Interstitial Collagen Remodeling in Chronic Heart Failure

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Abstract

Myocardial fibrillar collagen provides for muscle fiber and cardiac myocyte alignment, maintains ventricular shape and size, and contributes to tissue stiffness. The collagen matrix is in intimate contact with the myocyte, muscle fiber and coronary microcirculation. In renovascular and genetic hypertension, there is a progressive remodeling of this matrix which includes thickening of existing fibrillar collagen, and the addition of new collagen fibers to all components of the matrix. In ischemic and cardiomyopathic heart disease evidence is accumulating to indicate that part of the remodeling process of interstitial collagen includes a phase of collagenase-induced disruption of the components of the collagen matrix which are responsible for maintaining myocyte alignment and ventricular size and shape. This deleterious remodeling leads to ventricular dilatation and wall thinning, and eventually congestive heart failure. Much of the adverse remodeling appears to be preventable with chronic angiotensin converting enzyme inhibition or adrenoceptor blockade. Whether the adverse remodeling of the interstitial collagen matrix during heart failure is reversible remains to be determined.

Key words: myocardial collagenase, fibrillar collagen, interstitial collagen remodeling, hypertension, ischemic heart disease, infarction, cardiomyopathy, heart failure.

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The myocardium consists of myocytes, connective tissue, coronary vasculature and nerves. The major component of connective tissue is the fibrillar collagen matrix which surrounds, supports and interconnects the other myocardial elements. As a result of this intimate contact, several functional roles have been attributed to this collagen network. These include: the coordinated transmission of force generated by myocytes to the ventricular chamber [49]; a significant contribution to myocardial relaxation and diastolic stiffness [27, 63]; the determination of ventricular size and shape [10, 11, 28]; and the prevention of myocardial edema [28], ventricular aneurysm and rupture [16, 20]. Most of these functional roles were determined experimentally from animal models which develop either excess or inadequate amounts of myocardial fibrillar collagen. The collagen matrix is known to remodel in response to chronic physiologic and pathophysiologic alterations in vascular impedance, ventricular filling volume or circulating hormones and in cardiac disease. For example, an abnormal increase in myocardial collagen concentration secondary to genetic hypertension [6, 25, 39] or activation of the renin-angiotensin-aldosterone system [17, 26, 64] results in an increase in myocardial passive stiffness and ventricular diastolic stiffness. Conversely, collagen matrix degradation leads to myocardial edema [28], ventricular dilatation [10, 11, 28] and a decrease in ventricular diastolic stiffness [10, 27, 28]. Our knowledge of myocardial fibrillar collagen remodeling in heart failure will be the subject of this review. We will begin with a description of the composition, organization and maintenance (i.e., collagen synthesis and degradation) of this matrix.

The myocardial collagen matrix

Composition

Normally the amount of collagen in the myocardium is small; morphometric measurements reveal that only 2 to 4% of the normal myocardium is occupied by collagen. However, because collagen is a relatively stiff material with a high tensile strength, its presence, even in small amounts, would be expected to have a marked influence on the mechanical properties of the myocardium. Fibrillar collagen found in the heart is composed of collagen types I, III and V. Even though the relative proportions of these

types are species dependent [34], the predominant collagen types in adult hearts are type I and type III, where the percentage of type I is typically greater than type III [18, 34, 64]. Large diameter type I collagen fibers are found in tissues typically subjected to high stresses (e.g., tendons). Type III collagen fibers are smaller in diameter, and are found in abundance in tissues which tend to be relatively compliant (e.g., skin). The myocardial collagen fibers that surround individual [14, 48, 54] as well as groups of myocytes [14, 54] appear to be a copolymerization of both types.

Organization

The extracellular matrix of the myocardium has three distinct components: the epimysium, perimysium and endomysium (figure 1). The epimysium is defined as the sheath of connective tissue that surrounds a muscle [47]. In the case of papillary muscle, the collagen fibers of the epimysium form a weave pattern that tends to be aligned with the long axis of the muscle [47]. For the ventricular myocardium, the epimysium has been described as the collagenous matrix that lies below the endothelium of the epicardium and endocardium [62]. The perimysium originates from the epimysium in the form of tendinous cords which appear as coiled fibers running parallel or oblique to the axis of muscle fibers (figure 2) or terminate in a fibrillar weave that surrounds and groups myocytes into myofibrils. Adjacent perimysial weaves are joined to each other by collagen fibers referred to as strands. The endomysium (figure 3) consists of thin fibrillar collagen fibers that surround individual myocytes and collagen struts that join myocyte to myocyte or myocyte to neighboring capillaries.

Myocardial collagen synthesis and degradation

Once deposited in fibrillar form and subsequently cross-linked, extracellular collagen is extremely stable and resistant to degradation. As a result of this stability, myocardial collagen turnover is relatively slow. In the rat heart, total collagen synthesis within the fibroblasts was reported to be $5.2 \pm 0.7\%$ of total myocardial collagen per day, and of this amount, $53 \pm 5\%$ was destroyed prior to secretion [32]. The net synthesis rate of collagen for the right and left ventricles in dogs was determined to be only 0.56% of total ventricular collagen per day [5]. If an equilibrium between collagen synthesis and degradation is assumed, then the half-life of collagen is around 90 to 120 days.

Interstitial collagen consists of three peptide chains which intertwine to form a right-handed super-helix. This conformation makes it highly resistant to all proteinases except specific collagenases [69]. Thus the rate limiting step in the degradation of fibrillar collagen is the catalytic cleavage by interstitial collagenase (matrix metalloproteinase, MMP-1). This enzyme cleaves the three α chains of collagen types I, II, and III. It does this by hydrolyzing the peptide bond that follows the Gly residue of the partial sequence Gly-[Ile or Leu]-[Ala or Leu] located at a distance of three-fourths from the amino terminal [24, 37]. Gelatinase (MMP-2) then degrades these products into smaller peptides that then become substrate for several nonspecific proteases [68].

The presence of myocardial collagenase in the interstitial spaces between myocardial fiber bundles was first described by Monfort and Pérez-Tamayo [38]. While the intensity of the collagenase antibody staining patterns is variable, collagenase is present throughout the myocardium. Moreover, when one compares the pattern of collagenase staining to the distribution of collagen in the myocardium, the two are essentially identical, suggesting that latent collagenase is bound to collagen. In all likelihood the antibody used by Montfort and Pérez-Tamayo labelled both latent and active collagenase. Woolley et al. [70], using an antibody with a proven high affinity for active collagenase, reported little collagenase activity in the heart. Thus, while collagenase in the normal heart is plentiful, most of it appears to be in a proenzyme or latent form. Such was the conclusion of Tyagi et al.[58] who used zymographic techniques and estimated that, in rat myocardial tissue, only 1 to 2% of total collagenase is normally active. In a subsequent report, this group demonstrated the existence of a tissue inhibitor of metalloproteinase (TIMP) in the myocardium [59].

Myocardial collagen remodeling

Cells that synthesize collagen and collagenase are influenced extensively by their environment. This controlling environment includes resident cell populations in connective tissue as well as migratory cells that infiltrate a region in response to inflammation, disease or injury. Factors secreted by such cells play a prominent role in the remodeling of connective tissue through the local regulation of collagen synthesis and degradation. Remodeling of the fibrillar collagen matrix occurs naturally with normal growth and development. Also, myocardial interstitial collagen remodeling is a response to chronic physiologic and pathophysiologic alterations in vascular impedance, ventricular filling volume or circulating hormones and in cardiac disease. Here the remodeling process is dependent on the nature of the stimulus. Compensated left ventricular (LV) hypertrophy secondary to renovascular and genetic hypertension is associated with excessive myocardial collagen deposition [6, 17, 25, 26, 39, 41, 64]. Generally this remodeling occurs at both the microscopic and ultrastructural levels. Alterations of the peri- and endomysial components include: thickening of collagen fibrils, fibers and tendons; increased density of the weave and collagen network surrounding myocytes; newly formed collagen fibers; expansion of the area occupied by perivascular collagen; and occasional microscopic scars [1, 9, 17, 39, 45]. In contrast, chronic ventricular volume overload results in dilatation and compensated LV hypertrophy with normal collagen concentration [2, 36, 65]. The interstitial collagen remodeling that occurs with cardiac disease and associated with myocyte necrosis includes excessive reparative or replacement and reactive (i.e., newly syn-

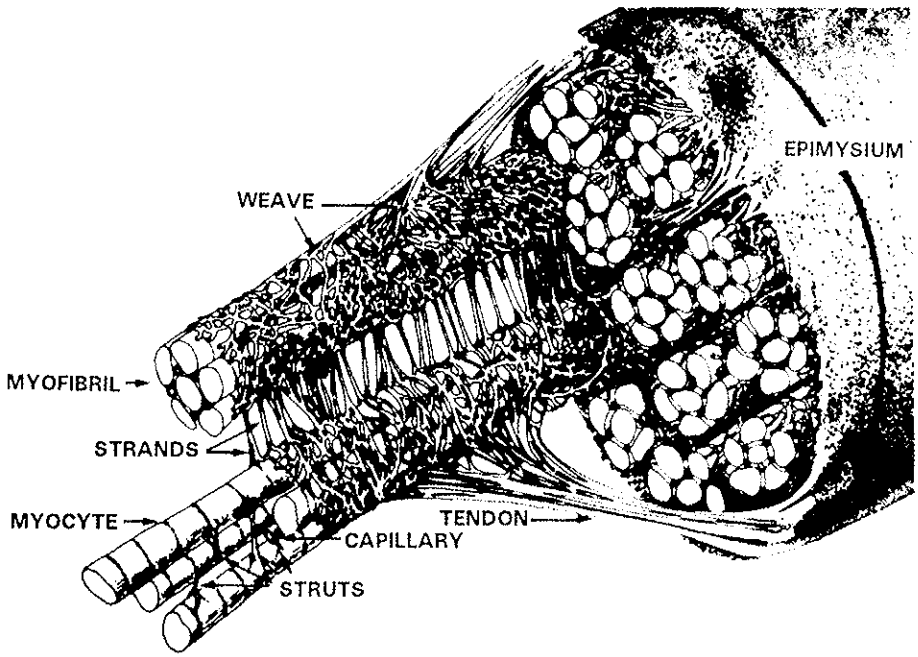

Figure 1. Schematic portrayal of the myocardial interstitial collagen matrix and its epimysial, perimysial (i.e., tendon, weave and strands) and endomysial (i.e., struts) elements. Reproduced with permission from Weber et al [63].

thesized collagen fibers and thickening of existing fibers in non-necrotic areas) fibrosis [4, 23, 51, 53, 71]. LV collagen concentration was found to be 30 and 100% greater in explanted hearts from patients with coronary heart disease and dilated cardiomyopathy, respectively, than in normal postmortem hearts. Contributing to this greater concentration of collagen was an increase in both the size and number of endomysial and perimysial thick fibers, particularly those surrounding individual myocytes [23, 51, 71]. While the concentration of collagen types I and III were both found to be elevated in these diseased hearts, the relative increase in type I was greater than that of type III [4].

It should be stressed that most of the studies dealing with remodeling of the collagen matrix were focused primarily on the end-point of a dynamic process. Thus a biochemical, histological or morphological assessment of interstitial collagen several weeks after initiating a sustained increase

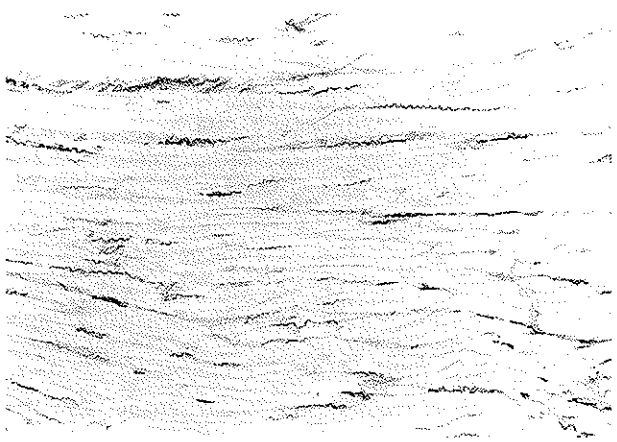

Figure 2. Normal myocardium stained with collagen specific Sirius Red demonstrating typical amounts of collagen. Darkly stained, coiled perimysial fibers in between muscle bundles are apparent.

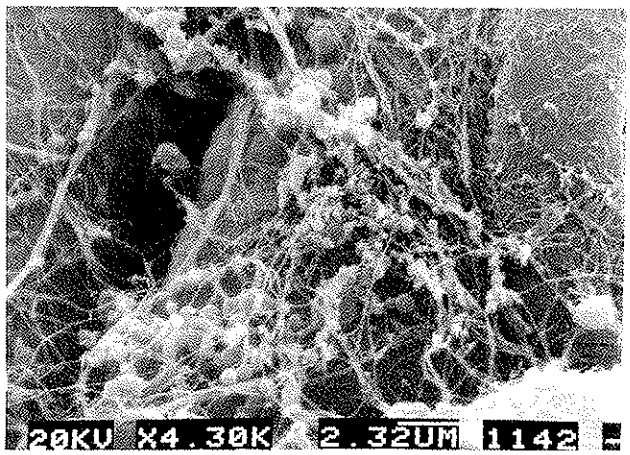

Figure 3. Scanning electron microscope photomicrograph of rat myocardium showing fibrillar collagen components of the perimysial weave and the endomysial network and struts.

in ventricular loading conditions, at the time of cardiac transplantation, or at autopsy provides a description of the collagen network "after the fact" and sheds no insight into the temporal relation of the remodeling process that may have preceded. Such information, which could include both a breakdown and subsequent reconstruction of the collagen matrix, can only be obtained from longitudinal studies of which there is a sparsity. Our understanding, albeit limited, of this process will now be considered for several pathophysiological conditions.

Collagen matrix remodeling secondary to chronic ventricular pressure overload

Many studies have documented an increase in myocardial collagen concentration in the compensated pressure overloaded, hypertrophied myocardium [1, 6, 7, 14, 25-27, 36, 39, 41, 45, 52, 63, 64]. Moreover, in experimental renovascular and perinephritic hypertension, the myocardial remodeling process has been shown to be progressive. At 4 weeks, type III collagen was found to rise significantly from its normal value of 11% to 16% or more [64]. There was a disproportionate amount of newly formed thin perimysial fibers, which in all likelihood were type III collagen fibers, and there was slight thickening and increased density of the weave [1, 52]. Evidence of disrupted collagen with expansion of many intermuscular spaces and muscle fiber slippage was also present. As will be discussed, these changes are indicative of collagen degradation and an early wound healing process. Beyond four weeks of experimentally induced hypertension, collagen concentration is significantly elevated and newly formed perimysial fibers are evident. As the hypertrophic process continues, further increases in collagen concentration are modest despite the appearance of patchy areas of reactive (i.e., unrelated to myocyte necrosis) fibrosis extending over muscle fibers. Late in the hypertrophic process, some of these areas become quite extended to the point where they completely encircle muscle. In many of these isolated muscle areas, cell necrosis is present [17, 45]. Between 35 and 88 weeks of hypertension there is a restoration of a normal proportion of type III collagen relative to type I, resolution of the myocardial edema evident at 4 weeks, and a greater number of interstitial spaces contain thick perimysial fibers [45, 64]. In addition to previously mentioned changes in the weave which occur during the hypertrophic process, the collagen strands become thicker and pillar-like, the tendons are increased in number and thickness, and some myocytes are encased in collagen [1, 52]. While it is not presently known what happens to the fibrillar collagen matrix as the hypertrophied myocardium begins to decompensate, degeneration of myocytes and increased fibrosis in the latter stages of the hypertrophic process have been reported [17, 45, 52]. This would then be expected to lead to a worsening of diastolic dysfunction and the onset of systolic dysfunction [26].

Collagen matrix remodeling secondary to ischemia

The remodeling of the myocardium following a prolonged period of ischemia includes early damage to the interstitial fibrillar collagen matrix, scar formation and, if the damage is sufficiently severe, progressive ventricular dilatation. A rapid breakdown of collagen within 24 h after the induction of experimental myocardial infarction has been noted. Takahashi et al. [56] found collagen content in the infarcted region to decrease by approximately 50% as early as 3 hours post-infarction. The collagenolysis corresponded to significant (two- to threefold) increases in tissue collagenase and lysosomal serine protease activities. Subsequent to the degradation of the supportive fibrillar collagen matrix, a thinning and an outward expansion of the infarcted ventricular wall occurred during systole. Rapid disruption of collagen struts and loss of collagen weaves also was found to occur in non-infarcted stunned (i.e., ischemia-induced) myocardium [12, 72].

In rats with and without experimental leukopenia, collagen degradation in the infarcted hearts has been shown to be markedly greater when there was a normal leukocyte response [8]. While these results implicate inflammatory cell collagenase in infarction-related collagen breakdown, significant collagen degradation occurs in the damaged area prior to inflammatory cell infiltration. This may be due to the increase in oxidized glutathione (GSSG) that occurs in the ischemic zone immediately post-infarction [50]. GSSG has recently been shown by Tyagi et al. [59] to be capable of activating myocardial collagenase. This would then explain the rapid collagen disruption which occurs in stunned [12, 72] and infarcted [56] myocardium where inflammatory infiltrate is not yet present.

Within days following an infarction, a replacement fibrotic process is evident. At about 6 weeks post-infarction, the collagen content in the necrotic area increases by as much as 500% [29]. The orientation of collagen fibers within the scar typically corresponds to that of the muscle fibers that had previously occupied the space [66]. Collagen fibers that are oriented in the same direction as the local stresses contribute significantly to the strength of the tissue as opposed to a negligible influence of fibers aligned perpendicular to the stress direction. For example, Wiegner and co-workers [67] found strips of pericardium exhibited the greatest stiffness when the majority of collagen fibers were oriented parallel to the direction of the elongating force. In papillary muscle the orientation of the epimysial collagen fibers changes with stretch. Resistance to elongation increases significantly when the collagen fibers become predominantly oriented parallel to the major axis of the muscle [48].

The collagen concentration in areas remote to the infarcted region increases in experimental animals [35, 60] and humans [4, 61]. The stimulus for excess collagen deposition in these non-infarcted areas is unknown but may be related to remote necrosis [15], increased workload on the remaining viable myocardium and/or circulating endocrine factors. Despite an extensive remodeling of the

interstitium and myocyte post-infarction, the ventricle progressively dilates and becomes stiffer; the extent of dilatation is related to the location, size and duration of infarction [19]. Significant thinning of the ventricular wall also accompanies the LV dilatation [19, 43]. Although this dilatation may at first bring about a compensatory increase in stroke volume, it ultimately results in a mechanical disadvantage which leads to progressive dysfunction and heart failure.

The fate of the myocardial collagen matrix as the heart dilates post-infarction is unknown. However, it has been our working hypothesis that progressive dilatation secondary to myocardial injury is the result of myocardial collagen disruption and degradation secondary to myocardial collagenase activation. Preliminary data from our laboratory indicate that a sustained elevation in ventricular volume secondary to the creation of an infra-renal abdominal aorta-vena cava fistula is associated with a significant activation of the myocardial collagenase system. Twelve hours after the creation of the fistula, collagenase activity was elevated by 50% relative to control activity. Over the next 5 days of volume overload, it further increased to levels that were 80% greater than control levels. Also during this period a significant decline (i.e, 40%) in collagen concentration occurred. Over the remainder of the study (i.e., 8 weeks), collagenase activity decreased to a level which was 33% above control collagenase activity. These alterations to the fibrillar collagen matrix resulted in a significant ventricular enlargement and increased compliance.

A schematic representation of the events post injury which lead to ventricular dilatation and heart failure is shown in figure 4. Following an injury that produces myocyte necrosis, there is a compensatory remodeling of the ventricle involving all of the myocardial components. If ventricular dysfunction results from this injury, then there is a compensatory increase in filling volume or preload. It is at this point that the ventricle dilates to accommodate this larger volume at a lower filling pressure [19]. It is our hypothesis that a collagenase-induced disruption of the myocardial collagen matrix must precede this dilatation. With the onset of heart failure there are other compensatory mechanisms such as increased levels of circulating catecholamines, angiotensin II and aldosterone. Pathophysiologic plasma levels of these hormones have been shown to cause myocyte necrosis [3, 7, 30], leading to a vicious cycle which ultimately results in death. As discussed below, experimental and clinical evidence supporting our hypothesis has been reported in dilated cardiomyopathic hearts.

Collagen matrix remodeling secondary to idiopathic dilated cardiomyopathy

Several investigative groups have demonstrated that experimentally induced myocardial collagen degradation leads to ventricular enlargement and an increase in ventricular compliance [10, 11, 16, 28, 40]. That is, the ventricular pressure-volume relation is shifted to the right

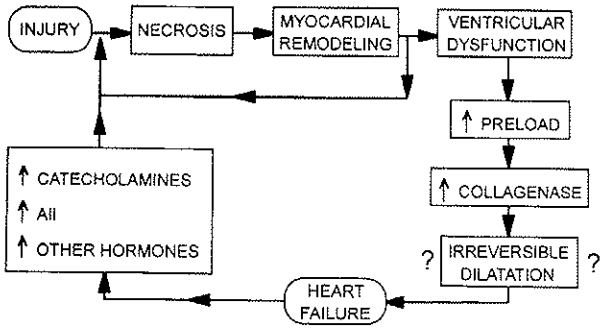

Figure 4. Model depicting mechanisms of progressive ventricular dilatation in heart failure (see text for explanation). AII = angiotensin II.

following the loss of many of the collagen struts that connect adjacent myocytes and the collagen weave that surrounds groups of myocytes. Thus, a collagenase-induced disruption of muscle bundle to muscle bundle tethers and other elements of the collagen matrix would be expected to lead to ventricular dilatation and wall thinning. In addition, muscle fiber slippage and a sphericalization of the ventricle are likely to occur. Recently Reddy et al. [46] used zymography to assess collagenase activity in endomyocardial biopsy tissue obtained from patients with end-stage dilated cardiomyopathy and from post-transplant patients with presumably normal hearts. Collagenase activity in the cardiomyopathic biopsy samples was increased eightfold above that measured in normal hearts. Echocardiographic measurements revealed that the cardiomyopathic left ventricles were significantly dilated with thinner walls compared to the post-transplant left ventricle. Also, the shape of the diseased left ventricle was more spherical than normal.

These findings of Reddy and co-workers support the hypothesis that enhanced collagenase activity results in fibrillar collagen degradation that then leads to progressive ventricular dilatation and sphericalization. However, they do not provide insight into the remodeling that precedes this phase of end-stage heart failure due to idiopathic dilated cardiomyopathy. Such temporal information can be obtained from the cardiomyopathic Syrian hamster. This animal model of cardiomyopathy, which develops progressive ventricular enlargement and heart failure, has the advantages of a known, age-related pathophysiologic course. Four distinct histological and clinical phases of the disease process have been identified [21]. During the first phase (i.e., prenecrotic < 45 days of age) both the histology of the heart and the clinical appearance of the hamsters are normal. The second or necrotic phase is characterized by the incidence of multifocal myocytolytic necrosis which continues until approximately 120 days of age. There are also alterations in the connective tissue network adjacent to the necrotic myocardial lesions which are noted at 90 days of age and become progressively larger with age. The

lesion was characterized by a marked absence of connective tissue along the edges of the scar tissue formations and the presence of long, thick fibers which apparently tethered the post-necrotic foci to the surrounding normal muscle. In the interstitium distal to this "halo-like", collagen-deficient region, the connective tissue was normal [13]. The authors speculated that the loss of connective tissue surrounding confluent fibrotic areas may result in myofiber slippage and wall thinning and that the effects of the tethering fibers may result in an increase in wall stiffness. Near the end of the necrotic phase, healing is essentially complete with only a few new areas of myocyte necrosis developing. The next phase is referred to as the hypertrophic compensated phase. This phase continues until the development of significant dilatation and wall thinning which usually occurs around the age of 240 days. The final or terminal stage begins at this point, and during this fourth stage, congestive heart failure is clinically present.

To further test the hypothesis regarding increased myocardial collagenase activity leading to collagen degradation and ventricular dilatation, hearts from cardiomyopathic hamsters were examined at 150, 180, 210, 240, and 300 days of age and compared to age-matched golden Syrian hamsters which served as controls [28]. Collagenase activity in the cardiomyopathic hamster heart was found to progressively increase with age as opposed to the golden Syrian hamsters which exhibited an age-invariant myocardial collagenase activity. An example of myocardial collagenase activity as measured using zymography is presented in figure 5. The lanes of the gel were loaded with myocardial extract from animals in both groups at several ages. In all cases, the brighter and wider lytic bands (i.e. greater collagenase activity) are associated with the cardiomyopathic hearts. Typically, myocardial collagenase activity was significantly greater (i.e., 2 to 3 times) in the cardiomyopathic hearts compared to control hearts at the ages examined. Collagen volume fraction (CVF) for the control hearts did not vary with age. In contrast, CVF was significantly greater than control values for the 150 day old cardiomyopathic group and continued to increase up to 210 days of age. At 240 and 300 days, CVF began to decline (CVF at 300 days was similar to that obtained at 150 days of age) and the LV became dilated with a notably thinner wall. Significant ultrastructural fibrillar collagen degradation was also seen in non-necrotic areas of myocardium at 240 and 300 days of age. Thus, in the cardiomyopathic hamster, there is a continued increase in collagenase activity with collagen degradation eventually exceeding collagen synthesis. Microscopic evidence of fibrillar collagen degradation was found in remote areas [28] as well as in and around necrotic areas [13] resulting in an inadequate interstitial collagen matrix. The fact that this collagen degradation becomes significant around the age associated with development of marked ventricular dilatation and wall thinning is indicative of a strong cause and effect relation between collagenase activity and ventricular remodeling.

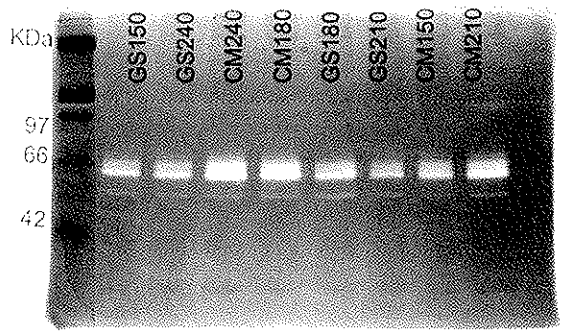

Figure 5. Example of myocardial collagenase activity using zymography in cardiomyopathic (CM) and age-matched golden Syrian (GS) hamsters at 150, 180, 210, and 240 days of age. The CM lytic bands (55 to 60 KDa) are denser and wider indicating enhanced collagenase activity.

These observations in the cardiomyopathic hamster indicate that significant degradation could be occurring, even though total myocardial collagen concentration is significantly greater in diseased hearts than in age-matched control hearts. That is, most of the excess collagen consists of a reparative or replacement fibrosis. Whether or not the scar tissue is undergoing degradation is unimportant with regard to the shape and size of the ventricle. Instead, it is degradation of the collagen matrix component responsible for the maintenance of myocyte alignment that will result in significant ventricular dilatation. Thus, in heart failure, it is not possible to discern the integrity of interstitial remodeling by simply measuring the concentration of myocardial collagen. Instead, one needs to assess the status of the collagen matrix which surrounds and interconnects myocytes and groups of myocytes.

Prevention of interstitial remodeling and reverse interstitial remodeling in heart failure

Little is known regarding the prevention of interstitial remodeling in heart failure. However, chronic therapy with an angiotensin converting enzyme (ACE) inhibitor has been shown to attenuate progressive ventricular enlargement and significantly improve one year survival following myocardial infarction [42, 44, 57]. Patients so treated were found to have less ventricular dilatation, fewer clinical indications of heart failure, a decreased number of hospitalizations due to heart failure, and a reduction in the number of deaths attributed to heart failure. Additionally, LV shape of patients at greatest risk for ventricular enlargement was normal with chronic ACE inhibition while the LV of patients receiving placebo became progressively more spherical [31]. Chronic therapy with ACE inhibitors in cardiomyopathic hamsters beginning at an age of 180 days and continuing for 120 days also prevented the decline of LV contractile performance, coronary flow and dilatation, and prolonged survival time by 33% [22]. The mechanism underlying the cardioprotective nature of ACE

inhibition, however, remains to be determined. Also, whether ACE inhibitors directly or indirectly reduce or prevent the enhanced myocardial collagenase activity following myocardial infarction and cardiomyopathy is not known.

Another unresolved issue concerns the possible reversibility of the interstitial remodeling process. Spinale and colleagues [55] reported a trend towards restoration of the myocardial collagen network following cessation of chronic supraventricular rapid pacing in a pig model of congestive heart failure. Following 3 weeks of rapid pacing, congestive heart failure was evident; there was significant LV dilatation and myocardial collagen concentration was significantly reduced. Electron microscopic analysis of the collagen ultrastructure revealed disruption of struts and thinning of collagen fibers. Following deactivation of the pacemaker and a 4 week recovery period, collagen concentration was significantly greater than control and there was a trend for ventricular size to return to normal. The increased collagen concentration in the recovered hearts was the result of thickened endo- and perimysial collagen components. McDonald et al. [33] also reported a trend towards a reduction in LV volume in their model of heart failure following 3 months of therapy with either an ACE inhibitor or beta-adrenoceptor blockade. They, however, did not examine the interstitial collagen matrix.

Summary

From the above, the following pathophysiologic scenario regarding interstitial collagen remodeling in heart failure can be proposed. In hearts with myocardial damage secondary to myocardial infarction, chronic ischemia, inflammation, or cardiomyopathy there is a complex sequence of compensatory events that eventually result in an adversely remodeled myocardial collagen matrix and a dilated, thin-walled, spherical ventricle. For a period of time, a state of preclinical heart failure exists where there is ventricular dysfunction due to myocardial damage but no clinical evidence of cardiac insufficiency, circulatory congestion or edema. As a result of progressive myocyte necrosis, there may be an excessive amount of fibrillar collagen due to replacement fibrosis and a compensatory remodeling of the collagen matrix elements which are responsible for maintaining myocyte alignment. However, in an attempt to maintain a compensated state, there are ongoing myocardial and peripheral adaptations including activation of the renin-angiotensin-aldosterone and sympathetic nervous systems, elevations in circulating blood volume and ventricular preload, cardiac myocyte hypertrophy, and progressive heart enlargement. A continual state of remodeling with progressive ventricular dilatation and myocyte loss, and increased collagenase activity is present. The net effect is a loss of balance between collagen synthesis and degradation which leads to an inadequate fibrillar collagen matrix, progressive ventricular dilatation with wall thinning and sphericalization and eventually congestive heart failure. Much of this adverse remodeling is preventable with chronic angiotensin converting enzyme inhibition or adrenoceptor blockade. However, the mechanism underlying the efficacy of these treatment modalities remains to be determined. Also, future research regarding the reversibility of adverse interstitial fibrillar collagen remodeling is required.

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