The clinical perspective

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Abstract

Acute myocardial ischaemia is known to impair contractile function, but if the ischaemic event is not lethal and reperfusion occurs, contractility is restored. Differences in response to reperfusion on contractility is due to the admixture of scar tissue including 'stunned' and 'hibernating' myocardium. All but the irreversibly scarred myocardium is viable and the proportion of viable but dysfunctional myocardium due to stenosed coronary arteries offers an index to contractility restoration on revascularisation. A range of imaging techniques have been developed to identify viable reversibly dysfunctional myocardium and assist in the decision-making of the suitability of revascularisation in an individual patient.

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Acute myocardial ischemia impairs contractile function [1], but, if the ischemic event is not lethal and reperfusion occurs, contractility is restored [2]. However, despite reperfusion, contractile dysfunction may persist for several hours and this phenomenon is termed ''myocardial stunning'' [3–5]. Thus in myocardial stunning there is a mismatch of perfusion and contraction. Repeated episodes of ischemia may lead to repetitive stunning with a cumulative reduction in contractility, and this may be one mechanism of chronic postischemic left ventricular dysfunction [6].

The phenomenon of ''myocardial hibernation'' was proposed to explain the finding that revascularization in patients with coronary artery disease (CAD) and chronic postischemic left ventricular dysfunction could lead to an improvement in left ventricular function [7–9]. Initially, it was proposed that, during a prolonged state of sublethal ischemia, contractility and metabolism could be depressed in parallel with the reduced blood supply [9]. Thus hibernating myocardium is adaptive, with necrosis prevented by a reversible downregulation of function and energetics, but with retained perfusion–contraction matching in affected segments [10]. Hibernating myocardium may not, therefore, be ischemic at rest, as a result of the matched reduction in energy requirement [11,12].

The stress of oxygen and substrate deprivation activates endogenous mechanisms of cell survival [13]. These adaptations may differ between repetitive stunning and hibernating myocardium [14]. Hibernating myocardium has greater concentrations of cAMP, whereas the cardioprotective heat-shock protein, Hsp-72, is increased in myocardial stunning [14]. In hibernating myocardium, depletion of contractile elements, cytoskeletal disorganization, and alterations in adrenoreceptor density have been reported, together with activation of the inflammatory cascade, induction of cytokines and chemokines, recruitment of leucocytes, interstitial remodeling, and fibrosis [15]. These findings are progressive and reflect the severity of the cumulative ischemic insult.

In normal myocardium, myocardial blood flow increases in parallel with an increased contractile demand during stress. Both repetitive stunning and hibernation represent an inability to enhance

myocardial blood flow across the range of demand: a reduction in coronary flow reserve [6,16]. Restoration of coronary flow reserve allows post-stunning recovery and upregulation of metabolism and contractility in hibernation. Any segment of chronic postischemic left ventricular dysfunction may contain an admixture of scar tissue resulting from lethal ischemia, hibernating myocardium, stunned and repetitively stunned myocardium, and normally contractile myocytes [17]. All but the irreversibly scarred myocardium is viable, and the proportion of viable but dysfunctional myocardium subtended by stenosed epicardial coronary arteries amenable to revascularization becomes an index of how much contractility could be restored by correction of coronary flow reserve [18,19].

This concept of viable reversibly dysfunctional myocardium is important. CAD is the most common cause of congestive heart failure [20,21], and many patients will retain a significant quantum of viable reversibly dysfunctional myocardium in which function could be improved [22]. As myocardial function is an exquisite index of prognosis, interventions that improve function are also likely to improve prognosis [23,24]. Typically, patients with CAD and chronic postischemic left ventricular dysfunction have multivessel disease and increased left ventricular volumes [20]. Dysfunction in one region leads to increased demands in others and promotes adverse remodeling [25]. Successful revascularization can improve function in viable reversibly dysfunctional myocardium segments, improving overall left ventricular function and reducing adverse remodeling in affected and remote segments.

Viable reversibly dysfunctional myocardium has several features that can be used to facilitate its identification. Except in its most severe forms, it remains responsive to β-adrenergic stimulation [26]. Thus dobutamine stress echocardiography can detect increased wall motion in segments of viable reversibly dysfunctional myocardium, whereas wall motion in predominantly scarred segments remains unchanged [27]. With high-dose dobutamine stress echocardiography, initially improved contractility can diminish, reflecting inducible ischemia. This ''biphasic'' response is highly predictive of recovery [26].

Echocardiography can also detect wall thinning, most probably as a result of transmural infarction and scarring. Scarring results in obstruction of the coronary microcirculation. The reduced perfusion can be detected by myocardial contrast echocardiography, which uses small (<7 μm; smaller than the red corpuscle) gaseous microbubbles to determine tissue capillary blood flow [28,29]. Myocardial contrast echocardiography also improves chamber opacification and identification of left ventricular wall borders, facilitating assessment of function and wall thickness. Intramyocardial contrast enhancement detects [30] viable reversibly dysfunctional myocardium, whereas lack of enhancement indicates non viability. The utility of myocardial contrast echocardiography in detection of viable reversibly dysfunctional myocardium is increased when combined with dobutamine stress echocardiography [31,32].

Viable reversibly dysfunctional myocardium retains the functional integrity of the myocyte sarcolemma to exchange potassium and other ions [33]. This can be examined by single photon emission computed tomography, which uses the labeled potassium analog, thallium-201, or technetium-99m. Initial administration of tracer provides an index of myocardial blood flow, whereas delayed tracer uptake reflects sarcolemmal integrity and viability; absence of delayed uptake indicates non viability [33,34].

Unlike scar, viable reversibly dysfunctional myocardium also retains the ability to metabolize significant amounts of glucose [35,36]. This can be probed using positron emission tomography (PET) and the glucose analog, [^{18}F]fluoro-deoxyglucose (FDG) [37]. FDG-PET is often combined with a perfusion tracer study. Regions demonstrating a parallel reduction of flow and FDG uptake may be considered irreversibly injured, whereas maintenance of FDG uptake, even in the presence of a perfusion abnormality, may indicate viability with ischemia [35]. During FDG-PET, the use of insulin as a hyperinsulinemic euglycemic clamp reduces free fatty acids and promotes entry of glucose or FDG, enhancing image quality [38–40]. On occasion, some segments display DG-PET viability, but not contractile reserve. In this circumstance, contractile recovery may be delayed and occur to a lesser extent, suggesting a more advanced downregulation of the myocyte [17].

Cardiac magnetic resonance imaging can be used in conjunction with dopamine stress echocardiography to assess both contractile reserve and assesses wall thickness [41,42]. Importantly, it can be used with gadolinium-chelated contrast agents, which gradually accumulate in areas of scar. This allows assessment of the transmurality of infarction [43,44]. The absence of late gadolinium accumulation, even in thinned (<5 mm) hypokinetic ventricular wall, is associated with postrevascularization recovery.

Although we do not have controlled prospective randomized studies indicating that the revascularization of viable reversibly dysfunctional myocardium improves prognosis, there are studies that suggest benefit [20]. Several investigators have found that revascularization of viable reversibly dysfunctional myocardium increases left ventricular ejection fraction by at least 5% and that the increase is related to the number of viable reversibly dysfunctional myocardium segments [37,45,46]. To achieve an increase of at least 5% in left ventricular ejection fraction,

approximately 25% of the left ventricle needs to be viable in dopamine stress echocardiography [22]. Meta-analyses have suggested a prognostic advantage of revascularization in the presence of viable reversibly dysfunctional myocardium, and a prognostic disadvantage if that tissue is not revascularized [47]. Symptoms of heart failure and objective measures of exercise tolerance may improve [48]. Importantly, delayed revascularization of viable reversibly dysfunctional myocardium allows further deterioration, and frustrates the benefits accrued by prompt treatment [49,50].

Chronic postischemic left ventricular dysfunction in CAD is common, and contributes to the epidemic of heart failure. Although hibernation and repetitive stunning may both be contributory mechanisms, currently, the distinction is less relevant than an overall assessment of viability and the subsequent decision-making process of whether revascularization, often applied in combination with other heart failure therapies, is applicable in the individual patient. ■

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