Mechanisms leading to reversible mechanical dysfunction in severe CAD: alternatives to myocardial stunning

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Mazzadi, Alejandro N., Xavier André-Fouët, Nicolas Costes, Pierre Croisille, Didier Revel, and Marc F. Janier. Mechanisms leading to reversible mechanical dysfunction in severe CAD: alternatives to myocardial stunning. Am J Physiol Heart Circ Physiol 291: H2570–H2582, 2006. First published July 21, 2006; doi:10.1152/ajpheart.01249.2005.—Patients with severe chronic coronary artery disease (CAD) exhibit a highly altered myocardial pattern of perfusion, metabolism, and mechanical performance. In this context, the diagnosis of stunning remains elusive not only because of methodological and logistic considerations, but also because of the pathophysiological characteristics of the myocardium of these patients. In addition, a number of alternative pathophysiological mechanisms may act by mimicking the functional manifestations usually attributed to stunning. The present review describes three mechanisms that could theoretically lead to reversible mechanical dysfunction in these patients: myocardial wall stress, the tethering effect, and myocardial expression and release of auto- and paracrine agents. Attention is focused on the role of these mechanisms in scintigraphically “normal” regions (i.e., regions usually showing normal perfusion, glucose metabolism, and cellular integrity as assessed by nuclear imaging techniques), in which stunning is usually considered, but these mechanisms could also operate throughout the viable myocardium. We hypothesize that reversion of these three mechanisms could partially explain the unexpected functional benefit after reperfusion recently highlighted by high-spatial-resolution imaging techniques.

stunned myocardium; hibernating myocardium; inotropic reserve; cardiac imaging; myocardial wall stress; ventricular remodeling

SUMMARY OF CLINICAL PROBLEM

In recent years, widespread utilization of noninvasive cardiac imaging methods has greatly improved the synergy between clinical and basic investigation of cardiac ischemic pathophysiology. Thus imaging methods have shown that the reversible left ventricular (LV) dysfunction arising from brief coronary occlusion and reflow (myocardial stunning), first described in animal models (80), occurs in humans. Two major hypotheses explain this phenomenon: 1) the oxyradical hypothesis, which proposes that oxidant stress impairs LV function (18), and 2) the calcium hypothesis, which postulates that stunning results from disturbed myocyte calcium homeostasis (98). On the other hand, the hibernating myocardium (136, 137) was first discovered by imaging methods in humans, and it was originally defined as “resting LV dysfunction due to reduced coronary blood flow that can be partially or completely reversed by myocardial revascularization and/or by reducing myocardial oxygen demand” (136). The concept was refined when ultrastructural investigations showed a distinctive morphology for hibernating myocardium, generally without necrosis, but with loss of sarcomeres and myofibrils (suggesting a “dedifferentiation” process toward an embryonic phenotype), with loss of mitochondria and increased glycogen storage (9, 19, 27, 162).

The clinical recognition that reperfusion could improve mechanical performance of an unscarred dysfunctional ischemic region of the myocardium was motivation for the study of so-called myocardial viability. Clinical interest in the issue in terms of management has been widely recognized: if myocardial hibernation or stunning occurs, reperfusion may positively impact not only local, but also overall, myocardial function, heart failure symptoms, and survival. Consequently, various imaging methods have been employed to detect viability, with the ultimate aim of predicting outcome (and especially functional outcome) after reperfusion therapy. Scintigraphic meth-
ods such as single-photon-emission computed tomography (SPECT) and positron-emission tomography (PET) have been incorporated into clinical practice for the assessment, at rest or under pharmacological stress, of myocardial cellular integrity, perfusion, and metabolism (e.g., glucose and fatty acid uptake or oxygen consumption). Thus it has been demonstrated scintigraphically that stunned myocardium shows normal glucose uptake and perfusion, that hibernating myocardium often shows increased glucose uptake relative to perfusion ("flow-metabolism mismatch"), and that infarcted (scarred) myocardium shows correspondingly reduced glucose uptake and perfusion ("flow-metabolism match") (110, 156). Furthermore, it was suggested that inotropic reserve (i.e., improved contractile function during inotropic stimulation) might indicate individuals or myocardial regions liable to show functional improvement after reperfusion (34, 36), and this approach has been extensively used in combination with imaging methods classically employed for mechanical performance assessment (echo-cardiography or MRI). Periodic in-depth review of the ability of the various imaging methods to detect viability (and to predict functional outcome) has provided guidelines for investigation and patient management (159, 167).

Despite sustained efforts and methodological advances, however, the study of myocardial viability has important limitations. These limitations have been attributed to several factors, such as technical limitations of the imaging methods and lack of a standardized protocol and definition of viability, which result in difficulty in comparison of the results (167). Viability assessment may be especially problematic in patients with chronic severe coronary artery disease (CAD; i.e., multivessel CAD, severe LV dysfunction, and risk factors), where the underlying complexity of the disease could introduce confounding factors that hinder accurate interpretation of the phenotyping given by the imaging methods. For example, clinical assessment of regional functional performance may be difficult because of the dynamic interplay of adjacent dyskinetic, hypokinetic, and hyperkinetic regions. Thus, in patients with LV dysfunction, nonischemic regions often exhibit functional abnormalities that are due, at least in part, to changes in stress-strain relations (the so-called “tethering effect”). Moreover, in patients with chronic CAD, some degree of overlap could occur between stunning, hibernation, and scarring (see below).

STUNNING, HIBERNATION, AND SCARRING: PATHOPHYSIOLOGICAL CASCADE IN SEVERE CAD

Many studies of patients with chronic severe CAD sought to assess the incidence of various scintigraphic imaging patterns reflecting the pathophysiological consequences of ischemic injury, for instance, hibernating or stunned myocardium. Over and above the recognized clinical interest, such assessment has also sought to elucidate the so-called “natural history of the disease” (77, 112, 131, 142). The underlying hypothesis is that stunning, hibernation, and scarring are not circumscribed pathophysiological entities but, rather, represent interrelated gradual ultrastructural alterations at the myocyte level (26). In several PET studies (79), the finding that resting perfusion is reduced in hibernating regions supports the idea that decreased contractile performance is downregulated by hyperperfusion. More recently, first-pass MRI (147), an imaging technique that can follow the progression of the intramyocardial signal during the first pass of injected contrast medium, also showed hyperperfused hibernating regions (87). However, other PET studies reported relatively normal perfusion and oxygen consumption in such regions (79, 163). The former results, combined with the finding of abnormal perfusion reserve in hibernating regions (i.e., minimal increment in perfusion during pharmacological vasodilation) (163), suggest that repetitive transient ischemia (“repetitive stunning”) finally leads to chronic hibernation (108, 163). In turn, chronic hibernation, in the absence of reperfusion, can undergo progressive cellular alteration, leading to cell death and scarring (51, 52, 73, 145). The inflammatory process implicated in heart failure (24, 144) (see below) completes the view that severe CAD is a permanent evolutive cascade of gradual myocyte degeneration accompanied by cellular infiltration, cytokine release, residual edema, hemorrhage, and resorption.

USUAL IMAGING VIEW OF MYOCARDIAL STUNNING

According to the evolutive view of the disease, the mechanically dysfunctional, but scintigraphically “normal,” myocardium (i.e., regions usually showing normal resting values of perfusion, glucose metabolism, and cellular integrity, as assessed by nuclear imaging techniques) is frequently considered in cardiac imaging to be one of the first clinical features in the disease cascade. Repetitive stunning secondary to increased oxygen demand is taken to underlie a mechanical dysfunction that could hypothetically be reversed by reperfusion (reversible mechanical dysfunction) (129). Thus, although repetitive transient regional ischemia cannot be unequivocally documented in the clinical setting, it is usually agreed that repetitive stunning occurs in dysfunctional, but scintigraphically normal regions, with relatively rapid functional improvement after reperfusion. Consequently, some recent investigations involving patients with severe CAD reported a high incidence of dysfunctional, but scintigraphically normal, regions that were considered to be stunned (12, 21, 77, 142). According to some authors, up to 72% of dysfunctional regions in patients with CAD present scintigraphically normal patterns (77). In such normal regions, the time course of functional recovery after reperfusion was reported to be shorter than in hibernating regions (12), which might suggest that myocardial stunning should be equated with dysfunctional scintigraphically normal regions showing relatively rapid and spontaneous postoperative functional recovery. However, there might be some degree of overlap between stunned and hibernating regions in terms of the time course of the functional improvement after reperfusion. Whereas improved mechanical performance 3 mo after reperfusion has been found in 61% of regions defined as stunned (12), functional improvement after reperfusion in hibernating regions has been reported to follow a monoexponential time course with a median time constant of 23 days (161).

WORKING HYPOTHESIS

Our group recently reported on functional outcome after revascularization in patients with severe CAD (114). The consequences of the ischemic injury were characterized by integration of PET measurements of perfusion and glucose uptake. Inotropic reserve was assessed preoperatively with dobutamine (a β-adrenergic agonist) to identify the regions
susceptible to postoperative functional improvement. Intramyocardial mechanical performance was quantitatively assessed by tagged MRI, an imaging technique that creates “tags” (Fig. 1d) by presaturating planes of tissue, which appear on the image as a dark grid pattern moving and deforming along with the myocardium (37, 173). Revascularization was found to provide greater intramyocardial functional benefit than would be expected from the preoperative inotropic reserve assessment. Postoperative functional improvement was observed in a large proportion of regions that were found to be viable by PET (i.e., normal, hibernating, and moderately scarred regions) without dobutamine response (Fig. 2) (114). Although they are not new, these findings confirm and complement previous reports of a reduced negative predictive value of inotropic testing for functional improvement after reperfusion. Thus, in patients with CAD undergoing dobutamine echocardiography before angioplasty, Afridi et al. (2) noted that “interestingly, 35% of segments with a worsening response during dobutamine had recovery of resting function.” In another study with a similar patient population (126), a negative dobutamine response in dysfunctional regions with preserved or only moderately reduced perfusion (as assessed by SPECT) was found to be an “unreliable predictor of functional outcome” (as assessed by echocardiography). Moreover, tagged-MRI studies of viability after infarction also demonstrated the ability of intramyocardial mechanical performance to increase “markedly” on follow-up in dysfunctional regions that did not respond to dobutamine (65).

The above-mentioned findings concern the relation between perfusion and inotropic reserve, and their rationale is therefore likely to be complex. Despite the recognized complexity of the issue, however, it is generally agreed that dysfunctional regions displaying contractile reserve can increase perfusion during stimulation, whereas those without contractile reserve cannot (61, 99). Thus it is usually accepted that most regions showing inotropic reserve (before reperfusion) could benefit from reperfusion in terms of mechanical performance because of regionally enhanced perfusion. Conversely, a direct functional benefit from reperfusion is usually considered less probable in regions without inotropic reserve, in which perfusion could be expected to remain basically unchanged. Consequently, the post-operative functional improvement in these regions (2, 65, 114, 126) suggests that factors other than regionally enhanced perfusion after reperfusion could be playing a role. In dysfunctional, but scintigraphically normal, regions, such factors may represent an alternative to myocardial stunning to account for functional improvement after reperfusion.

The hypothesis of the present review is that pathophysiological mechanisms other than stunning could play a major role in the reversible mechanical dysfunction observed in severe CAD. In dysfunctional, but scintigraphically normal, regions, these mechanisms may act by mimicking the functional effects often attributed to repetitive stunning. We believe that a reversion of these mechanisms could be partially responsible for the functional benefit following reperfusion in regions without inotropic reserve by high-spatial-resolution imaging methods.

OBJECTIVES

The present review discusses the causal role attributed to myocardial stunning in the reversible mechanical dysfunction observed in scintigraphically normal regions in patients with severe CAD. First, we briefly present the complexities underlying imaging diagnosis of stunning in these patients. Next, we review three pathophysiological mechanisms (other than those involved in stunning) that could lead to such reversible me-
in severe CAD is not an easy task. The most convincing studies of stunning in humans were generally performed under well-controlled conditions (cardioplegic arrest during cardiac surgery or angioplasty balloon inflation in the coronary arteries) (5, 93, 150) or in patients with at least one of the following characteristics: one-vessel CAD, relatively well-preserved LV ejection fraction (LVEF), modest regional dysfunction at rest, and no signs of scarring in the region of interest (3, 64, 125, 146).

Stunned myocardium refers to prolonged, but reversible, posts ischemic LV dysfunction after coronary occlusion of a severity or duration insufficient to produce myocardial necrosis (22). Consequently, as reported by Ambrosio and Tritto (4), “evidence of the presence of stunning requires evidence that contractile dysfunction persists at a time when perfusion has returned to baseline values. It is necessary to perform accurate and reliable determination of regional function; to demonstrate that dysfunction persists after resolution of the ischemic episode; to document that myocardial blood flow has returned to baseline and that function eventually recovers. It is thus mandatory to perform serial simultaneous measurement of flow and function.” In other words, the diagnosis of stunning is complex and could be hindered by several methodological and logistic considerations (17). Unequivocal demonstration of contraction-perfusion mismatch at the time of dysfunction, for instance, remains controversial. PET, the reference technique for quantitative perfusion studies, has revealed a wide variation in perfusion within and between individuals (31, 78), rendering the use of absolute perfusion values in assessment of the normality of perfusion after reperfusion questionable. Subtle reductions in regional perfusion due to moderate ongoing ischemia or moderate endocardial necrosis (Fig. 1c) may not be detected by PET (Fig. 1b). Moreover, most clinical studies fail to define mechanical performance: they give semiquantitative scores, rather than absolute values, for full wall thickening (Fig. 1a), generally in large myocardial regions and with use of echocardiography.

In addition, identification of myocardial stunning by evaluation of physiological characteristics could be hindered by confounding factors associated with severe mechanical LV dysfunction. For instance, experimental data indicate that stunned myocardium typically enhances functioning under inotropic stimulation (i.e., the presence of inotropic reserve) (115). However, because the normal pattern of inotropic reserve can be greatly altered during severe LV dysfunction, such an observation in this context is unlikely. Experimental data from MRI have revealed a blunted inotropic response in the remote myocardium of rats with drastic drop of cardiac output due to chronic coronary stenosis (122). In patients with severe LV dysfunction, Skopicki et al. (151) reported that an abnormal response to dobutamine frequently occurred in regions that contracted normally, which were classified as normal by PET, with a normal hyperemic response to adenosine, and were fed by a patent coronary vessel. The authors concluded that the absence of inotropic reserve was only partially explained by the inability of normal regions to increase blood flow, and they attribute a major role to the mechanical effect of tethering (see below) in this impairment: dobutamine-unresponsive regions were much more likely to be adjacent to regions that were dysfunctional at rest (151). More recently, we confirmed the observations of Skopicki et al. in a group of patients with

**Fig. 2.** Tagged MRI enables quantitative assessment of intramyocardial change in circumferential shortening (Ecc). Ecc changes with dobutamine (gray bars; Ecc<sub>dob</sub> - Ecc<sub>baseline</sub>) should predict changes after reperfusion (at follow-up; solid bars; Ecc<sub>follow-up</sub> - Ecc<sub>baseline</sub>). These intramyocardial changes were computed in regions with (A) and without (B) inotropic reserve on different PET patterns. After successful reperfusion by surgical revascularization, a consistent functional improvement was observed in regions without preoperatative inotropic reserve (B) and considered viable on PET. Of the 242 regions without inotropic reserve, 114 (47%) showed postoperative functional improvement. Values are means ± SE; n, number of studied regions. *P < 0.05 vs. infarcted regions. [From Mazzadi et al. (114).]
severe CAD in whom the dobutamine response (assessed by tagged MRI) was related to different PET patterns of perfusion and glucose uptake; we showed an abnormal intramyocardial dobutamine response in a large proportion of regions that appeared normal by PET, including those fed by angiographically patent coronary vessels (113).

In conclusion, all these findings are consistent with a greatly altered myocardial pattern of inotropic reserve in patients with severe LV dysfunction. Consequently, the utility of inotropic reserve testing for stunning is probably moderate in these patients.

REVIEW OF MECHANISMS LEADING TO REVERSIBLE MECHANICAL DYSFUNCTION

Myocardial Wall Stress

It is well known that ventricular wall stress is an essential factor that increases myocardial energetics (66); less well known, however, is its role as a negative modulator of cardiac mechanics under pathophysiological conditions.

With regard to myocardial energetics, early experiments in papillary muscles showed that passive stress-mediated myocardial stretch significantly increases resting heat production (106). A positive effect of stretch on oxygen consumption was demonstrated in intact quiescent rat hearts exposed to increased ventricular preload (15) and also in humans; a good direct linear correlation was found in normal volunteers and in patients (with chronic pressure overload, chronic volume overload, or CAD) between end-diastolic and peak systolic stress, on the one hand, and LV oxygen consumption, on the other (72, 153). Increased energetic demand caused by wall stress could explain experimental (46, 63) and clinical findings of surprisingly high oxygen consumption and, consequently, impaired mechanical efficiency in dysfunctional regions in patients with CAD (70). It is of note that mechanical efficiency...
was also reduced in animal models of myocardial stunning (94, 115) and in dysfunctional human myocardium after unstable angina (i.e., suspected acute stunning) (64).

The negative modulation of cardiac mechanics by wall stress was explored by tagged MRI in patients presenting first-reperfused myocardial infarction (MI) (135). Rademakers et al. (135) studied regional ejection fraction as a function of corresponding regional loading. Regional ejection fraction reflects the contribution of each region to the global LVEF; regional loading was computed by a parameter approximating wall stress. Regional ejection fraction showed a significant inverse correlation with regional loading, suggesting that regional mechanical performance decreases as regional wall stress increases (135). Inverse correlations between regional parameters of systolic function and wall stress were similarly reported in patients with first-reperfused MI (with use of 3-dimensional MRI) (38), in patients with known or suspected CAD (with use of echocardiography) (172), and in hypertensive patients with concentric remodeling (with use of echocardiography) (139). The explanation for such observations is unclear, and further studies are necessary to correctly interpret these correlations in patients presenting ischemic or hypertrophic territories, in which systolic function is also influenced by factors other than wall stress.

Wall stress drastically increases myocardial energy expenditure and represents a loading component that negatively influences mechanical deformation. These findings support the idea that a pathological rise in wall stress may greatly contribute to mechanical impairment.

**LV remodeling and wall stress in animal models and first-MI patients.** Ischemic insult contributes to the appearance and progression of the alteration in LV architecture known as ventricular remodeling (54–56), a complex process defined as molecular, cellular, interstitial, and genome expression changes that manifest clinically as changes in the size, shape, and function of the heart after cardiac injury (35). In this review, we have basically focused on macroscopic anatomic alterations affecting wall stress that, according to Laplace’s equation, are directly proportional to LV pressure and chamber radius and inversely proportional to wall thickness.

Experimental studies have revealed that ventricular remodeling involves ventricular dilation (6, 102, 123) accompanied by a severalfold increase in LV end-diastolic pressure (6, 7, 102). Recently, the time course and geometry of these alterations have been described (59) by late contrast-enhanced MRI, an imaging technique using injected gadolinium-diethylene triamine pentaacetic acid (an extracellular contrast agent), which results in late high-resolution images in which myocardial damage appears hyperenhanced (Fig. 1c) (165, 167). In this study, consistent ventricular dilation, together with changes in LV shape leading to an increased curvature radius, was shown in dogs subjected to coronary occlusion. Hypertrophy in viable myocardium (even when total LV mass did not increase) and infarct expansion followed by resorption and concomitant regional thinning (i.e., wall thickness reduction) were also observed (59).

The above-described experimental findings are consistent with observations in first-MI patients undergoing tagged MRI and PET (16). Increased end-diastolic volumes and diffuse changes in LV shape and morphology were reported. Geometric changes notably involved an evolution of LV shape from conical to spherical (even in remote scintigraphically normal regions), as previously reported using other imaging techniques (10, 38, 118).

In animal models of myocardial damage or after MI in humans, ventricular remodeling alters the major determinants of wall stress; consequently, it is not surprising that an increase in wall stress has been found in both settings (6, 7, 38, 102). Interestingly, in both settings, functional impairment has been reported in the remote myocardium of dilated LV presenting geometrical alteration (16, 96, 122). Whether increased wall stress causes this functional impairment remains unknown.

**LV remodeling and wall stress in CAD.** All the above-mentioned architectural alterations also occur, although in a more complex fashion, in severe CAD and contribute to progression of the systolic and diastolic abnormalities reported in these patients. The ischemic systolic dysfunction, superimposed on the use of preload to increase cardiac output (e.g., during exercise) (29, 71, 85), can cause an even greater increase in LV chamber volume because of the inability to eject blood. Thus severe CAD is associated with several degrees of LV end-diastolic and end-systolic volume enlargement (33, 134) as well as with increased LV end-diastolic pressure (20, 29, 152). In addition, LV end-diastolic pressure can increase in the presence of altered myocardial compliance (caused by tissue stiffening), which can boost resistance to mechanical deformation. Thus increased stiffness is a factor leading to decreased systolic function. Myocardial stiffness has been shown to be increased in infarct scar areas (14, 130), but several experimental and clinical studies further indicate that it is also increased in noninfarcted regions, including nonischemic, scintigraphically normal, myocardium (14, 49, 97, 109).

Finally, alterations in LV volume, pressure, shape, and morphology are consistent with the increased peak systolic and diastolic wall stress reported in severe CAD (33, 132–134, 164). Such increased wall stress would tend to alter myocardial energetic and mechanical performance.

**Reverse remodeling and wall stress.** Does reperfusion reverse the above-mentioned changes during ventricular remodeling?

A postoperative decrease in wall stress can be inferred from the morphological changes associated with reverse remodeling. Most recent studies addressing the impact of surgical revascularization in large populations of patients with CAD have shown a consistent reduction or a clear trend to a reduction in LV end-diastolic and end-systolic volume (20, 28, 30, 73, 86). These echocardiographic results were confirmed by quantitative gated SPECT (81), an imaging technique that uses electrocardiography to synchronize image frame acquisition and enables imaging of the cardiac cycle (166). The reduction in LV volume relates to a reduction in chamber radius and, thus, wall stress. Reduced intracavity pressure could also account for the reduction in wall stress. Although the above-mentioned studies did not examine the associated impact on intracavity pressure (probably for ethical reasons), evidence from small groups of patients shows that the reduction in LV volume is accompanied by a reduction in intracavity pressure (29, 82). Finally, improved wall thickness could also reduce wall stress; gated SPECT and MRI studies demonstrated that reperfusion improves wall thickness not only in revascularized (81, 89, 147), but also in nonrevascularized, regions (81), as in remote, scintigraphically normal, myocardium.
On the other hand, reduced wall stress may be accompanied by changes in myocardial compliance, which should theoretically contribute to mechanical improvement. Although reperfusion is unlikely to reduce chronic stiffening caused by gross structural change (such as postinfarction scarring), it has been reported that abnormally increased stiffness is partially reversible in viable regions (82, 117, 130).

Briefly, despite the lack of direct measurements, a consistent reduction in wall stress associated with reverse remodeling after reperfusion is a logical and, indeed, very likely hypothesis. However, such a reduction would not necessarily reverse the mechanical consequences of chronically enhanced wall stress. The following question, therefore, remains: Does the reversion of wall stress after reperfusion attenuate its negative chronic impact on systolic function?

Clinical studies of surgical ventricular restoration support the idea that total or partial reversion of chronically increased wall stress has a positive impact on cardiac mechanics. Surgical ventricular restoration consists in rebuilding the chamber by exclusion of scarred myocardium and is thus associated with rapid and drastic LV change, leading to a sharp reduction in parameters influencing wall stress. Surgical ventricular restoration could be considered a "model" for studying the interrelation between LV shape and wall stress and mechanics. In addition, the change in LV morphology after reconstructive surgery, to some extent, matches that described in severe CAD after reperfusion: reduction in LV volume, intracavity pressure, and chamber radius and changes in LV geometry leading to a more normal shape (44, 53). Moreover and, again, similar to reperfusion in CAD, surgical ventricular restoration also generally improves LV diastolic compliance (90) and intraventricular mechanical asynchrony (42). All these changes subsequent to surgical ventricular restoration have been shown to be associated with increased LVEF and improved regional function, as indicated by increased wall thickening (41, 44, 53). Tagged MRI has revealed improved intramyocardial lengthening in terms not only of extent but also a more radial orientation (95), rendering contraction more "effective" in terms of ejection. Finally, two points are worth stressing in regard to the functional changes associated with surgical ventricular restoration: 1) systolic functional improvement was mostly reported in normal remote regions (44, 95), and 2) in all the studies referred to above, follow-up assessments were made shortly after surgical ventricular restoration, showing that the time course of the observed functional change was rapid, as reported in the case of suspected myocardial stunning (12, 64).

In conclusion, it is possible that reversion of wall stress after reperfusion positively influences systolic function in severe CAD. Such a possibility could help explain why improvement in LVEF after revascularization in patients with severe CAD correlates significantly with reduction in LV end-diastolic volume (86).

Tethering Effect

Impaired systolic performance in ischemic regions contributes to a fall in LVEF in severe CAD. However, decreased LVEF could also be partially caused by the functional abnormality secondary to ischemia found in remote myocardial regions fed by patent vessels (47, 62, 83, 168). In animal models of coronary occlusion, it has been demonstrated that regional systolic alterations are not restricted to the center and lateral border of an ischemic region, rather, that their severity is a function of proximity to the ischemic region (83). Thus systolic shortening in remote regions (assessed by length gauges) has been found to be 65% of control values (168). In contrast to the narrow border zones for perfusion and metabolism found in acute ischemia (75, 170), functional border zones were reported up to 25 mm from the ischemic border (104).

This effect, called "tethering," displays a rapid time course that parallels changes in the ischemic region (168) and has usually been explained in terms of physical phenomena. Since the classic studies by Henderson et al. (76) and Tyberg et al. (158) in an isolated muscle preparation, it has been recognized that dysfunctional ischemic fibers contracting alongside normal fibers cause mechanical resistance. Consequently, in patients with severe LV dysfunction, dysfunctional ischemic fibers acting "in parallel" with normal fibers might be expected to function as a parallel resistance, altering the systolic performance of the normal fibers. Additionally, two factors in CAD patients may amplify the tethering effect: 1) LV asynchrony due to reciprocal contraction and relaxation in opposing myocardial regions (141) and 2) increased myocardial stiffness (14, 49, 97).

Given the causes of the tethering effect and its amplification, it should be inferred that it could be, at least partially, reversed by reperfusion. First, reperfusion improves systolic mechanical performance in ischemic regions capable of interacting via the tethering effect with nonischemic myocardium. Second, reperfusion has been shown to partially reverse abnormal LV pressure decay and LV asynchrony during ejection. That is, enhanced relaxation and contraction in the previously ischemic myocardium help correct interregional functional asynchrony (50, 68). Finally, reperfusion also improves myocardial stiffness (82, 117, 130).

Myocardial Expression and Release of Auto- and Paracrine Agents

Severe CAD is accompanied by interactive changes in myocardial gene expression and release of a variety of auto- and paracrine agents. The balance between the distinct patterns of myocardial response to these agents will modulate phenotypic outcome, for instance, mechanical performance and myocardial hypertrophy, which shows a varied geometric pattern in severe CAD (172). It may be speculated that the time course of these processes could be longer than for the other pathophysiological mechanisms that are thought to lead to mechanical dysfunction in severe CAD, such as wall stress and the tethering effect.

Two of several inducers of myocardial expression and release play a key role in the development of CAD: 1) hemodynamic overload and 2) inflammation. Both act over the whole of the heart, including any scintigraphically normal regions.

Hemodynamic overload. The notion that hemodynamic overload, and the associated ventricular dilation and increased wall stress, could act as a trigger for myocardial gene expression and release of numerous agents is entirely consistent with experimental and clinical observations. For instance, the influence of wall stress on increased release of ANG II (an agent that modulates cardiac hypertrophy) was demonstrated in iso-
lated stretched myocytes (140) and, subsequently, in isolated rat heart preparations exposed to ventricular dilation (84). In turn, ANG II formation was increased by wall stress in patients with aortic regurgitation (i.e., volume overload) (149) and in patients with heart failure secondary to dilated cardiomyopathy or ischemic cardiomyopathy (148).

In the experimental setting, increased wall stress secondary to ventricular dilation was shown to modulate expression of several agents, such as endothelin-1 (105), atrial natriuretic peptide (105), IL-6 (127), TNF-α (127), and insulin-like growth factor (IGF-I) (119, 120, 127).

In humans, IGF-I and TNF-α have been particularly implicated as causes of mechanical dysfunction secondary to increased wall stress. Generation of IGF-I (an agent that displays a positive inotropic effect) is no longer detectable within severely stretched myocardium, whereas TNF-α (displaying a negative inotropic effect) is upregulated. These findings have been promoted as partially accounting for the functional depression in dilated stretched myocardium (148, 149).

On the other hand, seminal studies of the link between mechanical forces and myocardial remodeling have pointed out that wall stress triggers programmed myocyte cell death (apoptosis). In normal rat papillary muscles, myocardial stretch is associated with markedly increased apoptosis, increased production of endogenous superoxide (a suicide program activator), and increased expression of Fas protein (a cytotoxic death receptor) (32). These initial in vitro simulations of in vivo diastolic overload suggest that myocardial wall stress acts directly by increasing apoptosis. Subsequent studies in isolated rat myocyte (100) and in a sheep model of chronic moderate heart failure (88) confirmed the association between wall stress and myocardial apoptosis.

In humans, the association between wall stress and apoptosis has not been established in a substantial number of patients with ischemic disease. However, apoptosis, particularly in the subendocardium, was reported in a small number of patients with dilated cardiomyopathy (in some cases caused by ischemic disease) (43). In addition, high apoptosis rates have been reported in postmortem specimens from patients with three-vessel CAD, especially in remote noninfarcted myocardium (13). Further studies, however, are necessary to determine the role of wall stress in these findings.

Inflammation. Although inflammation is less well known than the inflammatory process in experimental models of myocardial ischemic injury, a growing body of evidence suggests that inflammation in CAD patients modulates pathophysiological changes. The inflammatory processes involved in atherosclerosis are similar to those in chronic inflammatory fibroproliferative disease (e.g., rheumatoid arthritis and chronic pancreatitis) (143). The phenomenon involves several pathogenic processes, such as altered endothelial permeability (which allows macromolecule infiltration), high proinflammatory cytokine content, and inflammatory cell infiltrates. There is also evidence to suggest that immune activation accompanies inflammation (25, 160). Importantly, the cardiac inflammatory process is not confined to a single culprit, plaque, but may involve other segments of the coronary tree (24, 138). Thus the inflammatory infiltrate may affect all three vascular layers (121). Such diffuse inflammatory activation has been invoked (1), for example, to explain clinical cases characterized by multiple ruptured plaques (69), altered coronary perfusion, and abnormal perfusion in remote myocardial regions (8, 67).

In patients with CAD, the presence of myocardial inflammatory processes was first suggested by increased plasma levels of inflammatory markers (101, 155). Subsequently, evidence of the cardiac inflammatory process has been essentially confined to endothelial cells, interstitial cells, and adipose tissue (111, 124). Cardiac expression and release of several cytokines that mediate tissue inflammation (103, 107, 111, 128, 154, 157) and upregulation of monocyte chemotactic protein-1 and active leukocyte recruitment (60) have been reported. Furthermore, an active inflammatory infiltrate (activated T lymphocyte) was recently demonstrated not only in peri-infarct areas, but also in regions remote from the infarct area, in patients with recent MI (1).

Among the cytokines implicated in the pathogenesis of the disease, proinflammatory TNF-α has repeatedly been suggested to be an important contributor to myocardial contractile dysfunction. Several experimental findings point to a causal role for this cytokine in cardiac dysfunction. In cats, for instance, TNF-α exerts a negative inotropic effect in isolated myocytes and intact LV (171). In addition, transgenic mice with cardiac-specific TNF-α overexpression develop cardiac failure (23), and TNF-α has proved to be the mediator responsible for contractile dysfunction during experimental local inflammation by microembolization (45).

In humans, TNF-α leads to nitric oxide production via inducible nitric oxide synthase (91), the expression of which is increased in hypoxic and ischemic human hearts (48, 57, 58, 74). Thus TNF-α expression and release have been closely correlated to increased levels of nitric oxide, which in turn has a negative inotropic effect on the heart (48). It has been suggested that the negative inotropic effect of TNF-α may be mediated by increasing nitric oxide production. Nevertheless, it is likely that TNF-related myocardial dysfunction is due to nitric oxide-dependent and -independent mechanisms (92) and that increases in nitric oxide and TNF-α levels contribute directly to myocardial dysfunction in the ischemic heart.

In summary, hemodynamic overload and inflammation lead to myocardial expression and release of several agents potentially affecting mechanical performance. Whether such a gene expression and its phenotypic outcome are reversed by reperfusion remains obscure and speculative. As previously described, reperfusion is associated with wall stress diminution, which, in turn, could reduce the genetic expression and apoptosis associated with myocardial stretching. It is also possible that reperfusion may, as suggested by certain authors (60), promote resolution of ongoing inflammation, preventing further tissue injury. On the other hand, a certain degree of hypertrophy regression would be expected after reperfusion: some evidence in CAD patients shows that an increased LV wall mass index can be expected to regress after surgical revascularization (116). LV hypertrophy regression usually results in improved LV function (40).

CONCLUDING REMARKS

In conclusion, at least three pathophysiological mechanisms, in addition to stunning and hibernation, could lead to reversible mechanical dysfunction in severe CAD patients: 1) myocardial...
wall stress, 2) the tethering effect, and 3) myocardial expression and release of auto- and paracrine agents (Fig. 3). After reperfusion, the partial or total reversion of such mechanisms may account for the functional improvement in dysfunctional, but scintigraphically normal, regions, where stunning is usually considered. Thus, according to this view, the incidence of stunning may well be overestimated in these patients.

The above-mentioned mechanisms lead to reversible mechanical dysfunction throughout the viable myocardium. It is with this consideration in mind that we interpret recent results indicating that reperfusion provides a unexpected functional benefit that is not related to regionally enhanced postoperative perfusion. Further studies, however, are necessary to evaluate the impact of these mechanisms in reversible mechanical dysfunction.

An increasing body of evidence supports the idea that reperfusion has multiple benefits over and above myocardial salvage and functional improvement in stunned and hibernating myocardium. The magnitude of such benefits does not seem to be entirely predictable by current imaging methods used in myocardial viability studies. On the other hand, an increasing number of patients can benefit from safe reperfusion procedures, as demonstrated by decreased postoperative rates of mortality and cardiac events. In this context, clinicians should probably reconsider in which cases it is necessary to order sophisticated and expensive imaging studies to predict the functional outcome of reperfusion at a regional level.

REFERENCES


Review


