outcome data at long term and also relevant information on the adverse cardiac effects of excess aldosterone.

**Baseline Evaluation**

Consistently with the view that PA is common among patients with stage 2 and 3 and with resistant hypertension, at baseline the patients with PA had higher BP and required more antihypertensive drugs to achieve BP control than patients with PH. They also had more LVH than PH patients even after adjustment for the BP values, in keeping with findings in a smaller cohort. Hence, the rate of LV mass that was inappropriately
high for the workload and sex was higher in patients with PA than in PH. These results accord with those of most\textsuperscript{1,4,9,19,21–23,28} albeit not all previous cross-sectional studies.\textsuperscript{2,24–27} Difficulties of diagnosing unequivocally PA, inadequate patients matching and insufficient statistical power in some negative studies, along with differences of severity and also of duration of hypertension at diagnosis can account for these discrepancies. In fact, in this large cohort of patients with PA who were submitted to a systematic search for the disease, and, therefore, were diagnosed at a much earlier stage of their PA, the left ventricular mass index was not markedly elevated as it was in previous studies.\textsuperscript{3,4}

In our patients with PA, the LV adapted to the hyperaldosteronism-induced increase of pre-load (blood volume) and after-load (high BP) by developing LVH mainly through an increase of LV volume, as shown by the minimal thickening of the LV walls and the decrease of LV volume after correction of the hyperaldosteronism with treatment (Table 3). This accords well with the shift of the ex vivo LV pressure–volume curve to the right observed in normotensive rats infused with aldosterone.\textsuperscript{39}

At baseline, the rate of major cardiovascular events was similarly low in PA and PH, but that of previous or current AF was \(\approx 7\)-fold higher in the former than in the latter patients. This figure is lower than the 12.3 relative risk found in a smaller retrospective study,\textsuperscript{8} likely because of the different study design and selection criteria. A Kaplan–Meier analysis of the time from the first diagnosis of high BP to the last available follow-up (Figure 3) showed a worse AF-free survival in the patients with PA than in PH. Apparently this could not be reversed by specific treatment during the time frame of this study, but the small number of incident events likely minimized the between-group differences and thus the power to detect a significant difference. Thus, collectively previous and current findings establish a link between PA and AF, which accords well with studies showing that the arrhythmia could be induced by atrial pacing in 100% of normotensive rats infused with aldosterone, but only in 20% of those receiving a vehicle,\textsuperscript{39} and also with the reduction of AF with the MR antagonist eplerenone in the Eplerenone in Mild Patients Hospitalization And Survival Study.\textsuperscript{40}

**Effect of Correction of Hyperaldosteronism**

A marked reduction of systolic and diastolic BP (\(P < 0.001\)) was seen at long-term follow-up in both the surgically and the medically treated patients with PA (Table 2). In the former, this fall occurred in spite of a marked decrease of the antihypertensive treatment that could be withdrawn in 45.2% of the patients, and markedly reduced in the rest (Figure S2). More than 50% still required medical treatment, which accords with previous observations,\textsuperscript{2} and could be explained by the following: (1) long-standing hyperaldosteronism causing vascular remodeling and thereby high BP even after normalization of the aldosterone;\textsuperscript{2} and (2) coexisting primary (essential) hypertension that can concur with PA in \(\leq 40\)% of the patients and can develop over time in long-term studies as in this one. This rate of BP normalization was associated with correction of the biochemical picture of PA in practically all of our surgically treated patients, which renders our results comparable with the 98% cure rate reported at Mayo Clinic using a definition of cure that included either biochemical normalization of aldosterone or normalization of BP.\textsuperscript{41}

In contrast with the outcome of the adrenalectomized patients, the medically treated PA patients and those with primary hypertension showed an increase over time of the antihypertensive treatment needed to achieve BP control (Figure S2). Thus, on the whole these findings indicate that a precise early diagnosis is a key for achieving control of BP and tapering the antihypertensive treatment.

**Changes of LV Wall and Dimension After Treatment**

The demonstration of regression of LVH after correction of hyperaldosteronism could furnish the final proof of a causal role of aldosterone excess in LVH, but thus far evidence for this was limited to small cohorts, mostly after removal of an adrenal adenoma, with a short-term follow-up.\textsuperscript{3,4} In 1997, we reported a fall of LV mass and a normalization of indexes of LV filling 1 year after adrenalectomy;\textsuperscript{3} Catena et al thereafter reported that both adrenalectomy and also spironolactone treatment decreased LV mass in patients with PA, although this seemed to occur earlier after surgery.\textsuperscript{4} The present larger series of patients with PA submitted to a longer follow-up allowed us to document a prominent and persistent decrease in LV mass index in the adrenalectomized patients, and a borderline significant fall in the medically treated patients with PA (Table 3), which might suggest the superiority of adrenalectomy over medical treatment in regressing LVH. However, the smaller size of this group, with ensuing lower statistical power, might also account for the lack of statistical significance.

In spite of the prominent fall of pre-load (LV volume index), after-load (BP), LV mass index, and rate of LVH, the proportion of patients with a LV mass that was inappropriately elevated for sex and for cardiac workload unexpectedly increased (Table 4), suggesting that specific treatment of PA was unable to induce complete regression of the adverse changes involving the LV. Whether this could be achieved with an earlier diagnosis needs further investigation.
A further important novel finding of this study was that LV mass decreased mainly by reverse inward LV remodeling (eg, through a reduction in LV diameters and volume; Figure S3), which supports the notion of LV remodeling toward higher volumes in human PA as a consequence of increased pre- and after-load. Ex vivo studies of the LV pressure–volume curves in rats infused with aldosterone support this interpretation. This reverse inward LV remodeling was peculiar to PA, as much as it was not seen in the patients with primary hypertension, in whom the regression of LVH occurs through a decrease of the LV wall thickness (Table 3). Regardless of the mechanisms, the fall of LV volume and the ensuing inward remodeling, have profound consequences in that they markedly decreased LV workload (Table 3), which is a known determinant of oxygen and nutrients demand. Moreover, it implied an improvement in LV diastolic filling properties, as suggested by the significant prolongation of the E wave deceleration time (Table 3).

The correction of hyperaldosteronism, the LV remodeling around a smaller cavity (reverse inward), and the ensuing improvement in diastolic function, might explain why incident AF was no longer more common, but rather showed a trend toward regression during follow-up. Hence, overall our results can provide a mechanistic explanation for both the increased cardiovascular risk of patients with PA and for the improved prognosis of those submitted to adenectomy.

Some limitations of this study are to be underlined: first, our patients were referred to tertiary centers and, therefore, might not be representative of the population of PA at large. However, because of this they could be carefully subtyped and thus submitted to an adrenal vein sampling–guided treatment. It might also be argued that the higher rate of AF could have precluded the assessment of echocardiography and Doppler indexes at baseline in the patients with PA. Given the large sample size of our cohort and the relatively low proportion of patients with AF this potential bias was, however, likely minimal.

**Perspectives**

This study showed that a targeted surgical and medical treatment of PA induced a long-term reduction in BP and LV mass via LV inward remodeling. Although underscoring the importance of a timely identification of PA to accomplish regression of LV abnormalities and lower cardiovascular risk, these findings are relevant for understanding the cardiac changes occurring in the increasing population of congestive heart failure patients, who have secondary aldosteronism, and in whom MR blockade enhanced diastolic function, and strikingly due to Conn’s adenoma.

Several meta-analysis and prospective studies have confirmed that some components of the renin-angiotensin-aldosterone system are involved in the pathogenesis of hypertension, heart failure, and vascular diseases. 

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**Disclosures**

None.

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Gian Paolo Rossi, Maurizio Cesari, Cesare Cuspidi, Giuseppe Maiolino, Maria Verena Cicala, Valeria Bisogni, Franco Mantero and Achille C. Pessina

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Long-Term Control Of Arterial Hypertension
And Regression Of Left Ventricular Hypertrophy With
Treatment Of Primary Aldosteronism

Short title: Cardiac effects of hyperaldosteronism

Gian Paolo Rossi, MD, FACC, FAHA; Maurizio Cesari, MD, PhD; Cesare Cuspidi,1 MD;
Giuseppe Maiolino, MD, PhD; Maria Verena Cicala, MD; Valeria Bisogni, MD;
Franco Mantero, MD; Achille C. Pessina, MD, PhD.
EXPANDED MATERIALS AND METHODS

Echocardiography

M-mode and 2-D echocardiography (Megas, Esaote Biomedica, Italy and Vivid 7 Pro, General Electric, USA) was performed in all patients with a 3.5-MHz transducer by a Cardiologist blind to the cause of hypertension and ongoing medical therapy. All measurements were performed on the average of at least three cardiac cycles according to the American Society of Echocardiography guidelines. In the PA cohort the first 34 echo studies at baseline were performed by a different Cardiologist on the cohort reported\(^1\) albeit in the same laboratory with the same overall methodology. Thus, 81% of all echocardiograms of the PA patients at baseline and 100% of the follow-up examinations were performed by the same Cardiologist (M.C.) at the same echo-laboratory, both for the Clinica Medica 4 and for the Endocrinology patients.

Two different echo machines were used over this period: first an Esaote Megas (Esaote Biomedica) and thereafter (from 2008) a Vivid 7 Pro (General Electrics). When used in parallel in a pilot study overall the two machines provided almost identical results, particularly as regards the M-mode parameters used to assess LV mass and Doppler parameters to evaluate diastolic function.

The Cardiologist who performed the echo study was instructed to remain blind to the diagnosis and to record the images for the measurements, which were thereafter performed offline without access to the medical history of the patient. The data collected were thereafter entered in a database by another investigator blind to the final diagnosis. A file with the latter was thereafter merged. In the essential hypertensive patients examined at the University of Milan all the echo were performed by the same operator (CC) using a similar procedure. A comparison of their echo parameters of these patients with those of the essential hypertensive patients recruited in Padua showed no systematic differences. Hence, the likelihood that there were observer-related biases in our analysis was minimized.

LV wall thickness and internal dimensions were measured from 2-D-guided M-mode echocardiographic tracings obtained at mid-chord level in the parasternal long axis view. The LV mass (LVM) was estimated according to Devereux et al.\(^2\) LV mass index (LVMI) was calculated by indexing LV mass to height\(^{2.7}\). Relative wall thickness (RWT) was calculated at end-diastole to estimate LV geometry, as

\[
RWT = \frac{\text{inter-ventricular septum thickness + posterior wall thickness}}{\text{LV diameter}}.
\]

The criteria for LV hypertrophy (LVH) were LVMI>50 g/m\(^2\) and >47 g/m\(^2\) for men and women, respectively. LVH was classified as concentric or eccentric using a cut off for RWT>0.45 or <0.45, respectively; an RWT > 0.45 along with a normal LVMI identified LV concentric remodeling.\(^3,4\) LV end-diastolic and end-systolic volumes were calculated with the Teicholz’s correction of the cube formula.\(^5\) Ejection fraction was calculated by standard methods.\(^6\) Stroke work (SW) was estimated as systolic BP (measured after the echocardiographic study) times stroke volume and converted into gram-meters by multiplying by 0.0144.

The theoretical (predicted) value of LV mass, which provides an estimate of LV mass expected for cardiac workload, height\(^{2.7}\) (used as surrogate for genetically programmed lean body mass for that height) and gender,\(^6,7\) was calculated using an indicator variable for gender, height\(^{2.7}\), and stroke work, as a measure of cardiac workload.
Predicted LV mass (preLVM) was $= 55.37 + 6.64 \times \text{height (m}^2) + 0.64 \times \text{SW} - 18.07 \times \text{gender}$ (where gender was coded as male = 1 and female = 2). The observed LV mass divided by the preLVM expressed as a percentage (observed LV mass/predicted LV mass*100) was categorized as inappropriate when in excess >35% from the predicted value using the 97.5\textsuperscript{th} percentiles of the distribution in normotensive, taken as a normal reference adult population.8

**Statistical Analysis**

The data are expressed as mean ± SD (or SEM, or median and range), as appropriate. Variables that were not normally distributed were analyzed after appropriate transformations. The group comparison was performed with one-way ANOVA and post-hoc Bonferroni’s test when needed. The within-patient comparison of baseline and follow-up echocardiographic and hemodynamic variables was carried out on normally distributed value with student t-test for paired data. ANCOVA using baseline systolic, diastolic or mean BP, each in separate analyses, as covariate was performed to test for differences in LVMI, either normalized for BSA or for height\textsuperscript{27}. Moreover, as regression analysis on LVMI showed that BP values predicted LVMI, the BP-predicted values were saved and examined with ANOVA. Again the results and conclusions were identical as mentioned in the text. Statistical significance was defined as $P< 0.05$. SPSS 20.00 for Mac (SPSS Italy Inc., Bologna, Italy) was used for all analyses.
References for expanded materials and methods


**APA diagnosis by the four corners criteria.**

<table>
<thead>
<tr>
<th>1) Biochemical diagnosis of PA:</th>
</tr>
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<tbody>
<tr>
<td>a) Aldosterone ≥ 15 ng/dl, and</td>
</tr>
<tr>
<td>i) baseline aldosterone-renin ratio ≥ 26 or</td>
</tr>
<tr>
<td>ii) post captopril aldosterone-renin ratio ≥ 11;</td>
</tr>
<tr>
<td>2) Lateralized aldosterone secretion;</td>
</tr>
<tr>
<td>3) Identification of an adrenal adenoma at imaging and/or pathology;</td>
</tr>
<tr>
<td>4) Cure of the hyperaldosteronism and cure or improvement of hypertension post-adrenalectomy.</td>
</tr>
</tbody>
</table>

Supplemental table S1. APA diagnosis by the four corners criteria.
Supplemental Figure S1: Flow chart of the study.
Supplemental Figure S2: Panel A. The graph shows the mean systolic and diastolic blood pressure at baseline and follow-up in the surgically- and medically-treated PA patients and in the primary hypertensive patients group. Panel B. The bar graph shows the change in the average number of anti-hypertensive drugs needed to achieve BP control at long-term follow-up in the surgically- and medically-treated PA patients and in the PH group. All changes were significant from baseline. Moreover, there was a significant difference across group by ANOVA due to the fall in the surgically-treated PA patients and the increase in the medically-treated PA and in the PH group.
Supplemental Figure S3: Left ventricular changes during primary aldosteronism and after specific treatment. LV: left ventricular; LVH: left ventricular hypertrophy; MR: mineralocorticoid.