Letter by Csont and Ferdinandy Regarding Article, “Ischemic Conditioning Protects the Uremic Heart in a Rodent Model of Myocardial Infarction”

To the Editor:

Ischemic pre- and postconditioning confer powerful protection to the ischemic/reperfused myocardium. Nevertheless, >25 years after the discovery of preconditioning, we still do not have cardioprotective drugs on the market. One of the reasons may be that most experimental studies on cardioprotection have been undertaken in healthy animal models, in which ischemia/reperfusion is imposed in the absence of other diseases.1 However, ischemic heart disease in humans is a complex disorder caused by or associated with known cardiovascular risk factors including hypertension, aging, and metabolic diseases such as hyperlipidemia, diabetes mellitus, insulin resistance, etc. These diseases are associated with fundamental molecular alterations that potentially affect ischemia/reperfusion injury and responses to cardioprotective interventions.

Indeed, the loss of the cardioprotective action of preconditioning has been shown first in hypercholesterolemic animals and patients. Since then, the disruption of known cardioprotective cellular signaling pathways have been shown in the presence of hyperlipidemia, diabetes mellitus, and aging.1 Therefore, there is an emerging interest in the investigation of cardioprotective mechanisms and cardioprotective drug candidates in the presence of comorbidities.

Uremia, resulting from kidney failure, is a metabolic disease associated with a high prevalence of ischemic heart disease. One may speculate that the uremic state may also lead to the attenuation of endogenous cardioprotection. However, in a preliminary study, Kocsis et al2 have demonstrated first that the cardioprotective effect of postconditioning was still present 10 weeks after subtotal nephrectomy resulting in uremia in rats. In an extensive study recently published in Circulation, Byrne et al3 reported that ischemic preconditioning, remote conditioning, and postconditioning are still cardioprotective after 4 or 8 weeks of subtotal nephrectomy or adenine-enriched, diet-induced uremia in rats. These studies suggested that the uremic heart can still be protected by conditioning techniques. However, an experimental model of even 10 weeks of uremia may not properly reflect the clinical situation, because uremia frequently remains unexplored until its late stages.4 Moreover, characterization of uremia in these experimental models was limited to measurement of serum creatinine and hematocrit.

The effect of prolonged experimental uremia (eg, >6 months) on the cardioprotective effect of endogenous cardioprotective mechanisms is still unknown; however, the duration of an altered metabolic condition may be an important determinant of the efficacy of pre- and postconditioning. Indeed, it was shown that 2 weeks of experimental diabetes mellitus protected the myocardium against ischemia/reperfusion injury; however, 4 or 8 weeks of diabetes mellitus abolished the protection by preconditioning.1,5 Moreover, systematic characterization of the evolution of the uremic state including measurement of serum urea, creatinine, lipids, inflammatory markers, glomerular filtration rate, urine parameters, and metabolism of the heart in uremic animal models would give more insight into the systemic and cardiac metabolic changes during uremia and their interaction with cardioprotective mechanisms.

In conclusion, animal models of relatively short-term uremia show that conditioning techniques can protect the ischemic heart; however, further preclinical studies in long-term uremia and clinical studies will be necessary to show if conditioning and cardioprotective drugs that enhance the signaling pathways of pre- and postconditioning can still protect the heart in uremic patients.

Sources of Funding

This work was supported by grants from the National Office for Research and Technology (Baross DA-TECH-07-2008-0041 and TÁMOP-4.2.1/B-09/1/KONV-2010-0005). Dr Csont holds a “Bolyai Fellowship” from the Hungarian Academy of Sciences.

Disclosures

None.

References

Letter by Csont and Ferdinandy Regarding Article, "Ischemic Conditioning Protects the Uremic Heart in a Rodent Model of Myocardial Infarction"
Tamás Csont and Péter Ferdinandy

Circulation. 2012;126:e212
doi: 10.1161/CIRCULATIONAHA.112.110189

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2012 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/126/13/e212