Left Ventricular Myocardial Edema
Lymph Flow, Interstitial Fibrosis, and Cardiac Function

Glen A. Laine and Steven J. Allen

We hypothesized that both acute and chronic accumulation of myocardial interstitial edema (extravascular fluid [EVF]) would compromise cardiac function. We also postulated that excess fluid within the myocardial interstitial space would potentiate interstitial fibrosis, thus further compromising function. Dogs were divided into three groups: 1) control, 2) chronic pulmonary hypertensive with right heart failure, and 3) chronic arterial hypertensive. The quantity of EVF, expressed as the unitless blood-free (wet weight−dry weight)/dry weight ratio, and interstitial fibrosis (collagen content) were determined and correlated with cardiac function at baseline and after acute elevation of coronary venous pressure and reduction of cardiac lymph flow. Control EVF was 2.90±0.20 (mean±SD), which increased to 3.45±0.16 after acute (3-hour) elevation of coronary sinus pressure. This EVF significantly compromised cardiac function. The EVF in chronically hypertensive dogs and in dogs with chronic right heart pressure elevations was 3.50±0.30 and 3.50±0.08, respectively. End-diastolic left ventricular interstitial fluid pressure increased from a control value of 14.9±3.1 (at EVF=2.9) to 24.8±3.7 (at EVF=3.5). An EVF of 3.5 produced ~30% reduction of the heart’s ability to maintain cardiac output at a left atrial pressure of 15 mm Hg. The compromised function in these chronic models is exacerbated after acute elevation of coronary venous pressure and reduction of cardiac lymph flow. Collagen levels were elevated by at least 20% in the chronic hypertensive dogs and in the nonhypertrophied left ventricles of dogs with chronic right heart pressure elevation. We conclude that acute myocardial edema compromises cardiac function and that chronic right heart pressure elevation and chronic arterial hypertension produce left ventricular myocardial edema, which also compromises function in these common pathological conditions. The presence of myocardial edema in these chronic models also potentiates interstitial fibrosis, leading to a further decrease in the heart’s ability to function normally. (Circulation Research 1991;68:1713–1721)

The presence of excess myocardial interstitial fluid or myocardial edema increases the stiffness and decreases the compliance of the left ventricle.1–3 The accumulation of myocardial edema has been demonstrated in a number of acute and chronic conditions, including cardiac transplantation,4 decreased plasma colloid osmotic pressure during cardioplegia,5 altered microvascular permeability by chronic arterial hypertension,6 elevation of myocardial microvascular pressures,7 and chronic reductions in myocardial lymph flow (Qlv) rate.8 The presence of chronic edema within the interstitium has also been shown to stimulate fibrosis within the myocardial interstitial matrix.9–11 The increased deposition of collagen within the myocardial interstitial space during chronic arterial hypertension and ventricular hypertrophy compromises cardiac function.12 We believe this deposition of collagen may result from the combined effects of cardiac interstitial remodeling during hypertrophy and the presence of small volumes of myocardial edema.6,13

We hypothesized that acute and chronic accumulation of myocardial edema could directly compromise cardiac function in a predictable manner. We also postulated that myocardial fibrosis secondary to small volumes of chronic edema could diminish the heart’s ability to function normally. Both the presence of myocardial edema and the edema-induced deposition of interstitial matrix material could increase myocardial stiffness, increase oxygen diffusion distances, and alter the structural elements of the interstitium, thus compromising cardiac function under both control and stressed conditions.

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Materials and Methods

Animal Preparation

Forty-eight mongrel dogs (drawn from acute and chronic populations) with body mass >15 kg and of either sex were used. Anesthesia was induced with thiopental sodium (20 mg/kg) and maintained with 0.5–1.5% halothane. The dogs were intubated and artificially ventilated with a respirator (Harvard Apparatus, South Natick, Mass.) set to deliver room air at a volume of 25 ml/kg and at a rate appropriate to maintain PaCO₂ between 35 and 40 mm Hg. Fluid-filled catheters were placed into the femoral artery, femoral vein, and left jugular vein. A Fogarty balloon-tipped catheter (8/22F, 43.0 ml), cardiac output thermodilution catheter (7F), and Swan-Ganz (5F) catheter (all from Edwards Laboratories, Santa Ana, Calif.) were placed into the right jugular vein. The chest was then opened using a midline incision, and the major lymphatic trunk draining the left ventricular myocardium was identified and cannulated as previously described.14,15 With the chest open, the Fogarty balloon was secured in place just above the entry of the azygos vein into the superior vena cava. The thermodilution catheter was advanced into the pulmonary artery, and the Swan-Ganz balloon-tipped catheter was sutured into the coronary sinus in a nonocclusive manner as described previously.15 A solid-state microtipped pressure transducer (Millar, Houston) was placed into the left carotid artery and advanced into the left ventricular cavity. A fluid-filled catheter was also inserted into the left atrial appendage and secured with a purse suture.

Five dogs from this group had chronic (2-month) elevation of right ventricular and central venous pressures. We produce chronic right ventricular pressure elevations by banding the pulmonary artery.16–18 As right heart pressures increase, pressure within the thebesian veins and coronary sinus increases. This elevates microvascular pressure within the left ventricle, thus potentiating left ventricular myocardial edema. As microvascular fluid and protein flux increase, a phenomenon referred to as “washdown”19,20 reduces the concentration of plasma proteins in the interstitial fluids, resulting in low-protein edema. Elevation of superior vena caval pressure (SVCP) in this model also reduces the volume of cardiac lymph that can flow into the central venous circulation.21 This model produces right-sided pressures within the heart and vasculature analogous to those seen in right heart failure or cor pulmonale.

Seven dogs were drawn from a chronic population of one-kidney, one-clip Goldblatt hypertensive dogs and prepared in the preceding manner. These dogs had a sustained elevation of systemic arterial pressure for 9±1 weeks before their use in the acute preparation.19 These hypertensive dogs have been shown to exhibit a significant increase in microvascular permeability over time.6,7 The increase in permeability allows plasma proteins from the microcirculation to enter the interstitial space more easily and to produce relatively high-protein edema. In 18 of the dogs from the various groups, porous polyethylene capsules were chronically implanted in the left ventricular myocardium for the measurement of end-diastolic interstitial fluid pressure.6,15 Three porous polyethylene capsules (35-μm pores) were implanted in each left ventricular myocardium. Capsules were placed in the midmyocardium, since interstitial hydraulic continuity produces rapid hydraulic equilibrium within the interstitial space.15 When viewed under the microscope, sections of tissue that contained capsules revealed normal myocytes surrounding loose connective tissue, which had encased the porous polyethylene.

Physiological Measurements and Tissue Analysis

All fluid-filled catheters were connected to Statham pressure transducers (model P23Db, Hato Rey, Puerto Rico), and all data were recorded on a chart recorder (Grass Instrument Co, Quincy, Mass.). The femoral artery catheter was used to measure systemic arterial pressure, and the femoral vein catheter was used to administer fluids or drugs as necessary. The catheter within the left jugular vein was used to measure SVCP above the azygos vein and Fogarty balloon. The Swan-Ganz balloon catheter within the coronary sinus was used to record and manipulate coronary sinus pressure (CSP). Lymph from the left ventricle was allowed to flow through a calibrated pipette and was returned to the superior vena cava system through a set of pressure-tight fittings. This allowed the evaluation of true QLV as SVCP varied.22 This arrangement emulates the normal in vivo circumstances in which myocardial lymph drains into the superior vena cava system. Lymph samples were obtained by temporarily disconnecting the pressure-tight lymphatic catheter and allowing lymph to flow into heparinized test tubes. Cardiac output was repetitively determined by injection of 3 ml cold Ringer’s solution through the thermodilution catheter, and the data were recorded from an Edwards 9520 cardiac output computer. Cardiac function curves were generated by recording cardiac output and left atrial pressure (from the previously implanted left atrial pressure catheter) as incremental volumes of Ringer’s and albumin solutions were infused. Albumin was added to maintain plasma colloid osmotic pressure near control levels. This prevented the accumulation of interstitial fluid resulting from a decrease in colloid osmotic pressure during cardiac output determinations.

The amount of myocardial edema or extravascular fluid (EVF) was obtained from the unitless blood-free (wt weight–dry weight)/dry weight ratio for the left ventricle. After removal of tissue for biochemical and histological analysis, the myocardium was weighed and homogenized, and a lipid extraction with a 2:1 mixture of chloroform and methanol was performed. The homogenate was then dried to a constant weight. A spectrophotometric correction for blood volume was included, since the volume of
blood, and consequently water, found within the coronary vasculature may vary significantly throughout the course of an experiment. Total tissue water content is comprised of vascular water, interstitial water, and cellular water. Each of these water volumes may be accurately determined. Total water content was obtained from the EVF of the tissue sample. Vascular water volume was obtained both spectrophotometrically, using the technique of Pearce et al., and by chromium-51 labeling of red blood cells combined with hematocrit determinations. Interstitial fluid volume was determined using technetium-99m-labeled diethylenetriaminepentaacetic acid as an extracellular marker. Subtraction produces cellular water volume. Four-micron sections were cut from samples of midmyocardium and stained (hematoxylin–eosin). Histological examination of these tissue samples was performed to determine if myocytes were swollen from water accumulation, as seen in ischemic myocardium. A determination of hydroxyproline concentration within the myocardium was carried out using the method described by Weber et al. and confirmed with an amino acid analyzer. Since collagen contains ~13.4% hydroxyproline, the collagen content of the specimen was calculated by multiplying the hydroxyproline content by 7.46. The concentration of collagen was expressed as milligrams of collagen per 100 mg dry ventricular weight. Protein concentration within the lymph draining the myocardial interstitium was determined in each dog by use of a refractometer.

Experimental Protocol

Each protocol was carried out for 3 hours before determining the amount of myocardial edema or EVF present in the left ventricle. The various groups used are summarized in Tables 1 and 2. Eight normotensive controls were used to determine the baseline EVF of the canine left ventricular myocardium.

Myocardial tissue fluid exits the heart primarily in the form of lymph. Since lymph normally flows into the superior vena caval system, elevation of SVCP reduces QLV. To determine the effect of reducing QLV alone for 3 hours, SVCP was elevated to 20 mm Hg in three dogs (Fogarty balloon inflation). In 12 dogs, myocardial microvascular pressure was elevated by inflation of the Swan-Ganz balloon catheter within the coronary sinus, which elevated CSP. This was done since the rate at which fluid enters the myocardial interstitial space can be increased by elevation of pressure within the ventricular microvascular exchange vessels. In these dogs, cardiac function curves were generated before and after 3 hours of CSP elevation. In 13 dogs, QLV was reduced and CSP was elevated simultaneously. Cardiac function curves were also generated for these dogs before and after the combined reduction of QLV and elevation of CSP. Questions have been raised as to whether increases in CSP, such as those in our preparation, could produce a decrease in coronary artery flow that would result in compromised cardiac function. We have not been able to demonstrate a sustained decrease in coronary artery flow after CSP elevation. This observation has recently been confirmed by Ward et al. Baseline left ventricular EVF and cardiac function were determined in five dogs with chronic right ventricular hypertension. Control EVF and cardiac function data for dogs with chronic arterial hypertension were obtained in three dogs; four hypertensive dogs were exposed to elevated CSP for 3 hours. End-diastolic left ventricular interstitial fluid pressure was determined in control and hypertensive dogs at baseline and after CSP elevation. Cardiac lymph samples were obtained from all dogs and underwent analysis for plasma protein concentrations. At the conclusion of each 3-hour protocol, dogs were killed with an overdose of thiopental sodium and 20 ml saturated potassium chloride solution injected intravenously. The left ventricle (without the septum) was removed in a consistent manner from each heart. Since the absolute value for hydroxyproline concentration may vary, both as a function of species and sampling site, full thickness samples of myocardium were removed from a consistent site in the middle of the ventricle. The remaining ventricular muscle was evaluated for the presence of edema by determining EVF as previously described.

Statistical Analysis

All data are presented as mean±SD. Data analysis was carried out on an IBM 4381 using the SAS software package. Groups of data were compared by analysis of variance and F test. After analysis of variance, specific groups were tested using a t statistic with a Bonferroni correction for multiple comparisons. A value of p<0.05 was considered significant.

Results

Data from a total of 48 dogs are presented. Table 1 summarizes the myocardial edema data from 36 dogs. Myocardial EVF was not significantly elevated after 3 hours of reduced QLV alone. Elevation of CSP and the resultant increase in coronary microvascular
pressure caused significant edema formation over the 3-hour protocol (EVF, 3.45±0.16). The combined reduction of \( Q_{LV} \) and elevation of CSP also resulted in edema formation that was greater than the EVF found after CSP elevation alone (EVF, 3.90±0.19). \( Q_{LV} \) under control conditions and during each of the experimental interventions is also shown on Table 1.

Table 2 summarizes the data from 12 additional dogs and the eight normotensive controls. Baseline or control data are presented for three groups: 1) normotensive dogs, 2) dogs with chronic right heart pressure elevations, and 3) dogs with chronic arterial hypertension. Dogs with right-sided pressure elevations had significantly more left ventricular edema than did normotensive controls. The EVF of control dogs with chronic arterial hypertension was also significantly greater than the EVF for normotensive controls. After elevation of CSP in dogs with arterial hypertension, EVF was significantly elevated above that in both the normotensive and hypertensive controls. Control left ventricular interstitial fluid pressure at end diastole was 14.9±3.1 mm Hg.\(^{15} \) Control myocardial interstitial fluid pressure increased to 24.8±3.7 mm Hg when EVF rose to 3.5±0.30 in chronic arterial hypertension. Interstitial fluid pressure continued to increase to 47±7 mm Hg when EVF rose to 4.20±0.15 in hypertensive dogs with CSP elevation. We found that hypertensive dogs with CSP elevation were prone to cardiac arrest when stressed. Consequently, the volume infusions necessary to generate cardiac function curves were not administered to this group.

Figure 1 demonstrates how SVCP, CSP, and \( Q_{LV} \) varied throughout an experimental protocol. Additional time was added to the beginning of this protocol so that variations in \( Q_{LV} \) could be seen after changes in CSP and SVCP. As CSP was elevated and transmicrovascular fluid flux increased, \( Q_{LV} \) was seen to accelerate as well. When SVCP was elevated, the pressure that lymph must overcome in order to flow increased, and \( Q_{LV} \) decreased to <1% of control. After elevation of CSP and SVCP, the fluid that would normally be leaving via the myocardial lymphatics accumulates as myocardial edema.

Figure 2 presents the data for cardiac output plotted as a function of left atrial pressure for a single dog. All control cardiac output curves were obtained at the beginning of each protocol, and a second determination was made after the accumulation of myocardial edema. In Figure 2, a myocardial EVF of 3.9 can be seen to compromise cardiac function over a range of left atrial pressures. As seen in Table 1, cardiac function curves were significantly compromised after elevation of CSP alone for 3 hours. When \( Q_{LV} \) was reduced and CSP was elevated, cardiac function curves were further depressed. Cardiac function curves were also compromised in both the control right heart pressure elevation group and the control arterial hypertension group (Table 2).

Figure 3 presents the data from all dogs in which cardiac output and EVF were determined. Cardiac output at a left atrial pressure of 15 mm Hg is plotted as a percent of control and as a function of EVF or myocardial edema. This figure demonstrates the significant decrease in the heart’s ability to maintain cardiac output at a constant left atrial pressure as
myocardial edema increases within the interstitium. Left ventricular end-diastolic pressure was significantly increased in chronic dogs with elevated EVFs (from 4.5±1.0 to 15.2±2.5 mm Hg). Heart rate was significantly elevated in these halothane-anesthetized dogs (147±12 beats/min) and could not be shown to change after elevation of left atrial pressure or interstitial fluid accumulation.

Table 3 provides a comparison between various left ventricular parameters in control dogs and in those with chronic right heart pressure elevations. Left ventricles (without septum) were weighed after removal of a consistent full-thickness slice of myocardium for histological examination. No statistical increase could be demonstrated in the wet mass between the two groups. Left ventricular dry weights from the two groups, 12.45±0.85 g (normotensive controls) and 12.57±0.90 g (dogs with chronic right heart pressure elevation), also showed no difference. Dogs with chronic arterial hypertension had a left ventricular dry weight of 17.23±1.10 g, which is 28% greater than that for the control and right heart failure groups. We believe this statistically significant increase in left ventricular mass results from left ventricular hypertrophy. The percent blood content of ventricles from each group was not statistically different. The percentage of the left ventricle that is water and the percent of the left ventricle that is interstitium increased significantly in both the right-sided pressure elevation and chronic hypertension models. The percent of the left ventricle that is interstitium was determined using the extracellular marker technetium-99m-labeled diethylenetriaminepentaacetic acid. Knowing the total water volume in the left ventricular myocardium and subtracting blood volume and interstitial volume, we were unable to demonstrate any change in myocyte volume in the chronic right heart pressure elevation model. This was consistent with our histological findings. The quantity of collagen within the left ventricle increased significantly both in the right heart failure model (5.80±0.28) and in the chronic arterial hypertension model (5.1±0.6) when compared with controls (3.90±0.64). This is consistent with the findings of others. The lymph/plasma protein concentration ratio was significantly decreased in the chronic right heart pressure elevation model (from 0.83±0.05 to 0.70±0.03) and increased to 0.88±0.05 in the arterial hypertension model. These changes are consistent with a decrease in microvascular permeability in the
right heart failure (low-protein) model and an increase in microvascular permeability in the chronic arterial hypertension (high-protein) model.

Discussion

We studied the relation between left ventricular edema, myocardial interstitial fibrosis, and cardiac function. The sequential series of events depicted in Figure 4 provides an orderly framework around which a discussion of these relations may be structured.

Myocardial Transmicrovascular Fluid Flux

Myocardial edema originates as fluid that crosses the microvascular exchange vessels and enters the interstitial space. The factors that govern fluid movement into the myocardial interstitium and thus control myocardial tissue fluid volume may be expressed in the form of the Starling equation:

\[ J_v = K_f [(P_c - P_{int}) - \sigma (\pi_c - \pi_{int})] \]  

(1)

where \( J_v \) is the total volume of fluid crossing the microvascular exchange barrier and entering the myocardial tissue spaces, \( K_f \) is the filtration coefficient; \( P_c \) and \( P_{int} \) are hydrostatic pressures within the microvascular exchange vessels and within the interstitial space, respectively; \( \sigma \) is the reflection coefficient; and \( \pi_c \) and \( \pi_{int} \) are colloid osmotic pressures within the microvessels and within the interstitium, respectively. Normally, a volume of fluid equal to \( J_v \) is removed from the heart via the myocardial lymphatics (\( Q_{LV} \)) and via transudation across the surface of the heart into the pericardial sac; thus, the heart does not become edematous. A majority of myocardial tissue fluid exits the heart via the lymphatic system. As such, any reduction in \( Q_{LV} \) should potentiate edema formation. Since the lymphatics drain into the central venous circulation, any elevation in venous pressure tends to decrease \( Q_{LV} \), as seen in Figure 1. In the present study, elevation of SVCP and decreased \( Q_{LV} \) alone did not produce significant left ventricular edema formation over the 3-hour time course of the experimental protocol. This is consistent with findings in other organs that longer time periods may be necessary to generate sufficient volumes of edema for quantitation and that other factors within the Starling equation referred to as “defense mechanisms against edema formation” tend to protect the heart against fluid accumulation during acute insults.\(^{32}\) \( K_f \) is the filtration coefficient and is a function of the hydraulic conductivity of the microvascular exchange barrier as well as the surface area over which water exchange may take place. \( P_c \) is the hydrostatic pressure within the microvascular exchange vessels and acts to force fluid into the myocardial interstitium. When coronary venous pressures (coronary sinus and thebesian veins) were acutely elevated, \( P_c \) was elevated, and we found increased \( Q_{LV} \) (Figure 1) and significant left ventricular myocardial edema formation. This edema formation was significantly exacerbated by simultaneous

<table>
<thead>
<tr>
<th>Group</th>
<th>( n )</th>
<th>LV mass (g)</th>
<th>LV blood (blood %)</th>
<th>LV H_2O (blood-free %)</th>
<th>LV interstitium (%)</th>
<th>LV collagen (g%)</th>
<th>LV lymph (C_l/C_p)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normotensive controls</td>
<td>7</td>
<td>57.1±15.1</td>
<td>12.1±6.1</td>
<td>75.2±0.5</td>
<td>17±3</td>
<td>3.90±0.64</td>
<td>0.83±0.05</td>
</tr>
<tr>
<td>Chronic right heart pressure elevation</td>
<td>5</td>
<td>67.9±11.6</td>
<td>13.5±4.7</td>
<td>78.6±0.7*</td>
<td>26±4*</td>
<td>5.80±0.28*</td>
<td>0.70±0.03*</td>
</tr>
</tbody>
</table>

Values are mean±SD. \( n \), number of dogs; LV, left ventricular myocardium; \( C_l/C_p \), lymph/plasma protein concentration ratio.

*Significantly greater than normotensive controls.

![Figure 4](https://example.com/figure4.png)

**Figure 4.** Flow chart depicting several mechanisms that potentiate myocardial edema formation. Myocardial edema may compromise cardiac function directly or may alter the interstitial matrix, thus indirectly compromising function.
reduction of $Q_{LV}$. The synergistic relation between elevated coronary venous pressures and decreased $Q_{LV}$ potentiates left ventricular edema formation and is represented by the plus sign in Figure 4. It should be noted that our chronic right heart failure model increases the pressure experienced by the left ventricular coronary microvasculature both by elevating pressure to the thebesian veins draining into the right ventricle and, after fluid retention and redistribution, by elevating CSP. The increase in circulating fluid volume during right heart failure elevates central venous pressure and potentiates left ventricular edema formation through the “decreased myocardial lymph flow” mechanism as well (Figure 4).

$P_{int}$ is the hydrostatic pressure within the interstitial space and, as it increases, functions to oppose fluid movement into the interstitium. This increase in interstitial pressure is one of the factors that prevents significant edema formation after reduction of $Q_{LV}$ alone over the short time course of the acute studies. $\pi_c$ and $\pi_{int}$ are the colloid osmotic pressures within the microvessels and interstitium, respectively. The reflection coefficient ($\sigma$) is an index of microvascular permeability. Increases in microvascular permeability (or decreases in $\sigma$) allow additional plasma filtrate to cross the microvascular exchange barrier at normal pressures and to form high-protein edema. Decreases in microvascular permeability restrict plasma filtration and produce low-protein edema.

In the present study, we found that the increased permeability in chronic hypertension produced an elevated baseline level of left ventricular myocardial interstitial fluid, which was significantly exacerbated after elevation of CSP. It is important to note that the left ventricular edema levels found in both chronic arterial hypertension and chronic right heart pressure elevation (EVF, $-3.5$) are not apparent without careful quantitation and may be easily overlooked. As seen in Figure 5, a change in myocardial edema from control to 3.5 represents only a 3% change in myocardial water content and $\sim$12% change in heart weight.

**Myocardial Edema and Interstitial Fibrosis**

The fact that myocardial interstitial fibrosis can compromise cardiac function has been well documented and is portrayed schematically in Figure 4. Our primary concern was with the deposition of myocardial interstitial collagen stimulated by the presence of myocardial edema. Since interstitial fibrosis is a common sequela in response to the presence of interstitial edema, we were not surprised to find that left ventricular myocardial collagen concentration rose in response to the chronic edema associated with arterial hypertension and right heart pressure elevations (Table 3). We had speculated that the fibrotic changes seen in chronic arterial hypertension resulted not only from myocardial remodeling during hypertrophy but also from the presence of myocardial edema. Although we could detect significant volumes of edema in our hypertensive preparations, we were unable to differentiate fibrosis secondary to hyperproteinemia from that resulting from the presence of edema. Therefore, we began using a model of chronic myocardial edema in which no left ventricular myocardial hypertrophy could be demonstrated (Table 3). This model of pure myocardial edema was produced by chronically banding the pulmonary artery. In this preparation, central venous pressure is elevated, thus reducing lymph flow from the myocardial lymphatics and potentiating edema formation. Elevation of pressure within the coronary sinus and thebesian veins also caused an acceleration of fluid movement into the myocardial interstitium, thus further potentiating left ventricular interstitial fluid accumulation. Since the left ventricle in this preparation does not pump against an elevated pressure, no left ventricular hypertrophy takes place. We believe that a majority of the fibrosis seen in this preparation is reactive and not a reparative response to tissue damage. In this model of myocardial edema, significant collagen deposition was found at edema volumes similar to those found in the chronic arterial hypertension preparation.

We may speculate as to what signal is transduced by the fibroblasts to potentiate collagen gene activity in the presence of interstitial edema. Many investigators believe
that the presence of high-protein concentration within edema stimulates the deposition of fibrotic material.\textsuperscript{34} We believe that the protein concentration of the edema may influence the type of collagen deposited but not whether matrix will be formed, since we have seen collagen deposition in both a high-protein edema model (chronic arterial hypertension) and a low-protein edema model (right heart failure).

It has been demonstrated that collagen deposition may be stimulated in fibroblasts that are exposed to elevated pressure.\textsuperscript{39} Since the accumulation of myocardial interstitial edema increases interstitial fluid pressure (Table 2), fibroblasts may respond to this elevated pressure by increasing the strength of the collagen superstructure of the heart via fibrous deposits. It has also been speculated that compromised oxygen delivery, from reduced blood flow, and relative ischemia within the myocardium may lead to interstitial fibrosis.\textsuperscript{40} Ischemia may also result from increased interstitial diffusion distances between the capillaries and myocytes resulting from accumulation of edema (Table 3).\textsuperscript{41,42} In either case, the coronary angiogenesis associated with ischemia or increased workload results in the deposition of new tissue components.\textsuperscript{43} The evaluation of which factors associated with edema formation stimulate collagen deposition remains an active area of investigation. We should point out that, when chronic arterial hypertension is brought under control or systemic venous pressure is lowered in our chronic right heart failure model, edema regresses very slowly, and the elevated collagen concentrations and compromised cardiac function curves (relative to control) remain for extended periods of time.\textsuperscript{44}

**Myocardial Edema and Cardiac Function**

As expressed schematically in Figure 4 and graphically in Figures 2 and 3, both acute and chronic myocardial edema compromise cardiac function. As pointed out in the previous section, cardiac function is also compromised by the deposition of interstitial fibrosis associated with chronic edema. An increase in myocardial interstitial fluid from a control EVF value of 2.9 to 3.5, as seen during chronic arterial hypertension and chronic right heart pressure elevations, represents a change from a control myocardial water content of 75% to 78%. This small change in the percentage of the myocardium that is water significantly compromises function. This same change accounts for a 12% increase in the total weight of the heart (Figure 5). Such changes in myocardial water volume account for a decrease of \(\approx 30\%\) in the heart’s ability to maintain cardiac output at a left atrial pressure of 15 mm Hg (Figure 3). As with other factors that can compromise cardiac function, compromised function due to myocardial edema formation manifests itself as a decrease in cardiac reserve and an inability of the heart to perform when stressed. When the EVF value increased to \(-4\), the amount of water within the myocardial tissue only increased by 5%, and total heart weight increased by 25%. As seen in Figure 3, this increase in interstitial fluid volume resulted in more than a 50% decrease in the heart’s ability to maintain the elevated cardiac output that the controls could develop.

As we have demonstrated in normal hearts, elevation of CSP alone requires several hours to produce sufficient edema to quantitate and to compromise cardiac function.\textsuperscript{7} Acute elevations in healthy subjects, for a period of minutes, will not produce significant myocardial edema or compromise cardiac function.\textsuperscript{26} In contrast, elevation of CSP in subjects with chronic disease, such as elevated systemic venous pressure, produces rapid accumulation of edema and compromised cardiac function.\textsuperscript{7,45}

Several mechanisms may account for the compromised cardiac function seen in the presence of myocardial edema. We believe that all of the following mechanisms may in fact act in concert to compromise function. As myocardial edema accumulates within the interstitial spaces, interstitial pressure rises, thus increasing the stiffness of the myocardium. This stiffness combined with the viscous effects of moving excess interstitial water on a beat-to-beat basis can compromise the heart’s ability to contract efficiently.\textsuperscript{46} Although interstitial collagen has great tensile strength, increases in interstitial volume and pressure may displace the collagen fibers and potentially uncouple or break collagen struts loose from their anchoring points on fibroblasts.\textsuperscript{33,47} Because of the heart’s reliance on a well-organized interstitial matrix around which to contract, a disruption in the collagen structure could also compromise function. As myocardial edema accumulates within the interstitium, the diffusion distance for oxygen to the myocytes increases. This is of particular importance in an organ such as the heart, which operates near maximum oxygen extraction capacity at all times. Recent reports document that myocardial infarctions grow more rapidly in the hearts of subjects with chronic arterial hypertension.\textsuperscript{52} These reports speculate that increased diffusion distances for oxygen and relative ischemia,\textsuperscript{41} due to the presence of myocardial edema, may exacerbate the rapid infarction growth.

We conclude that acute myocardial edema compromises cardiac function and that chronic right heart failure and chronic arterial hypertension also produce left ventricular myocardial edema, which compromises function in these common models of interstitial heart disease. The presence of myocardial edema in these chronic models also potentiates interstitial fibrosis, leading to a further decrease in the heart’s ability to function normally.

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