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Go with the flow

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Reperfusion is essential and urgent. In ST-segment elevation myocardial infarction (STEMI), this urgency is recognized by dedicated emergency plans and the medical student mantra, "time is muscle". It seems rather strange, therefore, to dedicate an issue of *Heart and Metabolism* to such an obvious necessity.

Reperfusion is the only means by which myocardium that remains viable within the ischemic zone can survive. The only exceptions to this rule are the 25% of individuals with sufficient collateral support to maintain resting myocardial blood flow despite acute obstruction of an epicardial coronary artery [1]. However, it is likely that such individuals never present with STEMI, but may instead have stable angina resulting from a collateral dependent circulation with abnormal flow reserve [2]. For the remaining 75%, with acute coronary artery occlusion, reperfusion is mandatory. So what are the controversies to which this issue is dedicated?

The prime controversy underpinning the Basic Article by Reffelmann and Kloner, Refresher Corner by Dhalla and Duhamel, and the discussion of New Therapeutic Approaches by Thibault and colleagues is the concept of reperfusion injury. The premise that underlies this concept is that myocardium maybe viable at the very onset of reperfusion, but dies subsequently; moreover, this death is not "predestined" by events occurring during ischemia, and hence can be prevented by manipulations during reperfusion. Despite more than two decades of intense debate, the arguments as to whether reperfusion injury even exists rage on. One of the authors of the Basic Article, Robert Kloner, helped originally publicize the dual role of reperfusion as both slayer and saviour, or double-edged sword [3]. However, it is clear from his Basic Article that he remains sceptical as to its existence. One of the difficulties with the concept of reperfusion injury is that it is very difficult to measure myocardial infarction, even histologically,

without reperfusion. Thus the arguments as to its existence revolve around the events that are known to accompany reperfusion and, in particular, the ionic fluxes, mitochondrial depolarization, and cell rupture with release of creatine kinase and troponin – events that are succinctly summarized in Refresher Corner. However, for the concept of reperfusion injury itself to be viable, and not die in the ensuing debate, there needs to be evidence that myocardial salvage can be enhanced by interventions after ischemia. There is now ample evidence from the basic laboratory that agents added to the reperfusate (eg, insulin, adenosine, opioids, and cyclosporin), and not present during ischemia, can reduce ultimate infarction. The only way this can occur is that an injurious component of reperfusion is attenuated. Thus, by definition, they are proof of the existence of reperfusion injury.

The presence and manipulation of reperfusion injury is of direct therapeutic importance, because it is clinically accessible. One of the fundamental problems with most cardioprotective therapies is the need, for maximal effect, for the protective agent to be present at the moment of coronary occlusion [4]. Unfortunately, for most patients, STEMI is unheralded and, for those with premonitory symptoms resulting in admission to hospital, efforts focus on preventing occlusion, rather than allowing occlusion and then alleviating its consequences. However, as pointed out by Thibault and colleagues, the increase in primary percutaneous coronary intervention (PCI) for STEMI provides an unprecedented opportunity to manipulate the moment of reperfusion and, thus, not only terminate ischemic injury, but also prevent subsequent injury during reperfusion. The seminal proof of concept of this strategy was originally reported by Ovize's group [5] and appears in detail within their New Therapeutic Approaches article in this issue. This group harnessed the concept of post-conditioning, which is also explained in detail in

Refresher Corner and the Basic Article. In essence, postconditioning is the slowing/interruption of the hyperemic phase of reperfusion to ease the accompanying chaos. By simply re-inflating the angioplasty balloon to obstruct flow immediately after successful primary PCI, Ovize's group were able to reduce infarction by 30% on average. Thus the concept of injury at early reperfusion has been translated, from laboratory observations made just 4 years [6] ago, into an intervention that may benefit patients.

Despite reperfusion injury being a focus of research in the laboratory, for the jobbing interventional cardiologist, the focus remains the attainment of prompt and high-quality reperfusion for all. Hence the Clinical Article by Webb and Redwood describes techniques for measuring the quality of reperfusion in the catheter laboratory. The premise underlying these techniques is that, because low reflow is associated with a poor outcome, it needs to be improved. Unfortunately, it is not clear which interventions will improve flow in the treated and unobstructed infarct-related artery. Furthermore, as Reffelmann and Kloner point out, low-reflow is most probably a manifestation of substantial infarction, rather than its cause. Thus it seems unlikely that agents to improve reperfusion will have a substantial impact. What about agents to worsen reperfusion? In view of the

findings of the study by Ovize et al [5], perhaps it is time to realize that there may be circumstances in which too much flow during the first minute or two of reperfusion should be avoided. I wonder if we will ever be measuring flow during primary PCI in order to prevent it being too good? For the time being, at least, we should definitely "go with the flow". ■

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Consequences of reperfusion

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Abstract

Coronary artery reperfusion after temporary coronary occlusion is the only measure that can prevent irreversible damage of cardiac tissue. The later that reperfusion is established, the less myocardial tissue can be salvaged: in the dog, complete salvage can be achieved after brief episodes of ischemia of less than 20 min, whereas nearly complete necrosis of the area at risk occurs with reperfusion after more than 6 h. Consequences of reperfusion may manifest as progressive microvascular damage (“no reflow”) in infarcted myocardium and reversible contractile dysfunction (“stunning”) in salvaged cardiomyocytes. Very brief ischemic episodes followed by reperfusion can put the heart into a “preconditioning” state, a condition that increases myocardial tolerance towards a long ischemic insult.

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Keywords: Ischemic preconditioning, myocardial salvage, no reflow, reperfusion, stunning

Introduction

In most species, coronary artery occlusion results in myocardial ischemia because the collateral circulation is insufficient to maintain adequate supplies of oxygen and substrate [1]. In effect, coronary reperfusion is the only means of restoring aerobic metabolism and preventing irreversible damage of cardiac tissue. Therefore, the consequences of reperfusion – the most important of which will be discussed in this review – are always implicitly the consequences of the preceding period of temporary ischemia. Factors that potentially determine the final consequences of reperfusion, in a qualitative or quantitative manner, are: the duration and severity of ischemia, the volume of the ischemic area at risk, adjunctive therapeutic interventions before and during ischemia, and energetic demands during ischemia. Whether the specific mode of reperfusion and adjunctive therapy given during reperfusion can influence the ultimate volume of necrosis remain under investigation.

Salvage of myocardium at risk

In the dog, proximal coronary artery occlusion for up to 20 min, followed by re-opening of the artery, results in reversible alterations to the myocardium; however, after more than 20 min, significant amounts of necrosis develop (*Figure 1*) [1–3]. In their landmark publication in 1977, Reimer et al [4] described a wavefront of myocardial necrosis progressing from the endocardial towards the epicardial surface of the canine heart as the duration of the coronary artery occlusion was increased. When the occluded circumflex coronary artery was re-opened after 40 min of ischemia, 38% of the myocardium at risk had become necrotic; after 3 h 57% developed necrosis, after 6 h 71% was necrotic, and after 24 h 85% became necrotic. In most experimental studies in the dog, reperfusion within a period of 6 h after the onset of ischemia was associated with significant subepicardial salvage, with variation depending upon the amount of collateral flow; after 6 h of coronary occlusion, nearly the entire area at risk was already necrotic [5,6]. However, if ischemia during coronary occlusion is more severe, for instance in

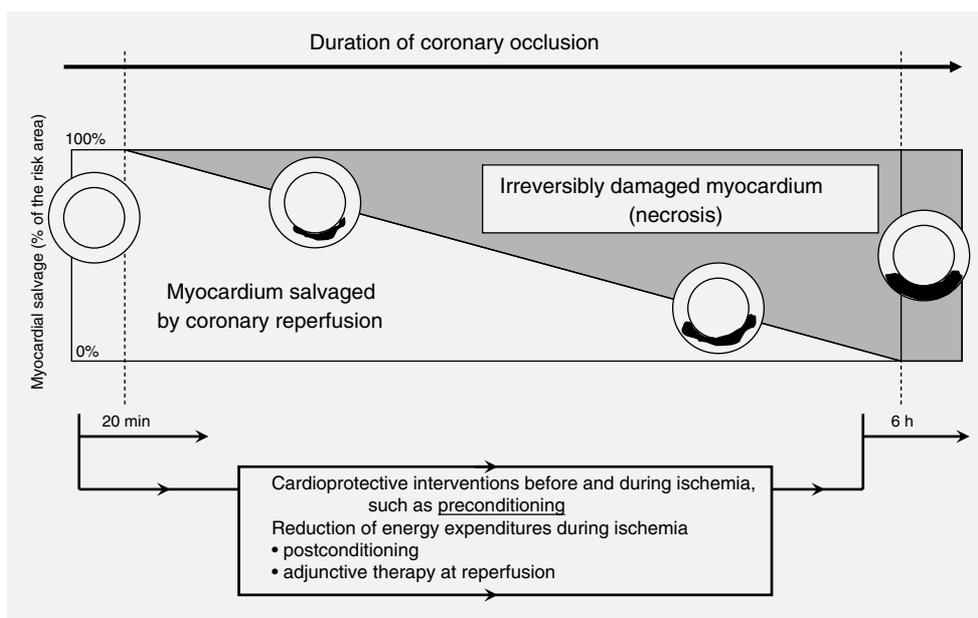


Figure 1. Schematic diagram illustrating the fundamental relationship between myocardial salvage and the time point of initiating coronary artery reperfusion in the dog. Myocardial salvage may be complete after very brief durations of ischemia; however, a progression of myocardial necrosis from the subendocardium towards the subepicardium occurs thereafter. When the coronary artery is reperfused very late, almost the entire area at risk becomes necrotic. Several factors and therapeutic interventions may shift the time frame into the direction of increased tolerance towards the ischemic insult.

species with negligible collateral flow, or when energy demands during ischemia are greater (for example as a result of increased tissue temperature or increased contractility), earlier reperfusion may be required in order to achieve myocardial salvage [7,8]. Moreover, certain cardioprotective interventions before or during ischemia such as ischemic preconditioning or pharmacologic interventions, and hypothermia during ischemia, may extend the period up to which reperfusion still results in complete or partial myocardial salvage [9–11]. In addition, final infarct size may not be invariably determined at the time when reflow is initiated: a “stuttering” reperfusion, termed “postconditioning” and referring to brief re-occlusions of the coronary artery early during the reperfusion period, may result in a smaller infarct size than occurs after an immediate, single and complete re-opening of the occluded artery [12]. The findings of many experimental investigations have also suggested that various adjunctive pharmacologic interventions during the reperfusion period may further reduce the size of the infarct. However, not all laboratories have observed benefits from therapies, such as postconditioning, that are initiated only at reperfusion [13].

Whether initiating reperfusion at a time when myocardial salvage is no longer achievable is of significant benefit (“open artery hypothesis”) remains a matter of debate [14]. Data from experimental studies have suggested that healing of infarcted tissue may be favorably influenced even by late coronary artery reperfusion, which could attenuate infarct expansion,

scar thinning, and aneurysmal dilatation beyond myocardial salvage [15].

In summary, reperfusion of ischemic myocardium will result in necrotic and salvaged myocardium within the risk area, ranging from complete salvage with very early reperfusion to almost complete necrosis with late reperfusion. Necrotic myocytes will eventually be replaced by scar tissue, but salvaged cardiomyocytes are characterized by various abnormalities that will normalize after a variable time course.

Morphologic and metabolic changes induced by reperfusion

With initiation of reflow, marked hyperemia (up to approximately 500% of basal flow) develops for approximately 15 min, restoring aerobic metabolism in reversibly altered myocardium [2–5]. Re-phosphorylation of adenine nucleotides to adenosine triphosphate, a pronounced increase in creatine phosphate, and normalization of lactate concentrations and pH are accompanied by transient swelling of mitochondria and cardiomyocytes [16,17]. During the first 10 min of reperfusion, oxygen-derived free radicals show a marked peak in concentration [18]. In addition, activation of a pattern of genes occurs during reperfusion, eventually leading to increased tissue concentrations of (for example) heat shock proteins and inducible nitric oxide synthase after 1 day of reperfusion [19].

Reversible contractile dysfunction: stunning

Prolonged, postischemic dysfunction of viable myocardial tissue salvaged by reperfusion, termed “stunning”, develops reproducibly after brief periods of ischemia followed by reperfusion. Despite adequate restoration of coronary flow, contractile dysfunction, in particular also diastolic dysfunction, may persist for periods ranging from hours to several days, depending on the duration and completeness of the initial ischemic insult. Besides this typical flow–contraction mismatch in stunning, another of its characteristics is that inotropic stimulation of stunned myocardium results in enhanced contractility without altering further recovery of the myocardium. Experiments using free radical scavengers have indicated that a major part of the stunning effect appears to be the result of desensitizing of the sarcolemmal contractile apparatus caused by the burst in oxygen-derived free radicals – mainly hydroxyl radical – during the first minutes of reperfusion [20]. Therefore, stunning can be described as a form of reperfusion injury that is, at least in part, induced by the reperfusion-induced burst in free radicals. Notably, contractile dysfunction is not completely preventable by oxygen-radical scavenging, which might reflect the incomplete effect of the radical scavengers or might point to additional, yet unidentified mechanisms leading to stunned myocardium.

Microvascular alterations

Paradoxically, re-opening of the coronary artery, the prerequisite for restoration of tissue reperfusion, may simultaneously initiate progressive microvascular damage, termed the “no-reflow phenomenon”. Despite complete restoration of epicardial artery patency, discrete perfusion defects may develop within the previously ischemic cardiac tissue during the first hours of reperfusion [21]. In the rabbit, regional myocardial blood flow, which was 2.06 ± 0.01 mL/min per g before ischemia, increased to 3.78 mL/min per g after 2 min of reperfusion following a period of 30 min of coronary occlusion; this was followed by a decline within 2 h of reperfusion, and a final plateau at about 0.9 mL/min per g by 2 and 8 h of reperfusion. Concomitantly, sizeable anatomic perfusion defects developed within the risk area, increasing from 12.2% of the area after 2 min of reperfusion to 30.8% and 34.9% at 2 and 8 h of reperfusion, respectively. These areas of no reflow were contained within the necrotic zone and finally comprised approximately 80% of the infarct size in this model [22]. Several pathophysiologic mechanisms for this phenomenon (including endothelial swelling and bleb formation, progressive leukocyte plugging, and vascular com-

pression by tissue edema) are under debate; however, this progressive vascular obstruction may be regarded as reperfusion injury at the microvascular level, with potentially significant prognostic implications [23].

Putting the heart in the “preconditioned” state by reperfusion

Brief coronary occlusions beneath the threshold for irreversible damage, followed by reperfusion, can induce cardioprotective effects via a complex, as yet incompletely understood, cascade of signals that renders the myocardium more tolerant towards a subsequent more prolonged ischemia insult [10]. This process is termed “ischemic preconditioning”. In the dog, infarct size is substantially reduced if an episode of 3–10 min of ischemia, followed by 5 min of reperfusion – the preconditioning procedure – precedes a longer episode of ischemia and reperfusion [24]. The cardioprotection conferred by such a preconditioning stimulus may no longer be detectable if the final ischemic insult is instituted after more than 3 h, but there seems to be a second window of delayed protection, evident if the long-duration coronary occlusion is performed 24–96 h after the preconditioning stimulus [25].

Summary

The earlier the coronary reperfusion is established, the greater the portion of myocardium that can be salvaged, thereby limiting the amount of myocardial necrosis. Nonetheless, reperfusion itself may also result in unfavorable consequences. The most important are progressive microvascular alterations (no reflow), and reversible contractile dysfunction of salvaged myocardium (stunning). Reduction of irreversible cardiomyocyte damage may be accomplished by administration of cardioprotective therapies before ischemia, such as preconditioning or drugs that mimic preconditioning or cardioprotective interventions during ischemia, such as hypothermia. Whether modifying the specific procedure for reperfusion (for example, postconditioning) or administering adjunctive therapy only at reperfusion reduces irreversible myocyte injury remains controversial. ■

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Measuring reperfusion in the catheter laboratory

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Abstract

Primary angioplasty has evolved as the reperfusion strategy of choice in acute ST-segment elevation myocardial infarction. Unlike thrombolytic therapy, it allows for direct visualization of the coronary anatomy and a targeted approach to revascularization. This is associated with significant improvements in culprit artery patency, distal myocardial perfusion, and, ultimately, patient prognosis. Assessment of reperfusion in this setting is heavily dependent upon the angiographic profile of the infarct-related artery after intervention. This incorporates both anatomical and physiological aspects of coronary function, with further delineation of epicardial and microvascular components of total coronary flow. More recent advances in contrast echocardiography and Doppler flow analysis have allowed for increasingly sophisticated and diverse measures of reperfusion that complement angiography and can all be used at the time of intervention in the catheter laboratory. Such information can guide immediate adjuvant therapy during angioplasty, in addition to identifying higher-risk groups of patients.

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Keywords: Microvascular dysfunction, primary angioplasty, reperfusion

Introduction

The main therapeutic strategy in ST-segment elevation myocardial infarction is the prompt restoration of blood flow to the distal myocardial bed of the culprit coronary artery. Primary percutaneous intervention is now widely accepted as the therapeutic treatment of choice. An invasive strategy allows for direct angiographic assessment of the epicardial coronary anatomy before and after targeted intervention is delivered, thereby eliminating the need for surrogate markers of reperfusion. Angiography remains the gold standard for measuring reperfusion. It provides both anatomical and physiological information about coronary flow, reflecting primarily, but not exclusively, the relative contribution of epicardial

and microvascular resistances, respectively. The distinction between epicardial and myocardial reperfusion is of increasing importance as our understanding and our capacity to measure microvascular function improve. Indeed, microvascular integrity beyond the stented lesion is now recognized as an independent outcome marker of revascularization [1–3]. More contemporary measures of the microvasculature, such as myocardial contrast echocardiography and Doppler coronary flow profiling, now complement the angiogram and electrocardiogram (ECG). These can all be measured simply in the catheter laboratory in order to guide delivery of treatment and identify those individuals at risk from incomplete epicardial or myocardial reperfusion.

Anatomical reperfusion

Epicardial reperfusion: the Thrombolysis In Myocardial Infarction (TIMI) flow grade and corrected TIMI frame count

Coronary angiography allows for both a two-dimensional quantitative analysis of residual lumen stenosis after percutaneous intervention and an assessment of coronary flow beyond the lesion intervened upon. These two components are not mutually exclusive, and both are important considerations in determining the success of revascularization in acute myocardial infarction. The first angiographic score of reperfusion was devised by the Thrombolysis In Myocardial Infarction (TIMI) study group for use in the early major trials of thrombolytic agents [4]. The TIMI flow grade provides a simple score of epicardial flow, graded 0–3 according to set angiographic criteria:

TIMI 3: Normal antegrade flow and contrast clearance from the epicardial artery beyond the (stented) obstruction (*complete perfusion*).

TIMI 2: Full opacification of the distal artery, but with slower contrast flow or clearance, or both, beyond the (stented) obstruction compared with a non-culprit artery or the culprit artery proximal to the lesion (*partial reperfusion*).

TIMI 1: Contrast flow in part, but not all, of the artery distal to the (stented) obstruction (*penetration without perfusion*).

TIMI 0: No antegrade contrast flow beyond the point of occlusion (*no perfusion*).

TIMI flow grade is now regarded as the benchmark by which coronary flow is assessed before and after intervention (*Figure 1*), and has become established as one of the most important markers of reperfusion in contemporary interventional trials.

Early use of the TIMI flow grade in thrombolysis trials defined a clear and stepwise improvement in patient outcome with each individual TIMI flow grade [5]. This has translated itself into a variety of interventional settings for acute myocardial infarction, including rescue angioplasty [6], revascularization in cardiogenic shock [7], and intra-aortic balloon-pump-supported therapy [8]. Unlike the thrombolysis trials, however, the prognostic merit of TIMI flow usually relates to a binary comparison of “successful” and “unsuccessful” revascularization, defined by a set TIMI flow grade threshold with or without reference to residual lumen stenosis after the intervention.

The major disadvantage of the TIMI flow grade is the subjective nature of reporting into a somewhat artificial and rigid classification of coronary flow. There is at least moderate interobserver variability reported, particularly in culprit arteries with TIMI 2

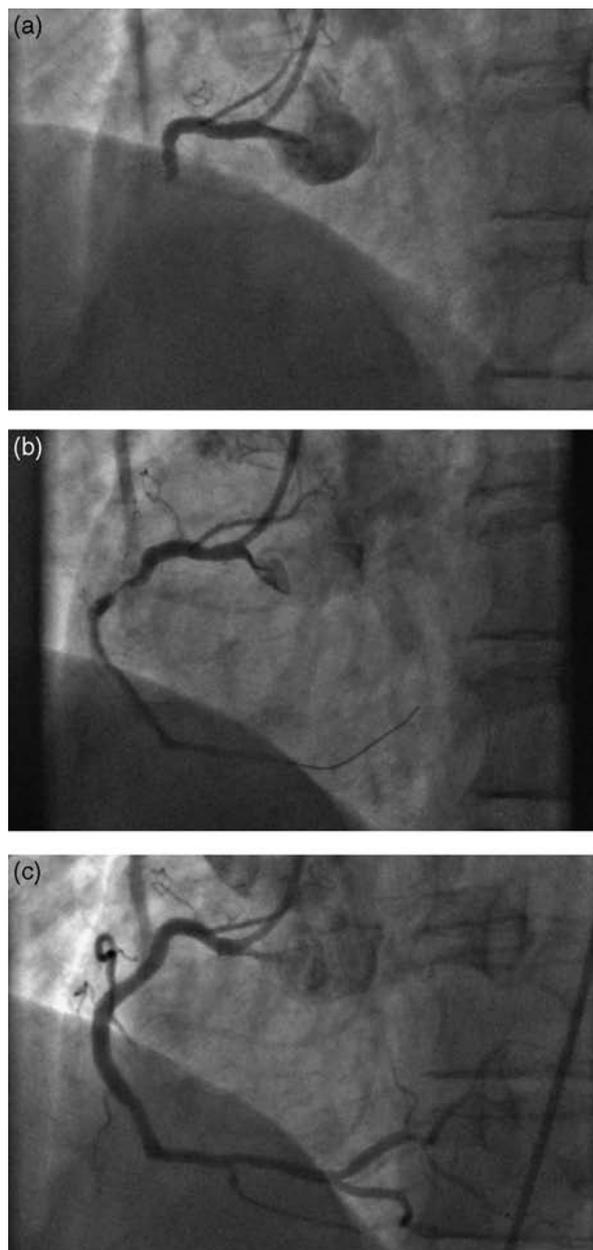


Figure 1. Thrombolysis In Myocardial Infarction (TIMI) 0 flow (a) in the right coronary artery of a patient presenting with an acute inferior myocardial infarction. Passage of the guidewire through the obstruction resulted in TIMI 1 flow (b) beyond a tight proximal lesion, which subsequently improved to TIMI 3 flow (c) after successful angioplasty and stenting.

and 3 flow after reperfusion [9]. Accordingly, the corrected TIMI frame count (cTFC) was devised in order to provide a more objective and less variable assessment of reperfusion. This angiographically derived measure describes the number of cineframes required for dye to reach defined distal landmarks of the three main epicardial arteries:

- (1) Left anterior descending (LAD): the distal bifurcation point of the left anterior descending artery.

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- (2) Right coronary artery (RCA): the first branch of the posterolateral artery of the right coronary artery.
- (3) Left circumflex artery (LCx): the most distal bifurcation of the obtuse marginal branch of the left circumflex system.

The cTFC depends upon a set acquisition frame-rate of 30 frames per second, standardized guide catheters, and sustained maximal epicardial vasodilatation. Otherwise, there is a remarkably low variance in measurements regardless of force of injection, dye contrast used, cardiac output, and heart rate [9,10]. The normal cTFC for the RCA and circumflex vessels is approximately 21 frames; for the LAD it is 36 frames. This disparity is in part a result of the longer course of the LAD in most individuals, but it also reflects a slightly slower flow – another confounding issue in using the TIMI flow grade. Conversely, the cTFC is a continuous measure and a correction factor of 1.7 is therefore used for LAD measurements [10].

Many studies now have identified an association between patient outcome and the cTFC in primary angioplasty trials [11,12]. Although certain prognostic threshold parameters are likely, the particular merit of the cTFC is its sensitivity to detect relative improvements in epicardial flow within TIMI flow grades. This is particularly true within TIMI 3, in which, in the absence of any residual stenosis, subtle hindrances in flow are probably caused by downstream microvascular obstruction or dysfunction.

Myocardial perfusion: myocardial contrast echo and the myocardial perfusion scores

Restoration of TIMI 3 epicardial flow remains the key target of interventional revascularization in acute myocardial infarction. However, up to 40% of the patients will fail to achieve adequate perfusion of the microvasculature beyond the stented lesion and

this, in itself, is associated with a worse prognostic outcome [13,14]. Myocardial contrast echocardiography (MCE) provided the first measure of this “no reflow” effect in humans and has remained an important modality against which other techniques have subsequently been tested [1]. Inert, echo-dense microbubbles between 2 and 4 μm in size can now be administered peripherally to determine capillary blood volume and regions of hypoperfusion/obstruction. This correlates well with gold-standard histological assessment and more contemporary measures of microvascular obstruction such as cardiac magnetic resonance imaging – both equally unhelpful in the catheter laboratory. MCE also allows for an accurate assessment of left ventricle dimensions and determination of immediate postinfarct contractile function, and is suggested as the most sensitive and accurate of microvascular measures in predicting longer-term left ventricular recovery [15].

Angiography-derived microvascular perfusion can be assessed from the myocardial blush grade and TIMI myocardial perfusion grade [2,10]. These are both simple descriptive scores of myocardial opacification with contrast, distinct from the epicardial vessel, and provide a score of between 0 (no myocardial blush) and 3 (normal blush and clearance of dye from myocardium) (Table 1). Angiographic myocardial reperfusion correlates well with MCE in the setting of primary angioplasty, and accordingly is an important prognostic outcome marker of myocardial salvage and mortality in spite of TIMI 3 epicardial flow [16,17]. More recently, the TIMI study group have proposed a 12-point angiographic perfusion score as a composite of pre- and postintervention TIMI flow grade (0–3) and TIMI myocardial perfusion grade (0–3) scores, in order to combine epicardial and microvascular perfusion. This has provided robust outcome data and a close correlation with infarct size determined by single photon emission computed tomography, but has yet to prove any more useful than existing angiographic indices [18].

Table 1. The myocardial blush grade and Thrombolysis In Myocardial Infarction (TIMI) myocardial perfusion grade.

Myocardial blush	Grade	TIMI myocardial perfusion
No myocardial blush or contrast density	0	Minimal or absent myocardial blush in the territory of the infarct-related artery
Minimal myocardial blush or contrast density	1	Myocardial blush present, but incomplete clearance of dye between injections (at least 30s)
Moderate myocardial blush or contrast density, but less than that of a non infarct-related artery	2	Myocardial blush present, but slow entry and clearance of dye (strongly persistent opacification beyond 3 cardiac cycles after injection)
Normal myocardial blush or contrast density, comparable to that of a non infarct-related artery	3	Myocardial blush present with normal entry and exit of dye (mild/moderate persistence of dye beyond 3 cardiac cycles but notably reduced during washout phase)

Both are angiographically derived scores of microvascular perfusion, describing the ground-glass or “blush” effect of distal myocardial contrast opacification beyond the infarct-related epicardial artery.

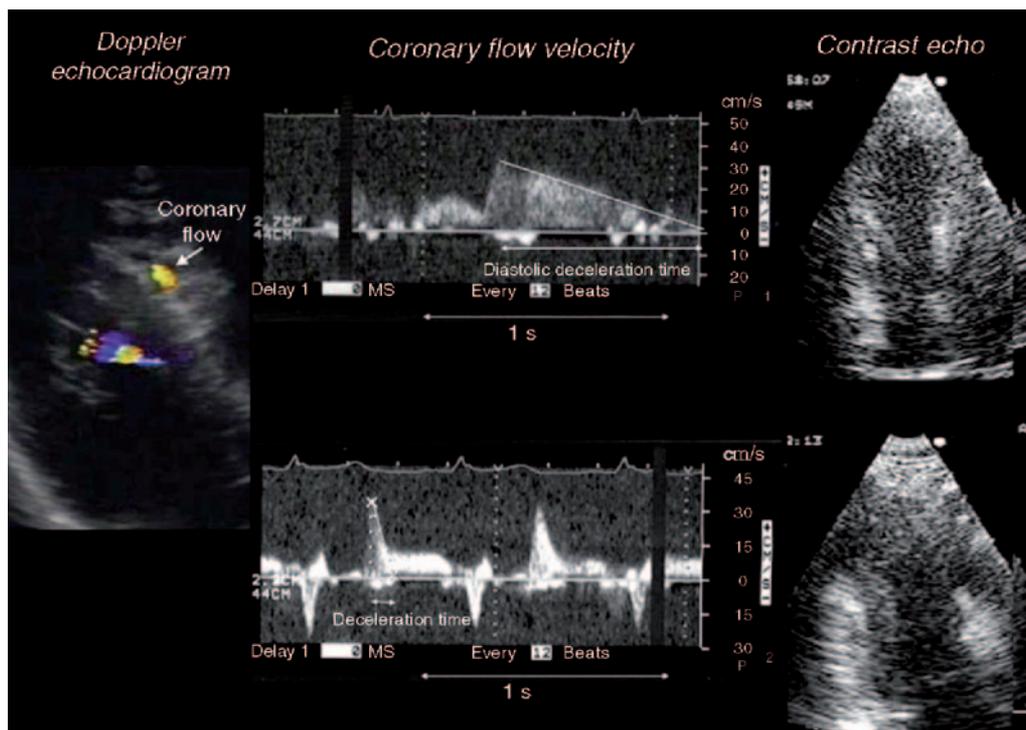


Figure 2. Transthoracic Doppler profile of the left anterior descending (LAD) coronary artery (left and centre) and myocardial contrast echo (right), in two patients who underwent successful revascularization for acute anterior myocardial infarction. The patient with “no reflow” on myocardial contrast echo (bottom images) demonstrated a characteristic coronary flow velocity pattern of increased diastolic peak velocity with rapid deceleration, diminished systolic peak velocity, and systolic flow reversal. (From Ikawura et al [21], with permission.)

Physiological reperfusion

Doppler analysis and the electrocardiogram

The advent and expansion in use of fine intracoronary measuring devices has also extended the capacity to define myocardial reperfusion on a “physiological” basis. Intracoronary Doppler interrogation of upstream epicardial flow after primary angioplasty, for example, provides a surrogate measure of downstream microvascular integrity, with both impairment of coronary flow reserve and progressive flow characteristics correlating with deteriorating perfusion defects on MCE, in the following order [19,20]:

- (1) Rapid diastolic deceleration time.
- (2) Systolic flow reversal.
- (3) Diminished antegrade systolic flow.

These findings are reproducible in transthoracic echo Doppler interrogation of LAD flow (Figure 2), and have been suggested as more sensitive of microvascular no-reflow than angiographic or ECG criteria [21].

Finally, although primary angioplasty has rendered the surface ECG redundant as a surrogate marker of epicardial reperfusion, the absence of reperfusion dysrhythmias and persistence of ST-segment elevation in the face of successful intervention and restoration of TIMI 3 epicardial flow correlate

strongly with other measures of microvascular dysfunction. This reflects sustained electrical transmural injury, and less than 50% resolution of ST segments in the infarct-related territory is associated with larger infarct size and significant long-term major adverse cardiac events [22,23]. ■

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Scoring reperfusion by contrast-enhanced magnetic resonance imaging

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Abstract

After acute myocardial infarction, the immediate therapeutic goal is to establish patency of the infarct-related artery. However, because a patient's prognosis after acute myocardial infarction relates directly to the extent of myocardial injury produced during coronary occlusion, attention has shifted away from achieving epicardial artery patency towards the achievement of adequate tissue reperfusion. On the basis of myocardial and microvascular injury assessed by contrast-enhanced magnetic resonance imaging after primary percutaneous coronary intervention, four patterns of tissue reperfusion score might be identified: I, aborted myocardial infarction; II, transmural necrosis limited to less than two left ventricular segments without severe microvascular damage; III, transmural necrosis in more than two left ventricular segments without severe microvascular damage; IV, transmural necrosis in more than two left ventricular segments plus severe microvascular damage.

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Keywords: Acute myocardial infarction, magnetic resonance imaging, primary angioplasty

Introduction

After acute myocardial infarction, the immediate therapeutic goal is to establish patency of the infarct-related artery. Nevertheless, the successful restoration of epicardial coronary artery patency by thrombolysis, primary angioplasty or bypass does not necessarily translate into improved myocardial reperfusion [1–3]. Patients' prognosis after acute myocardial infarction relates directly to the extent of myocardial injury produced during coronary occlusion [4–9]. Postinfarction electrocardiography, echocardiography, and contrast ventriculography are often used as an indirect means of assessing the degree of myocardial damage [10,11], whereas radionuclide studies with ^{99m}Tc sestamibi- and gadolinium-contrast-enhanced magnetic resonance imaging (ceMRI) can measure

infarct size directly [12–14]. In addition to the extent of infarcted myocardium, the magnitude of structural obstruction or disruption of the microvasculature, called the “no reflow” or “low reflow” phenomenon, that is sustained before or during primary percutaneous coronary intervention (PCI) has been related to a worse clinical outcome [14,15], despite successful epicardial revascularization. Therefore, attention has shifted away from merely achieving epicardial artery patency towards the achievement of an adequate myocardial and microvascular reperfusion.

Studies performed in experimental animal models have shown that, after ligation of a coronary artery and subsequent re-opening of the epicardial vessel, the territory injured by the prolonged ischemia is composed primarily of non viable myocardial tissue in which myocytes perish first, followed eventually by

necrosis of the endothelial cells that line intramyocardial capillaries [16,17]. An exact quantification of the final extent of both myocardial and microvascular damage might be possible. In contrast, unlike most animal models of mechanical coronary occlusion, the clinical setting of acute myocardial infarction is more complex: the duration of true ischemia might not be clearly determinable, micro- and macro-embolic events might be involved, the collateral circulation may be variable, and preconditioning and myocardial oxygen consumption may have major roles in determining the final amount of myocardial and microvascular injury. ceMRI has emerged as a useful tool with which to undertake a form of “in-vivo histology” to examine the infarct characteristics accurately, and has proven useful in both research and clinical areas of cardiology. This article summarizes the pathophysiologic and clinical evidence supporting the importance of scoring tissue reperfusion by ceMRI after successful recanalization of the infarct-related artery by primary PCI.

Magnetic resonance imaging assessment of myocardial and microvascular injury

After acute myocardial infarction, four different zones of myocardium can readily be defined by ceMRI [3,18]: (1) non necrotic, salvaged (stunned) myocardium, (2) necrotic myocardium without microvascular damage, (3) necrotic myocardium with microvascular damage, and (4) normal myocardium. These zones are defined by examining contractility using cine MRI and tissue characteristics using contrast-enhanced techniques, most commonly after administering a gadolinium-based contrast agent. In the case of myocardial necrosis, areas of hyperenhancement (bright) reflect necrotic tissue with intact microvasculature, whereas areas of hypoenhancement (dark) within areas of hyperenhancement reflect necrotic tissue with damaged microvasculature (so-called no-reflow zones). Myocardial necrosis is usually labeled as transmural if hyperenhancement extends to at least 75% of the thickness of the left ventricular segment.

A standard approach to imaging microvascular obstruction has yet to be defined. Two of the most commonly used methods for assessing no-reflow involve first-pass perfusion [14,19], and delayed-enhancement imaging [3,19,20]. A comparison between these two techniques undertaken by Lund and colleagues [19] found some differences in sensitivity between first-pass perfusion ceMRI and delayed-enhanced ceMRI, but overall there was a high level of concordance between these two approaches. The investigators suggested that the difference could be explained by extensive microvascular damage resulting in persistent hypoenhancement, even with late imaging.

We favor delayed-enhancement ceMRI for the evaluation of no reflow zones, because we have found this technique to be more specific for severe forms of microvascular damage with persistent contrast filling defects, which have been shown to be related to worse remodeling and outcome [7,9]. When first-pass ceMRI is used, patients with chronic, healed infarcts could be wrongly interpreted as having no reflow zones secondary to the reduced capillary density of scar tissue relative to healthy myocardium. Finally, we and others [21] feel that it is more clinically meaningful to evaluate microvascular injury concomitantly with the evaluation of the extent and the amount of necrosis (hyperenhancement), as they provide additional information regarding the extent and the type of myocardial necrosis and recovery of function [9].

Scoring of tissue reperfusion after primary percutaneous coronary intervention: the tissue reperfusion score

In experimental animal studies, both transmural and microvascular dysfunction are strongly dependent on the duration of ischemia before reperfusion, and the extent of no reflow is driven by the extent of infarct size for any given delay in time to treatment [22]. We have provided support for the ability of ceMRI to assess myocardial and microvascular damage in patients [3]. In a study of 77 patients with first-time acute myocardial infarction who underwent primary PCI, we found a continuous relationship between duration of ischemia and probability of transmural necrosis and severe microvascular damage assessed by ceMRI. Interestingly, for each 30 min delay in the treatment of patients undergoing successful primary PCI, the risk of transmural necrosis or severe microvascular damage increased by 37% and 21%, respectively (*Figure 1*). Although there was also a close correlation between the presence of severe microvascular damage and evidence of transmural necrosis, it is noteworthy that, for any time of reperfusion the probability of transmural necrosis was greater than that of severe microvascular damage (*Figure 1*). In other words, severe microvascular damage occurs later than transmural necrosis, suggesting that, from a pathophysiological point of view, severe microvascular damage lags behind transmural necrosis, being present exclusively in left ventricle in which at least two segments have transmural necrosis. In a series of patients with acute myocardial infarction, other authors similarly found that the extent of transmural necrosis was the strongest predictor of severe microvascular obstruction on delayed-enhancement ceMRI [23]. So, in summary, this suggests that “time is muscle and microvasculature damage follows on behind”, and not vice versa.

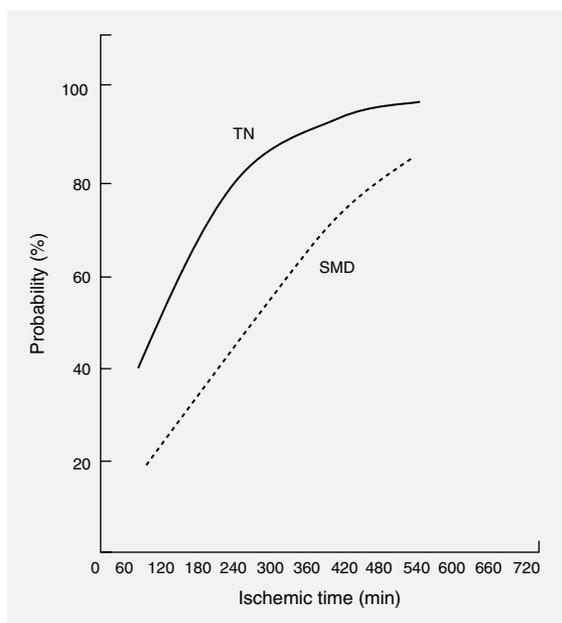


Figure 1. Relationship between duration of ischemia and patients' (in-hospital) probability of transmural necrosis (TN) or severe microvascular damage (SMD). (Modified from Tarantini et al [3], with permission. © Elsevier).

According to the myocardial and microvascular injury assessed by ceMRI after primary PCI, a tissue reperfusion score (TSR) showing four patterns might be identified (Figure 2) [3,9,24]:

- I Aborted myocardial infarction.
- II Transmural necrosis limited to fewer than two left ventricular segments without severe microvascular damage.
- III Transmural necrosis in more than two left ventricular segments without severe microvascular damage.
- IV Transmural necrosis in more than two left ventricular segments plus severe microvascular damage.

In a clinicopathologic study in two patients in the TSR IV category, who died of cardiogenic shock after reperfused acute myocardial infarction, we demonstrated for the first time that the peculiar signal features of late gadolinium hypoenhancement within the myocardial infarction core can be related to hemorrhage as a result of irreversible vascular injury within transmural acute myocardial infarctions that underwent late reperfusion (at least 5 h) [25]. This finding is consistent with those from experimental models of coronary occlusion and reperfusion, in which hemorrhage always occurs within the area of necrosis and is significantly related to the infarct size and to the coronary occlusion time [1,2,4]. At present, the clinical implications of hemorrhagic as compared with white infarcts remain undetermined.

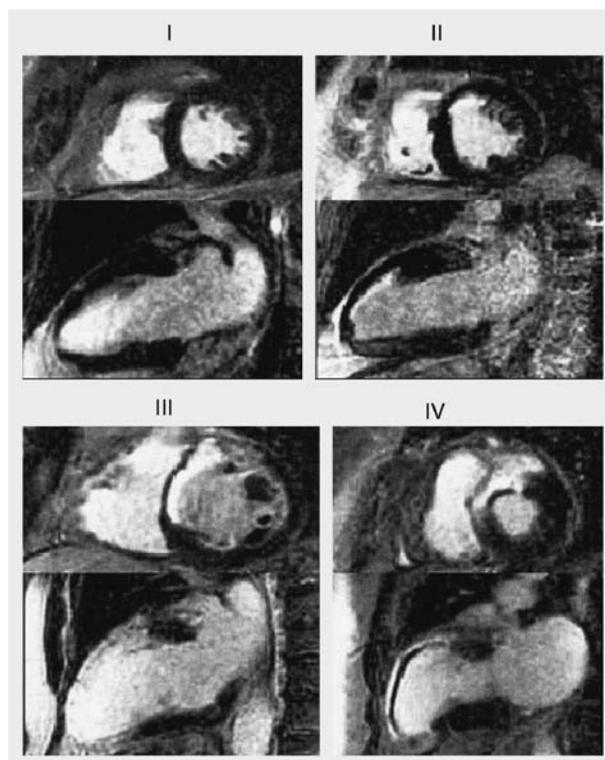


Figure 2. Typical examples of the different tissue reperfusion scores detected by contrast-enhanced magnetic resonance imaging (ceMRI) in patients undergoing primary percutaneous coronary intervention at increasing time delays from the onset of chest pain (see text for details). Upper and lower panels respectively show results of ceMRI obtained at the short-axis level and in the long-axis two-chamber plane. I: Anterior ST-segment elevation myocardial infarct (STEMI); pain to balloon time 70 min; troponin I peak 11.7 ng/mL. At 6 days from the acute event, no signs of necrosis are evident on ceMRI ("aborted" infarct). II: Anterior STEMI; pain to balloon time 170 min; troponin I peak 38.6 ng/mL. At 6 days from the acute event, ceMRI shows a non transmural necrosis in the middle and apical segments of the anterior wall. III: Anterior STEMI; pain to balloon time 240 min; troponin I peak 199 ng/mL. At 8 days from the acute event, ceMRI shows a transmural necrosis of more than two ventricular segments, without evidence of severe microvascular damage. IV: Anterior STEMI; pain to balloon time 310 min; troponin I peak 258 ng/mL. At 7 days from the acute event, ceMRI shows transmural necrosis of more than two ventricular segments, with evidence of a subendocardial dark zone referred to as severe microvascular obstruction. (Modified from Tarantini G et al [3], with permission. © Elsevier).

Summary

Cardiac magnetic resonance after acute myocardial infarction could help: (1) in the evaluation of the effectiveness of reperfusion after primary PCI by the characterization of myocardial and microvascular damage, (2) the early stratification of patients with acute myocardial infarction, to improve the clinical identification of patients at risk of adverse remodeling and outcome, (3) in studies of the effects of hemorrhage after acute myocardial infarction, and (4) to

clarify the consequences of new therapeutic strategies, such as platelet glycoprotein IIb/IIIa inhibitors [26]. ■

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Postconditioning the human heart

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Abstract

Acute myocardial infarction is a frequent and disabling disease. Ischemic postconditioning, consisting of repeated brief cycles of ischemia-reperfusion performed immediately after reperfusion following a prolonged ischemic insult, dramatically reduces infarct size in experimental models. A recent clinical study demonstrated that repeated brief episodes of inflation-deflation of the angioplasty balloon performed immediately after re-opening of the culprit coronary artery reduced infarct size by 36% in patients with current acute myocardial infarction. This proof-of-concept study identified lethal reperfusion injury as a new target for future pharmacological treatments. Future therapeutic strategies for acute myocardial infarction should include mimetics of postconditioning.

■ *Heart Metab.* 2007;37:19–22.

Keywords: Ischemia, myocardial infarction, postconditioning, reperfusion

Postconditioning protects the human heart

Acute myocardial infarction is a frequent and disabling disease, with heart failure as a common outcome. Infarct size is recognized as a major determinant of myocardial functional recovery and mortality after acute myocardial infarction [1]. Limitation of infarct size appears thus to be an appropriate strategy with which to prevent postinfarction heart failure and to improve survival. Current strategies to limit infarct size include emergency re-opening of the culprit coronary artery (coronary angioplasty or thrombolysis) and prevention of re-occlusion (antiplatelet agents). It is not questionable that myocardial reperfusion improves outcomes. Treatments adjunctive to reperfusion, including β -blockers and angiotensin converting enzyme inhibitors, can ameliorate morbidity or mortality, or both, but not via a reduction in infarct size.

Zhao et al [2] first reported that, in the dog heart, three episodes of 30 s of reperfusion and 30 s of ischemia performed immediately after a prolonged 60 min ischemic insult dramatically attenuated irreversible myocardial injury. This cardioprotective effect was comparable to that observed with the powerful

phenomenon of preconditioning [3]. Several other investigators have now been able to reproduce this initial experiment and found that ischemic postconditioning is also efficient in pig, rabbit, rat, and mouse hearts. This description of “postconditioning” demonstrated the existence of a lethal myocardial reperfusion injury and thereby helped us to consider potential new ways to achieve further attenuation of infarct size.

Unlike preconditioning, postconditioning can be triggered at the onset of reperfusion. It can therefore be manipulated in clinical situations in which reperfusion can be controlled, for example during coronary angioplasty or cardiac surgery. In a proof-of-concept trial, Staat et al [4] aimed to determine whether postconditioning might be protective in patients with current acute myocardial infarction. In a multicenter, controlled, randomized study, they enrolled patients with a first ST-segment elevation myocardial infarction, chest pain of less than 6 h duration, and a need for revascularization via angioplasty. Patients were allocated randomly to either a control or a postconditioned group. Major determinants of infarct size were assessed using methods that would be possible in an emergency clinical situation. The area at risk was

New therapeutic approaches

Hélène Thibault, Denis Angoulvant, Cyrille Bergerot, and Michel Ovize

estimated by left ventricular angiography. Duration of ischemia was estimated as time from the onset of chest pain to time of re-opening the coronary artery. Patients with overt collateral circulation to the region at risk were excluded from the study. After direct stenting, control patients underwent no additional interventions, whereas postconditioned patients underwent four cycles of inflation–deflation of the angioplasty balloon, starting within 1 min after the initial reperfusion. Each inflation and deflation lasted for 1 min. This procedure was simple and feasible in each patient, and was without any adverse event. Infarct size was first assessed by measuring the release of creatine kinase over the first 3 days of reperfusion. The area under the curve of creatine kinase release was significantly reduced (by 36%; $P < 0.05$) in the postconditioned group compared with the control group. Analysis of covariance revealed that the reduction in infarct size persisted whatever the size of the area at risk (Figure 1). This study demonstrated for the first time that postconditioning can protect the human heart.

Revisiting the pathophysiology of acute myocardial infarction

With their initial observation, Zhao et al [2] demonstrated that an unexpected intervention, performed after ischemia during the first minutes of reperfusion, was capable of reducing infarct size by approximately 40%. In other words, 40% of the overall myocardial damage (infarct size) occurs after ischemia – that is, during reperfusion. This observation is apparently paradoxical: reperfusion can both protect and kill. Reperfusion protects simply because it prevents additional lesions that would have occurred if ischemia (and subsequent reperfusion) had persisted. It kills because reflow is associated with dramatic ionic and metabolic disturbances that overwhelm the endoge-

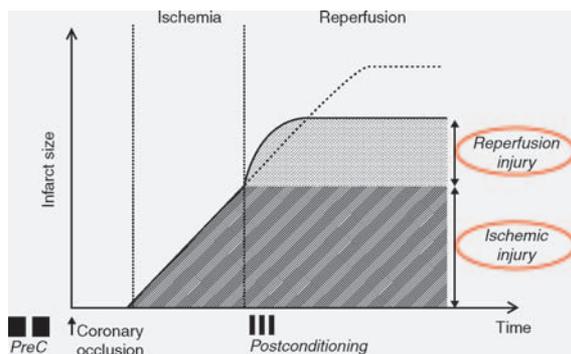


Figure 1. Lethal reperfusion injury. A proportion of the cardiomyocytes that die after prolonged ischemia-reperfusion are irreversibly injured during ischemia (dark gray area); the remainder are killed during reperfusion (light gray area). PreC, preconditioning.

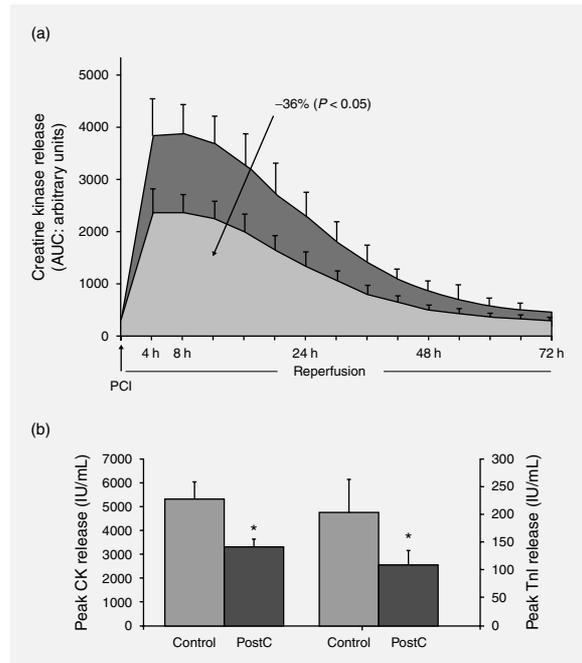


Figure 2. Release of creatine kinase (CK) and troponin I (TnI) during reperfusion. (a) The area under the curve (AUC) of creatine kinase release was assessed in control groups (dark gray area) and postconditioned groups (light gray area). Infarct size was reduced by 36% in the postconditioned group ($P < 0.05$). PCI, percutaneous coronary intervention. (b) Peak release of CK and TnI during reperfusion in control and postconditioned (PostC) groups. $*P < 0.05$.

nous defenses of jeopardized cardiomyocytes. Thus the final irreversible damage to cardiac tissue observed after a prolonged ischemia-reperfusion represents the superposition, in nearly equal amounts, of irreversible damage occurring before re-opening of the occluded coronary artery (ischemic damage) on irreversible damage occurring just at the time of reflow (reperfusion damage) (Figure 2). According to studies performed in experimental preparations, the window of time during which protection by postconditioning could be triggered would be very narrow (longest duration less than 1 min). Whether a comparable time course applies to the human heart remains to be determined, but it would represent valuable information in the targeting of therapeutic strategies in patients with current acute myocardial infarction.

Postconditioning in clinical practice

The initial study by Staat et al [4] was designed as a proof-of-concept study aimed at determining whether ischemic postconditioning was able to protect the human heart in a clinical setting that would be as close as possible to that of experimental preparations. Although the findings of the trial were very encouraging, key questions remain to be addressed, including: (1) does postconditioning afford a persistent limitation

New therapeutic approaches

Postconditioning

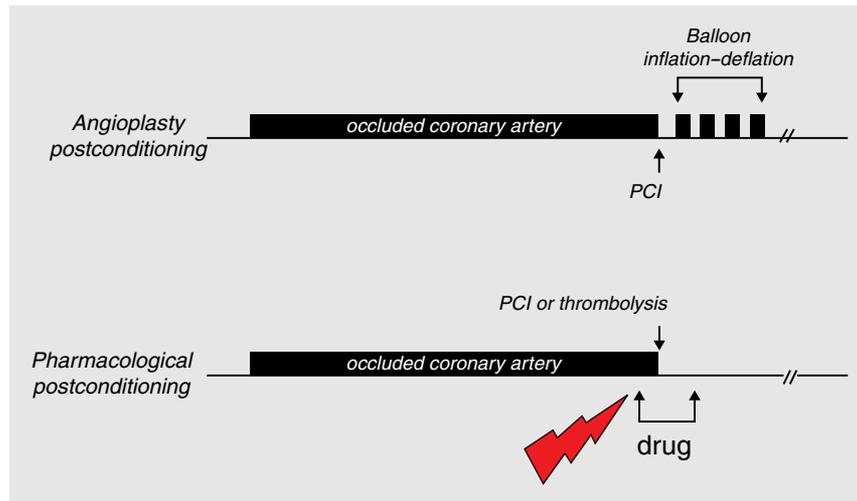


Figure 3. New strategies for patients with current acute myocardial infarction. Angioplasty (percutaneous coronary intervention, PCI) postconditioning is feasible and efficient in patients with acute myocardial infarction. Future research will address whether a pharmacological approach using postconditioning mimetics (drug) may protect patients with acute myocardial infarction when administered at reperfusion achieved by angioplasty (PCI) or thrombolysis.

of infarct size?, (2) does postconditioning improve recovery of myocardial contractile function, left ventricular remodeling, and survival?, and (3) is postconditioning feasible in all patients with current acute myocardial infarction?

The protective effect of postconditioning has been assessed as the release of cardiac enzymes over the first 3 days of reperfusion. Complementary studies are required to determine whether myocardial salvage by angioplasty is maintained over time: infarct size should be measured several months after the acute event, by magnetic resonance imaging or single photon emission computed tomography. Investigations are currently in progress to determine whether ischemic postconditioning improves clinical outcomes. It remains to be determined whether postconditioning might reduce mortality.

If one admits that postconditioning may improve patients' prognosis and if the approach becomes widely used in daily practice, two options appear to be available: first, to use it as it is – that is, as an angioplasty intervention – or, secondly, try to extend its availability to all patients by means of a pharmacological mimetic.

Postconditioning by angioplasty is technically simple and safe. Additional studies may help to determine what would be the shortest, safest, most efficient postconditioning procedure. One may question whether there might exist a wider window of time (which is supposedly limited to 1 min in animal species) for triggering postconditioning in patients. It would be useful to determine whether comorbidities (eg, diabetes, lipid disorders, age, hypertension) might attenuate the degree of protection.

A large number of patients achieve reperfusion via thrombolysis; these patients cannot benefit from

angioplasty postconditioning. There is then an obvious need for a pharmacological mimetic of ischemic postconditioning. In view of the narrow window of time defined in experimental studies, one has to consider the possibility that such a postconditioning drug should be administered before reperfusion, in order to obtain significant drug plasma concentration at the time of coronary reflow. It could then be administered in all patients with current acute myocardial infarction, either as an adjunct to thrombolysis, or even just before coronary angioplasty (in place of ischemic postconditioning) (Figure 3).

A considerable amount of experimental research has been performed since the discovery of pre- and, more recently, postconditioning. Several molecular targets have been identified as key players in cardioprotection by pre- or postconditioning, including signaling pathways (eg, protein kinase C, phosphatidylinositol 3-kinase, Akt, endothelial nitric oxide synthase, extracellular-signal regulated kinases 1/2, glycogen synthetase kinase 3 β), and, more recently, processes at the level of mitochondria. Growing evidence suggests that a change in mitochondrial permeability is involved in lethal reperfusion injury [5]. At the onset of reperfusion after a prolonged ischemic insult, abrupt accumulation of Ca^{2+} in the matrix, and overproduction of reactive oxygen species, render the inner mitochondrial membrane permeable through the opening of a non specific mega-channel (called the "permeability transition pore"). The opening of this pore, and the spread of permeability changes among neighboring mitochondria throughout the cardiomyocyte may at some point result in irreversible damage. In experimental preparations, pharmacological inhibitors of the mitochondrial permeability transition (including cyclosporin A) do reduce infarct size to an extent

New therapeutic approaches

Hélène Thibault, Denis Angoulvant, Cyrille Bergerot, and Michel Ovize

similar to that in ischemic postconditioning [6,7]. Current trials are under way to determine whether inhibition of the transition in mitochondrial permeability may limit infarct size in patients with current acute myocardial infarction.

Postconditioning represents a new major hope of improving the prognosis of patients with acute myocardial infarction.

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Clinical benefits of a metabolic approach in the treatment of ischemic heart disease: focus on Vastarel MR

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Abstract

Despite the recent decline in cardiovascular mortality, Ischemic Heart Disease (IHD) remains the leading single cause of death in the western world. Great hopes were provoked by the introduction of surgical and percutaneous myocardial revascularization techniques that promised to be a safe and effective alternative to control symptoms and to improve prognosis in these patients. Unfortunately, clinical results do not correspond to these expectations: most revascularized patients remain symptomatic, a large fraction continues to require antianginal medications, and about 10% suffer of either death or myocardial infarction within 2.5 years.

In the meantime, the clinical profile of chronic ischemic heart disease is rapidly changing, with a growing prevalence of elderly patients, diabetics, and heart failure patients. These associate conditions are relevant to patients compliance, to drug efficacy and safety, and may contribute to the failure of classic therapeutic strategies in so many instances. Pharmacologic manipulation of cardiac energy metabolism, by partial inhibition of free fatty acid oxydation by trimetazidine appears as an innovative and attractive alternative to treat patients with chronic IHD.

■ *Heart Metab.* 2007;37:23–25.

Keywords: Angina, cardiac energy metabolism, ischemic heart disease, trimetazidine

Introduction

Chronic stable angina is the initial manifestation of ischemic heart disease in approximately 50% of patients. It is difficult to estimate the number of patients with chronic chest pain syndromes, but clearly it is measured in the millions. In the USA, the reported annual incidence of angina is 213/100 000 population older than 30 years, and about 50% of patients presenting at hospital with myocardial infarction have preceding angina. Given that, in the USA, there are 1 100 000 patients with myocardial infarction each year, and about 50% of these (550 000) survive until

admission to hospital, it can be estimated that there are 30 patients with stable angina for every patient with infarction who is admitted to hospital. As a result, the number of patients with stable angina in the USA can be estimated as $30 \times 550\,000$, or 16 500 000 [1]. If we include in this estimation all industrialized countries, the figures become incredibly high.

Ischemic heart disease is important, not only because of its prevalence, but also because of its associated morbidity and mortality. Despite the well documented recent decline in cardiovascular mortality, ischemic heart disease remains the leading single cause of death in the western world. The morbidity associated with

this disease is also considerable: each year, millions of patients experience myocardial infarction, or are admitted to hospital for unstable angina. Beyond the need for admission to hospital, many patients with chronic chest pain syndromes are temporarily unable to perform normal activities for hours or days, thereby experiencing a reduced quality of life.

Myocardial revascularization: promise unfulfilled

Great hopes were inspired by the introduction of surgical and percutaneous myocardial revascularization techniques that promised to be safe and effective alternatives for the control of symptoms in patients resistant to optimal medical therapy. These techniques rapidly gained great popularity, but, unfortunately, they do not seem to have lived up to initial expectations, in either the short or the long term. According to the data from the Bypass Angioplasty Revascularization Investigation [2], about 30% of patients never return to work after coronary revascularization, and 15–20% of patients rate their own health as fair or poor despite revascularization.

Two more recent studies, one comparing clinical outcomes of patients treated medically with those of patients who underwent revascularization [3], and another comparing percutaneous transluminal coronary angioplasty and coronary artery bypass grafting [4], provided additional data on long-term prognosis, and cast additional doubts on the effective benefits of these procedures in patients with chronic ischemic heart disease. The first of these studies, although indicating that revascularized patients do better than patients treated medically, revealed that, at follow-up, many revascularized patients complain of angina, that most continue to receive antianginal medication, and that about 10% suffered either death or myocardial infarction within 2.5 years [3]. The second study, which was designed as a comparison between state-of-the-art surgical revascularization and percutaneous revascularization in multivessel coronary disease, proved the two strategies to be equally effective and safe. However, within 1 year, 10% of patients who had undergone revascularization had suffered a major adverse cardiac event, regardless of the procedure received [4].

It can be concluded that, despite increasing pharmacological and mechanical treatment options, ischemic heart disease continues to be associated with considerable patient mortality and morbidity. Obviously, this also translates in an enormous economic burden. The estimates of the direct and indirect costs associated with chronic stable angina are measured in tens of billions of dollars. Given the epidemiologic and economic magnitude of the problem, the need for more effective therapies is self-evident.

The broad clinical profile of chronic ischemic heart disease: implications for treatment

On the basis of current guidelines, the management of ischemic heart disease has progressively broadened to include risk-factor modification, patient education, and pharmacologic therapy. The pharmacologic agents fall into two categories:

- (1) Classic antianginal agents such as β -blockers, calcium antagonists, and nitrates.
- (2) Drugs for secondary prevention, such as aspirin, clopidogrel, statins, and angiotensin-converting enzyme inhibitors.

Tailoring therapy to individual needs has become even more challenging because of the marked changes occurring in the clinical profile of patients with chronic ischemic heart disease. As compared with those of the past, today's patients tend to be older, to have undergone revascularization procedures, and to present frequently with associated illnesses, including heart failure and diabetes.

Congestive heart failure is the single most common medical cause for admission to hospital, and is the leading cause of death in industrialized countries. Recent therapeutic advances have improved symptoms and prolonged survival; nevertheless, prognosis remains poor, and rates of re-admission to hospital high. Registry data suggest that the prognosis of patients admitted to hospital with heart failure is even worse than is indicated by clinical trials, with a median survival time of 1.5 years and a mortality rate of 50% within 1 year [5].

Diabetes mellitus is closely associated with coronary heart disease. The prevalence of coronary artery disease increases from the 2–4% found in the general population to a figure as high as 55% among adult patients with diabetes [6].

The prevalence of coronary artery disease also increases rapidly with advancing age, affecting approximately 10% of the population aged over 70 years, with one study reporting an incidence of up to 25% in patients older than 75 years. Elderly patients with ischemic heart disease would appear to be a high-risk subset of patients who may derive substantial benefit from appropriate therapy. Congestive heart failure affects approximately 10% of those over 80 years old and carries a uniformly less good prognosis, regardless of the level of cardiac dysfunction.

The clinical profile of chronic ischemic heart disease is thus characterized by a growing prevalence of elderly patients, diabetic individuals, revascularized patients, and patients with heart failure. These conditions, together with sex and race, are relevant to patient compliance, drug efficacy, drug safety, and

other factors that contribute to the success or otherwise of therapy.

Role of cardiac energy metabolism in the pathogenesis of myocardial ischemia

Significant progress has been made in recent years in understanding the role of cardiac energy metabolism in the pathogenesis of myocardial ischemia, and the better understanding of metabolic derangements associated with ischemia and reperfusion is being translated into innovative therapeutic approaches [7].

In normoxic conditions, the healthy heart derives most of its energy from the free fatty acid pathway that accounts for approximately two-thirds of energy (ATP) production, other sources of energy being derived from glucose oxidation and lactate. In hypoxic conditions, myocardial cells respond to mild-to-moderate ischemia by accelerating glucose uptake to generate sufficient ATP to maintain ionic gradients and calcium homeostasis. Severe ischemia rapidly induces an imbalance between the coronary blood supply and the requirement of cardiac tissue for oxygen, producing functional, metabolic, and morphological alterations to the myocardium, including arrhythmia, failure of contractility, and electrophysiological abnormalities. At the cellular level, glucose uptake is decreased and conversion to lactate is increased, lactate uptake by the heart is switched to lactate production, and pyruvate is mostly transformed into lactate, thus increasing cell acidosis. The free fatty acid pathway is slowed down, resulting in reduced production of ATP. These various forms of metabolic damage lead to a disruption of cell homeostasis, alterations in membrane structure, and, ultimately, cell death [7].

Given this pathophysiologic background, and given the failure of classic hemodynamic agents in many patients, it seems logical to consider the pharmacologic manipulation of cardiac energy metabolism as an alternative therapeutic option for patients with myocardial ischemia.

Optimization of cardiac energy metabolism: trimetazidine

Optimization of cardiac energy metabolism is based on promoting cardiac glucose oxidation. This has been proved to enhance the function of the heart and

to protect myocardial tissues against ischemia-reperfusion injury. Stimulation of myocardial glucose oxidation can be achieved either directly or indirectly through inhibition of fatty acid β -oxidation. A new class of metabolic agents, known as the 3-ketoacyl coenzyme A thiolase (3-KAT) inhibitors, is able to elicit an increase in glucose and lactate combustion secondary to partial inhibition of fatty acid oxidation, achieving demonstrable clinical benefits in patients with ischemic heart disease [8].

A modified-release formulation of the first 3-KAT inhibitor, trimetazidine MR, is now available for clinical use. Its optimized pharmacologic profile has made a twice-daily administration regimen possible, and provides round-the-clock cardioprotection. This new formulation has been shown to improve anti-anginal efficacy, to enhance anti-ischemic properties in ischemic patients with ventricular dysfunction, to exert a cardioprotective action in patients undergoing coronary artery bypass grafting or percutaneous coronary intervention, and to be of particular value in high-risk subgroups such as the elderly or patients with diabetes [8]. ■

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Primary angioplasty: worth the trouble?

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Abstract

Primary angioplasty is an increasingly common strategy for the treatment of patients with myocardial infarction. However, although the technique is associated with improved early reperfusion and prevention of recurrent ischemia compared with thrombolysis, this Case Report illustrates that performing primary angioplasty safely not only requires significant expertise and resources, but also introduces unique problems.

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Keywords: Acute myocardial infarction, bifurcation disease, clopidogrel, kissing balloons, primary angioplasty

Case report

A 57-year-old man presented to the local cardiac centre 4 h after the onset of typical cardiac ischemic pain. Clinical examination demonstrated a pulse of 75 beats/min, blood pressure of 130/80 mm Hg, a clear chest, and normal heart sounds. A 12-lead electrocardiogram (ECG) confirmed the diagnosis of acute anterolateral myocardial infarction (*Figure 1*). Morphine, oxygen, 300 mg aspirin and 600 mg clopidogrel were given before the patient was transferred to the cardiac catheter laboratory for primary angioplasty.

A 6-French sheath was inserted into the right femoral artery. A bolus dose of abciximab and 5000 units of heparin were administered. A diagnostic right Judkins catheter was used to intubate the right coronary artery, which contained non flow-limiting disease. There was no evidence of collateral filling of the left coronary arteries. Next, a 3.5-Voda left guide catheter was used to engage the left coronary system. After injection of contrast, the left anterior descending artery (LAD) was found to be occluded (*Figure 2*). A Luge angioplasty

guidewire was passed in to the vessel beyond the occluded segment, with little resistance. However, subsequent partial restoration of flow revealed that the guidewire was located in the first diagonal vessel, and not the LAD. Furthermore, the culprit lesion appeared to be situated at the origin of the bifurcation of the LAD and diagonal vessel (*Figure 3*). A second wire was therefore passed into the main vessel. Several balloon inflations were required to dilate this lesion before placement of drug-eluting stents. The diagonal stent was placed first, following which the guidewire within this vessel was removed. The LAD stent was then placed, crossing the diagonal and “crushing” the layers of the first stent in the process. After several high-pressure balloon inflations to compress the resilient culprit lesion, in addition to “kissing balloon” inflation simultaneously in the LAD and diagonal stents (*Figure 4*), Thrombolysis in Myocardial Infarction (TIMI) 3 flow was established in both the LAD and diagonal vessels (*Figure 5*). ST segments immediately resolved, as did the patient's symptoms. The patient was discharged after five uneventful days, with a life-long prescription for clopidogrel.

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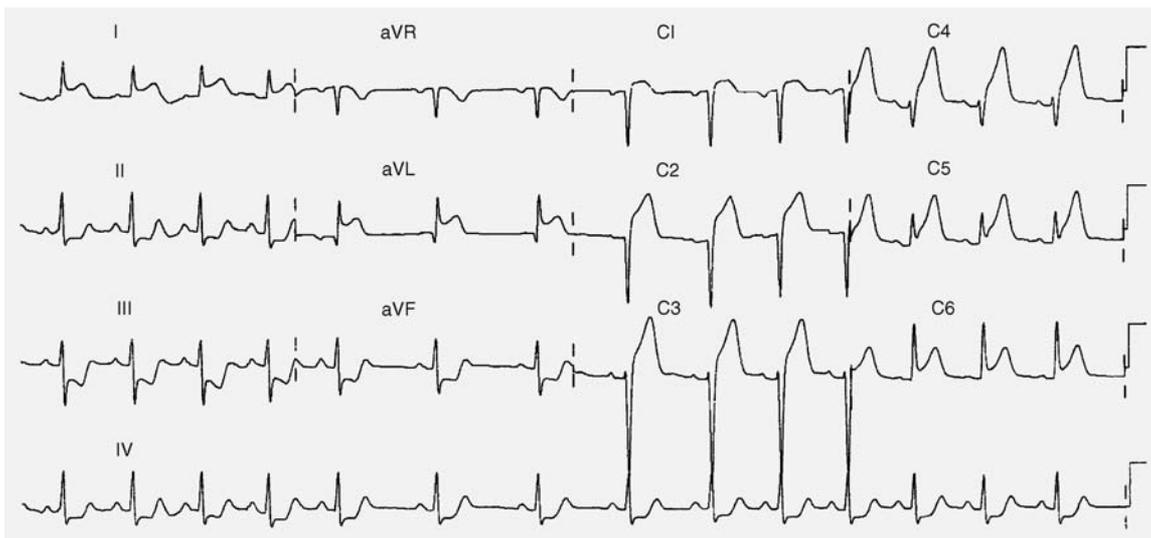


Figure 1. 12-Lead electrocardiogram showing anterolateral ST-segment elevation.

Discussion

Rationale for primary angioplasty

Management of acute myocardial infarction in a clinical setting is focused upon urgent restoration of flow in order to abrogate permanent damage to the heart. The critical relationship between infarct size and time was established by seminal experiments that demonstrated myocardial necrosis appearing within just 3 h after coronary artery occlusion [1]. The underlying pathology in most cases of acute myocardial infarction is believed to be a ruptured atherosclerotic plaque leading to thrombotic occlusion of the vessel [2]. Hence thrombolytic treatment has been established as the cornerstone of reperfusion therapy for many years. Despite percutaneous coronary interven-

tion having been introduced in 1977 for the treatment of stable coronary lesions [3], and primary angioplasty being performed just 2 years later [4], the routine management of acute myocardial infarction has remained largely confined to thrombolysis.

Recently, however, evidence has emerged suggesting that mechanically augmented vessel opening has advantages over pharmacological means alone, irrespective of the agent used [5]. The patient reported here illustrates one of the possible mechanisms for this disparity. A significant residual obstruction to flow persisted, despite repeated intracoronary balloon inflations, ultimately requiring both stent deployment and balloon inflations within the stented segment in order to restore TIMI 3 (ie, normal) flow. Hence, the culprit lesion may not have been adequately treated

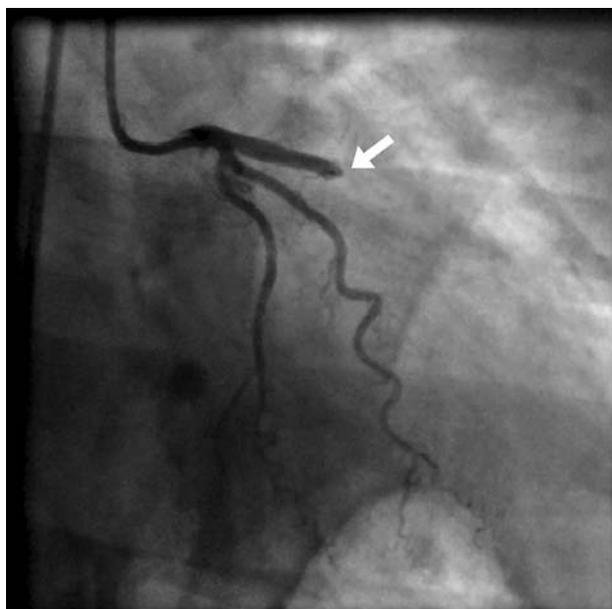


Figure 2. Occluded left anterior descending artery (arrow).

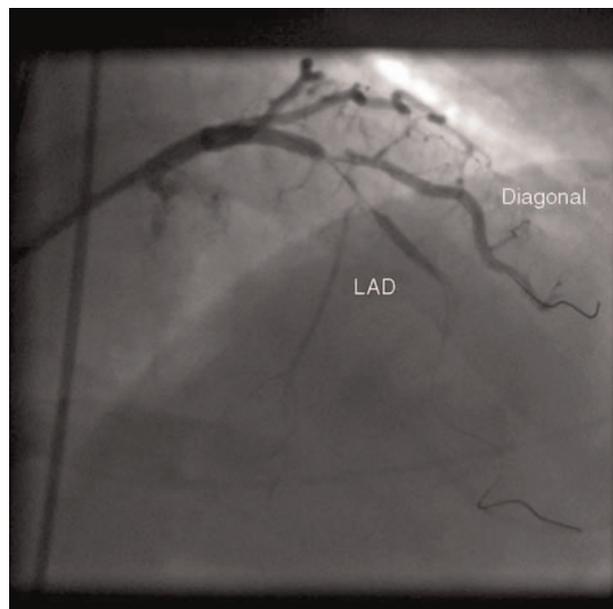


Figure 3. Bifurcation disease involving the left anterior descending (LAD) and diagonal vessels.

Case report

Primary angioplasty: worth the trouble?

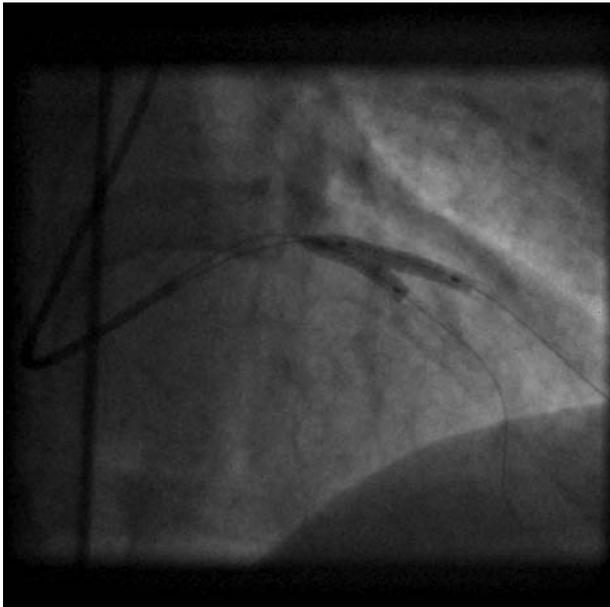


Figure 4. Kissing balloons after crush procedure.

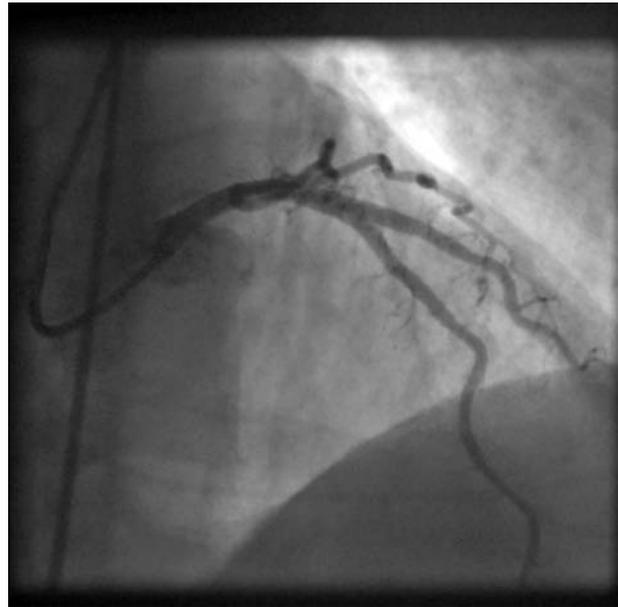


Figure 5. Final angiographic result.

with thrombolysis, despite full dispersion of the thrombus. This observation may explain the significant reductions demonstrated in those receiving primary angioplasty compared with thrombolysis for recurrent ischemia and recurrent non fatal myocardial infarction in both the short term (within 4–6 weeks) and longer-term (6–18 months) [5]. However, either strategy appears to confer similar benefits if applied within 3 h of the onset of pain, suggesting that the prompt administration of thrombolysis, such as by an ambulance crew, may be as effective as primary angioplasty in restoring perfusion. Nevertheless, after 3 h of the onset of pain, as in this patient, those receiving primary angioplasty instead of thrombolysis appear to obtain an overall benefit with respect to mortality [5]. Perhaps in light of these observations, the Department of Health has invested £1 million to determine the feasibility of implementing primary angioplasty as a nationwide strategy [6]. Furthermore, treatment of acute myocardial infarction by percutaneous coronary intervention is now enshrined in the most recent European Society of Cardiology guidelines [7].

Technical problems specific to primary angioplasty

Although primary angioplasty may seem to be an effective treatment for thrombotic coronary occlusion, this Case Report highlights several technical considerations that require further discussion.

Overall strategy

Unlike elective angioplasty, in the case of primary angioplasty the vessel to be treated has not been

visualized. Therefore the choice of initial catheter is determined primarily by the ECG, in order that the non culprit vessel may be imaged first. This strategy allows for the distal part of the occluded vessel to be revealed if collaterals are present. If the distal vessel cannot be seen, the possibility of encountering complex lesions should be considered, such as a bifurcation disease in this patient. Furthermore, the absence of forward flow may result in the guidewire advancing into an unwanted territory, such as a side branch, the vessel intima, or even outside the vessel. Currently, there are no trials that have investigated the optimum strategy for treating bifurcation lesions in acute myocardial infarction, although this patient demonstrates that techniques such as the “crush” [8] can be safely adapted from an elective situation, if the bifurcation angle is less than 50° and kissing balloons are used [9].

Antiplatelet agents

In our patient, clopidogrel was given in a dose of 600 mg as opposed to 300 mg. Although no trials have determined if the greater dose is superior in the context of myocardial infarction, platelet inhibition appears to be more effective during elective angioplasty when 600 mg is used [10]. Data from the only randomized trial comparing these doses in an elective setting suggest that there is less periprocedural myocardial injury with the greater dose, without increased bleeding complications [11]. Abciximab is also believed to be less than beneficial in the short term, by reducing target-vessel revascularization, although these benefits are not seen after one year, perhaps reflecting a lack of effect upon restenosis [12].

Case report

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Choice of stent

Data from two recent large trials [13,14] have indicated that drug-eluting stents may be used safely in primary angioplasty, and reduce the likelihood of repeat revascularization. However, given the cost of the prolonged treatment with clopidogrel that is necessitated by their use, and the corresponding bleeding risk, indications for the use of these stents should perhaps not exceed those used in elective cases.

Conclusion

Primary angioplasty is being recognized as a treatment that is superior to thrombolysis for some patients with myocardial infarction. This may account for the large national investment in the development of primary angioplasty as a 24 h service. However, establishing coronary flow in recently occluded vessels introduces challenges unique to this strategy, many of which will require further investigation before the widespread use of primary angioplasty can be advocated. ■

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The paradoxes of reperfusion in the ischemic heart

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Abstract

Although reperfusion is essential for salvage of the ischemic heart, reperfusion beyond a certain period of ischemia may cause injury to the myocardium. Dramatic changes in contractile function, arrhythmias, and ultrastructure occur in the ischemic-reperfused heart as a consequence of the generation of oxyradicals, loss of cation homeostasis, depletion of energy stores, and changes in subcellular activities. These acute effects of reperfusion appear to be the result of the occurrence of oxidative stress and intracellular Ca^{2+} overload in the heart. Alterations in cardiac gene expression may account for delayed recovery of subcellular organelles in the ischemic myocardium.

■ *Heart Metab.* 2007;37:31–34.

Keywords: Calcium-overload, cardiac dysfunction, ischemic myocardium, oxidative stress, reperfusion injury, subcellular remodeling

Introduction

Myocardial ischemia occurs when there is a reduction of blood flow as a result of narrowing of the coronary arteries during atherosclerosis, blockage of perfusion as a result of thrombosis, or development of coronary spasm. It is well known that myocardial ischemia results in the loss of contractile function and produces myocardial damage as a consequence of cell death from both necrosis and apoptosis [1–6]. It is therefore essential to restore coronary flow to the ischemic myocardium by interventions such as angioplasty, thrombolytic treatment or coronary bypass surgery [1]. However, if the coronary flow is not restored within a critical period of time, reperfusion itself may cause a wide variety of harmful effects in the ischemic heart – a

phenomenon referred to as “reperfusion injury” [4–6]. For example, reperfusion of ischemic tissue may intensify pathological processes that contribute to the generation of oxyradicals, disturbances in cation homeostasis, and depletion of cellular energy stores, which may elicit arrhythmias, contractile dysfunction, and ultrastructural damage, in addition to endothelial dysfunction and coronary vasoconstriction (*Figure 1*). These paradoxical effects of reperfusion become evident quite rapidly upon the restoration of perfusion [7–11], and may last for periods of several weeks to months. In particular, depressed cardiac function (myocardial stunning) of the ischemic-reperfused heart is commonly seen under chronic conditions after coronary bypass surgery or in patients with a heart transplant.

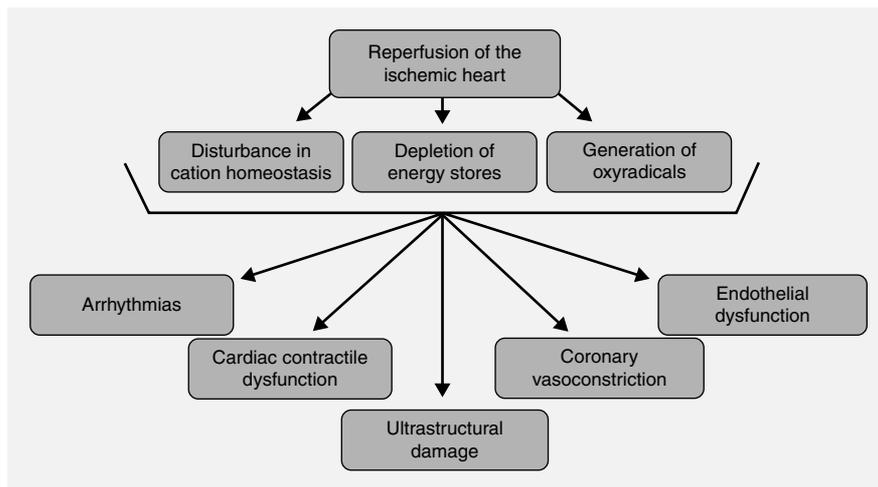


Figure 1. Paradoxical effects of reperfusion in the ischemic heart.

Ischemic injury or reperfusion injury

As ischemia reduces the delivery of oxygen and substrates to the myocardium, the initial process contributing to ischemic injury is a reduction of cellular energy status as a result of compromised mitochondrial production of ATP via impaired oxidative phosphorylation and electron transport [1,2,9,10]. Although there is an increase in anaerobic glycolysis in ischemic hearts, this metabolic change is not sufficient to meet the high energy demands for maintaining cardiac function [1,5,10]. Derangement of the mitochondrial electron transport system also promotes the generation of oxyradicals and development of oxidative stress in the ischemic heart [6,12]. Nonetheless, increased anaerobic glycolysis is considered to result in the accumulation of H^+ , stimulation of the Na^+-H^+ exchanger, activation of the Na^+-Ca^{2+} exchanger in the reverse mode, and development of intracellular Ca^{2+} overload [3,6]. Oxidative stress has also been shown to produce intracellular Ca^{2+} overload, and vice versa.

The degree of oxidative stress and the magnitude of intracellular Ca^{2+} overload in cardiomyocytes seem to be dependent upon the duration of ischemia. In fact, both oxidative stress and intracellular Ca^{2+} overload are considered to be the major mechanisms for the development of ischemic injury, and reperfusion appears to exacerbate the impact of these pathological processes [2,6,7]. Thus it is probable that ischemic injury and reperfusion injury are two facets of the same problem, in which ischemic injury is associated with alterations in myocardial metabolism, including depletion of energy stores, and the reperfusion injury is associated with additional changes, including the development of oxidative stress and the occurrence of intracellular Ca^{2+} overload (Figure 2).

Oxidative stress and the ischemia-reperfusion injury

Reactive oxygen species (ROS) are short-lived oxygen-derived free radicals, which act as signaling molecules at low concentrations, but adversely influence cell function by promoting lipid peroxidation and the oxidation of cardiac proteins when present in high concentrations. The major sources of ROS in the ischemic heart include the enzyme xanthine oxidase, the mitochondrial electron transport chain, and the NADPH oxidase system [8]. Oxidative stress may increase by as much as 100-fold during ischemia and reperfusion, as ROS production is greatly accelerated [8,12,13]. In addition, the cellular conditions associated with ischemia-reperfusion favor the

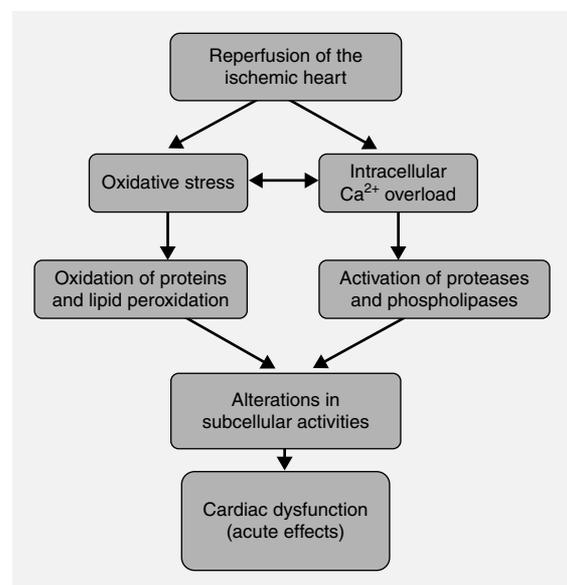


Figure 2. Mechanisms for the acute effects of reperfusion in the ischemic myocardium.

conversion of less reactive oxidants to more reactive species (e.g., the conversion of hydrogen peroxide to hydroxyl radicals or nitric oxide to peroxynitrite) [13,14]. These increases in ROS concentration and potency overwhelm the intracellular free-radical scavenger systems and leads to cellular injury during ischemia-reperfusion.

It has been demonstrated that ROS contribute to altered cation homeostasis through direct effects on membrane proteins involved in the regulation of cation transport and lipid peroxidation, which causes a change in membrane permeability [5] in addition to an increased inflammatory response to ischemia-reperfusion as a result of leukocyte activation. Prolonged oxidative stress also exerts chronic effects, as ischemia-reperfusion has been shown to produce expression of cardiac genes and associated remodeling of subcellular organelles [15,16] (Figure 3). Therapeutic treatments such as the administration of antioxidants or the overexpression of proteins that attenuate oxidative stress have been found to enhance the recovery of contractile function and to reduce infarct size, during ischemia and reperfusion [6,17].

Calcium overload and ischemia-reperfusion injury

Accumulation of intracellular Na^+ and Ca^{2+} during ischemia occurs in response to the loss of energy homeostasis and as a result of changes in the acute regulation of sarcolemmal and sarcoplasmic reticulum cation transport mechanisms. Specifically, ischemia reduces the activity of sarcolemmal Na^+/K^+ -ATPase,

increases the activity of the Na^+-H^+ exchanger, and promotes the activation of the $\text{Na}^+-\text{Ca}^{2+}$ exchanger in a reverse mode. Calcium transport is also affected by ischemia-reperfusion, because oxidative stress adversely influences Ca^{2+} -handling proteins in the sarcoplasmic reticulum (Ca^{2+} pump, sarcoplasmic reticulum Ca^{2+} -ATPase, and the Ca^{2+} release channel) and sarcolemma (sarcolemmal Ca^{2+} pump and the L-type Ca^{2+} channels) [6,18] and thus contributes to the development of an intracellular Ca^{2+} overload.

The pathological effects induced by intracellular Ca^{2+} overload are mediated by Ca^{2+} -induced activation of membrane phospholipases and proteases, and these changes may explain the acute effects of ischemia-reperfusion injury (Figure 2). Mitochondrial dysfunction [19] also contributes to the pathological effects associated with ischemia, because it is known that intracellular Ca^{2+} overload influences the opening of mitochondrial K_{ATP} channels and mitochondrial permeability transition pores, which activate apoptotic pathways [20]. Therapeutic treatments such as Ca^{2+} antagonists [21] and Na^+-H^+ exchange inhibitors [22], which attenuate intracellular Ca^{2+} overload, have been suggested to reduce the size of infarcts resulting from ischemia-reperfusion. Thus the development of intracellular Ca^{2+} overload can be seen to contribute to the acute effects of ischemia-reperfusion injury.

Subcellular remodeling in the ischemic-reperfused heart

During prolonged ischemia-reperfusion, significant changes in expression of cardiac genes occur such that subcellular organelles (eg, mitochondria, myofibrils, sarcolemma, and sarcoplasmic reticulum) are remodeled (Figure 3). As both oxidative stress and intracellular Ca^{2+} overload induced by ischemia-reperfusion are known to produce changes in gene expression, these factors seem to contribute to the remodeling of subcellular organelles and lead to a delayed recovery of contractile function [1,2,6]. These effects are not limited to the cardiomyocyte, as the pathological process may be amplified by the activation of neutrophils, which promote the formation of proinflammatory mediators, oxygen radicals, and the reduction of nitric oxide formation in the endothelium, leading to coronary constriction. Reperfusion-induced functional changes in vascular smooth muscle may also compound the injury process, as altered vascular reactivity may adversely influence the coronary flow and may result in a "no reflow" phenomenon. It may be noted that myocardial stunning, myocardial infarction [9,10,23], and potentially lethal arrhythmias are also associated with reperfusion of the ischemic heart [11]. Although preconditioning,

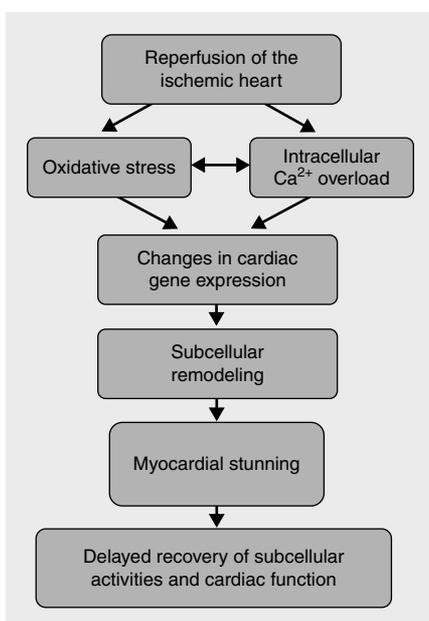


Figure 3. Mechanisms for the chronic effects of reperfusion (myocardial stunning) in the ischemic myocardium.

which is achieved by subjecting the heart to brief periods of ischemia, is known to limit both the size of the infarct and the cardiac dysfunction caused by ischemia-reperfusion [24], it is difficult to use this experimental intervention in clinical settings. Because Ca^{2+} handling by cardiomyocytes from ischemic reperfused heart becomes defective as a consequence of oxidative stress [25], it is to be emphasized that both intracellular Ca^{2+} overload and oxidative stress should be targeted, to avoid the adverse effects of ischemia-reperfusion injury.

Summary

Reperfusion of ischemic myocardium is invariably associated with arrhythmias and cardiac dysfunction as a consequence of the generation of oxyradicals, disturbance in cation homeostasis, and depletion of energy stores. Marked alterations in expression of cardiac genes as a result of ischemia-reperfusion are seen to explain subcellular remodeling and delayed recovery of cardiac function. These paradoxical effects of reperfusion appear to be attributable to the occurrence of oxidative stress and intracellular Ca^{2+} overload in the myocardium. ■

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Featured research

Abstracts and commentaries

The pH hypothesis of postconditioning. Staccato reperfusion reintroduces oxygen and perpetuates myocardial acidosis

Cohen MV, Yang X-M, Downey JM. *Circulation*. 2007;115:1895–1903.

Timely reperfusion salvages myocardium from tissue injury after prolonged ischemia. However, there is convincing evidence that sudden restoration of blood flow to ischemic myocardium may paradoxically exaggerate injury that is not present at the end of ischemia. A few years ago the evidence was presented that, in anesthetized open-chest dogs, several very brief coronary occlusions immediately after relief of a prolonged occlusion (ie, postconditioning) significantly reduced infarct size [1]. The degree of myocardial salvage with postconditioning was comparable to that observed with preconditioning. Postconditioning is protective in animals <http://circ.ahajournals.org/cgi/content/full/115/14/1895> and has had beneficial functional effects in patients who underwent coronary angioplasty for acute coronary occlusion. Until we understand its mechanism, however, it will be impossible to design an optimal postconditioning procedure.

The formation of mitochondrial permeability transition pores (MPTPs) leads to catastrophic consequences for reperfused cells, such as necrosis and apoptosis. Preconditioning suppresses the formation of MPTPs early in reperfusion as does postconditioning. In addition, cyclosporin A, which is a closer of MPTPs, is cardioprotective when infused at reperfusion, whereas atractyloside, which opens MPTPs, aborts the protection of preconditioning. Because acidosis prevents the formation of MPTPs by blocking Ca^{2+} binding to adenine nucleotide translocase (a component of MPTP) and displacing cyclophilin from it, the authors speculated that postconditioning might prevent the formation of

MPTPs by maintaining acidosis during the first minutes of reperfusion.

Commentary

After 30 min of regional ischemia in isolated rabbit hearts, reperfusion with buffer at physiological pH (7.4) caused $34.4 \pm 2.2\%$ of the risk zone to infarct, whereas 2 min of postconditioning (six cycles of 10 s reperfusion/10 s occlusion) at reperfusion resulted in $10.7 \pm 2.9\%$ infarction. One minute (three cycles) of postconditioning was not protective. Hypercapnic (ie, mildly acidic) buffer (pH 6.9) for the first 2 min of reperfusion in lieu of postconditioning caused equivalent cardioprotection ($15.0 \pm 2.6\%$ infarction), whereas 1 min of acidosis did not protect. Delaying postconditioning (six cycles) aborted protection. Reperfusion with alkaline buffer (pH 7.7) blocked postconditioning protection, but addition of the MPTP closer, cyclosporin A, restored protection. The protein kinase C antagonist, chelerythrine, and the mitochondrial K_{ATP} channel closer, 5-hydroxydecanoate, each blocked protection from 2 min of acidosis, as they did for postconditioning.

This study points to an important aspect of intracellular pH in controlling mitochondrial signals for protection of cardiomyocytes against reperfusion injury. Acidic perfusion had to be commenced immediately after release of the coronary occlusion. Indeed, myocardium becomes acidic during ischemia, but this acidosis is quickly relieved after reperfusion. MPTPs that could not open in an acidic milieu during ischemia quickly open as pH increases upon reperfusion. Opening of MPTPs leads to collapse of the mitochondrial transmembrane potential, cessation of ATP production, and subsequent cell death.

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Danielle Feuvray

Inhibition of free fatty acids metabolism as a therapeutic target in patients with heart failure

Fragasso G. *Int J Clin Pract.* 2007;61:603–610.

Recent studies have provided evidence that alterations in cardiac metabolism can be present in several cardiac syndromes. In heart failure, wasting of subcutaneous fat and skeletal muscle is relatively common, and suggests an increased utilization of non carbohydrate substrates for energy metabolism. In fact, fasting blood ketone bodies, in addition to fat oxidation during exercise, have been shown to be increased in patients with heart failure. This metabolic shift determines a reduction in myocardial oxygen consumption efficiency. A direct approach to manipulate cardiac energy metabolism consists in modifying substrate utilization by the heart. To date, the most effective metabolic treatments include several pharmacological agents that directly inhibit fatty acid oxidation. Clinical studies have shown that these agents can substantially increase the ischemic threshold in patients with effort angina. However, the findings of current research are also supporting the concept that shifting the energy substrate preference away from fatty acid metabolism and towards glucose metabolism could be an effective adjunctive treatment in patients with heart failure, in terms of improvement in left ventricular function and glucose metabolism. In fact, these agents have also been shown to improve overall glucose metabolism in diabetic patients with left ventricular dysfunction. In this paper, the recent literature on the beneficial therapeutic effects of modulation of the utilization of cardiac metabolic substrates in patients with heart failure is reviewed and discussed.

Commentary

The need to improve the management of heart failure is widely recognized, even though many advances have been made over the past decade.

The metabolic approach to heart failure is assuming increasing importance. Fragasso reviews in detail a metabolic approach that has the inhibition of free fatty acid metabolism as the therapeutic target. We

know myocardial energy metabolism may be normal in the early stages of heart failure, but, as the failure progresses, mitochondrial oxidative metabolism is reduced and glycolysis is increased, with downregulation of glucose and fatty acid oxidation. With the evidence that reducing fatty acid oxidation at the same time as increasing glucose oxidation can improve cardiac function and slow the progression of heart failure has come the concept of metabolic manipulation with drugs designed to inhibit fatty acid oxidation and simultaneously promote glucose oxidation.

The most widely studied metabolic agent is trimetazidine, which inhibits 3-ketoacyl coenzyme A thiolase, the last enzyme involved in β -oxidation. Importantly, trimetazidine has also shown good experimental evidence of efficacy, and important subjective and objective evidence of benefit in patients with heart failure. It is effective when used in addition to current-evidence based treatments, with minimal adverse effects and no drug interactions. The documented improvement in ejection fraction with this drug may be prognostically important, but this is as yet unproven (although the findings of one small study are very encouraging).

Fragasso's excellent review sets the benchmark for the use of a metabolic approach to the treatment of heart failure. Both Fragasso and I are in agreement that the "time has come to test this huge potential therapeutic advancement in heart failure syndromes which still suffer high morbidity and mortality". The potential to prolong life and with an improved quality is the optimal medical target, giving patients with heart failure new hope for the future.

Graham Jackson

Postconditioning the human heart

Staat P, Rioufol G, Piot C, et al. *Circulation.* 2005;112:2143–2148.

In animal models, brief periods of ischemia performed just at the time of reperfusion can reduce infarct size – a phenomenon called postconditioning. In this prospective, randomized, controlled, multicenter study, we investigated whether postconditioning may protect the human heart during coronary angioplasty for acute myocardial infarction. Thirty patients, submitted to coronary angioplasty for ongoing acute

myocardial infarction, took part in the study. Patients were randomly assigned to either a control or a postconditioning group. After reperfusion by direct stenting, control patients underwent no further intervention; in the other group, postconditioning was performed within 1 min of reflow by four episodes of 1 min of inflation and 1 min of deflation of the angioplasty balloon. Infarct size was assessed by measuring total creatine kinase release over 72 h. Area at risk and collateral blood flow were estimated on left ventricular and coronary angiograms. No adverse events occurred in the postconditioning group. Determinants of infarct size, including ischemia time, size of the area at risk, and collateral flow, were comparable between the two groups. The area under the curve of creatine kinase release was significantly reduced in the postconditioning group compared with controls (averages of $208\,984 \pm 26\,576$ arbitrary units (AU) and $326\,095 \pm 48\,779$ AU, respectively) representing a 36% reduction in infarct size. Blush grade, a marker of myocardial reperfusion, was significantly increased in the postconditioned group compared with controls: 2.44 ± 0.17 and 1.95 ± 0.27 , respectively ($P < 0.05$). These findings suggest that postconditioning by coronary angioplasty protects the human heart during acute myocardial infarction.

Commentary

Reperfusion is the definitive treatment to salvage ischemic myocardium from infarction. A primary determinant of infarct size is the duration of ischemia. In myocardium that has not been irreversibly injured by ischemia, reperfusion induces additional injury in the area at risk. The heart has potent innate cardioprotective mechanisms against ischemia-reperfusion that reduce infarct size and other presentations of postischemic injury. Ischemic preconditioning applied before the prolonged ischemia exerts the most potent protection observed among known strategies. It has been assumed that it exerts protection during ischemia. However, recent data suggest that cardioprotection is also exerted during reperfusion. Postconditioning, defined as brief intermittent cycles of

ischemia alternating with reperfusion applied after the ischemic event, has been shown to reduce infarct size, in some cases equivalent to that observed with ischemic preconditioning.

Although there are similarities in mechanisms of cardioprotection by these two interventions, there are key differences that go beyond simply exerting these mechanisms before or after ischemia. A significant limitation of ischemic preconditioning has been the inability to apply this maneuver clinically, except in situations in which the ischemic event can be predicted. In contrast, PoC is applied at the point of service in the hospital (catheter laboratory for percutaneous coronary intervention, coronary artery bypass grafting and other cardiac surgery) where and when reperfusion is initiated. Initial clinical studies are in agreement with the success and extent to which postconditioning reduces infarct size and myocardial injury, even in the presence of several comorbidities.

Percutaneous transluminal coronary angioplasty postconditioning is possibly not the easiest, and probably not the best, solution for all patients with acute myocardial infarction, and several questions remain to be addressed, including whether postconditioning protects the hearts of patients with comorbidities (diabetes, hyperlipidemia, age), the window of time for its application in humans, and whether it improves functional recovery and clinical outcome. We believe that pharmacological postconditioning is the most promising approach. Administration, at the time of reperfusion, of a given drug that will mimic ischemic postconditioning will make this protection available to all patients with acute myocardial infarction. An open question remains the route of administration of the protective agent. If reperfusion damage, mediated by oxygen free radicals, occurs instantaneously at the return of oxygenated blood in the ischemic territory, then the only means of successfully preventing reperfusion damage will be "preloading" the area with the protective agent (eg, adenosine) before vessel recanalization.

Mario Marzilli

Glossary

Gary D. Lopaschuk

cMR

cMR stands for cardiac magnetic resonance. MRI (magnetic resonance imaging) is a procedure that creates images of the body using powerful magnets and radio waves. cMR involves the imaging of the heart using this procedure.

MRI

MRI stands for magnetic resonance imaging. MRI is a procedure that creates images of the body using powerful magnets and radio waves. This non-invasive technique relies on the magnetic properties of atoms, rather than radiation. The imaging procedure utilizes extremely powerful magnets to create the radiowaves that produce the image.

Na⁺/Ca²⁺ exchanger

The Na⁺/Ca²⁺ exchanger is a membrane ion transporter that exchanges Na⁺ for Ca²⁺. During and following ischemia, the accumulation of intracellular Na⁺ can exchange with extracellular Ca²⁺. This can lead to Ca²⁺ overload and cell injury.

Na⁺/H⁺ exchanger

The Na⁺/H⁺ exchanger is a membrane ion transporter that exchanges Na⁺ for H⁺. In the heart, it is one of a number of pathways to extrude protons (H⁺) from the heart. However, this is coupled with a net inward flux of Na⁺. During and following ischemia, Na⁺/H⁺ exchanger activity increases, due to the ischemic-induced increase in intracellular acidosis. The increased Na⁺/H⁺ exchanger activity can lead to Na⁺ overload in the ischemic heart, which can decrease cardiac efficiency (energy is needed to extrude this Na⁺) and contribute to cell injury.

Na⁺/K⁺ ATPase

Na/K-ATPase is an ion pumps involved in the transport of Na⁺ and K⁺ across membranes. This involves the pumping of these ions against a concentration gradient, and therefore energy is required, which is

provided by the hydrolysis of ATP, the main energy currency in cells (hence the name ATPases). Na/K-ATPase pumps Na⁺ out of cells, while simultaneously pumping K⁺ into cells.

PCI

PCI stands for percutaneous coronary intervention, commonly known as coronary angioplasty. It is an invasive therapeutic procedure that involves passing a catheter into the coronary arteries of the heart. This catheter is used to open a blocked artery, either by inflating a balloon to open the artery, or by delivering a metal stent into the stenotic coronary artery. PCI can reduce the symptoms of coronary artery disease, including angina and congestive heart failure. PCI is also used to stop an acute myocardial infarction by reintroducing coronary blood flow into an area of the heart that is ischemic.

TIMI

TIMI is an acronym for thrombolysis in myocardial infarction; a large multicenter controlled clinical trial. This clinical trials group that performed this and other trials established a universally used coronary flow grading system to assess epicardial reperfusion, and demonstration of correlation between TIMI flow grade and survival in patients with STEMI. This uses a TIMI Frame Count to enhance reproducibility of the angiographic assessment of coronary blood flow. The TIMI Myocardial Perfusion Grade to assess tissue level reperfusion with demonstration of independent effects of these measures on survival.

SERCA2a

SERCA stands for sarcoplasmic/endoplasmic reticulum calcium ATPase. SERCA is the enzyme primarily involved in the transport of calcium into intracellular sarcoplasmic reticulum and endoplasmic reticulum. The sarcoplasmic reticulum (SR) is an intracellular organelle in heart and skeletal muscle that stores calcium. During excitation-contraction coupling, release of calcium from the SR is the major source of calcium that initiates muscle contraction.

Glossary

Gary D. Lopaschuk

STEMI

An acute coronary event is associated with the sudden rupture of plaque inside the coronary artery. This can cause changes in electrocardiogram, which include ST segment elevation. A myocardial infarction that is accompanied by this ST segment elevation is called a STEMI (ST segment elevation myocardial infarction).

TRS

TRS stands for TIMI Risk Score. TRS for unstable angina, STEMI, or nonSTEMI acute coronary events use simple risk scores derived from baseline clinical information to predict clinical outcomes and improve therapy in patients with unstable angina, STEMI, or nonSTEMI.