Myocardial viability and hibernation: still an incomplete picture

Pasquale Perrone Filardi, Shahbudin H. Rahimtoola*

*Division of Cardiology, "Federico II" University, Naples, Italy, *Section of Cardiology, University of Southern California, Los Angeles, CA, USA*

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Address:

Dr. Pasquale Perrone Filardi

Cattedra di Cardiologia
Università degli Studi "Federico II"
Via S. Pansini, 5
80131 Napoli
E-mail:
fpperron@unina.it

In recent years the term viability has entered the vocabulary of clinical cardiologists to indicate the possibility that in patients with ischemic left ventricular dysfunction improvement of contraction may occur following myocardial revascularization. In fact, this possibility was already recognized in the early '70s although its clinical relevance was at that time underestimated. Since evaluation of ventricular function before and after revascularization has been more systematically investigated it became evident that a substantial increase of ejection fraction may occur in up to 25 to 30% of patients with left ventricular dysfunction[1]. From a pathophysiological standpoint the recovery of regional systolic function is attributed to restoration of myocardial blood flow to myocardial territories consisting of viable yet functionally quiescent cells, a condition that has been termed hibernating myocardium[2]. The fascinating concept of hibernation has gained so much popularity in the cardiology community that this definition is being used interchangeably to indicate viability in its broadest significance or to simply indicate potential recovery of systolic function. However, this oversemplification, although appealing for clinicians, is conceptually incorrect for a number of pathophysiological and clinical considerations. First, it assumes that the mechanism of hibernation explains entirely the pathophysiology of reversible contractile dysfunction. As outlined by Heusch and Schulz[3] in their article, impairment of flow reserve in the presence of an epicardial stenosis, with or without a substantial reduction of basal flow, may also contribute in some patients (or in some myocardial regions of the same heart) to sustain a stable impairment of contractile function. Whatever the pathophysiology of sustained contractile dysfunction in hibernating myocardium, the subcellular processes leading to reduced contraction remain largely unknown. Recently, alterations of the contractile apparatus, leading to selective degradation of troponin I thin filaments, have been called in the pathogenesis of an experimental model of progressive left ventricular dysfunction in the mouse[4]. Whether similar mechanisms are operative in the human model of ischemic left ventricular dysfunction remains to be investigated. In addition, it became evident that the condition of hibernation is more a degenerative progressive than a static phenomenon, leading, if untreated, to continuing loss of viable cells and impairment of ventricular function[5].

Clinically, the equivalence between hibernation and viability implies that areas of so-called viable myocardium are necessarily hibernating, hence, they are underperfused and capable of functional recovery. This may not be the case in many circumstances, for instance in patients following thrombolysis, where the dysfunctional region consists of an admixture of necrotic and viable myocardium with normal perfusion at rest. In such a case no intervention can resume basal contraction if the amount of subendocardial necrosis is substantial, but the behavior of that region may still be relevant during inotropic stimulation, like physical exercise. In fact, demand ischemia, due to residual stenosis of the epicardial vessel, may occur and limit functional capacity and, therefore, it may represent an indication for revascularization independently of the recovery of basal contraction[6].

This introduces the last but not least argument to be cleared up concerning viability and its common understanding, i.e., the gold standard of viability. Obviously evaluation of viability is aimed at figuring out whether global ejection fraction will improve after revascularization. This is undoubtedly a straightforward task in a patient with reduced global contractile function. To date all noninvasive techniques have been tested to predict the recovery of regional and global ejection fraction. As outlined by Beller[7], different techniques show quite different accuracy to predict recovery of contractile function due to their inherent different approach, namely evaluation of contractile reserve for echocardiography or of metabolic integrity for nuclear scintigraphy and, recently, nuclear magnetic resonance[8-10]. In fact, contractile reserve may be absent in viable dysfunctional myocardium subtended by an occluded coronary vessel, thus limiting the sensitivity of dobutamine echocardiography compared to indices of metabolic integrity[11]. Alternatively, contractile reserve may be undetectable when the amount of viable cells is reduced despite evidence of residual metabolic activity in the same territory[12]. Another important limitation of current most used techniques is their spatial resolution that allows only transmural evaluation of perfusion and function, thus preventing assessment of the subendocardium. However, as outlined by Bonow[13], recent technical progresses of magnetic resonance imaging allow *in vivo* evaluation of subendocardial perfusion and function, thus making evaluation of subendocardial viability feasible in patients[14]. Whether these advantages of magnetic resonance imaging will substantially affect the clinical evaluation of viability is uncertain at this time and deserves further evaluation in comparative prospective studies.

It has recently been reported that the benefit of revascularization on survival of patients with moderate to severe ischemic dysfunction is independent of the recovery of ejection fraction[15]. In fact, this observation strongly supports the possibility that alternative pathophysiological effects of revascularization in the presence of residual viable myocardium may confer survival and functional advantages independently of the recovery of resting global function (Table I). Preservation of subepicardial viable myocardium may prevent adverse remodeling of the ventricle[16]; recovery of diastolic function may also contribute to survival and functional benefits[17]; finally, areas of viable jeopardized myocardium may trigger malignant arrhythmias. Whatever the mechanism(s), several studies have reported that untreated viable myocardium is associated with adverse prognosis, whereas patients with viable myocardium have better perioperative and long-term survival[18-20]. This benefit seems to occur also in patients with reduced amount of viable myocardium, presumably not leading to significant changes in resting ejection fraction[18]. However, the limitation of all these studies is their retrospective analysis. In addition, it is unclear whether patients remaining in medical treatment were receiving optimal maximized drug therapy. In fact, it is uncertain and worth to be investigated the effect of optimal therapy on viable myocardium. Clarification of this aspect in the upcoming NIH trial will be particularly welcome as it is crucial for an appropriate selection of candidates to risky revascularization procedure.

Table I. Potential benefits of myocardial revascularization in patients with ischemic left ventricular dysfunction.

Improvement of left ventricular ejection fraction at rest
Prevention of inducible ischemia
Reversal of diastolic dysfunction
Prevention of remodeling
Prevention of malignant arrhythmias

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