European Heart Journal (1993) **14** (*Supplement C*), 24–29

Ventricular remodelling: consequences and therapy

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KEY WORDS: Myocardial infarction, heart failure, ventricular function, angiotensin converting enzyme inhibitors.

The mammalian left ventricle can change its size and shape in response to a variety of stimuli including loss of tissue and external work. These changes in size and shape, defined as remodelling, are the sum total of a number of processes that involve the myocyte and the interstitial fibrous structures which provide the matrix in which the myocyte functions. The adapted mechanisms which occur are affected by humoral and cellular phenomena and can be modified by pharmacological agents. This paper reviews the remodelling process that occurs in myocardial infarction and heart failure and the effect of various pharmacological agents on this remodelling process.

Introduction

It has long been recognized that the constituent chambers of the mammalian heart (ventricles and atria) undergo considerable topographical changes in response to external and internal stimuli. Classic examples include the development of ventricular hypertrophy in response to chronic pressure overload and ventricular dilation in response to volume overload. In the setting of myocardial infarction, ventricular architecture may undergo multiple alteration including expansion of the infarcted region, hypertrophy of the residual viable myocardium and progressive left ventricular dilation. A progressive increase of left ventricular end-systolic and end-diastolic volumes has also been observed in animals[1] and in patients[2] with heart failure and reduced left ventricular ejection fraction. Both hypertrophy and dilation are compensatory responses that maintain stroke volume in the face of a large loss of functional cardiac units.

In recent years, the term 'ventricular remodelling' has been used to describe many of these adaptations or maladaptations and others as well. The term, remodelling, is used to infer global changes of ventricular chamber size, shape, and mass, as well as changes occurring at the cellular level, including alterations in both the myocyte and non-myocyte compartments, including the collagen matrix and interstitium. It is not very difficult to imagine that stimuli, which act to disrupt the homogeneity of the cellular and structural elements of the myocardium, can also lead to topographical modifications of the ventricular chamber manifested by changes of chamber size, shape and mass. If one accepts this broad definition of ventricular remodelling as an interplay between global and cellular events, one must also ask if this remodelling process is a beneficial adaptation or a maladaptation that should be corrected. If it is to be corrected, are there means available by which one may accomplish this correction? In the following discussion, an attempt will be made to reconcile some of these issues, while raising others which require further investigation before a comprehensive understanding of this phenomenon is reached.

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Topographical and cellular components of ventricular remodelling

The acute and chronic alterations that take place in the left ventricular myocardium after a transmural myocardial infarction is one example of the remodelling process that combines both alterations of global topography and cellular modifications. A myocardial infarction, if sufficiently large, can result in complex alterations of ventricular architecture, involving both the infarcted and non-infarcted regions[3]. The infarcted myocardium can undergo expansion with subsequent regional and global distortion of ventricular topography[4]. The dramatic loss of viable muscle mass imposes a greater workload on the residual non-infarcted myocardium which, in turn, responds with compensatory dilation[5] and hypertrophy[6] both of which influence global ventricular topography.

INFARCT EXPANSION

Infarct expansion defined as 'acute dilation and thinning of the area of infarction not explained by additional myocardial necrosis'[7] is a typical manifestation of an acute ventricular remodelling process. Infarct expansion occurs before and during the period of resorption of necrotic tissue, but prior to extensive deposition of collagen[3]. During this period, the myocyte fibrous support may be lost preventing proper 'tethering'[8], a requisite of normal contractility. Subsequent collagen deposition in expanded and thinned infarcted segments fix the topographic deformation of the ventricle during the healing phase[9] and provide resistance to further stretching[10]. Infarct expansion also represents an ideal example of the coupling between global alterations of ventricular topography and underlying cellular adaptations. Weisman and associates have shown that thinning of the infarct region is manifested histologically

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by a rearrangement of groups or bundles of myocytes (slippage) resulting in a decreased number of cells across the infarcted wall[11]. Cell stretch and a decrease in the intercellular space was also found in regions of infarct expansion, but was felt to contribute far less than slippage to infarct thinning[11].

REMODELLING OF THE NON-INFARCTED MYOCARDIUM

In addition to expansion, myocardial infarction induces time-dependent secondary changes in the non-infarcted myocardium[3]. Studies in both patients[5] and experimental animals[6,12] provided strong evidence of dilation of the non-infarcted myocardium. Dilation of the non-infarcted myocardium was attributed to side-to-side slippage of myocytes[6]. This association was based on studies in rats with large infarcts (63% of the left ventricular free wall) that showed a 36% decrease in the number of myocytes and a 40% decrease of capillary profiles in the spared region[6]. Expansion of the infarcted region and dilation of the residual viable myocardial wall, in combination, result in overall enlargement of the left ventricle. In patients with Q-wave myocardial infarction, ventricular enlargement was detectable 2 weeks after the onset of symptoms[13]. There is little doubt that the extent of ventricular remodelling during the acute and healing phase of a myocardial infarction and subsequent chamber enlargement reflects the magnitude of the primary damage induced by the acute ischaemic event.

Remodelling of the residual non-infarcted myocardium is not limited to acute movements of cells within the wall (slippage) but is also dictated by the hypertrophic characteristics of the myocytes. Reactive hypertrophy of the residual viable myocytes is a characteristic response to increased workload resulting from loss of functional cardiac units[6]. This cellular growth continues to occur throughout the healing process and thereafter[14,15] leading to progressive increase in the size of the spared myocytes[6]. Studies by Anversa and colleagues[6] suggest that hypertrophy of myocytes of the residual viable myocardium may play an important role in the chronic phase of ventricular remodelling. Their data suggest that eccentric ventricular hypertrophy develops after myocardial infarction rather than concentric hypertrophy. This is a plausible interpretation in that myocyte hypertrophy by cell lengthening alone could be expected to result in a large cavity volume without altering wall thickness, whereas increases in the lateral dimension of myocytes would have the effect of increasing wall thickness with no change or a decrease in chamber volume[6]. Cardiomyocytes isolated from explanted hearts of patients with end-stage ischaemic cardiomyopathy were found to be longer but not wider than myocytes of non-failed hearts[16]. This structural remodelling of cardiomyocytes was postulated to be the primary cause of left ventricular dilation in ischaemic cardiomyopathy rather than myocyte slippage[16].

VENTRICULAR SHAPE AS A COMPONENT OF THE REMODELLING PROCESS

The components of ventricular remodelling described thus far have taken into account cellular alterations, such as myocyte slippage and myocyte hypertrophy and their role in modifying ventricular chamber size. Another component of ventricular remodelling that follows the loss of viable myocardium is a change of left ventricular shape. Changes in ventricular geometry with a shift from the conventional elliptical shape to a more globular or spherical shape have been described in patients following anterior myocardial infarction[4,17] and in patients with heart failure secondary to coronary artery disease[18] or dilated cardiomyopathy[18,19]. It is easy to assume that changes of ventricular shape are a mere consequence of ventricular dilation. Recent data from our laboratory suggest that such an assumption is not fully warranted. Serial ventriculographic studies in dogs with chronic heart failure produced by multiple intracoronary embolizations showed a marked increase of end-diastolic chamber sphericity before the onset of an overt increase of left ventricular end-diastolic volume[20]. In a subset study, we also showed that dogs with identical left ventricular end-systolic volumes had marked differences in their end-systolic sphericity index[20]. This observation was also confirmed in patients with heart failure[18]. Despite close similarities in left ventricular end-diastolic and end-systolic volumes, different cohorts of patients showed marked differences of left ventricular shape. These data suggest that ventricular shape changes are not necessarily a pure reflection of ventricular enlargement; instead, these shape changes may represent an independent component of the remodelling process. At present, we can only speculate that regional heterogeneities of myocyte hypertrophy and remodelling of the extracellular matrix and interstitium are potential contributors to the observed shape changes. The fact that these shape changes have been observed in both animal models[20] and patients with heart failure[19] indicates that this maladaptative remodelling continues to be present in the setting of the functionally impaired left ventricle.

REMODELLING OF THE MYOCARDIAL EXTRACELLULAR MATRIX AND INTERSTITIUM

Participation of the cellular components of the nonmyocyte compartment of the ventricular wall is also important in the overall remodelling of the ventricular wall that accompanies either a diffuse or focal loss of myocytes, such as occurs with myocardial ischaemia and infarction. In 1989, Weber suggested that the anatomical requisite for myocyte slippage in either concentric or eccentric hypertrophy resides in the disruption of collagen tethers that normally maintain muscle fibre alignment[8]. A disappearance of collagen tethers has been observed in rats with concentric hypertrophy due to renovascular hypertension[21] and in humans with advanced heart failure due to primary myocardial disease[22]. This process of collagen degradation is thought to occur early in the remodelling process and disappears with the established phase of hypertrophy[8]. The mechanism of this degradation is uncertain, but may be related to activation of myocardial collagenase[23].

Once hypertrophy is established, a different form of remodelling of the nonmyocyte compartment appears to take place. At this stage, increased collagen synthesis becomes evident[8]. Accumulation of perivascular and

interstitial collagen (reactive interstitial fibrosis) has been shown to occur in the hypertrophied and failing left ventricle[21]. In dogs with chronic heart failure produced by intracoronary microembolization, we observed considerable interstitial fibrosis in regions of viable myocardium[1]. The mechanisms responsible for the perivascular and extracellular accumulation of collagen is not clear. There is some evidence which implicates angiotensin-II in this process. Angiotensin-II may be a direct stimulus to cell growth[24] and may be mytogenic to fibroblasts[23]. Fibroblasts which normally reside in the myocardium contain the messenger RNA responsible for gene expression of type-I and type-III collagen[25], the major fibrillar collagens of the myocardium. One possible signal for enhanced collagen synthesis is abnormal coronary vascular permeability which can allow growth factors to gain access to the extravascular space and its fibroblasts[23]. There is some evidence that angiotensin-II can mediate alterations of endothelial cell integrity[26]. Regardless of the signal which initiates the process of collagen accumulation with the non-cardiomyocyte compartment of the ventricular wall, it would appear, at present, that this process is most likely the result of fibroblast proliferation, augmentation in local fibroblast activity or both[27].

Ventricular remodelling: a positive adaptation or a maladaptation

LEFT VENTRICULAR ENLARGEMENT

Acute and chronic ventricular dilation after myocardial infarction may be viewed as a compensatory response which serves to maintain stroke volume (through operation of the Frank-Starling mechanism) as ejection fraction declines. From this prospective, it would appear that ventricular dilation is a positive response. An increase of ventricular size, however, occurs at the expense of increasing systolic and diastolic wall stress which, in turn, stimulates further ventricular dilation[28]. This is particularly true if the cumulative loss of viable myocardium, as a result of the infarction, is large[3]. Among patients with acute myocardial infarction, an increase of left ventricular volume was distinctly associated with poor long-term prognosis[29,30]. White *et al.* clearly showed that survival after myocardial infarction is inversely correlated with left ventricular end-diastolic and end-systolic volumes[29], with end-systolic volume being the most powerful predictor of death[29,30]. These findings suggest that even though ventricular enlargement may initially be beneficial in maintaining stroke volume, progressive ventricular dilation carries with it a poor long-term prognosis. The observation that this process is attenuated or even prevented by angiotensin converting enzyme inhibitors, which themselves are known to improve survival, emphasizes the maladaptive role of ventricular dilation in the remodelling process.

MYOCARDIAL HYPERTROPHY

Loss of viable myocardium following myocardial infarction triggers a compensatory hypertrophy of the residual viable myocardium. The increase in cardiomyocyte volume occurs in response to a chronic increase in workload mediated by the loss of functional cardiac units. Hypertrophy, once established, can act to offset ventricular wall stress and, as such, reduce a major stimulus of progressive ventricular dilation[3]. This positive attribute of myocyte hypertrophy, however, is largely dependent on the extent of tissue loss following infarction. Studies in experimental animals with large myocardial infarctions have shown that hypertrophy of the residual myocardium with up to 78% increase of mean myocyte volume was inadequate to compensate for muscle loss[31]. The notion that inadequacy of hypertrophy of the residual myocardium after infarction may contribute to chamber dilation and the development of heart failure is supported by a study in rats with large myocardial infarctions. In this animal model, induction of hypertrophy with an inhibitor of long-chain fatty acid oxidation retarded the process of left ventricular dilation and produced beneficial effects on systolic function[32]. Viewed from this prospective, one can argue that compensatory hypertrophy after acute myocardial infarction, may, in general, be a positive development. Having said that, one must also be aware that pathological hypertrophy may also carry with it long-term deleterious effects. There is strong evidence that coronary flow reserve is reduced with hypertrophy[33]. Most laboratories report a 20–30% reduction in capillary density of the hypertrophied myocardium[33] and there is also evidence of a biochemical defect in the hypertrophied myocardium[34] suggested by decreased levels of high-energy metabolites[35]. These abnormalities, and possibly others as yet undefined, may have deleterious effects on the myocardium. Ultrastructural studies of cardiomyocytes from hypertrophied hearts have shown various degrees of cell degeneration, including loss of contractile elements and changes in virtually every cellular organelle[36]. Thus, as in ventricular enlargement, myocardial hypertrophy appears to possess both a positive effect on the ventricle by reducing wall stress and deleterious long-term intrinsic effects.

LEFT VENTRICULAR SHAPE

Changes in ventricular shape with a shift from the conventional ellipic to a more spherical shape is without doubt a component of remodelling that results in a marked mechanical disadvantage. Both physiological and clinical studies suggest that the shape of the left ventricle has an important effect on overall myocardial viability and clinical outcome. Among patients studied 2–4 weeks after an acute myocardial infarction, those who developed a spherical ventricle had the lowest exercise capacity and accumulated the highest heart rate score, suggesting a greater propensity for the development of heart failure, compared with those who did not manifest a spherical ventricle[17]. Increased left ventricular sphericity has also been shown to be associated with increased wall stress[37,38], abnormal distribution of fibre shortening and poor long-term survival[19]. Studies in our laboratory in both patients and dogs with heart failure showed a close association between left ventricular sphericity and the development of functional mitral regurgitation; an event which directly impacts on an already compromized pump function[18,39]. The mechanism by which increased ventricular sphericity can lead to mitral

regurgitation is not fully understood. In a spherical left ventricle, the papillary muscle may undergo a lateral migration with a resulting misalignment with the mitral annulus. Under such circumstances, the forces exerted on the mitral leaflets during systole through the chordae tendineae may become more lateral than vertical and prevent complete leaflet coaptation during systole rendering the valve incompetent[40].

INTERSTITIAL FIBROSIS

Accumulation of interstitial collagen is another important component of remodelling of the hypertrophied and failing ventricle. It has been suggested that this reactive fibrosis is an important determinant of left ventricular stiffness and pump function[8,41]. Its progressive accumulation is thought to account for a spectrum of left ventricular dysfunction that first appears during diastole and subsequently involves systole[8,41]. Late in left ventricular hypertrophy, Weber *et al.* suggested that myocyte necrosis may be the result of compromised blood flow mediated by interstitial fibrosis or strangulation of intramyocardial arteries[42]. Additional studies are required to fully elucidate the role of myocardial collagen remodelling and extracellular collagen deposition on the mechanical properties of the left ventricle and their impact on the viability of the collagen encircled cardiomyocyte.

Therapeutic modification of the remodelling process

The cumulative evidence presented thus far suggests that the process of ventricular remodelling that results from the loss of functional cardiac units, is not a desirable adaptation and can lead to progression of ventricular dysfunction, overt heart failure and poor long-term survival. Prevention or retardation of the remodelling process, therefore, may be beneficial for preserving overall ventricular viability. Given this choice, the obvious question becomes, can the remodelling process be prevented or attenuated given existing therapeutic options? In the setting of acute myocardial infarction, any intervention that limits infarct size is likely to have a salutary effect on the remodelling process. Patients surviving an infarction with minimal regional wall motion abnormalities do not exhibit marked changes of ventricular size or shape[3]. Myocardial reperfusion with thrombolytic therapy, during the period in which salvage of myocardium is possible, has been shown to reduce infarct size and improve regional and global left ventricular function[43,44]. Even late coronary reperfusion, at a time when myocardial salvage is unlikely, can minimize infarct expansion[45]. Restoration of flow under such circumstances may promote healing and as such, prevent or retard infarct expansion[3]. In contrast, administration of glucocorticosteroids and non-steroidal anti-inflammatory agents during the acute phase of infarction have been shown to augment infarct expansion by delaying the healing process[46,47]. Intravenous nitroglycerine therapy during the acute phase of a myocardial infarction has also been shown to reduce infarct expansion, infarct size and in-hospital mortality[48].

In patients who survive the acute ischaemic insult, focus must shift to addressing the issue of long-term ventricular enlargement. At present, there exists considerable clinical evidence to suggest that ventricular enlargement after acute myocardial infarction can be influenced by pharmacological therapy. In rats with experimental myocardial infarction, Pfeffer and colleagues demonstrates that long-term therapy with the angiotensin converting enzyme (ACE) inhibitor captopril, initiated long after any reduction of infarct size was possible (14 days after coronary ligation), was associated with lower ventricular volumes, reduced filling pressures and improved survival[49]. In experimental infarction in dogs, Jugdutt *et al.* demonstrated that therapy with captopril, initiated 2 days after ligation of the left anterior descending coronary artery, conferred a positive influence on the ventricular remodelling process[50]. In comparison with dogs randomized to placebo, dogs treated with captopril had lower mean arterial and left atrial pressures, a lesser degree of infarct expansion and a lesser increase in left ventricular end-systolic and end-diastolic volumes[50]. In patients with anterior myocardial infarction, Pfeffer and colleagues demonstrated that therapy with captopril, initiated 3 weeks after the acute onset of symptoms, prevented the progression of left ventricular dilation despite persistent occlusion of the infarct related artery, whereas patients randomized to placebo showed further chamber enlargement at 1 year[51]. In a study of 100 patients with Q-wave myocardial infarction randomized to long-term (3 monthh) therapy with captopril or placebo, Sharp *et al.* demonstrated that therapy initiated as early as 24–28 h after onset of symptoms can have a salutary effect on left ventricular function[52]. In their study, patients treated with captopril showed an improvement of ejection fraction and minimal changes of left ventricular end-diastolic and end-systolic volume indices in comparison with the placebo treated group. In a study of 52 patients with transmural anterior myocardial infarction and depressed left ventricular function (ejection fraction <40%) randomized to long-term (1 year) therapy with captopril or digoxin, Bonaduce *et al.* showed that captopril therapy initiated 7–10 days after the onset of symptoms was more effective in retarding progressive left ventricular enlargement (increase of end-systolic and end-diastolic volumes) in comparison with digoxin[53]. Among 56 patients with mild to moderate heart failure enrolled in the SOLVD (Studies of Left Ventricular Dysfunction) trial randomized to therapy with enalapril or placebo for 1 year, those treated with enalapril showed a significant reduction of left ventricular end-diastolic and end-systolic volumes and a significant increase in ejection fraction compared to those treated with placebo in whom these indices tended to increase during the 1 year follow-up period[2]. Initial data from the Survival and Ventricular Enlargement (SAVE) multicentre trial presented at the 41st Annual Scientific Sessions of the American College of Cardiology in April 1992 appear to confirm many of the findings of these studies, namely that therapy with ACE inhibition (captopril) in survivors of myocardial infarction who manifest left ventricular dysfunction (ejection fraction ≤40%), can prevent the progressive deterioration of left ventricular function after infarction.

The mechanisms by which ACE inhibition prevents, retards or reverses progressive ventricular dilation and improves long-term survival after myocardial infarction is uncertain. Reduction of both preload and afterload with a subsequent decrease in left ventricular wall stress are likely components of this beneficial effect[3]. In rats with large myocardial infarctions, comparisons between captopril, a presumed arterial and venodilator, with hydralazine, which is thought primarily to be an arterial vasodilator, showed that the venodilatory capability of captopril accounted for the improvement in ventricular volume[54]. Rats treated with captopril manifested venodilation, decreased blood volume and decreased operating end-diastolic volume and pressure. In contrast, hydralazine had no effect on the venous circulation and did not alter left ventricular end-diastolic pressure or operating left ventricular end-diastolic volume.

ACE inhibitors may also have a favourable impact on other components of the remodelling process and by doing so, improve left ventricular function and long-term survival. In patients with anterior infarction who are at high risk of ventricular enlargement because of persistent occlusion of the infarct-related vessel, Mitchell *et al.* demonstrated that long-term (1 year) therapy with captopril prevented the progressive increase in left ventricular sphericity[4]. In contrast, patients randomized to placebo showed a significant increase in left ventricular end-systolic and end-diastolic sphericity indices after 1 year of follow-up[4]. The mechanisms underlying this beneficial effect of ACE inhibition remains unknown. ACE inhibitors may also influence the remodelling process by having a direct effect on myocardial hypertrophy. Angiotensin-II may be a direct stimulus of in-vivo cardiac muscle cell growth independent of its effects on afterload augmentation. In cardiomyocyte cell cultures, angiotensin-II was shown to be a potent stimulus for protein synthesis and cardiomyocyte growth[55]. In spontaneously hypertensive rats, captopril therapy was shown to reduce cardiac hypertrophy and improve ventricular performance[56]. Other studies in rats with aortic banding and left ventricular hypertrophy showed that the ACE inhibitor, ramipril, prevented the development of hypertrophy in this model independent of its afterload-reducing properties[57]. Ramipril-induced potentiation of bradykinin was postulated to contribute to this beneficial effect[57]. Angiotensin-II may also play a role in the accumulation of collagen in the extravascular compartment and interstitium of the hypertrophied left ventricular wall. In a recent study, Jalil *et al.* showed that in rats with renovascular hypertension, pretreatment with enalapril attenuated the expected perivascular fibrosis of intramyocardial coronary arteries[58]. Whether these effects are unique to ACE inhibitors is not entirely clear. Because of the multiplicity of actions expressed by this class of drugs, the specific means by which they exert a beneficial effect on ventricular remodelling remains to be determined.

In conclusion, many of the components of ventricular remodelling have been defined. Additional studies are needed to further define the interplay among these components and their cumulative and individual roles in modifying ventricular function. Research is also needed to confirm and more fully elucidate the secondary and potentially beneficial effects of ACE inhibition on ventricular remodelling, including limitation of ventricular hypertrophy, attenuation of ventricular shape changes (sphericity) and prevention of reactive interstitial fibrosis. Despite some limitations, there are sufficient data at present to conclude that long-term therapy with ACE inhibitors can attenuate left ventricular remodelling and, in doing so, improve long-term survival.

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