The renin-angiotensin-aldosterone system plays a key role in the regulation of blood pressure and water/ electrolyte homeostasis. Classically, angiotensin II causes arteriolar vasoconstriction and increases aldosterone levels, whereas aldosterone promotes sodium and water reabsorption and potassium secretion via renal mineralocorticoid receptors. It is now well-accepted that inappropriate activation of the renin-angiotensin-aldosterone system not only increases blood pressure but also can play an important role in end-organ damage. Although Selye et al have demonstrated that administration of a mineralocorticoid combined with sodium promotes malignant hypertension and end-organ damage, subsequent clinical and experimental studies have focused on the pathological effects of angiotensin II, rather than aldosterone, and demonstrated that angiotensin-converting enzyme inhibitors, as well as angiotensin II receptor antagonists, confer significant cardiovascular protection.

Recent discoveries have revolutionized our view of aldosterone and its biological actions, and identified mineralocorticoids as important mediators of cardiovascular injury. The demonstration of rapid aldosterone effects challenged the exclusive role of mineralocorticoid receptor-mediated genomic actions in aldosterone signaling. Furthermore, it is now well-established that aldosterone can exert effects in non-epithelial and extrarenal tissues. Moreover, mineralocorticoids not only exert effects on extrarenal tissues but also can be synthesized outside the adrenal cortex. Aldosterone has now been shown to promote cardiovascular inflammation, endothelial dysfunction, and fibrosis. Furthermore, the effects of aldosterone can be independent of blood pressure, because mineralocorticoid receptor blockade can confer cardiovascular protection without lowering the blood pressure.

In this issue of *Hypertension*, an interesting article by Blanco-Rivero et al extends our understanding of aldosterone-mediated endothelial dysfunction by demonstrating the role of prostacyclin in aldosterone-induced endothelial dysfunction. The authors demonstrate that chronic administration of aldosterone does not affect blood pressure but promotes endothelial dysfunction in normotensive Wistar Kyoto (WKY) and in spontaneously hypertensive rats (SHR). This supports previous observations that aldosterone promotes cardiovascular injury without raising the blood pressure, and that mineralocorticoid receptor antagonism can exert significant protective effects without lowering the blood pressure.

It should be noted, however, that the authors used tail-cuff plethysmography to measure the blood pressure, which can be less accurate compared with direct inline measurements. Thus, their results do not exclude the possibility of aldosterone promoting subtle changes or perhaps altering the diurnal variations in blood pressure. In fact, another article has showed that the renoprotective effect of aldosterone blockade depends on its ability to lower the blood pressure. Though this issue needs further clarification, it appears that aldosterone can promote vascular injury without major changes in blood pressure, and conversely aldosterone receptor blockade can exert cardiovascular protection without normalizing the blood pressure.

The authors also investigate the role of prostanoids in aldosterone-mediated endothelial dysfunction. They show that aldosterone increases vascular cyclooxygenase-2 protein expression in both WKY and SHR. By using selective and nonselective cyclooxygenase-2 inhibitors, they can improve endothelial dysfunction in both strains, indicating the participation of cyclooxygenase-2 metabolites in the attenuated endothelium-dependent vasodilation in both strains.

With respect to eicosanoid metabolism, the most commonly accepted cyclooxygenase-derived vasoconstrictor metabolite is thromboxane A2. In this study, the authors showed that a thromboxane receptor antagonist improved endothelium-dependent relaxation in both aldosterone-treated SHR and WKY, but a thromboxane synthesis inhibitor had no effect. Furthermore, they could not show increased release of thromboxane A2 metabolites from vessels with aldosterone-induced endothelial dysfunction. Collectively, these data challenge the primary role of thromboxane A2 in aldosterone-induced endothelial dysfunction.

Numerous studies demonstrated that prostacyclin (PGI2) promotes vasodilation in various vascular beds. However, it is often forgotten that prostacyclin can also promote vasoconstriction via thromboxane receptors. As an additional novel aspect of this study, the authors demonstrate that aldosterone-induced endothelial dysfunction is associated...
with increased vascular release of prostacyclin metabolites and inhibition of prostacyclin synthesis can improve endothelium-dependent relaxation. Therefore, they conclude that increased prostacyclin production contributes to aldosterone-induced endothelial dysfunction.

Interestingly, a previous study suggested that a rapid nongenomic vascular effect of aldosterone is vasodilation. This vasodilatory effect is most likely caused by increased nitric oxide synthase activation, but the role of vasodilatory prostanooids could not be ruled out. Thus it appears that long-term administration of aldosterone exerts opposite effects on vascular endothelial function, perhaps caused by vascular inflammation. This represents an interesting diversity in the short-term versus long-term actions of aldosterone and underlines the pathological significance of chronic inappropriate activation of the renin-angiotensin-aldosterone system in vascular injury.

The use of aortic rings to assess vascular reactivity in the study by Blanco-Rivero et al potentially limits its applicability to changes in vascular resistance or blood flow. The aorta is a large conduit vessel and as such does not appreciably affect vascular resistance. However, in large conduit vessels endothelial dysfunction has been suggested to contribute to atherosclerosis. As such, these studies could have implications to human macrovascular disease.

It should also be mentioned that the authors specifically adjusted the tension of the aortic ring preparations to eliminate the initial differences in vascular reactivity between the normotensive WKY and hypertensive SHR strains. Though this makes the preparations more comparable for easier demonstration of the aldosterone effects, it is may not accurately reflect their in vivo state. It is possible that in vivo when the aortas are subjected to altered tensions caused by the differences in blood pressure, the aldosterone-induced endothelial dysfunction affects vascular reactivity to a different degree.

Collectively, this interesting study demonstrates that aldosterone promotes endothelial dysfunction independent of blood pressure. They also show that aldosterone-induced endothelial dysfunction is most likely mediated by increased cyclooxygenase-2-derived prostacyclin-mediated vasoconstriction in normotensive and hypertensive animals. Clearly, this original study contributes to our understanding in the role of aldosterone in vascular injury.

Finally, in the Perspectives section of their article, the authors hypothesize that cyclooxygenase-2 inhibitors could be used to restore endothelial function and prevent vascular injury. Whereas this is a logical extension of their current data, in the light of other serious side effects of cyclooxygenase-2 inhibitors in patients with cardiovascular disease and the current controversy over the use of cyclooxygenase-2 inhibitors in these patients, this approach currently may be inadvisable. Further studies are needed to examine the role of cyclooxygenase-2 metabolites in vascular injury and establish safer methods to limit their production. However, this does not detract from the pathophysiological significance of these findings.

References
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