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TIME COURSE OF MYOCARDIAL INTERSTITIAL EDEMA RESOLUTION AND ASSOCIATED LEFT VENTRICULAR DYSFUNCTION

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Abstract

Objective—Although the causal relationship between acute myocardial edema and cardiac dysfunction has been established, resolution of myocardial edema and subsequent recovery of cardiac function have not. The time to resolve myocardial edema and the degree that cardiac function is depressed after edema resolves are not known. We therefore characterized temporal changes in cardiac function as acute myocardial edema formed and resolved.

Methods—Acute myocardial edema was induced in the canine model by elevating coronary sinus pressure for three hours. Myocardial water content and cardiac function were determined before and during coronary sinus pressure elevation, and after coronary sinus pressure restoration.

Results—Although no change in systolic properties was detected, accumulation of water in myocardial interstitium was associated with increased diastolic stiffness. When coronary sinus pressure was relieved, myocardial edema resolved within 180 min. Diastolic stiffness, however, remained significantly elevated compared to baseline values, and cardiac function remained compromised.

Conclusions—The present work suggests that the cardiac dysfunction caused by the formation of myocardial edema may persist after myocardial edema resolves. With the advent of new imaging techniques to quantify myocardial edema, this insight provides a new avenue for research to detect and treat a significant cause of cardiac dysfunction.

Keywords

Edema-induced dysfunction; edema resolution

INTRODUCTION

Myocardial edema

Myocardial edema, the excess accumulation of fluid in the myocardial interstitium, develops when there is an imbalance between filtration from the coronary microvasculature and removal of interstitial fluid via lymphatic vessels and epicardial transudation [14, 28]. Myocardial edema can form with acute conditions such as ischemia-reperfusion injury [33, 44], myocardial infarction [1, 46], cardiopulmonary bypass [7, 30], or sepsis [13, 17], and

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with chronic conditions such as pulmonary hypertension [9, 27] or arterial hypertension [26]. In each case, myocardial edema forms by causing changes in microvascular filtration or lymphatic drainage [32]. Cardiac dysfunction under these acute and chronic conditions has conventionally been ascribed to either acute impairment of the myocardium or chronic changes leading to cardiac remodeling [32]. However, using acute, nondestructive experimental conditions, cardiac dysfunction in the presence of myocardial edema without myocardial injury has been reported [6, 27, 39], suggesting that the cardiac dysfunction under acute and chronic conditions may also be ascribed to the presence of myocardial edema.

Presence of myocardial edema results in cardiac dysfunction

The presence of myocardial edema has been reported to cause both systolic and diastolic cardiac dysfunction. Myocardial interstitial edema diminishes contractility, decreasing both preload recruitable stroke work [10, 39] and the maximum rate of change in left ventricular pressure during isovolumic contraction [6]. Myocardial edema also inhibits ventricular filling, increasing diastolic chamber stiffness [11, 35, 38] and the isovolumic relaxation time constant [10, 35, 39]. As a consequence, both decreased cardiac output [27, 39] and decreased cardiac efficiency [14] have been reported with increased myocardial interstitial water content. The changes in systolic and diastolic cardiac function in the presence of myocardial edema have been ascribed to several mechanisms. These include changes in myocardial viscoelastic properties [8, 12, 42], disruption of electrical conduction pathways [34], and a decrease in myocardial oxygen supply caused by decreased coronary perfusion and increased myocardial oxygen diffusion distance [41, 45, 50]. Each potential mechanism may persist following edema resolution.

Resolution of myocardial edema is not documented

Although the causal relationship between myocardial edema and cardiac dysfunction has been established, time course of resolution of myocardial edema and the subsequent recovery of cardiac function have not been documented. While characterizing the effect of myocardial edema on cardiac function, Pratt et al. found that myocardial water content remained higher than baseline and cardiac function was still compromised 30 min after relieving elevated coronary sinus pressure [39]. These findings suggest that myocardial edema resolution takes longer than 30 min and cardiac function can be depressed for at least 30 min after an edemagenic stimulus is removed [39]. It is not known how long it takes to resolve the myocardial edema and to what degree cardiac function is depressed after edema resolves. Therefore the purpose of the present study was to characterize the temporal changes in myocardial water content and cardiac function before, during and after exposure to an edemagenic challenge.

METHODS

Animal preparation

Animal care and all experimental procedures were performed in compliance with the Texas A&M University Institutional Animal Care and Use Committee and Guide for the Care and Use of Laboratory Animals. Seven heartworm-free dogs (22 to 30 kg) were anesthetized with 25mg/kg thiopental sodium administered intravenously and were placed in dorsal recumbency on heated water blankets. The dogs were intubated endotracheally and were ventilated mechanically with 100% oxygen using a volume-cycled ventilator (Harvard Apparatus, South Natick, MA). Anesthesia was maintained with isoflurane (~2%). A fluid-filled catheter was introduced into the femoral artery and advanced into the distal aorta. Similarly, a 5F and a 7F Swan-Ganz catheter were inserted into the right jugular vein. The 5F catheter was directed into the cranial vena cava. The chest was then opened with a

median sternotomy. The 7F catheter was directed into the coronary sinus through right atrium and was sutured to the coronary sinus wall. This Swan-Ganz catheter in the coronary sinus was used to obstruct flow and increase coronary sinus pressure while simultaneously measuring coronary sinus pressure. A loop of umbilical tape was placed around the caudal vena cava just before its confluence with the right atrium. Two pairs of ultrasonic crystals (Sonometrics Corporation, London, ONT, Canada) were inserted into the left ventricular subendocardium, with one pair across the freewall-septal axis and the other pair spanning the base-apical axis. A 5F micro-tipped pressure transducer (MPC-500, Millar Instruments, Houston, TX) was introduced transmurally via the apex into the left ventricle. The transducer position within the ventricle was maintained by marking the catheter. To prevent the evaporative fluid losses, the open chest was covered with plastic wrap.

Data acquisition

The fluid-filled catheters used to measure pressure in the aorta, cranial vena cava, and coronary sinus were connected to pressure transducers (Isotec Disposable Transducer, Healthdyne Cardiovascular, Irvine, CA) zeroed to the level of the right atrium. The signals from pressure transducers were amplified, digitally converted (MacLab/8, Analog Digital Instruments, Castle Hill, NSW, Australia), and simultaneously displayed and recorded at 200 Hz by computer. The signals from the sonomicrometry crystals and the left-ventricular pressure transducer were displayed and recorded on another computer at 200 Hz, allowing us to generate left ventricular pressure-volume loops.

Myocardial edema quantification

Myocardial water content was determined from myocardial biopsies using a microgravimetric technique reported previously [7, 15]. Briefly, transmural biopsy samples (6 to 8 mm³) were obtained with biopsy forceps (Cordis Corporation, Miami, FL) using the same hole created for the left ventricular pressure catheter. Specific gravity of each sample was determined using a linear density gradient prepared from a mixture of kerosene (specific gravity 0.99) and bromobenzene (specific gravity 1.08). The density gradient was calibrated with K₂SO₄ solutions of known specific gravity, and linearity was confirmed. Each myocardial sample was gently loaded into the density gradient column, and the depth of each sample was recorded at 2 min. Biopsies were obtained in duplicates, and the mean specific gravity was used to determine myocardial water content (MWC, in %) using Eq. 1.

$$\text{MWC} = \left\{ 1 - \left[\frac{(SG_{myo} - 1)}{\left(1 - \frac{1}{SG_{dry}}\right)} \cdot SG_{myo} \right] \right\} \cdot 100 \quad (1)$$

where SG_{myo} and SG_{dry} are the specific gravities of the myocardial sample and of dry myocardium, respectively. SG_{dry} was determined at the end of the experiment using isolated left ventricular free wall samples. After trimming all fat and valvular tissue, left ventricular wall samples were weighed and dried at 60°C in an oven to a constant weight. With wet (W) and dry (D) weights, SG_{dry} was calculated using Eq. 2, assuming that SG_{dry} did not change during the experiment [7, 15].

$$SG_{dry} = \frac{1}{1 - \left[\frac{W \cdot (SG_{myo} - 1)}{D \cdot SG_{myo}} \right]} \quad (2)$$

Data analysis and left ventricular function assessment

After the experiment, left ventricular pressure and sonomicrometric (base-apical and free wall-septum axes length) data were analyzed using the LV Loop Analysis Tool (ADInstruments, Colorado Springs, CO). Left ventricular volume was calculated using Eq. 3, assuming the volume of an ellipsoid with equal minor axes lengths (i.e., the free wall-septum axis length),

$$V = \frac{4}{3} \cdot \pi \cdot \left(\frac{BA}{2}\right) \cdot \left(\frac{FS}{2}\right)^2 \quad (3)$$

where BA and FS are the base-apical and free wall-septal axes, respectively. The left ventricular pressure-volume loops were plotted and assessed visually to confirm the integrity of all recorded data. The first and last incomplete loops were eliminated from analysis. Left ventricular systolic function was assessed by calculating the systolic contractility (E_{sys}), the maximum rate of change of left ventricular pressure (dp/dt_{max}), preload recruitable stroke work ($PRSW$), and relative time in systole (T_s/T_d). E_{sys} was determined from the slope of the linear regression analysis of the end-systolic pressure-volume relationship. $PRSW$ was determined from the slope of the linear regression analysis of the stroke work and end-diastolic volume relationship. T_s/T_d was estimated from the ratio of left ventricular systolic duration to diastolic duration. Left ventricular diastolic function was assessed using ventricular chamber stiffness (E_{dia}) and the time constant of isovolumic relaxation (τ). E_{dia} was derived from the slope of the linear regression analysis of the end-diastolic pressure-volume relationship. The value of τ was determined by fitting an exponential function (Eq. 4) to the left ventricular pressure data using non-linear least squares regression [31, 47].

$$P(t) = P\left(\frac{dp}{dt}\right)_{min} \cdot e^{-\frac{t}{\tau}} \quad (4)$$

where $P\left(\frac{dp}{dt}\right)_{min}$ is the left ventricular pressure at dp/dt_{min} and t is time. For each pressure-volume loop, ventricular pressure data were analyzed beginning at the time of dp/dt_{min} ($t=0$) to the first point where the pressure was less than or equal to end-diastolic pressure.

Experimental Protocol

All the dogs were surgically prepared, and arterial pressure, central venous pressure, coronary sinus pressure, left ventricular pressure, and base-apical and free wall-septum axis lengths were continuously monitored. Baseline (BL0) left ventricular function and hemodynamic variables were measured. Data were recorded for 15 sec to determine the isovolumic τ and dp/dt_{max} at baseline. Data were recorded for another 15 sec while the caudal vena cava was progressively occluded to allow determination of $PRSW$, E_{sys} , and E_{dia} at baseline (BL0). Myocardial biopsy samples were obtained and loaded on the density gradient. This sequence was repeated each time data were recorded throughout the experiment. 30 min after the first baseline measurement, second baseline measurements were made (BL30). Immediately following the second baseline measurement, the balloon of the Swan-Ganz catheter in the coronary sinus was inflated for 180 min to induce coronary venous hypertension and acute myocardial edema. Data were recorded for 60 min (CSH60), 120 min (CSH120) and 180 min (CSH180) after coronary sinus pressure elevation. Then the balloon in the coronary sinus was deflated and the dogs were allowed to recover for 180 min. Data were recorded at 60 min (REC60), 120 min (REC120) and 180 min (REC180) during the recovery period. Myocardial biopsies during recovery were obtained at 90 min (REC90) and 180 min (REC180). At the end of the experiment, dogs were euthanized while under anesthesia with intravenous administration of saturated solution of potassium chloride,

and the left ventricular free wall was rapidly removed for SG_{dry} determination. The pulmonary artery and right ventricle were then inspected and each dog was verified to be heartworm free.

Statistical Analyses

Data are presented as mean $\pm$ SEM. Linear regression analysis was performed with a standard statistical software package (SigmaPlot 11, Systat Software Inc.). Variables during the baseline period, the 3-hr coronary sinus hypertension period, and the 3-hr recovery period were compared using one-way repeated measures analysis of variance (SigmaPlot 11, Systat Software Inc.). All pairwise multiple comparisons tests were performed using the Student-Newman-Keuls Method. A value of $p < 0.05$ was considered significant.

RESULTS

Hemodynamic variables

One dog presented with an arrhythmia at baseline and periodically throughout the experiment; therefore data from this dog were eliminated from analysis. Coronary sinus pressure, mean arterial pressure, central venous pressure, heart rate, end-systolic volume, and cardiac output for the remaining six dogs are listed in Table 1. No significant variations in hemodynamic variables at the two baseline measurements were observed. Coronary sinus pressure was elevated from 0.9 ± 0.7 to 14.5 ± 1.0 mmHg for the 3-hr period. Coronary sinus hypertension led to a significant decrease in cardiac output and ejection fraction. By the end of the 3-hr recovery period, coronary sinus pressure had returned to values not significantly different from baseline. However, cardiac output and ejection fraction remained significantly lower after the 3-hr recovery period. No significant differences in mean arterial pressure, central venous pressure, and heart rate were observed between baseline, 3-hr coronary sinus hypertension period, and 3-hr recovery period.

Myocardial water content

Figure 1 depicts the myocardial water content recorded at different time periods. During the 3-hr period of coronary sinus hypertension, myocardial water content was significantly elevated ($76.8 \pm 0.3\%$ at BL0 versus $78.9 \pm 0.6\%$ at CSH60, $78.5 \pm 0.7\%$ at CSH120, and $79.7 \pm 0.7\%$ at CSH180). During the 3-hr recovery period, myocardial water content returned to values not significantly different from baseline (78.0 ± 0.6 at REC90 and 77.4 ± 0.2 at REC180). Myocardial water content at the end of the 3-hr recovery period (REC180) was significantly lower than that of CSH180.

Left-ventricular pressure-volume loop analysis

Representative left-ventricular pressure-volume loops at BL0, CSH180, and REC180 and their corresponding end-systolic pressure volume relationships, end-diastolic pressure volume relationships, and preload recruitable stroke work plots are depicted in Fig. 2.

Systolic function

Variables used to assess left ventricular systolic function are listed in Table 2. There were no significant differences in systolic contractility (E_{sys}), maximum rate of change in left ventricular pressure (dp/dt_{max}), preload recruitable stroke work ($PRSW$), or relative time in systole (T_s/T_d) between the two baseline measurements (BL0 and BL30). Coronary sinus pressure elevation did not result in significant changes in these four variables. Furthermore, during the recovery period, the values of these parameters were not significantly different from baseline.

Diastolic function

Variables used to assess left ventricular diastolic function are listed in Table 3. No significant difference in these variables was observed between the two baseline measurements (BL0 and BL30). The time constant of isovolumic relaxation did not change significantly during the experiment. End-diastolic volume decreased during 3-hr coronary sinus hypertension period, although not significantly lower than baseline values. However, during the 3-hr recovery period, end-diastolic volume was significantly lower than baseline values. End-diastolic pressure during the 3-hr coronary sinus hypertension period and the 3-hr recovery period were not significantly different from baseline values. Left-ventricular chamber stiffness was significantly elevated during the 3-hr coronary sinus hypertension period and the 3-hr recovery period. Figure 3 depicts the relationship between myocardial water content and left ventricular chamber stiffness.

DISCUSSION

Although previous investigations have demonstrated the cardiac dysfunction in the presence of edema, the present work is the first to investigate the time course of edema resolution as well as cardiac function following edema resolution. In accord with previous studies [39], coronary sinus hypertension induced a significant increase in myocardial interstitial water content (Fig. 1). Although no change in systolic properties was detected, accumulation of water in the myocardial interstitium was associated with an increased diastolic stiffness (Fig. 3). When coronary sinus pressure was relieved, myocardial edema resolved within 180 min. However, diastolic stiffness remained significantly elevated compared to baseline values, and cardiac function remained compromised. Thus, the present work suggests that the formation of myocardial edema may lead to depressed cardiac function that persists after myocardial edema is resolved. Unlike previous studies that elevated coronary sinus pressures to 35–50 mmHg [25, 27], the relatively small increase in pressure used in this study suggests this effect may be clinically relevant under a wide range of conditions that elicit similar changes in coronary microvascular pressures.

Experimental challenges

The three most notable methodological limitations of the present study are common to acute experimental investigations. First, it is possible that the observed cardiac dysfunction may be the direct result of anesthesia and surgical trauma. Previous studies have reported that anesthesia and surgical trauma in control groups cause little or no change in cardiac output [6, 27, 39]. Not only did coronary sinus hypertension in experimental groups increase myocardial water content relative to these control groups, but also compared to their own baseline measurements. Therefore, the observed cardiac dysfunction in the present study cannot be ascribed to anesthesia or surgical trauma. Second, it is possible that the longer experimental period (6-hr) may have contributed to cardiac dysfunction. However, in previous studies that lasted for more than 4 hours, no significant changes were observed in systolic (E_{sys} and $PRSW$) or diastolic (τ , EDV, EDP, E_{dia}) function in the control group animals [39]. Cardiac function was compromised only in the experimental group animals exposed to coronary sinus hypertension. Furthermore, it is expected that if the extended experimental period itself had an effect on diastolic function, it would have also affected systolic function. No significant changes in systolic function were observed in the present study. Third, unlike previous studies [39], no intravascular saline was administered during the experiment to maintain arterial pressure. We chose not to administer saline to minimize the confounding effects on end-diastolic pressure and volume. The choice not to administer saline can explain why our study resulted in a decrease in end-diastolic volume compared to previous studies [39]. The change in diastolic stiffness, however, is nonetheless similar.

Acute myocardial edema induced by coronary sinus hypertension is easily reversible

Despite its clinical relevance, the difficulty in reversing the complex interventions used to induce myocardial edema has led to a notable lack of studies focusing on the characterization of resolution of myocardial edema and recovery of cardiac function. Perhaps the fundamental limitation has been that common procedures produce multiple edemagenic stimuli, each of which may be difficult to reverse. For instance, cardiopulmonary bypass induces edema through cardiac arrest, ischemia, and hemodilution [32]. Hemodilution in particular can take too long to reverse to study the process of edema resolution [16]. Furthermore, ischemia directly impacts cardiac function, masking the potential effects of myocardial edema. We therefore used coronary sinus hypertension, which induces myocardial edema by increasing microvascular pressure and thus microvascular filtration [32]. Not only does edema form relatively quickly, this particular insult can be quickly reversed.

Active processes are minimally affected by the experimental preparation

Previous studies have measured coronary blood flow and myocardial oxygen consumption to address the overall balance between myocardial blood flow and metabolism before and during the onset of acute myocardial edema [21, 41]. Such measurements have been deemed necessary, because significant decreases in the perfusion pressure (by increasing coronary sinus pressure) may not be compensated by the coronary flow reserve [8, 18, 45]. Similarly, some investigators believe that edema may increase the oxygen diffusion distance [10, 27], and an increase in myocardial interstitial fluid pressure may increase coronary vascular resistance [27, 50]. Indeed, studies suggest edema could yield an increase in diffusion distance [2, 3]. Furthermore, experimental studies have correlated changes in intramyocardial pressure to changes in the zero-flow pressure as well as peak diastolic flows [19, 43]. Collectively, reduced coronary blood flow and increased oxygen diffusion distance may lead to a mismatch in myocardial oxygen supply and demand, resulting in compromised cardiac function and a sustained myocardial ischemia-induced inflammatory response [33, 41, 51]. However, it has been long-established that a mismatch in myocardial oxygen supply and demand has a profound and immediate impact on energy utilization, and thus manifests in a change in myocardial energy-dependent (active) processes and function. Indices of systolic function such as E_{sys} , $PRSW$, and dP/dt_{max} [5, 23] and index of diastolic relaxation, τ [4, 20, 22, 52] has been reported to be altered with a mismatch in myocardial oxygen supply and demand. In this study, we could detect no changes in E_{sys} , $PRSW$, dP/dt_{max} , or τ . The lack of changes in τ is particularly telling, because τ is the accepted index used to detect changes in myocardial active relaxation [52]. Therefore, the observed diastolic dysfunction may not be ascribed to changes in active relaxation secondary to a reduced oxygen supply. The increase in coronary sinus pressure used in the present study (14 mmHg) is significantly lower than 30–50 mmHg reported previously [8, 39, 45], which may have limited the impact on coronary blood flow and resulting ischemia and ischemia-induced inflammation.

Acute myocardial edema induced by coronary sinus hypertension leads to diastolic dysfunction

Previous studies using coronary sinus hypertension to characterize the impact of myocardial edema have reported systolic and diastolic dysfunction in the presence of myocardial edema [6, 11, 25, 27, 39]. However, our results indicate that moderate coronary sinus hypertension primarily inhibits the passive relaxation phase of diastolic function (Fig. 3). We observed no change in the active phase of diastolic relaxation, and no change in heart rate or indices of systolic function. Furthermore, the higher levels of coronary sinus hypertension (35–50 mmHg) are reported to increase left ventricular diastolic pressure and thus the left ventricular diastolic stiffness [8, 42]. However, increased diastolic stiffness during the 3-hr

recovery period in our study cannot be ascribed to this mechanism. Our results therefore may be different, because we elected to use a more modest increase in coronary sinus pressure. The observed increase in diastolic stiffness in the present study during coronary sinus hypertension as well as after relieving the coronary sinus pressure is consistent with a previous study limited to a 30 min recovery period [39].

Potential mechanisms

Diastolic dysfunction did not resolve by the end of the 3-hr recovery period. The primary mechanisms, previously identified to cause compromised cardiac function in the presence of myocardial edema, may be at work after edema resolution. It is possible that the myocardial interstitial matrix and its physico-chemical properties are altered. In the presence of myocardial edema, the quantity of water is increased, thus requiring movement of excess free-flowing fluid on a beat-to-beat basis [48]. The presence of myocardial edema may also affect conformation as well as composition of the matrix constituents, affecting interstitial permeability to fluids [40] and excluded volume [36, 37]. Furthermore, it is possible that the presence of myocardial edema may directly disrupt the myocardial interstitial matrix either via physical damage or degradation of the constituents [49]. Collectively, these changes may affect the viscoelastic properties of the myocardial interstitial matrix, resulting in persistent diastolic dysfunction [49]. Furthermore, the altered mechanotransduction has also been reported to directly affect the cardiac function by initiating several signal transduction pathways [24, 29].

Perspectives

The present work expands the list of potential mechanisms responsible for cardiac dysfunction following numerous clinical interventions [14, 32]. Furthermore, we demonstrated that changes in coronary sinus pressure do not have to be large to have a significant impact. Relatively innocuous interventions, such as fluid volume resuscitation, may have persistent effects on cardiac function. Perhaps the lasting effects of myocardial edema had not been appreciated because myocardial edema was so difficult to measure clinically. Not only has ischemia and inflammation been much easier to detect, but they may have masked the effects of myocardial edema. With the new insights of the present work, there is a new urgency to apply relatively new techniques [14] to measure myocardial edema to detect an underappreciated cause of persistent cardiac dysfunction. The present study also catalyzes future studies focused on the cause and reversal of the detrimental effects of edema formation that persist well after edema resolves.

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Figure 1.

Myocardial water content (% mean ± SEM) was recorded at 0 and 30 min of baseline (BL0 and BL30); at 60, 120 and 180 min of acute coronary sinus hypertension (CSH60, CSH120 and CSH180); and at 90 and 180 min of recovery from acute coronary sinus hypertension (REC90, REC180). Myocardial water content increased significantly (compared to baseline, indicated by *, $p < 0.5$) during coronary sinus hypertension, but returned to baseline levels within the 3-hr recovery period. Myocardial water content at the end of the recovery period (REC180) was significantly lower than that during the coronary sinus hypertension period (indicated by †, $p < 0.5$).

Figure 2.

Representative left ventricular pressure-volume loops and relationships between left ventricular pressure (LVP) and volume (LVV); end-diastolic pressure (P_{ed}) and volume (V_{ed}); and stroke work (SW) and end-diastolic volume (V_{ed}). End-diastolic volume decreased, end-diastolic pressure increased, and left ventricular chamber stiffness (E_{dia} , slope of P_{ed} and V_{ed} relationship) increased significantly in response to the 3-hr period of coronary sinus hypertension. These changes persisted after the 3-hr recovery period. However, no significant change in the end-systolic pressure volume relationship (E_{sys} , slope of end-systolic pressure (P_{es}) and volume (V_{es}) relationship) and preload recruitable stroke work ($PRSW$, slope of SW and V_{ed} relationship) was observed.

Figure 3.

Relationship between myocardial water content and left ventricular chamber stiffness. Arrows indicate progression of left ventricular chamber stiffness and myocardial water content with time. Although myocardial water content returned to baseline level after the 3-hr recovery period (following the 3-hrs of coronary sinus hypertension), left ventricular chamber stiffness remained significantly elevated and did not return to baseline level. (■ – baseline, BL; ○ –during coronary sinus hypertension period, CSH; ×–during recovery period, REC)

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Table 1

Hemodynamic variables measured at 0 and 30 min of baseline (BL0 and BL30); at 60, 120 and 180 min of coronary sinus hypertension (CSH60, CSH120 and CSH180); and at 60, 120 and 180 min of recovery from coronary sinus hypertension (REC60, REC120 and REC180). In response to coronary sinus pressure (CSP) elevation (from 0.9±0.7 to 14.5±1.0 mmHg) for three hours, mean arterial pressure (MAP), central venous pressure (CVP), heart rate (HR), and end-systolic volume (ESV) did not change significantly. However, cardiac output (CO) was significantly decreased during coronary sinus hypertension period and during recovery period.

Period	CSP (mmHg)	MAP (mmHg)	CVP (mmHg)	HR (min ⁻¹)	ESV (ml)	CO (L/min)
BL0	1.0±1.0	82.7±4.1	3.1±0.6	131.7±7.3	56.3±8.5	2.44±0.42
BL30	0.8±1.1	75.8±6.0	3.3±0.9	128.5±7.3	58.8±10.2	2.27±0.39
CSH60	14.9±1.4 [*]	76.7±5.7	3.1±0.8	133.9±7.5	58.3±10.1	2.00±0.29 [*]
CSH120	14.6±2.1 [*]	73.9±7.0	4.1±0.8	137.8±7.1	58.3±10.5	1.82±0.31 [*]
CSH180	14.1±1.7 [*]	74.4±8.6	5.0±0.7	146.7±6.4	59.9±11.5	1.69±0.33 [*]
REC60	1.5±1.1 [‡]	75.2±8.6	4.8±0.6	136.8±5.8	59.9±13.0	1.97±0.39 [*]
REC120	1.7±1.0 [‡]	69.6±7.9	4.3±0.9	136.6±5.6	59.5±12.8	1.86±0.35 [*]
REC180	1.1±2.0 [‡]	71.6±8.9	4.4±0.7	138.8±6.4	59.7±10.4	1.68±0.36 [*]

^{*} indicates significant change compared to baseline values (p<0.05).

[‡] indicates significant change compared to values during coronary sinus hypertension (p<0.05).

Table 2

Systolic contractility (E_{sys}), maximum rate of change of left ventricular pressure (dP/dt_{max}), preload recruitable stroke work ($PRSW$), and relative time in systole (T_s/T_d) were calculated to assess the effect of myocardial edema on left ventricular systolic function. Coronary sinus hypertension and the subsequent myocardial edema did not affect left ventricular systolic function.

Period	E_{sys} (mmHg/ml)	dP/dt_{max} (mmHg/sec)	$PRSW$ (mmHg)	T_s/T_d
BL0	4.0±1.0	1426.9±129.6	50.1±4.1	0.86±0.0
BL30	4.1±1.18	1422.2±129.4	51.3±3.9	0.81±0.0
CSH60	4.2±0.9	1472.4±98.9	58.2±8.2	0.84±0.0
CSH120	4.6±1.0	1543.0±157.6	50.6±4.5	0.91±0.0
CSH180	4.6±1.5	1449.4±90.8	51.7±5.4	0.86±0.0
REC60	6.5±1.8	1459.3±58.6	57.7±5.5	0.88±0.1
REC120	7.4±2.9	1398.4±70.3	54.0±5.5	0.89±0.1
REC180	5.3±0.8	1435.5±43.4	50.0±8.6	0.91±0.1

Table 3

Coronary sinus hypertension and the subsequent myocardial edema did not affect the left ventricular isovolumic relaxation time constant (τ) or the end-diastolic pressure (EDP). End-diastolic volume (EDV) decreased during the 3-hr period of coronary sinus hypertension, although significant reduction in EDV was recorded during the recovery period. Left ventricular chamber stiffness (E_{dia}) was significantly elevated throughout during the 3-hr period of coronary sinus hypertension as well as the 3-hr recovery period.

Period	τ (sec)	EDV (ml)	EDP (mmHg)	E_{dia} (mmHg/ml)
BL0	21.4±1.8	74.5±10.4	0.4±1.9	0.18±0.02
BL30	23.4±2.4	74.1±11.6	1.8±2.8	0.19±0.02
CSH60	24.5±2.0	71.6±10.8	2.6±1.6	0.25±0.02 *
CSH120	24.7±2.4	69.6±11.7	3.8±1.9	0.30±0.02 *
CSH180	23.8±3.2	70.6±13.0	3.2±2.2	0.31±0.02 *
REC60	25.1±3.5	69.4±13.8	5.5±1.9	0.25±0.03 *
REC120	19.4±4.0	66.8±12.4 *	1.2±2.7	0.28±0.02 *
REC180	20.7±3.9	66.2±10.0 *	2.2±2.6	0.29±0.02 *

* indicates significant change compared to baseline values ($p<0.05$).