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EDITORIAL

A neurohumoral activation of renin-angiotensin-aldosterone system in endothelial dysfunction modulating immunity in heart failure

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This editorial refers to 'Nox2$^+$ myeloid cells drive vascular inflammation and endothelial dysfunction in heart failure after myocardial infarction via angiotensin II receptor type 1' by M. Molitor *et al.*, pp. 162–177.

Several risk factors are recognized in the onset, as well as in the long-term sequelae, of coronary artery disease. Heart failure (HF) ensuing from myocardial infarction (MI) is a complex event that overall causes a reduced supply of oxygen to organs and tissues. Resulting from the dysregulation of various pathophysiological components, HF is a challenging clinical condition. Endothelial dysfunction accompanying post-MI evolution towards HF, typically represents an unfavourable predictor of the clinical outcome.[1] At the molecular level, it has been recognized that when the generation of nitric oxide is reduced and the formation of reactive oxygen species within the vessel wall is increased, endothelial dysfunction occurs.[2] A growing body of evidence highlights the clinical importance of ameliorating endothelial function to hamper the recurrence of secondary fatal events in post-MI patients.[3] On another notice, the contribution of immune cells that participate to the process of acute and post-MI remodelling is a well-consolidated notion. Few years ago, Wenzel *et al.*[4] showed that angiotensin II (AngII) promotes vascular infiltration of proinflammatory monocytes and contributes to endothelial dysfunction in an animal model of arterial hypertension. Also, effects of AngII in promoting the release of leukocytes from the spleen after MI were identified.[5] Whether the recruitment of splenic myeloid cells in arterial walls of mice subjected to MI could contribute to the development of endothelial dysfunction, besides the known effects on cardiac remodelling, remained unidentified.

Molitor *et al.*[6] investigate the potential connection established between systemic effects of inflammation activated by AngII signalling and vascular function in post-MI remodelling. Here, the authors hypothesized that myelomonocytic cells, activated by AngII in the experimental setting of MI, play a crucial role in the onset of vascular dysfunction accompanying post-MI HF. By testing the effects of myeloid cells depletion after MI-induced remodelling, they were able to show an amelioration of endothelial function, despite no effect was observed in cardiac function. At the molecular level, the authors also tested the strategy of a systemic blockade of AngII effects with telmisartan, revealing an improved vascular function due to attenuation of vascular inflammation. To evaluate the process of endothelial dysfunction that occurs after MI, the authors used the organ chamber for isolated aortic rings, dissected out from mice with permanent left anterior descending artery (LAD) ligation compared to sham-operated control mice. Their results demonstrated that MI leads to an early onset of endothelial dysfunction, characterized by reduced vasodilator response to acetylcholine and increased production of reactive oxygen species. The presence of leukocytes infiltrating the vessel walls with abundant populations of monocytes-macrophages and increased aortic mRNA expression of vascular cell adhesion molecule 1, CC-chemokine ligand-2, the proinflammatory cytokines interleukin-6, interleukin-1β, tumour necrosis factor-α, the angiotensin II receptor type 1 (AT1R), and inducible NO-synthase (Nos2) was suggestive of a role of the vascular and immune response in causing endothelial dysfunction. To test this hypothesis, the authors depleted monocyte and macrophagic populations using a mouse model carrying a Cre-inducible diphtheria toxin receptor under a myeloid promoter (LysMCre^{iDTR} mice) 28 days after LAD-ligation. While the echocardiographic analysis did not show effects on left ventricular function of post-MI mice, myeloid cell depletion ameliorated endothelial function in aortic rings. In addition, the flow cytometry analysis of aortic lysates revealed that the functional effect was accompanied with a reduction of infiltrating CD11b$^+$ F4/80$^-$ Ly6G$^-$ Ly6C^{high} monocytes and CD11b$^+$ F4/80$^+$ macrophages. A concomitant reduction in vascular and plasma reactive oxygen species (ROS) suggested that the immune cells infiltrating aortic walls impaired endothelial function through an oxidative stress-mediated effect. Taken together these data indicate that post-MI HF induces a systemic inflammatory and oxidative stress response that, by activating myelomonocytic cells infiltration in the vasculature, further deteriorate endothelial function, leading to an overall unfavourable outcome.

Interestingly, the authors also found that the depletion of myeloid cells reduced mRNA expression of AT1R in LAD-ligated mice. This observation raised an intriguing relationship with the frequently reported beneficial effect of AT1R blockade in HF patients, pursuing the authors

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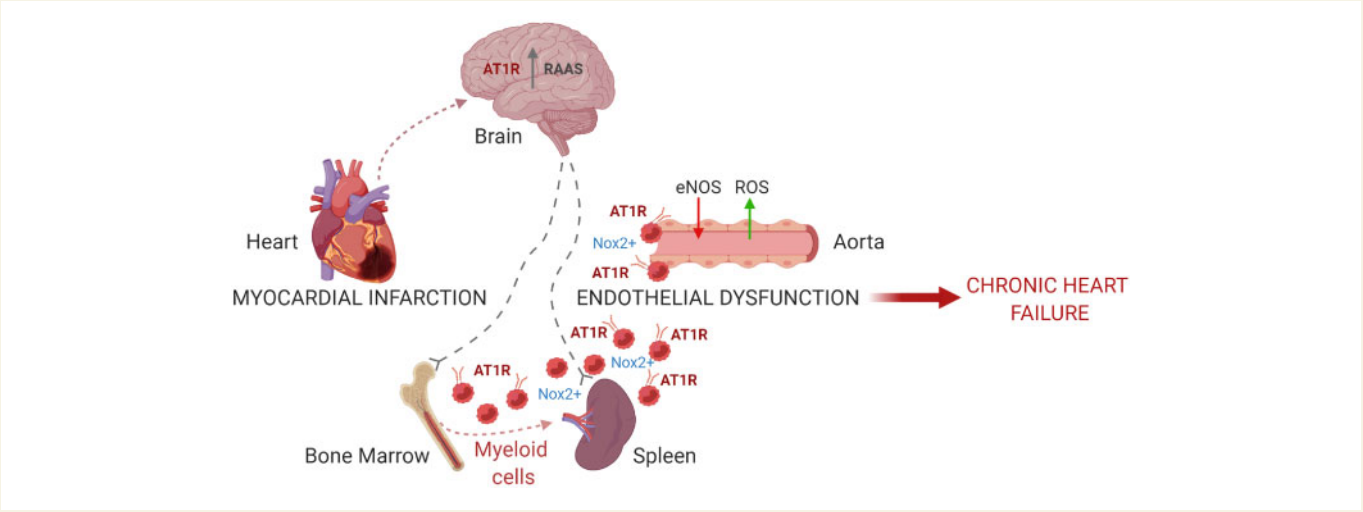

Figure 1 Myocardial infarction induces endothelial dysfunction promoting the recruitment of myeloid cells to aortic walls, contributing to evolution of chronic heart failure. Molitor *et al.* show that angiotensin II type 1 receptors (AT1R) are highly expressed on Nox2+ myeloid cells and endothelial cells after MI and promote endothelial dysfunction by increasing ROS production and concomitantly reducing endothelial NO synthase. RAAS system in the brain could contribute to Nox2+ myeloid cells migration from bone marrow and spleen towards aortic walls, through neural driven signals. Created with Biorender.com.

to further explore the possibility that MI-induced neurohumoral activation of renin-angiotensin-aldosterone system (RAAS) triggers an immune response that exerts deleterious effects on endothelial function further aggravating the clinical outcome. To validate this hypothesis, the authors investigated the effect of AT1R pharmacological inhibition with telmisartan, which revealed results comparable those induced by the depletion of myeloid cells, resulting in an overall reduction of infiltrating cells and oxidative stress, and improved endothelial function.

While these findings support the involvement of an AngII-dependent mechanism regulating the activation of myeloid cells that migrate and infiltrate aortic walls promoting endothelial dysfunction in the chronic phase of HF that occurs after MI, they also offer further perspectives that should be explored. Swirski *et al.*[5] elegantly showed that AngII mobilizes immune cells from the spleen after MI-induced emergency extramedullary haematopoiesis. Interestingly, it has also been shown that AngII modulates immune responses in the spleen through neural driven signals,[7,8] hence advancing the hypothesis that the AT1-mediated post-MI endothelial dysfunction could also result from the integration of neuroimmune mechanisms with vascular inflammation (*Figure 1*). Worth noticing, telmisartan is an AT1R-blocker highly blood–brain barrier permeable. Hence, it is possible to speculate that the beneficial effects obtained with telmisartan administration could derive from combined neuroimmune and vascular actions.

Conflict of interest: none declared.

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