Effects of hypoproteinemia-induced myocardial edema on left ventricular function


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Miyamoto, M., D. E. McClure, E. R. Schertel, P. J. Andrews, G. A. Jones, J. W. Pratt, P. Ross, and P. D. Myerowitz. Effects of hypoproteinemia-induced myocardial edema on left ventricular function. Am. J. Physiol. 274 (Heart Circ. Physiol. 43): H937–H944, 1998.—In previous studies, we observed left ventricular (LV) systolic and diastolic dysfunction in association with interstitial myocardial edema (IME) induced by either coronary venous hypertension (CVH) or lymphatic obstruction. In the present study, we examined the effects of myocardial edema induced by acute hypoproteinemia (HP) on LV systolic and diastolic function. We also combined the methods of HP and CVH (HP-CVH) to determine their combined effects on LV function and myocardial water content (MWC). We used a cell-sparing device to lower plasma protein concentration in HP and HP-CVH groups. CVH was induced by inflating the balloon in the coronary sinus. Six control dogs were treated to sham HP. Conductance and micromanometer catheters were used to assess LV function. Contractility, as measured by preload recruitable stroke work, did not change in control or HP groups but declined significantly (14.5%) in the HP-CVH group. The time constant of isovolumic LV pressure decline (τ) increased significantly from baseline by 3 h in the HP (24.8%) and HP-CVH (27.1%) groups. The end-diastolic pressure-volume relationship (stiffness) also increased significantly from baseline by 3 h in the HP (78.6%) and HP-CVH (42.6%) groups. Total plasma protein concentration decreased from 5.2 ± 0.2 g/dl at baseline to 2.5 ± 0.0 g/dl by 3 h in the HP and HP-CVH groups. MWC of the HP (79.8 ± 0.2%) and HP-CVH groups (79.8 ± 0.2%) were significantly greater than that of the control group (77.8 ± 0.3%) but not different from one another. In conclusion, hypoproteinemia-induced myocardial edema was associated with diastolic LV dysfunction but not systolic dysfunction. The edema caused by hypoproteinemia was more than twice that produced by our previous models, yet it was not associated with systolic dysfunction. CVH had a negative inotropic effect and no significant influence on MWC.IME may not have the inverse causal relationship with LV contractility that has been previously postulated but appears to have a direct causal association with diastolic stiffness as has been previously demonstrated.

colloid osmotic pressure; contractility; compliance; myocardial water content

INTERSTITIAL MYOCARDIAL EDEMA OCCURS IN NUMEROUS CLINICAL AND EXPERIMENTAL CONDITIONS AND HAS GENERALLY BEEN ASSOCIATED WITH LEFT VENTRICULAR (LV) DYSFUNCTION. DESPITE THIS FREQUENT ASSOCIATION, A CAUSAL RELATIONSHIP HAS NOT BEEN ESTABLISHED. IN ORDER TO ESTABLISH A CAUSAL RELATIONSHIP BETWEEN INTERSTITIAL MYOCARDIAL EDEMA AND VENTRICULAR DYSFUNCTION, THE EXPERIMENTAL DATA SHOULD FULFILL SEVERAL BASIC CRITERIA. HOWEVER, BEFORE THESE CRITERIA ARE CONSIDERED, VENTRICULAR DYSFUNCTION

should be considered in terms of the three independent properties of contraction and relaxation: contractility, rate of active relaxation, and stiffness. Given this definition, the criteria used to establish a causal relationship between interstitial myocardial edema and ventricular dysfunction should be applied independently to each of these properties of ventricular function. One criterion that should be met is that interstitial myocardial edema should invariably result in ventricular dysfunction regardless of the method by which the edema is induced. For the properties outlined above, this means that edema should result in one or more of the following changes: a decline in contractility, a prolongation of the rate of active relaxation, and/or an increase in diastolic stiffness. Another criterion that should be met is that the degree of interstitial edema [myocardial water content (MWC)] should correlate with the degree of dysfunction. Although this relationship need not be linear, there should be some form of significant correlation. The literature on these issues strongly supports a relationship between stiffness and MWC (3, 20, 24) but is more controversial for contractility (1, 4, 7, 10, 14, 15, 17, 18, 22). The active phase of relaxation has not been as extensively studied (4, 16–18, 21, 22).

To examine these relationships in the context of the criteria described above, we previously performed two studies in dogs in which interstitial myocardial edema was produced by independent methods: coronary venous hypertension (CVH) and cardiac lymphatic obstruction (16, 21). CVH resulted in mild edema (0.3% increase over control group) that was accompanied by a decline in contractility, increase in the time constant of isovolumic relaxation (τ), and increase in diastolic stiffness (21). Cardiac lymphatic obstruction resulted in less edema (0.14% increase over control group) but caused a similar decrease in contractility and increase in τ but no change in stiffness (16). With the assumption that the two methods of creating edema affected these functional parameters by the change in MWC, we concluded that contractility and τ may be more sensitive to increased water content than stiffness is. Our data were consistent with that from some other laboratories in terms of directional change, if not in terms of degree.

To further examine the hypothesis that interstitial myocardial edema causes contractility to decline and τ and stiffness to increase, we performed a study in which interstitial myocardial edema was created by a third and independent method that involved lowering plasma protein concentration. We used techniques to examine ventricular function that were identical to those of our previous studies in a group of dogs during...
baseline conditions and after plasma protein concentration was lowered to 50% of baseline. In a separate group of dogs, we combined the hypoproteinemia (HP) method of inducing edema with that of CVH to determine their combined influence on water content and ventricular function. We also measured coronary blood flow and arteriovenous oxygen content difference to assess myocardial oxygen consumption, coronary vascular resistance, and mechanical efficiency.

MATERIALS AND METHODS

Experimental preparation. Twenty-one mature male, heartworm-free, semiconditioned dogs (wt range 20.5–25.5 kg) were anesthetized by intravenous pentobarbital sodium (25–30 mg/kg) followed by continuous administration (5 mg·kg⁻¹·h⁻¹). The dogs were intubated, placed in dorsal recumbency on a water-circulating heating blanket, and ventilated with 100% oxygen using a volume of 15–20 ml/kg and respiratory rate of 8–15 breaths/min. Isotonic sodium chloride was administered as a continuous infusion of 5 ml·kg⁻¹·h⁻¹. Arterial pH, P CO₂, and P O₂ were measured periodically (ABL30, Radiometer, Denmark) during instrumentation and maintained within normal limits by adjusting tidal volume and ventilatory rate and by intravenous administration of sodium bicarbonate. The left femoral artery was cannulated for arterial blood pressure measurement and blood sampling for blood gas measurements. The left femoral vein was cannulated for fluid and drug administration. The right femoral artery was cannulated for microsphere reference volume (V) over each cardiac cycle.

LV function and hemodynamic parameter assessment. LV volume was assessed by determining the electrical conductance catheter system was calibrated utilizing the relationship between end-diastolic volume and V 0,sw is the volume-axis intercept. The least-squares linear regression of the rate of change of pressure over time (dP/dt) and LV pressure for the isovolumic period of relaxation yielded a slope (A) equal to −1/τ and a pressure-axis intercept of P asy. The value for τ reported for each experimental period represents the mean value of a 1-min recording period. LV contractility was evaluated utilizing preload recruitable stroke work (PRSW). Stroke work (SW) was calculated as the integral of LV transmural pressure (P) and volume (V) over each cardiac cycle

\[
SW = \int PdV
\]

PRSW was determined from the slope of the linear regression analysis of the relationship between stroke work and end-diastolic volume (SWEDVR)

\[
SW = \text{PRSW} (V_{ed} - V_{0,sw})
\]

where PRSW is the slope of the linear SWEDVR, V ed is the end-diastolic volume and V 0,sw is the volume-axis intercept. Preload was varied by transiently occluding venous return for ~10 s at end expiration with the ventilator turned off. Eight to fifteen consecutive beats were analyzed, starting from the point of reduction of LV pressure. A minimum of three venous occlusions were performed at each experimental period. Extra systolic beats and beats where end-systolic pressure decreased below 70 mmHg were excluded from analysis.

The time constant of isovolumic relaxation τ was derived from the following relationship (30)

\[
dP(t)/dt = A_P(t) - A_{asy}
\]

The least-squares linear regression of the rate of change of pressure over time (dP/dt) and LV pressure for the isovolumic period of relaxation yielded a slope (A) equal to −1/τ and a pressure-axis intercept of P asy. The value for τ reported for each experimental period represents the average of the values calculated from each cardiac cycle over a 1-min recording period. To measure stiffness, we altered loading conditions of the LV by transiently inflating the occlusion balloon in the aorta followed by veno caval occlusion. Stiffness was considered to be the slope of the linear regression analysis of the relationship between end-diastolic pressure and volume (EDPVR)

\[
P_{ed} = S (V_{ed} - V_{0,d})
\]

S is stiffness and slope and V 0,d is the volume-axis intercept.
Three transient aortic and venous occlusions were performed each experimental period to obtain an average stiffness value.

Blood flow and myocardial oxygen consumption measurements were determined from stroke work divided by oxygen consumption. The methods for fluorescent microsphere determination of blood flow have been previously described in detail (9) and are briefly reported here. Myocardial blood flow was measured at intervals described in the protocol utilizing 15-µm fluorescent microspheres. Two million microspheres, sonicated for 10 min and vortexed immediately before injection, were injected into the left atrium for each measurement. Reference blood samples were collected from the abdominal aorta at a rate of 10 ml/min. At the end of the experiment, tissue specimens weighing ~1 g were collected from the left and right kidneys and the whole wall of the heart. The reference blood and tissue specimens were then digested.

Aortic and coronary sinus blood samples for oxygen content determination were taken immediately before blood flow determination and at time periods defined in the protocol. Oxygen content was determined by cooximetry (OSM3, Radiometer) using a canine dissociation curve and correction for dissolved oxygen. Myocardial oxygen consumption was determined from the arterial and coronary sinus blood oxygen content difference multiplied by myocardial blood flow. LV efficiency was determined from stroke work divided by oxygen consumption.

Protocol. After instrumentation, all dogs were stabilized for 30 min before each experiment and were assigned to one of three groups: control (n = 6), HP (n = 7), and HP with CVH (HP-CVH; n = 8). After the stabilization period, baseline measurements were performed. After baseline period measurements, plasma protein concentration was lowered in the HP and HP-CVH groups using a cell-saving device (Haemonetics, Braintree, MA). Blood was separated by this device into plasma, which was discarded, and red blood cells, which were suspended in a balanced electrolyte solution and returned to the dogs. Coronary vascular resistance was calculated by taking the difference between mean arterial pressure and coronary sinus pressure, and dividing this difference by coronary blood flow.

Aortic and coronary sinus blood samples for oxygen content determination were taken immediately before blood flow determination and at time periods defined in the protocol. Oxygen content was determined by cooximetry (OSM3, Radiometer) using a canine dissociation curve and correction for dissolved oxygen. Myocardial oxygen consumption was determined from the arterial and coronary sinus blood oxygen content difference multiplied by myocardial blood flow. LV efficiency was determined from stroke work divided by oxygen consumption.

Protocol. After instrumentation, all dogs were stabilized for 30 min before each experiment and were assigned to one of three groups: control (n = 6), HP (n = 7), and HP with CVH (HP-CVH; n = 8). After the stabilization period, baseline measurements were performed. After baseline period measurements, plasma protein concentration was lowered in the HP and HP-CVH groups using a cell-saving device (Haemonetics, Braintree, MA). Blood was separated by this device into plasma, which was discarded, and red blood cells, which were suspended in a balanced electrolyte solution and returned to the dogs. Blood separation was continued until plasma protein concentration was ~2.5 g/dl. Mean arterial pressure and hematocrit values were maintained at or near baseline values by administration of balanced electrolyte solution. In the HP-CVH groups, the coronary sinus pressure was gradually increased to 25 mmHg over 1 h by inflating the balloon catheter within the coronary sinus. Coronary sinus pressure was maintained at 25 mmHg for an additional 2 h. Measurements were repeated at 1, 2, and 3 h after onset of hemodilution.

The dogs were euthanized with KCl (100 mg/kg iv) after the final data collection. The heart was rapidly excised, and tissue specimens for myocardial blood flow and water content determinations were collected. Right and left kidney specimens were also collected for blood flow measurement.

MWC determination. Samples of LV were placed in preweighed pans and the wet weight was recorded. The samples were dried to a constant weight in a 70°C vacuum oven. MWC (in %) was determined by calculating the ratio, (wet wt – dry wt)/dry wt.

Statistical analysis. Data are presented as means ± SE. Comparisons within and between groups were made using a two-way repeated-measures analysis of variance. Student-Newman-Keuls multiple comparisons tests were performed when a significant (P < 0.05) within-group or between-group variation occurred. MWC values were compared between groups with the Student t-test.

RESULTS

Contractile function. The only significant decline in PRSW occurred at 3 h in the HP-CVH group when PRSW decreased by ~14.5% from baseline (Fig. 1). PRSW values did not differ between the groups at any
period in the study. The mean values of $V_{0.02}$ of the SWEDVR ranged from -3 to 27 in the three groups, but there were no significant differences between or within groups for this variable.

Isovolumic relaxation. The $\tau$ values increased significantly from baseline in both the HP and HP-CVH groups at 1, 2, and 3 h (Fig. 1). There were no differences between groups in $\tau$ values at any time during the study. The $\tau$ values did not change in the control group over the course of the study.

EDPVR. Stiffness increased significantly from baseline in the HP-CVH group at 1 h and remained at this elevated pressure for the rest of the study. Heart rate did not change during the study in any of the groups and did not differ between groups. In addition, there was no change in the mean arterial pressure over the course of the study and no difference between groups. Cardiac output increased significantly from baseline in the control and HP groups at 1 h and decreased significantly from baseline in the HP group at 3 h but did not differ between groups. Pulmonary arterial pressure increased significantly from baseline in the HP group at 1, 2, and 3 h and in the HP-CVH group at 2 and 3 h, but there were no between-group differences. Right atrial pressure increased significantly in the HP group at 1 h and then remained at this elevated pressure for the rest of the study, but there were no between-group differences.

MWC. MWC of the HP (79.76 ± 0.25%) and HP-CVH (79.80 ± 0.20%) groups were not different from one another, but both were significantly greater than that of the control group (77.84 ± 0.28%) (Fig. 2). Coronary hemodynamics. Coronary blood flow increased significantly from baseline at 1 h in the HP group but was not different from baseline at 2 and 3 h (Table 2). Coronary vascular resistance decreased significantly in the control and HP groups at 1 h but did not change in the HP-CVH group. Myocardial oxygen consumption decreased significantly in the control group at 2 and 3 h but did not change in the other groups. Efficiency increased significantly from baseline in the control group at 1, 2, and 3 h and decreased significantly at 3 h in the HP group.

Blood gas and acid-base values. The arterial PO$_2$ values did not differ between groups, and the mean values ranged from 282 to 430 Torr. The pH values did not differ between or within groups, and the mean values ranged between 7.32 and 7.37. The mean arterial PCO$_2$ values did not differ within or between groups and ranged from 35 to 41 Torr.

Electrolytes. There were no differences between any of the groups for the electrolytes or total protein concentration at baseline (Table 3). Total protein concentration significantly decreased in all groups at 1, 2, and 3 h. However, the total protein concentrations in the HP and HP-CVH groups were significantly less than that of the control group. Packed cell volume was found to decrease significantly in the control group at 2 and 3 h after baseline but not in the other groups. There were no differences between the groups for packed cell volume. Ionized calcium concentration decreased significantly at 1, 2, and 3 h in the HP group and at 2 and 3 h in the HP-CVH group. Calcium concentration did not change in the control group, and there were no significant differences between groups. There were no significant within-group or between-group differences in sodium concentration. Potassium increased significantly from baseline in the HP group at 1, 2, and 3 h but did not differ between groups.

**DISCUSSION**

The hypoproteinemia induced in this study resulted in significant myocardial edema reflected by an average MWC value that was 2% greater than that of the control group. Ventricular diastolic stiffness and the time constant of isovolumic relaxation increased pro-

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**Table 1. Mean values for hemodynamic parameters for 3 different groups**

<table>
<thead>
<tr>
<th>Group</th>
<th>Baseline</th>
<th>1 h</th>
<th>2 h</th>
<th>3 h</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR, beats/min</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>134 ± 6</td>
<td>131 ± 7</td>
<td>131 ± 7</td>
<td>131 ± 7</td>
</tr>
<tr>
<td>HP</td>
<td>127 ± 6</td>
<td>128 ± 7</td>
<td>129 ± 8</td>
<td>129 ± 8</td>
</tr>
<tr>
<td>HP-CVH</td>
<td>117 ± 5</td>
<td>116 ± 4</td>
<td>114 ± 4</td>
<td>113 ± 4</td>
</tr>
<tr>
<td>$P_{ra}$, mmHg</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>12.6 ± 11</td>
<td>13.5 ± 10</td>
<td>14.2 ± 10</td>
<td>14.9 ± 11</td>
</tr>
<tr>
<td>HP</td>
<td>11.5 ± 08</td>
<td>13.9 ± 13*</td>
<td>13.1 ± 07*</td>
<td>14.1 ± 08*</td>
</tr>
<tr>
<td>HP-CVH</td>
<td>12.2 ± 08</td>
<td>13.4 ± 06</td>
<td>13.8 ± 07*</td>
<td>14.9 ± 06*</td>
</tr>
<tr>
<td>MAP, mmHg</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>3.5 ± 03</td>
<td>3.2 ± 04</td>
<td>3.4 ± 04</td>
<td>3.4 ± 04</td>
</tr>
<tr>
<td>HP</td>
<td>2.5 ± 04</td>
<td>3.8 ± 05*</td>
<td>3.6 ± 05*</td>
<td>3.5 ± 05*</td>
</tr>
<tr>
<td>HP-CVH</td>
<td>3.4 ± 07</td>
<td>3.7 ± 07</td>
<td>3.5 ± 05</td>
<td>3.7 ± 04</td>
</tr>
<tr>
<td>CO, l/min</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>1.99 ± 016</td>
<td>2.37 ± 025*</td>
<td>2.35 ± 027*</td>
<td>2.23 ± 028</td>
</tr>
<tr>
<td>HP</td>
<td>2.45 ± 013</td>
<td>3.14 ± 025*</td>
<td>2.34 ± 009*</td>
<td>1.98 ± 010*</td>
</tr>
<tr>
<td>HP-CVH</td>
<td>2.54 ± 025</td>
<td>2.55 ± 014</td>
<td>2.39 ± 028</td>
<td>2.05 ± 019</td>
</tr>
<tr>
<td>CSP, mmHg</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Control</td>
<td>5.2 ± 1.3</td>
<td>4.4 ± 0.5</td>
<td>4.3 ± 0.5</td>
<td>4.3 ± 0.4</td>
</tr>
<tr>
<td>HP</td>
<td>2.2 ± 0.6</td>
<td>2.6 ± 0.5</td>
<td>2.5 ± 0.7</td>
<td>2.3 ± 0.7</td>
</tr>
<tr>
<td>HP-CVH</td>
<td>8.2 ± 1.3†</td>
<td>25.4 ± 07*†</td>
<td>25.3 ± 10*†</td>
<td>24.7 ± 0.9*†</td>
</tr>
</tbody>
</table>

Values are means ± SE. HP, hypoproteinemia; CVH, coronary venous hypertension; HR, heart rate; $P_{ra}$, pulmonary arterial pressure; MAP, mean arterial pressure; CO, cardiac output; CSP, coronary sinus pressure. Significantly different: *P < 0.05 vs. baseline value; †P < 0.05 vs. control group.
gressively with edema formation, reflecting deterioration of the passive and active components of ventricular diastolic function. In a finding inconsistent with our hypothesis, contractility did not change in association with hypoproteinemia and myocardial edema. The autonomic nervous system was not responsible for these results because autonomic blockade was performed. In experiments where CVH was combined with HP (HP-CVH group), MWC did not differ from that of the HP group, suggesting that CVH had little additional influence on the degree of edema formation. In response to HP-CVH, stiffness and τ changed in a manner similar to that observed in the HP group. However, in contrast to what was seen in the HP group, contractility decreased significantly. These results suggest that CVH had a negative inotropic effect that was independent of the myocardial edema created by these two methods. The effects of the experimental preparation and time on ventricular function were not found to be significant because there were no changes in LV systolic and diastolic function in the control group.

**Table 2.** Mean values for CBF, CVR, $\dot{V}O_2$, and mechanical efficiency for 3 different groups

<table>
<thead>
<tr>
<th>Group</th>
<th>Baseline</th>
<th>1 h</th>
<th>2 h</th>
<th>3 h</th>
</tr>
</thead>
<tbody>
<tr>
<td>CBF, ml·min⁻¹·g⁻¹</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>0.70±0.05</td>
<td>0.81±0.09</td>
<td>0.72±0.07</td>
<td>0.74±0.09</td>
</tr>
<tr>
<td>HP</td>
<td>0.77±0.09</td>
<td>1.04±0.13*</td>
<td>0.83±0.05</td>
<td>0.73±0.07</td>
</tr>
<tr>
<td>HP-CVH</td>
<td>0.80±0.12</td>
<td>0.81±0.08</td>
<td>0.70±0.06</td>
<td>0.62±0.06</td>
</tr>
</tbody>
</table>

| CVR, mmHg·min·g·ml⁻¹ |          |      |      |      |
| Control            | 161±15   | 132±19* | 147±15 | 152±21 |
| HP                 | 149±13   | 107±14* | 128±10 | 146±16 |
| HP-CVH             | 139±12   | 111±12  | 125±13 | 141±15 |

| $\dot{V}O_2$, 10⁻²·ml·min⁻¹·g⁻¹ |          |      |      |      |
| Control             | 8.4±0.54 | 7.9±0.78 | 6.9±0.60* | 7.1±0.55* |
| HP                  | 6.9±0.89 | 7.8±1.01 | 6.6±0.50  | 6.6±0.62  |
| HP-CVH              | 8.0±1.18 | 8.3±1.08 | 8.4±0.71  | 7.3±0.72  |

| Mechanical efficiency, 10⁶erg·min·g·ml⁻¹ |          |      |      |      |
| Control          | 180±10  | 233±9* | 260±19* | 245±22* |
| HP               | 324±64  | 327±49 | 291±47  | 234±37* |
| HP-CVH           | 284±31  | 302±50 | 233±26  | 218±20  |

Values are means ± SE. CBF, coronary blood flow; CVR, coronary vascular resistance; $\dot{V}O_2$, myocardial oxygen consumption. Significantly different: *P < 0.05 vs. baseline value.

When we compare the results of the current study with those of our previous studies of interstitial myocardial edema induced by either CVH (21) or cardiac lymphatic obstruction (16), there are several interesting findings. In our first study, CVH resulted in a decline in contractility (−23%) and increases in stiffness (35%) and τ (41%) that were associated with a very mild increase in MWC (0.3%) compared with the control group (21). Cardiac lymphatic obstruction also resulted in a decline in contractility (−32%) and increase in τ (41%) but no change in stiffness (16). Those latter results were associated with an even smaller increase in MWC (0.14%) compared with the control group. The findings of our previous studies are clearly inconsistent with those of the current study with regard to contractility. In fact, when we examined the relationships between MWC of the control and treatment groups of the three studies with that of the percent change from baseline for contractility, stiffness, and τ, we found that stiffness was the only index of function that correlated significantly with MWC (Fig. 3). The data strongly suggest that the three methods employed to induce edema had effects on contractility and τ that were independent of their effects on MWC. The question of which study or studies accurately reflect the true physiological relationship between edema and ventricular function cannot be answered from the existing data. However, the finding in the present study that HP-CVH induced a decline in contractility, but HP did not, despite nearly identical MWC values, suggests that CVH had a negative inotropic effect that did not depend on myocardial edema. Although the alternative explanation that hypoprotein-
emia may have had a positive inotropic effect on contractility that masked a negative inotropic effect of edema must be considered, this scenario is less likely given that the increase in MWC of the HP group was at least sixfold greater than that observed with either CVH or lymphatic obstruction. If interstitial myocardial edema causes a decline in contractility, then given the degree of edema seen in the HP group, systolic dysfunction should have been observed.

There have been numerous studies by other investigators that have directly or indirectly examined the causal association between interstitial myocardial edema and systolic dysfunction. In studies of the effects of edema induced by elevation of coronary perfusion pressure on systolic function, Cross et al. (3) found no evidence that myocardial edema influenced the contractile strength of the ventricles in dogs. Laine (14) and Laine and Allen (15) reported that CVH in dogs resulted in myocardial edema and an associated decrease in LV systolic function as assessed by the maximum rate of change of pressure over time (dP/dt max) and cardiac output. Ilbawi and colleagues (12) found that elevation of coronary sinus pressure in dogs resulted in a decline in cardiac index and dP/dt, whereas another group of investigators (29) did not observe changes in these indexes of contractile function in sheep subjected to similar conditions. These investigations were limited by the fact that the indexes utilized to assess contractility were not load independent and that techniques of MWC determination were not standardized. Mehlhorn and associates (17, 18) found that contractility (PRSW) was depressed after cardiopulmonary bypass and cardioplegic arrest, using either cold-crystallloid or warm blood. Cardiopulmonary bypass and cardioplegia induced interstitial edema by a reduction in lymph flow, lowered blood colloid osmotic pressure (hypoproteinemia), and reduced workload and (in the case of cold-crystallloid) intracellular edema by creating ischemia. These latter effects complicate interpretation of the influence of interstitial edema on function because of the dysfunction caused by ischemia. Acute cardiac lymphatic obstruction has been found by our laboratory to result in very mild edema and a decrease in contractility (16). Studies by other investigators (27, 28) support those findings. Consistent with our current study, three independent groups of investigators (8, 11, 13) found that hemodilution-induced myocardial edema was not associated with depressed systolic function. However, interstitial myocardial edema induced by acute pulmonary hypertension was found to be associated with diminished contractility (4). Developed pressure in isolated rat hearts did not decline despite marked changes in MWC (7% greater than control) induced by colloid-free perfusate (25). Finally, contractility was not affected when myocardial edema (1.2% greater than control) was produced in association with acid aspiration-induced acute lung injury (26). Thus, when we consider all these data, we find that interstitial myocardial edema is not regularly associated with depressed contractility, and, from our studies, the degree of edema does not correlate with the degree of systolic dysfunction.

Ventricular diastolic stiffness has been invariably found to increase in association with interstitial water content of the heart regardless of the method used to create the edema (3, 6, 21, 24). We found that there was a direct and significant linear relationship between MWC and stiffness in our three studies in which edema was created by different mechanisms (Fig. 3). On the basis of the cumulative evidence, it is possible to conclude that there is a causal relationship between development of interstitial myocardial edema and increased diastolic stiffness.
The time constant $\tau$ has been found to be affected by the same conditions that influence contractility; $\tau$ varies inversely with contractility but is thought to be more sensitive to changes in ventricular function than contractility is. This time constant has been found to vary with the position of the micromanometer within the ventricle (5). The variation in $\tau$ with micromanometer position may contribute to interanimal variability in $\tau$ values and account for the lack of correlation between MWC and $\tau$ (Fig. 3). The consistency of the finding of $\tau$ prolongation with interstitial edema supports a causal association, but further studies are needed to verify this.

Coronary blood flow did not vary over the course of the study except for a transient increase at 1 h in the HP group when it was significantly increased from the baseline value. This transient increase in blood flow was likely related to the volume exchange that occurred when use of the cell-saving apparatus was initiated. There was no evidence of increased coronary vascular resistance with edema formation as has been suggested to occur in isolated heart studies (23). Myocardial oxygen consumption did not vary in the HP or HP-CVH groups but was found to decline slightly at 2 and 3 h in the control group. The decline in mechanical efficiency that occurred in the HP group at 3 h reflects the declining stroke work and relatively constant myocardial oxygen consumption. The decline in total protein concentration in the control group reflected the general tendency for hemodilution in experimental animals that have undergone surgery and received fluids. In the HP and HP-CVH groups, we estimated the change in colloid osmotic pressure from total protein concentration using the formula $\Pi = 1.4C + 0.22C^2 + 0.005C^3$, where $\Pi$ is colloid osmotic pressure and C is plasma protein concentration (19), and found that colloid osmotic pressure declined from an estimated baseline value of 15 mmHg to 5 mmHg at 3 h. This was based on the assumption that the ratio of albumin to globulin did not change during the experiment. The hypoalbuminemia we induced was not associated with anemia to any significant degree in either the HP or HP-CVH groups, eliminating the influence of variation in oxygen-carrying capacity on the results in these groups. However, the significant decline in packed cell volume in the control group may have influenced the oxygen-transport related results of these animals. There were similar decreases in the calcium concentrations in the HP and HP-CVH groups, although these changes were probably not responsible for the difference in contractility between the HP and HP-CVH groups.

In summary, interstitial myocardial edema created by lowering colloid osmotic pressure was associated with increases in stiffness and $\tau$, indexes of the passive and active components of diastolic function. Interstitial myocardial edema created by this method was not, however, associated with any change in contractility. When CVH was combined with lowered colloid osmotic pressure to create interstitial myocardial edema, contractility was significantly depressed despite the fact that the MWC value of the HP-CVH group was not significantly greater than that of the HP group. This latter finding suggests that CVH has an effect on contractility that does not involve myocardial edema as a mechanism. When these results were considered in the context of our previous studies and those of other investigators, it appears very likely that a causal relationship exists between myocardial edema formation and increased diastolic ventricular stiffness. The existence of a similar relationship between interstitial myocardial edema and contractility is less likely. The relationship between interstitial edema and $\tau$ must be further examined. The degree of edema created in this study had no appreciable effect on myocardial oxygen delivery, myocardial oxygen consumption, or mechanical efficiency.

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