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## **Effects of Aldosterone on the Heart : Beyond Systemic Hemodynamics?** Javier Díez

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## Effects of Aldosterone on the Heart Beyond Systemic Hemodynamics?

Javier Díez

As predicted by Laplace's law, the ability of the left ventricle to compensate for increasing loading conditions requires the thickening of the ventricular wall and the growth of left ventricular mass (LVM), defined as left ventricular hypertrophy (LVH) when it exceeds partition values based on distribution in normal reference populations. The presence of LVH, however, does not discriminate between a compensatory and excessive increase in LVM. Therefore, the term "inappropriate LVM" (iLVM) has been applied to conditions in which the observed level of LVM exceeds the theoretical value predicted by sex, body size, and stroke work.<sup>1</sup> iLVM is associated with clustered geometric and functional abnormalities of the left ventricle<sup>2</sup> and appears to be a marker of adverse cardiovascular prognosis independent of LVH.<sup>3</sup> Recent data suggest that changes in the appropriateness of LVM from baseline to follow-up during treatment may predict a subsequent cardiovascular event in hypertensive patients.<sup>4</sup> It has been proposed that the pathophysiological process that yields iLVM is probably linked to the protracted activity over time of humoral mediators of LV growth, such as proto-oncogenes, growth factors, hormones, and cytokines, inducing modifications that initially compensate imposed overload but eventually change the structure of myocardial tissue (eg, remodeling) and, as a consequence, impair LV function.<sup>5</sup>

The study by Muiesan et al in this issue of *Hypertension*<sup>6</sup> points to aldosterone as one of the candidate hormones that may contribute to iLVM. The authors evaluated the inappropriateness of LVM in 125 patients with a diagnosis of primary aldosteronism (PA) and in 125 age-, sex-, and blood pressure-matched patients with essential hypertension. The prevalence of iLVM (defined by a ratio of observed:predicted LVM >135%) was greater in PA patients than in essential hypertension patients, irrespective of the presence or absence of traditionally defined LVH. In addition, direct correlations were observed between the ratio of observed:predicted LVM and the ratio of aldosterone:plasma renin activity levels or the postsaline infusion aldosterone concentration in PA patients. The study by Muiesan et al<sup>6</sup> is timely, because PA is much

more common than previously held, and it implies excessive organ damage to the heart, vessels, and kidney, which translates into an excess of cardiovascular events. One of the main features of the study is the careful biochemical, morphological, and hormonal methodology for the screening and confirmation of PA, as well as the adequate estimation of the appropriateness of LVM for individual cardiac load from the echocardiographic measurements. Thus, the reported findings provide compelling evidence that the chronic augmentation of aldosterone could contribute to the increase of LVM exceeding the amount needed to compensate for hemodynamic load in patients with PA.

Findings from a number of experimental studies suggest that aldosterone has the potential to directly stimulate LV growth independent of its effects on renal sodium (Na<sup>+</sup>) regulation and secondary modulation of blood pressure. For instance, transgenic mice overexpressing 11 $\beta$ -hydroxysteroid dehydrogenase type 2 in cardiomyocytes, which facilitates aldosterone occupancy of the mineralocorticoid receptor (MR), exhibit normal blood pressure values but spontaneously develop severe LVH.<sup>7</sup> In addition, subcutaneous infusion of nonhypertensive doses of aldosterone to normotensive rats leads to LVH independent from blood pressure.<sup>8</sup> Finally, also in normotensive rats, a high-salt intake for 8 weeks produces LVH associated with increased cardiac aldosterone production and aldosterone-synthase overactivity in the absence of blood pressure elevation.<sup>9</sup>

Several studies have investigated the direct hypertrophic effects of aldosterone on rat cardiac myocytes. In one study,<sup>10</sup> aldosterone caused a 27% increase in protein incorporation and a 29% increase in myocyte surface area. This response was associated with increased mRNA levels of atrial natriuretic factor and  $\alpha$ - and  $\beta$ -myosin heavy chain, and it was suppressed by the MR antagonist spironolactone. Aldosterone stimulation acutely translocated protein kinase C- $\alpha$  to the membrane fraction and increased the levels of phosphorylated extracellular signal-regulated kinases 1/2 and c-Jun N-terminal kinase. PD 98059, an inhibitor of the extracellular signal regulated kinase activator mitogen-activated protein kinase, and bisindolylmaleimide I, an inhibitor of protein kinase C activation, each blocked aldosterone-stimulated hypertrophy. In another study,<sup>11</sup> aldosterone significantly increased cell size by 61% and expression of atrial natriuretic peptide by 2-fold. Na<sup>+</sup>/H<sup>+</sup> exchanger type 1 mRNA expression and protein abundance were significantly increased, and intracellular Na<sup>+</sup> levels were elevated. Both hypertrophy and elevated Na<sup>+</sup> levels were prevented by the NHE-1-specific inhibitor EMD87580, as well as by spironolactone, although the increased Na<sup>+</sup>/H<sup>+</sup> exchanger type 1 levels were prevented only by spironolactone. Finally, it has been reported that

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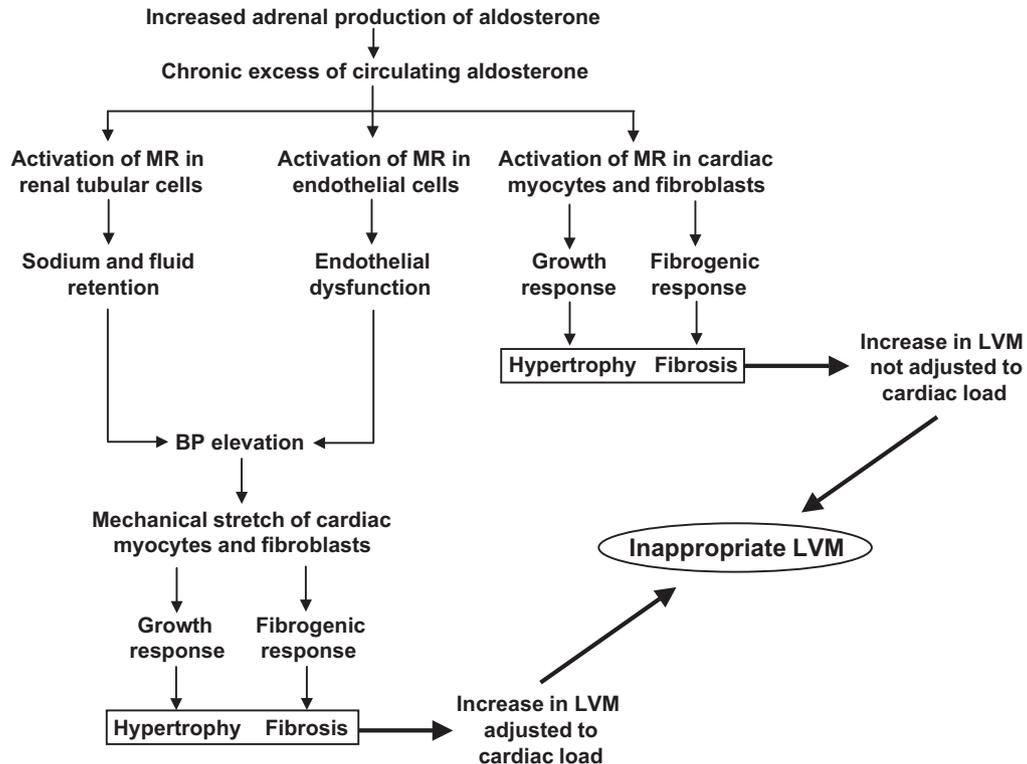
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**Figure.** Schematic view of the systemic and cardiac pathways involved in the ability of aldosterone to produce the structural remodeling of the myocardium responsible for the inappropriate growth of LVM present in conditions associated with an excessive synthesis and secretion of the hormone by the adrenal gland. BP indicates blood pressure.

aldosterone provoked expression of hypertrophic markers (genes encoding for atrial and brain natriuretic peptides, and skeletal  $\alpha$ -actin) and phosphorylation of protein kinase D.<sup>12</sup> Inhibition of protein kinase D abrogated the hypertrophic effects, as did spironolactone. Collectively, these data suggest that the growth response elicited by aldosterone in myocytes depends on stimulation of the MR and is associated with activation of several kinase-mediated pathways and stimulation of  $\text{Na}^+/\text{H}^+$  exchanger type 1 expression and activity.

Other than hypertrophy of cardiac myocytes, aldosterone may also contribute to interstitial and perivascular fibrosis, another histomorphologic component of myocardial remodeling associated with exaggerated LV growth. In fact, chronic aldosterone infusion causes myocardial fibrosis in rat models in the setting of high-salt intake.<sup>13</sup> The development of fibrosis is preceded by coronary and myocardial inflammation characterized by monocyte and macrophage infiltration and increased production of reactive oxygen species. The inflammatory and oxidative changes and subsequent fibrosis can be blocked by MR antagonism. Because animal models of aldosterone-stimulated cardiac fibrosis involve the systemic administration of aldosterone and salt excess, it has been difficult to dissect local fibrotic effects of aldosterone from systemic effects of  $\text{Na}^+$  retention. Nevertheless, it is to be noted that aldosterone has been shown to directly stimulate the expression of several profibrotic molecules that may contribute to the pathogenesis of cardiac fibrosis. For example, aldosterone increases the activity of transforming growth factor- $\beta_1$  in cultured cardiac myocytes and its expression in cultured cardiac fibroblasts, these effects being abrogated by

MR antagonists.<sup>14</sup> In addition, aldosterone increases angiotensin II type 1 receptor mRNA expression and angiotensin II type 1 receptor binding in the heart, whereas MR antagonism decreases angiotensin II type 1 receptor mRNA and density in the heart and abrogates many of the adverse cardiac effects of aldosterone, including fibrosis.<sup>15</sup>

Thus, a relationship is emerging between aldosterone and the heart, beyond the ability of the hormone to facilitate  $\text{Na}^+$  retention and increase blood pressure, involving the activation of MR-dependent pathways in cardiac cells by the hormone (Figure). Continuing research *in vitro* and *in vivo* in animal models is required to discern a number of aspects, such as the ligand specificity of MR activation, the role for MR-dependent compared with -independent effects, and the importance of genomic compared with nongenomic pathways, as well as the potential contribution of an intracardiac synthesis of aldosterone. A general question raised by the study of Muiesan et al<sup>6</sup> is whether the association of aldosterone with iLVM could be also translated to other conditions in which inappropriately high aldosterone concentrations coexist with increased blood pressure and exaggerated prevalence of LVH (eg, resistant hypertension and sleep apnea) or with the presence of iLVM (eg, obesity and metabolic syndrome).<sup>16</sup> In this context, clinical trials are needed to evaluate whether MR antagonists exert a beneficial effect on LVM in patients with the above conditions and whether this effect is not only because of their ability to reduce blood pressure but also because of their ability to block the cardiac hypertrophic actions of aldosterone.

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### Disclosures

None.

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