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Aims and Scope

Heart and Metabolism is a quarterly journal focusing on the management of myocardial ischemia. Its aim is to inform cardiologists and other specialists about the newest findings of the role of metabolism in cardiac disease and to create awareness of its potential clinical implications. The management of patients with angina, as well as those with heart failure and hypertrophic or dilated cardiomyopathy, will also be discussed. Moreover, the effects of metabolic diseases such as diabetes mellitus on the heart will be highlighted. Each issue will include an editorial, followed by articles on a key topic. Experts in the field will explain the metabolic consequences of cardiac disease and the multiple potential targets for pharmacotherapy in ischemic and non-ischemic heart disease.

The figure on the cover shows MR cine images (top row) and MR tissue tagging images (bottom row) at enddiastole (left) and endsystole (right). The tag line distance is 7 mm. The cine images demonstrate wall thickening during contraction, but intramural deformation is not visualized. In the tagged images, the tags are a temporary property of the myocardium and therefore the tag lines move along with the tissue. The deformed tag lines visualize directly the underlying motion of the myocardium.

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Left ventricular remodeling after acute myocardial infarction

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Following acute myocardial infarction the left ventricle can undergo progressive dilatation and alterations in shape. This phenomenon, termed 'postinfarction left ventricular remodeling', is mainly determined by the site and extent of the infarcted myocardium.

In the last two decades postinfarction left ventricular remodeling has been the object of increasing scientific and clinical interest for a number of reasons: (1) the phenomenon can now be easily explored in vivo thanks to accurate cardiac imaging techniques, such as echocardiography and MRI, which enable serial noninvasive and safe evaluation of changes in left ventricular volume and shape over time; (2) recognition of the relevant prognostic importance of left ventricular volume (especially endsystolic) after acute myocardial infarction;¹ (3) demonstration of the relevant beneficial functional and clinical impact of therapeutic strategies that, although via different mechanisms, are able to reduce the left ventricular remodeling process after acute myocardial infarction.²

Our understanding of this complex and clinically important phenomenon is continually increasing, not only because of the more systematic use of cardiac imaging techniques both in the acute and subacute phase of myocardial infarction, but also because of our improved knowledge of the pathophysiology of acute myocardial infarction and better grasp of the mechanisms involved. The articles in this issue of *Heart and Metabolism* provide a clear example of our improved knowledge in the field.

Initial investigations into the phenomenon of left ventricular remodeling focused mainly on its 'mechanical' determinants: the site and extent of infarcted myocardium, the overall mass, myocardial thickness, etc. Nowadays, however,

other aspects related to the development of remodeling are better understood, for example inflammation, which is an important determinant of the occurrence of acute myocardial infarction and its prognosis. The role of inflammation and the potential clinical implications of different selective interactions with its various mechanisms, are discussed by Wim Lagrand and colleagues. The therapeutic consequences, in the context of postinfarction left ventricular remodeling, are explored by Luigi Biasucci and colleagues. However, the prevention and treatment of postinfarction left ventricular remodeling are the objects of various therapeutic strategies based on identification and comprehension of the different mechanisms underlying it. In his article, Ronnie Willenheimer offers a comprehensive overview of the most important strategies in this context, from the classical use of ACE inhibitors to the possible utilization of peptide growth factor inhibitors.

Advanced cardiac imaging techniques can further improve the treatment of postinfarction left ventricular remodeling now that some aspects related to its development can be identified easily and early in its course. Examples of these new potential uses are presented by Marco Götte et al and by Leonardo Bolognese and Giampaolo Cerisano. In the first of these two articles Dr Götte examines the potentials of cardiac MRI in evaluating patients at risk of postinfarction left ventricular remodeling. Of particular interest is the possibility of using cardiac tagging to explore the characteristics of intramyocardial contractility and viability. This aspect of ventricular mechanics is not otherwise explorable, and its relevance in influencing postinfarction left ventricular remodeling has become progressively clearer in recent years. In their article, Drs Bolognese and

Cerisano present an interesting case of acute anterior myocardial infarction. This clinical case underlines the importance, after acute myocardial infarction, of exploring not only myocardial but also microcirculatory characteristics. It is well known that even in the presence of adequate and prompt recanalization of the infarct-related artery, myocardial perfusion can be absent due to microcirculatory dysfunction, known as the 'no-reflow' phenomenon. This phenomenon has important functional consequences and is a possible cause of postinfarction left ventricular remodeling. Thanks to myocardial contrast echocardiography, the no-reflow phenomenon can be explored in humans in the acute phase of myocardial infarction.

The metabolic therapeutic approach presents a new opportunity for the prevention and/or treatment of postacute myocardial infarction left ventricular remodeling. Awareness of the importance of the metabolic alterations during acute myocardial infarction and the functional³ and clinical implications⁴ of metabolic treatment

have substantially increased the attention given to this therapeutic option. The last article of this issue of *Heart and Metabolism* summarizes the potentials of a metabolic agents such as trimetazidine in the context of coronary artery disease and acute myocardial infarction. ■

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From the Editor-in-Chief

In order to further improve the educational quality of our journal the editorial board has decided to expand the number of sections presented in each issue.

Our first new section will be *Featured Research*. Each issue will present and briefly discuss a number of abstracts from the recently published literature. This is to help the reader keep track of the most important basic and clinical research in cardiac metabolism.

The second new section is called *Refresher Corner*. There are many aspects of physiolo-

gy, biochemistry, pharmacology, pathology, etc, which we all learned during our medical training but which we may since have forgotten. The *Refresher Corner* section will renew our knowledge of the facts as they are taught to medical students today.

The third new section is the *Glossary*. Often when I read articles on Basic Metabolism I stumble over names and notions that I cannot place in context. The *Glossary* will therefore give a short explanation of the terms used, to give the reader a better understanding of the concepts under discussion.

F.C. Visser

Ventricular remodeling

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During the past 20 years it has been acknowledged that large transmural myocardial infarcts in particular may result in complex alterations in left ventricular architecture, involving both the infarcted and noninfarcted zone. These alterations, usually referred to as 'left ventricular remodeling', can profoundly affect the patient's prognosis.

From a clinical point of view, left ventricular remodeling is a dynamic process, starting in the acute phase with infarct expansion and progressing to left ventricular dilatation and hypertrophy.¹ The remodeling process has regional and global effects on wall thickness and chamber size, shape, and function.

Full patency of the infarct-related artery is crucial for reducing both infarct expansion in the early phase of infarction and subsequent left ventricular enlargement.² There is increasing evidence to support the use of late reperfusion therapy, ie, after the 6-h window, and thus beyond the timeframe for myocardial salvage. Furthermore, studies investigating residual stenosis or reocclusion after reperfusion therapy support efforts to establish full patency of the infarct-related artery and to maintain patency in the long term. A subset analysis of the APRICOT trial (which evaluated the efficacy of antithrombotics in preventing reocclusion) demonstrated the deleterious effect of reocclusion without reinfarction, in terms of increased left ventricular dilatation combined with a lack of improvement in both global and regional left ventricular function.³

Apparently, an open infarct-related artery may provide a scaffold that limits the distensibility of the infarct zone and therefore the extent of dyskinesia, and may also obviate left ventricular dilatation.

Various pharmacological interventions have been studied, and some show great promise in their ability to alter the remodeling process. Based on experimental data, three large studies, SAVE,⁴ Consensus II,⁵ and GISSI,⁶ examined the effects of ACE inhibitors in this respect, and all of them showed a reduction in left ventricular dilatation. This beneficial effect has been translated into improved survival with long-term treatment.^{7,8} It is generally agreed and recommended that infarct patients with left ventricular dilatation or heart failure be treated with ACE inhibitors without undue delay.

Nitrate therapy has also been suggested to have a beneficial effect on cardiac remodeling and survival, despite the fact that there is no clear evidence of long-term benefit.^{7,9}

Furthermore, there is growing evidence that inflammation may also play a role in this respect, yielding potential new therapeutic avenues.

Summary

Development of left ventricular remodeling after acute myocardial infarction is a complex process influenced by multiple factors, some of which have yet to be elucidated. Nevertheless, a variety of potential targets for limiting postinfarct remodeling have been identified. It is clear, however, that a successful strategy is likely to involve a combination of interventions that provide additive, or even synergistic, benefits by altering one or more factors that influence this process.

Finally, based on current evidence, a rational strategy for preventing left ventricular remodeling should involve intervention starting very early after infarction, spanning the entire healing process, and continuing well beyond. ■

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Anti-inflammatory interventions: a promising pathophysiological approach in the treatment of acute myocardial infarction?*

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Introduction

Acute myocardial infarction (AMI) is one of the major causes of mortality and morbidity in the Western world. Mortality after AMI is due to arrhythmia, acute heart failure, and cardiac rupture, whereas morbidity often results from chronic heart failure. AMI is considered to be caused by myocardial cell death from oxygen depletion resulting from acute coronary occlusion by thrombus formation on preexisting atherosclerotic lesions. An important prognostic determinant is the total amount of myocardial necrosis, ie infarct size. Studies in animals have shown that irreversible myocardial cell injury starts about 30 min after occlusion of the coronary vessel and proceeds for hours. It is, however, remarkable that the primary oxygen deficit is only in part responsible for the total extent of myocardial necrosis (infarct size). The local processes in infarcted myocardium point to elicitation of immunologic reactions of both the α -specific and specific immunologic system. The local inflammatory response ensuing in the infarcted myocardium is characterized by the local production of chemotactic factors, the infiltration and activation of neutrophils, the local production of cytokines (such as

tumor necrosis factor- α [TNF α], interleukin [IL]-6, and IL-8), elicitation of the acute-phase response, expression of adhesion molecules, and local activation of the complement system.¹ The later phase of myocardial cell injury, in part, results from these acute inflammatory reactions ensuing in the ischemic myocardium, as infarct size can be effectively reduced by anti-inflammatory agents. For example, corticosteroids given as late as 6 h after coronary occlusion can reduce infarct size by up to 35% in comparison with untreated control animals.²

Reperfusion injury

Early reperfusion of ischemic myocardium is a major goal in the treatment of AMI, since reperfusion results in an overall reduction in infarct size and a better prognosis in time. However, reperfusion of ischemic myocardium itself may induce inflammatory reactions, which, amongst others, involve further activation of complement and neutrophils, and the generation of oxygen radicals.^{3,4} These inflammatory reactions may damage the cardiac tissue and limit the beneficial effects of a restored circulation ('reperfusion injury'). Reperfusion therapy in AMI can therefore be regarded as a 'double-edged sword'.

All observations, described above, have resulted in an increase in interest in the subject, since intervention in the inflammatory

*This study was financially supported by the Netherlands Heart Foundation, grant number 97-088 and 93-119. Dr Niessen is a recipient of the Dr E. Dekker program of the Netherlands Heart Foundation (D99025).

Table 1. Infarct reduction by inhibition of inflammation during AMI.

Modality	Intervention method	Agent	Study population	Results ^a	Authors	Ref.
Corticosteroids	Exogenous suppletion	Cortisone	Dogs	1	Johnson et al (1953)	5
		Hydrocortisone	Dogs	1	Libby et al (1973)	2
		Methylprednisolone	Cats	1	Spath et al (1976)	6
		Methylprednisolone	Humans	1	Morrison et al (1976)	7
PMN	Depletion	Antineutrophil mAb	Dogs	1	Romson et al (1983)	8
		Antineutrophil mAb	Dogs	1	Jolly et al (1986)	9
		Antineutrophil mAb	Dogs	1	Simpson et al (1988)	10
		Extracorporeal leukocyte filtration	Dogs	1	Litt et al (1989)	11
Complement	Depletion	CoVF	Dogs	1	Maroko et al (1978)	12
		CoVF	Baboons	1	Crawford et al (1988)	13
	Inhibition (classical pathway)	sCR1	Rats	1	Weisman et al (1990)	14, 15
		sCR1	Rats	2	Shandelya et al (1993)	16
		C1-INH	Cats	1, 2	Buerke et al (1995)	17
		C1-INH	Pigs	1, 2	Horstick et al (1997)	18
		C1-INH	Rats	1	Buerke et al (1998)	19
	C1-INH vs. sCR1	Rats	1	Murohara et al (1995)	20	
	Inhibition of specific complement factor	Anti-C5a mAb	Pigs	1	Amsterdam et al (1995)	21
		Anti-C5 mAb	Rats	1	Vakeva et al (1998)	22
Adhesion molecules	Inhibition of PMN adhesion	Anti-CD18 mAb	Rabbits	1	Williams et al (1994)	23
		P-selectin inhibition	Rats	1	Scalia et al (1996)	24
		Anti-ICAM-1 mAb	Dogs	1	Hartman et al (1995)	25
		Anti-ICAM-1 mAb	Rabbits	1	Zhao et al (1997)	26
		Anti-CD11b/CD18 mAb	Dogs	1	Simpson et al (1988)	10
Cytokines	Inhibition of neutrophil activation/migration	Anti-IL-8 mAb	Rabbits	1	Boyle et al (1998)	27
		Anti-TNF α	Rabbits	1	Li et al (1999)	28

^a1 = reduction in infarct size, 2 = improvement of hemodynamics.
 PMN, polymorphonuclear cells; mAb, monoclonal antibody; CoVF, cobra venom factor; sCR1, soluble complement receptor type 1; C1-INH, C1 esterase inhibitor; ICAM-1, intercellular adhesion molecule-1.

processes may provide new possibilities for (additional) treatment in patients with AMI. In this manuscript we discuss potential therapeutic approaches for anti-inflammatory interventions in AMI. In *Table 1* we have grouped and summarized studies in which anti-inflammatory interventions during AMI were investigated.

Corticosteroids

Corticosteroids such as prednisone and dexamethasone are potent inhibitors of the inflammatory response. As early as 1953, Johnson et al⁵ reported the cardioprotective effects of cortisone by its ability to limit myocardial damage during myocardial infarction in dogs. In subse-

quent animal studies the infarct size-reducing effects of corticosteroids were also observed.^{2,6,7} Several clinical trials with both positive and inconclusive results followed thereafter.^{29,30} Corticosteroids, however, presumably because of their effects on cytokine and growth factor production, impair wound healing processes. Prob-

ably due to these effects, a higher incidence of left ventricular rupture was reported in some clinical trials in patients receiving high-dose corticosteroid therapy.^{31,32} Because of these negative effects on wound healing and scar tissue formation, corticosteroids were considered inappropriate for the treatment of AMI in humans.

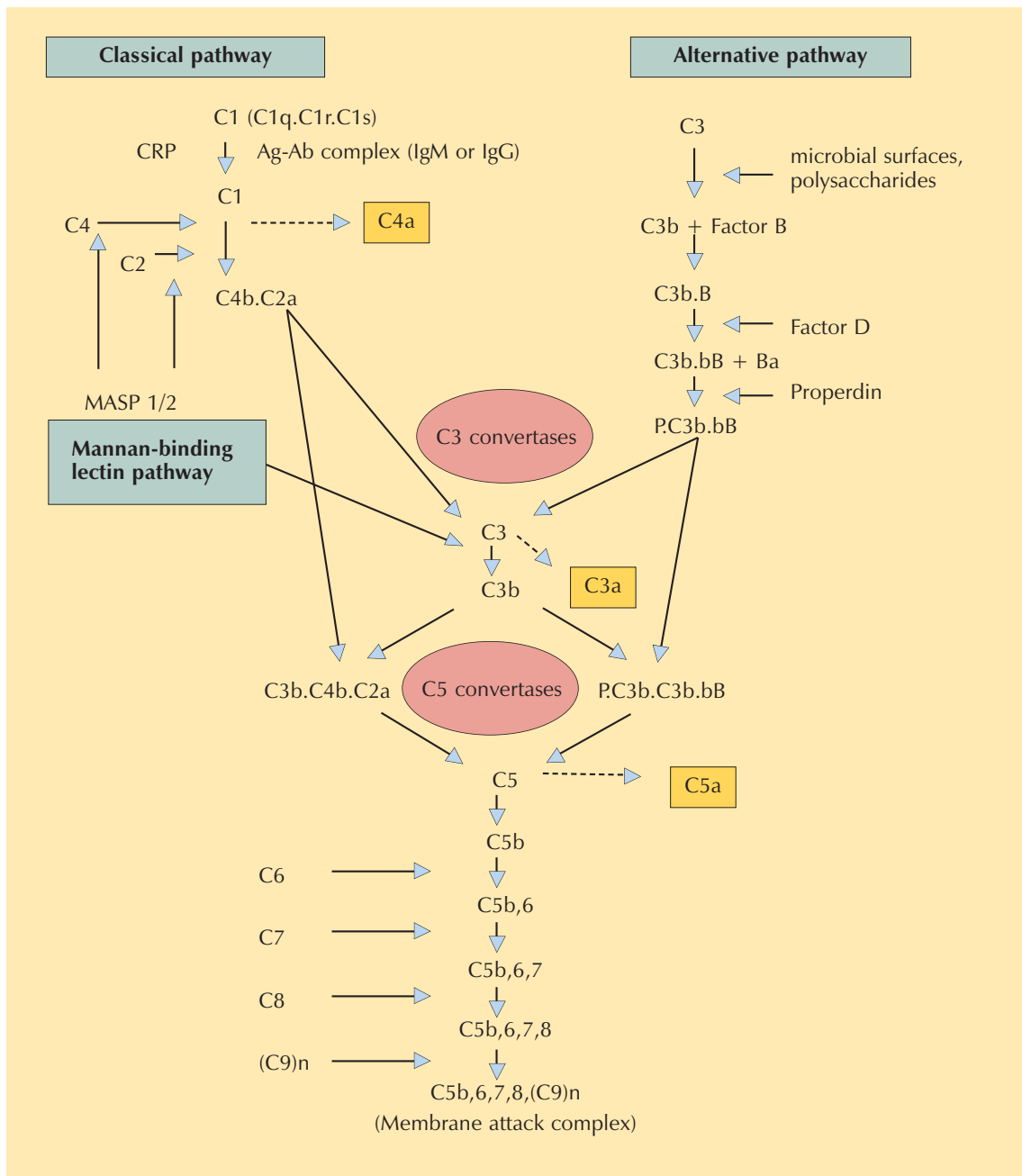


Figure 1. The complement system.

Neutrophils

During AMI, polymorphonuclear cells (PMN) infiltrate, accumulate, and degranulate in the infarcted parts of the myocardium. Results from animal studies point to an important role for PMN in the inflammatory reactions during AMI. Activated PMN are able to generate oxygen radicals and proteolytic enzymes, thereby exacerbating myocardial tissue injury.^{8,9} Reduction, depletion, or inactivation of PMN during AMI indeed resulted in a significant reduction in myocardial necrosis in several animal models of AMI (Table I).⁸⁻¹¹ Also, inhibition of the infiltration of PMN into the infarcted myocardium, by inhibition of intercellular adhesion molecule-1 (ICAM-1) upregulation on endothelium, significantly reduced neutrophil activity locally in the ischemic myocardium in ischemia-reperfusion experiments, resulting in cardioprotection.²⁵

The complement system

The complement system consists of more than 30 serum and cellular proteins linked in three biochemical cascades: the classical, the alternative, and the mannan-binding lectin pathway (Figure 1). All three pathways end in one final common pathway resulting in the formation of the membrane attack complex (MAC). Complement activation occurs during myocardial ischemia and infarction, which was first demonstrated by Hill and Ward³³ who showed that complement activation products generated in the infarcted myocardium were responsible for the infiltration of neutrophils. Later studies suggest that ischemic myocardium indeed activates complement: plasma levels of activated complement components increase in patients following AMI,³⁴ and several complement components become localized in the infarcted area during the course of AMI, as has been shown in animals as well as in humans.^{3,13,35,36} Complement and its activation products, in particular C5a, have the ability to provoke stimulation, aggregation, and degranulation of PMN. Thus complement activation may be responsible for the progressive leuko-

cyte capillary plugging during myocardial ischemia, which may impair full restoration of the capillary flow upon reperfusion, the so-called 'no-reflow' phenomenon.³⁷

How the complement system during myocardial ischemia is activated is still unclear. Ammonia,³⁸ reperfusion,³⁹ and mitochondrial constituents⁴⁰ are possible activators, but thrombolytic agents are also able to activate complement.⁴¹ In our own studies we have obtained evidence that C-reactive protein (CRP) is involved since CRP is able to activate complement *in vitro* as well as *in vivo*,⁴² and CRP colocalizes with activated complement in infarcted sites of the myocardium during AMI.⁴³ Recently, Griselli et al⁴⁴ demonstrated that such a role for CRP in cardiovascular disease is very likely.

A detrimental role for complement is suggested by the presence of MAC on damaged muscle fibers in ischemic myocardial areas.⁴⁵ More conclusive evidence for such a role was obtained in rabbits deficient in complement factor C6, which cannot assemble a fully active MAC. These animals have a reduced infarct size in cardiac ischemia-reperfusion models compared with C6-sufficient rabbits.⁴⁶ MAC may mediate effects via various mechanisms. The pore-forming ability of the MAC on the cell membrane can cause direct cell lysis.⁴⁷ MAC, inserted in the cell membrane, facilitates the movement of the electrolytes across the cell membrane, resulting in a rapid increase in intracellular Ca^{2+} concentration, which enhances the rate of cell death.⁴⁸ A sudden influx of calcium may also be harmful to the cell in other ways, for example, by activation of calcium-dependent phospholipases, increase in ATPase activity, and the uncoupling of oxidative phosphorylation in mitochondria.⁴⁹ In addition to these direct cytotoxic effects, MAC at sublytic concentrations may also have a number of other effects on target cells, such as induction of cytokines and changes in prostaglandin production.⁵⁰ Thus, activation of complement by ischemic myocardium has pathogenic significance: complement activation products like the anaphylatoxins and MAC may have deleterious effects on the myocardium by mechanisms dependent on, and independent of, neutrophils, which may result in

vasoconstriction, an impaired microcirculation, an increase in coronary perfusion pressure, ischemia, contractile failure of the myocardium, tachycardia, and impairment of atrioventricular conduction.^{1,51,52}

Complement activation can also facilitate activation of the coagulation cascade. For example, MAC insertion in cell membranes is accompanied by the formation of membrane vesicles on the cell surface. These vesicles express binding sites for factor Va and support prothrombinase activity.⁵³ Complement activation with subsequent MAC formation can also result in the upregulation of tissue factor activity.⁵⁴ All these effects promote coagulation and are therefore potentially harmful in AMI.

The deleterious effects of complement activation products on the myocardium have been substantiated by observations that in animal models, complement inhibition before or shortly after permanent occlusion of a coronary vessel significantly reduces the amount of myocardial necrosis.^{12,13} Administration of cobra venom factor (CoVF) *in vivo* rapidly produces profound and sustained depletion of C3 and C5.^{55,56} As for a long time it was the only agent available to manipulate complement in animals, in most experimental studies of AMI, CoVF was used to inhibit complement activation. Cardioprotective effects of CoVF, resulting in reduced myocardial tissue damage, were also demonstrated in animal ischemia-reperfusion experiments.^{12,13} These cardioprotective effects were accompanied by reduced deposition of complement factors, except for C4, in the ischemic myocardium.¹³ Positive hemodynamic effects of CoVF, such as an increase in blood flow in the jeopardized area, with subsequent increase in oxygen utilization, have also been demonstrated.⁵⁷

Administration of soluble complement receptor type 1 (sCR1) in rats exposed to ischemia-reperfusion of the heart, reduced both infarct size and the deposition of MAC in the infarcted myocardium.^{14,15} Furthermore, infiltration of leukocytes in the ischemic myocardial areas was significantly attenuated in comparison with control animals,^{14,15} as was also confirmed in a later study.¹⁶ In the latter study, administration of sCR1 resulted in improved hemodynamic

variables, eg better postischemic contractile function, after reperfusion of the ischemic myocardium.¹⁶

Inhibition of C5 activation, by a monoclonal antibody directed against C5, was found to prevent the formation of C5a and MAC in an ischemia-reperfusion model in rats.²² This monoclonal antibody was shown to reduce infarct size significantly and reduce PMN infiltration locally in the infarcted myocardium. Interestingly, these phenomena were accompanied by reduced apoptosis in the ischemic area.²² Administration of an antibody that specifically inhibits the activity of C5a resulted in improved hemodynamic parameters and less tissue injury (necrosis) after ischemia-reperfusion.²¹ As expected, the deposition of MAC was not significantly changed by anti-C5a, in line with the specificity of the monoclonal antibody. The anti-C5a also inhibited (in vitro) neutrophil cytotoxic activity but not neutrophil accumulation in the ischemic myocardium, indicating that fragments of the complement system other than C5a contribute to this phenomenon.²¹

C1 esterase inhibitor (C1-INH) is a primary inhibitor of the classical pathway of the complement system. C1-INH is also an important regulator of the intrinsic pathway of coagulation. Hence, among complement inhibitors, C1-INH is unique in that it also inhibits other inflammatory systems. Moreover, this inhibitor does not impair the alternative pathway and does not prevent all defense functions of complement. Buerke et al^{17,19} showed that C1-INH significantly reduced infarct size in an ischemia-reperfusion model in cats. Contractility of the heart was improved in comparison with control animals. Furthermore, PMN accumulation was shown to be reduced in the ischemic area. Intracoronary C1-INH treatment during ischemia-reperfusion reduced circulating C3 and slightly attenuated C5a plasma concentrations. This was accompanied by a significant reduction in plasma markers of myocardial cellular injury such as creatine kinase and troponin-T. No differences were observed with respect to global hemodynamic parameters, but local myocardial contractility was markedly improved in the ischemic zone in C1-INH-

treated animals.^{18,20} In our own studies, we have observed beneficial effects of C1-INH (reduction in infarct size by up to 40%) in a dog model for AMI, not only in ischemia-reperfusion, but particularly under conditions of permanent occlusion (Kleine et al, manuscript submitted for publication).

All studies discussed above show that inhibition of the complement system may markedly limit myocardial infarct size and improve myocardial function after AMI. Unfortunately, only limited data are available regarding a potentially detrimental role of complement inhibition in the formation of scar tissue in the infarcted myocardium after AMI, since insufficient scar formation would eliminate the clinical use of complement inhibitors in AMI such as was observed with corticosteroids (as discussed above). In one study, CoVF was shown to reduce slightly the ventricle wall thickness of the infarcted area in rats 3 weeks after induction of AMI.¹² Regarding C1-INH, we found no effect on scar formation in dogs treated with C1-INH 3 months after experimental AMI (Kleine et al, manuscript submitted for publication). In a limited clinical trial with C1-INH in patients with AMI, we observed promising effects with respect to infarct size (Hermens et al, manuscript in preparation). As described above, inhibition of complement activation reduces myocardial infarct size considerably in animals both after permanent coronary occlusion and during induction by reperfusion of ischemic myocardium.^{14,21} Whether the molecular mechanisms underlying this ischemia-reperfusion-induced complement activation are similar to those occurring during permanent occlusion, remains to be established.

Adhesion molecules

Adhesion molecules are expressed on endothelial and inflammatory cells during AMI. This expression is probably initiated by the inflammatory reactions ensuing in the infarcted myocardium. P-, L- and E-selectins, CD11/ - CD18 and other (vascular and intercellular) adhesion molecules are expressed, both on endothelial and inflammatory cells (PMN).

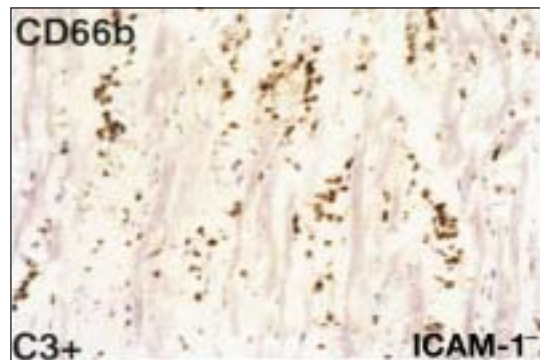


Figure 2A. Localization of CD66b in extravascular nonadherent PMN. In this area of myocardial infarction cardiomyocytes stained positively for C3d but negatively for ICAM-1 (magnification $\times 250$).

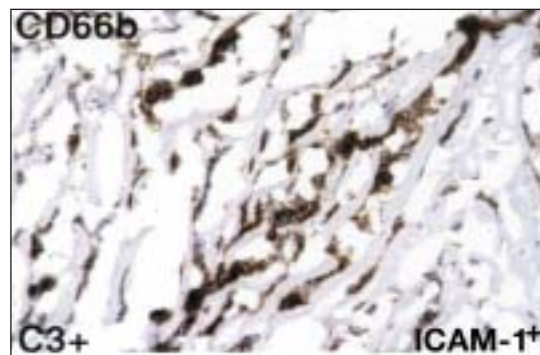


Figure 2B. Localization of CD66b in PMN adhering to infarcted cardiomyocytes that stained positively for both C3d and ICAM-1. Positive staining for CD66b also was found in cardiomyocytes, unrelated to (adherent) PMN (magnification $\times 250$).

ICAM-1 effectively promotes the adherence of activated leukocytes, including PMN. Complement, in particular anaphylatoxin C5a, is able to upregulate ICAM-1 by endothelial cells.⁵⁸ ICAM-1 expression in ischemic myocardium is upregulated upon reperfusion.⁵⁹ In post-mortem studies in humans who died following AMI we found increased ICAM-1 expression by nonviable cardiomyocytes in areas containing deposits of complement factors.⁶⁰ Moreover, the presence of CD66b on cardiomyocytes strongly suggested degranulation of PMN in these ICAM-1-positive areas, which was not observed in ICAM-1-negative areas (Figure 2). Hence, ICAM-1 upregulation by cardiomyocytes may be an important event in the processes ultimately leading to the death of

these cells. Although the precise trigger for ICAM-1 expression by ischemic cardiomyocytes is not known, the time sequence between complement deposition and the expression of ICAM-1 as well as the observation that ICAM-1 expression is strictly restricted to complement-positive areas, suggest that complement plays a role.

Blockade of ICAM-1 during reperfusion was shown to be cardioprotective through limitation of infarct size by inhibiting neutrophil adhesion to coronary endothelium.²⁶ Inhibition of neutrophil accumulation in the infarcted myocardium by use of an anti-CD18 monoclonal antibody resulted in a significantly smaller infarct size.²³ Reduction in endothelial P-selectin expression by N,N,N-trimethylsphingosine also significantly attenuated myocardial necrotic injury.²⁴

Cytokines

During myocardial ischemia and infarction several cytokines are released by macrophages, endothelial cells, and fibroblasts of the jeopardized tissue. The main cytokines involved are IL-6, IL-8, and TNF α .⁶¹ IL-6 is the main cytokine initiating the acute-phase response. The acute-phase response is a well-known clinical phenomenon consisting of leukocytosis, fever, alterations in metabolism of many organs, and changes in plasma concentrations of various so-called acute-phase proteins.⁶² The function of the acute-phase response is not well understood: possible hypotheses are prevention of ongoing tissue damage, neutralization of the inflammatory agent, or activation of tissue repair processes. IL-8 is a very potent chemoattractant and is thought to play an important role in the activation and transmigration into interstitium of neutrophils. Boyle et al²⁷ demonstrated that a specific monoclonal antibody that neutralizes IL-8 activity was able to reduce the degree of myocardial necrosis in rabbits subjected to ischemia-reperfusion. In agreement with the results described for anti-IL-8, Li et al²⁸ observed significant cardioprotective effects of anti-TNF α in a similar rabbit model for AMI.

Mechanisms of cell death

Cell death during AMI with reperfusion not only occurs via necrosis ('accidental cell death') but may also result from apoptosis ('programmed cell death').⁶³ In contrast to 'accidental cell death', apoptosis is energy-requiring and highly orchestrated by several regulatory proteins. The expression of two such proteins, bcl-2 and Bax, has been studied in human hearts from patients who died following AMI. Bcl-2, an apoptotic inhibitor, was found in the border zone of myocardial infarction. Bax, when overexpressed, a protein with proapoptotic abilities, was also found in these areas but especially in older infarctions. The Bax/bcl-2 ratio in these areas may therefore be an indicator of the extent of apoptotic activity.⁶⁴

The link between inflammation and the different mechanisms of cell death is not fully understood. Recent experimental studies identified, for example, the MAC of the complement system as proapoptotic.⁶⁵ To what extent the MAC, and other inflammatory phenomena, contribute to apoptosis in ischemic myocardium remains to be determined. In line with this, the exact clinical and therapeutic implications of apoptotic phenomena for humans with AMI are still unclear. Inhibition of the caspase system, however, was found to result in a marked reduction in myocardial tissue damage.⁶³

Conclusions

During myocardial ischemia, inflammatory reactions are elicited locally in the infarcted myocardium. These reactions comprise complicated interactions between ischemic cardiomyocytes, inflammatory cells (such as PMN), cytokines, complement factors, acute-phase proteins, and adhesion molecules. Whether the inflammatory reactions in humans with AMI with reperfusion may differ from those without reperfusion is still unclear, but in both situations the inflammatory reactions may considerably contribute to the final myocardial tissue injury. Anti-inflammatory interventions have been demonstrated to be effective in reducing overall infarct size. It is, however,

notable that most results originate from animal studies, the results of which cannot be translated directly to the human situation.

Future studies should reveal whether anti-inflammatory interventions are efficacious and safe in humans with AMI. Analysis of these studies should be accurately performed since the corticosteroid studies in the 1970s have demonstrated that anti-inflammatory therapies may have very severe detrimental consequences. ■

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Identification of patients at risk for left ventricular remodeling: role of magnetic resonance tissue tagging and strain analysis

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Introduction

Early identification of patients at risk for left ventricular remodeling after myocardial infarction will enable therapy to be adjusted before significant remodeling occurs. This may contribute to the prevention of heart failure. Metabolic imaging techniques using SPECT or PET are widely used for assessing myocardial ischemia and viability,¹ and for identifying patients who may potentially benefit from revascularization.² Most studies using these techniques, however, are carried out in patients with already severely depressed left ventricular function, and although they provide important data with respect to prognosis and patient management, they do not address the identification of patients prone to remodeling.

The remodeling process, characterized by progressive dilatation and impaired global function, is attended by regional differences in myocardial function and mechanical loading, both important stimuli that contribute to the progression of the postinfarct ventricle toward endstage heart failure.^{3–7}

Magnetic resonance (MR) imaging has emerged as an important imaging modality for accurate assessment of global ventricular function.⁸ MR tissue tagging offers the unique feature of noninvasively quantifying regional, intramural myocardial function *in vivo*.^{9–15} This imaging modality thus enables study of the relationship between both global and regional function after infarction.

This article will discuss the potential value of MR tissue tagging and strain analysis for the detection of patients at risk for ventricular remodeling.

Mechanical implications of ventricular remodeling

Left ventricular remodeling has been suggested to play an important role in the progression of heart failure in patients with ventricular dysfunction,¹⁶ and therefore contributes to the increased morbidity and mortality after myocardial infarction.¹⁷ Serial follow-up studies of left ventricular dimensions and regional myocardial function after infarction have demonstrated that ventricular remodeling is attended by an early^{18–20} and persistent⁴ difference in segmental performance of the myocardium. In the early phase after infarction, adaptive responses are initiated in the noninfarcted remote myocardium to preserve stroke volume. Infarct expansion causes deformation of the infarct border zone and remote myocardium. This change in geometry alters the Frank-Starling relationship and augments shortening.²¹ As a result, the remote myocardium becomes hyperkinetic and a — temporary — circulatory compensation is achieved.

Infarct expansion in the acute phase after myocardial infarction results in wall thinning and ventricular dilatation and causes elevation of wall stress, a major determinant of ventricular performance and an important stimulus for hypertrophy.

Late after infarction, alterations in myocardial wall architecture and ventricular geometry develop to distribute the increased wall stress more evenly. The rearrangement of bundles ('slippage') of myocytes²² and myocyte hypertrophy²³ in response to the elevated wall stress cause a reduction in function of the remote

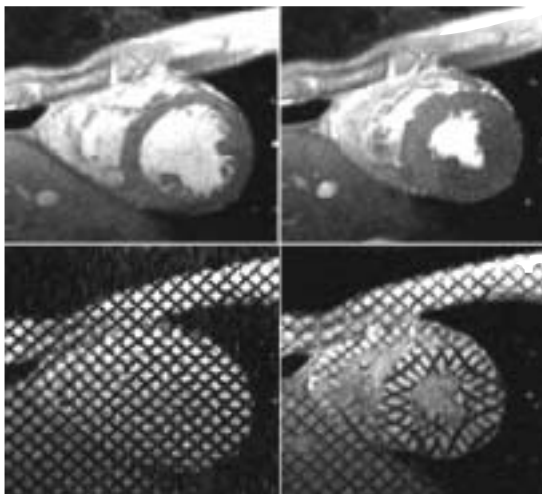


Figure 1. MR cine images (top row) and MR tissue tagging images (bottom row) at end-diastole (left) and end-systole (right). The tag line distance is 7 mm. The cine images demonstrate wall thickening during contraction, but intramural deformation is not visualized. In the tagged images, the tags are a temporary property of the myocardium and therefore the tag lines move along with the tissue. The deformed tag lines visualize directly the underlying motion of the myocardium.

myocardium and progressive impairment of global ventricular performance.

These findings suggest that besides humoral factors,^{18,24,25} functional and mechanical factors play an important role in the process of remodeling,^{3,5-7} and support the concept that remodeling is a regional process, induced by the local myocardial damage due to infarction, which involves the entire ventricle as more and more contractile units become exposed to the damaging effects of mechanical overload.

To improve understanding of the interaction between regional and global function in relationship to postinfarction remodeling, accurate quantification of regional myocardial function in different parts of the ventricular wall and changes in ventricular geometry are required.

MR tissue tagging

Until a decade ago, because of the need for identifiable landmarks or material points within the ventricular wall which can be followed during contraction, quantification of myocar-

dial deformation was restricted to animal experiments and patients undergoing coronary angiography or cardiac surgery.

In 1988, Zerhouni et al⁹ introduced MR tissue tagging, a method for noninvasive selective labeling of myocardial tissue. This was followed by the introduction of grid tagging, which provides a large number of traceable tags within the myocardium.^{11,12}

The basic idea of grid tagging is to alter locally the magnetization properties of the tissue prior to image acquisition. The modulation of the magnetization appears as dark ('tag') lines on the images (Figure 1, bottom row). Because the magnetization is a property of the tissue, the tag lines move along with the tissue in which they are created (Figure 1, top right). The tag intersection points of the grid serve as intramural landmarks. The deformed tagging pattern reflects the underlying motion of the heart wall. By tracking the motion of the tag lines throughout the cardiac cycle, the intramural myocardial deformation can be quantified.¹⁰

Myocardial strain

The tag intersection points are used to define triangular elements of the myocardium across the heart wall (Figure 2). Homogeneous strain

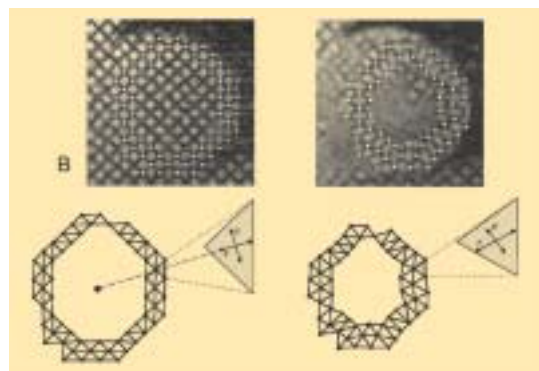


Figure 2. On the tagged images, the white diamonds indicate the intersection points of the tagging grid. By using groups of three intersection points, multiple triangular elements of myocardium can be created. The variables r and c both represent a line segment in the undeformed state, in radial and circumferential direction, respectively. The variables r' and c' represent the same line segment in the deformed state.

analysis is used to compute the deformation of each triangle.^{12,13} The strain components — radial stretch (ϵ_r) and circumferential shortening (ϵ_c) — are computed with respect to the radial and circumferential directions, respectively (Figure 2). Positive radial strains (ϵ_r) represent the local contribution to wall thickening. Negative values for ϵ_r imply local wall thinning. Negative circumferential strains (ϵ_c) quantify local circumferential shortening or myocardial contraction. Positive circumferential strains represent circumferential lengthening, associated with local dilatation.

Global ventricular function after infarction

Ventricular mass and volume can be measured accurately using cine MR imaging.⁸ In the semi-acute phase after infarction, the ratio of the end-diastolic volume and muscle mass reflecting the overall ventricular wall tension (Figure 3)²⁶ is equal in patients who demonstrate ventricular remodeling at follow-up and in patients without remodeling (0.99 ± 22 mL/g vs. 1.03 ± 0.13 mL/g, $P = ns$, respectively). These values are comparable to the normal value (0.9 mL/g) reported in the literature.²⁷ However, at 3 months' follow-up, a significant increase in global wall stress ($P < 0.05$) was observed, mainly due to progressive ventricular dilatation (end-diastolic volume index from 84 ± 23 mL/m² to 108 ± 26 mL/m², $P < 0.01$), in patients with a poor ejection fraction (<40%). The global wall stress remained unchanged in patients with an ejection fraction 40%. These observations emphasize that wall stress is an important determinant of global ventricular function.

Regional myocardial function after infarction

At follow-up after infarction, changes in myocardial function are observed not only in the infarcted area but also in the noninfarcted adjacent and remote myocardium. In the semi-acute phase after infarction, function in the infarcted area is severely depressed compared

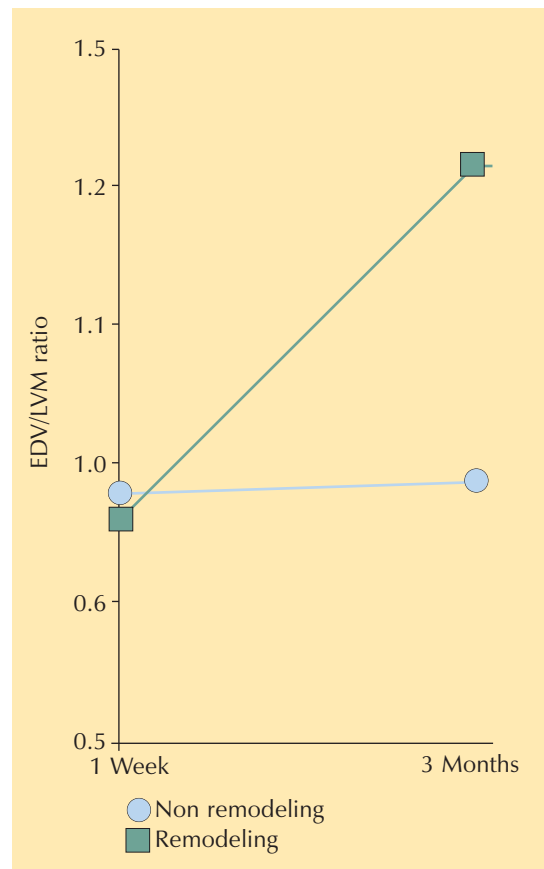


Figure 3. Ratio of end-diastolic volume to left ventricular mass (EDV/LVM), a reflection of global wall stress, at two different time points after infarction in patients with remodeled and nonremodeled ventricles.

with that in the adjacent and remote regions ($P < 0.001$). The radial stretch (Figure 4A) in the infarcted area continues to fall during follow-up in patients with ventricles subject to remodeling. In addition, the radial stretch in the remote myocardium falls from $24 \pm 7\%$ to $16 \pm 5\%$ ($P < 0.005$).

The same observations were made for circumferential shortening (Figure 4B). Shortening was severely impaired in the infarcted area ($P < 0.001$) compared with the adjacent and remote regions. During follow-up, no improvement in shortening was observed in the infarcted area, while a significant reduction in circumferential shortening in the remote region occurred (from -15 ± 5 to $-12 \pm 4\%$, $P < 0.01$).

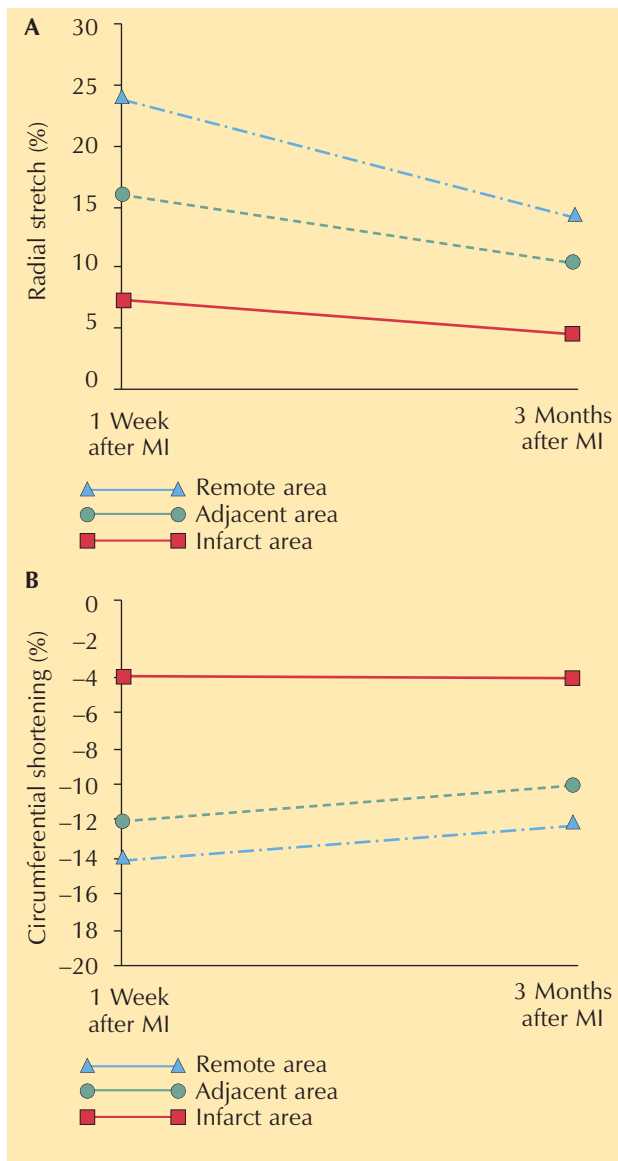


Figure 4. Percent radial stretch (A) and circumferential shortening (B) in the infarct, adjacent and remote regions at 1 week and 3 months after myocardial infarction (MI), in patients with a remodeled ventricle at follow-up.

Of both strain parameters, circumferential shortening in the semiacute phase after infarction was demonstrated to have the best predictive value for the development of ventricular remodeling. An increased value for circumferential shortening (less negative) in the remote area implicating reduced systolic shortening is associated with an increase in volumes and a

decrease in ejection fraction during follow-up (regression coefficient obtained from generalized estimating equations: 2.525, $P < 0.01$).

Conclusion

Ventricular remodeling is associated with a poor long-term prognosis and can be considered a primary target for treatment. To assess the impact of ventricular shape on regional function and reverse, accurate noninvasive measurements of ventricular geometry and function are required.

MR imaging provides the unique feature of noninvasively quantifying regional, intramural myocardial function in vivo and offers even greater accuracy for assessment of global ventricular function. These features enable study of the relationship between both global and regional function, may provide new insights into the mechanical aspects of remodeling, and lead to reductions in sample size requirements for interventional studies.

Two-dimensional myocardial strain quantified in the semiacute phase after first infarction provides noninvasive data which are predictive of ventricular remodeling. Impaired shortening is associated with an increase in ventricular volumes at follow-up. ■

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Postinfarction myocardial remodeling: current treatment

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Introduction

The myocardial remodeling process can be adaptive in response to intermittent physiological stimuli such as exercise training. However, after a myocardial infarction the stimuli are continuous and pathological. Therefore, the process becomes maladaptive, leading to progressive myocardial dysfunction.¹ Even if the infarction is so small that it causes no immediate cardiac dysfunction the remodeling process is triggered. The progressive changes in myocardial structure and deterioration of myocardial function can go on silently for a long time. Consequently, in the absence of further clinical ischemic events, overt heart failure may not develop until several years after an infarction. Since the remodeling process is triggered in virtually all patients with a myocardial infarction, it is imperative to counteract this process immediately following the infarct in order to decrease morbidity and prolong life.

What is remodeling?

In clinical practice 'remodeling' usually denotes left ventricular dilatation and altered geometry with a more spherical left ventricle, which is seen in a number of cardiac disorders.¹ This is usually accompanied by a decreased ejection fraction. However, at the microscopic level a number of changes are found (Table 1).

Table 1. Features of remodeling.

- Phenotype alteration
- Myocyte hypertrophy
- Fibrosis
- Blood vessel deficit
- Mitochondria deficit
- Defective handling of Ca²⁺
- Slower myosin
- Myocyte death

The basis for myocardial remodeling is the phenotype alteration, caused by reexpression of fetal genes in response to pathological stimuli (Figure 1).^{2,3} This leads to rapid myocardial growth, attempting to compensate for the increased mechanical load imposed on the myocardium following a myocardial infarction.⁴ The increased myocardial mass is partly due to myocyte hypertrophy. However, the quality of these proteins is not appropriate to meet the demands on the myocardium of the adult human, which eventually leads to myocardial dysfunction.

Another result of the altered gene expression is collagen deposition, causing diffuse interstitial fibrosis, perivascular fibrosis, and focal, reparative fibrosis.^{1,5} As a result the myocardium becomes less compliant and diastolic dysfunction develops. Perivascular fibrosis impairs the coronary artery compliance and decreases the coronary reserve, which increases myocardial ischemia (Figure 2).⁶ Furthermore, fibrosis may promote ventricular arrhythmia.^{5,7} The fibrous tissue is vital and contains viable cells. Thus, there is a continuous deposition of collagen by fibroblasts and consumption by macrophages. These cells consume oxygen, energy, and nutrients, causing a corresponding deficiency in the working myocytes. This leads to continuous myocyte death and systolic ventricular dysfunction.

In the remodeled myocardium there is a vascular deficit (Figure 3) which further contributes to impaired supply of oxygen and nutrients to vital myocardial cells¹ and promotes progressive cell death and remodeling. Myocyte hypertrophy also causes a relative decrease in the density of mitochondria, leading to insufficient energy production and myocardial dysfunction.¹

The remodeled myocardium is also characterized by deficient Ca²⁺ handling due to a relative decrease of sarcoplasmic reticulum, Ca²⁺ channels, and Ca²⁺ pumps.^{1,3,8} Due to the altered gene expression there is also an impaired

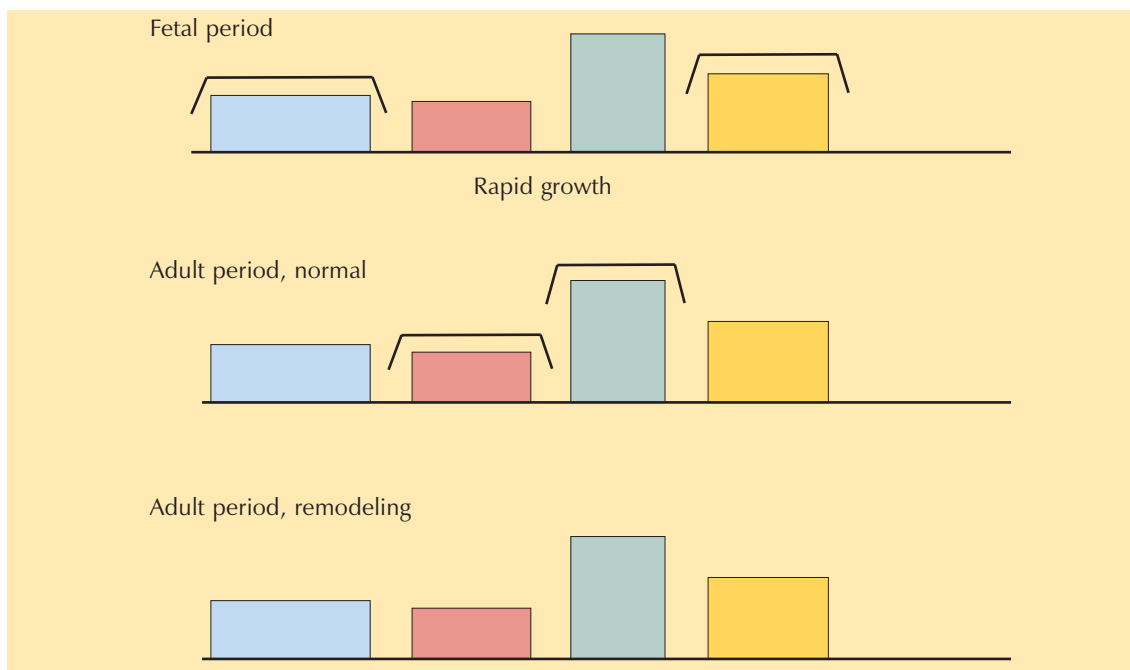


Figure 1. In response to pathological stimuli, genes coding for fetal proteins, which normally are not expressed in the adult human, once again become available for transcription.

quality of Ca^{2+} handling proteins.⁹ This contributes to the myocardial dysfunction.

Another feature of myocardial remodeling is a shift towards slower isoforms of myosin,¹⁰ causing slowing of myocardial contractility and contributing to the myocardial dysfunction.

An important characteristic of myocardial remodeling is myocyte death, which can be either necrotic or apoptotic.¹¹ Death of myocytes leads to fibrosis and thus increased remodeling, since the lost cells are replaced by collagen in order to avoid empty spaces in the myocardium (Figure 4).¹¹

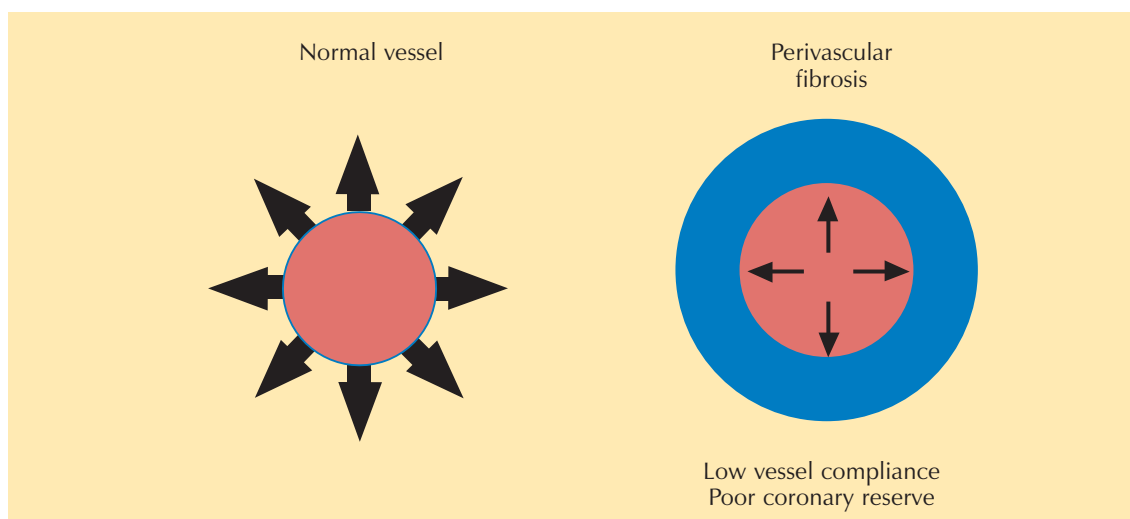


Figure 2. Perivascular fibrosis impairs coronary vessel compliance and decreases the ability of the coronary arteries to increase the blood flow in response to increased demand, ie, the coronary reserve (reproduced from reference 1).

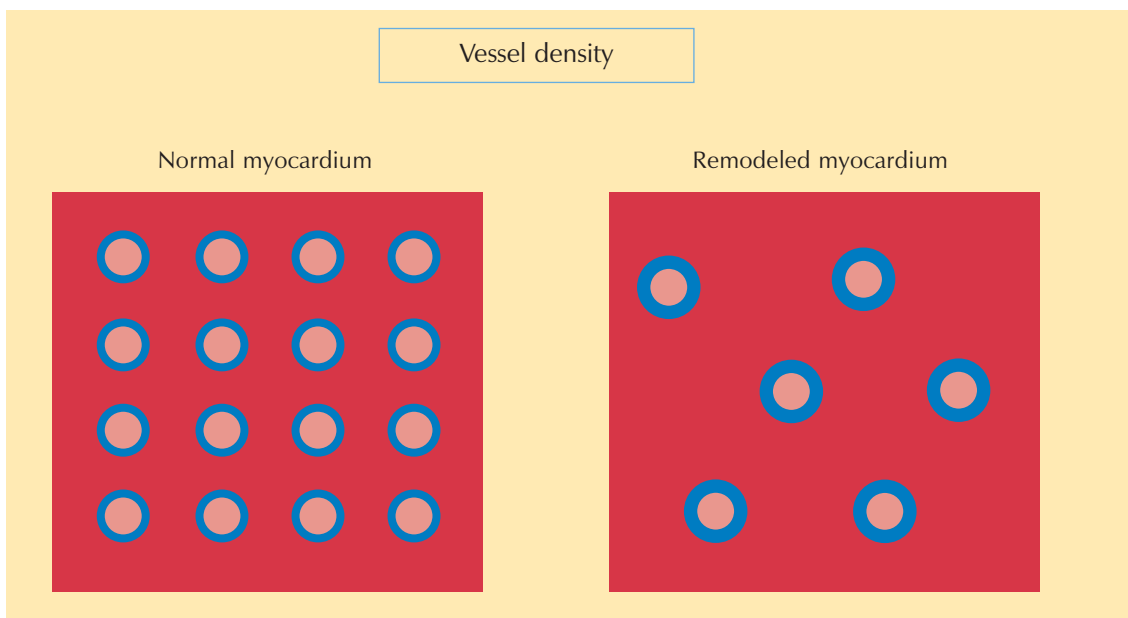


Figure 3. The remodeled myocardium is characterized by reduced vessel density (reproduced from reference 1)

Main stimuli for remodeling

The main stimuli for myocardial remodeling are mechanical overload and activation of neuro-hormonal systems such as the angiotensin and sympathico-adrenergic systems.¹² The mechani-

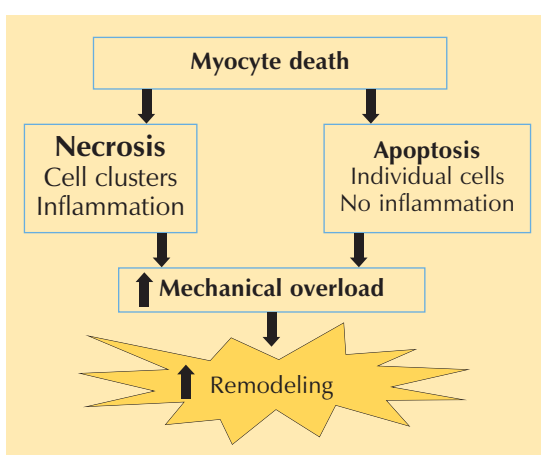


Figure 4. Death of myocytes leads to increased remodeling. The load on the remaining myocytes is increased, which further promotes the remodeling process. Furthermore, lost myocytes are replaced by collagen (reparative fibrosis) in order to avoid empty spaces in the myocardium. This constitutes an increase of the remodeling per se (reproduced from reference 1).

cal overload triggers neurohormonal activation¹³ and other cellular mediators of remodeling (Table II). Together they cause the remodeling events (Figure 5). Consequently, the mechanical overload and the remodeling mediators are the targets for therapy aimed at slowing or possibly stopping the remodeling process.

Antiremodeling therapy

β-*Receptor blockers*

Norepinephrine can induce remodeling events such as reinduction of fetal genes, growth of cardiac myocytes, increased synthesis of DNA and protein in cardiac fibroblasts, downregulation of calcium-regulating genes, expression of

Table II. Remodeling mediators and targets for antiremodeling therapy.

- Norepinephrine
- Angiotensin II
- Aldosterone
- Endothelin
- Oxygen radicals
- Cytokines
- Growth factors

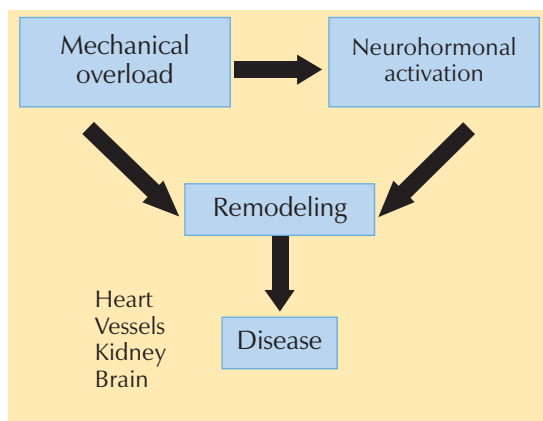


Figure 5. The main stimuli for myocardial remodeling are mechanical overload and activation of neurohormonal systems. The mechanical overload triggers neurohormonal activation and other cellular mediators of remodeling. Together they cause the remodeling events leading to disease.

tumor growth factors, and apoptosis.^{1,2} β -Receptor blocking agents may inhibit remodeling by counteracting these effects of norepinephrine. Mortality and morbidity were substantially reduced in postinfarct patients with asymptomatic left ventricular systolic dysfunction treated by carvedilol (the CAPRICORN trial, presented by H. Dargie at the 2001 ACC meeting in Orlando), and in patients with chronic heart failure treated by carvedilol¹⁴ (the COPERNICUS trial, presented by M. Packer at the 2001 ACC meeting in Orlando), bisoprolol,¹⁵ and metoprolol.¹⁶ The mortality reduction has been shown to be associated with a beneficial effect on myocardial remodeling.¹⁷

ACE inhibitors and angiotensin receptor blockers

Besides the circulating, endocrine renin-angiotensin-aldosterone system, there is a local paracrine/autocrine angiotensin system in the myocardium.¹⁸ After a myocardial infarction this system is further activated and there is an upregulation of ACE,¹⁹ angiotensinogen mRNA,²⁰ and angiotensin receptors.²¹ Angiotensin II causes remodeling through several mechanisms, including protein synthesis in cardiac myocytes, DNA synthesis in cardiac fibroblasts, and apop-

tosis.¹ ACE inhibitors and angiotensin receptor blockers (ARBs) may inhibit these events by counteracting the formation of angiotensin II and by blocking the effects of angiotensin II on the angiotensin type-1 receptor, respectively. Indeed, both the ACE inhibitor captopril and the ARB losartan have been found to prevent changes in gene expression and subsequent cellular remodeling in the remodeled rat heart.²²

Clinically, ACE inhibition attenuates remodeling following myocardial infarction.²³ Furthermore, ACE inhibition reduces mortality and morbidity in chronic heart failure,²⁴ in cardiac failure after myocardial infarction,²⁵ as well as in asymptomatic left ventricular systolic dysfunction.^{25,26} However, there are some suggestions of formation and deleterious effects of angiotensin II despite ACE inhibition.²⁷ Therefore, ARBs alone or in combination with ACE inhibitors may prove more efficacious.²⁷ However, in the Val-HeFT trial (presented by J. Cohn at the 2000 AHA meeting in New Orleans), treatment with an ARB on top of an ACE inhibitor failed to reduce one of the primary objectives (all cause mortality) in heart failure patients compared with ACE inhibition alone. This combined treatment reduces the second primary objective of mortality and hospitalization. Several clinical studies in cardiovascular disease have shown that angiotensin receptor blockers are at least equal to ACE inhibitors in terms of clinical effects.²⁷ However, to date there is no evidence that angiotensin receptor blockers are better than, or even similarly efficacious to, ACE inhibitors with regard to mortality and morbidity.²⁸

Aldosterone receptor blockers

Aldosterone is especially important to the development of myocardial fibrosis.²⁹ By inhibiting the formation of aldosterone and/or by blocking the effects of aldosterone at the receptor level myocardial fibrosis may be counteracted. Some of the beneficial effects of ACE inhibition are most likely due to inhibition of aldosterone effects. However, despite treatment with target doses of ACE inhibitors there is considerable formation of aldosterone,³⁰ and the addition of an aldosterone receptor block-

er, spironolactone, on top of an ACE inhibitor further reduced mortality in patients with chronic heart failure.³⁰

Endothelin-1 receptor blockers

Endothelin-1 is a potent peptide vasoconstrictor produced by several cell types in the myocardium. Endothelin-1 and endothelin receptors are upregulated in the remodeled myocardium.³¹ In the rat, endothelin-1 increases collagen synthesis in cardiac fibroblasts,³² and ventricular myocyte protein synthesis.³³ Blockade of the endothelin-A receptor may counteract remodeling,³⁴ and has been shown to increase survival in rats after myocardial infarction.³⁴ Preliminary clinical data suggest beneficial effects of endothelin-inhibiting agents in patients with heart failure.^{35,36} However, so far no benefit has been demonstrated on morbidity and mortality. The Randomized Intravenous Tezosentan 1 (RITZ-1) trial (www.theheart.org, April 20, 2001) was recently reported to show no such benefit of the dual endothelin receptor blocker tezosentan in acute heart failure.

Antioxidants

Free oxygen radicals are associated with cardiac myocyte apoptosis, fetal gene expression, and excessive myocardial growth due to increased protein synthesis and fibroblast proliferation.^{1,2} There is thus a potential role for antioxidant therapy in conditions with cardiac remodeling. Some of the beneficial effects of carvedilol in patients with heart failure may be due to such an effect.³⁷ Nitric oxide-releasing agents may counteract apoptosis by attenuating free oxygen radicals.¹

Cytokine antagonists

Inflammatory cytokines such as tumor necrosis factor- α (TNF α) and interleukin-6 are increased in heart failure,³⁸ and TNF α correlates with survival in patients with heart failure.³⁸ Cytokines

are associated with remodeling and may act via receptors on myocytes and fibroblasts.³⁹ TNF α antagonism has been well tolerated and seemingly effective in small clinical studies in heart failure patients.^{40,41} Nevertheless, two morbidity/mortality trials investigating the TNF α blocker etanercept were recently prematurely halted because of a lack of efficacy (www.theheart.org, March 23, 2001).

Peptide growth factor inhibitors

Peptide growth factors such as fibroblast growth factors, transforming growth factor- β_1 , and platelet-derived growth factor, are involved in the remodeling process by inducing fetal gene expression and stimulating growth of cardiac myocytes and fibroblasts.⁴² Today they may be indirectly inhibited by therapies reducing mechanical overload and by agents blocking the neurohormonal activation responsible for their activation, such as β -receptor blockers.²

Therapeutic strategies

Despite ACE inhibitor treatment, mortality remains extremely high in heart failure.^{24,25} Although the addition of a β -receptor blocker¹⁴⁻¹⁶ or spironolactone³⁰ on top of an ACE inhibitor has improved survival somewhat further, it may be necessary to further block the remodeling-mediating pathways in order to completely prevent or stop the remodeling process. However, it has been suggested that it might be dangerous to block the neurohormonal systems too vigorously, and polypharmacy has potential drawbacks.⁴³ Therefore, individual tailoring of heart failure therapy is probably a useful approach, about which we need to learn more.⁴³

When heart failure has developed, the remodeling process is already advanced. It will probably be extremely difficult to fundamentally affect prognosis if therapy is not initiated until the late stages of remodeling. Therefore, it is imperative that we find and appropriately treat patients at risk of developing remodeling,

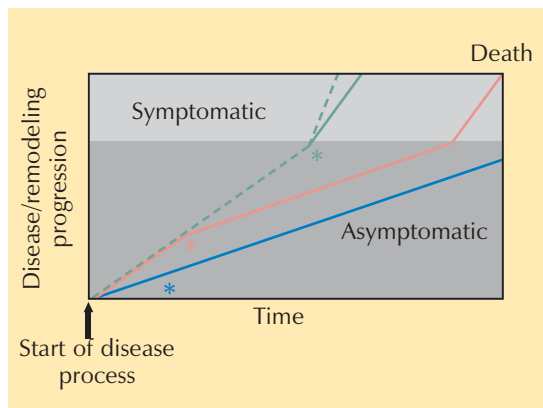


Figure 6. The impact of earlier initiated antiremodeling therapy on disease progression, symptom development, and survival. The y-axis depicts the progression of the disease and remodeling processes. The x-axis represents time. The light grey field indicates that the patient is asymptomatic, and the darker grey field that the patient is symptomatic. Dotted green line: Natural course of the disease (eg, post myocardial infarction). The disease progresses silently with time. After some time the patient becomes symptomatic. At this stage the disease and remodeling processes progress even faster, and the patient eventually dies. Solid green line: If antiremodeling therapy is not initiated until symptoms of heart failure have developed (green asterisk), the disease and remodeling processes are advanced. Although the speed of progression can be slowed, this therapeutic strategy has a small effect on survival and the patients usually continue to be symptomatic. Pink line: When antiremodeling therapy is initiated in early stages of the disease (pink asterisk) the remodeling process is less advanced. Therapy will slow down the remodeling process and disease progression. This therapeutic strategy has a greater impact on survival and the patient may stay asymptomatic for long time. Blue line: The start of antiremodeling therapy in very early stages of the disease or even in patients at risk of developing remodeling has a great impact on survival. The patient may remain asymptomatic for a long time.

or with remodeling in earlier stages (Figure 6). Indeed, the HOPE trial⁴⁴ showed that in patients who mainly had coronary artery disease, early ACE inhibitor therapy has substantial beneficial effects on disease progression and mortality, despite the absence of heart failure and clear left ventricular systolic dysfunction. ■

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Anti-inflammatory treatment in postinfarction left ventricular remodeling

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Left ventricular remodeling after myocardial infarction is the sum total of various processes involving myocytes and the interstitial fibrous structures which provide the matrix in which the myocytes function, causing an increase in ventricular mass and cavity dimensions. These changes in size and shape of the ventricle, defined as remodeling, are a continuous phenomenon. Progressive changes in myocardial structure lead to deterioration in myocardial function and, if not treated, may lead to clinical heart failure.

Multiple mechanisms, including inflammatory reactions, are involved in remodeling. Initially these mechanisms may be adaptive but become maladaptive if left untreated. A better understanding of these mechanisms may lead to novel preventive pharmacotherapeutic approaches. In the past, therapy was focused on the use of drugs (eg, diuretics) to obtain symptomatic improvement in patients in whom heart failure had already occurred. Various clinical trials subsequently provided insight into the potential of certain agents to prevent or delay the onset or worsening of heart failure. These agents include ACE inhibitors and, in addition to the former β -blockade, the vasodilator β -blocking agent carvedilol.¹⁻⁵

Although these therapeutic strategies have consistently improved survival and quality of life after myocardial infarction, no specific therapy toward remodeling is yet available; however, much interest has been focused on the role of inflammation and on the potential use of anti-inflammatory agents to prevent remodeling after myocardial infarction.

New anti-inflammatory therapeutic approaches

Although no data are available on the effects of anti-inflammatory agents in left ventricular remodeling, recent evidence suggests that anti-

Table 1. Potential anti-inflammatory therapeutic approaches in postinfarction left ventricular remodeling.

Function	Molecule
Anti-TNF α activity	<ul style="list-style-type: none"> • Etanercept (sTNF-R-Fc fusion protein) • IL-1 receptor antagonist
Anti-inflammatory cytokines	<ul style="list-style-type: none"> • Intravenous immunoglobulin (induces a rise in plasma levels of anti-inflammatory cytokines) • TGF-β
MMP activity inhibitors	<ul style="list-style-type: none"> • Doxycycline • Anti-MMP2 antibody
Anti-CRP activity	<ul style="list-style-type: none"> • Anti-CRP antibodies • Statins
Adenosine	<ul style="list-style-type: none"> • Counteracts neurohumoral factors including cytokines

inflammatory therapy, targeted at specific cytokines or other proinflammatory molecules, may be helpful (Table 1).

Anti-tumor necrosis factor- β (TNF α) activity

Recently, etanercept was used in patients with heart failure. Etanercept, a soluble recombinant anti-tumor necrosis factor- α (TNF α) receptor (sTNF-R-Fc fusion protein) was used in a randomized, double-blind, placebo-controlled, multidose trial in 47 patients with heart failure (NYHA class III-IV). The results demonstrated a dose-dependent improvement in left ventricular ejection fraction and left ventricular remodeling (reduction in left ventricular enddiastolic and endsystolic volume), with a trend toward an improvement in patient functional status.⁶ Because of the pivotal role of TNF α in the

inflammatory reaction following myocardial infarction,⁷ its use might lead to an even more pronounced improvement of the remodeling process also in the early postinfarction phases. More information on the clinical utility of this molecule will be available as soon as three ongoing multicenter trials have been completed (RENAISSANCE, RECOVER, and RENEWAL).

A similar effect is likely to be obtained by interleukin (IL)-1 receptor antagonist, a molecule with anti-TNF α and anti-IL-1 activity which is also under investigation in patients with rheumatoid arthritis.⁸ This molecule has similar characteristics to etanercept and therefore is likely to have similar, or improved, clinical efficacy also on left ventricular remodeling.

Anti-inflammatory cytokines

Anti-inflammatory cytokines have been shown to be effective in preventing atherosclerosis in animal models, but to our knowledge no data are available on congestive heart failure and postinfarction remodeling. However, Gullestad et al⁹ demonstrated that intravenous immunoglobulin improved left ventricular ejection fraction in patients with congestive heart failure through a net anti-inflammatory effect, which was determined by a rise in plasma levels of anti-inflammatory cytokines.

Another molecule with modulatory activity on inflammation, transforming growth factor (TGF)- β , a family of multifunctional proteins that regulate cell growth, differentiation, migration, and extracellular matrix production, plays an important role in tissue remodeling.¹⁰ Schenowitz et al¹¹ demonstrated that systemic administration of basic fibroblast growth factor following myocardial infarction in rats prevents left ventricular dilatation and induces hypertrophy of the noninfarcted myocardium.

Matrix metalloproteinase (MMP) activity inhibitors

Recently the possibility to counteract matrix metalloproteinase (MMP) activity by the use of doxycycline, a commercially available tetracy-

cline modified antibiotic, has opened the way for the use of this molecule in left ventricular remodeling following myocardial infarction.¹² MMP is involved in many remodeling processes in the organism¹³⁻¹⁵ and its level is raised after myocardial infarction: in a rat model of ischemia reperfusion injury MMP2 was raised in the coronary effluent and correlated negatively with left ventricular function. In this model the use of doxycycline and anti-MMP2 antibody improved left ventricular function after ischemia reperfusion.¹⁶

Anti-C-reactive protein (CRP) activity

There is growing evidence that C-reactive protein (CRP), the prototypic acute-phase reactant produced in the liver under IL-1 and IL-6 stimulation,¹⁷ is an important and independent predictor of cardiac events following myocardial infarction.¹⁸⁻²² Colocalization of CRP and complement in the infarcted myocytes has been demonstrated. Recently, Griselli et al²³ demonstrated that injection of human CRP into rats after ligation of the coronary artery reproducibly enhanced infarct size by 40%: human CRP binds to damaged cells and activates complement, but rat CRP does not activate complement. These authors showed that in vivo complement depletion completely abrogated this effect and markedly reduced infarct size. These observations suggest that human CRP and complement activation are major mediators of ischemic myocardial injury and identify them as therapeutic targets in coronary heart disease. Anti-CRP antibodies are under investigation and may result in a new therapeutic option in the treatment of postinfarction remodeling.

Evidence that statins may reduce CRP levels in patients with ischemic heart disease^{24,25} suggests that early treatment with high doses of statins may help in reducing infarct size and improve remodeling.

Adenosine

Adenosine therapy has been proposed as a new treatment for the prevention and attenua-

tion of chronic heart failure due to its various possible cardioprotective activities. Adenosine induces collateral circulation by inducing growth factors and triggering ischemic preconditioning; reduces the release of norepinephrine and endothelin production, and attenuates the activation of the renin-angiotensin system, all of which contribute to cardiac hypertrophy and remodeling; reduces the severity of ischemia and reperfusion injury; and counteracts neurohumoral factors, including cytokine systems, known to be related to ventricular remodeling and progression towards heart failure.²⁶

It is also intriguing to note that drugs we currently use for the treatment of postinfarction left ventricular failure have anti-inflammatory effects, as is the case of ACE inhibitors and β -blocking agents.^{27,28}

Conclusion

The identification of stimuli that initiate and maintain the processes of cardiac hypertrophy and remodeling, and eventually heart failure, remains a major pursuit in cardiac molecular biology and remodeling. The growing evidence that inflammation plays a role in these mechanisms suggests that new drugs with a specific anti-inflammatory activity targeted to the molecules involved in remodeling will play an important role in the future pharmacological armamentarium of cardiologists. ■

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3-KAT inhibition: a new approach to cardioprotection

Cardiovascular disease represents a major health care problem worldwide.^{1,2} Coronary artery disease (CAD) remains the leading cause of morbidity and mortality in cardiovascular disease and its treatment remains challenging.

The phenomenon of coronary atherosclerosis mediates the development of myocardial ischemia through a complex interaction of fixed atherosclerotic plaque, impaired coronary vasomotion, hematologic, and metabolic abnormalities.³ Despite improvement in the management and treatment of CAD, the prognosis and quality of life of patients remain to be improved. The complex mechanism of myocardial ischemia requires a combined approach using revascularization procedures (PTCA + stent, CABG) and medical treatments.⁴⁻⁶

New developments in the field of cardiovascular research have recently underlined the importance of metabolic abnormalities and the deleterious consequences of ischemia for the myocardial cells.^{7,8} Therefore, new drugs which act on metabolic control of the myocardial cells have been developed. Trimetazidine (Vastarel 20) is the first in a new class of metabolic agents known as 3-KAT inhibitors, which exerts its anti-ischemic effect without affecting myocardial blood supply, and which operates independently of any hemodynamic changes. Kantor et al⁹ have recently identified the exact mechanism of action of trimetazidine: it selectively inhibits a mitochondrial enzyme of fatty acid β -oxidation: the long-chain 3-ketoacyl-CoA-thiolase (3-KAT). This specific enzyme inhibition allows trimetazidine to redirect cardiac metabolism towards glucose oxidation, to the detriment of fatty acid β -oxidation, hence increasing the energy performance of the myocardial cell and improving cardiac work (Figure 1).

In experimental studies, trimetazidine was shown significantly to reduce acidosis during

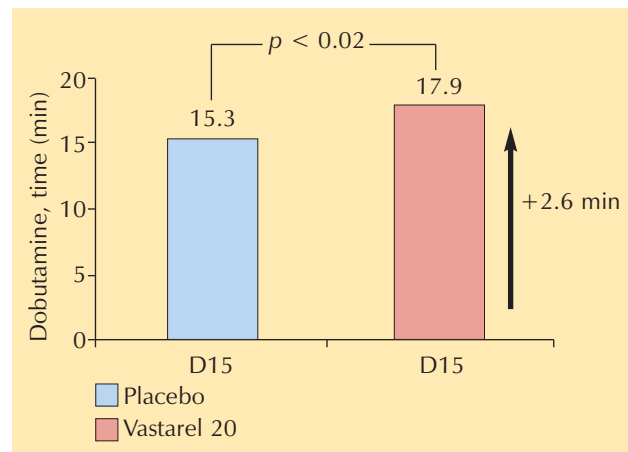


Figure 1. Trimetazidine increases the ischemic threshold on dobutamine echocardiography.

ischemia, preserve ATP synthesis, and improve functional recovery during ischemic reperfusion. These findings have been confirmed in numerous clinical studies.

Trimetazidine has proved to be an effective drug in chronic stable angina, both in monotherapy and in combination with a hemodynamic agent (β -blocker or calcium antagonist).¹⁰⁻¹⁴ The original metabolic mechanism of action allows trimetazidine to be effective and safe, even in high-risk populations such as diabetics and the elderly, for whom both quality of life and prognosis remain particularly poor.^{15,16}

More recent studies have reported promising results with trimetazidine in other fields of CAD. The LIST study group demonstrated that trimetazidine, compared with placebo, led to earlier resolution of ST-segment elevation in 94 patients treated with PTCA for acute myocardial infarction.¹⁷

Two recent studies confirmed the value of trimetazidine in patients with ischemic left ventricular dysfunction, in whom the contractile response of chronically dysfunctional myocardium to dobutamine was improved by trimetazi-

Table 1. Results at 2 months' follow-up (adapted from reference 18).

	Placebo	Trimetazidine	P-Value
Left ventricular end-systolic volume (mL) at rest	112.7 ± 11	110 ± 13	0.003
Left ventricular end-systolic volume (mL) at peak	108.0 ± 11.8	97.7 ± 11.6	<0.001
LVEF (%) at rest	33.6 ± 3.4	39.5 ± 5.9	<0.001
LVEF (%) at peak	38.9 ± 3.5	42.9 ± 4.4	<0.001
SWTI at rest	1.88 ± 0.13	1.71 ± 0.15	<0.001
SWTI at peak	1.83 ± 0.16	1.41 ± 0.09	<0.001

LVEF, left ventricular ejection fraction; SWTI, systolic wall thickening index.

dine without hemodynamic changes.^{18,19} Belardinelli and Purcaro¹⁸ have recently underlined these benefits in a randomized, double-blind study. Forty-four patients (52.7 ± 8 years) with postnecrotic left ventricular dysfunction (33 ± 5%) and multivessel CAD were randomized into matched groups. Group 1 received trimetazidine 20 mg tid, while group 2 received a placebo during 2 months of follow-up. At baseline and after 2 months, all patients underwent low-dose dobutamine echocardiography (5–20 µg/kg per min) and a symptom cardiopulmonary exercise test. Patients taking trimetazidine, compared with the placebo group, had a significant improvement in systolic wall thickening index. This effect was accompanied by an improvement in left ventricular function ($P < 0.001$) and peak VO_2 ($P = 0.001$) (Table 1). Improvement in left ventricular function in coronary patients treated with trimetazidine was also confirmed in a double-blind, placebo-controlled crossover study by Lu et al¹⁹ (Figure 1). These data clearly support the value of cardiac metabolism manipulation with metabolic agents such as trimetazidine and offer new perspectives for the management and the prognosis of patients with CAD.

Conclusion

Trimetazidine, the first of a new class of metabolic agents known as 3-KAT inhibitors, is effective and safe in all subgroups of patients with CAD. Coronary patients with or without diabetes, elderly patients, women with documented CAD, and patients with ischemic cardiomyopathy, may benefit from a metabolic anti-ischemic treatment with trimetazidine. ■

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Perfusion after AMI

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Introduction

A case is presented of a 62-year-old man with acute myocardial infarction successfully treated by means of primary coronary angioplasty of the culprit vessel. A myocardial contrast echocardiography (MCE) study was performed during infarct-related artery occlusion, shortly after PTCA, and 48 h afterwards to assess microvascular status after optimal recanalization of the epicardial vessel.

Early MCE showed an evident contrast enhancement in the infarct area associated with a brisk epicardial flow (using conventional contrast dye angiographic assessment) indicating tissue level reperfusion. However, late MCE study at 48 h showed, in spite of the persistence of a brisk epicardial flow, the absence of a significant contrast effect in the infarct area after injecting the bubbles (sonicated contrast dye) in the infarct-related vessel, indicating an extensive microvascular obstruction.

The subsequent course was uneventful and a mild regional and global functional recovery was observed at the predischarge echocardiographic study and the calculated ejection fraction (EF) was 45%. Repeat echocardiography 1 month after the index infarction revealed a dilated, poorly contracting left ventricle and an EF of 25%.

This case illustrates the dynamic behavior of microvascular status after acute myocardial infarction and highlights the importance of optimal and sustained tissue reperfusion for preserving left ventricular geometry. In fact, despite restoration of epicardial blood flow, early or late microvascular obstruction may negatively influence left ventricular remodeling after reperfusion.

Case report

The patient was a 62-year-old male with a history of hypertension who presented to the emergency department of our hospital com-

plaining of severe and persistent chest pain lasting about 2 h.

On admission, the patient was slightly tachypnoic. Heart rate was 98 bpm and blood pressure 115/70 mm Hg. Heart sounds were normal and at the apex a soft protomesosystolic murmur was audible, compatible with mitral regurgitation. Rales were audible over the bases of the lungs.

The ECG on admission showed marked ST-segment elevation in leads V₁–V₅ compatible with acute anterior infarction. There were also mild repolarization abnormalities in the inferior leads.

The echocardiogram showed severe left ventricular regional motion abnormalities (akinesia) involving the anterior wall, anterior septum, and apex, and a moderate left ventricular dysfunction (EF 38%). The left ventricular end-diastolic and endsystolic dimensions were 51 and 40 mm, respectively. There was a mild mitral regurgitation.

Due to the short time elapsed from the onset of symptoms and the extension of the area at risk, the patient was commenced on intravenous infusion of heparin and abciximab and promptly transferred to the catheterization lab-



Figure 1. Left: Coronary angiography; right: myocardial contrast echocardiogram (long axis view) in a patient with acute anterior myocardial infarction before recanalization. The angiogram shows occlusion of LAD in the mid portion after the first diagonal branch. Myocardial contrast echocardiogram reveals the absence of opacification in the medium segment of the septum and apex (area at risk).



Figure 2. Repeat myocardial contrast echocardiogram shortly after successful primary PTCA of the LAD (left) shows an homogeneous contrast enhancement of the risk area (right).

oratory for emergency coronary angiography and primary coronary angioplasty if suitable. Coronary angiography revealed the occlusion of the midportion of the left anterior descending (LAD) coronary artery after the first diagonal branch (Figure 1). MCE was performed (by injecting 3 mL hand-agitated iopamidol) during coronary occlusion and revealed the absence of contrast effect in the medium segment of the septum and apex (area at risk) (Figure 1). A successful (TIMI flow grade 3 and residual stenosis <30%) PTCA and stenting of the LAD were performed (Figure 2). Repeat MCE, shortly after infarct-related artery recanalization, showed an homogeneous contrast enhancement of the risk area (Figure 2).

After primary PTCA the patient remained asymptomatic and was transferred to the coronary care unit where intravenous infusion of abciximab and low-dose heparin was continued for 12 h and oral antiplatelet (aspirin 300 mg/day and ticlopidin 500 mg/day) and ACE inhibitor therapy was instituted. Creatine phosphokinase peaked at 2357 IU/L after 7 h from

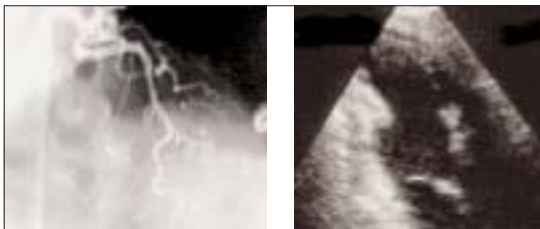


Figure 3. Forty-eight hrs follow-up coronary angiography (left) showing the persistence of an optimal epicardial patency. Myocardial contrast echocardiogram (right) revealing the disappearance of a significant contrast enhancement in the risk area.

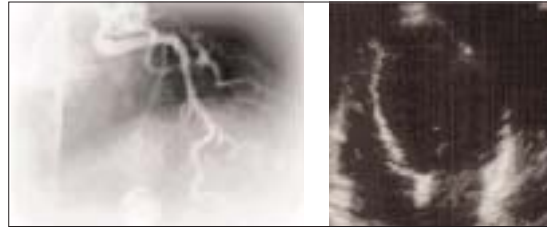


Figure 4. Four weeks after discharge repeat coronary angiogram demonstrates the persistence of LAD patency (left) but 2D-Echo (four chamber view) shows a dilated, poorly contracting left ventricle (right).

onset of acute myocardial infarction.

During the first 48 h after primary PTCA the patient recovered quickly. There were neither recurrent ischemic episodes nor significant arrhythmias, and no rales were subsequently heard; no signs of congestion were seen on chest x-ray and his ECG showed a progressive disappearance of ST-segment shift with T waves becoming negative in the infarct leads. Repeat MCE at 48 h showed the absence of a significant contrast enhancement in the risk area despite the persistence of a brisk epicardial flow (TIMI 3) at coronary angiography (Figure 3). Predischarge (day 5) echocardiogram showed a mild regional and global functional recovery and the calculated EF was 45%.

Four weeks after discharge the patient started to complain of dyspnea on intensive exercise. Again, repeat coronary angiography revealed the persistence of LAD patency, but 2-D echocardiography showed a dilated, poorly contracting left ventricle and EF was 25% (Figure 4).

Discussion

In acute myocardial infarction early restoration of antegrade flow can limit the progression of myocardial necrosis and should enhance the functional recovery of postischemic dysfunctioning myocardium, improving left ventricular function and geometry, and early and late survival.¹ However, the adequacy of reperfusion depends not only on persistent patency of the infarct-related artery but also on the integrity of distal circulation. Embolization of plaque con-

tents of platelet thrombus or platelet aggregation in the microcirculation with loss of endothelial integrity may compromise the recovery of perfusion at tissue level. Until recently, we have had limited access to diagnosing microvascular obstruction in patients with acute myocardial infarction. With the availability of imaging technology, such as MCE, microvascular dysfunction after optimal recanalization of the epicardial vessel has been documented in a far greater proportion of patients than was previously thought possible.

The link between microvascular dysfunction and unfavorable clinical outcome has been documented in many studies.²⁻⁴ Thus, MCE performed in the catheterization laboratory during the acute phase of myocardial infarction, looking beyond epicardial coronary patency, may identify higher risk patients with microvascular dysfunction.

The mechanism of microvascular dysfunction after optimal recanalization of the infarct-related artery is not completely understood. Duration of ischemia and time to recanalization are the most powerful determinants of microvascular dysfunction. However, the amount of tissue perfusion in infarcted patients is dependent on many other complex and interrelated factors including extent of collateral circulation, residual stenosis, extent of reperfusion injury, and loading conditions. This may explain some recent results showing progressive microvascular obstruction within the infarcted territory beyond coronary reflow up to 48 h,⁵ supporting the hypothesis that microvascular damage might be caused by mechanisms activated after coronary artery reflow,⁶ and not only during the occlusion period.⁷ On the other hand, some recent studies have also shown that microvascular dysfunction may improve over time, indicating that microvascular impairment is not always irreversible.⁸ Thus, microvascular dysfunction is a dynamic process. In this regard, the case reported is paradigmatic. Serial MCE, performed shortly after recanalization and at 48 h from the index infarction, showed a clear reversal of initial microvascular reflow, despite persistent patency of the infarct-related artery. There are two potential alternative explanations for this behavior. (1) Because of

hyperemia during the early hours of reperfusion, MCE may have underestimated the infarct size and overestimated the myocardial salvage. This may be particularly true when the residual stenosis is not severe enough to attenuate hyperemic flow, as in the present case. (2) After initial reflow an extensive reperfusion injury might have induced a late and progressive microvascular obstruction. Whatever the truth may be, this case highlights the issue of the appropriate timing of microvascular assessment after reperfusion. Sakuyama et al⁹ reported that most of the changes in the distal circulation occur by day 1 after recanalization of the infarct-related artery, and that microvascular assessment 2 days after recanalization better predicts early and late clinical events. Thus, a very early MCE assessment of microvascular status may foster the 'illusion of reperfusion'.

Finally, the second important message arising from this case is that microvascular dysfunction complicating mechanical reperfusion has clinical and prognostic consequences. Patients with microvascular dysfunction by MCE demonstrate progressive ventricular dilatation, as opposed to the reduction in ventricular volume seen in patients with restored microvascular perfusion.¹⁰ They also have more clinical events at follow-up compared with patients who achieved restoration of normal microvascular flow.¹⁰ Thus, microvascular status after restoration of epicardial flow may be the missing link between reperfusion, left ventricular function and geometry, and clinical outcome in acute myocardial infarction. ■

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Featured Research

Abstracts and commentaries

A novel mouse model of lipotoxic cardiomyopathy

Chiu H-C, Kovacs A, Ford DA, et al. *J Clin Invest*. 2001;107:813–822.

Inherited and acquired cardiomyopathies are associated with marked intracellular lipid accumulation in the heart. To test the hypothesis that mismatch between myocardial fatty acid uptake and utilization leads to the accumulation of cardiotoxic lipid species, and to establish a mouse model of metabolic cardiomyopathy, Chiu et al generated transgenic mouse lines that overexpress long-chain acyl-CoA synthetase in the heart (MHC-ACS). This protein plays an important role in vectorial fatty acid transport across the plasma membrane. MHC-ACS mice demonstrate cardiac-restricted expression of the transgene and marked cardiac myocyte triglyceride accumulation. Lipid accumulation is associated with initial cardiac hypertrophy, followed by the development of left ventricular dysfunction and premature death. Terminal deoxynucleotidyl transferase-mediated dUTP nick-end labeling staining and cytochrome c release in transgenic heart suggest that a cardiac myocyte death occurs, in part, by lipid-induced programmed cell death. Taken together, the authors' data demonstrate that the fatty acid uptake/utilization mismatch in the heart leads to accumulation of lipid species toxic to cardiac myocytes. This novel mouse model will provide insight into the role of perturbations in myocardial lipid metabolism in the pathogenesis of inherited and acquired forms of heart failure.

Lipotoxic heart disease in obese rats: implications for human obesity

Zhou YT, Grayburn P, Karim A, et al. *Proc Natl Acad Sci USA*. 2000;97(4):1784–1789.

To determine the mechanism of the cardiac dilatation and reduced contractility of obese Zucker diabetic fatty rats, myocardial triacylglycerol (TG) was assayed chemically and morphologically. TG was high because of underexpression of fatty acid oxidative enzymes and their transcription factor, peroxisome proliferator-activated receptor- α . Levels of ceramide, a mediator of apoptosis, were two to three times those of controls, and inducible nitric oxide synthase levels were four times greater than normal. Myocardial DNA laddering, an index of apoptosis, reached 20 times the normal level. Troglitazone therapy lowered myocardial TG and ceramide and completely prevented DNA laddering and loss of cardiac function. The authors conclude that cardiac dysfunction in obesity is caused by lipoapoptosis and is prevented by reducing cardiac lipids.

Commentary

These two papers describe a new and potentially very important form of cardiovascular disease, 'lipotoxic heart disease' or 'lipotoxic cardiomyopathy'. The concept is that abnormally high circulating fatty acid levels or excessive uptake of fatty acids by the heart can lead to the development of a cardiomyopathy or heart failure associated with accumulation of intracellular lipid and accelerated apoptosis (programmed cell death). This form of cardiomyopathy has potential clinical relevance in obesity or diabetes and insulin resistance syndromes, often termed 'metabolic syndrome X'. It also may be relevant in various genetic disorders of abnormal fatty acid metabolism.

The papers highlight the need for further research to better understand the cellular events that contribute to lipotoxic cardiomyopathy, as well as the potential to develop therapeutic interventions to treat these cardiomyopathies.

G.D. Lopaschuk

No-flow ischemia inhibits insulin signaling in heart by decreasing intracellular pH

Beauloye C, Bertrand L, Krause U, et al. *Circ Res.* 2001;88(5):513–519.

Insulin signaling is initiated by its binding to the insulin receptor. This activates the tyrosine kinase activity of the receptor, leading to insulin receptor autophosphorylation and to subsequent phosphorylation of insulin receptor substrates. This in turn activates downstream components of the signaling pathway which mediate some of the metabolic effects of insulin including recruitment of insulin-sensitive glucose transporters GLUT4 to the plasma membrane.

Beauloye et al studied the insulin response of ischemic myocardium by analyzing insulin signaling in isolated perfused rat hearts submitted to no-flow ischemia. Intracellular pH was measured in these hearts by nuclear magnetic resonance spectroscopy.

Commentary

The important conclusion reached from this study is that there is an inhibition of insulin signaling during severe ischemia, and that this inhibition parallels the development of intracellular acidosis (at intracellular pH values below 6.75). Therefore, inhibition of insulin signaling is expected to depend on the severity and duration of ischemia. Inhibition of insulin signaling by severe ischemia may indicate that all insulin effects are abolished. Conversely, insulin signaling was soon fully restored on reperfusion, suggesting that the hormonal effects could resume as normal intracellular pH recovers.

The implications of these findings on cell protection, heart function, glucose metabolism, or other heart responses to insulin remain to be investigated.

D. Feuvray

Hypertrophied rat hearts are less responsive to the metabolic and functional effects of insulin.

Allard MF, Wambolt RB, Longnus SL, et al. *Am J Physiol Endocrinol Metab.* 2000;279(3):E487–E493.

The authors determined the effect of insulin on the fate of glucose and contractile function in isolated working hypertrophied hearts from rats with an aortic constriction ($n = 27$) and control hearts from sham-operated rats ($n = 27$). Insulin increased glycolysis and glycogen in control and hypertrophied hearts. The change in glycogen was brought about by increased glycogen synthesis and decreased glycogenolysis in both groups. However, the magnitude of change in glycolysis, glycogen synthesis, and glycogenolysis caused by insulin was lower in hypertrophied hearts than in control hearts. Insulin also increased glucose oxidation and contractile function in control hearts but not in hypertrophied hearts. Protein content of glucose transporters, protein kinase B, and phosphatidylinositol 3-kinase was not different between the two groups. Thus, hypertrophied hearts are less responsive to the metabolic and functional effects of insulin. The reduced responsiveness involves multiple aspects of glucose metabolism, including glycolysis, glucose oxidation, and glycogen metabolism. The absence of changes in content of key regulatory molecules indicates that other sites, pathways, or factors regulating glucose utilization are responsible for these findings.

Commentary

Decreased insulin responsiveness of skeletal muscle is a hallmark of type 2 diabetes, which is associated with increased cardiovascular morbidity and mortality. The subcellular mechanism leading to impaired insulin stimulation is largely unknown and may differ among tissues. The study by Allard et al demonstrates that left ventricular hypertrophy in response to pressure overload in nondiabetic rats elicits insulin resistance in the myocardium, with reduced glycolysis, glycogen synthesis, and glucose oxidation. The consequences of reduced insulin responsiveness on myocardial function and survival are presently not known. However, the findings of this study may be of clinical importance because hypertrophied and failing myocardium relies more on glucose metabolism than does normal myocardium. Stimulation of glucose oxidation and/or restoration of insulin responsiveness may be a target for therapeutic intervention.

R. Lerch

Myoblast transplantation for heart failure

Menasché P, Hagege AA, Scorsin M, et al. *Lancet*. 2001;357(9252):279B280.

Intramyocardial skeletal muscle transplantation has been shown experimentally to improve heart function after infarction. Menasché et al report success with this procedure in a patient with severe ischemic heart failure. They implanted autologous skeletal myoblasts into the postinfarction scar during coronary artery bypass grafting of remote myocardial areas. Five months later, there was evidence of contraction and viability in the grafted scar on echocardiography and PET. Although encouraging, this result requires validation by additional studies.

Commentary

Myocytes are terminally differentiated cells, which means that lost cells cannot be replaced by mitosis. Accordingly, transplantation of contractile cells, cardiomyocytes, or myoblasts is presently being explored by a number of groups. The article by Menasché et al reports one of the first clinical cases in which myoblasts, or satellite cells, harvested from skeletal muscle of the patient have been transferred to an infarcted area during coronary bypass surgery. Five months after surgery, PET following intravenous injection of ^{18}F -fluorodeoxyglucose documented tracer uptake in the previously infarcted region, which was attributed to the transplanted cells. This case report highlights the interest of using PET with metabolic tracers to document the viability of transplanted cells in future studies.

R. Lerch

Beneficial haemodynamic effects of insulin in chronic heart failure

Parsonage WA, Hetmanski D, Cowley AJ. *Heart*. 2001;85:508–513.

A single-blind, placebo-controlled study was carried out at a university teaching hospital to characterize the central and regional hemodynamic effects of insulin in 10 patients with stable chronic heart failure. A hyperinsulinemic-euglycemic clamp was performed and noninvasive hemodynamic measurements carried out to evaluate change in resting heart rate, blood pressure, cardiac output, and regional splanchnic and skeletal muscle blood flow. Insulin infusion led to a dose-dependent increase in skeletal muscle blood flow of 0.36 (0.13) and 0.73 (0.14) mL/dL per min during low- and high-dose insulin infusions ($P < 0.05$ and $P < 0.005$ vs. placebo, respectively). Low- and high-dose insulin infusions led to a fall in heart rate of 4.6 (1.4) and 5.1 (1.3) beats/min ($P < 0.05$ and $P < 0.005$ vs. placebo, respectively) and a modest increase in cardiac output. There were no significant changes in superior

mesenteric artery blood flow. The authors concluded that in patients with chronic heart failure, insulin is a selective skeletal muscle vasodilator that leads to increased muscle perfusion primarily through redistribution of regional blood flow rather than by increased cardiac output. These results provide a rational hemodynamic explanation for the apparent beneficial effects of insulin infusion in the setting of heart failure.

Commentary

The use of glucose-insulin-potassium (GIK) infusion has been studied in patients since 1962. So far, clinical studies have concentrated

on acute myocardial infarction and patients undergoing cardiac surgery. In the present study Parsonage et al studied patients with chronic heart failure caused by ischemic and idiopathic cardiomyopathy and found a decrease in forearm vascular resistance and an increase in cardiac output by GIK infusion. Although many questions remain unanswered (see also the editorial in the same issue of *Heart*), this study is the first to demonstrate a possible beneficial effect in patients with chronic heart failure and this hopefully will lead to many other studies on the same subject.

F. Visser

Myocardial remodeling: wall stress and the supply-demand ratio

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Introduction

Cardiac remodeling, characterized by changes in ventricular size, shape, wall thickness, myocardial structure, and ultra structure,¹ is generally interpreted as an adaptation of the heart to myocardial damage, as in myocardial infarction, and to chronic pressure or volume overload. It is triggered by mechanical stress but modified by a variety of other unrelated factors.² Although the changes of remodeling are most likely adaptive, the process may become a double-edged sword if pump function is maintained at the cost of increased myocardial oxygen demand while at the same time oxygen delivery is reduced because of the restructured coronary circulation and a

reduced capillary-to-myocardial-cell ratio.

In this short review, we describe, in the left ventricle, the factors that determine the supply-demand ratio during remodeling of the pressure-overloaded, the nonfailing volume-overloaded, and the infarcted nonfailing heart.

The supply-demand ratio in the normal heart

Demand

One of the simplest models to examine the relationship between supply and demand is the isolated ventricular trabecula or the papillary muscle. These preparations, like all muscle,

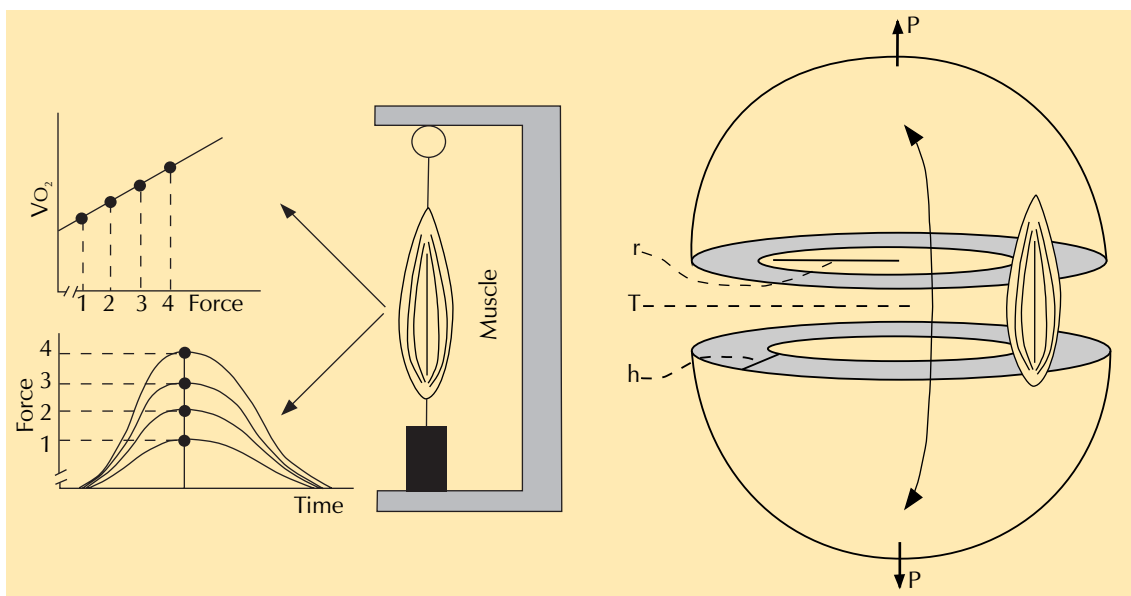


Figure 1. Myocardial muscle mechanics and Laplace's law in the heart. (A) In isolated contracting papillary muscles, oxygen consumption is approximately linearly related to developed force or the force-time integral (area under the force tracing). (B) Laplace's law: if an imaginary plane cuts a sphere into two equal halves, the force (tension) in the wall will keep the parts together while the pressure in the sphere will try to separate them. T , wall force or wall stress; P , intraventricular pressure; r , radius; h , wall thickness.

generate force when stimulated and consume oxygen and substrates (Figure 1A). When oxygen consumption (VO_2) during a series of graded contractions is plotted as a function of maximal developed force the relation is approximately linear, with an intercept on the VO_2 axis dependent on basal oxygen use. A similar relationship is obtained when the area under the force tracings, approximating mean systolic force, instead of maximal force is used.

In the intact heart during systole the contracting fibers also develop force which is used to raise intraventricular pressure to overcome aortic pressure and to eject stroke volume. This force (T), usually called wall force or wall stress, is difficult to measure but can be calculated using Laplace's law if intraventricular pressure (P), radius (r) and wall thickness (h) are known:

$$T = Pr/2h$$

T is the theoretical force that holds the two halves of a sphere intersected by an imaginary plane together when the pressure within this sphere tries to separate them (Figure 1B). The

oxygen and substrate consumption of the muscle fibers in the intact heart, like those in isolated papillary muscle, depend on fiber stress and fiber shortening, but the contribution of the former is so much greater that shortening can be neglected.³

Laplace's law, illustrated in the above equation, shows that wall stress increases if intraventricular pressure (P) and/or radius (r) increase, but it falls if the wall (h) of the ventricle thickens. In other words, a higher pressure and a larger ventricle cause a greater demand. In the normal heart, wall stress thus is a valid index of oxygen and substrate demand.

Although wall force can be calculated, systolic pressure or its time integral, the 'tension-time index' (Figure 2), is easier for determining predictors of oxygen demand.³ Wall force and the tension-time index estimate demand per beat; to arrive at demand in a certain time period these indices have to be multiplied by heart rate, the so-called 'rate-pressure product' or 'double product'.⁴

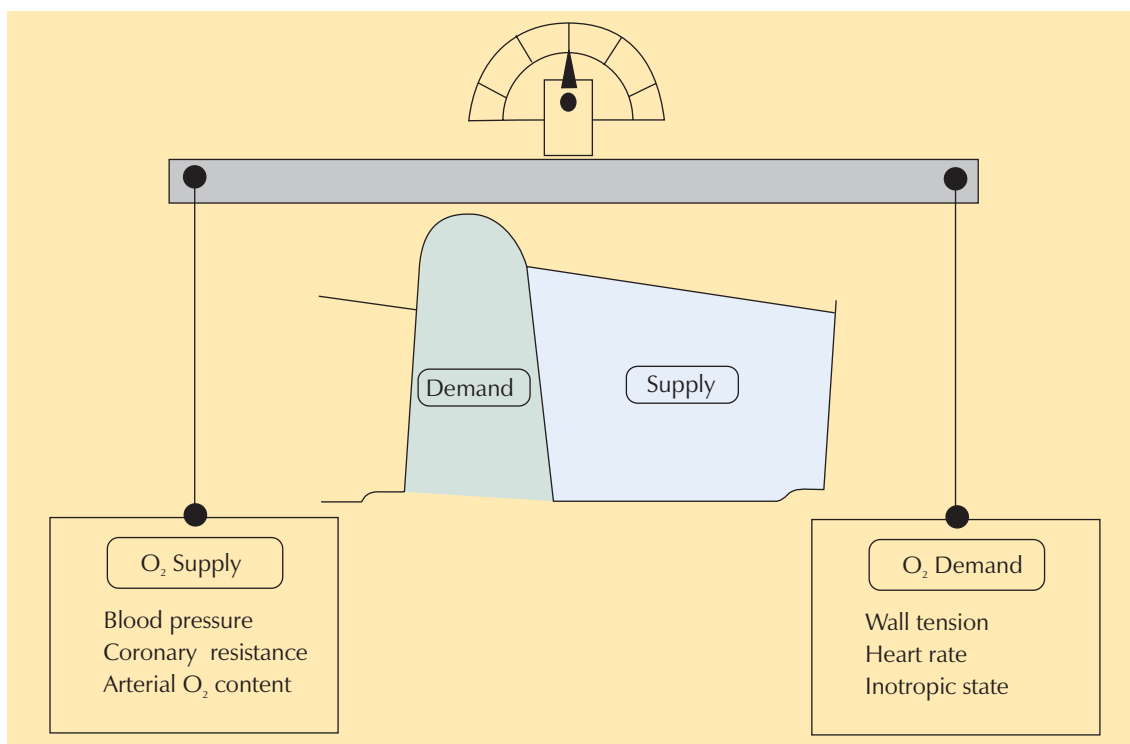


Figure 2. Factors which determine myocardial oxygen supply and demand: area under the systolic pressure trace is an estimate of demand, area under the diastolic pressure trace is an estimate of supply.

Supply

The myocardial oxygen supply is determined by the product of the arterial oxygen content and the coronary blood flow. Normally, when respiration is adequate, arterial oxygen content is constant and is thus not subject to regulation or adaptation. In the left ventricle, coronary blood flow mainly occurs during diastole when cardiac muscle is relaxed, and thus supply is chiefly dictated by diastolic blood pressure and coronary diastolic resistance. The latter is a function of vascular geometry and vasomotor tone (cardiac muscle itself does not contribute to diastole because intramyocardial pressure is approximately zero).

Supply-demand ratio

In the normal left ventricle, supply and demand are balanced (Figure 2). In most other organs, but not the heart, some compensation for a greater demand or a decreased supply is possible through increased extraction, but in the normal heart, even at rest, extraction is almost maximal so that the only alternative is increased coronary perfusion. The supply-demand ratio per beat can thus best be obtained from the diastolic (supply) and systolic (demand) blood pressure, as shown in Figure 2. When this ratio is 0.7 or more, supply is considered sufficient for even subendocardial layers to function well.⁵

The supply-demand ratio in the stressed heart

Chronic stress to the heart, whether caused by pressure overload, volume overload (Figure 3), or myocardial infarction, will to some extent alter myocardial demand and possibly also supply. Moreover, it may create circumstances in which neither the tension-time index and the double product for demand nor the diastolic pressure-time index for supply may be valid.

Pressure overload

When pressure overload is instantaneous and short-lasting, wall tension increases according to Laplace's law even if the ventricular dimensions do not change. Oxygen demand also rises, but in the normal heart, supply will cover this through coronary vasodilatation. When the overload becomes chronic, as in hypertension, the stress causes remodeling and the myocardial cells hypertrophy, leading to increased wall thickness, so that wall tension normalizes. This does not necessarily mean that oxygen demand is also normal: if systolic pressure increases by 50%, wall thickness, ie, the amount of wall tissue, needs to increase also by 50% to normalize wall tension. Therefore, the oxygen demand increases with hypertrophy in spite of the normalized wall stress because the

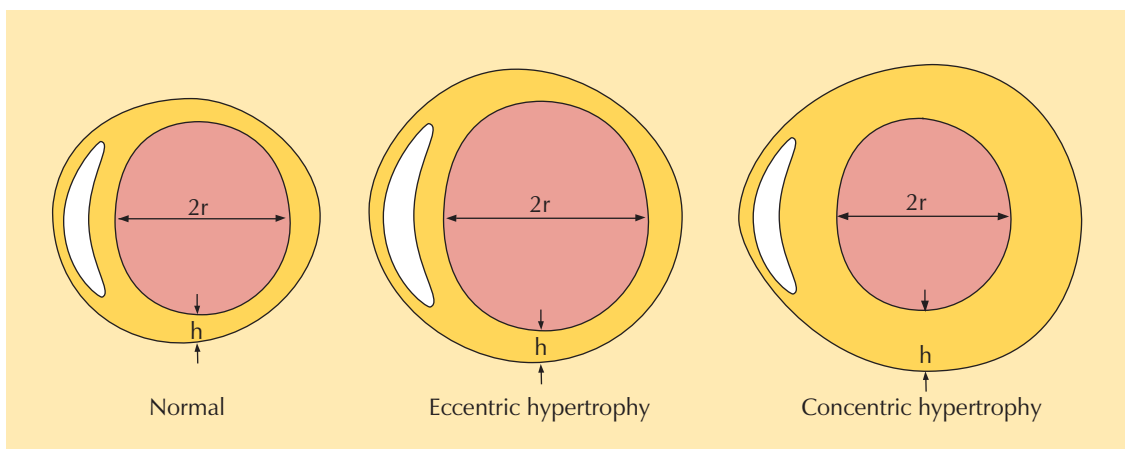


Figure 3. Cross-sections of normal, volume-overloaded and pressure-overloaded left ventricles. In the latter two cases the right ventricle is assumed to be normal.

mass of working muscle has increased. The increased demand can no longer be accurately estimated from wall tension because it has been returned to normal, but it will be directly related to the developed pressure because this has not changed in proportion to the tissue mass.

In the heart with concentric hypertrophy, diastolic perfusion still mainly depends on diastolic coronary resistance. Capillarization may not keep pace with myocardial growth so that resistance per gram of tissue may increase. Also, since myocardial cell diameter increases, the diffusion distances rise. Moreover, since remodeling also involves myocardial fibrosis,² diastolic stiffness increases so that intramyocardial pressure during diastole may no longer be negligible. Consequently, supply may be limited in the remodeled heart with concentric hypertrophy. The increased resistance and intramyocardial pressure in diastole, together with the decreased amount of oxygen reaching the heart cells by diffusion, may limit the usefulness of the diastolic pressure-time integral as an index of supply.

Volume overload

When volume overload is instantaneous, ventricular diameter increases and wall thickness decreases so that wall tension and thus oxygen demand rise. In chronic volume overload, as in hyperthyroidism and physical training (sports heart), ventricular diameter remains increased while ventricular wall thickness is normal or only slightly increased: wall stress thus remains increased. Under these conditions the use of developed pressure alone is no longer a good index of oxygen demand; instead, wall stress should be calculated from pressure according to Laplace's law.

Whether supply to the heart with eccentric hypertrophy is changed is at present not entirely clear, but the literature suggests that this is not the case. Diffusion distances will not change, however, because the myocardial cells increase mainly in length.

Thus, in eccentric hypertrophy the systolic developed pressure cannot be used to estimate

demand, but the use of the diastolic pressure-time area as an index of supply seems to be appropriate.

The infarcted heart

Whatever the size of the infarct, the altered loading conditions will always result in asymmetric, ie, heterogeneous, increases in wall stress: to keep heart function as near normal as possible, the noninfarcted tissue has to compensate for the noncontractile areas (remodeling). The remodeling which takes place is not only caused by the increased wall force but also by the volume overload hypertrophy in the noninfarcted tissue, and the amount of tissue lost by the ischemia is fully compensated by the hypertrophy through an unknown regulatory mechanism.² Local wall stress, which can still be calculated from pressure, local radius, and local wall thickness according to Laplace's law, is only a predictor of local demand.

Although overall wall stress cannot be used as an index of demand, the systolic pressure and the tension-time index can, but neither will give information about local demand.

The use of the diastolic aortic pressure as an index of supply is even more hazardous because the index indicates overall but not local perfusion. In the normal heart this is not a problem because distribution of coronary flow is to a large extent homogeneous, but in the infarcted heart this is obviously not the case.

If more information is needed about local relationships in the infarcted heart, the methods described by Götte et al⁶ should be followed.

Conclusion

We have presented an overview of the pros and cons of the use of mechanical parameters to estimate oxygen supply and demand. The diagram given in *Figure 4* summarizes these principles. For simplicity we have treated the results of the three forms of remodeling as if they were independent phenomena, but in reality pure concentric or pure eccentric hyper-

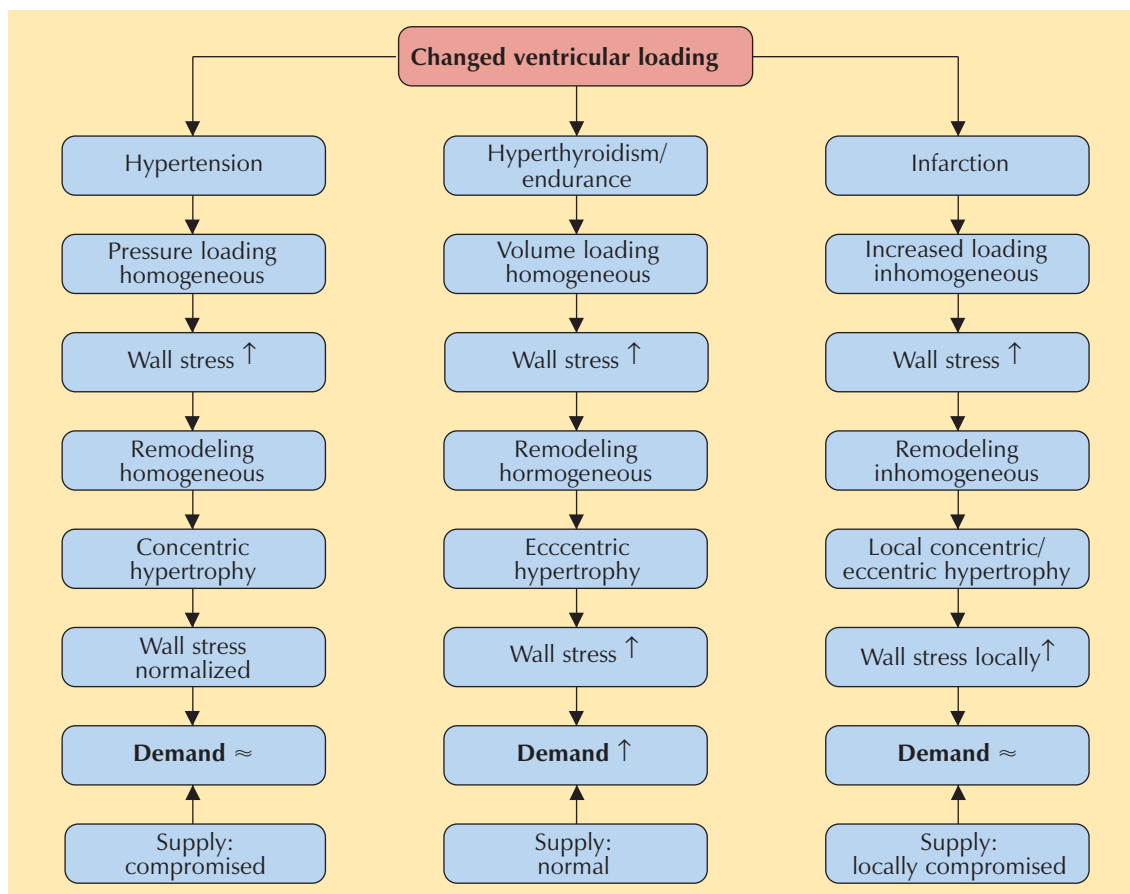


Figure 4. Summary of changes in supply and demand in the overloaded heart.

trophy seldom occurs, while the changes in the infarcted heart are even more complex.

There are better but infinitely more complex ways to estimate demand. One of these is the method described by Suga⁷ in which demand is calculated from the area under a pressure-volume loop described when pressure is plotted as a function of volume; it is mainly used in experimental studies in animals because the method requires intensive instrumentation. For these reasons we have limited our discussions to the more conventional indices and considered all other methods to be beyond the scope of this brief review. ■

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Glossary

Gary Lopaschuk and William Stanley

Anti-C-reactive protein (CRP) activity

C-reactive protein (CRP) is a protein that is produced in the acute phase of an inflammatory reaction. Recent interest has focused on the measurement of CRP as an indicator of various inflammatory diseases, as well as to assess the degree of cardiovascular risk. For example, measurement of CRP has been used to measure inflammation associated with an acute myocardial infarction or unstable angina. Anti-CRP is an antibody against CRP that can be used to assess CRP levels/activity in the serum of patients.

Anti-tumor necrosis factor- α (TNF α)

Tumor necrosis factor- α (TNF α) is a cytokine that has diverse actions in the body. With regard to the heart, TNF α binds to cardiac receptors and mediates a number of cellular processes, including the promotion of apoptosis (programmed cell death), and activation of inducible nitric oxide synthase.

Ceramide

Ceramide is a specialized lipid that is derived from sphingomyelin and glycosphingolipids present in the plasma membrane of cardiac cells. Various cytokines can release ceramide, which then acts as an important intracellular signaling molecule. Considerable interest has recently focused on ceramide as a signaling molecule involved in apoptosis (programmed cell death).

Cytochrome *c*

Cytochrome *c* is a mitochondrial protein that has an important electron-transport function in mitochondrial respiration. Recently, cytochrome *c* release from the mitochondria has been shown to be an important early event in the apoptotic (programmed cell death) pathway. Release of cytochrome *c* from the mitochondria triggers a series of events leading to cell death.

Cytokines

Cytokines refer to a group of compounds that are produced under a variety of conditions, including the immune response and inflammatory reactions. TNF α and IL-1 are examples of two cytokines.

Endothelin-1

Endothelin-1 is a vasoactive peptide that is primarily produced by endothelial cells. This peptide is a very potent vasoconstrictor.

GLUT4

GLUT4 is a protein that transports glucose across cell membranes. In insulin-responsive tissues (such as the heart), insulin will cause GLUT4 to be translocated from inside the cell to the plasma membrane, thereby stimulating glucose uptake.

Interleukin (IL)-1

Interleukin (IL)-1 is a proinflammatory cytokine which is involved in many immune responses, including physiological stress reactions. IL-1 has a diverse number of biological actions, part of which occur through ceramide signaling.

3-KAT

3-KAT is the abbreviation for 3-ketoacyl-CoA thiolase (see below).

3-ketoacyl-CoA-thiolase (3-KAT)

3-ketoacyl-CoA-thiolase (3-KAT) is the last enzyme in the intramitochondrial pathway that is involved in the metabolism of fatty acids (fatty acid β -oxidation). Recent interest has focused on 3-KAT, since inhibition of this enzyme decreases fatty acid oxidation and protects the ischemic heart.

Long-chain acyl-CoA synthetase

Long-chain acyl-CoA synthetase is one of the first enzymes in the fatty acid metabolic pathway. It converts long-chain fatty acids to long-chain acyl-CoA within the cell. Long-chain acyl-CoA is then either metabolized by the mitochondria to produce energy, or is used to produce membrane and cellular lipids.

Matrix metalloproteinase (MMP)

Matrix metalloproteinase (MMP) is an extracellular matrix-degrading enzyme that is involved in tissue remodeling. Alteration in MMP activity have been shown to contribute to heart remodeling in heart failure or following an acute myocardial infarction.

Nitric oxide synthase

Nitric oxide synthase is the enzyme responsible for synthesizing nitric oxide (NO). NO has received considerable research attention, since it is not only a vasodilator, but is also important in numerous other processes, including apoptosis.

Peroxisome proliferator-activated receptor- γ (PPAR γ)

Peroxisome proliferator-activated receptor- γ (PPAR γ) is a nuclear receptor involved in transcriptional regulation of proteins. PPAR γ has many functions, including regulating enzymes involved in insulin sensitivity and lipid metabolism. PPAR γ agonists have potential therapeutic use in treating insulin resistance and atherosclerosis.

Phosphatidylinositol 3-kinase (PI3K)

Phosphatidylinositol 3-kinase (PI3K) is an intracellular kinase involved in a number of important cellular pathways. PI3K is activated by insulin, and will promote glucose metabolism.

Protein kinase B (PKB)

Protein kinase B (PKB) is an intracellular kinase that is important in regulating glucose metabolism. It is a kinase downstream of PI3K, and insulin activation of PKB will result in GLUT4 translocation to the cell membrane, thereby stimulating glucose uptake.

Terminal deoxynucleotidyl transferase-mediated dUTP nick-end labeling (TUNEL)

Terminal deoxynucleotidyl transferase-mediated dUTP nick-end labeling (TUNEL) is an assay used to detect double-strand DNA breaks. This assay is used for in situ identification of apoptotic cells by detecting DNA damage.

Transforming growth factor (TGF)- β

Transforming growth factor (TGF)- β is a growth factor that has an important role in controlling fibroblast growth and accumulation of extracellular matrix proteins. Increases in TGF- β have been implicated in the maladaptive response to cardiac hypertrophy.

Triacylglycerol (TG)

Triacylglycerol (TG) is the major storage form of fatty acids in the body and consists of three fatty acids attached to a glycerol backbone. Fatty acid storage in adipocytes primarily occurs in the form of TG. The heart also contains sizable TG stores as a source of fatty acids for energy production.

Troglitazone

Troglitazone is an agonist of PPAR γ . It belongs to a class of compounds called thiazolidinediones. Activation of PPAR γ with troglitazone has potential clinical application in the treatment of insulin resistance and atherosclerosis.

Tyrosine kinase

Tyrosine kinase is a kinase that phosphorylates tyrosine residues on proteins. Many different tyrosine kinases exist, an important one being the insulin receptor. Insulin binding to the receptor stimulates a tyrosine kinase to initiate the downstream insulin-signaling pathway.