Experimental Physiology

Connections

Cardiovagal activity confers cardioprotection after myocardial infarction: recent advances

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It has been known for many years that normal functioning of the cardiovascular system depends on an adequate sympathetic–parasympathetic interaction. Also, it is known that a decreased parasympathetic tone is detrimental for the myocardium and is associated with a worse prognosis of cardiovascular diseases, particularly heart failure secondary to a myocardial infarction. Ischaemic preconditioning is among a number of myocardial protection strategies in ischaemic heart disease that have been developed in recent years. In this physiopathological entity described in 1996, brief episodes of ischaemia protect the myocardium from subsequent prolonged ischaemia. However, cardiologists do not have easy access to the heart to perform short preconditioning ischaemia; therefore, this form of preconditioning is difficult for clinical application. Thus, cardiovascular researchers looked for another method of myocardial protection. A variant is remote ischaemic preconditioning (RIPC), in which the preconditioning stimulus is delivered in an organ or tissue away from the heart. Somehow, these short periods of ischaemia at a site distant from the target organ protect the heart in the same way that local ischaemic preconditioning does. Although this new method of distant heart protection has attracted considerable interest among researchers, which is reflected in the numerous papers published in recent years, the mechanisms involved are not yet known in detail.

In our 2013 paper in *Experimental Physiology* (Donato *et al.* 2013), we hypothesized that in RIPC the preconditioning stimulus in the remote organ could activate the efferent vagus nerve pathway and reduce the infarct size through a muscarinic cholinergic mechanism. To confirm our hypothesis, we studied the afferent and efferent components of this reflex arc. Specifically, we induced three episodes of brief ischaemia in a rabbit hindlimb model, followed by 30 min of ischaemia and 3 h reperfusion in the heart. To evaluate the afferent pathway during the RIPC protocol, we used two groups of animals, one in which the femoral and sciatic nerves were sectioned, and the other in which the spinal cord was sectioned (T9–T10 level). To study the efferent neural pathway, both vagus nerves were sectioned. In another group, atropine was administered. As expected, the RIPC protocol reduced the infarct size from 40.8 ± 3.1 to 16.4 ± 3.5%. This protection was abolished by the section of the spinal cord, and also by vagal nerve section and the administration of atropine. Also, vagal stimulation mimicked the beneficial effect, reducing the infarct to 15.2 ± 4.7%.

In previous studies, it has been hypothesized that different substances (adenosine, bradykinin, calcitonin gene-related peptide, etc.) could activate a neural reflex, whose afferent branches correspond to some of the sensitive nerves (autonomic or somatic) and whose efferent branch corresponds to an autonomic motor nerve. One of the proposed efferent autonomic pathways was the vagus nerve, which would transmit the stimuli to the ischaemic heart, thus activating preconditioning. A pioneer contribution to the understanding of the vagal participation in the myocardial protection mechanisms was made in 2009 (Kawada *et al.* 2009). In that study, the authors showed, for the first time, that acute myocardial infarction increased the levels of interstitial acetylcholine in the ischaemic region. In the same study, they demonstrated that vagal electrical stimulation also increased interstitial acetylcholine in the myocardium, suggesting that the release during an ischaemic episode may have been mediated by a central activation of the efferent vagal fibres. However, the ischaemia induced by occlusion of the circumflex artery did not decrease the heart rate. An increased sympathetic nerve activity during the ischaemia may have accounted for the lack of a decrease in heart rate, even though it would seem possible that parasympathetic activity might still be increased. Finally, these same authors showed that a short episode of ischaemia (5 min) produced a significant increase of acetylcholine concentrations in the rabbit

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left ventricle, suggesting that this release of acetylcholine could act as a trigger to activate local ischaemic preconditioning. Taking the abundant and original information produced by this elegant work as a whole, it could be concluded that the efferent vagal activation contributes to the cardioprotective effect against an ischaemic insult in an important way. However, a local mechanism to increase acetylcholine release independent of parasympathetic nerve activity is also possible.

These speculations were confirmed experimentally in our study a few years later (Donato *et al.* 2013), in the sense that the release of acetylcholine by the left ventricular vagal nerve endings has a protective effect. Also, it shows that there is an afferent pathway transmitting the stimulus from the periphery and an efferent pathway for the cardioprotective signal that reaches the heart via the vagus nerve. The released acetylcholine activates the ischaemic preconditioning phenomenon when it acts on the muscarinic receptors, as demonstrated by the fact that atropine abolished the protective effect. Taking the foregoing as a whole, it can be concluded that vagal stimulation has a clear beneficial effect on ischaemic heart disease. Confirming the pre-ischaemic myocardial protection through vagal activation, we showed in a recent paper from our laboratory (Buchholz *et al.* 2015) that intermittent vagal stimulation before 30 min of ischaemia followed by 3 h of reperfusion reduced the infarct size by antagonizing the sympathetic nervous system and activating the Akt/Glycogen synthase kinase - 3β pathway.

Thus, we have shown strong experimental evidence that vagal activation is related to the protective mechanisms in myocardial ischaemia. However, there is also evidence that vagal activation in relation to reversal of ST segment elevation, reflecting the degree of reperfusion, soon after percutaneous coronary intervention in patients with acute myocardial infarction has a clinical application. In this sense, a study published in 2014 (De Ferrari *et al.* 2014), conducted in patients provided the first evidence that baroreflex sensitivity can be assessed reliably in the early hours after myocardial infarction and established its behaviour relative to tissue reperfusion. In more detail, the authors detected an increase in vagal tone evaluated through the baroreceptor reflex in a group of patients with acute myocardial infarction who were undergoing angioplasty. This finding was correlated with the ST segment resolution, used as an index of tissue reperfusion after angioplasty. It is important to remark that the baroreceptor reflex in these patients was measured using the sequence method, which does not require the administration of vasopressors, as opposed to the classical technique. It can therefore be applied to patients with acute myocardial infarction in a safe and easy manner. The results showed that the patients with an increased baroreceptor reflex sensitivity also presented a beneficial ST segment resolution, indicating an improved myocardial perfusion. These findings very early after myocardial infarction might allow for risk stratification and help to determine the therapeutic approach in patients with myocardial infarction.

In summary, vagal activation is a powerful tool that explains not only the myocardial protective mechanisms in ischaemia, but also allows, in relation to other myocardial reperfusion variables, the establishment of the basis for the treatment of a group of patients with acute myocardial infarction. The question that arises is, does the activation of vagal mechanisms also allow the prediction of ischaemic events? The answer to this question, however, lies in the development of future basic and clinical research projects.

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