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What becomes of the brokenhearted?

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I’m searching though I don’t succeed,
But someone look, there’s a growing need.
Oh, he is lost, there’s no place for beginning,
All that’s left is an unhappy ending.

Witherspoon, Riser and Dean

This Motown hit by Jimmy Ruffin from the summer of 1966 is one of my all-time favorites and provides the ideal introduction, summary, and conclusion for this issue of *Heart and Metabolism* that is devoted to the subject of the prevention of left ventricular remodeling.

Remodeling of the heart is broadly divided into physiological and pathological. Physiological remodeling encompasses the normal developmental growth of the heart as the rest of the body grows (eutrophy), in addition to the hypertrophy (increase in heart muscle mass with respect to body weight) that accompanies “healthy” stresses such as pregnancy and frequent exercise. It is generally accepted that, during physiological remodeling, the cellular and extracellular components of the heart remain normal and the process is therefore completely reversible. Thus heart size has been documented to increase and decrease without any decrement in function during bed rest, weightlessness, and seasonal athletic training. In contrast, pathological remodeling is the term used to describe the complex alterations in the cellular and extracellular components of the heart that occur in response to pathological “unhealthy” stresses – predominantly, hypertension and ischemic heart disease. It is this latter form of irreversible left ventricular remodeling, characterized by interstitial fibrosis, that is the focus for this issue.

As hypertension is treated more aggressively, the etiology of pathological remodeling has changed. Thirty to forty years ago, the principal cause was hypertension. However, since the mid-1990s, the main underlying causes have been myocardial ischemia and infarction. Obviously, these conditions commonly co-exist.

In survivors of acute myocardial infarction, prognosis and the symptoms of heart failure are principally determined by left ventricular size. At any particular timepoint after infarction, left ventricular size is determined by the interplay of processes that: precede infarction (such as hypertension, valvular heart disease, and previous myocardial infarction); coincide with infarction (such as the location, size, and transmurality of the infarct, and the success/rapidity of reperfusion); and follow infarction (such as hypertension, valvular disease, and neurohormonal activation).

Largely as a result of the complexity and temporal interplay of these factors, it is difficult to separate the influence that the process of healing has on ventricular shape and size from other events occurring before, during, or after infarction. However, it seems likely that as many as 30% of patients surviving anterior myocardial infarction develop progressive left ventricular dilatation and eventual heart failure.
as a consequence of adverse left ventricular remodeling. This issue of *Heart and Metabolism* focuses on the description, measurement, and manipulation of these processes.

The new “Hot Topics” section includes a short summary of the features of left ventricular remodeling and the strategic points in its natural history at which interventions have been shown to be of benefit. This overview by Dr Huqi provides an excellent starting point from which to explore the role of the renin–angiotensin–aldosterone system (RAAS) that is the focus of the Main Clinical Article by Drs Morrone and Marzilli. Their article provides an excellent refresher of the basic biology, in addition to an overview of the pivotal outcome studies involving manipulation of this system early after myocardial infarction and later in the remodeling process once symptoms of heart failure are established. Although the role of the RAAS has been well established through clinical trials, there are biological processes, believed to be of crucial importance, for which there are no specific therapies.

In their New Therapeutic Approaches article, Drs Frantz and Bauersachs discuss an evolutionarily very primitive immune recognition system based on Toll-like receptors (TLRs). These receptors are present, not only on cells of the immune system, but also on cardiac myocytes, where they are designed to recognize the molecular characteristics of pathogens directly. Unfortunately, the receptors also recognize damage-associated molecular patterns and trigger responses that harm, rather than protect, the heart. TLRs have not yet been specifically targeted in patients post myocardial infarction, although some of the relevant downstream kinases, for example p38 mitogen-activated protein kinase, are under investigation in Phase 2 studies and are known to lead to programmed cell death. This is the topic reviewed by Dr Foo, who provides a very detailed overview of the processes that lead to apoptosis. It is quite possible that β-blockers and angiotensin-converting enzyme inhibitors have an impact on apoptosis but, as yet, as in the case of TLRs, no drugs that specifically target the cell death pathway have demonstrated success in clinical trials.

It is likely that the process of remodeling shows individual variability as a result of patient-specific biology. Currently, most of these biological processes go unrecognized because we lack the tools to distinguish them. Drs Coelho-Filho, Kwong and Jerosch-Herold provide a state-of-the-art overview of cardiac magnetic resonance imaging and how it can be used to gain better understanding of the processes leading to pathological remodeling in an individual patient. One such process that can be recognized early after myocardial infarction by means of gadolinium-based contrast agents is microvascular obstruction within the zone of infarction. This seems to predict subsequent poor healing, and probably identifies patients in whom it is particularly important to uptitrate medications to their full evidence-based dose. The advantages of cardiac magnetic resonance imaging are further reinforced in the striking case report, by Drs Nijveldt and van Rossum, of a patient in whom extensive microvascular obstruction within an anteroseptal ST-segment elevation myocardial infarction predicted early and marked adverse remodeling.

As illustrated in this issue, we understand more and more about the biology underlying pathological remodeling. Moreover, imaging techniques are fast evolving, which will help us identify these processes and discover those at risk. As this story of discovery unfolds ... all that’s left is a happy ending.

"see glossary for definition of this term."
Basic mechanisms in apoptosis and heart failure

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Conflicts of interest: None.

Abstract

The syndrome of heart failure may arise from different causes but there are features that are common to all: myocardial fibrosis, desensitization of β-adrenergic receptor signalling, excitation-contraction uncoupling, myosin isoform switch, altered energy utilization and “cell loss”. These unifying features imply that the molecular pathways that underpin them are activated in most, if not all, instances of heart failure. Good response to therapy such as angiotensin receptor or β-adrenergic receptor blockade, is also not selective to only specific causes of heart failure. Thus many molecular mechanisms now form important targets in the heart failure drug discovery pipeline.

The best-understood form of “cell loss” in the myocardium is APOPTOSIS. Both evolutionarily conserved pathways of apoptosis: extrinsic and intrinsic, are activated in heart failure. Apoptotic cell death involves the recruitment of death activating complexes whose formation is dependent on specific protein motifs called death domain motifs. Apoptotic cell death also characteristically requires the activation of caspases that selectively cleave proteins, eventually leading to cell disassembly. This review covers the basic mechanisms involved in apoptosis and heart failure.

Keywords: Apoptosis, caspases, death domain motifs, heart failure

Introduction

Molecular mechanisms in heart failure are increasingly well understood [1], and many aspects of these mechanisms currently form important targets in the heart-failure drugs-discovery pipeline [2]. Although heart failure may result from a variety of heterogeneous causes, it is striking that these are nonetheless linked by distinct unifying features such as myocardial fibrosis, desensitization of β-adrenergic receptor signalling, excitation-contraction uncoupling, myosin isoform switch, and altered energy utilization [2]. “Cell loss” is another unifying feature found in nearly all forms of cardiomyopathy [3–5], and loss of myocytes is predicted to decrease contractility and promote cell slippage, wall thinning, and chamber dilatation. Currently, the best understood form of cell loss or cell death in heart failure is apoptosis. This review aims to cover the mechanisms of the basic science involved in apoptosis.

Apoptosis is a regulated mode of cell death in multicellular organisms [6]. It is critical for sculpting tissue during development, and is also activated when tissues are exposed to injury, when irreparable damage is done and affected cells have to be eliminated. Apoptosis is often contrasted to necrosis, in which cell death involves cell lysis and produces a surrounding inflammatory response. Recently, however, tightly regulated processes in necrosis have also been identified [7]. Even so, there are biochemical and morphological changes that classically characterize apoptosis: cellular and nuclear shrinkage, chromatin condensation, cell membrane blebbing, formation of apoptotic bodies, and DNA fragmentation [8]. Most of these
features, best seen on electron microscopy, remain the hallmarks of apoptotic cell death.

There are two evolutionarily conserved pathways of apoptosis. The extrinsic pathway utilizes cell-surface death receptors and links external stimuli to intracellular apoptotic cell death machinery. The intrinsic pathway involves the mitochondria and endoplasmic reticulum, which, again, sense stimuli and transduce signals to execute apoptosis via another distinct set of molecules.

The extrinsic apoptotic pathway

In the extrinsic pathway, death ligands (such as FasL) interact and bind with their respective cell-surface death receptors (such as Fas ligand receptor), reorganizing the inactive receptor and stimulating the recruitment of adaptor proteins [such as Fas-associated via death domain (FADD)], which in turn recruits procaspase-8 into a multiprotein complex called the death-inducing signaling complex (DISC) [9]. Clustering of these interacting proteins within the DISC promotes autoproteolytic processing and activation of the caspase-8 by induced proximity [10]. In some cells, processed caspase-8 is sufficient to activate the other downstream effector caspases directly, leading to the execution phase of apoptosis (see below). In other cells, activation of downstream effector caspases further requires the amplification loop, where caspase-8 mediates cleavage of the proapoptotic Bcl-2 family member, Bid, which subsequently releases mitochondrial proapoptotic factors [11], linking the extrinsic pathway to the intrinsic pathway of apoptosis (see below). Figure 1 summarizes the interlinked pathways of the extrinsic and intrinsic apoptotic cascades.

Figure 1. The apoptotic cascade. ARC, apoptosis repressor with a caspase recruitment domain; cyt c, cytochrome c; DISC, death-inducing signaling complex; FADD, Fas-associated via death domain; FLIP, FADD-like interleukin-1b-converting enzyme-like inhibitory protein; XIAP, X-linked inhibitor of apoptosis. (Adapted from Foo et al [27], with permission.)
Formation of the multiprotein DISC complex is critically mediated by interactions between “death domain motifs” that are present on each of the components in the protein complex (eg, Fas, FADD, caspase-8). Death domain interactions are characteristic in the formation of “death” complexes in both pathways of apoptosis. Fasl–Fas interaction and DISC complex formation are regulated by the soluble endogenous decoy receptor, DcR3 [12], by various Fas isoforms lacking the death domain [13], or by soluble Fasl generated by proteolytic processing or alternative splicing [14]. The FasL gene is often transcriptionally inactive, and upregulated by transcription factors such as nuclear factor kappa B (NFκB), and nuclear factor of activated T cells (NFAT) [15]. Expression of Fas may, similarly, be regulated by the transcription factor, p53 [16]. The extrinsic pathway of apoptosis is also held in check by the endogenous anti-apoptotic FADD-like interleukin-1b-converting enzyme-like inhibitory protein (FLIP) [17]: FLIP binds to and inhibits procaspase-8. The protein, Ithc, is a ubiquitin E3 ligase for FLIP, mediating FLIP ubiquitination and degradation. In death receptor tumor necrosis factor-α signaling, Jun kinase-mediated activation of Ithc is proapoptotic because it leads, downstream, to FLIP protein degradation [18].

**The intrinsic apoptotic pathway**

The intrinsic pathway transduces extracellular and intracellular stimuli, including nutrient depletion, radiation, hypoxia, oxidative stress, ischemia-reperfusion, and DNA damage. Direct signaling from each of these is unclear, but they converge on the pivotal event of mitochondrial outer membrane permeabilization (MOMP) [19]. At the mitochondria, MOMP often follows dissipation of the mitochondrial inner transmembrane potential (Δψm), which may involve opening of the mitochondrial permeability transition pore [19]. A separate mechanism for MOMP involves members of the Bcl-2 family of proteins acting at the outer mitochondrial membrane. Bcl-2 (the mammalian homologue of ced-9) is the prototype of the important family of genes in this intrinsic pathway of apoptosis [20]. Bcl-2 family members share Bcl-2 homology (BH) domains. The BH123 (multidomain) members, Bax and Bak, are proapoptotic proteins that, upon apoptotic stimuli, undergo conformational change, oligomerize, and translocate to the mitochondrial outer membrane, promoting MOMP. Cells lacking the Bax and Bak genes fail to undergo MOMP, reflecting the critical role for these multidomain proteins in the intrinsic pathway of apoptosis. The other subfamily, BH3-only proteins, are proapoptotic and can activate Bax/Bak either directly (effectors; eg, Bid and Bim) or by interfering with anti-apoptotic Bcl-2 family members (sensitizers; eg, Puma, Noxa, Bad). Anti-apoptotic Bcl-2 family proteins such as Bcl-2 itself, Bcl-xL and Mcl-1 prevent MOMP by sequestering BH3-only proteins, and probably also Bax and Bak themselves. Recently, p53 was shown to have a nontranscription-related role in apoptosis by translocating to the mitochondria and directly promoting the oligomerization of Bax and Bak (acting like an effector), or by binding and neutralizing anti-apoptotic members Bcl-xL and Mcl-1 (acting like a sensitizer) [21]. An emerging theme is of other nuclear proteins that function in the cytosol through interaction with Bcl-2 family proteins; these include Ku70 which, apart from being involved in DNA repair, also inhibits the translocation of Bax to the mitochondria [22]. Nuclear protein TR3 also binds Bcl-2 and promotes MOMP [23]. Histone 1.2, released from the nucleus after DNA damage, triggers MOMP – again via an interaction with Bcl-2 family members [24].

After MOMP, critical apoptogens (eg, cytochrome c) are released from the mitochondrial intermembrane space into the cytosol [25]. When in the cytosol, cytochrome c binds to the adaptor protein, Apaf-1. Apaf-1 oligomerizes into an apoptosome, which recruits and activates caspase-9. Like DISC in the extrinsic pathway, recruitment of caspase-9 in the apoptosome is dependent on “death domain motifs” on both caspase-9 and Apaf-1 [19]. As with caspase-8, activated caspase-9 activates downstream effector caspases and leads to the execution phase of apoptosis. This sequence of events is depicted at bottom left in Figure 1.

**Caspases**

This family of cysteine proteases recognize specific peptide sequences and cleave proteins only after an aspartic acid residue. The specificity of caspases is consistent with the characteristic that apoptosis does not involve indiscriminate protein digestion, but rather a selection of proteins is cleaved in a coordinate manner, resulting in cell disassembly. Specific substrates of downstream effector caspases (traditionally believed to be 3 and 7) include inhibitor of caspase-activated DNase (the inhibitor of the nuclease responsible for DNA fragmentation), the nuclear lamina, and cytoskeleton regulators such as focal adhesion kinase. In unstressed conditions, effector caspases are inhibited by endogenous X-linked inhibitor of apoptosis (XIAP). Upon apoptotic stimuli, another set of mitochondrial apoptogens (Smac/DIABLO and Omni/HtrA2) are released from the mitochondria [26]. These bind and inactivate XIAP and thereby activate effector caspases.
Significance of apoptosis in heart failure

Heart failure is characterized by a very low, but significantly increased prevalence of myocyte apoptosis (0.08–0.25%) in individuals with dilated cardiomyopathy, compared with 0.001–0.002% in controls [27]. Several mouse models demonstrate that myocyte apoptosis itself directly causes dilated cardiomyopathy [28–30], and increased apoptosis may mark the transition from compensated hypertrophy to decompensated cardiomyopathy [31]. Moreover, both extrinsic and intrinsic pathways of apoptosis operate in the stressed myocardium [27]. Loss of survival signals demonstrates that accelerated apoptosis aggravates cardiomyopathy [29], and overexpression of anti-apoptotic proteins such as Bcl-2 [32] provides proof of concept that apoptosis is a valid target for the design of novel heart failure therapy.

REFERENCES

Role of RAAS inhibition in preventing left ventricular remodeling in patients post myocardial infarction

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Conflicts of interest: Prof. Marzilli has given lectures on Ischemic Heart Disease for Servier International.

Abstract

Left ventricular remodeling after myocardial infarction has been identified as a predictor of adverse outcome and as a relevant therapeutic target. It has been shown that upregulation of the renin–angiotensin–aldosterone system (RAAS) has an important role in the pathogenesis of cardiac remodeling. In this paper we summarize evidence on the role of the RAAS in the development of left ventricular remodeling and review major trials based on the addition of an RAAS inhibitor to standard therapy in the post myocardial infarction setting to prevent remodeling and improve outcome.

Heart Metab. 2010;47:9–13.

Keywords: Aldosterone blockers, angiotensin converting enzyme inhibitors, angiotensin receptor blockers, left ventricular remodeling, renin–angiotensin–aldosterone system

Introduction

Mechanical reperfusion therapy and current pharmacological treatment can, to some extent, limit cardiac dysfunction and adverse ventricular remodeling in patients with acute myocardial infarction; however, progressive ventricular dilatation is still observed in a substantial proportion of patients [1]. Left ventricular remodeling includes changes in ventricular structure, volume, and shape after an acute myocardial infarction. The process develops in two phases: an early one, with expansion limited to the infarct zone, and a late one, the so-called late remodeling phase, when the entire left ventricle undergoes progressive dilatation. Left ventricular remodeling eventually results in chamber dilatation and sphericity [2]. Initially, ventricular dilatation may be useful in maintaining an adequate cardiac output despite the loss of contractile elements; however, at the same time, it is a detrimental process because it renders the ventricle more prone to dysfunction and eventually to heart failure. Importantly, left ventricular remodeling may also be associated with an increased risk of ventricular arrhythmias.

Left ventricular remodeling is most pronounced in patients with a large anterior infarction or microvascular dysfunction, or both. Endocrine/autocrine/paracrine neurohormonal signaling is the driver for the process, the acute phase of myocardial infarction being characterized by a short-lived but intense neuroendocrine activation, with plasma concentrations of angiotensin II peaking at 3 days. Myocyte hypertrophy and excess extracellular deposition of collagen are key histologic components.
Activation of the renin–angiotensin–aldosterone system (RAAS) participates actively in the process of left ventricular remodeling. Renin is a proteolytic enzyme that is released into the circulation primarily by the juxtaglomerular cells. Its release is stimulated by renal artery hypotension and is followed by sympathetic nerve activation and by decreased delivery of sodium to the distal renal tubules. When renin is released into the blood, it acts upon a circulating substrate, angiotensigen, that undergoes a proteolytic cleavage to form the decapetide, angiotensin I. Vascular endothelium, particularly in the lungs, has an enzyme, angiotensin converting enzyme (ACE), that cleaves off two amino acids to form the active octapeptide, angiotensin II.

Under pathological conditions, the RAAS is activated by several factors – in particular, inflammation and endothelial dysfunction. Its stimulation, with the spillover of aldosterone, is responsible for extracellular matrix proliferation and contributes to the increased deposition of fibrous tissue within the ventricular myocardium [3]. The presence of myocardial fibrosis and endothelial dysfunction may affect the coronary microcirculation; in particular, the decrease in myocardial capillary density can contribute to the progression of left ventricular remodeling towards heart failure [4]. For this and other reasons, therapeutic interventions in patients with post infarction left ventricular dysfunction should be aimed at preventing the activation of the RAAS, with possible beneficial effects on left ventricular structure, size, and function. In this respect, a number of pharmacological approaches have demonstrated their efficacy and have significantly reduced mortality and morbidity in patients with a history of acute myocardial infarction.

**Inhibition of the renin–angiotensin–aldosterone system**

ACE inhibitors were the first drugs to be used to block the RAAS. Inhibition of ACE results in a decrease in the concentration of angiotensin II at the angiotensin receptor sites. Over the past 25 years, several clinical trials have demonstrated the beneficial effects of ACE inhibitors in patients with acute myocardial infarction, with favorable prognostic implications.

The Survival And Ventricular Enlargement (SAVE) trial was a landmark study by Pfeiffer et al [5]. They enrolled patients with left ventricular dysfunction (ejection fraction no greater than 40%) after acute myocardial infarction, who were treated with captopril, starting between 3 and 16 days after admission to hospital. An attenuation of ventricular enlargement became apparent after 12 months and was associated with a significant reduction in morbidity and mortality. In the Studies Of Left Ventricular Dysfunction Treatment and Prevention (SOLVD) trial [6], patients with acute myocardial infarction, ejection fraction <35%, with or without signs and symptoms of heart failure, were allocated randomly to groups receive to enalapril or placebo within the 24–36 hours from their admission to hospital. The study again showed an improved survival in patients receiving the ACE inhibitor. An echocardiographic substudy of the SOLVD trial demonstrated a trend toward reduction in left ventricular end-diastolic volume in the enalapril group with respect to those receiving placebo [7] (Figure 1). In the Gruppo Italiano per lo Studio della Sopralevvenza dell’Infarto Miocardico (GISSI-3) trial, administration of lisinopril was associated with an improved outcome in patients treated after 24–36 hours from an acute myocardial infarction. The beneficial effects of the drug on left ventricular volumes have been documented in an echocardiography substudy [8] of the main trial. A significant reduction in left ventricular enlargement was already present after 6 weeks of lisinopril treatment. According to the study investigators, early RAAS blockade should be included in a systematic strategy of prevention of post infarction left ventricular remodeling.

Most of the above-mentioned trials did not include elderly patients. As aging is a factor well known to be involved in the process of left ventricular remodeling, a study was designed to investigate the effects of a relatively new ACE inhibitor, perindopril, in elderly patients diagnosed with acute myocardial infarction. In the Perindopril and Remodeling in Elderly With Acute Myocardial Infarction (PREAMI) trial, 1252 post myocardial infarction patients aged at least 65 years with ejection fractions of at least 40% were allocated randomly to groups to receive perindopril or placebo. The study showed that the administration of perindopril was associated with a 0.22 absolute risk reduction in the composite endpoint of death, admission to hospital because of heart failure, or remodeling (95% confidence intervals [CI], 0.16 to 0.28; \( P < 0.001 \) [9]. In a recent echocardiographic sub-study of that trial, it became apparent that the administration of a daily dose of 8mg of perindopril was associated with prevention of progressive left ventricular dilatation [10].

The selective blockade of the angiotensin II receptor type 1 is another means by which to inhibit the RAAS that is associated with favorable effects on left ventricular structure and function. This is likely to be one of the mechanisms that contribute to the improved outcome of patients with heart failure secondary to postischemic left ventricular dysfunction, as shown by several clinical trials (eg, Candesartan in Heart failure – Assessment of Reduction in Mortality and Morbidity [CHARM] [11], Optimal Trial in Myocardial Infarction with Angiotensin II Antagonist...
Losartan [OPTIMAAL] [12], Valsartan Heart Failure Trial [Val-HeFT] [13]). A positive impact on remodeling has also been observed in patients treated with aldosterone antagonists [14]. Aldosterone exerts several actions that may contribute to adverse left ventricular remodeling: worsening tissue injury, myocyte loss, and reparative myocardial fibrosis. Additional mechanisms include myocyte apoptosis and direct stimulation of collagen synthesis, which may derive from repetitive stunning and oxidative stress. Two large trials evaluated the use of aldosterone receptor antagonists: the Eplerenone Post–Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS) and the Randomized Aldactone Evaluation Study (RALES). The EPHESUS trial compared placebo with the selective aldosterone blockade, eplerenone, added to a background ACE inhibitor – and, in most cases, β-blocker treatment – in patients with post ischemic left ventricular systolic dysfunction. Eplerenone significantly reduced mortality (by 15%), supporting the strategy of adding an aldosterone receptor blocker to an ACE inhibitor or an angiotensin II type 1 receptor blocking agent (ARB). This makes sense from a pathophysiological standpoint, because aldosterone is regulated independently of angiotensin II. Aldosterone blockade is therefore a complementary, rather than a competing, treatment for the survivors of acute myocardial infarction [15]. The RALES trial, which was discontinued early because an interim analysis determined that spironolactone to candesartan (an angiotensin type II receptor blocker) in patients who had suffered acute myocardial infarction. They reported a significant reduction in left ventricular end-diastolic and end-systolic volumes and an improvement in left ventricular ejection fraction. Therapeutic perspectives

Although ACE inhibitors and ARBs have both been shown to be effective in improving mortality and morbidity in acute myocardial infarction complicated by left ventricular systolic dysfunction, left ventricular remodeling remains a frequent and adverse consequence of myocardial infarction. Left ventricular remodeling contributes to the progression from left ventricular dysfunction to heart failure, and markedly affects clinical outcome and quality of life of patients who have suffered myocardial infarction. For this reason, alternative therapeutic options that may be implemented in these patients are actively sought (Table I).

A number of new therapeutic interventions targeting left ventricular remodeling have been proposed. Because aldosterone stimulation is recognized to have a negative effect on left ventricular remodeling [16], Chan et al [17] undertook a magnetic resonance imaging study to investigate the addition of spironolactone to candesartan (an angiotensin type II receptor blocker) in patients who had suffered acute myocardial infarction. They reported a significant reduction in left ventricular end-diastolic and end-systolic volumes and an improvement in left ventricular ejection fraction.

Aliskiren, a direct renin antagonist, improved left ventricular function and prevented cardiac remodeling in experimental mice submitted to an acute ischemic injury [18].

After myocardial infarction, excessive deposition of extracellular collagen matrix (ECCM) has been
associated with evidence of left ventricular diastolic dysfunction. Modulation of collagen formation and degradation and control of extracellular matrix deposition have been proposed as possible therapeutic approaches. Preservation of a correct balance between matrix metalloproteinase activity and endogenous tissue inhibitors of matrix metalloproteinases could be an effective therapeutic strategy with which to prevent ventricular remodeling [19].

Collagen formation occurs by eight enzymatic steps: intracellular synthesis of pro-chains, hydroxylation, glycosylation, formation of procollagen triple helixes, secretion into the extracellular space, conversion into less soluble molecules, assembly into fibrils, and aggregation into fibers. Prolyl-4-hydroxylase catalyzes the hydroxylation of proline on α monomers to yield stable protocollagen molecules that are secreted into the ECCM; this enzyme could be a possible therapeutic target. Both ACE inhibitors and ARBs, in addition to aldosterone blockers, decrease ECCM. The aldosterone antagonist, spironolactone, decreases collagen turnover and ARBs also decrease prolyl-4-hydroxylase [20–23]. Protecting the ECCM post myocardial infarction could be a promising target for treatment.

A new pharmacological option may be offered by agents that inhibit both the ACE and neutral endopeptidase enzymes: vasopeptidase inhibitors (Figure 2). Lapointe et al [24] demonstrated that the neutral endopeptidase inhibitor, omapatrilat, improved post myocardial infarction cardiac function and prevented cardiac remodeling in a rat model.

However, not all treatments that were associated with a beneficial effect on left ventricular remodeling

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Table 1. Potential therapeutic strategies to prevent left ventricular remodeling.
have later been associated with an improved clinical outcome, suggesting that disease progression may also occur through alternative mechanisms, independent of cardiac remodeling [25]. It is possible that sex differences could have a critical role in this respect, based on different concentrations of the sex-related hormones, estrogens and testosterone [26].

Summary

RAAS inhibition in the setting of acute myocardial infarction represents an established strategy to reduce cardiovascular mortality and morbidity. The beneficial effects of RAAS inhibition with ACE inhibitors, ARBs, and aldosterone antagonists can be attributed, at least in part, to the prevention or attenuation of left ventricular remodeling.

* see glossary for definition of these terms.

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Magnetic resonance imaging to assess ventricular remodeling

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Conflicts of interest: None.

Abstract

Ventricular remodeling has a key role in the pathology of ventricular dysfunction. During the reaction to a myocardial insult, the ensuing genetic, structural, and biochemical changes will result in the deterioration of the functional ability of the heart in the long term. Non invasive imaging plays a central part in the diagnosis of heart failure, assessment of ventricular remodeling, prognosis, and monitoring of therapy. Cardiovascular magnetic resonance offers a unique and comprehensive assessment of patients with heart failure and has attained a role as gold standard among imaging techniques to assess myocardial anatomy, regional and global function, and viability.

Heart Metab. 2010;47:14–18.

Keywords: Cardiovascular magnetic resonance, heart failure, imaging, ventricular remodeling

Introduction

Heart failure is a multifaceted clinical syndrome with high rates of admissions to hospital and mortality; coronary artery disease (CAD) is its main etiology in developed countries. Ventricular remodeling leading to heart failure can have many causes, including hypertension, CAD [1], high-intensity endurance training [2], and non-CAD causes such as infiltrative myocardial diseases and viral myocarditis. Adverse ventricular remodeling has been defined as the “genomic expression resulting in molecular, cellular and interstitial changes that are manifested clinically as changes in size, shape and function of the heart after cardiac injury” [3]. An accurate quantitative assessment of ventricular remodeling is instrumental both for prognosis and to follow the effectiveness of therapeutic interventions. Cardiovascular magnetic resonance (CMR) can add novel markers of structural alterations that initiate or accompany early phases of ventricular remodeling. The integration of CMR into the clinical work-up of patients with heart failure is furthered by its capacity to answer a range of clinical questions without the need for additional tests. A recent European survey of the clinical utility of CMR revealed a broad range of clinical indications, from myocarditis and post myocardial infarction to assessment of cardiac masses, with CMR having a direct impact on patient management in up to two-thirds of cases [4]. The current review will focus on recent developments in CMR that are relevant to the assessment of the pathophysiological changes associated with ventricular remodeling.

Ventricular function, volume, and shape

Changes in ventricular geometry and ventricular function reflect the most obvious aspects of adverse remodeling, but may in fact reveal only the “tip of the iceberg”. Cine CMR imaging of parallel, contiguous short-axis slices covering the entire heart over
a user-defined number of cardiac phases has become a reference standard by which to assess ventricular function and structure. Global left ventricle and right ventricle volumes and mass are derived from cine CMR without the need for any geometrical assumptions, applying to ventricles of all sizes and shapes, even to those that have experienced extensive remodeling [5]. Cine CMR with steady-state free precession (SSFP) – a relatively recent innovation with high signal-to-noise and tissue-to-blood contrast – enables an accurate identification of even subtle regional wall motion abnormalities [6].

In patients with heart failure, cine CMR demonstrates superiority over other non invasive techniques, showing less inter-study variability and better reproducibility of the volumetric results. Bellenger et al [7] argued that the excellent reproducibility of cardiac cine CMR would translate into smaller sample sizes in clinical trials. As evidence of their foresight and predictions, we point out a recent randomized study with CMR in 41 patients [8] that demonstrated that β-blocker therapy has antiremodeling effects on the left ventricle in patients with chronic heart failure – a result that is consistent with the highly significant decrease in mortality from worsening heart failure among 4000 patients in the Metoprolol Randomized Intervention Trial in Congestive Heart Failure (MERIT-HF) [9]. The most common measures quantifiable by cardiac cine CMR are the ventricular dimensions and volumes, myocardial mass, and derived quantities such as ejection fraction, stroke volume, and cardiac output. Additional measures relate to the shape of the ventricle, such as the ratio of the long axis to the short axis, which plays an important part in the pathogenesis of mitral regurgitation. A related measure of left ventricular shape is the sphericity index, defined as the ratio of the major axis to the minor axis of the left ventricle [10].

Flow, or wall, velocities can be quantified with CMR, using the phase-contrast technique. In the presence of a single valvular insufficiency, such as mitral regurgitation or aortic regurgitation alone, comparison of right and left ventricular stroke volumes by either cine CMR or phase-contrast blood flow measurements can accurately estimate the degree of valvular dysfunction – for example, that of stenotic aortic valves [11].

Wall stress and strain

Wall stress has an important role in ventricular remodeling, both as a powerful stimulus for remodeling, and as a marker of the adverse ventricular adaptation [12]. Ventricular dilatation increases the radius of curvature and is accompanied by wall thinning, both changes leading to increased wall shear stress. Estimates of regional wall stress require determination of wall thickness and wall curvature, highly accurate measures of which are accessible by cine CMR. An average measure of wall stress [13] can be obtained from the modified Laplace equation. The approach introduced by Grossman et al [14] can be adapted to CMR to estimate the regional peak systolic wall stress in the radial direction (σr) by measuring the inner radius of the left ventricle (R) and wall thickness (t) at end systole:

\[ σ_r = \frac{(0.133 \times SP \times R)}{(2t \times (1 + (t/2R)))} \]

where SP is peak systolic ventricular blood pressure in millimeters of mercury. In healthy individuals, the principal stress component was estimated by finite element analysis to be greatest near the base of the heart; it decreases by about 40% towards the apex of the heart, even without accounting for a ventricular pressure gradient from base to apex [15]. Using CMR, Blom et al [16] demonstrated the benefits of a ventricular constraint device that provided passive mechanical diastolic support to curb ventricular remodeling and reduce ventricular wall stress in sheep with myocardial infarction.

Myocardial viability and infarct remodeling

Gadolinium contrast used with CMR remains confined to the extracellular space in normal myocardium. Within infarcted myocardium, the volume of distribution for gadolinium contrast is significantly expanded, reaching 60–70% in scar tissue. As early as 3 or 4 min after administration of gadolinium contrast, the expanded distribution volume can be reliably detected with CMR to demarcate non viable myocardium [17], with at least 4–6-fold greater spatial resolution and a greater contrast-to-noise ratio than can be achieved with nuclear scintigraphy. The focal signal hyperintensity of infarcted myocardium, or myocardial scar tissue, is highlighted by suppressing the signal from normal myocardium [18]. Late gadolinium enhancement (LGE) images delineate the transmural extent of infarction (Figure 1), thereby distinguishing between reversible and irreversible myocardial injury, regardless of the extent of wall motion at rest, the age of the infarct, or the reperfusion status [19,20]. In a landmark study of patients with CAD, the probability of improvement in regional contractility after successful coronary revascularization decreased in inverse proportion to the transmural extent of LGE before revascularization, showing that LGE provides important information regarding ventricular remodeling and recovery in function after a myocardial infarction [21].

LGE imaging is consistently more sensitive and specific than any other techniques in detecting and
sizing the spatial extent of myocardial infarction [22,23]; the transmural extent of LGE can predict the response of left ventricular function to β-blocker therapy in patients with heart failure [24]. Orn et al [25] found that scar size assessed by CMR was the strongest independent predictor of ejection fraction and left ventricular volumes in acute myocardial infarction, and of patients with heart failure. Even in patients with suspected CAD, but without a history of myocardial infarction, LGE involving a small amount of myocardium carries a high cardiac risk, including in patients with very few signs of ventricular remodeling [26]. It was shown recently that CMR measurements of gadolinium distribution volumes in viable myocardium provide a novel marker of extracellular remodeling and diffuse fibrosis in patients with heart failure and dilated cardiomyopathy [27,28], pointing to the versatility of CMR for extensive tissue characterization in patients with heart failure.

CMR can also assess complications after myocardial infarction, such as left ventricular mural thrombus, aneurysmal dilatation, and papillary muscle involvement causing mitral regurgitation and rupture of the interventricular septum [29]. Because thrombus is an avascular structure, on LGE images it usually appears as a mass with low signal intensity surrounded by areas of high signal intensity such as cavity blood (Figure 2).

After an acute myocardial infarction, infarct remodeling is governed by the status of coronary reflow, degree of ischemia, collateral formation, and infarct location. CMR techniques can capture and characterize the multifaceted process of infarct remodeling, and shed light on novel markers beyond infarct and scar size, cavity enlargement, and left ventricular function. The border zone of infarction with intermediate signal intensity on LGE images provides a stronger association with electrophysiological substrates of ventricular arrhythmias than with left ventricular ejection fraction. The border zone was strongly associated with post myocardial infarction mortality in a small group of patients post myocardial infarction [30]. The myocardial extent of no-reflow (microvascular obstruction) (Figure 3), despite successful coronary revascularization after acute myocardial infarction, was shown to be an independent and significant prognostic factor [31], and is associated with adverse

Figure 1. Cardiovascular magnetic resonance image of a patient with a myocardial infarction in the mid-left anterior descending artery territory. (a) Systolic cine steady-state free precession images demonstrating moderate left ventricular dysfunction (left ventricular ejection fraction 38%) with akinesis of anteroseptal walls. (b) Late gadolinium enhancement image showing a full-thickness myocardial infarction (arrows) matching the wall motion abnormality, and implying a very low likelihood of recovery after revascularization. LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle.

Figure 2. Four-chamber late gadolinium enhancement image of a 63-year-old man with a recent history of an anterior ST-segment elevation myocardial infarction referred to cardiovascular magnetic resonance imaging for left ventricular function. There is a transmural myocardial infarction involving the entire mid to distal anterior and anteroseptal wall of the left ventricle, associated with a large thrombus located in the left ventricular apex (arrow). LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle.
ventricular remodeling [32]. T2-weighted imaging has been used to characterize the extent of myocardial edema as the “at-risk region” as a result of ischemia [33], and to differentiate between acute and chronic CAD [34].

Conclusions

The application of CMR in the evaluation of patients with heart failure is bound to expand substantially in the coming years, to the point that most patients with heart failure will undergo CMR imaging as part of their diagnostic work-up, as an aid to guide management, and as a means to stratify risk. Novel CMR techniques aiming at the identification and quantification of diffuse fibrosis [27,28] will further improve in-vivo, non invasive assays of myocardial pathology. Careful application of this technology has the potential to improve both diagnostic efficiency and the care of patients with heart failure.

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Toll-like receptors (TLRs) have been identified as central innate immune receptors. They distinguish among different patterns of pathogens and rapidly activate an innate immune response. However, TLRs can also be stimulated by host-derived molecules. They are expressed in the cardiovascular system and could thus be a key link between cardiovascular diseases and the activation of the immune system. Good experimental evidence is now available suggesting that TLR signaling promotes injury in the heart in response to ischemia, ischemia-reperfusion or hypertrophic stimuli.

**Keywords:** Heart failure, innate immunity, ischemic injury, myocardium, Toll-like receptors (TLR)

**Introduction**

At first glance, pathologic mechanisms in cardiac diseases seem far from involving pathogen defense mechanisms. However, several lines of evidence link the activation of the immune system with cardiovascular diseases. For example, in patients and animal models with heart failure, the immune system is robustly activated, although there is no evidence for a specific pathogen in its etiology. Activation of the immune system is associated with unfavorable outcome, and experimental studies suggest it also has a role in adverse cardiac remodeling and survival after myocardial infarction. Most of the activated immune mechanisms are part of the innate immune system, an evolutionarily ancient, non clonal immune recognition and effector system present in both invertebrates and vertebrates, and distinct from adaptive immunity, which has evolved only in vertebrates.

Toll-like receptors (TLRs) have emerged as central receptors of the innate immune system. To date, 11 human and 13 mouse TLRs have been cloned [1]. The ligands for TLRs are molecular motifs produced by pathogens, not by the host; for example, TLR4 recognizes cell wall components of Gram-negative bacteria. However, they can also be activated by host-derived molecules released upon events such as tissue injury. For example, heat-shock protein 60 (HSP-60), a molecular chaperone conserved in both invertebrates and vertebrates, can activate nuclear factor kappa B (NF-kB) through both TLR2 and TLR4 [2]. Thus these endogenous TLR ligands may activate the innate immune response in cardiovascular diseases such as ischemic cardiac injury, thereby explaining immune activation in a primary non immune disease.

**Toll-like receptor signaling**

TLR signaling is complex (Figure 1) and beyond the scope of this article (for a detailed description see [3]).

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**Abstract**

Toll-like receptors (TLRs) have been identified as central innate immune receptors. They distinguish among different patterns of pathogens and rapidly activate an innate immune response. However, TLRs can also be stimulated by host-derived molecules. They are expressed in the cardiovascular system and could thus be a key link between cardiovascular diseases and the activation of the immune system. Good experimental evidence is now available suggesting that TLR signaling promotes injury in the heart in response to ischemia, ischemia-reperfusion or hypertrophic stimuli.

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At first glance, pathologic mechanisms in cardiac diseases seem far from involving pathogen defense mechanisms. However, several lines of evidence link the activation of the immune system with cardiovascular diseases. For example, in patients and animal models with heart failure, the immune system is robustly activated, although there is no evidence for a specific pathogen in its etiology. Activation of the immune system is associated with unfavorable outcome, and experimental studies suggest it also has a role in adverse cardiac remodeling and survival after myocardial infarction. Most of the activated immune mechanisms are part of the innate immune system, an evolutionarily ancient, non clonal immune recognition and effector system present in both invertebrates and vertebrates, and distinct from adaptive immunity, which has evolved only in vertebrates.

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Signaling converges on the activation of the transcription factor, NF-κB.

**Toll-like receptors in heart failure**

In addition to the role of TLR signaling in atherosclerosis, which has been the focus of other reviews [4,5] and is beyond the scope of this article, several reports suggest a regulation of TLRs in patients with ischemic heart disease [6]. For example, an increase in circulating TLR2- or TLR4-positive monocytes has been observed in unstable angina, acute myocardial infarction, and chronic heart failure [7,8]. Activation of TLR4 in monocytes is associated with the development of heart failure after acute myocardial infarction [9]. In patients with ST-segment elevation myocardial infarction, activated TLR4 is independently predictive of 30-day major adverse clinical outcome [10].

Whereas the clinical evidence is only indirect, direct hints for a role of TLRs in ischemic heart disease come from in-vitro and in-vivo data. Indeed, TLRs are readily detectable in cardiac myocytes. TLRs 2, 3, 4, 6, 7 and 9 are expressed in ventricular myocytes,
whereas TLR1 and 5 are not [11–13]. In vitro, a potential role of TLR2 in the response to oxidative stress has been established in neonatal rat cardiac myocytes. Blockade of TLR2 function was found to inhibit hydrogen peroxide-induced activation of NF-κB and diminished cytotoxicity and apoptosis [11]. In contrast, TLR4 activation can reduce apoptosis of cardiac myocytes, an effect mediated by nitric oxide synthase 2 [14]. Activation of TLRs 2 and 4 reduces myocyte contractility and cytokine secretion in HL-1 cells, an immortalized cell line with adult cardiac myocyte properties [13]. This suggests that TLR signaling may be important for myocardial diseases.

In vivo, TLRs and their signaling components are upregulated in experimental or clinical heart failure. Expression of TLR4 is increased in the myocardium of patients with advanced heart failure [12,15]. In addition, there is a change in the pattern of expression of TLR: whereas in normal murine and human myocardium, TLR4 expression is diffuse and predominantly confined to cardiac myocytes, myocardium from patients with advanced heart failure displays focal areas of intense TLR4 staining (Figure 2). The reason for this change in expression of TLR4 in the remodeled failing myocardium is not yet known [12]. TLR signaling converges on the activation of interleukin receptor-associated kinase 1 (IRAK1) and the transcription factor NF-κB (Figure 1). In line with the previous findings, both IRAK1 and NF-κB are activated by cardiac ischemia or in experimental and human heart failure [16–18]; NF-κB is also increased in peripheral leukocytes of patients with stable heart failure [19]. Taken together, the evidence is strong that TLR and its signaling components are activated by ischemic heart failure.

The coronary artery ligation model is the best established and clinically most relevant experimental model of heart failure. After coronary artery ligation, mortality and left ventricular dilatation were significantly reduced, and left ventricular function was preserved in TLR2−/− mice compared with wild-type mice. These effects may be mediated by TLR-dependent changes in extracellular matrix remodeling [20]. Furthermore, left ventricular remodeling and...
survival are improved in TLR4-deficient mice, together with a reduction in proinflammatory cytokines, alterations of extracellular matrix remodeling, but no change in the rate of apoptosis [21,22].

In parallel, mice with targeted deletion of the NF-κB subunit, p50, are protected from left ventricular dilation after myocardial infarction and have preserved left ventricular function. Collagen content and expression of matrix metalloproteinase-9 are significantly lower in p50-knockout mice after myocardial infarction and may account for improved left ventricular remodeling [16]. Thus TLRs and their downstream signaling components are important in left ventricular remodeling after myocardial infarction.

**Conclusion**

Toll-like receptors are an important family of innate pattern recognition receptors that trigger the activation of an immune response. TLRs are readily detectable in the cardiovascular system and upregulated in ischemic cardiac diseases. There is good experimental evidence that inhibition of TLR2 and TLR4 signaling could reduce cardiac damage after ischemic injury. Unfortunately, a transfer of these results to the clinic is hampered by the fact that an intact immune system is necessary for many protective pathways. However, prolonged immune activation may also activate unfavorable signal cascades that drive disease progression. Thus further research in this field is necessary to find a consensus as to the specific role played by the innate immune system and the potential therapeutic impact in these diseases.

**Summary**

TLRs, central receptors of the innate immune system, are expressed in the heart and activated in experimental and human heart failure. TLR activation is associated with adverse outcome. Inhibition of TLR2 and TLR4 improves left ventricular remodeling after experimental myocardial infarction. The therapeutic role of TLR inhibition in humans remains to be defined.

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Clinical overview of trimetazidine (Vastarel MR) in patients with heart failure

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Conflicts of interest: None.

Abstract

Myocardial energy metabolism may be normal in the early stages of heart failure but, as failure progresses, mitochondrial oxidative metabolism is reduced and glycolysis is increased, with downregulation of glucose oxidation. Reducing free fatty acid oxidation and a concomitant increase in glucose oxidation improve cardiac contraction and slow the progression of left ventricular failure. Trimetazidine (TMZ) acts as a partial inhibitor of fatty acid oxidation and in turn stimulates glucose oxidation. In several studies, treatment with TMZ was found to result in a significant improvement in functional ability, left ventricular function, and the remodeling process in non diabetic, diabetic, ischemic, and non ischemic left ventricular dysfunction. Therefore, there is a compelling argument to advocate the use of TMZ in addition to conventional evidence-based treatments in the management of heart failure.

Keywords: Heart failure, trimetazidine

The failing heart has been described as an energy-starved organ. Through several mechanisms, modulation of cellular energetics has the potential to improve cardiac performance and reduce symptoms in patients with heart failure, without relying on alterations in hemodynamics or further modulation of neurohormones [1]. Inhibition of free fatty acid oxidation with trimetazidine (TMZ) shifts cardiac energy metabolism from fatty acid oxidation to glucose oxidation by inhibiting mitochondrial long-chain 3-ketoacyl coenzyme A thiolase [2], which can decrease the consequences of recurrent ischemia, facilitating the maintenance of myocardial function and enhancing left ventricular performance [3]. By decreasing fatty acid oxidation, TMZ stimulates glucose utilization, restoring coupling between glycolysis and carbohydrate oxidation, and leading to the production of ATP with the consumption of less oxygen [2]. It has also been demonstrated that TMZ has antioxidant properties and improves endothelial-dependent vasorelaxation in heart failure [4]. In conditions of high oxidative stress, such as chronic heart failure, production of free radicals is increased and contributes to endothelial dysfunction. In this setting, TMZ decreases plasma concentrations of both free radicals and endothelin-1. In addition, in patients with heart failure, improvement in the phosphocreatine (PCr)/ATP ratio has been observed in response to TMZ, indicating preservation of intracellular concentrations of myocardial high-energy phosphate [5]. These results deserve interest, especially in view of previous evidence suggesting the PCr/ATP ratio to be a significant predictor of mortality in the patients with heart failure [6]. Although the exact mechanism of action is not fully understood, experimental and clinical results have shown that TMZ has a number...
of potentially useful cytoprotective features [3,7]: it has been reported to limit intracellular acidosis and the accumulation of sodium and calcium, preserve contractile function, and limit cytolysis and membrane damage caused by oxygen free radicals. Protection of the cell against the changes induced by oxygen deficit, by preservation of mitochondrial function and energy metabolism, may reduce ischemic left ventricular dysfunction [3].

To date, TMZ has been studied extensively in heart failure predominantly of ischemic origin [5,8–15]. Apart from the well known antianginal effect of TMZ [2,3,16], several clinical studies have demonstrated consistently that TMZ improves left ventricular function and quality of life in ischemic patients with left ventricular dysfunction [5,8,10–15]. The improvement in left ventricular function estimated by echocardiography has been confirmed in several short- or medium-term studies [10–13,17]. The first observation of functional benefit in patients with ischemic cardiomyopathy with TMZ came from Brottier et al [17]. Fragasso et al [12] and Rosano et al [13] reported a relevant improvement in clinical status and left ventricular ejection fraction after 6 months of treatment with TMZ in diabetic individuals with ischemic cardiomyopathy. This effect was associated with enhanced left ventricular diastolic filling and systolic function [12,13]. Belardinelli et al [11] demonstrated that, compared with placebo, 2 months of treatment with TMZ in 44 patients with ischemic cardiomyopathy resulted in a significant improvement in left ventricular ejection fraction at rest and enhanced left ventricular wall motion during dobutamine stress test in those with New York Heart Association (NYHA) class II–III heart failure.

In a blinded crossover study of 15 patients with chronic coronary artery disease, TMZ has been shown, not only to protect from dobutamine-induced ischemic dysfunction, but also to improve resting regional left ventricular function [10]. These results could indicate that TMZ may make the myocardium less vulnerable to ischemic myocardial dysfunction. In all studies, the beneficial effects of TMZ have been shown to occur without any significant changes in systemic hemodynamics as assessed by heart rate and arterial blood pressure [10–15,18]. The explanation for this is that TMZ does not depend on alterations in oxygen supply or demand, acting directly on the ischemic cell [18]. In addition, 6 months of treatment with TMZ in ischemic cardiomyopathy resulted in significant improvement in functional capacity associated with a relevant reduction in plasma concentrations of brain natriuretic peptide (BNP) [19]. The same was demonstrated in left ventricular dysfunction of various etiologies [14]. Taking into consideration that BNP is a marker of myocardial load, these findings confirm that treatment with TMZ has a positive effect on the neurohormonal pathway in patients with ischemic cardiomyopathy and reduces the cellular damage that characterizes chronic evolution of left ventricular remodeling [20]. Improvement in left ventricular remodeling by TMZ is noteworthy as, in the progression of heart failure, left ventricular remodeling is considered to be the pivotal mechanism linked to neurohormonal activation and contributing to the evolution from left ventricular dysfunction to irreversible heart failure [21] (Figure 1).

In patients with coronary artery disease, left ventricular dysfunction is the result of myocardial fibrosis, or hibernating and stunned myocardium [16].

Figure 1. Biological and metabolic effects of trimetazidine in patients with ischemic heart disease [16]. CoA, coenzyme A; IHD, ischemic heart disease; 3-KAT, 3-ketoacyl coenzyme A thiolase; PCr/ATP ratio, phosphocreatine/adenosine triphosphate ratio; PDH, pyruvate dehydrogenase; PL, phospholipids.
The therapeutic management of hibernating and stunned myocardium is fundamental in ischemic cardiomyopathy, because they are potentially reversible conditions. In a recent study, a more marked improvement has been observed with TMZ in patients with more severe reversible perfusion defects at entry, suggesting that a crucial requirement for the effects of TMZ is the amount of ischemic/hibernating myocardium [22]. In the study by El-Kady et al [9] of 200 patients with ischemic left ventricular dysfunction as a result of multivessel coronary artery disease, the addition of TMZ to conventional treatment improved ischemic attacks clinically and also improved both exercise performance and perfusion as assessed by single photon emission computed tomography (SPECT). From the standpoint of viability testing, an important study was performed in 12 patients with previous myocardial infarction who underwent technetium-99m sestamibi SPECT and echocardiography before revascularization [23]. Patients taking TMZ showed a significant increase in tracer uptake, mainly in viable segments that improved function postoperatively [23]. These results suggest that viable ischemic segments benefit from treatment with TMZ. All these data could explain the reduction in left ventricular remodeling and the preservation of left ventricular function that are observed during treatment with TMZ.

Apart from the studies in ischemic heart failure, the effects of TMZ on cardiac performance and left ventricular function have been estimated in patients suffering from non ischemic dilated cardiomyopathy [14,24]. Fragasso et al [14] conducted a prospective, open-label, parallel group, randomized study comparing add-on TMZ against conventional treatment in 65 consecutive, mostly non diabetic and well-treated patients with symptomatic chronic systolic heart failure. The results were promising: TMZ was associated with significant improvement in functional capacity, quality of life, and plasma natriuretic peptide concentrations compared with conventional treatment; the improvement was equally apparent in patients with non ischemic and ischemic cardiomyopathy. The mean improvement in left ventricular ejection fraction was 7%, which is consistent with prior observations [25]. As in previous studies, TMZ was well tolerated and did not induce any hemodynamic changes [14]. In the more recent study by Tuunanen et al [24], TMZ was shown to improve left ventricular function in idiopathic dilated cardiomyopathy in which overt myocardial ischemia had been excluded. In addition, the positive effects of TMZ on left ventricular function were especially evident in patients with a high degree of β-blockade as estimated by a β1-adrenoreceptor occupancy test, strongly suggesting a synergistic effect of these two modalities of treatment [23]. TMZ and β-blockers partially inhibit different enzymes in the free fatty acid pathway [2,26], so their metabolic effects could be additive.

The finding that, in idiopathic dilated cardiomyopathy, TMZ decreases cardiac free fatty acid oxidation modestly, by only 10% [24], raises the possibility of additional mechanisms of action TMZ. In support of this, recent studies have found that TMZ improves whole-body insulin sensitivity and glucose control in insulin-resistant idiopathic dilated cardiomyopathy [26] and in diabetic patients with ischemic heart failure [12]. This is of particular note given the high prevalence of diabetes in patients with idiopathic dilated cardiomyopathy. Enhanced glucose metabolism improves cardiac function and prevents the development of systolic dysfunction in patients with diabetes [27]. Overall, such extracardiac metabolic changes may indirectly improve myocardial glucose metabolism and glycolysis with TMZ, amplifying the effects mediated by the modest decrease in free fatty acid oxidation observed in cardiac tissue.

Lately, in view of the positive effects of TMZ on left ventricular remodeling in patients with non ischemic cardiomyopathy, some authors have challenged the long-standing working hypothesis that TMZ counteracts the "metabolic switch" in the setting of myocardial ischemia [28]. However, the finding may be consistent with those of a prior study in animal models that suggested that there is a down-regulation of the enzymes of fatty acid oxidation; the switch to carbohydrate oxidation may be only a late-stage phenomenon in the heart failure phenotype, and may not be present in otherwise chronic compensated states [7]. Accordingly, the exact phenotype for those who had a response to TMZ remain to be clearly identified.

The question of whether TMZ has prognostic benefits in patients with heart failure needs to be addressed, given the evidence of an improved left ventricular ejection fraction in these patients. Various studies have provided evidence that TMZ could positively influence the prognosis and quality of life in patients with heart failure [14,16]. To date, reduction in cumulative events when TMZ was added to standard therapy has been reported in ischemic heart failure [8,9]. In the study by El-Kady et al [9], survival at 2 years was 92% among patients treated with TMZ and 62% among those treated with placebo. Clearly, this observation is of significance, given the poor prognosis in cardiac failure even when all evidence-based treatment has been deployed. In the post-hoc analysis obtained from the 48-month extension of Villa Pini d’Abruzzo Trimetazidine Trial, it was found that TMZ treatment reduced all-cause mortality and admission to hospital because of heart failure, improved NYHA functional class and exercise tolerance, and reduced left ventricular remodeling in ischemic heart failure [15].
Focus on Vastarel MR
Tiina Uuetoa

Summary

There is increasing evidence that TMZ, an approved drug for which there is long-standing clinical experience in treating angina, has the potential to improve cardiac performance and reduce symptoms in patients with heart failure, without relying on alterations to hemodynamics or further modulation of neurohormones. Agents acting via the “metabolic” approach are likely to complement modern pharmacotherapy, and hold a possibility for clinical benefit in patients with heart failure. Larger, long-term randomized trials with heart failure, without relying on alterations to cardiac performance and reduce symptoms in patients such as overall mortality are warranted.

* see glossary for definition of this term.

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Left ventricular remodeling after acute myocardial infarction with microvascular obstruction

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Abstract

Accurate assessment of myocardial function and determinants of adverse functional outcome after acute myocardial infarction are essential in further therapeutic management of affected patients. Although echocardiography is most commonly used for this purpose, cardiovascular magnetic resonance (CMR) is emerging as an important diagnostic tool in the evaluation of ischemic heart disease. The advantage of CMR in comparison with other techniques is the ability to combine anatomical and functional information in a single non-invasive examination, with superior spatial and temporal resolution, and without dependence on the patient’s acoustic window or the use of ionizing radiation. This case report demonstrates a comprehensive CMR evaluation of a patient with a large myocardial infarction, and its complications.

Keywords: Cardiovascular magnetic resonance, ischemic heart disease, left ventricular remodeling, microvascular obstruction, myocardial infarction

Case report

After a day at work, a 35-year-old man presented to the emergency department because of severe chest pain, with nausea and dyspnea. The symptoms began an hour after he had started work; however, he did not go to the emergency department until after his shift. He had smoked a pack of cigarettes a day since the age of 15 years and his family history was positive for cardiovascular disease. At the time of presentation, the patient still had chest pain and ST-segment elevation involving leads aVL and V1–V5, with reciprocal ST-segment depression in leads II, III, and aVF, which did not respond to vasodilative medication. He then was brought to the catheterization laboratory, where the left anterior descending artery was found to be proximally occluded. After primary percutaneous coronary intervention with stenting there was suboptimal epicardial flow (Thrombolysis In Myocardial Infarction [TIMI] grade 2), and the electrocardiogram revealed minimal ST-segment resolution after reperfusion. Laboratory testing showed a peak creatine kinase concentration of 11,515 U/L, with an MB fraction of more than 500 U/L. Six days after admission to hospital, the patient was referred to our imaging department for evaluation of ventricular function and the extent of infarction.

Cine imaging was used to assess cardiac function, revealing severely impaired left ventricular function (Figure 1a and c), with akinesia of the entire septum, anterior and anterolateral walls, and the apex, with preserved wall thickness. There was mitral valve regurgitation as a result of a dilated left ventricle, and a pericardial effusion. Assessment of the right ventricle also showed akinesia of the apex. In addition, there was a mass in the left ventricular apex suggesting a thrombus. Ten to 15 minutes after the administration of a gadolinium-based contrast agent, late contrast-enhanced images were acquired (Figure 1b), demonstrating a thrombus in the left...
ventricular apex. There was transmural hyperenhancement of the akinetic segments of the left ventricle, with hypoenhanced areas in the infarct core, attributed to delayed wash-in of the contrast agent because of severe injury of the microvasculature. In addition, hyperenhancement of the distal right ventricular apex confirmed myocardial infarction, not stunning, to be the cause of the wall motion abnormalities. Before the patient was discharged from the hospital, a repeat CMR was performed, 16 days after the percutaneous coronary intervention. Cine imaging demonstrated further deterioration of left ventricular function and geometry, with wall thinning of the transmurally infarcted myocardium. Despite a low-flow state in the left ventricle, anticoagulation therapy had dissolved the thrombus.

Discussion

This case report illustrates that CMR offers a comprehensive evaluation of a patient after acute myocardial infarction in one single non-invasive study. It provides information on the size and extent of myocardial infarction, its complications (eg, thrombus, mitral regurgitation) and other sequelae of infarction (eg, microvascular obstruction, right ventricular involvement), improving the risk stratification of these patients [1–3]. In this patient, large areas of microvascular obstruction were found; this was the result of impaired reperfusion at the myocardial tissue level, caused by mechanisms including the development of tissue edema, platelet plugging, neutrophil adhesion, myonecrosis, and intracapillary red blood cell stasis, also known as the “no-reflow” phenomenon [4]. Several studies have shown that microvascular obstruction is strongly associated with a greater incidence of left ventricular remodeling, congestive heart failure, and death [5,6]. In a comparative study, the prognostic value of microvascular obstruction detected by CMR was stronger than the commonly used criteria of microvascular injury (eg, TIMI flow, myocardial blush grade, ST-segment resolution) for the prediction of ventricular...
function; in addition, it appeared to be more relevant than infarct size or the transmural extent of infarction [7]. Furthermore, typical findings of no-reflow measured by functional intracoronary Doppler flow (eg, systolic retrograde flow, rapid deceleration of diastolic flow, reduced coronary flow velocity reserve) are associated with the anatomical extent and size of microvascular obstruction revealed by CMR [8]. Therefore, CMR should be considered in patients after acute myocardial infarction with severe impairment of left ventricular function, to predict functional outcome and prognosis, and to assess the presence and extent of suspected infarct-related complications.

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Ivabradine (Procoralan) alone or with β-blockers in myocardial ischemia

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Conflicts of interest: Prof. Alain Berdeaux has received honoraria for lectures and served as consultant to Servier.

Abstract

Both ivabradine (Procoralan), the first I(f) current inhibitor of the cardiac pacemaker cells, and β-blockers reduce heart rate and exhibit potent anti-ischemic effects. Although β-blockers are still the first choice of medication to treat patients suffering from myocardial ischemia, numerous experimental and clinical arguments are now available from which to conclude that ivabradine not only is the drug of choice when β-blockers are not well tolerated or contraindicated, but is the drug that can be associated with β-blockers at the commonly used dosage in clinical practice for an optimal therapeutic efficacy in ischemic disease.

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Keywords: Angina pectoris, β-blockers, ivabradine (Procoralan), myocardial ischemia

Introduction

Because an increase in diastolic perfusion time simultaneously reduces myocardial oxygen demand and increases oxygen supply, a reduction in heart rate has always been a primary pharmacological target for the treatment of myocardial ischemic disease (Figure 1). All available epidemiological studies demonstrate that, after myocardial infarction or in heart failure, heart rate reducing therapies such as β-blockers reduce cardiac mortality [1]. β-Blockers remain the drugs of first choice to treat patients suffering with myocardial ischemia and have been for at least 40 years, although their usefulness is often limited by their numerous side effects or contraindications. These limitations are usually linked to the fact that the pharmacological blockade of β1-adrenoreceptors, which is the basis of heart rate reduction, is always associated with reductions in myocardial contraction/relaxation and conduction time, limiting their therapeutic usefulness in ischemic patients with altered basal contractile function, rhythmic disorders, or both, even though β-blockers are also indicated in heart failure and some rhythmic disorders. More recently, a reduction in the rate of admission to hospital of patients with coronary artery disease with a cardiac rate greater than 70 beats/min was reported in a subgroup analysis of the Morbidity-Mortality Evaluation of the I(f) Inhibitor Ivabradine in Patients with CAD and Left Ventricular Dysfunction (BEAUTIFUL) study after treatment with the I(f) current inhibitor, ivabradine (Procoralan), a pure heart rate reducing drug [2].

The discovery of ivabradine, which can selectively reduce heart rate without concomitant negative
effects on myocardial contraction/relaxation, conduction time, and coronary vasomotor tone [3–5], was thus a truly innovative discovery among drugs previously used for the treatment of myocardial ischemia. This also partly explains why, after the introduction of ivabradine as a new antianginal drug, the initial medical opinion was to consider ivabradine and β-blockers as mutually exclusive. However, because of a real synergy in their mechanisms of action, this concept was totally revisited recently, leading now to their use as combined therapy, especially in patients with angina pectoris who cannot tolerate a full dose of β-blockers.

Ivabradine versus β-blockers

Although both ivabradine and β-blockers improve the balance between oxygen supply and demand during myocardial ischemia, they promote this result through quite different mechanisms. As shown in Table I, β-blockers, regardless of their pharmacological spectrum, reduce myocardial oxygen consumption (mVO₂) by simultaneously reducing cardiac rate and contractility. They also increase coronary vascular resistance, through the direct blockade of β-adrenoreceptors and indirect unmasking of α-adrenoreceptors [6,7].

As a result, β-blockers usually reduce coronary blood flow or at least limit its increase during exercise, but their simultaneous and potent reduction of mVO₂ always leads, through metabolic autoregulation, to an improvement in the global transmural perfusion per unit of cardiac work, especially within the endocardial layers.

At least three main mechanisms illustrate the contrast between β-blockers and ivabradine (Table I):

- Ivabradine reduces mVO₂ through its selective reduction of the heart rate.
- Ivabradine preserves the maximal reserve of coronary vasodilatation at exercise because there are no I(f) channels on these arteries and thus no coronary constriction – a difference from β-blockers.
- Ivabradine causes a greater increase (exactly 10%) in the diastolic perfusion time of the coronary vascular bed for the same reduction in heart rate compared with β-blockers, because the diastolic filling time of coronary arteries in protodiastole is significantly longer (6 s/min) with ivabradine than with a β-blocker such as atenolol [8]. These differences are of major importance when the relationship between coronary blood flow (or myocardial oxygen supply) and mVO₂ reaches the ischemic threshold for a patient with limited exercise-induced angina pectoris [9].

Taking these differences together, for a similar reduction in heart rate ivabradine probably improves the balance between oxygen supply and demand to the ischemic myocardium more favorably than do β-blockers. This could partly explain why ivabradine tended to exert more anti-ischemic effects than atenolol in the 939 patients with angina pectoris who were included in the International Trial on the Treatment of Angina with Ivabradine vs. Atenolol (INITIATIVE), although this large trial finally concluded that the difference in efficacy between the drugs was non significant, regardless of the exercise test and the challenges of doses used [10].

Table I. Comparative anti-ischemic effects of ivabradine and β-blockers at equivalent reduction of heart rate

<table>
<thead>
<tr>
<th></th>
<th>β-blockers</th>
<th>Ivabradine</th>
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<tbody>
<tr>
<td>Heart rate</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Myocardial contractile force</td>
<td>↓</td>
<td>0</td>
</tr>
<tr>
<td>Relaxation</td>
<td>↓</td>
<td>0</td>
</tr>
<tr>
<td>Myocardial oxygen consumption</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td>Coronary vascular resistance</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td>Ejection/diastolic perfusion time ratio</td>
<td>↑</td>
<td>↑</td>
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<tr>
<td>Myocardial distribution of flow between endo- and epicardium</td>
<td>↑</td>
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<tr>
<td>Anti-ischemic effect (reduction in ST-segment) for a similar heart rate reduction</td>
<td>↑</td>
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<tr>
<td>Increase in myocardial oxygen supply for a similar heart rate reduction</td>
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Ivabradine in combination with β-blockers

Inasmuch as a half-filled bottle can be viewed as half full or half empty, the pharmacological spectra of ivabradine and β-blockers as viewed above can also be viewed as complementary or even additive. Indeed, both drugs reduce myocardial ischemia and infarct size [11] and reduce heart rate.

With this in mind, and because any decrease in myocardial oxygen demand per unit of heart rate reduction is the most important endpoint to reach for reducing exercise-induced myocardial ischemia, we compared the relationships between reductions in measured mVO_2 and heart rates in normal conscious dogs during repeated treadmill exercises at different workloads when ivabradine and atenolol were administered separately and at doses inducing the same final reduction in heart rate [12,13]. As shown in Figure 2, this relationship is negatively and linearly related with ivabradine, but hyperbolic with atenolol and thus, for a small reduction in heart rate, there is a strong reduction in mVO_2 with the latter, above all when basal heart rate is high. Unfortunately, we did not investigate this relationship when the drugs were administered together at a chosen dose inducing the same heart rate reduction as when they were administered separately, but one can postulate that, at lower doses for each drug, their combination should induce a larger reduction in mVO_2 than when they are administered separately. Such a scenario could possibly explain the recent data reported in ASSOCIATE study in which 889 patients with stable angina receiving atenolol 50 mg/day were allocated randomly to groups to receive either a placebo or ivabradine 5 mg twice daily for 2 months, which was then increased to 7.5 mg twice daily for a further 2 months. On the basis of the results with classical treadmill exercise tests, it was concluded that the combination of 7.5 mg twice daily ivabradine and atenolol administered at the commonly used dosage in clinical practice in patients with chronic stable angina pectoris produced additional efficacy, with no untoward effect on safety or tolerability [14].

Conclusion

From experimental studies, we have learned that ivabradine and β-blockers possess complementary and perhaps even additive pharmacological properties linked to their common ability to reduce heart rate: in the short term, they improve the balance between oxygen supply and demand in the ischemic myocardium [5,11–13]; in the long term, they reduce the activity of the renin–angiotensin system [15–17], they reduce oxidant stress and endothelial dysfunction [18], and they reduce left ventricular remodeling of the post-infarcted myocardium [15–17]. From the BEAUTIFUL study, we learned that ivabradine in combination with β-blockers is safe for the patient and may afford a further reduction in their risk of admission to hospital [2]. From the ASSOCIATE study, we learned that ivabradine associated with atenolol produces additional efficacy in patients with chronic stable angina pectoris [14]. Thus it is time now to consider that ivabradine not only is the drug of choice when β-blockers are not well tolerated by or are contraindicated in a patient, but is the drug that can be combined with β-blockers for an optimal therapeutic effect in patients with ischemic disease. ■

References


Strategies to prevent left ventricular remodeling

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Left ventricular maladaptive remodeling after ST-segment elevation myocardial infarction (STEMI) has been consistently associated with an increased incidence of congestive heart failure and impaired prognosis [1,2]. Among other factors such as anterior localization and quality of collateral circulation, infarct size is one of the major predictors of left ventricular remodeling. Once the myocardial damage has been established, pharmacological or device-based treatments are intended to treat, prevent, or slow the progression towards the heart failure syndrome ("secondary" prevention). However, the most effective treatment strategy with a recognized significant impact on the prognosis of patients with STEMI is "primary" prevention through limitation of infarct size [3].

Final infarct size is dependent on two major determinants: total ischemic time and reperfusion-related myocardial damage. Experimental models of coronary occlusion have shown that a large fraction of the myocardium at risk remains viable when reperfusion occurs within 30–60 min, with the percentage of salvageable myocardium rapidly decreasing beyond the first 1 h of ischemia [4]. On the basis of this evidence, prompt reperfusion, either mechanical or pharmacological, is recognized as the optimal treatment strategy for the management of patients with STEMI in all recent guidelines, which strongly recommend 30-min door-to-needle and 90-min door-to-balloon times [5]. Time delays have been identified as the central point in the decision-making process concerning the best treatment strategy, superiority of primary percutaneous coronary intervention (PCI) over fibrinolysis having been demonstrated only in so far as the time to reperfusion is not exceedingly increased by opting for PCI. However, despite considerable progress in myocardial reperfusion strategies achieved over the past 20 years, the in-hospital rate of death for acute myocardial infarction in the "real world" still approaches 10%, and the incidence of subsequent cardiac failure is almost 25%. Registry data show that the established goals for total ischemic time are extremely difficult to achieve. In particular, door-to-balloon times are often much longer than reported in randomized clinical trials because, in the "real world", transfer of patients for PCI, local factors (ie, geographic location), and poor management strategies lead to longer delays [6]. In the National Registry of Myocardial Infarction, only 4.2% of patients undergoing primary PCI achieved a door-to-balloon time less than 90 min [7]. Moreover, up to one-third of patients eligible for fibrinolytic therapy did not receive effective early reperfusion because of factors such as late presentation or lack of efficacy of thrombolytic agents [8].

The current challenge is therefore the implementation of protocols capable of reducing the time between symptom presentation and effective reperfusion (total ischemic time). Possible strategies could include, for example: educating patients to be prompt in the recognition of symptoms and in alerting the emergency services; transmission of the electrocardiogram recorded in the field; bypassing the emergency room. Nonetheless, rapid restoration of coronary flow does not always result in myocardial salvage and consistently guarantee a reduction in the infarct size. In about one-third of patients, myocardial reperfusion is followed by microvascular damage resulting in the so-called no-reflow phenomenon, as originally described by Kloner et al [9]. This phenomenon is associated with a sevenfold increase in mortality (from 0.7% to 5.4%) and heart failure [10–12].

The capillary structure is damaged by ischemia, with tissue compression, myocyte edema, and neutrophil infiltration [13]. This pathologic process can be accentuated by coronary reperfusion, leading to progressive decline in coronary flow [14]. In this way, reperfusion has the potential to add to the damage produced by the ischemic insult, thereby offsetting the beneficial effects of flow restoration. Studies of AMI in animal models suggest that lethal reperfusion injury, which starts immediately after the opening of the culprit coronary artery, accounts for up to 50% of the final infarct size [15]. Thus reperfusion injury should be regarded as a major therapeutic target in patients with STEMI.
Several strategies have been shown to reduce reperfusion injury in animal models, including administration of cardioprotective agents (e.g., adenosine, cariporide, metabolic agents, calcium channel blockers), mechanical prevention of distal coronary embolization, intermittent reperfusion (postconditioning), and thrombus aspiration. Unfortunately, translation to the clinical setting has not yielded consistent benefits.

The negative results of most clinical trials addressing ischemia-reperfusion injury have led us to question the clinical relevance of reperfusion injury. Several confounding factors should be taken into consideration when discussing the effects of cardioprotective agents. First, difficulties in reproducing the human disease in animal models. Secondly, variability in the route of administration of the cardioprotective agents (intravenous administration of adenosine in the Acute Myocardial Infarction Study of Adenosine [AMISTAD] II trial). Thirdly, but not least, a lack of a predefined and homogenous duration of ischemia before the initiation of treatment. The clinical impact of reperfusion injury may be negligible when reperfusion is achieved after several hours of ischemia, when all myocardium at risk is irreversibly damaged. Conversely, reperfusion damage may be much more relevant when the vessel is reopened early and a sizeable part of viable myocardium is still present.

At present, there are two strategies that have been shown to limit reperfusion injury in the setting of AMI: postconditioning and intracoronary administration of adenosine. Brief episodes of ischemia, at the time of reperfusion, have been reported to reduce infarct size dramatically [16–18]. Similarly, intracoronary adenosine, as an adjunct to primary percutaneous transluminal coronary angioplasty, has been shown to ameliorate flow, prevent the no-reflow phenomenon, improve ventricular function, and to be associated with a more favorable clinical course [19]. Thrombectomy, which improves surrogate endpoints, does not affect 30-day mortality, reinfarction, and stroke, according to the findings of a recent meta analysis [20].

In conclusion, timely reperfusion of the infarct-related artery and effective cardioprotection must be combined to limit infarct size and prevent left ventricular remodeling.

REFERENCES

Early diagnosis of myocardial infarction with sensitive cardiac troponin assays

The rapid and reliable diagnosis of acute myocardial infarction is a major unmet clinical need. We conducted a multicenter study to examine the diagnostic accuracy of new, sensitive cardiac troponin assays performed on blood samples obtained in the emergency department from 718 consecutive patients who presented with symptoms suggestive of acute myocardial infarction. Cardiac troponin concentrations were determined in a blinded fashion with the use of four sensitive assays (Abbott-Architect Troponin I, Roche High-Sensitive Troponin T, Roche Troponin I, and Siemens Troponin I Ultra) and a standard assay (Roche Troponin T). The final diagnosis was adjudicated by two independent cardiologists. Acute myocardial infarction was the adjudicated final diagnosis in 123 patients (17%). The diagnostic accuracy of measurements obtained at presentation, as quantified by the area under the receiver operating characteristic curve (AUC), was significantly greater with the four sensitive cardiac troponin assays than with the standard assay (AUC values: Abbott-Architect Troponin I, 0.96, 95% confidence interval [CI] 0.94 to 0.98; Roche High-Sensitive Troponin T, 0.96, 95% CI 0.94 to 0.98; Roche Troponin I, 0.95, 95% CI 0.92 to 0.97; Siemens Troponin I Ultra, 0.96, 95% CI 0.94 to 0.98; standard assay, 0.90, 95% CI 0.86 to 0.94). Among patients who presented within 3 h after the onset of chest pain, the AUCs were 0.93 (95% CI 0.88 to 0.99), 0.92 (95% CI 0.87 to 0.97), 0.92 (95% CI 0.86 to 0.99), and 0.94 (95% CI 0.90 to 0.98) for the sensitive assays, respectively, and 0.76 (95% CI 0.64 to 0.88) for the standard assay. We did not assess the effect of the sensitive troponin assays on clinical management. We conclude that the diagnostic performance of sensitive cardiac troponin assays is excellent, and that these assays can substantially improve the early diagnosis of acute myocardial infarction, particularly in patients with a recent onset of chest pain. (ClinicalTrials.gov number, NCT00470587.)

Sensitive troponin I assay in early diagnosis of acute myocardial infarction

Cardiac troponin testing is central to the diagnosis of acute myocardial infarction. We evaluated a sensitive troponin I assay for the early diagnosis and risk stratification of myocardial infarction. In a multicenter study, we determined concentrations of troponin I as assessed by a sensitive assay, troponin T, and traditional myocardial necrosis markers in 1818 consecutive patients with suspected acute myocardial infarction, on admission to hospital and 3 h and 6 h after admission. For samples obtained at the time of admission, the diagnostic accuracy was greatest with the sensitive troponin I assay (area under the receiver operating characteristic curve [AUC] 0.96), as compared with the troponin T assay (AUC 0.85) and traditional myocardial necrosis markers. With the use of the sensitive troponin I assay (cutoff value 0.04 ng/mL) on admission, the clinical sensitivity was 90.7% and the specificity was 90.2%. The diagnostic accuracy was virtually identical in baseline
and serial samples, regardless of the time of onset of chest pain. In patients presenting within 3 h after the onset of chest pain, a single sensitive troponin I assay had a negative predictive value of 84.1% and a positive predictive value of 86.7%; these findings predicted a 30% increase in the troponin I concentration within 6 h. A troponin I concentration of more than 0.04 ng/mL was independently associated with an increased risk of an adverse outcome at 30 days (hazard ratio 1.96; 95% confidence interval 1.27 to 3.05; $P = 0.003$). We conclude that the use of a sensitive assay for troponin I improves early diagnosis of acute myocardial infarction and risk stratification, regardless of the time of onset of chest pain.

**Commentary**

By coincidence, two very similar studies appear in this issue of the *New England Journal of Medicine*. Although the design of these studies differs, their conclusions are remarkably similar and consistent, and should have a significant impact on the way we use troponins to diagnose early acute myocardial infarction (AMI).

Troponins I, C, and T form a complex that regulates the interaction between myosin and actin in response to calcium. These proteins are embedded in the sarcomere, although there maybe a small cytosolic pool. Hence, compared with the release of cytoplasmic proteins traditionally used to mark myocardial infarction (creatine kinase, creatine kinase myocardial band [CK-MB], lactate dehydrogenase, and myoglobin), that of troponin is delayed, with a peak between 10 and 18 h after the onset of chest pain. However, the cardiac-specific expression of particular isoforms of troponins I and T confers such a significant advantage as markers that they have largely usurped creatine kinase and myoglobin, which are expressed more ubiquitously. Thus, since the late 1990s, with the revised definition of myocardial infarction, the advantage of troponins as biomarkers of myocardial infarction has become widely acknowledged. The cutoffs we use clinically as our lower limit of normal for troponins are the result of a combination of early studies comparing troponins with CK-MB and of early assays that did not perform well at their lower limits of detection, having relatively high coefficients of variation. Since their clinical introduction, the assay for troponin T and the various assays for troponin I have evolved through a number of generations. Consequently, the currently available assays have much lower coefficients of variation when measuring troponins in the sub-0.1 ng/mL range. This lower coefficient of variation allows the upper limit of the normal range to be set at the 99th centile of a reference “normal” population.

In the study by Reichlin et al., a number of the new ultrasensitive assays for troponins I and one for troponin T were compared with the standard assay for troponin T; in the study by Keller et al., only one vendor’s assay for troponin I was compared with the standard assay from troponin T. In combination, the conclusions of the two studies are very clear, and they demonstrate that the newer assays perform well and hence are capable of reliably identifying the release of troponin at earlier timepoints after the onset of chest pain than is possible with the standard assay. This is likely to have a number of consequences for clinical practice.

The ability of the new assays to detect troponins reliably at an early point in their profile of temporal release should enable a more prompt “rule out” of AMI and reduce the needless waiting and overnight admissions that currently occur for many low-risk patients. In my view, this is likely to be their main benefit. Conversely, the earlier “rule in” of AMI will enable more prompt treatment of patients. However, by and large, these earlier diagnosed AMIs will be non-ST-segment elevation myocardial infarctions, and towards the lower end of the risk spectrum where the benefits of early intervention are less clear. Perhaps the most daunting consequence of these new assays is their reduced specificity, which comes as an almost inevitable consequence of their greater sensitivity. The reduced specificity and greater false “rule in” rate of AMI are best illustrated in the study by Reichlin et al., in which the positive predictive value of the new assays was as low as 50%. What this actually means in real terms is complex. In both studies, AMI was defined by expert cardiologists and there were insufficient numbers of patients to analyze clinical outcome. It is quite possible that a patient in whom troponin release is detected using the new sensitive assays does not meet the clinical threshold for AMI but nevertheless has sustained cardiac damage and could be at increased risk of subsequent events. Moreover, this could still be the case when the coronary arteries appear angiographically normal. These new assays are likely to increase the prevalence of this group of patients with an indeterminate diagnosis or the default diagnosis of myocarditis.

Unfortunately, the amount of myocardial damage required to increased troponins above the 99th centile of a reference population is probably of too low a volume to be detected by magnetic resonance imaging with late gadolinium enhancement, unless the pathology is current or repetitive. Thus, for patients with detectable release of troponin, the benefit of these sensitive assays over those traditionally available is unclear. Furthermore, even if outcome studies confirm that low levels of troponin release confer a decrement in prognosis, it will be some time before intervention studies clarify the management of these patients.
Summary

These studies illustrate that we have a new tool with which reliably to exclude AMI as early as 3 h after the onset of chest pain. However, in those patients with normal hearts in whom low-level release occurs, we will have an increasing clinical dilemma and associated cost of investigation.

* see glossary for definition of this term.
Apoptosis

Apoptosis is a highly regulated and ATP-dependent mechanism of cell death mediated by a death receptor/extrinsic pathway and/or mitochondrial/intrinsic pathway. Apoptosis is characterized by caspase activation, chromosomal DNA fragmentation leading to DNA ladder formation, and cell shrinkage.

Caspases

Caspases are a family of cysteine aspartyl proteases that are activated following cleavage at specific aspartate residues. Caspase activation is a critical step involved in carrying apoptosis following activation of either the extrinsic or intrinsic apoptotic pathway.

Cytochrome C

Cytochrome C is a protein found associated with the inner mitochondrial membrane that is a component of the electron transport chain and is also involved in initiating the mitochondrial/intrinsic pathway of apoptosis. Following the loss of integrity of the outer mitochondrial membrane, cytochrome c (and other proapoptotic factors) is (are) released into the cytosolic compartment of the cell, where following formation of the apoptosome leads to well characterized cellular changes observed in cell death mediated by apoptosis.

Renin-angiotensin-aldosterone-system

The renin-angiotensin-aldosterone-system is the physiological hormone system responsible for the regulation of blood pressure and fluid balance. Renin (originating from the kidneys) stimulates the production of angiotensin, which induces blood vessel constriction and increases blood pressure. Angiotensin also stimulates the production of aldosterone, which acts on the kidneys to increase sodium and water reabsorption into the blood, also contributing to an increase in blood pressure.

MicroRNA(s)

MicroRNA(s) are a class of highly conserved, endogenous, non-coding RNA molecules of approximately 22 nucleotides that silence gene expression at the post-transcriptional level by either promoting the degradation of messenger RNA (mRNA), or inhibiting the translation of protein from mRNA by translational repression.

Natriuretic peptide(s)

The natriuretic peptides are a family of peptides that are involved in the induction of natriuresis, which is the discharge of sodium through the urine. Peptide members include atrial natriuretic peptide, brain natriuretic peptide, and C-type natriuretic peptide.

Bradykinin

Bradykinin is a 9 amino acid peptide belonging to the kinin group of proteins that is involved in vasodilation and the lowering of blood pressure.

Endothelin-1/2

Endothelin-1/2 are isoforms of the human protein, endothelin, which is a 21 amino acid peptide produced by the endothelium that is involved in blood vessel constriction and increasing blood pressure.

Troponin (Troponin-1 and Troponin-2)

Troponin (Troponin-1 and Troponin-2) are heterotrimeric complexes present in striated muscle (skeletal and cardiac muscle) that is comprised of a Ca\(^{2+}\) binding subunit (troponin-C), an inhibitory subunit (troponin-1), and an elongated troponin molecule (troponin-2) which binds both troponin- C and 1. In conjunction with tropomyosin, the troponin heterotrimer forms a regulatory complex that controls the interaction of actin and myosin. The binding of Ca\(^{2+}\)
to troponin permits muscle contraction. Cardiac troponins (troponins-1 and 2) are released from cardiac myocytes following myocardial damage and loss of membrane integrity, and serve as highly sensitive and specific biomarkers for establishing the diagnosis of myocardial infarction.