Coronary Microcirculation
– A Neglected Target of Cardioprotection –
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Cardioprotection aims at the salvage of myocardium from infarction, whereas the atherosclerotic epicardial coronary artery as the primary culprit of coronary occlusion and reperfusion and the coronary microcirculation, as both a confounder and target of cardioprotection are often neglected. Ischemic preconditioning is the original experimental paradigm of cardioprotection and refers to the reduction of infarct size from sustained myocardial ischemia with reperfusion by prior brief episodes of myocardial ischemia and reperfusion. Pre-infarction angina is the natural clinical counterpart of ischemic preconditioning and associated with a better outcome from infarction, in terms of reduced infarct size, less arrhythmias, better LV function and prognosis.

Microvascular obstruction is another consequence of myocardial ischemia-reperfusion injury beyond that by and closely related to infarction. Particulate debris and soluble vasoconstrictor, pro-inflammatory and prothrombotic factors which are released from the culprit lesion, contribute to microvascular obstruction as do leukocyte-platelet aggregates, tissue edema and capillary destruction. Embolizing particles, which cause patchy microinfarcts, contribute to aggregate infarct size before and after myocardial ischemia-reperfusion, but do not interfere with the protection by ischemic pre- or postconditioning per se. In fact, ischemic preconditioning in pigs and postconditioning in humans reduce microvascular obstruction after myocardial ischemia-reperfusion.

In this issue of the Journal, Niccoli et al recruited 200 patients with acute ST-segment elevation myocardial infarction undergoing primary PCI and reported less angiographic (TIMI flow <2) and ECG (ST segment elevation resolution <70%) evidence of microvascular obstruction in patients with pre-infarction angina within 48 h before infarct onset, confirming protection of the coronary microcirculation by pre-infarction angina. Importantly, such microvascular coronary protection was attenuated in the presence of hypertension, smoking and dyslipidemia, but not confounded by diabetes, body mass index or a positive family history of cardiovascular diseases, which probably reflects the genetic burden. Such attenuation of cardioprotection by typical risk factors and confounders, which are frequently found in patients suffering an acute myocardial infarction, is well established for infarct size as an endpoint. In fact, such attenuation of cardioprotection by typical confounding risk factors and comorbidities is largely responsible for the less than perfect translation of the promising experimental cardioprotective strategies to the clinical area. It is the unequivocal merit of the present study to highlight the importance of these confounding risk factors and comorbidities for the protection of the coronary microcirculation by preconditioning/pre-infarction angina in humans. The present study by NICCOLI et al thus extends a prior study by UCHIDA et al who reported both larger infarct size, as reflected by serum creatine kinase levels, and greater coronary microvascular dysfunction, as reflected by TIMI count and ST-segment elevation resolution, in patients with reperfused acute myocardial infarction when confounded by metabolic syndrome.

In future studies, the exact site and mechanisms of such attenuation of protection remain to be identified: is the protective stimulus weaker in the presence of risk factors/comorbidities or is the target tissue less responsive to the stimulus? Is there possibly a specificity of a given risk factor/comorbidity and/or target tissue (myocardium vs. microcirculation) in the attenuation of protection? In fact, a certain specificity both for the given risk factors/comorbidities and the endpoints is suggested by the present study, because hypertension, smoking and dyslipidemia confounded protection of the coronary microcirculation by pre-infarction angina with the angiographic endpoint, but diabetes, body mass index and positive family history did not; however, then again, a positive family history confounded protection with ECG ST segment elevation resolution as the endpoint. Answers to these questions might help to overcome the impediment of protection by risk factors/comorbidities and improve the translation of protective strategies for the myocardium and coronary microcirculation to the clinical setting.

References
1. Heusch G. Cardioprotection: Chances and challenges of its translation to the clinic. *Lancet* 2013; 381: 166–175.
2. Heusch G, Kleinbongard P, Skyshchly A, Levkau B, Schulz R, Erbel R. The coronary circulation in cardioprotection: More than just one confounder. *Cardiovasc Res* 2012; 94: 237–245.
3. Murry CE, Jennings RB, Reimer KA. Preconditioning with ischemia: A delay of lethal cell injury in ischemic myocardium. *Circulation* 1986; 74: 1124–1136.
4. Heusch G. Nitroglycerin and delayed preconditioning in humans: Yet another new mechanism for an old drug? *Circulation* 2001; 103: 2876–2878.
5. Rezkalla SH, Kloner RA. Ischemic preconditioning and preinfarction angina in the clinical arena. *Nature Clin Pract Cardiovasc Med* 2004;
1: 96–102.
6. Heusch G, Kleinbongard P, Skyschally A. Myocardial infarction and coronary microvascular obstruction: An intimate, but complicated relationship. *Basic Res Cardiol* 2013; **108**: 380.
7. Heusch G, Kleinbongard P, Boese D, Levkau B, Haude M, Schulz R, et al. Coronary microembolization: From bedside to bench and back to bedside. *Circulation* 2009; **120**: 1822–1836.
8. Kleinbongard P, Boese D, Baars T, Mohlenkamp S, Konorza T, Schoener S, et al. Vasoconstrictor potential of coronary aspirate from patients undergoing stenting of saphenous vein aortocoronary bypass grafts and its pharmacological attenuation. *Circ Res* 2011; **108**: 344–352.
9. Kleinbongard P, Baars T, Mohlenkamp S, Kahlert P, Erbel R, Heusch G. Aspirate from human stented native coronary arteries vs. saphenous vein grafts: More endothelin but less particulate debris. *Am J Physiol Heart Circ Physiol* 2013; **305**: H1222–H1229.
10. Skyschally A, Schulz R, Gres P, Koenitzka I, Martin C, Haude M, et al. Coronary microembolization does not induce acute preconditioning against infarction in pigs: The role of adenosine. *Cardiovasc Res* 2004; **63**: 313–322.
11. Skyschally A, Gres P, Heusch P, Martin C, Haude M, Erbel R, et al. Preinfarction angina: No interference of coronary microembolization with acute ischemic preconditioning. *J Mol Cell Cardiol* 2005; **39**: 355–361.
12. Skyschally A, Walter B, Heusch G. Coronary microembolization during early reperfusion: Infarct extension, but protection by ischemic postconditioning. *Europace* 2013; **15**: 3314–3321.
13. Posa A, Pavo N, Hemetsberger R, Csonka C, Cson T, Ferdinandy P, et al. Protective effect of ischemic preconditioning on ischemia/ reperfusion-induced microvascular obstruction determined by on-line measurements of coronary pressure and blood flow in pigs. *Thromb Haemost* 2010; **103**: 450–460.
14. Mewton N, Thibault H, Rouhille F, Lairez O, Rioufol G, Sportouch C, et al. Postconditioning attenuates no-reflow in STEMI patients. *Basic Res Cardiol* 2013; **108**: 383.
15. Niccoli G, Scalone G, Cosentino N, Fabretti A, Mirizzi AM, Gramenga M, et al. Protective effect of pre-infarction angina on microvascular obstruction after primary percutaneous coronary intervention is blunted in humans by cardiovascular risk factors. *Circ J* 2014; **78**: 1935–1941.
16. Uchida Y, Ichimiya S, Ishii H, Kanashiro M, Watanabe I, Yoshikawa D, et al. Impact of metabolic syndrome on various aspects of microcirculation and major adverse cardiac events in patients with ST-segment elevation myocardial infarction. *Circ J* 2012; **76**: 1972–1979.