PEROXISOME PROLIFERATOR γ COACTIVATOR 1 AND MITOCHONDRIAL FUNCTION IN HIBERNATING MYOCARDIUM

To the Editor:

We read with great interest the very good article by Kelly and colleagues¹ showing reduced mitochondrial function manifested both as downregulated oxygen consumption and as a modified expression of mitochondrial proteome in a swine model of myocardial hibernation despite a successful coronary artery bypass grafting. The hypothesis of the authors is intriguing, and a depression in mitochondrial activity could provide the key to deciphering cellular survival in the setting of the chronically ischemic myocardium and the appearance of the apoptosis in the late phase of myocardial hibernation, as well as the incomplete recovery after bypass.

One molecular switch that could explain the modifications in the mitochondrial function in the hibernating myocardium is peroxisome proliferator-activated receptor γ coactivator-1 (PGC-1), reduction of which has already been demonstrated by Page and coworkers² in the setting of experimentally induced chronically hibernating myocardium. The reduced activity of PGC-1 in chronically ischemic myocardium through the reduced mitochondrial biogenesis and the reduced synthesis of the proteins of the electron transport chain could be the root of the reduced oxygen consumption and of

the induction of apoptosis. In a recent article, Adhihetty and colleagues³ showed that in a model of PGC-1 knockout mice the lack of PGC-1 resulted in muscle in a reduced cellular mitochondrial content and respiratory function, in altered mitochondrial composition, and in the increased release of proapoptotic cytochrome C in response to exogenous hydrogen peroxide. If the results demonstrated in skeletal muscle also proves valid for the myocardial muscle, many of the experimental results of Kelly and colleagues¹ and the various steps in the evolution of chronically ischemic myocardium might be explained on such a basis.

The role of PGC-1 and of mitochondrial biogenesis in myocardial hibernation is yet incompletely known. In our opinion, this role should be further studied and clarified.

Luca Siracusano, MD

Viviana Girasole, MD

Department of Neuroscience,
Psychiatric, and Anesthesiological
Sciences

University of Messina School of
Medicine

Policlinico Universitario G. Martino
Messina, Italy

References

1. Kelly RF, Cabrera JA, Ziemba EA, Crampton M, Anderson LB, McFalls EO, et al. Continued depression of maximal oxygen consumption and mitochondrial proteomic expression despite successful coronary artery bypass grafting in a swine model of hibernation. *J Thorac Cardiovasc Surg.* 2011;141:261-8.
2. Page B, Young R, Iyer V, Suzuki G, Lis M, Korotchkina L, et al. Persistent regional downregulation in mitochondrial enzymes and upregulation of stress proteins in swine with chronic hibernating myocardium. *Circ Res.* 2008;102:103-12.
3. Adhihetty PJ, Uguccioni G, Leick L, Hidalgo J, Pilegaard H, Hood DA. The role of PGC-1 α on mitochondrial function and apoptotic susceptibility in muscle. *Am J Physiol Cell Physiol.* 2009;297:C217-25.

doi:10.1016/j.jtcvs.2011.04.047

Reply to the Editor:

We appreciate the constructive comments of Drs Siracusano and Girasole. We agree that the depressed mitochondrial activity of complex V in the

electron transport chain might be a critical factor in the delayed functional recovery after revascularization of the hibernating myocardium. Whether this is the cause or effect of the persistent abnormalities in maximal oxygen consumption or contraction, however, will need additional studies to elucidate.

In our recent commentary,¹ we acknowledged the importance of the observation that adenosine triphosphatase expression was reduced in hibernating myocardium, as elegantly shown by Page and colleagues.² We considered that the cause of this decrease was a program induced by increased reactive oxygen species to offset subsequent oxidant damage. It is conceivable that a program to promote cardiomyocyte survival downregulates critical proteins in the mitochondria that contribute to reactive oxygen species formation, and this might result in either an inefficiency or an inability to maximally drive electron transport during high work states. Our findings support this hypothesis. Determining the possible disruption of a molecular switch, such as peroxisome proliferator γ coactivator 1 α and mitochondrial biogenesis,^{3,4} clearly warrants further scientific study in our revascularized hibernating myocardial swine model.

In summary, we believe that the physiologic status of the mitochondria plays a critical role in the cardiomyocyte's capacity to restore maximal myocardial oxygen consumption and contractility within hibernating myocardium after revascularization. By understanding the regulation of mitochondrial responses after revascularization, we hope to identify therapeutic measures that can ameliorate persistent heart failure after optimal coronary artery bypass grafting.

Rosemary F. Kelly, MD

Jesús A. Cabrera, MD, PhD

Edward O. McFalls, MD, PhD

Divisions of Cardiothoracic Surgery
and Cardiology

VAMC/University of Minnesota
Minneapolis, Minn

The Editor welcomes submissions for possible publication in the Letters to the Editor section that consist of commentary on an article published in the Journal or other relevant issues. Authors should: • Include no more than 500 words of text, three authors, and five references. • Type with double-spacing. • See <http://jtcvs.ctsnetjournals.org/misc/fora.shtml> for detailed submission instructions. • Submit the letter electronically via jtcvs.editorialmanager.com. Letters commenting on an article published in the JTCVS will be considered if they are received within 6 weeks of the time the article was published. Authors of the article being commented on will be given an opportunity of offer a timely response (2 weeks) to the letter. Authors of letters will be notified that the letter has been received. Unpublished letters cannot be returned.