Journal of Clinical and Basic Cardiology

An Independent International Scientific Journal

Journal of Clinical and Basic Cardiology 1999; 2 (1), 113-116

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Indexed in
Chemical Abstracts
EMBASE/Excerpta Medica

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Remodeling of the cardiac interstitium in the progression of heart failure

H. N. Sabbah, V. G. Sharov, S. Goldstein

A characteristic feature of heart failure is the progressive deterioration of left ventricular (LV) function that occurs in the absence of clinically apparent intercurrent adverse events. The mechanism or mechanisms responsible for this haemodynamic deterioration are not known but may be related to progressive intrinsic contractile dysfunction of cardiomyocytes and/or to ongoing degeneration and loss of viable cardiomyocytes. We examined the concept that progressive LV dysfunction in heart failure is associated with remodeling of the cardiac interstitium manifested by progressive accumulation of interstitial collagen (reactive interstitial fibrosis) that can potentially lead to chronic hypoxia of the collagen encircled cardiomyocytes, the latter a trigger of cardiomyocyte apoptosis.

Studies were performed in dogs with progressive LV dysfunction and failure produced by multiple sequential intracoronary microembolizations. In all dogs, embolizations were discontinued when left ventricular ejection fraction was 30 % to 40 %. Subsequently, dogs were randomly selected to sacrifice at 2 weeks and 4 months after the last embolization and left ventricular tissue was obtained for histologic examination. Ejection fraction decreased significantly between 2 weeks and 4 months (33 ± 3 vs. 20 ± 2 %, $p < 0.05$). This was associated with increased volume fraction of interstitial fibrosis (8.7 ± 0.8 vs. 12.2 ± 0.7 %, $p < 0.05$), reduced capillary density (capillary per fiber ratio 0.93 ± 0.01 vs. 0.98 ± 0.01, $p < 0.05$) and increased oxygen diffusion distance (14.6 ± 0.32 vs. 12.2 ± 0.09 μm, $p < 0.05$).

The observations suggest that in heart failure, progressive LV dysfunction is accompanied by remodeling of the interstitial compartment manifested as progressive accumulation of collagen in the cardiac interstitium that is associated with decreased capillary density and increased oxygen diffusion distance. All of these maladaptations can lead to hypoxia of the collagen encircled cardiomyocyte, a potential trigger of ongoing cardiomyocyte apoptosis or programmed cell death. The latter may contribute to ongoing loss of functional cardiac units and consequently progressive global LV dysfunction. *J Clin Basic Cardiol 1999; 2: 113–6.*

Key words: animal models, capillary density, congestive heart failure, ventricular function, apoptosis

Left ventricular (LV) dysfunction, once established as a consequence of a primary event such as an acute myocardial infarction, can deteriorate over time, despite the absence of clinically apparent intercurrent adverse cardiac events [1–3]. This progressive deterioration of LV function often culminates in chronic heart failure. The mechanism or mechanisms responsible for this haemodynamic deterioration are not known but have been attributed, in part, to entry into a so-called "vicious circle" whereby compensatory mechanisms intended to maintain homoeostasis, such as compensatory LV hypertrophy and dilation [4, 5] and enhanced activity of the sympathetic nervous system and renin-angiotensin system [6, 7], themselves become factors that accelerate the process of progressive LV dysfunction. A working hypothesis is that activation of these compensatory mechanisms leads directly or indirectly to ongoing intrinsic contractile dysfunction of residual viable cardiomyocytes and/or to ongoing degeneration and loss of cardiomyocytes.

Structural maladaptations of both cardiomyocytes and the cardiac interstitium occur in heart failure which, acting individually, or in concert, can adversely influence global LV contractile performance. These include hypertrophy of cardiomyocytes [4], abnormalities of myocyte contractile structures [8], abnormalities of mitochondria [9] and accumulation of collagen in the interstitium [10] termed "reactive interstitial fibrosis". In the present study, we tested the hypothesis that the progressive deterioration of LV function in the setting of heart failure is associated, in part, with progressive accumulation of collagen in the cardiac interstitium. The rationale was based on earlier findings from our laboratory [11]. In the LV of dogs with chronic heart failure, we showed that severe reactive interstitial fibrosis is associated with reduced capillary density, increased oxygen diffusion distance and increased myocyte lactate dehydrogenase activity; conditions that favor the development of hypoxia [11]. Studies in dogs with chronic heart failure [12] and in explanted failed human hearts have documented the occurrence of cardiomyocyte apoptosis based on nuclear DNA fragmentation [13, 14]. The high incidence of cardiocyte apoptosis in regions bordering old infarcts [12] and the susceptibility of these regions to ischaemia/hypoxia provides rationale for hypoxia as a possible trigger of cardiomyocyte apoptosis.

Methods

Animal model

The dog model of chronic heart failure used in the study was previously described in detail [15]. The model manifests many of the sequelae of heart failure seen in humans, including marked and sustained depression of LV systolic and diastolic function, LV hypertrophy and dilation, reduced cardiac output, increased systemic vascular resistance and enhanced activity of the sympathetic nervous system evidenced by marked elevation of plasma norepinephrine concentration [15]. In the present study, chronic LV dysfunction was produced in 12 dogs by multiple sequential intracoronary embolizations with polystyrene latex microspheres (77–102 μm in diameter). Coronary microembolizations were performed one to 3 weeks apart

Received June 25th,1998; accepted July 23rd, 1998.
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during cardiac catheterizations. All procedures were conducted under general anaesthesia and sterile conditions. Anaesthesia consisted of intravenous injections of oxymorphone hydrochloride (0.22 mg/kg), diazepam (0.17 mg/kg) and sodium pentobarbital (150–250 mg to effect). In all dogs, coronary microembolizations were discontinued when LV ejection fraction, determined angiographically, was between 30 % and 40 %. When this target ejection fraction was reached, dogs were randomized for sacrifice at 2 weeks (n = 6) or at 4 months (n = 6) after the last microembolization. In each group, LV function was assessed at the time of randomization and repeated just prior to sacrifice. At the end of the follow-up period (2 weeks or 4 months), the dogs were euthanized and the hearts were removed and prepared for histologic examination. The study was approved by the institution Care of Experimental Animals Committee and conformed to the guiding principles of the American Physiological Society.

Angiographic assessment of LV function

Left ventriculograms were obtained during cardiac catheterization with the dog placed on its right side and were recorded on 35 mm cine at 30 frames/sec during the injection of 20 ml of contrast material (Hypaque meglumine 60 %, Winthrop Pharmaceuticals). Correction for image magnification was made with a radiopaque calibrated grid placed at the level of the LV. Left ventricular end-systolic and end-diastolic volumes were calculated from ventricular silhouettes using the area-length method [16]. Left ventricular ejection fraction was calculated as the difference between end-diastolic and end-systolic volume divided by end-diastolic volume times 100.

Immunohistochemical methods

At the end of the final angiographic assessment, and while under general anaesthesia, the dog's chest was opened via a left thoracotomy, the pericardium was opened and the heart was rapidly removed and placed in ice-cold cardioplegia solution. From each heart, transverse slices (3–4 mm thick) were obtained from the LV at the basal, middle and apical levels. Each slice was cut into several 8 transmural blocks each labeled for anatomical location and rapidly frozen in isopentane cooled to -160 °C in liquid nitrogen. Cryostat sections, 8–10 μm thick, were prepared and double stained with rabbit anti-human collagen type III polyclonal antibody (Chemicon International, Inc.) to visualize interstitial collagen and with Griffonia Simplicifolia Lectin I to visualize capillaries [18]. Immunofluorescent staining was evaluated with an epifluorescent microscope. Collagen was visualized under fluorescent light and capillaries under rhodamine light. Sections obtained from each dog were used for quantifying volume fraction of interstitial collagen, capillary density and oxygen diffusion distance. For each analysis, 10 fields (magnification x 40), away from any infarct, were selected at random for analysis. The volume fraction of interstitial fibrosis defined as the area occupied by interstitial collagen as a percent of total surface area, was quantified using computer-assisted videodensitometry (JAVA Video Analysis Software, Jandell Scientific). Capillary density was calculated using the index capillary per fiber ratio (C/F) [19]. The oxygen diffusion distance was measured as half the distance between two adjoining capillaries [19]. Average myocyte cross sectional area was measured in radially oriented fields using computer-assisted planimetry [11]. LV sections from 6 normal dogs were prepared and examined in an identical fashion.

Data analysis

To establish the presence of progressive LV dysfunction in this canine model of heart failure, comparisons of LV ejection fraction were made within each group between measurements made at the time of randomization and at the time of sacrifice. For this comparison, a Student's paired t-test was used and a p-value < 0.05 was considered significant. For comparison of morphologic measures among normal dogs and the two heart failure groups (those sacrificed at 2 weeks after the last embolization and those sacrificed at 4 months after the last embolization), a one way analysis of variance was performed with alpha set at 0.05. If ANOVA reached statistical significance, pairwise comparisons were made using the Student-Newman-Keuls test. For this test, a probability of ≤ 0.05 was considered significant. All data are reported as the mean ± standard error of the mean.

Results

In dogs sacrificed 2 weeks after randomization, LV ejection fraction was not significantly different between the time of randomization and time of sacrifice (33 ± 2 % vs. 33 ± 3 %) indicating no progression of LV dysfunction. In contrast, in dogs sacrificed 4 months after randomization, LV ejection fraction at the time of sacrifice was significantly lower than that measured at the time of randomization (20 ± 2 % vs. 33 ± 3 %, $p < 0.05$), indicating progressive deterioration of LV function. There was no difference in LV ejection fraction between the 2 groups at the time of randomization (33 ± 2% vs. 33 ± 3 %). LV ejection fraction, however, differed significantly between the two groups at the time of sacrifice (33 ± 3 % vs. 20 ± 2%, $p < 0.05$).

Morphological findings

In LV myocardium of normal dogs, the volume fraction of interstitial collagen that constitutes normal matrix was 3.5 ± 0.3 %, capillary density was 1.00 ± 0.02, oxygen diffusion distance was 11.8 ± 0.1 μm and the average cardiomyocyte cross-sectional area was 616 ± 18 μm^2 (Fig. 1). Reactive interstitial fibrosis was present in viable LV myocardium of all dogs with heart failure with considerable heterogeneity in location. In general, regions of viable myocardium adjacent to old infarcts manifested considerably more interstitial fibrosis compared to other LV regions. The overall volume fraction of interstitial collagen was higher in dogs sacrificed at 4 months compared to dogs sacrificed at 2 weeks (12.2 ± 0.27 % vs. 8.7 ± 0.8, $p < 0.05$) (Fig. 1). This increase in interstitial fibrosis was associated with a significant decrease in capillary density (0.93 ± 0.01 vs. 0.98 ± 0.01, $p < 0.05$) and a significant increase in oxygen diffusion distance (14.6 ± 0.32 μm vs. 12.2 ± 0.09 μm, $p < 0.05$) in dogs sacrificed at 4 months compared to dogs sacrificed at 2 weeks after randomization (Fig. 1). Average cardiocyte cross-sectional area was significantly larger in dogs sacrificed at 4 months compared to dogs sacrificed at 2 weeks (988 ± 37 μm^2 vs. 718 ± 20 μm^2, $p < 0.05$).

Discussion

A wide gap of knowledge has existed for many years with respect to the underlying factors responsible for the progressive deterioration of LV function in patients with heart failure. The lack of understanding of this process may have resulted, in part, from limitations of detailed studies of this phase of the disease in humans and from the lack of an appropriate animal model that can act as surrogate to the human disease. It has become abundantly evident in recent years that preventing the transition to congestive heart failure in patients with established LV dysfunction through early pharmacologic intervention is potentially a desirable alternative to the treatment

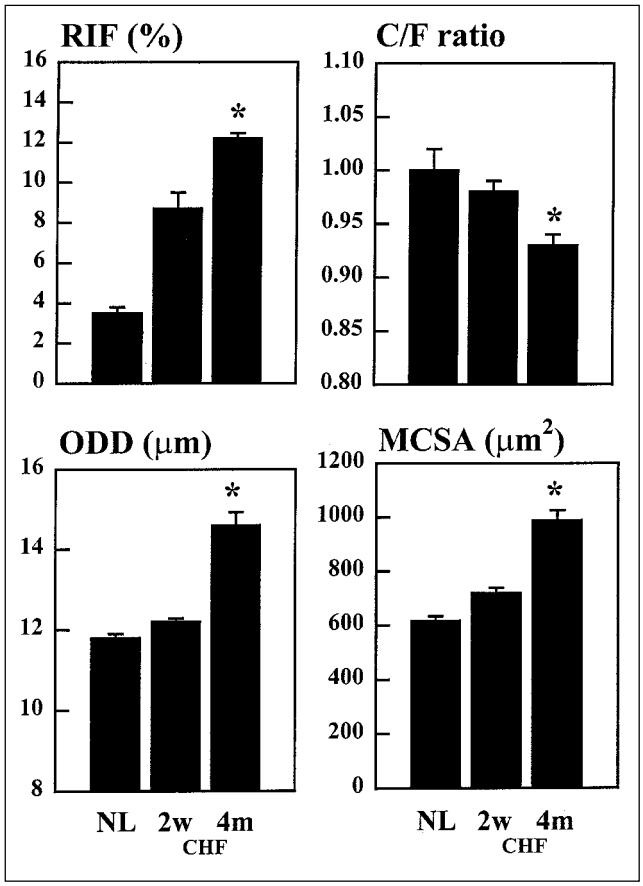

Figure 1. Bar graph (mean ± SEM) depicting changes in volume fraction of reactive interstitial fibrosis (RIF), capillary density (C/F Ratio), oxygen diffusion distance (ODD) and average myocyte cross-sectional area (MCSA) in LV myocardium of normal dogs (NL), dogs with heart failure (CHF) sacrificed at 2 weeks (2w) and 4 months (4m) after the last embolization. *= $p < 0.05$ 2w vs. 4m

of overt end-stage heart failure. Recognition of the positive merits of this approach to therapy in patients with LV dysfunction has spurred considerable interest in research aimed at increasing understanding of the factors that promote progressive deterioration of LV function in patients who are at high risk of developing congestive heart failure. The investigations described in this report, using a canine model of heart failure that manifests progressive LV dysfunction [15, 20], identifies a physiological factor that may play a key role in the progression of LV dysfunction in heart failure. The present study clearly showed that progressive accumulation of collagen occurs in the cardiac interstitium during the development of progressive LV dysfunction and heart failure and is likely to promote hypoxia of the collagen encircled cardiomyocyte.

Cardiomyocyte contractile dysfunction, structural degeneration and loss in the failing heart are often attributed, albeit with very limited direct evidence, to compensatory systems intended to maintain homoeostasis. Key among these is the enhanced activity of the sympathetic nervous system [6], enhanced activity of local and circulating renin-angiotensin system [7, 21] and the development of compensatory cardiac hypertrophy [4]. Activation of the sympathetic nervous system and renin-angiotensin system can have adverse haemodynamic consequences in heart failure by inducing vasoconstriction, promoting sodium and water retention [22] and possibly by exerting a direct cytotoxic effect on cardiomyocytes [23–25]. Although circulating norepinephrine and angiotensin-II are elevated in the failing heart, it is not likely that their concentrations in plasma are sufficiently high to promote direct cell toxicity. Structural degenerative changes of residual cardiocytes have been reported in both patients and animal models of heart failure [8]. According to the concept of the three stages of hypertrophy outlined by Meerson, this adaptation alone can potentially lead to progressive cardiomyocyte degeneration and loss [26]. Considerable interest has emerged in recent years with regard to alterations in the cardiac interstitium of the hypertrophied and failing heart. It is now recognized that accumulation of collagen occurs in the interstitial space of the hypertrophied and failing heart, a process termed "reactive interstitial fibrosis" [27, 28]. The exact mechanism or mechanisms that promote the accumulation of collagen in the interstitial compartment are not known but have been attributed, in part, to enhanced activity of the renin-angiotensin-aldosterone system [27]. The fibrous tissue response of the cardiac interstitium is thought to be responsible for abnormal ventricular stiffness and has also been suggested to account for a spectrum of ventricular abnormalities that involve either the systolic or diastolic phase of the cardiac cycle or both [27]. Although, intuitively, it is easy to imagine how increased accumulation of collagen in the interstitial space can affect ventricular stiffness and consequently diastolic function, its ability to influence LV systolic function is not readily apparent. Interstitial fibrosis has been shown to be associated with reduced capillary density and increased oxygen diffusion distance [11]. In the present study, progressive LV dysfunction was accompanied by increased volume fraction of interstitial fibrosis, decreased capillary density and increased oxygen diffusion distance. The observations may be used to advance the concept that interstitial fibrosis, when present, may be associated with localized chronic hypoxia; a condition which is likely to adversely influence the functional capacity and ultimately the viability of the collagen encircled cardiomyocyte. The increase in the capillary-to-myocyte oxygen diffusion distance appears to be due primarily to expansion of the interstitial space mediated by the deposition of collagen, with some contribution from increase in cardiocyte size. Model studies by Rakusan have shown that a small increase in the oxygen diffusion distance, when the remaining oxygen determinants are normal, can result in hypoxia, while an increase to 70 % of normal can decrease myocardial pO_2 to zero [19]. The concept that interstitial fibrosis can lead to hypoxia of the collagen encircled cardiocyte is supported by studies from our laboratory [29]. In LV tissue obtained from dogs with chronic heart failure, histological evaluations revealed a near 2-fold increase in lactate dehydrogenase activity in constituent myocytes of myocardial regions of severe interstitial fibrosis compared to myocytes of regions manifesting little or no fibrosis [29].

Studies in our laboratory in dogs with heart failure [12] and studies by others in explanted failed human hearts have documented the occurrence of cardiomyocyte apoptosis [13, 14] providing, for the first time, direct evidence of cell loss in the failing heart. In contrast to passive necrosis which occurs in response to lethal injury, apoptosis is an active, strongly regulated, energy requiring process which appears to be under genetic control. That is why the terms "apoptosis" and "programmed cell death" become synonymous [30–32]. It is now recognized that terminally differentiated cells, such as cardiocytes, may also retain the ability to die by apoptotic mechanisms [33]. An important characteristic of cardiomyocyte apoptosis in heart failure is that it occurs with significantly higher frequency in myocardial regions bordering old infarcts compared to regions remote from any infarcts [12–

14]. Myocardial regions bordering old infarcts, the so-called "periinfarct zone", are characterized by severe interstitial fibrosis and are susceptible to ischaemia/hypoxia. In dogs with heart failure, constituent cardiomyocytes of the border zone of old infarcts manifest severe structural degeneration [34], increased lactate dehydrogenase activity [29] and ultrastructural features consistent with apoptosis [12].

Several studies provide support for the role of hypoxia as a potential physiologic trigger of cardiomyocyte apoptosis. Exposure of cultured rat neonatal cardiac myocytes to hypoxia was shown to induce apoptosis as evidenced by positive labeling for nuclear DNA fragmentation [35]. In the same study, enhanced expression of Fas antigen was also noted in response to hypoxia. Consistent with this finding is the observation in cardiac myocytes that hypoxia/reoxygenation can stimulate Jun kinase activity through redox signaling [36]. Exposure of cultured rat cardiac myocytes to hypoxia has also been shown to activate Raf-1 and MAPK [37]. ICE-like proteases have been shown to be involved in the hypoxia-induced apoptosis in cardiac myocytes [38]. In addition, hypoxic stress has also been suggested to increase the expression and nuclear accumulation of specific protooncogenes such as c-fos, c-jun and c-myc that are also involved in the induction of cell cycle progression and apoptosis [39–41].

In conclusion, the observations made in this study indicate that the progression of LV dysfunction in dogs with heart failure is associated with remodeling of the cardiac interstitium. The remodeling of this cardiac compartment is manifested by a progressive increase in reactive interstitial fibrosis, a reduction of capillary density and an increase of oxygen diffusion distance; abnormalities that are likely to promote cardiomyocyte hypoxia. The latter being a potential trigger of cardiomyocyte apoptosis. From this perspective, remodeling of the cardiac interstitium in heart failure can be viewed as a maladaptation that contributes to the progressive deterioration of LV function characteristic of this disease state.

Acknowledgments

Supported by a Grant from the National Institutes of Health, National Heart, Lung and Blood Institute HL49090-04.

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