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

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Abstract

Patients with severe chronic coronary artery disease 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 present in 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 article reviews three of these 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 para-crine 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 over the whole 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.
Introduction

Summary of clinical problem

In recent years, the 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 the reversible left ventricular (LV) dysfunction arising from brief coronary occlusion and reflow (myocardial stunning), first described in animal models (80), to occur in humans. There are presently two major hypotheses to explain it: the oxyradical hypothesis proposes that oxidant stress impairs LV function (18), whereas the calcium hypothesis postulates that stunning results from disturbed myocyte calcium homeostasis (98). In 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 thereafter refined when ultrastructural investigations found that hibernating myocardium shows a distinctive morphology, generally without necrosis, but with loss of sarcomeres and myofibrils (suggesting a “de-differentiation” process towards an embryonic phenotype), with loss of mitochondria and increased glycogen storage (9, 19, 27, 162).

The clinical recognition that dysfunctional ischemic regions without signs of scarring could potentially improve their mechanical performance after reperfusion gave rise to the study of so-called myocardial viability. The clinical interest of 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 functioning, heart failure symptoms and survival. Consequently, various imaging methods have been deployed to detect viability, with the ultimate aim of predicting outcome (and especially functional outcome) after reperfusion therapy. Scintigraphic methods 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 pharmacologic stress, of myocardial cellular integrity, perfusion and metabolism (for example, 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, the presence of inotropic reserve (i.e., improved contractile function during inotropic stimulation) was suggested as an indicator of 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 (echocardiography or Magnetic Resonance Imaging (MRI)). The ability of the various imaging methods to detect viability (and to predict functional outcome) has been periodically reviewed in depth, providing guidelines for investigation and patient management (159, 167).

Despite sustained efforts and methodological advances, however, the study of myocardial viability still suffers from important limitations. This has been attributed to several factors such as technical limitations of the imaging methods used, or the lack of a standardized protocol and definition of viability, making it difficult to compare the existing results (167). Viability assessment may be especially problematic in chronic severe coronary artery disease (CAD) patients (i.e., presenting multi-vessel CAD, severe LV dysfunction and risk factors), where the underlying complexity of the disease could introduce confounding factors hindering accurate interpretation of the phenotyping given by the imaging methods. For example, regional functional performance may be difficult to assess clinically, given 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 these chronic CAD patients some degree of overlap could occur between stunning, hibernation and scarring (see below).

**Stunning, hibernation and scarring: the 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 inter-related gradual ultra-structural alterations at myocyte level (26). Several studies using PET (79) reported reduced resting perfusion in hibernating regions, supporting the idea that decreased contractile performance is downregulated by hypoperfusion. More recently, hibernating regions were also found hypoperfused using first-pass MRI (147), an imaging technique that can follow the progression of the intramyocardial signal during the first pass of injected contrast medium (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 vasodilatation) (163), suggest that repetitive transient ischemia (“repetitive stunning”) finally leads to chronic hibernation (108, 163). In turn, chronic hibernation - in 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 of severe CAD as a permanent evolutive cascade of gradual myocyte degeneration accompanied by cellular infiltration, cytokine release, residual edema, hemorrhage and resorption.

The 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 as 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 as yet be unequivocally documented in the clinical setting, it is usually agreed that repetitive stunning does occur in dysfunctional but scintigraphically normal regions displaying relatively rapid
functional improvement after reperfusion. Consequently, some recent investigations involving severe CAD patients reported a high incidence of dysfunctional but scintigraphically normal regions, considered as stunned (12, 21, 77, 142). According to some authors, up to 72% of dysfunctional regions found in CAD patients present scintigraphically normal patterns (77). In such normal regions, the time course of functional recovery after reperfusion was previously 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. It is noteworthy, however, that some degree of overlap between stunned and hibernating regions could exist in terms of the time course of the functional improvement after reperfusion. Whereas 61% of regions defined as stunned have been found to improve mechanical performance 3 months after reperfusion (12), the 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 functional outcome after revascularization in severe CAD patients (114). The consequences of the ischemic injury were characterized by integrating perfusion and glucose-uptake PET measurements. Inotropic reserve was assessed preoperatively with dobutamine (a beta-adrenergic agonist) to identify those regions susceptible of postoperative functional improvement. Intramyocardial mechanical performance was quantitatively assessed by tagged MRI, an imaging technique that creates “tags” (Fig. 1, d), by presaturating planes of tissue, which appear on the image as a dark grid pattern moving and deforming along with the myocardium (37, 173). The study found revascularization to provide greater intramyocardial functional benefit than would be expected from the preoperative inotropic reserve assessment. In fact, postoperative functional improvement was observed in a large proportion of PET-viable regions (i.e., normal, hibernating and moderately scarred regions) without dobutamine response (Fig. 2) (114). Although not actually new, these findings confirm and complement certain previous reports highlighting a reduced negative predictive value of inotropic testing.
for functional improvement after reperfusion. Thus, in CAD patients undergoing dobutamine echocardiography before angioplasty, Alfridi et al. highlighted the finding that “interestingly, 35% of segments with a worsening response during dobutamine had recovery of resting function” (2). In another study with a similar patient population, 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) (126). Moreover, tagged-MRI studies of viability after infarction also demonstrated that intramyocardial mechanical performance can increase “markedly” on follow-up in dysfunctional regions that had not responded to dobutamine (65).

The above findings concern the relationship between perfusion and inotropic reserve, and its 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). It is with this consideration in mind that it is usually accepted that most regions showing inotropic reserve (before reperfusion) could benefit from reperfusion in terms of mechanical performance, thanks to 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 postoperative functional improvement found 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 article is that pathophysiological mechanisms other than stunning could play a major role in explaining 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 partially be responsible for the functional benefit following reperfusion highlighted in regions without inotropic reserve by high spatial resolution imaging methods.
Objectives

The present article discusses the causal role attributed to myocardial stunning in the reversible mechanical dysfunction observed in scintigraphically normal regions in severe CAD patients. First, we shall briefly present the complexities underlying imaging diagnosis of stunning in these patients. Next, we shall review three pathophysiological mechanisms (other than those involved in stunning) that could lead to such reversible mechanical dysfunction: myocardial wall stress, the tethering effect, and myocardial expression and release of auto- and para-crine agents. These mechanisms are generally seen as concerning scintigraphically normal regions – in which stunning is usually suspected; but they can also operate over the whole viable myocardium.

The proposed mechanisms, taken singularly, have been in general investigated by basic researchers. Few information exists concerning the participation of these mechanisms in severe CAD. In this article we compile the evidence suggesting the presence of these mechanisms in severe CAD, and we specially focus, when available, on the imaging findings testifying for such a presence. The Fig. 3 schematically illustrates the proposed mechanisms involved in reversible mechanical dysfunction in severe CAD. Of note that, since the outcome of revascularization has been shown to be quite variable, we shall focus on those patients in whom functional improvement after successful reperfusion is usually seen (11, 39, 169).

Imaging diagnosis of stunning in severe CAD

While myocardial hibernation and scarring can now be fairly reliably demonstrated in the clinical setting by cardiac imaging techniques, unequivocal demonstration of myocardial stunning 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
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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 a prolonged but reversible postischemic LV dysfunction occurring in the aftermath of a coronary occlusion of a severity or duration insufficient to produce myocardial necrosis (22). Consequently, as underlined by Ambrosio et al. (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 wide perfusion value variation within and between individuals (31, 78), rendering the use of absolute perfusion values in assessing the normality of perfusion after reperfusion questionable. In fact, subtle reductions in regional perfusion due to moderate ongoing ischemia or moderate endocardial necrosis (Fig. 1, c) may go unnoticed on PET (Fig. 1, b). Moreover, most clinical studies fail to define mechanical performance, giving semi-quantitative scores rather than absolute values for full wall thickening (Fig. 1, a), generally in large myocardial regions and using echocardiography.

In addition, identifying myocardial stunning by testing 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., presence of inotropic reserve) (115). However, the normal pattern of inotropic reserve can be greatly altered during severe LV dysfunction, casting doubt on such an observation in this context. Experimental data from MRI have revealed that the inotropic response is blunted in the remote myocardium of rats showing a drastic drop in cardiac output (122). In patients with severe LV dysfunction, Skopicki et al. (151) reported that an abnormal response to dobutamine frequently occurred in regions contracting...
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normally and classed as normal by PET, with a normal hyperemic response to adenosine, and fed by a patent coronary vessel. The authors conclude that the absence of inotropic reserve is 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 Skopiki's observations in a group of severe CAD patients in whom the dobutamine response (assessed by tagged MRI) was related to different PET-patterns of perfusion and glucose uptake, highlighting an abnormal intramyocardial dobutamine response in a large proportion of PET-normal regions, 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.

Concerning 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 both 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 in CAD patients (70) of surprisingly high oxygen consumption and consequently impaired mechanical
efficiency in dysfunctional regions. Of note that mechanical efficiency was also found to be 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). The authors 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 likewise reported in patients with first reperfused MI (using 3-D MRI) (38), with known or suspected CAD (using echocardiography) (172), and in hypertensive patients with concentric remodeling (using echocardiography) (139). The explanation for such observations is unclear, and further studies will be necessary to correctly interpret these correlations in patients presenting ischemic or hypertrophic territories, in which the systolic function is also influenced by factors other than wall stress.

In fact, 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 humans with first MI. 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 work, we basically focus on macroscopic anatomical alterations affecting wall stress that, according to Laplace’s equation, is 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 several-fold 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-DTPA (an extracellular contrast agent) that results in late high-resolution images in which myocardial damage appear hyperenhanced (Fig. 1, c) (165, 167). This study, in dogs subjected to coronary occlusion, showed consistent ventricular dilation together with changes in LV shape leading to an increased curvature radius. 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 experimental findings are in agreement 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. Geometrical 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).

Ventricular remodeling, in animal models of myocardial damage or following MI in humans, alters the major determinants of wall stress: it is consequently not surprising that wall stress has been found to be increased in both settings (6, 7, 38, 102). Interestingly, in both of these 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 architectural alterations also occur - although in a more complex fashion - in severe CAD and contribute to the 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 (for instance, 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 presence of altered myocardial compliance (caused by tissue stiffening), a booster factor in resistance to mechanical deformation. Thus, increased stiffness represent itself a factor leading to decreased systolic function. Myocardial stiffness has been shown to be increased in
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Infarct scar areas (14, 130), but several experimental and clinical studies further indicate that it is also increased in non-infarcted regions, including non-ischemic scintigraphically normal myocardium (14, 49, 97, 109).

Finally, the alterations in LV volume, pressure, shape and morphology are in line 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 both myocardial energetic and mechanical performance.

Reverse remodeling and wall stress.

Does reperfusion reverse the above changes during ventricular remodeling?

A postoperative decrease in wall stress can be inferred from the morphologic changes associated with reverse remodeling. Most recent studies addressing the impact of surgical revascularization in large CAD populations have shown a consistent reduction – or a clear trend to 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 using electrocardiography to synchronize image frame acquisition and that enables the imaging of the cardiac cycle (166). It is noteworthy that the reduction in LV volume relates to a reduction in chamber radius, and thus in wall stress. Reduced intracavity pressure could also account for the reduction in wall stress. Although the above studies did not examine the associated impact on intracavity pressure (probably for ethical reasons), evidence from small groups of patients shows that LV volume reduction is accompanied by a reduction in intracavity pressure (29, 82). Finally, improved wall thickness could additionally reduce wall stress: gated SPECT and MRI studies demonstrated that reperfusion improves wall thickness not only in revascularized (81, 89, 147) but also in non-revascularized regions (81), as is the case with 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. While reperfusion is unlikely to reduce chronic stiffening caused by gross structural change (such as post-infarction 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 reduction would not necessarily reverse the
mechanical consequences of chronically enhanced wall stress. The following question, therefore, remains as to whether the reversion of wall stress following reperfusion attenuates 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 excluding scarred myocardium, and is thus associated with rapid and drastic LV change leading to a sharp reduction in parameters influencing wall stress. In this regard, surgical ventricular restoration could be considered as a “model” for studying the inter-relationship between LV shape, 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 similarly to reperfusion in CAD, surgical ventricular restoration also generally improves LV diastolic compliance (90) and intraventricular mechanical asynchrony (42). All these changes following surgical ventricular restoration have been shown to be associated with increased LVEF and improved regional functioning as indicated by increased wall thickening (41, 44, 53). Tagged MRI has moreover revealed improved intramyocardial lengthening in terms not only of extent but also of 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: a) systolic functional improvement was mostly reported in normal remote regions (44, 95); and b) 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, the possibility is open that wall-stress reversion after reperfusion positively influences systolic functioning in severe CAD. Such a possibility could help to explain why improvement in LVEF after revascularization in severe CAD patients 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, but 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, parallel with changes in the ischemic region (168), and has usually been explained in terms of physical phenomena. Since the classic studies by E.H. Sonnenblick’s group in isolated muscle preparation (76, 158), 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 existing in CAD patients may amplify the tethering effect: LV asynchrony due to reciprocal contraction and relaxation in opposing myocardial regions (141), and 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. Firstly, reperfusion improves systolic mechanical performance in ischemic regions capable of interacting via the tethering effect with non-ischemic myocardium. Secondly, 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 helps correct inter-regional functional asynchrony (50, 68). Finally, reperfusion also improves myocardial stiffness (82, 117, 130).
Myocardial expression and release of auto- and para-crine agents

Severe CAD is accompanied by interactive changes in myocardial gene expression and release of a variety of auto- and para-crine 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 thought to lead to mechanical dysfunction in severe CAD: i.e., wall stress and the tethering effect.

Two of the several inducers of myocardial expression and release play a key role in the development of CAD: hemodynamic overload, and 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 angiotensin II release (AII, an agent modulating cardiac hypertrophy) was demonstrated in isolated stretched myocytes (140) and subsequently in isolated rat heart preparations exposed to ventricular dilation (84). In turn, AII formation was found to be 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 to ischemic cardiomyopathy (148).

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

In humans, two of the above factors, IGF-1 and TNF-\(\alpha\), have been particularly implicated as causing mechanical dysfunction secondary to increased wall stress. Generation of IGF-1 (an agent displaying a positive inotropic effect) is no longer detectable within severely stretched myocardium, whereas TNF-\(\alpha\) (displaying a negative inotropic effect) is up-regulated. These findings have been put forward as
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partially accounting for the functional depression present 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 cytokine 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 yet been established in a substantial number of patients with ischemic disease. However, apoptosis particularly located 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 post-mortem specimens from three-vessel CAD subjects, especially in remote non-infarcted myocardium (13). Further studies, however, will be necessary to determine the role of wall stress in these findings.

Inflammation. Although less well-known than the inflammatory process in experimental models of myocardial ischemic injury, a growing body of evidence suggests that inflammation does occur in CAD patients, modulating pathophysiological changes. In fact, the inflammatory processes involved in atherosclerosis are so far similar to those occurring in chronic inflammatory fibroproliferative disease (for instance, rheumatoid arthritis or chronic pancreatitis) (143). The phenomenon involves several pathogenic processes, such as altered endothelial permeability (allowing macromolecule infiltration), high pro-inflammatory 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 CAD patients, the presence of myocardial inflammatory processes was firstly suggested by the observation of increased plasma levels of inflammatory markers (101, 155). Subsequently, evidence of the cardiac inflammatory process has been found essentially confined to endothelial cells, interstitial cells and adipose tissue (111, 124). Cardiac expression and release of several cytokines, which mediate tissue inflammation (103, 107, 111, 128, 154, 157), and up-regulation of monocyte chemotactic protein-1 and active leukocyte recruitment (60) have been reported. Furthermore, the presence of 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 put forward as 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 have a negative inotropic effect on the heart (48). In fact, it has been suggested that the negative inotropic effect of TNF-α may be mediated by increasing nitric oxide production. Even so, it is likely that TNF-related myocardial dysfunction is due to both nitric oxide-dependent and nitric oxide-independent mechanisms (92), and that increases in both 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). As has been noted, LV hypertrophy regression usually results in improved LV function (40).

Concluding remarks

At least three pathophysiological mechanisms, in addition to stunning or hibernation, could lead to reversible mechanical dysfunction in severe CAD patients: myocardial wall stress, the tethering effect, and myocardial expression and release of auto- and para-crine agents (Fig. 3). After reperfusion, the partial or total reversion of such mechanisms may therefore 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 currently overestimated in these patients.

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

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

References
The alternatives to myocardial stunning


The alternatives to myocardial stunning


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FIGURE LEGENDS

Fig. 1: Late (1 month) imaging after first latero-inferior myocardial infarction. Reperfusion (re-opening of a marginal branch of the circumflex artery) was performed at the 6th hour. Troponin I culminated at 38 ng/ml. Echocardiographic assessment at day 6 showed moderate lateral hypokinesis and LV ejection fraction at 60%. One month later, wall thickening on cine-MRI (a) and perfusion by PET (b) were normal in the area previously characterized as hypokinetic by echocardiography. However, the late contrast-enhanced MRI image (c) highlighted a thin subendocardial necrosis (arrows) and tagged MRI (d) detected lateral intramyocardial dysfunction. While a) and b) suggest full recuperation, images c) and d) point to remaining damage. Thus, the characterization of regional tissue and conclusions about the disease’s evolution could differ with different imaging methods.

It is of note that the myocardial image of perfusion (b) (computed from PET series after the injection of H$_2^{15}$O) does not indicate perfusion defects in damaged territories (regions 1 and 2). Moreover, absolute myocardial perfusion values in these regions (computed using a one-compartment kinetic model) were in the range usually considered as normal: 0.86 and 0.83 ml/min/g (in 1 and 2 respectively). It is noteworthy that myocardial perfusion in a remote territory (region 3) was 0.91 ml/min/g.

Fig. 2: Tagged MRI enables the quantitative assessment of intramyocardial change in circumferential shortening (Ecc). The Ecc changes under dobutamine (grey bars; Ecc$_{doba}$- Ecc$_{baseline}$) should predict changes after reperfusion (at follow-up ) (black bars; Ecc$_{follow-up}$- Ecc$_{baseline}$). These intramyocardial changes were computed in regions with (Dob+) or without (Dob-) inotropic reserve on different PET-patterns. After successful reperfusion by chirurgical revascularization, a consistent functional improvement was observed in regions without preoperative inotropic reserve (Dob-) and considered viable on PET. Of the 242 regions without inotropic reserve, 114 (47%) showed postoperative functional improvement.

*p<0.05 vs infarcted regions. n= number of studied regions. Bars represent S.E.M. [from Mazzadi et al. (ref. 114)].
**Fig. 3:** Schematic recordings of regional mechanical performance (Illlllll) to illustrate the process involved in reversible mechanical dysfunction in severe CAD. The ischemic (Isch.) injury results in stunned (stunn.), hibernating (hibern.) and infarcted (scarred) regions. All these regions exhibit a varying degree of dysfunction that will influence the mechanical performance of adjacent regions, for instance, of remote normal regions. This “tethering effect” (Teth.) could be amplified by asynchrony (Async.) and increased myocardial stiffness (Stiff.). Moreover, increased stiffness represent itself a factor leading to impaired mechanical performance. Ventricular remodeling following ischemic injury greatly increases wall stress (increased left ventricular pressure (P) and radius, and wall thickness) and stretching, two factors playing a major role in myocardial energetics and mechanical dysfunction. For example, stretching is associated with tumor necrosis factor release (TNF-α, a negative inotropic agent), inhibition of insulin-like growth factor (IGF-1, displaying a positive inotropic effect) and increased apoptosis. In turn, inflammation related to CAD involves the release of TNF-α that leads to enhanced nitric oxide production (NO, displaying a negative inotropic effect). Functional and scintigraphic characterization before reperfusion therapy does not distinguish between normal and stunned regions, both of which presented normal perfusion and metabolism, mechanical dysfunction (in general, assessed qualitatively) and impaired mechanical efficiency (Mech. Effic.).

After reperfusion, functional improvement in stunned and hibernating regions could partially reverse the negative effect of tethering on mechanical performance. Normal and infarcted regions, for instance, could thus draw a functional benefit from reperfusion that is not essentially related to regionally enhanced perfusion. Moreover, diminution in wall stress associated with reverse remodeling and the hypothetic resolution of the inflammatory process after reperfusion could also contribute to improving mechanical performance over the whole myocardium. At the time of diagnosis, the “normal” mechanical performance observed in previously dysfunctional, scintigraphically normal regions could lead to such regions being wrongly considered as stunned.

Of note, this is a schematic view, and the time course and the magnitude of the involved process are hypothetic.