Oxidative stress is thought to play a key role in the initiation and progression of cardiovascular diseases. Increased formation of reactive oxygen species (ROS) leads to endothelial dysfunction through the breakdown of NO, promotes proinflammatory gene expression, and increases the sympathetic tone. A multitude of stimuli including inflammation, cardiovascular risk factors like hypertension and cigarette smoke as well as a broad spectrum of hormones increase the systemic oxidative stress. Among these elements, however, angiotensin II is probably the most robust stimulus for ROS, which derive from Nox1- and Nox2-containing NADPH oxidases. In fact, angiotensin II activates and induces these ROS-generating enzymes.

Angiotensin II is also the classic stimulus for the release of aldosterone. Interestingly, aldosterone is an independent stimulus for vascular ROS production. This steroid hormone induces components of the NADPH oxidase like p47phox1 and p22phox and acutely increases ROS production in vascular cells2 probably through EGF receptor transactivation. Importantly, ROS may be mandatory for the deleterious effects of aldosterone in the cardiovascular system: for example, genetic deletion of the Nox2-containing NADPH oxidases prevents the aldosterone-induced interstitial fibrosis in the mouse heart.3 Furthermore, antioxidants prevent the aldosterone-induced expression of intercellular adhesion molecule-1 and MCP-1 as well as tumor necrosis factor α in the rat heart.4

On such a basis it is possible that blockade of the mineralocorticoid receptor by either spironolactone or the more specific aldosterone antagonist eplerenone is beneficial for vascular function in situations of increased aldosterone formation such as chronic congestive heart failure5 or experimental application of angiotensin II.6

In this issue of Hypertension, Sartorio et al7 extend this concept and demonstrate that blockade of mineralocorticoid receptors at the time of myocardial infaracts to a large extent prevents the vascular dysfunction occurring in the early postinfarction period. Eplerenone attenuated the development of aortic endothelial dysfunction, and it prevented the loss of the stimulatory phosphorylation of endothelial NO synthase (eNOS) on serine 1177. Furthermore, this aldosterone antagonist blocked the vascular induction of the angiotensin converting enzyme (ACE) as well as of the p22phox component of the NADPH oxidase. Finally, eplerenone also prevented the infarction-induced downregulation of manganese superoxide dismutase (MnSOD). All these effects resulted in a blockade of the development of infarction-induced vascular oxidative stress.

These observations are remarkable and important for several reasons. From the clinical point of view, they may help to understand why an early initiation of therapy with eplerenone in the EPHEBUS trial resulted in less mortality than a late initiation. The pathophysiological situation shortly after a large myocardial infarction is also considerably different and more dynamic than the chronic heart failure situation. In the latter, neurohumoral activation dominates, which is just initiated in the early postsischemic time. Moreover, the resolution of the fresh myocardial infarction results in considerable systemic inflammation, a process that elicits oxidative stress per se and probably contributes to vascular dysfunction. It is intriguing that even in such a complex scenario the selective interference with the aldosterone system is sufficient to prevent vascular dysfunction.

Two aspects may aid to understand this phenomenon. The down-stream effectors of aldosterone overlap with those of inflammatory cytokines and angiotensin II, and sub-threshold concentrations of the individual hormone may lead to biological effects due to cross talk. Aldosterone, for example, potentiates the activation of ERK1/2 and JNK by angiotensin II.3 The neurohumoral activation that develops early after myocardial infarction is a consequence of several self-energizing loops, which involve aldosterone as a critical element. Aldosterone maintains AT1 receptor level8 and increases the expression of ACE9 as well as that of subunits of the NADPH oxidase,1 which will further increase and sustain neurohumoral activation. Even the oxidative stress induced by aldosterone is able to enter a vicious circle. The initial ROS, released in response to aldosterone and angiotensin II, promote an uncoupling of eNOS,2 as well as ROS-mediated activation of NADPH oxidase9 and even ROS-dependent induction of components of the NADPH oxidase10 (Figure). That such complex systems are indeed operative in vivo is impressively demonstrated by the observation of Sartorio et al that eplerenone prevents the vascular induction of p22phox as well as of ACE after myocardial infarction.7 Further evidence for such a self-energizing system comes from the observations that inhibition of the
angiotensin II receptor in part attenuates the vascular dysfunction occurring after in vivo aldosterone infusion.5,11 The effects of eplerenone, however, are not restricted to the vascular system. Cardiac function and even blood pressure were less affected by myocardial infarction when animals were treated with this mineralocorticoid receptor blocker. Therefore, one could speculate that the attenuation of vascular dysfunction reported by Sartorio et al is only a consequence of an improved cardiac function and consequently less neurohumoral activation. As eplerenone further increased the aldosterone level after myocardial infarction, however, a significant suppression of the renin-angiotensin system appears implausible.

In addition to aldosterone, cortisol levels are also elevated shortly after myocardial infarction because of the inflammation associated with the resolution of the infarcted tissue. Cortisol acts as an activator of the mineralocorticoid receptor in organs which do not express the 11β-HSD2. Yet, the role of cortisol for vascular dysfunction after myocardial infarct requires further investigation as vascular cells, different from the heart, express the 11β-HSD2. Moreover, in smooth muscle cells glucocorticoids, through the glucocorticoid receptor, have been shown to downregulate the expression of NADPH oxidase subunits.12

In conclusion, Sartorio et al demonstrated that aldosterone is a key player for vascular dysfunction early after myocardial infarction and that eplerenone has a great potential to prevent the initiation of the vicious circles leading to progressive neurohumoral activation and vascular dysfunction in heart failure.

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Disclosures

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References

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