Nongenomic Effects of Aldosterone in the Human Heart
Interaction With Angiotensin II

Wenxia Chai, Ingrid M. Garrelds, René de Vries, Wendy W. Batenburg, Jorge P. van Kats, A.H. Jan Danser

Abstract—Aldosterone exerts rapid “nongenomic” effects in various nonrenal tissues. Here, we investigated whether such effects occur in the human heart. Trabeculae and coronary arteries obtained from 57 heart valve donors (25 males; 32 females; 17 to 66 years of age) were mounted in organ baths. Aldosterone decreased contractility in atrial and ventricular trabeculae by maximally 34±3% and 15±4%, respectively, within 5 to 15 minutes after its application. The protein kinase C (PKC) inhibitor chelerythrine chloride, but not the mineralocorticoid receptor antagonists spironolactone and eplerenone, blocked this effect. Aldosterone also relaxed trabeculae that were prestimulated with angiotensin II (Ang II), and its negative inotropic effects were mimicked by hydrocortisone (at 10-fold lower potency) but not 17β-estradiol. Aldosterone concentrations required to reduce inotropy were present in failing but not in normal human hearts. Previous exposure of coronary arteries to 1 μmol/L aldosterone or 17β-estradiol (but not hydrocortisone) doubled the maximum contractile response (E_max) to Ang II. ΔE_max correlated with extracellular signal-regulated kinase (ERK) 1/2 phosphorylation (P<0.01). Spironolactone and eplerenone did not block the potentiating effect of aldosterone. Studies in porcine renal arteries showed that potentiation also occurred at pmol/L aldosterone levels but not at 17β-estradiol levels <1 μmol/L. Aldosterone did not potentiate the α1-adrenoceptor agonist phenylephrine. In conclusion, aldosterone induces a negative inotropic response in human trabeculae (thereby antagonizing the positive inotropic actions of Ang II) and potentiates the vasoconstrictor effect of Ang II in coronary arteries. These effects are specific and involve PKC and ERK 1/2, respectively. Furthermore, they occur in a nongenomic manner, and require pathological aldosterone concentrations. (Hypertension. 2005;46:701-706.)

Key Words: aldosterone ■ mineralocorticoids ■ angiotensin ■ human

The steroid hormone aldosterone is synthesized in the adrenal cortex in response to angiotensin II (Ang II). The primary cardiovascular effect of aldosterone has traditionally been ascribed to regulation of electrolyte homeostasis and extracellular fluid volume by promotion of sodium retention and potassium excretion in the renal collecting duct. The mechanism underlying this effect is of “genomic” nature (ie, it involves binding to the intracellular mineralocorticoid receptor [MR], followed by translocation of the steroid–receptor complex to the nucleus, where this complex acts as a transcription factor).

Two large clinical trials in patients with heart failure have recently shown that MR antagonists improve morbidity and mortality on top of angiotensin-converting enzyme inhibition.1,2 Because these beneficial effects could not be attributed solely to blockade of the renal MR-mediated effects on blood pressure, it has been proposed that aldosterone also exerts actions in extrarenal tissues. Evidence for this concept is now readily available. The nonrenal actions of aldosterone include inotropic effects in the heart and vasoconstrictor as well as vasodilator effects in various vascular beds.3–7 Unexpectedly, these effects occurred within minutes rather than hours and could not always be blocked by MR antagonists. Consequently, they are now known as “nongenomic” effects of aldosterone. Some of these nongenomic effects might in fact be exerted by aldosterone that has been synthesized locally in the heart or vessel wall, although not all studies agree on this possibility.8–10

The majority of the data on the nongenomic actions of aldosterone have been obtained in animals. It was the aim of the present study to investigate the nongenomic effects of aldosterone in the human heart, focusing on trabeculae and coronary arteries. To determine the specificity of the effects of aldosterone, we also assessed the effects of 17β-estradiol and hydrocortisone. Furthermore, because aldosterone exerts its effects, at least in part, via Ang II or Ang II type 1 (AT₁) receptors,7,11 and vice versa,10 we evaluated the interaction with Ang II in our experimental setup. Finally, we looked into the mediators of the effects of aldosterone in this study, focusing on those that have already been coupled to the nongenomic actions of aldosterone (protein kinase C [PKC], Ca²⁺, NO, and mitogen-activated protein kinase [MAPK]).

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protein kinases), and we determined the aldosterone levels in normal and failing human hearts to put our findings into a physiological perspective.

**Methods**

**Tissue Collection**

All studies were approved by the ethics committee of the Erasmus MC. Human trabeculae, human coronary arteries (HCAs), and left ventricular tissue were obtained from 57 heart-beating organ donors (25 men and 32 women; 46 ± 1 years of age [range 17 to 66]) who died of noncardiac causes (46 cerebrovascular accident, 5 head trauma, and 6 brain hypoxia) < 24 hours before the heart was taken to the laboratory. Hearts were provided by the Rotterdam Heart Valve Bank after removal of the heart valves. Hearts were stored in an ice-cold sterile organ-protecting solution after circulatory arrest. After arrival at the laboratory, right atrial and left ventricular trabeculae of ~1-mm thickness were dissected and mounted in organ baths. The trabeculae were paced at 1 Hz using electrical field stimulation. Resting tension was set at 750 mg and 1950 mg for atrial and ventricular trabeculae, respectively. Changes in contraction were recorded with a force transducer. HCAs were removed and stored overnight at 4°C, cut into segments of ~4-mm length, and suspended on stainless steel hooks in organ baths. Resting tension was set at 1.5 g. Left ventricular tissue pieces (5 to 10 g) were dissected from the heart and frozen at −70°C. Left ventricular tissue (3 to 5 g) was also obtained from 11 subjects (10 men and 1 woman; 48 ± 4 years of age [range 30 to 64]) with end-stage dilated cardiomyopathy undergoing cardiac transplantation.

Porcine renal arteries (PRAs) were removed from kidneys obtained at the slaughterhouse. Vessels were stored overnight and suspended in organ baths as described above. Resting tension was set at 2 g.

**Trabeculae Studies**

Trabeculae were allowed to equilibrate for ≥60 minutes, and organ bath fluid was refreshed every 15 minutes during this period. Next, a concentration-response curve (CRC) to norepinephrine was constructed to verify the viability of the tissue. After several washouts and stabilization at baseline contractile force, CRCs to aldosterone, spironolactone, eplerenone (a gift of Pfizer), hydralazine, their solvent (ethanol), or 17β-estradiol (dissolved in water) were constructed, either at baseline or after pretreatment with forskolin (dissolved in dimethylsulfoxide [DMSO]) or Ang II. To investigate the mechanism of the aldosterone-induced effects, CRCs to aldosterone were also constructed after pretreatment with spironolactone, eplerenone, the NO synthase inhibitor Nω-nitro-arginine methyl ester (L-NAME), the NO scavenger hydroxocobalamin (dissolved in methanol), the guanylyl cyclase inhibitor ODQ, the PKC inhibitor chelerythrine chloride (dissolved in DMSO), the intracellular Ca2+ blocker thapsigargin (dissolved in ethanol), or solvent. At the end of each experiment, viability was verified with norepinephrine.

**Vessel Studies**

Viability was evaluated as described previously. Next, segments were preincubated for 30 minutes with or without aldosterone, 17β-estradiol, spironolactone, eplerenone, or L-NAME, and CRCs to Ang II, aldosterone, hydralazine, spironolactone, 17β-estradiol, solvent (ethanol), or phenylephrine were constructed. Ang II CRCs were also constructed after completion of the CRCs to aldosterone, hydralazine, 17β-estradiol, or solvent (ethanol) without refreshing the organ bath fluid in between. To determine Ang II–induced extracellular signal-regulated kinase (ERK) 1/2 activation, segments were collected and frozen at −80°C within 10 minutes after exposure to the highest Ang II concentration.

**Biochemical Measurements**

To determine ERK 1/2 phosphorylation, frozen HCA segments were homogenized in Nonidet P-40 lysis buffer and kept on ice for 1 hour. Next, they were centrifuged at 14,000g for 15 minutes at 4°C, and the supernatants were collected and stored at −80°C until further analysis. Protein was determined using the Bradford assay. Western blotting was performed with 20 μg protein using phospho-ERK 1/2 and ERK antibodies (Westburg; 1:2000). Peroxidase-conjugated secondary antibodies were from Pierce (1:5000). Blots were developed with the chemiluminescence substrate and visualized on Kodak films. For semiquantification, the band obtained with Ang II alone was defined as 100%.

Aldosterone was measured by solid-phase radioimmunoassay (Diagnostic Products Corporation) after its extraction from left ventricular tissue. In short, tissue was homogenized 1:2 in methanol. The supernatant was collected after a 15-minute centrifugation at 3000 rpm at 4°C, vacuum dried, and dissolved in water. The detection limit was 10 pg/g wet weight.

Total renin (ie, renin plus prorenin) was measured by immunoradiometric assay in homogenized tissue after treatment with acid and plasmin to activate prorenin.

**Data Analysis**

Data are expressed as mean ± SEM or geometric mean and range, and n refers to the patient number. Trabeculae showing <25 mg response to norepinephrine at the start or end of the experiment were excluded from analysis. CRCs were analyzed as described previously to obtain pEC50 (−logEC50) values. Aldosterone levels below the detection limit were taken to be equal to the detection limit. Statistical analysis was by Mann–Whitney U test for unpaired observations, paired t test, or 1-way ANOVA, followed by post hoc evaluation according to Tukey. P < 0.05 was considered significant.

**Results**

**Trabeculae Studies**

Baseline contractile forces were 164 ± 11 mg and 233 ± 15 mg in atrial (n = 29) and ventricular (n = 15) trabeculae, respectively. Norepinephrine increased contractile force in both types of trabeculae in a concentration-dependent manner (pEC50 6.2 ± 0.1 and 6.1 ± 0.1, respectively). The contractile response to 10 μmol/L norepinephrine at the end of the experiment was not different from that at the start (±208 ± 16% versus ±205 ± 11% in atrial trabeculae and ±196 ± 20% versus ±198 ± 20% in ventricular trabeculae). This indicates that tissue viability did not decrease during the course of the experiment.

Aldosterone (pEC50 8.3 ± 0.1; n = 25) and hydrocortisone (pEC50 7.6 ± 0.2; n = 5; P < 0.01 versus aldosterone), but not 17β-estradiol (n = 4), reduced contractility in atrial trabeculae (Figure 1). The effects of aldosterone occurred within 5 to 15 minutes after its application. Aldosterone also reduced contractility in ventricular trabeculae (pEC50 8.1 ± 0.5; n = 7), although its effects in this preparation were more modest than in atrial trabeculae. The effects of spironolactone in atrial (pEC50 8.2 ± 0.4; n = 7) and ventricular (pEC50 8.7 ± 0.1; n = 6) trabeculae were comparable to those of aldosterone. Eplerenone did not exert effects in either atrial (n = 7) or ventricular (n = 4) trabeculae, nor did solvent (n = 4 and 6, respectively). In atrial trabeculae, the negative inotropic effect of aldosterone after pretreatment with either forskolin (n = 6) or Ang II (n = 6) was identical to that at baseline. Aldosterone also relaxed forskolin-prestimulated ventricular trabeculae (n = 6). Without aldosterone, the forskolin-induced increase in contractility remained stable for ≥45 minutes (ie, the time required to construct an aldosterone CRC).

Spironolactone (n = 7), eplerenone (n = 5), L-NAME (n = 5), hydroxocobalamin (n = 5), ODQ (n = 4), thapsigargin (n = 5), and solvent (methanol [n = 4] or DMSO [n = 5]) did not affect the...
aldosterone-induced negative inotropic effects (Figure 2), and with the exception of spironolactone (see above), none of these inhibitors affected baseline contractility. In contrast, chelerythrine chloride (n=H11005 7) not only blocked the effect of aldosterone, but tended to reverse it into a positive inotropic (P=H11005 NS) response. Chelerythrine chloride did not affect baseline contractility.

Vessel Studies
Ang II concentration-dependently constricted HCAs (pEC\textsubscript{50} 7.5±0.5; maximum contractile response [E\textsubscript{max}] 29±7%; n=13; Figure 3). Aldosterone (n=H11005 11), hydrocortisone (n=11), 17\beta-estradiol (n=10), or solvent (ethanol; n=5), at concentrations ranging from 1 pmol/L to 1 \mu mol/L, did not affect baseline contractility in HCAs (data not shown). However, when constructing an Ang II CRC after exposure to aldosterone or 17\beta-estradiol (without refreshing the organ bath fluid), E\textsubscript{max} doubled to 55±11% and 51±14%, respectively (P<0.05 versus control for both), with no change in pEC\textsubscript{50} (7.5±0.2 versus 7.5±0.2; Figure 3). Hydrocortisone tended to induce a similar potentiation (P=NS; Figure 3), whereas ethanol was without effect. Neither spironolactone

\begin{figure}[h]
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\caption{Inotropic effects of aldosterone (aldo), spironolactone (spiro), eplerenone (eple), solvent (ethanol), 17\beta-estradiol, and hydrocortisone in human right atrial (A and C) and left ventricular (B and D) trabeculae at baseline (A and B) and after prestimulation with 1 \mu mol/L forskolin (to 326±48% and 325±83% of baseline in atrial and ventricular trabeculae, respectively) or 100 \mu mol/L Ang II (to 32±7% of baseline; C and D). Data (mean±SEM of 4 to 25 experiments) are expressed as percent change from baseline contractile force or from the contractile force after prestimulation.}
\end{figure}

\begin{figure}[h]
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\includegraphics[width=\textwidth]{figure2}
\caption{Inotropic effects of aldosterone in atrial trabeculae in the absence (E) or presence (F) of spironolactone (SPIRO; 10 \mu mol/L), eplerenone (EPLE; 1 \mu mol/L), L-NAME (100 \mu mol/L), ODQ (10 \mu mol/L), hydroxocobalamin (HC; 200 \mu mol/L), chelerythrine chloride (CHEL; 1 \mu mol/L), thapsigargin (THAPS; 1 \mu mol/L), or solvent (methanol or DMSO). Data (mean±SEM of 4 to 7 experiments) were obtained in a paired setup and have been expressed as percent change from baseline contractile force. *P<0.05 vs control.}
\end{figure}

(n=8) nor eplerenone (n=8) blocked the effect of aldosterone (Figure 3). The amount of phosphorylated ERK 1/2 tended to be increased in the presence of 1 \mu mol/L aldosterone, hydrocortisone, and 17\beta-estradiol (P=NS versus Ang II alone; n=6 for all; Figure 4), with no change in the total

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\includegraphics[width=\textwidth]{figure3}
\caption{Contractions of HCAs to Ang II at baseline (control) or after previous exposure to aldosterone (aldo), hydrocortisone (hydrocort), or 17\beta-estradiol (17\beta-estr; 1 pmol/L-1 \mu mol/L) with or without preincubation with 10 \mu mol/L spironolactone (Spiro) or 1 \mu mol/L eplerenone (Eple). Data (mean±SEM; n=7 to 10) are expressed as a percentage of the response to 100 mmol/L KCl. *P<0.05 vs control.}
\end{figure}
amount of ERK 1/2. The increase in ERK 1/2 phosphorylation was limited to vessel segments displaying a large increase in $E_{\text{max}}$, as evidenced by the significant correlation between $\Delta E_{\text{max}}$ and ERK 1/2 phosphorylation ($r=0.56$; $P<0.01$; Figure 4).

The effects of aldosterone, 17$\beta$-estradiol, and hydrocortisone toward Ang II could be reproduced in PRAs: none of these steroids affected baseline contractility at concentrations ranging from 1 pmol/L to 1 $\mu$mol/L, and only previous exposure to aldosterone and 17$\beta$-estradiol increased the Ang II $E_{\text{max}}$ (n=9; Figure 5). Therefore, PRAs were used to test whether the effects of aldosterone and 17$\beta$-estradiol could also be observed at lower concentrations. Preincubation with 17$\beta$-estradiol concentrations $<1$ $\mu$mol/L did not result in potentiation (n=7; data not shown). In contrast, the effects of aldosterone could be mimicked at concentrations as low as 1 nmol/L (n=10; $P<0.05$) or, in the presence of t-NAME, 1 pmol/L (n=4; $P<0.05$; Figure 5). Furthermore, the potentiating effects were specific for Ang II because preincubation with 1 nmol/L aldosterone did not affect the phenylephrine CRC (n=4; Figure 5).

### Aldosterone Levels in the Human Heart

Aldosterone levels in failing hearts (184 [range 10 to 4710] pg/g; n=11) were ≈10-fold higher ($P<0.02$) than in normal hearts (26 [range 10 to 481] pg/g; n=12). This parallels our previous observations on cardiac renin.14 In fact, the levels of renin in the heart correlated significantly with those of aldosterone ($r=0.71$; $P<0.05$; Figure 6).

### Discussion

The present study is the first to demonstrate nongenomic actions of aldosterone in the human heart. Aldosterone exerted a negative inotropic effect in atrial and ventricular trabeculae at baseline and after prestimulation with the adenylyl cyclase activator forskolin. This effect was long lasting and, unlike the short-lasting negative inotropic effect of bradykinin,15 did not involve the NO–cGMP pathway. The PKC inhibitor chelerythrine chloride fully blocked the aldosterone-induced negative inotropy, suggesting that it is mediated via the diacylglycerol–PKC signal transduction pathway. Patch clamp studies in rabbit ventricular myocytes have revealed that aldosterone affects Na$^+$-K$^+$ pump activity via ePKC,12 thereby providing a mechanism for the negative inotropic response to aldosterone. The modest effect of aldosterone in ventricles is in agreement with the fact that atria have fewer sodium pumps than ventricles16 because low expression enhances inotropic sensitivity.

The lack of effect of MR antagonists suggests that the inotropic effects of aldosterone occur in an MR-independent manner. In fact, as in the isolated perfused rat heart,4,5 spironolactone exerted an inotropic effect that was comparable to that of aldosterone, whereas the more selective MR antagonist eplerenone did not. This further supports the MR independency of the effects of aldosterone and spironolactone. However, importantly, aldosterone and spironolactone exerted positive inotropy in the rat heart,4,5 as opposed to the negative inotropy observed here and in rabbit cardiomyocytes.12 Although this may relate to species differences, alternative explanations must be considered. First, inotropic effects in isolated trabeculae do not necessarily parallel inotropic effects in intact hearts because the latter also reflect responses on coronary flow. Second, similar diagnostically differing effects of aldosterone have been observed on flow, either because such effects involve different cells or because different second messengers are activated depending on the experimental circumstances.5,6,12,17 Finally, the consequences of PKC-induced regulation of Na$^+$-K$^+$ pump activity are tissue specific and range from stimulation to inhibition or no change.12,18
Hydrocortisone mimicked the inotropic effects of aldosterone at lower potency. This underlines the specificity of the aldosterone effect. However, because glucocorticoids circulate at levels that are several orders of magnitude higher than those of aldosterone, the inotropic effects of aldosterone and glucocorticoids may occur simultaneously in vivo.

The aldosterone levels in failing human hearts were found to be up to ~5000 pg/g (corresponding with ~15 nmol/L), that is, high enough to allow the inotropic effects of aldosterone to occur under pathological conditions in vivo. The levels in normal hearts (~25 pg/g or <0.1 nmol/L) appeared to be too low to exert inotropic effects. Although the origin of aldosterone in the heart is still under debate, our observation that the cardiac aldosterone levels correlate with the cardiac levels of renin (which is exclusively of renal origin\textsuperscript{14}), combined with previous findings on cardiac extraction of aldosterone,\textsuperscript{19} suggest that at least some cardiac aldosterone is of extracardiac origin.

The high renin levels in failing human hearts will result in high local Ang II levels.\textsuperscript{20} In agreement with previous studies,\textsuperscript{21} Ang II was found to induce a modest (compared with norepinephrine) positive inotropic effect. Aldosterone counteracted this effect. This observation contrasts with the aldosterone-induced potentiation of the vasoconstrictor effect of Ang II in HCAs. Hydrocortisone and 17β-estradiol similarly potentiated constriction, although significance was reached for 17β-estradiol only. The magnitude of potentiation (ie, the increase in E\textsubscript{max}) correlated with the increase in the level of phosphorylated ERK 1/2, in full agreement with a previous study on steroid–Ang II interaction in rat aortic vascular smooth muscle cells.\textsuperscript{7} None of the steroids applied in the present study exerted a constrictor or dilator effect of its own, and the Ang II–potentiating effects became apparent only after constructing a CRC to the steroid. Such construction requires 30 to 60 minutes, a time interval that is insufficient to allow the AT\textsubscript{1} receptor upregulation that underlies the Ang II potentiation after a 24- to 48-hour exposure to aldosterone and glucocorticoids.\textsuperscript{11,22}

Studies in HCA smooth muscle cells have already indicated that Ang II is capable of activating MR-mediated gene expression in an aldosterone-independent manner (suggesting MR activation by post-translational modifications such as phosphorylation).\textsuperscript{10} The present data extend this observation by demonstrating functional synergy when applying aldosterone together with Ang II. This synergy did not depend on MR activation, was selective, and occurred at physiological aldosterone levels.

In the rat aorta,\textsuperscript{3} as well as the human forearm,\textsuperscript{6} aldosterone has been reported to enhance vasoconstriction and vasodilation. The latter was endothelium dependent, whereas the former could only be observed during NO synthase blockade. The absence of aldosterone-induced vasodilation in HCAs may relate to our inability to observe endothelial NO release in these vessels.\textsuperscript{23}

Limited NO release could also underlie the absence of a vasodilator response to 17β-estradiol in HCAs. Despite the higher incidence of stroke, myocardial infarction, and dementia in postmenopausal women taking hormone replacement therapy,\textsuperscript{24} virtually all in vitro studies published so far claim that estrogen induces vasodilation through endothelium-dependent or endothelium-independent mechanisms.\textsuperscript{24} An alternative ex-
plation for the absence of estrogen-induced vasodilation in HCAs, at least in women, is the change in estrogen receptor cellular localization during perimenopause. Furthermore, estrogen inactivates reactive oxygen species like the vasodilator H$_2$O$_2$ and alters the AT$_1$/AT$_2$ receptor ratio. Both phenomena will directly affect Ang II–mediated vasoconstriction.

**Perspectives**

Aldosterone induces a negative inotropic response in human trabeculae (thereby antagonizing the positive inotropic actions of Ang II) and potentiates the vasoconstrictor effect of Ang II in HCAs. These effects occur in a rapid, nongenomic manner, independently of MR, and involve PKC and ERK 1/2, respectively. Combined with the nonhemodynamic effects of aldosterone in cardiac tissue, which result in inflammation and fibrosis, these data shed light on the wide variety of actions of aldosterone in the heart. Future studies should now address which receptor mediates the nongenomic cardiac effects of aldosterone and to what degree these effects occur in failing hearts. In view of the comparable beneficial effects of spironolactone and eplerenone in heart failure, such studies should also critically evaluate the physiological importance of the negative inotropic effect of spironolactone. The many nongenomic, non–MR-mediated effects of aldosterone suggest that aldosterone synthase inhibitors may yield effects on top of MR blockade.

**References**


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