JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY
VOL. 65, NO. 7, 2015

ISSN 0735-1097/$36.00
PUBLISHED BY ELSEVIER INC.
http://dx.doi.org/10.1016/j.jacc.2014.12.024

EDITORIAL COMMENT

Revascularization of Hibernating Myocardium

Uneven Reflorescence After the Drought*

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In a review paper published 3 decades ago, Dr. Rahimtoola first defined hibernating myocardium as the "…prolonged subacute or chronic stage of myocardial ischemia that is frequently not accompanied by pain and in which myocardial contractility and metabolism and ventricular function are reduced to match the reduced blood supply" (1). Severe coronary artery stenosis is the primary cause of hibernation, which can be partially or completely reversed by interventions of revascularization (2). An approximate PubMed search on the topic "hibernating myocardium" yields about 500 research papers published since 1985, not including many prior and subsequent clinical and experimental studies that defined and explored the peculiar changes occurring in chronically-hypoperfused myocardium. Despite the conspicuous published studies, our grasp of the pathophysiological and molecular processes leading to myocardial hibernation is still limited.

One of the phenomena that remain poorly understood is the variability of functional recovery observed in patients, even months after revascularization of chronically hibernating ventricular segments (3–4). This problem has important prognostic implications (5). Because prolonged hypoperfusion can cause partial necrosis/fibrosis, a proposed explanation is that the degree of post-revascularization improvement is highly dependent on the residual mass of viable myocardium; clinical and experimental studies have shown a linear, inverse correlation between the extent of transmural necrosis/fibrosis and contractile function of ischemic and post-ischemic ventricular walls (4,6,7). But, the interpretative paradigms in biology and medicine are very often not intuitive and obvious. Despite the absence of fibrosis, more than 20% of patients were reported to experience persistent contractile dysfunction in successfully revascularized ventricular segments (4). This phenomenon hints at possible alterations to viable cardiomyocytes that negatively affect their function.

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The study by Page et al. (8) in this issue of the *Journal* tested the hypothesis that persistent myocyte loss and/or altered protein expression influence the functional recovery of revascularized hibernating myocardium in the absence of infarction. The authors used an elegant and technically-challenging swine model of severe left anterior descending coronary artery stenosis to induce and maintain myocardial hibernation over a period of 3 months, followed by complete recanalization with an intravascular stent, and then 1 month of follow-up. This model was conveniently devoid of necrosis/fibrosis; yet, at 1 month after revascularization, ventricular wall systolic thickening was only partially restored. The role of transmural necrosis was ruled out. So, did revascularization largely fail to overturn cellular alterations?

The surprising finding was that, although vessel reopening did lead to numerous reverse changes, these were very heterogeneous. A thorough proteomic analysis revealed normalization of previously upregulated stress and cytoskeletal proteins, persistent down-regulation of some contractile proteins, and nonuniform changes in regulation of metabolic enzymes. Among the latter, the expression of pyruvate

*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.

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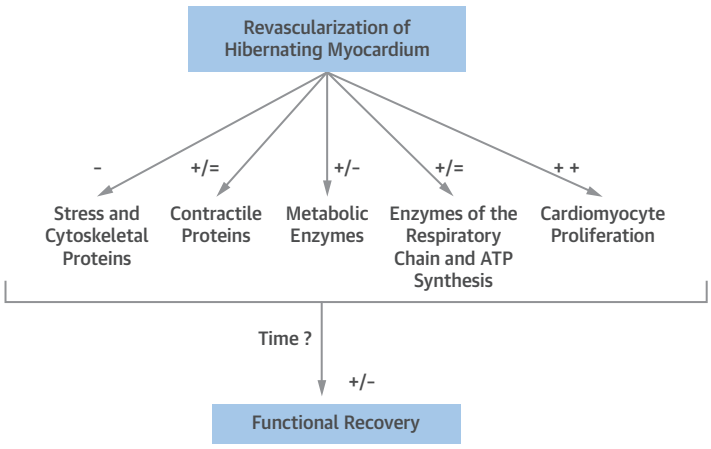
dehydrogenase, which is the entry point for the final mitochondrial oxidation of carbohydrates, was normalized. Conversely, long chain acyl-CoA dehydrogenase, a key enzyme in the beta-oxidation of long-chain fatty acids, which is the main energy source for healthy myocardium, displayed a paradoxical, further down-regulation. In contrast, the expression of electron transport chain and adenosine triphosphate synthesis enzymes returned to quasi-normal levels. The limited published data, which has been obtained from direct measurements of energy substrate metabolism, indicate enhanced glucose utilization and reduced fatty acid oxidation in hibernating myocardium (9). The study by Page et al. (8) suggests that abnormally high carbohydrate utilization may continue long after the therapeutic intervention, consistent with outcomes observed by others in treated patients (10).

As noted by the authors, an unexpected finding of their study was the stimulation of myocyte regeneration by revascularization. It was already known that hibernation causes apoptotic cell loss and compensatory hypertrophy of the surviving cardiomyocytes (2). Page et al. (8) reported a boost in cardiomyocyte number and in molecular markers of cell proliferation, whereas cell size decreased; therefore, the end-diastolic ventricular wall thickness remained unaltered. These findings remind us that perhaps the most powerful stimulus and the necessary condition for ischemic tissue regeneration by endogenous (or exogenous) stem cells is the re-establishment of adequate blood perfusion. Although the authors could not provide direct evidence for this, they speculated that the delayed maturation of newly-formed cardiomyocytes might influence the time course of functional recovery.

The study by Page et al. (8) prompts several considerations. First, it again confirms the high value of the pig model of myocardial hibernation, which proved particularly useful for the characterization of the pathophysiological, histological, and molecular changes occurring after revascularization. The authors acknowledged their study's limitations; for instance, the relatively short duration of the post-stent follow-up leaves open questions about longer-term reverse remodeling. Nonetheless, to date, no other model allows such a wealth of in vivo and ex vivo measurements of variables ranging from regional coronary flow, ventricular function, and metabolism to cellular and molecular adaptive modifications. The highlight of this study is the co-existence of reverse and persistent molecular changes after revascularization. Further complexity is added by the variable maturation rate of putative newly-formed cardiomyocytes, a previously unsuspected player. These findings suggest that the prediction of functional recovery after revascularization is, perhaps, much more complex than previously thought. It may depend not only on viable myocardial mass, but also on the net effect of all of these alterations, both negative and positive, at the cellular level (**Figure 1**).

FIGURE 1 Functional Recovery After Revascularization



Recovery may depend not only on viable myocardial mass, but also on the net effect of negative and positive alterations at the molecular and cellular level. At present, the complete time course of recovery remains undetermined and warrants further investigation. +/− = up- or down-regulation, or positive or negative effect; +/= = up-regulation or no change; ATP = adenosine triphosphate.

Ideally, new noninvasive cellular, molecular, and metabolic diagnostic imaging (11), combined with classical diagnostics, will, in the future, generate data that might be entered in computational models (12) to predict the functional outcome, with little room left for empiricism. This integrated approach might also provide important information regarding the hierarchy of the biological factors that should be potentiated by targeted therapies to accelerate the functional recovery: administration of pharmacological and/or hormonal metabolic modulators if metabolism is the key player; administration of growth hormones if the primary goal is to promote cardiomyocyte maturation; and so forth. Integrative pathophysiology will still be an invaluable compass for steering the advancement of cardiovascular medicine.

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JACC VOL. 65, NO. 7, 2015
FEBRUARY 24, 2015:698–700

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KEY WORDS cardiac, contractile proteins, cytoskeletal proteins, myocardial ischemia, myocytes, proteomics, regeneration, stents