Aldosterone Is Produced From Ventricles in Patients With Essential Hypertension

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Abstract—This study was designed to examine whether aldosterone is produced from the hearts of patients with essential hypertension without left ventricular systolic dysfunction (LVSD). The study population consisted of 20 patients with essential hypertension without LVSD and 22 control subjects. Plasma levels of aldosterone, serum ACE activity, and B-type natriuretic peptide levels were measured in the anterior interventricular vein (AIV), coronary sinus, and aortic root during cardiac catheterization. The plasma aldosterone levels were significantly higher in AIV than in aortic root (99±11 versus 88±10 pg/mL, P<0.01, and 100±12 versus 88±10 pg/mL, P<0.01, respectively) in the hypertension group. On the other hand, there were no significant differences in aldosterone levels for these sites in the control group. There were no significant differences in ACE activity levels between aortic root, AIV, and coronary sinus in either the hypertension or control group. The levels of B-type natriuretic peptide were significantly higher in AIV than in aortic root in both groups. The difference in aldosterone levels between AIV and aortic root (ΔAldo[AIV−Ao]) had a significant positive correlation with the difference in ACE activity between AIV and aortic root (ΔACE[AIV−Ao]) (r=0.501, P<0.05) in the hypertension group. Both ΔAldo[AIV−Ao] and ΔACE[AIV−Ao] had a significant positive correlation with diastolic blood pressure (r=0.498, P<0.05; r=0.577, P<0.01, respectively) in the hypertension group. We conclude that production of aldosterone is activated in the left ventricles in patients with essential hypertension without LVSD in proportion to the severity of hypertension. (Hypertension. 2002;39:958-962.)

Key Words: aldosterone ■ angiotensin-converting enzyme ■ natriuretic peptides ■ hypertension, essential ■ blood pressure

The renin-angiotensin-aldosterone system plays an important role in the control of body fluid and blood pressure.1–3 Aldosterone promotes the retention of sodium and the loss of potassium, activates the sympathetic nervous system and myocardial and vascular fibrosis, and causes baroreceptor dysfunction.1–4 Traditionally, aldosterone has been thought to be produced solely by the adrenal cortex in response to angiotensin II, making it an important component of the circulating renin-angiotensin-aldosterone system. Recently, aldosterone has also been reported to be produced in extrarenal tissues, including the heart and blood vessels in animals.5–8 The coronary sinus drains blood from the heart as a whole, and the anterior interventricular vein (AIV), which lies in the anterior interventricular groove, drains blood from the anterior left ventricle.9 The difference in the hormone levels between the AIV and the aortic root therefore reflects the level of the hormone from the left ventricle, and that between the coronary sinus and the aortic root reflects the hormone level from the whole heart. By using this method, we showed that the production of natriuretic peptides, A-type natriuretic peptide (ANP) and B-type natriuretic peptide (BNP), was activated in the left ventricle in proportion to the severity of left ventricular dysfunction in patients with heart failure.10–13 We also showed by this method that the production of aldosterone and ACE was activated in the left ventricle in patients with heart failure in proportion to the severity of left ventricular dysfunction.14,15 It is not known, however, whether aldosterone is also produced in the heart in patients with hypertension and without left ventricular systolic dysfunction.

The present study was designed to examine whether aldosterone is produced together with ACE and BNP in the hearts of patients with hypertension and without left ventricular systolic dysfunction by measuring the plasma levels of aldosterone and BNP and the serum ACE activity in the aortic root, AIV, and coronary sinus.

Methods

Subjects

The study population consisted of 42 patients divided into a hypertension group and a control group. The hypertension group consisted of 20 patients (14 men and 6 women; mean age, 52.4±2.9 years, ranging from 32 to 78 years). Hypertension was defined as a
systolic blood pressure of >140 mm Hg and a diastolic blood pressure of >90 mm Hg in subjects who were not taking antihypertensive medications. These patients had a history of chest pain and were suspected of having angina pectoris. All of them received diagnostic cardiac catheterization, including coronary angiography and left ventriculography. Nineteen of them had atypical chest pain with normal coronary angiograms, and 1 patient had coronary spastic angina. All of the patients had left ventricular ejection fraction (LVEF) >65%. Patients with myocardial infarction, other heart muscle diseases, valvular disease, electrolyte disturbance, renal impairment (serum creatinine >133 μmol/L), or secondary hypertension were excluded from the study. All antihypertensive medications—including ACE inhibitors, angiotensin II receptor antagonists, aldosterone receptor blockers, nitrates, calcium antagonists, adrenergic β-antagonists, or diuretics—were withheld for ≥4 days before the study in all patients.

The age- and gender-matched control group consisted of 22 patients (16 men and 6 women; mean age, 55.7 ± 2.4 years, ranging from 23 to 70 years) in whom diagnostic cardiac catheterization, including coronary angiography and left ventriculography, was performed. All of them had a systolic blood pressure of <140 mm Hg and a diastolic blood pressure of <90 mm Hg. Sixteen patients had atypical chest pain with normal coronary angiograms, and 6 had coronary spastic angina. All of the patients had LVEF >65%. None of them had hypertension, heart failure, myocardial infarction, cardiac hypertrophy, other heart muscle diseases, valvular disease, electrolyte disturbance, or renal impairment (serum creatinine >133 μmol/L). None of them was receiving any other therapy at the time of the study.

All patients were hospitalized and were on a 10-g sodium chloride diet. Heart rate and blood pressure were measured ≥3 times in the morning (6:00 to 8:00 AM) after patients had fasted overnight and rested supine for 30 minutes. The study protocol was in agreement with the guidelines of the ethics committee at our institution, and written informed consent was obtained from each patient before the study, including the withholding of medication.

Cardiac Catheterization Study
Cardiac catheterization was performed with patients in a fasting state. By use of a Swan-Ganz catheter inserted into the femoral or internal carotid vein, the following hemodynamic measurements were obtained: pulmonary artery pressure, pulmonary capillary wedge pressure, right atrial pressure, and cardiac output. Cardiac output was determined by the thermodilution technique in triplicate. After the right heart catheterization was performed, a 6F Goodale-Lubin catheter was placed in the coronary sinus via either a brachial or an internal carotid vein.

The catheter was then advanced into the AIV under ﬂuoroscopy by a guidewire.10–14 The position of the catheter tip in the AIV was conﬁrmed by injection of contrast dye medium. This was a critical part of the study: 5 patients (3 from the hypertensive group and 2 from the control group) in whom at least the proximal half of the AIV was not visualized were excluded from the study. A Judkins catheter was placed at the root of the aorta by way of a femoral or brachial artery. Then blood was sampled within 2 minutes at the aortic root, AIV, and coronary sinus. Care was taken to draw blood samples slowly from the AIV. Initial parts of the sample, including those forcibly drawn, were discarded, because forcibly drawing blood from the AIV resulted in spurious levels of hormone, probably because backflow from the coronary sinus occurred and contaminated the AIV.9,10 Systemic arterial pressure, heart rate, and left ventricular end diastolic pressure (LVEDP) were measured, and coronary arteriography and left ventriculography were performed. LVEF was determined by left ventriculograms.

Hormonal Analysis
Blood samples were taken into plastic syringes and transferred to chilled siliconized disposable tubes with and without EDTA (1 mg/mL), then immediately placed on ice and centrifuged at 4°C. An aliquot of plasma and serum were immediately frozen at −80°C and thawed only once at the time of assay within 1 week.

Plasma levels of aldosterone were measured in duplicate with commercially available radioimmunoassay kits (SPAC-S aldosterone kit, Dainabot Inc).16 This assay kit is based on a solid phase method in which the aldosterone antibody is absorbed on polystyrene. The minimal detectable quantity of aldosterone is 25 pg/mL. The intra-assay and interassay coefficients of variation were 4.7% and 4.5%, respectively.

Serum ACE activity was measured in duplicate by colorimetry using commercially available kits (ACE color, Fujirebio Inc).17 The intra-assay and interassay coefficients of variation of this method were 6.7% and 8.3%, respectively.

Plasma levels of BNP were measured with a specific immunoradiometric assay kit (Shionoria BNP kit, Shionogi Inc).18 The intra-assay and interassay coefficients of variation of this method were 5.3% and 5.9%, respectively.

Echocardiographic Study
Complete M-mode and 2D echocardiographic studies were performed using standard criteria.19 Left ventricular internal dimensions were measured at end diastole (LVDDd), and intraventricular septal wall thickness (IVST) and posterior wall thickness (PWT), at the level of the mitral valve leaflet tips, were measured from a left parasternal image obtained at end-diastole by electronic calipers.

Measurement of Left Ventricular Mass Index
Left ventricular mass was calculated using the regression equation described by Devereux and Reichek:20 left ventricular mass (g) = 1.04[(LVDDd + PWT)^2 − (LVDDd)^2] − 13.6. Left ventricular mass was normalized for body-surface area.

Statistical Analysis
All values are expressed as mean ± SE. Statistical significance was defined as a P < 0.05. Either unpaired t test or 1-way ANOVA was used to analyze the results of the hemodynamic or hormonal measurements.20 Hormonal levels in the aortic root, AIV, and coronary sinus within the group were compared by 2-way ANOVA with repeated measurements followed by Scheffe’s test. The correlation of the plasma levels of aldosterone, BNP, serum levels of ACE activity, and systolic and diastolic blood pressure were examined by linear regression analysis.

Results
Patients Characteristics
The clinical characteristics of the study groups are shown in the Table. The levels of systolic blood pressure, diastolic blood pressure, and mean blood pressure were significantly higher in the hypertension group than in the control group. There were no significant differences in age, gender, the incidence of diabetes mellitus, smoking, obesity (including body mass index), serum total proteins, sodium, and creatinine between the 2 groups, except serum potassium, which was significantly lower in the hypertensive group than in the control group (3.90 ± 0.08 versus 4.14 ± 0.07 mmol/L, P < 0.05). LVEF and cardiac index were not different between the 2 groups. The levels of LVEDP were significantly higher in the hypertension group than in the control group. The levels of left ventricular mass index were also significantly higher in the hypertension group than in the control group. There were no complications occurring from the experimental procedures.
Comparison of Hormonal Levels

Figure 1 shows plasma aldosterone levels, serum ACE activity, and plasma BNP levels in the aortic root, AIV, and coronary sinus in the hypertension group compared with the control group. In the hypertension group, the plasma levels of aldosterone were significantly higher in the AIV and coronary sinus than in the aortic root (99±11 versus 88±10 pg/mL, *P*<0.01, and 100±12 versus 88±10 pg/mL, *P*<0.01, respectively). On the other hand, there were no significant differences in the levels between the aortic root, AIV, and coronary sinus (67±7, 63±5, and 68±7 pg/mL, respectively) in the control group. Plasma aldosterone levels were significantly higher in the AIV (99±11 versus 63±5 pg/mL, *P*<0.01) and coronary sinus (100±12 versus 68±7 pg/mL, *P*<0.05) in the hypertension group than in the control group; however, there was no significant difference in the level in the aortic root between the 2 groups.

There were no significant differences in the serum ACE activity levels between the aortic root, AIV, and coronary sinus both in the hypertension group (13.0±1.5, 13.0±1.5, and 12.7±1.3 IU/L, respectively) and in the control group (11.0±0.7, 10.9±0.7, and 11.0±0.7 IU/L, respectively). The plasma BNP levels were significantly higher in the AIV and coronary sinus than in the aortic root (66±16 versus 19±4 pg/mL, *P*<0.01, and 51±9 versus 19±4 pg/mL, *P*<0.01, respectively) in the hypertension group. The plasma levels of BNP were also significantly higher in the AIV and coronary sinus than in the aortic root (45±8 versus 15±2 pg/mL, *P*<0.01, and 39±6 versus 15±2 pg/mL, *P*<0.01, respectively) in the control group. The plasma levels of BNP in the hypertension group tended to be higher at every sampling point compared with those of the control group, but these elevations were not significant.

Correlations Among the Cardiac Hormones in the Hypertensive Group

The difference in plasma aldosterone levels between the AIV and the aortic root had a significant positive correlation with the difference in serum ACE activity between the AIV and aortic root (∆ACE[AIV−Ao]), and the difference in plasma BNP levels between the AIV and aortic root (∆BNP[AIV−Ao]) in the hypertension group.

Figure 2. Correlations among differences in plasma aldosterone levels between the AIV and aortic root (∆Aldo[AIV−Ao]), the difference in serum ACE activity between the AIV and aortic root (∆ACE[AIV−Ao]), and the difference in plasma BNP levels between the AIV and aortic root (∆BNP[AIV−Ao]) in the hypertension group.
Correlation of the Cardiac Hormones With Blood Pressure Levels in the Hypertensive Group

The difference in plasma aldosterone levels between the AIV and aortic root had a significant positive correlation with diastolic blood pressure levels in the hypertension group ($r=0.498$, $P<0.05$) (Figure 3, left), but not with systolic blood pressure levels in the hypertension group ($r=0.021$, $P=NS$). The difference in serum ACE activity between the AIV and aortic root had a significant positive correlation with diastolic blood pressure levels in the hypertension group ($r=0.577$, $P<0.01$) (Figure 3, right), but not with systolic blood pressure levels in the hypertension group ($r=0.018$, $P=NS$). The difference in plasma BNP levels between the AIV and aortic root had no significant positive correlation with either systolic or diastolic blood pressure levels in the hypertension group ($r=0.273$, $P=NS$; $r=0.218$, $P=NS$, respectively).

Correlation of Cardiac Aldosterone Levels With Left Ventricular Mass Index in the Hypertensive Group

The difference in plasma aldosterone levels between the AIV and aortic root had no significant correlation with LV mass index ($r=0.090$, $P=NS$), although the hypertensive patients, as a whole, did have increased LV mass as shown in the Table.

Discussion

Several recent animal studies have shown that aldosterone is produced in extraadrenal tissues, including the heart, blood vessels, and brain.5–8 We demonstrated that the production of aldosterone is activated in the human failing ventricles.15 The present study demonstrates that the plasma levels of aldosterone are increased significantly between AIV and aortic root in patients with hypertension and without left ventricular systolic dysfunction, whereas there was no significant difference in the levels in the controls. The plasma aldosterone levels in the AIV and coronary sinuses were significantly higher in hypertensive patients than in the controls, although the levels were not significantly different in aortic root between the 2 groups. This indicates that aldosterone production is activated in the left ventricles of patients with hypertension but not in normotensive human hearts; however, the difference in the aldosterone level between AIV and aortic root was small, suggesting that the function of cardiac aldosterone may be autocrine or paracrine. The effects of aldosterone are mediated by the binding of the hormone to its specific receptor, the mineralocorticoid receptor, and both the mineralocorticoid receptor and the mineralocorticoid receptor–protecting 11β-hydroxysteroid dehydrogenase, have been shown to be expressed in human heart,21 providing the necessary components of mineralocorticoid action. Recently, Takeda et al.22 reported that cardiac aldosterone is activated in genetically hypertensive rats. There is also a possibility that cardiac aldosterone production may indeed be small and of unknown limited biological significance. As the aldosterone concentration is much higher in the heart tissue than in plasma, the step up of aldosterone level between the aortic root and AIV could reflect a leak of aldosterone from the heart. Young et al.23 could not detect aldosterone synthase mRNA in normal human hearts and could detect it only sporadically and in low concentrations in hearts of patients with heart failure, in accordance with the findings of Kayes-Wandover et al.24 The possibility that ACE inhibitors suppressed the expression of aldosterone synthase gene in patients with heart failure, however, could not be excluded in these studies.

We previously reported14,15 that cardiac ACE production was activated in failing human ventricles, but that the absolute difference in ACE activity between AIV and aortic root was small; this suggested that the biologic function of cardiac ACE is mainly autocrine and/or paracrine. In the present study, however, the levels of ACE activity were not significantly different between the AIV and aortic root in the hypertensive patients without left ventricular systolic dysfunction as in controls. It is possible that the method used in the present study may not be sensitive and/or reproducible enough to detect small increases of cardiac ACE in these patients without left ventricular systolic dysfunction.

On the other hand, there was a highly significant step-up in plasma BNP levels between AIV and aortic root both in the hypertensive hearts and in the control hearts. This indicates that BNP is produced in the ventricle and that the heart is the endocrine organ for circulating BNP. These results are in agreement with those of our previous studies.11,12,25 The precise mechanisms for the induction of aldosterone in the hypertensive heart are not clear. Aldosterone synthesis is mainly stimulated by angiotensin II, the active peptide of the renin-angiotensin system, but its production is also controlled by potassium, adrenocorticotropic hormones, and natriuretic peptides, including BNP.26–30 In the present study, the difference of plasma aldosterone levels between AIV and aortic root, or of cardiac aldosterone levels had a significant positive correlation with the difference of ACE activity between AIV and aortic root, or of cardiac ACE activity levels. Takeda et al.22 and Silvestre et al.8 showed that activation of cardiac aldosterone production is mediated primarily by cardiac angiotensin II in rat hearts with hypertension or myocardial infarction. We recently showed that cardiac aldosterone production is suppressed by administration of an ACE inhibitor in patients with heart failure.31

In the present study, cardiac aldosterone levels had a significant positive correlation with diastolic blood pressure. Cardiac ACE activity levels also had a significant positive correlation with diastolic pressure. These findings suggest that increased wall tension or stretch in the myocardium owing to high blood pressure may be a main stimulus for

Figure 3. Correlations among difference in plasma aldosterone levels between the AIV and the aortic root ($\Delta$Aldo[AIV-Ao]), the difference in serum ACE activity between the AIV and aortic root ($\Delta$ACE[AIV-Ao]), and diastolic blood pressure in the hypertension group.

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activation of cardiac aldosterone production by way of renin-angiotensin system in patients with hypertension.

Aldosterone was originally thought to be important in the pathophysiology of hypertension or heart failure only because of its ability to increase sodium retention and potassium loss. Weber et al.18 and Young et al.20 however, have shown that aldosterone promotes myocardial and vascular fibrosis independently of the hemodynamic effects. Aldosterone also causes direct vascular damage and baroreceptor dysfunction and prevents the uptake of norepinephrine by the myocardium.33–35 The present study shows that aldosterone production is activated in the ventricles of patients with hypertension. Myocardial levels of aldosterone are reported to be many times higher than those in plasma,8 suggesting that not only does cardiac tissue possess the capacity to synthesize its own aldosterone, but its retention within the heart is important for localized functions. We recently showed that aldosterone also induces ACE gene expression in rat cardiomyocytes, and we indicated that a positive feedback loop from aldosterone to ACE exists within the local cardiac renin-angiotensin-aldosterone system.36 It is thus possible that cardiac aldosterone may play an important role in the pathogenesis of hypertensive heart.

We conclude that production of aldosterone is activated in the ventricles of patients with hypertension in proportion to the severity of hypertension.

References
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