JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY
VOL. 72, NO. 9, 2018

PUBLISHED BY ELSEVIER

EDITORIAL COMMENT

Remote Endothelial Activation Following Myocardial Infarction

A New Target to Combat Recurrent Cardiovascular Events?*

Adam J. Brown, MD, PhD,[a] Martin R. Bennett, MD, PhD[b]

Atherosclerotic plaques occur at different stages of development within an individual, scattered in a nonuniform pattern across multiple vascular territories. Most lesions remain clinically silent and may even regress over time or following appropriate pharmacotherapy. However, acute plaque rupture or erosion leading to myocardial infarction (MI) remains a significant cause of morbidity and mortality. In addition to the culprit site, observational data demonstrate significantly increased risks of recurrent events at nonculprit sites soon after the index presentation (1). Indeed, around one-half of all recurrent cardiovascular events after MI are attributable to disease progression in nonculprit arterial locations (2,3). These data suggest that plaque rupture/erosion or subsequent infarction might "prime" the entire vasculature, making remote plaques more susceptible to a further cardiovascular event. This "priming" may be systemic, for example, through release and/or activation of blood-borne inflammatory cells; may act locally on individual plaques, for example, through release of local proinflammatory cytokines; or both. Animal studies show that infarction causes release of bone marrow-derived progenitor cells and amplified extramedullary myelopoiesis, leading to leukocytosis, increased plaque inflammation, and larger atherosclerotic lesions with a more advanced morphology in remote arterial regions (4). However, endothelial mechanisms that might promote monocyte recruitment at remote locations remain relatively unexplored, and there remains uncertainty on whether increased remote plaque inflammation following MI can be suppressed.

SEE PAGE 1015

In this issue of the *Journal*, Moccetti et al. (5) examined endothelial alterations in remote arterial regions following a closed-chest murine model of MI. The authors hypothesized that an acute ischemic event might enhance expression of endothelial cell (EC) adhesion molecules and augment platelet adherence to the EC surface. Using molecular imaging, the authors demonstrated up-regulation of EC P-selectin, vascular cell adhesion molecule-1, and von Willebrand factor-A1, and increased platelet deposition 3 days post-MI in both wild-type mice and mice lacking both the low-density lipoprotein receptor and apolipoprotein-B mRNA editing enzyme catalytic polypeptide 1 (Apobec-1) (double knockout). Adhesion molecule up-regulation persisted in double-knockout animals to 21 days, suggesting that EC adaptations are more sustained when concomitant atherosclerosis is present. Intravital microscopy showed decreased leukocyte rolling velocity in other remote vascular regions post-MI, while results from mice undergoing surgery followed by sham MI indicated that changes in EC adhesion molecules are not simply due to the surgical procedure. Expression of EC adhesion molecules was inhibited by platelet depletion, while administration of a metalloprotease enzyme that cleaves von Willebrand factor inhibited platelet adhesion. Finally, the authors show that administration of apocynin (an inhibitor of nicotinamide adenine dinucleotide phosphate oxidase enzymes, a major source of reactive oxygen species) attenuated remote EC adhesion molecule expression,

*Editorials published in the *Journal of the American College of Cardiology* reflect the views of the authors and do not necessarily represent the views of *JACC* or the American College of Cardiology.

From the [a]Monash Cardiovascular Research Centre, Monash University and MonashHeart, Clayton, Victoria, Australia; and the [b]Division of Cardiovascular Medicine, University of Cambridge, Cambridge, United Kingdom. Both authors have reported that they have no relationships relevant to the contents of this paper to disclose.

ISSN 0735-1097/$36.00
https://doi.org/10.1016/j.jacc.2018.05.068

suppressed monocyte accumulation, and reduced a number of higher-risk features. Overall, the study suggests that increased inflammation in remote plaques following MI might be due to increased expression of EC adhesion molecules and platelet deposition, as well as increased bone marrow production of pro-inflammatory leukocytes and progenitor cells. The study also suggests that inhibition of remote EC activation might present a novel therapeutic opportunity to prevent early recurrent cardiovascular events.

However, despite these advances in knowledge, the current study leaves a number of unanswered questions. In particular, the study does not determine the actual mechanism (or mechanisms) for remote EC activation post-MI. For example, adhesion molecule expression was measured in the aorta, and MI might have reduced aortic blood flow velocity leading to lower endothelial shear stress (ESS), which has profound effects on EC function. Low ESS enhances expression of EC adhesion molecules and promotes monocyte adhesion (6), which in turn augment local inflammation and accelerate plaque growth. Indeed, recurrent cardiovascular events occur more frequently in low ESS regions within the coronary arteries (7). Another possibility is that increased expression of EC adhesion molecules in remote arteries may occur through release of systemic signaling mediators, including microvesicles or danger-associated molecular patterns. Myocardial necrosis causes release of a range of intracellular factors that are recognized by the immune system (8). This sterile immune response is sensed and mediated through danger-associated molecular patterns, which not only promote recruitment of inflammatory cells to the site of injury, but could also signal the occurrence of "harm" to remote arterial regions. A systemic signaling mechanism that induces remote EC activation might represent a target for novel therapeutic interventions or act as a prognostic biomarker for future cardiovascular risk.

The study by Moccetti et al. (5) also reignites the debate on the role of antioxidant therapy in attenuating progression of atherosclerosis. The study showed that apocynin reduced EC adhesion molecule expression, monocyte recruitment, and plaque inflammation. Previous studies have shown that antioxidants, such as alpha-tocopherol, decrease monocyte adhesion to the arterial wall (9) and impair the ability of monocytes to release pro-atherogenic cytokines (10). However, in other studies in ECs, apocynin failed to block superoxide production and was thought to primarily act as an antioxidant (11). In addition, randomized trials of antioxidant therapy in humans show either a modest benefit (12) or lack of benefit associated with long-term therapy (13,14). Even when trial benefit was observed with antioxidant therapy, it tended to occur late, which would not necessarily mirror the early inhibition of remote EC adhesion.

Ultimately, the study by Moccetti et al. (5) lays the foundation for further studies to both confirm remote EC activation in the coronary arteries following MI and examine the mechanisms underlying this phenomenon. A comprehensive knowledge of the cellular and molecular pathways involved will be crucial to the development of targeted therapeutics that may assist clinicians to combat early recurrent cardiovascular events.

ADDRESS FOR CORRESPONDENCE: Dr. Adam J. Brown, Monash Cardiovascular Research Centre and MonashHeart, Monash Health, Clayton, Victoria, Australia. E-mail: adam.brown@monash.edu. Twitter: @MonashHeart, @Cambridge_Uni.

REFERENCES

1. Jernberg T, Hasvold P, Henriksson M, Hjelm H, Thuresson M, Janzon M. Cardiovascular risk in post-myocardial infarction patients: nationwide real world data demonstrate the importance of a long-term perspective. Eur Heart J 2015;36:1163–70.

2. Stone GW, Maehara A, Lansky AJ, et al. A prospective natural-history study of coronary atherosclerosis. N Engl J Med 2011;364:226–35.

3. Calvert PA, Obaid DR, O'Sullivan M, et al. Association between IVUS findings and adverse outcomes in patients with coronary artery disease: the VIVA (VH-IVUS in Vulnerable Atherosclerosis) Study. J Am Coll Cardiol Img 2011;4:894–901.

4. Dutta P, Courties G, Wei Y, et al. Myocardial infarction accelerates atherosclerosis. Nature 2012;487:325–9.

5. Moccetti F, Brown E, Xie A, et al. Myocardial infarction produces sustained proinflammatory endothelial activation in remote arteries. J Am Coll Cardiol 2018;72:1015–26.

6. Brown AJ, Teng Z, Evans PC, Gillard JH, Samady H, Bennett MR. Role of biomechanical forces in the natural history of coronary atherosclerosis. Nat Rev Cardiol 2016;13:210–20.

7. Stone PH, Maehara A, Coskun AU, et al. Role of low endothelial shear stress and plaque characteristics in the prediction of nonculprit major adverse cardiac events: the PROSPECT study. J Am Coll Cardiol Img 2018;11:462–71.

8. Rider P, Voronov E, Dinarello CA, Apte RN, Cohen I. Alarmins: feel the stress. J Immunol 2017;198:1395–402.

9. Faruqi R, de la Motte C, DiCorleto PE. Alpha-tocopherol inhibits agonist-induced monocytic cell adhesion to cultured human endothelial cells. J Clin Invest 1994;94:592–600.

10. Harris A, Devaraj S, Jialal I. Oxidative stress, alpha-tocopherol therapy, and atherosclerosis. Curr Atheroscler Rep 2002;4:373–80.

11. Heumuller S, Wind S, Barbosa-Sicard E, et al. Apocynin is not an inhibitor of vascular NADPH

oxidases but an antioxidant. Hypertension 2008; 51:211–7.

12. Stephens NG, Parsons A, Schofield PM, Kelly F, Cheeseman K, Mitchinson MJ. Randomised controlled trial of vitamin E in patients with coronary disease: Cambridge Heart Antioxidant Study (CHAOS). Lancet 1996;347:781–6.

13. Sesso HD, Buring JE, Christen WG, et al. Vitamins E and C in the prevention of cardiovascular disease in men: the Physicians' Health Study II randomized controlled trial. JAMA 2008;300:2123–33.

14. Yusuf S, Sleight P, Pogue J, Bosch J, Davies R, Dagenais G, for the Heart Outcomes Prevention Evaluation Study Investigators. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. N Engl J Med 2000;342:145–53.

KEY WORDS atherosclerosis, coronary artery disease, vascular endothelium