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Editorial

The recent publication of the **P**erindopril **R**emodeling in **E**lderly with **A**cute **M**yocardial **I**nfarction (PREAMI) study showed that perindopril significantly reduced the *composite* risk of death, hospitalisation for heart failure, and cardiac remodeling in an elderly population with preserved left ventricular (LV) function, following an acute myocardial infarction.[1,2,3]

In light of this trial, this edition of the Medifile reviews the process of cardiac remodelling post infarction, with specific focus on the role of the Renin-Angiotensin-Aldosterone System (RAAS). The results and clinical significance of PREAMI are then reviewed and discussed.

Introduction

Heart failure, defined as a clinical syndrome caused by cardiac disease which compromises ventricular systolic or diastolic function or both[4], is a serious disease with high morbidity and mortality[5] that is due primarily to progression of myocardial dysfunction.[2] The occurrence of heart failure during hospitalisation for acute myocardial infarction (AMI) is an important factor influencing short- and long-term morbidity and mortality.[6] Myocardial infarction (MI) can be differentiated based on the anatomic, morphologic and diagnostic clinical information. A transmural MI is characterised by ischaemic necrosis of the full thickness of the affected myocardial muscle segment i.e. from the endocardium through the myocardium to the epicardium. On the other hand with a non-transmural MI, the area of necrosis is limited to either the endocardium or the endocardium and myocardium.[7]

Kostis et al reported in 1997 that AMI ranks second to hypertension as a cause of heart failure.[6] A study of 438 patients (JAMA1999) which examined clinical predictors of heart failure in patients with their first acute myocardial infarction, reported that heart failure occurred in 41.6% of the patients during hospitalisation.[6] Other studies observed that the incidence of heart failure following AMI is 22% in patients having their first infarction and 33% in those individuals having a recurrent infarction.[6] Following hospital discharge heart failure occurs at a rate of 2% per year up to 10 years. The mortality rate in patients with AMI with heart failure was 3 fold higher in the pre-thrombolytic drug era, an indication that heart failure frequently occurs during the acute phase of AMI. The early recognition and prevention of heart failure during the acute course of AMI is therefore imperative in the reduction of morbidity and mortality rates.[6]

Cardiac Remodeling

There is a general acceptance that as AMI progresses into heart failure, there is remodeling of the left ventricle - called cardiac remodeling.[2,8] Cardiac remodeling is thought to be an important aspect of disease progression in heart failure regardless of the cause.[8,9,10] It is manifested by changes in cardiac size, shape and function in response to cardiac injury.[2,9,10]

The term "cardiac remodeling" may include the following processes:

- Geometric (or architectural) alterations in ventricular size and shape and the thickness of its walls
- Biochemical modifications of cardiac myocytes
- Structural changes of infarcted tissue, particularly fibrous formation, that appear in the infarcted and viable myocardium remote to the site of the AMI.[9]

This review focuses on the latter.

Cardiac remodeling post MI is one of the main causes of heart failure. The chronically failing heart of ischaemic origin is characterised by iterations in tissue structure, particularly fibrous tissue formation, that appear in infarcted and non-infarcted myocardium of both the right and left ventricles. In other words, fibrosis appears at the site of the MI (considered "the good" of tissues repair) as well as remote from it (considered "the bad" of tissue repair). Fibrosis remote from the infarct site is considered the major cause of ventricular remodeling in ischaemic cardiomyopathy. Such an adverse accumulation of extracellular matrix initially raises diastolic stiffness; its continued accumulation further increases diastolic stiffness and impairs contractile behaviour.[9,11]

Cellular Structure of the Myocardium

The cardiac tissue consists of:

- A muscular component composed of large cardiac myocytes. These account for one third of all cells in the cardiac tissue
- An extracellular compartment which is composed of fibroblasts, macrophages, endothelial cells and pericytes
- Fibrillar collagen scaffolding
- Adrenergic nerve terminals.[9]

Structural Changes following Acute Myocardial Infarction

Changes at the Site of Infarction:

Following a transmural MI, there is a segmental loss of cardiac myocytes. A reparative process is initiated after cardiac myocyte necrosis. This process results from a two-phase generation of angiotensin II (Ang II) and transforming growth factor ß1 (TGF ß1) both of which act as stimulator signals:

Phase 1: This initially depends on inflammatory cells, such as monocytes and macrophages that invade the site of injury. Macrophages are activated which then generate

angiotensin II (Ang II). Ang II in turn generates transforming growth factor ß1 (TGF ß1).

Phase 2: Fibroblasts are subsequently attracted to the site of injury, where they are converted to myofibroblasts (myoFbs) by TGF ß1. The myoFbs then also generate Ang II which again stimulates TGF ß1 expression. Scar tissue formation is produced by myoFbs and fibrogenic signals or stimuli which include angiotensin II (Ang II) and transforming growth factor ß1 (TGF ß1).[9]

Through a complex series of molecular events that include expression of immediate early response genes and activation of multiple second messenger systems which act synergistically to induce mitosis, these cells proliferate and lay down fibrillar collagen that replaces lost myocytes. Fibrous tissue formation is essential to preserve structural integrity of the infarcted myocardium at the site of myocyte loss.

Changes Remote to the Site of Infarction and the Vicious Cycle:

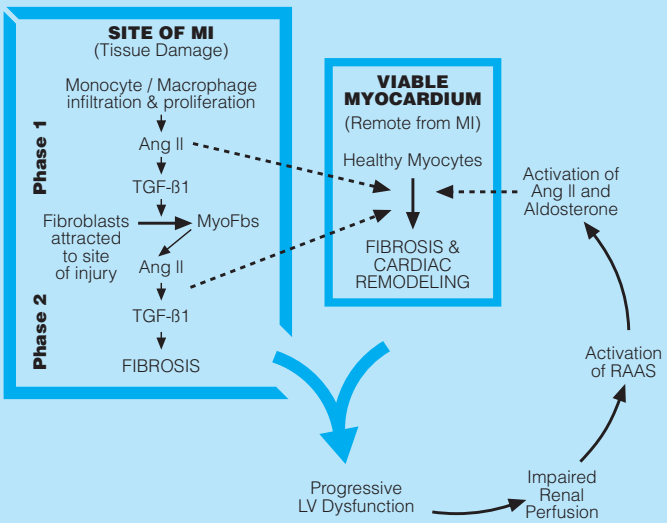
The stimulatory signals can, however, pass through the interstitial space and gain access to distal sites of viable myocardium where they cause an unwanted fibrous tissue response, or remodeling.[9] The circulating myoFbs result in continued generation of fibrogenic signals that promote progressive remodeling at remote sites.

The combination of progressive remodeling and the infarct scar adversely alter ventricular function, leading to impaired renal perfusion and activation of the RAAS. Chronic RAAS activation and thus increased levels of its effector hormones, Ang II and aldosterone, promotes progressive remodeling of cardiac tissue and the vicious cycle ensues. This can be considered as "the ugly" of tissue repair.[9]

MyoFbs persist in the infarct scar area for prolonged periods of time, where they continue to generate fibrogenic signals that perpetuate tissue repair and promote fibrosis at and remote to the MI.[9]

For a graphic representation see figure 1.

Figure 1: Process of Cardiac Remodeling



Source: *Adapted from Weber KT et al, Rebuilding and remodeling following myocardial infarction: The good, the bad and the ugly of tissue repair, Dialogues in Cardiovascular Medicine 1999; 4(1): 3-19*

The Role of ACE and Ang II in the Remodeling Process

Raised levels of ACE cause increased levels of Ang II and decreased levels of bradykinin.[12] These then act as stimuli or signals to induce a number of adverse effects of vascular function and structure as discussed above. In the normal heart, low-density ACE and Ang II receptor binding is found throughout ventricular myocardium and atria, whereas high-density binding is present at sites of high collagen turnover, including heart valve leaflets.[9] However, in an infarcted heart high density binding is present at the site of the MI.[9] Although Ang II is intimately involved in promoting tissue repair, it does so irrespective of the etiology of tissue damage.[9]

Stimulator and Inhibitor Signals of Cell Growth

Ang II is one of many different signals or stimuli that maintain cell growth and behaviour. An understanding of its relationship with other stimulator and inhibitory stimuli is important in the understanding of cardiac remodeling.

Maintenance of normal cardiac tissue is determined by the homeostatic balance between stimulatory and inhibitory signals. These signals regulate cell growth, apoptosis and metabolic behaviour (e.g. collagen turnover).[13,1]

Ang II is a potent vasoconstrictor, it also stimulates aldosterone, a sodium-retaining hormone.[8,12,14] Myocardial injury invokes stimulator overproduction.[15] Stimulators of repair, such as angiotensin II, aldosterone, and endothelin promote coagulation and platelet aggregation, vaso-constriction, tachycardia and increased contractility, and renal sodium retention.[13,15] Conversely inhibitors, such as nitric oxide, bradykinin, prostaglandins, natriuretic peptides, dopamine, and glucocorticoids, have opposing effects on homeostasis and repair.[13,15] The relative predominance and potency of stimulators versus inhibitors determine overall responses.[9,12,13] In advanced heart failure, for example, circulating levels of natriuretic peptides, Ang II, aldosterone, and noradrenalin are each increased.[18] Natriuretic peptides are regarded as "beneficial" hormones as they have vasodilatory and natriuretic properties. However, the potency of RAAS-effector hormones, supersedes natriuretic peptides[14], cardiac remodeling being the final result.[13,15]

Table 1 lists some of the stimulator and inhibitor signals of cell growth.

The Role of ACE-Inhibitors in Cardiac Remodeling

Angiotensin converting enzyme plays a significant role in cardiac remodeling as outlined above. The use of ACE inhibitors (ACE-I) post MI would therefore be beneficial in the prevention of cardiac remodeling.[10,12,16] ACE-I block the conversion of angiotensin I to angiotensin II, thereby decreasing the breakdown of bradykinin to inactive fragments. The result is an improved balance between bradykinin and Ang II. This has been attributed to many of the beneficial effects of ACE-I, such as the antihypertensive, anti-atherosclerotic and cardioprotective properties.[12]

The role of ACE-I in prevention of secondary heart failure has been well researched. Several trials provide evidence that ACE-I are important in the treatment of AMI and for secondary prevention in heart failure.[12] As a class, they have been shown to have various effects on the cardiovascular system, from their haemodynamic effect to improving the endothelial function, fibrinolytic stabilization, reduction in cell proliferation and migration and stabilization

of plaques. Hence their use in various patho-physiological disorders, such as hypertension, CAD and heart failure.[12]

ACE-I reduce mortality and the development of left ventricular (LV) remodeling and dysfunction, both when administered as *long term* treatment in patients with *severely impaired LV function and/ or heart failure* and as *short-term* treatment after acute myocardial infarction (AMI) in patients *without heart failure*. However, until recently, the clinical benefits of ACE inhibitors in *elderly* patients *with preserved or moderately impaired left ventricular function* were not well documented.[2,18]

The PREAMI Study

The **P**erindopril **R**emodeling in **E**lderly with **A**cute **M**yocardial infarction (PREAMI) study was designed to evaluate the effects of perindopril (a lipophilic ACE-I) in patients with AMI and *preserved* left ventricular function (LV ejection fraction ≥40%) on a combined outcome: death, hospitalisation for heart failure and cardiac remodeling (considered as a ≥8% increase in LV end-diastolic volume in the 12 month period after an AMI).[1,2,3] The hypothesis was that the use of Perindopril (8mg/day) for one year post AMI would reduce remodeling and the prevalence of heart failure and death in these patients.[1]

This double-blind, parallel-group, multicentre, placebo-controlled trial included 1252 patients 65 years and older. Patients were randomly allocated to either perindopril (4mg for 1 month, then 8mg for 11 months) or placebo.

In this study, the use of Perindopril had a beneficial effect in the long term prevention of heart failure due to cardiac remodeling. This anti-remodeling effect was responsible for the significant reduction in the combined primary endpoint, as the hospitalisation and mortality results of the two arms were not significantly different. See table 2 for results of the study.

Adherence is reported to have been good especially given the high dose of perindopril. The percentage of withdrawals was 25.2% in the perindopril group vs. 24% in the placebo group. The main reason cited for withdrawal was cough which accounted for 1.6% in the perindopril group vs. 0.5% in the placebo group.[2]

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Discussion

Advanced age appears to be an important determinant for LV remodeling, and can occur even in the presence of small infarct sizes. Therefore, the results of PREAMI could be clinically relevant in this group of patients for whom therapeutic decision making is still equivocal.[2]

The results of PREAMI are however somewhat disappointing: although treatment with perindopril reduced progressive left ventricular remodeling, it was not associated with significantly better clinical outcomes, such as hospitalisation for heart failure, and mortality. Angina, revascularization or subsequent AMI (other secondary outcomes) were also not modified by perindopril treatment, neither did the treatment result in a reduction in the use of other cardiovascular medication after 1 year.[2]

The authors of the study have attributed this to:

- The overall low morbidity and mortality rates, due to the well-conserved LV function
- Optimized treatment (including ACE-I after AMI)
- Relatively short duration of treatment (12 months)[2]

The PREAMI study has provided new pathophysiologic information, but only partially fills the gap regarding optimal treatment of elderly patients with AMI and preserved LV function.[2] The *therapeutic benefits* of perindopril and other ACE-I in this population therefore still remain unclear.

Table 1: The Cardiac Repair Process: Stimulator and Inhibitor Signals of Cell Growth

Inhibitors	***Stimulators***
Bradykinin[9,11,13,14,15]	TGF-ß1[9,11,16]
Nitric Oxide[11,12,13,14]	Endothelin[11,13,15]
Prostaglandin [8,11,13,14,15]	Aldosterone[11,13,15]
Natriuretic peptides[11,13,15]	Angiotensin II[11,13,15]
Glucocorticoids[11,13,15]	Catecholamines[11,13,15]

Table 2: Summary of the Results of the PREAMI Study[1,2,3]

Primary End Point	**Perindopril arm** (n=631)	**Placebo arm** (n=621)	**Relative risk reduction**	**p value**
Combined death, hospitalisation for heart failure & LV remodeling	181 patients (35%)	290 patients (57%)	38%	<0.001
Remodeling	126 patients (28%)	226 patients (51%)	46%	<0.001
Hospitalisation for heart failure	22 patients (4%)	30 patients (5%)	27%	0.24
Total mortality	40 patients (6%)	37 patients (6%)	0%	0.90

Studies with enalapril (CONSENSUS II) and lisinopril (GISSI-3), in younger patient groups who experienced an AMI, but in whom ejection fraction was not measured, showed inconsistent results.[12] CONSENSUS II did not detect a significant reduction in mortality, despite beneficial effects of ACE inhibition on LV volumes,[2,12] whereas GISSI-3 reported a reduction in mortality after only 4-6 weeks of ACE-I treatment.[12]

In EUROPA (**EU**ropean trial on **R**eduction **O**f cardiac events with **P**erindopril in stable coronary **A**rtery disease) perindopril 8mg per day led to a significant reduction in the combined primary outcome of cardiovascular death, nonfatal MI, and cardiac arrest with successful resuscitation after 3 years.[2,19] In particular, there was a significant 24% reduction in the recurrence of MI (fatal and non-fatal, p <0.001) and a 39% reduction in hospitalisation for heart failure (p = 0.002).[12] Patients did not have evidence of heart failure[12] or substantial hypertension at study entry.[19]

Analysis of a sub-group of EUROPA patients, corresponding to the PREAMI elderly population, demonstrated a significant 36.1% relative risk reduction in the primary end point of that study, but only after 3 years of treatment with perindopril.[2]

Conclusion

As opposed to PREAMI, the EUROPA study clearly shows significant benefits in terms of *clinical outcomes,* albeit over a longer period of time. Unfortunately reduction in LV remodeling was not included in the primary or secondary end points of EUROPA, therefore the relationship between decreased LV remodeling and better clinical outcomes cannot be established in this study. Based on PREAMI, it may well be that reduced LV remodeling eventually contributes to improved outcomes, but this benefit may be delayed.

More long-term studies are required to provide sufficient information on the benefits of ACE inhibition in terms of *hospitalisation for heart failure* and effects on *mortality* in elderly patients with preserved LV function.

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