Characterizing ventricular mechanics and energetics following repeated coronary microembolization

KOJI TODAKA, DAVID LEIBOWITZ, SHUNICHI HOMMA, PETER E. FISHER, CAROLYN DEROZA, RICHARD STENNETT, MILTON PACKER, and DANIEL BURKHOFF

Characterizing ventricular mechanics and energetics following repeated coronary microembolization. Am. J. Physiol. 272 (Heart Circ. Physiol. 41): H186-H194, 1997.—Myocardial mechanics and energetics were investigated in an animal model of moderate chronic heart failure (CHF) created by repeated coronary microembolizations in six dogs. The final fractional area change was 34 ± 4%. Hearts of these animals were isolated and cross-perfused, and balloons were placed in the left ventricle (LV). Chamber contractile state was markedly depressed in embolized hearts as assessed by the slope (Ees: 2.74 ± 0.49 vs. 4.00 ± 1.16 mmHg/ml, P < 0.01) and volume axis intercept (Vo: 8.7 ± 5.9 vs. 1.0 ± 3.2 ml, P < 0.01) of end-systolic pressure-volume relation compared with a group of six normal dogs. The end-diastolic pressure-volume relation of embolized hearts was shifted to the right, indicating a dilation of the LV. However, systolic and diastolic stress-strain relationships were similar in the two groups, suggesting that the average myocardial properties of the embolized hearts are similar to those of normal hearts. The relationship between oxygen consumption and pressure-volume area in embolized hearts had smaller intercept (2.98 ± 0.44 vs. 3.92 ± 0.39 × 10^5 ml O_2·beat^{-1}·100 g LV^{-1}, P < 0.01) compared with the control group, with no change in the slope.

These results contrast with previous findings in pacing CHF and serve as an important characterization of ventricular properties in this model of CHF from different etiology.

Methods

Heart Failure Model

Nine mongrel dogs were anesthetized (1–2% inhaled isoflurane), and a coronary angiographic catheter was engaged in the left main coronary artery under fluoroscopic guidance via a femoral approach. A pig-tail catheter was inserted via the contralateral femoral artery into the left ventricle (LV) to monitor LV pressure and for ventriculography. Glass microspheres (90 μm mean diameter, Spheriglass) suspended in contrast medium (~33,000 spheres/ml) were injected into the left anterior and circumflex branches in divided doses until LV end-diastolic pressure reached ~20 mmHg. Diuretics, intravenous nitroglycerine, and prolonged periods of intubation were employed when necessary to treat acute heart failure (manifest as excessive rise in LV end-diastolic pressure and decreases in arterial blood pressure). This procedure was repeated in each animal on an average of five (range 3–6) separate occasions over a 9-wk period until persistent global ventricular dysfunction was observed on transthoracic echocardiography (vide infra). Ventriculography was performed at the beginning of each of the subsequent embolization sessions to assess global and regional wall motion; to achieve incremen-
tal myocardial damage with each procedure, microspheres were selectively infused into the artery (left anterior descending or circumflex) which supplied the region with the best wall motion.

Two of the nine dogs that underwent embolization died due to acute heart failure within hours of embolization, and the third dog died unexpectedly 4 days after embolization. All data are from the six surviving animals. On average, a total of 310 ± 90 x 10^5 microspheres were injected per dog. These dogs were followed for a total period of 286 ± 66 days from the first embolization, over which time they developed persistent left ventricular dysfunction. The progression of left ventricular dysfunction was followed by periodic transesophageal echocardiograms performed in a conscious resting state. Echocardiograms were quantified off-line by determining LV end-systolic and end-diastolic areas (ESA and EDA, respectively) at the midapical muscle level in the short-axis view. Fractional area change was defined as 100 x (EDA - ESA)/EDA.

Isolated Heart Preparation

To assess LV systolic and diastolic properties, the hearts of the six embolized animals and the hearts of six body weight-matched controls were studied in a standard isolated heart preparation. Details of this preparation have been provided previously (4). Briefly, the heart from the dog of interest was excised and metabolically supported by blood provided from a second "support" dog. The femoral arteries of the support dog were cannulated and connected to a perfusion circuit consisting of two peristaltic pumps, a heater, a blood filter, and an air trap. The pressure in the aortic root of the isolated heart, which is the perfusion pressure for coronary flow, was measured on-line by a commercially available spectrophotometer (Transonic Systems model T108, Ithaca, NY). The difference between arterial and venous oxygen content was measured on-line by a commercially available spectrophotometer (AVOX Systems, San Antonio, TX). Oxygen consumption of the whole heart was determined by multiplying coronary flow by the arteriovenous blood oxygen difference.

A water-filled balloon was placed within the left ventricle via the mitral valve. The volume of the balloon, and therefore of the ventricle, was controlled by a piston pump servo system. A micromanometer (Millar Instruments model SPC-360, Houston, TX) placed within the balloon was used to measure ventricular pressure. The heart was paced from the LV apex and was constrained to contract isovolumically.

Protocol

After isolation, the heart was allowed to stabilize for ~30 min. LV pressure, coronary blood flow, and arteriovenous blood oxygen difference were measured at several different volumes chosen to provide a range of end-diastolic pressures between <0 and a minimum of 20 mmHg. The volume steps between different settings were between 5 and 10 ml depending on the size of the individual hearts. At each volume setting, enough time was allowed to attain steady-state conditions as judged from all signals recorded (usually 2-3 min). Upon completion of baseline data acquisition, continuous intracoronary infusion of isoproterenol was initiated to evaluate β-responsiveness. The rate of isoproterenol administration was adjusted so that peak isovolumic LV pressure (at a volume which provided end-diastolic pressure of ~10 mmHg) increased by 20%. The data were acquired digitally at a sampling frequency of 1,000 Hz.

Histology

After completion of the isolated heart study, the heart was fixed in 10% neutral buffered Formalin. At least nine samples were cut from each heart (anterior, posterior, septal samples from the basal, mid, and apical levels of the LV), embedded in paraffin, and sectioned. Masson's trichrome-stained tissue slides were scanned and digitized for image analysis (Polaroid Sprint Slide Scanner; Power Macintosh 6100). The number of blue pixels in each section of myocardium (corresponding to collagen) was counted and expressed as a percent of the total number of pixels analyzed (Adobe Photoshop; NIH Image).

Data Analysis

Assessment of global mechanics. Systolic properties of the LV chamber were assessed in the isolated hearts by the linear end-systolic pressure-volume relationship (ESPVR)

\[ P_{es} = E_{es}(V_{es} - V_0) \]  

where \( P_{es} \) is end-systolic pressure, \( V_{es} \) is end-systolic volume, \( E_{es} \) is the slope of the ESPVR, and \( V_0 \) is the volume axis intercept of ESPVR.

Diastolic properties were asasced by the end diastolic pressure-volume relationship (EDPVR). The EDPVR was fit to a logarithmic function (12) as follows

\[ P_{ed} = -S \ln \left( \frac{V_{ed} - V_0}{V_{ed} - V_u} \right) \]  

where \( P_{ed} \) is end-diastolic pressure, \( V_{ed} \) is end-diastolic volume, \( S \) is normalized chamber stiffness, \( V_u \) is the volume asymptote, and \( V_0 \) is the unstressed volume at which end-diastolic pressure equals zero. The parameters \( S, V_u, \) and \( V_0 \) are all determined by nonlinear least-squares fitting algorithm applied to the measured \( P_{ed} \) and \( V_{ed} \) data. According to a previous study (12), \( V_u \) corresponds to the hypothetical ventricular volume at which diastolic stiffness becomes infinitely large and represents the theoretically maximum volume that can be placed within the ventricular chamber.

Assessment of myocardial systolic and diastolic properties. To assess average regional systolic and diastolic myocardial properties, a stress-strain analysis was performed. Myocardial fiber stress (\( \sigma \)) and natural strain (\( \epsilon \)) were estimated by the following formulas (3), which assume a thick-walled rotationally symmetric chamber

\[ \epsilon = (1/3)\ln((1 + 3 \cdot LVV/V_u)/(1 + 3 \cdot V_u/V_w)) \]  

\[ \sigma \text{ (g/cm}^2\text{) = 1.355 LVP (1 + 3LVV/V_w)} \]  

where \( V_u \) is LV wall volume, which was set equal to ventricular mass divided by an assumed specific gravity of 0.96 g/ml, \( LVV \) is left ventricular volume, and LVP is left ventricular pressure. To determine the degree to which the results obtained from this analysis were dependent on the geometric model, circumferential stress and strain were also estimated using a model that assumes thick-walled spheric chamber (21)

\[ \epsilon = \ln((L/L_0) \)  

\[ \sigma = 1.355 LVP \pi r_0^2 (r_0^2 - r_f^2) \]  

where \( L \) is a constant, \( r_f \) is the radius of the internal, midwall, and external surface of the ventricle.
radii of the LV, respectively. Each of the radii is determined from the equation for the volume contained within the respective sphere of interest: \( r = (3V/4\pi)^{1/3} \).

Assessment of myocardial energetics. Energetic aspects of LV properties were assessed by the relationship between myocardial oxygen consumption (MVO\(_2\)) and the LV pressure-volume area (PVA) (19). MVO\(_2\) was calculated as detailed above. PVA was defined as the area circumscribed by the ESPVR, EDPVR, and systolic portion of pressure-volume loop in LV pressure-volume diagram. Both MVO\(_2\) and PVA were normalized to 100 g LV mass and then fit to a linear equation

\[
\text{MVO}_2 = A \text{PVA} + B
\]

where \( A \) is the slope and \( B \) is the intercept of the relation.

Statistics

Multiple linear regression analysis was used to test for statistical significance of differences between linear relations. For other comparisons between groups, the unpaired t-test was used. Repeated-measures analysis of variance with Tukey’s post hoc test was used for comparisons within groups. \( P < 0.05 \) was regarded as significant.

RESULTS

In Situ Ventricular Function

Coronary embolizations were completed within an average of 66 days, and animals were followed for an average of 286 days from the first embolization; thus the average observation period following completion of embolization was 220 days. The time course of EDA, ESA, and fractional area changes as a function of time after the first embolization are shown in Fig. 1 (all points reflect mean ± SD values). The points at time equals 0 days represent baseline values before embolization. The second point in each graph represents values obtained within 1 wk of the last embolization. The third data point in each graph represents data collected just before killing the animals for the isolated heart study. Asterisks indicate significant differences from baseline values. The EDA after the last embolization increased from baseline and remained elevated until death of the animal. The EDA showed a similar trend. As a result, fractional area change decreased from an average of 49% at baseline to 37% after the last embolization and then to 34% at the end of the observation period.

Two dogs developed massive ascites, and another dog became cachexic. The other dogs did not show overt heart failure symptoms at rest. From these data, we concluded that repeated coronary embolization produced an irreversible and slightly progressive model of moderate CHF.

Body weights and ventricular masses of the embolized and normal control animals are shown in Table 1. Although baseline body weights were matched between the two groups, there was an increase in body weight over time in the embolization group most likely due to fluid collection (\( P < 0.05 \) by paired t-test). Postmortem right ventricular masses were the same in the two groups. Left ventricular mass tended to be increased in the embolized hearts, although this trend did not reach statistical significance (\( P = 0.12 \)).

ESPVR and EDPVR

End-systolic and end-diastolic pressure-volume points from normal and embolized hearts are shown in Fig. 2. Different symbols indicate data from different animals. The solid lines show the average ESPVRs and EDPVRs of each group. The ESPVRs and EDPVRs of the embolization group are shifted to the right compared with the normal group. These differences are illustrated more clearly in Fig. 3, which shows the mean ± SD results. The ESPVR of the embolization group was shifted to the right and had a shallower slope as shown by the solid lines in Fig. 3A (dotted and broken lines indicate ± SD of the respective group). The average ESPVR slope (\( E_{SV} \)) and intercept (\( V_0 \)) values are shown in Table 2; multiple linear regression analysis indicated that the differences between groups in both of these values were statistically significant.

The average EDPVRs (Fig. 3B) also revealed a rightward shift in the embolized group compared with normal, indicating dilation and structural remodeling of the LV chamber. This was shown to be statistically significant by the differences in calculated \( V_m \) (referred to as the maximal attainable volume) and \( V_0 \) (the

Table 1. Body weight and postmortem data

<table>
<thead>
<tr>
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<th>Normal</th>
<th>Embolization</th>
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<tbody>
<tr>
<td>Original body weight, kg</td>
<td>20.3 ± 2.0</td>
<td>20.7 ± 1.4</td>
</tr>
<tr>
<td>Body weight at death, kg</td>
<td>20.3 ± 2.0</td>
<td>23.3 ± 2.2*</td>
</tr>
<tr>
<td>Left ventricular mass, g</td>
<td>114 ± 21</td>
<td>141 ± 34</td>
</tr>
<tr>
<td>Right ventricular free wall mass, g</td>
<td>43 ± 11</td>
<td>50 ± 14</td>
</tr>
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Values are means ± SD. *P < 0.05 vs. original by paired t test.
unstressed volume) between the groups (Table 2). In contrast, there was no difference in S, the index of global myocardial diastolic stiffness.

**Stress-Strain Relations**

Average (±SD) end-systolic and end-diastolic strain relationships calculated from the original pressure-volume data according to Eq. 3 are shown for the control and embolized hearts in Fig. 4. Each point represents the mean (±SD) strain at specified stress values; those strain values were obtained by interpolation of the exponential fits to data of individual hearts. The stress-strain relationships of the two groups were overlapping in both systole and diastole. To test whether this result was peculiar to one geometric model of calculating stresses and strains, a different model was also used for the calculations (Eq. 4). The results of that analysis (shown in Fig. 5) also indicated that there was no detectable difference in stress-strain relations between normal and embolized hearts. The only difference in results obtained from the two models was that the absolute values of stresses were lower when calculated via the spherical model (Eq. 4). This implies that despite the marked reduction in global chamber systolic strength and remodeling of the chamber (Figs. 1–3), average systolic and diastolic properties of embolized hearts remained similar to those of normal hearts.

**Table 2. Fit parameters**

<table>
<thead>
<tr>
<th></th>
<th>Normal</th>
<th>Embolization</th>
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<tbody>
<tr>
<td><strong>Ees, mmHg/ml</strong></td>
<td>4.00 ± 1.18</td>
<td>2.74 ± 0.49†</td>
</tr>
<tr>
<td><strong>Ees, mmHg/100 g LV/ml</strong></td>
<td>4.55 ± 1.65</td>
<td>3.88 ± 1.16</td>
</tr>
<tr>
<td><strong>V0, ml</strong></td>
<td>1.0 ± 3.2</td>
<td>8.7 ± 5.9‡</td>
</tr>
<tr>
<td><strong>r² (mean)</strong></td>
<td>0.98</td>
<td>0.98</td>
</tr>
<tr>
<td><strong>S, mmHg</strong></td>
<td>11.9 ± 3.2</td>
<td>9.7 ± 2.7</td>
</tr>
<tr>
<td><strong>Vas, ml</strong></td>
<td>57 ± 11</td>
<td>78 ± 18†</td>
</tr>
<tr>
<td><strong>Vu, ml</strong></td>
<td>18 ± 4</td>
<td>26 ± 9‡</td>
</tr>
<tr>
<td><strong>A, 10⁻⁵ ml O₂⁻¹·min⁻¹·100 g LV⁻¹</strong></td>
<td>1.43 ± 0.56</td>
<td>1.24 ± 0.31</td>
</tr>
<tr>
<td><strong>B, 10⁻² ml O₂·beat⁻¹·100 g LV⁻¹</strong></td>
<td>3.92 ± 0.39</td>
<td>2.98 ± 0.44‡</td>
</tr>
<tr>
<td><strong>Rab, 10⁻² ml O₂/beat</strong></td>
<td>4.47 ± 0.85</td>
<td>4.27 ± 1.43</td>
</tr>
</tbody>
</table>

Values are means ± SD. Ees, end-systolic elastance; Ees,n, end-systolic elastance normalized to left ventricle (LV) mass; V0, volume axis intercept of end-systolic pressure-volume relationship (ESPVR); r², correlation coefficient of ESPVR; S, normalized diastolic chamber stiffness; Vas, volume asymptote of end-diastolic pressure-volume relationship; Vu, unstressed volume; A and B, slope and intercept of relationship between myocardial oxygen consumption and LV pressure-volume area, respectively; Rabs, nonnormalized absolute value for B. †P < 0.05 by unpaired t-test. ‡P < 0.01 by multiple linear regression.
lized myocardium in the chronic setting are comparable to those from the normal group. Two other findings support this notion: 1) E\(\text{co}\) normalized to LV mass (E\(\text{co,n}\), Table 2), which provides a rough index of myocardial systolic properties, was comparable in the two groups; and 2) as noted above, the index of global myocardial diastolic stiffness (S, Table 2) was also not different between normal and embolized hearts.

\(\beta\)-Adrenergic Responsiveness

To test another aspect of myocardial properties known to be altered in heart failure, the dose of intracoronary isoproterenol necessary to induce an \(-20\%\) increase in peak isovolumic LV pressure (at a fixed end-diastolic pressure of \(-10\) mmHg) was determined. Results, summarized in Fig. 6, reveal that embolized hearts exhibited a blunted inotropic response to isoproterenol compared with normal hearts (\(P = 0.06\) by analysis of covariance).

**Myocardial Energetics**

Average (\(\pm\) SD) M\(\text{VO}_2\)-PVA relations obtained from the six embolized and six body weight-matched control hearts are shown in Fig. 7 and summarized quantitatively in Table 2; note that M\(\text{VO}_2\) in Fig. 7 is normalized to LV mass in the conventional manner. The relationship for the embolization group was shifted downward in a parallel manner; there was no change in the slope (A, Table 2), but there was a decrease in the M\(\text{VO}_2\) axis intercept (\(P < 0.05\) by multiple linear regression analysis). The M\(\text{VO}_2\) axis intercept represents M\(\text{VO}_2\) in the mechanically unloaded state normalized to LV mass (B, Table 2). However, if we compare the absolute nonnormalized values of the M\(\text{VO}_2\) axis-intercept (\(B_{\text{abs}},\) Table 2), there was no difference between normal and embolized hearts (see DISCUSSION).

**Histology**

An example of a digitized histological sample in which originally blue-stained pixels (collagen fibers) are shown in dark black is illustrated in Fig. 8, which shows a typical multifocal pattern of scarring due to the microembolization. The average collagen fractions determined by digital analysis of such images were \(7.7 \pm 4.1, 7.2 \pm 3.7,\) and \(8.8 \pm 5.3\%\) at base, mid, and apical levels of the LV, respectively, with the overall average of \(7.8 \pm 4.3\%\). Because microspheres tended to flow into the apical portion, that region had the largest collagen fraction.

**DISCUSSION**

Repeated coronary embolization resulted in sustained left ventricular dysfunction as evidenced by chamber enlargement and decreased wall motion detected by echocardiography in vivo which is consistent with previous reports (15, 16). The degree of ventricular dysfunction was moderate (final fractional area change of 34\%). When studied in isolation, chamber dilation was confirmed by direct measurement of diastolic pressure-volume relations, and chamber contractile dysfunction was confirmed by measurement of systolic pressure-volume relations. Heart mass tended
CHAMBER AND MUSCLE FUNCTION IN HEART FAILURE MODEL

Fig. 8. An example of a digitized image in which originally stained blue pixels (collagen fibers) are shown in dark black. Original magnification, ×8.7.

to be increased compared with normal, consistent with observations of other investigators (1, 13, 16), suggesting that the surviving myocytes had increased their mass (compensatory hypertrophy). The relative contributions of chamber dilation (remodeling) and muscle dysfunction to chamber contractile dysfunction were examined by performing a stress-strain analysis. This revealed that both the systolic and diastolic stress-strain relations of the ventricular wall in embolized hearts were not significantly different from those of normal control hearts.

These findings were confirmed by two different commonly used forms of stress-strain analysis, suggesting that the findings are not peculiar to one formulation. Consistent with this, $E_{\text{sv}}$ values normalized to ventricular mass and a geometry-independent diastolic chamber stiffness $S$ were both similar in normal and embolized hearts. Original expectations were that systolic wall stress would be depressed in the embolized animals because of the sustained and significant decrease in global ventricular performance detected both in situ and in vitro. The data suggest that in this model, global ventricular chamber contractile dysfunction is largely due to the chamber dilation (remodeling) but that hypertrophy in the surviving myocardium is adequate to normalize myocardial mass and that contractile function of the surviving hypertrophied myocardium is largely normal.

It was previously shown for the rapid pacing-induced heart failure model using stress-strain analysis that myocardial systolic properties are depressed (21). However, detailed examinations of those original data indicate that the differences in stress-strain relations between normal and heart failure animals are small compared with the large difference noted in the pressure-volume relations. This suggests that even in that model of severe heart failure it is difficult to document a significant reduction in myocardial contractile function despite overt chamber contractile dysfunction.

The finding of an unaltered diastolic stress-strain relationship was at first surprising in view of the scar tissue in infarcts throughout the myocardium of embolized hearts. It was expected that the diastolic stress-strain relationship would be elevated and that the myocardial stiffness parameter would be increased in embolized hearts compared with normal, reflecting the presence of stiff (scar) elements. This would certainly be the case if a region of the heart were acutely rendered noncontractile and stiff; however, the situation is different in the chronic setting where chamber remodeling and changes in properties of surviving muscles have occurred (15, 16). To explore how the stress-strain relationship may be affected by the introduction of stiff scar in the setting of ventricular remodeling, we performed a theoretical analysis that is summarized in the APPENDIX. The results of that analysis indicated that (subject to the assumptions detailed in the APPENDIX), for the case of a chronically remodeled heart in which the surviving muscle undergoes compensatory hypertrophy (1, 13), there is very little impact on either the systolic or diastolic stress-strain relationships even with marked changes in the composition of the myocardial wall. While based on theory and not direct observation, this analysis does provide a plausible explanation for the findings of the present study.

Observation in embolized hearts of an average of 7.8% (ranging up to 20%) is slightly smaller than the 12–21% noted by Sabbah et al. (16). This may be due in part to the fact that we calculated the percent of collagen fraction using a computer-based digital processing technique that generates an index of scar area based on the sum of pixels that have met our stringent color criteria. Our method, as compared with that used by Sabbah et al. (16), therefore most likely provides a more conservative estimate of scarring since the previous technique simply encircles areas stained by hand and may also include in its final estimation of degree of fibrosis speckled nonstained regions within the samples. Moreover, we waited for a longer time period (an average of 6 mo vs. the 3 mo in the Sabbah study) after the last ischemic insult; during that period, it is likely that the scars contracted further in the process of healing. Therefore, a greater amount of myocardium than the measured percent of scar must have been destroyed initially. In addition, Whittaker et al. (19a) reported that Masson trichrome staining per se underestimated the amount of collagen compared with picrosirius red staining, which is regarded as a more accurate method for that purpose.

Although the baseline myocardial mechanical properties as assessed by stress-strain analysis were not found to be altered in this model, responsiveness to β-adrenergic stimulation was blunted as shown in Fig. 6. This is consistent with what was found in the heart failure state in other animal models (11, 21) as well as in heart failure patients (5). Thus there is pharmacologi-
decreased after the last embolization, the ejection that the fractional area change by echocardiography was 28 ± 3%. When we take into consideration measured under anesthesia before the last embolization, heart. In fact, our ejection fraction by ventriculography taken into account dysfunction at other areas of the analyzed the wall motion at mid LV level, we may not have because the echocardiographic technique only evalu-

This is because for these scarred hearts, MVVo₂ normalized to total LV mass would be lower than MVVo₂ normalized to LV myocardial mass; myocardial mass is the pertinent denominator for normalization because it is the myocytes that consume oxygen and not the scar tissue. An average 8% of collagen fraction, which may have underestimated scar content as detailed above, may account for a considerable part of the 25% difference in R noted between the two groups. In this regard, it is of interest to note that there was no difference between the MVVo₂-PVA intercepts from the two groups of hearts when these values were not normalized to LV mass (Babs values, Table 2). Still, we cannot exclude the possibility that there is a fundamental change in energetics in these embolized hearts. A previous study of repeatedly embolized dog hearts revealed dramatic changes in mitochondrial structural appearance (15), suggesting that there may be an alteration in metabolic properties in this form of heart failure. However, a functional analysis of changes in metabolic capacity has not been performed.

In addition, it is also of interest to note that these energetics results contrast with data from the rapid pacing heart failure model, which showed no change in intercept but a significant decrease in slope of the MVVo₂-PVA relationship (21). This difference in findings may be due to the differences in etiology of heart failure as well as differences in the degree of heart failure.

**Limitations**

As stated above, the degree of left ventricular dysfunction achieved using the present methods was most likely not as severe as in the rapid pacing heart failure model or as in patients with end-stage heart failure. It is of note that previous studies with this model have shown more severe reductions in global volume ejection fraction (16). This may reflect differences in embolization techniques between the different groups of investigators. Alternatively, this may reflect differences in techniques used to evaluate ventricular function; that is, results obtained with the use of echocardiography in the conscious state (present study) may differ from results obtained using ventriculography under anesthesia (previous studies). Furthermore, because the echocardiographic technique only evaluated the wall motion at mid LV level, wc may not have taken into account dysfunction at other areas of the heart. In fact, our ejection fraction by ventriculography measured under anesthesia before the last embolization was 28 ± 3%. When we take into consideration that the fractional area change by echocardiography decreased after the last embolization, the ejection fraction value by ventriculography must have also decreased from this value. Nevertheless, the present results may not apply to the case of severe heart failure and should not be extrapolated to that condition. In particular, a small reduction in systolic stress-strain relations could be observed in severe heart failure, as has already been suggested for the pacing-induced heart failure model (21).

The main results of this study are observational in nature and are derived from direct measurements of pressure-volume relationships. However, one of the ancillary conclusions is based on the results of stress-strain analysis. Because this is a derived entity and not measured directly, it is important to explore the sensitivity and specificity of the analysis. As noted previously (3, 8, 22), there are many mathematical schemes used to calculate stress and strain. It has been shown, however, that while absolute values for these parameters may differ between the various schemes, the relative changes in parameter values are typically not affected and, accordingly, the qualitative conclusions made from the data are not different (22). As an example of this, we showed in the present data set, that the qualitative conclusions were the same using two very different means of determining stresses and strains despite marked differences in quantitative aspects of the results. Another limitation of stress-strain analysis is that it provides an assessment of average material properties which, in the case of the embolized heart, represent a composite of contracting myocardium and scar. To the extent that the scar tissue is much stiffer than the surviving myocardium, it is possible to assess the impact of the presence of scar on the results. As detailed above and in the Appendix, our analysis indicates that this does not introduce a major limitation in interpretation. Furthermore, because scar tissue does not actively contract, conclusions pertaining to active force generation (and specifically end systole) are even

![Fig. 9. Theoretical effect of scar in chronic settings on stress-strain relations. Although introduction of scar made both relations stiffer, effect was relatively small. See text for details of this analysis.](image-url)
less likely to be influenced by the nature of the analysis. On the other hand, the results we obtained and the theoretical analysis point to a lack of sensitivity of the stress-strain analysis for detecting major changes in the composition of the ventricular wall. This conclusion is noteworthy, since stress-strain analysis of one form or another is the only technique available for assessing myocardial properties in the intact heart.

**Summary**

In summary, repeated coronary embolization leads to moderate sustained left ventricular dysfunction. The left ventricles of such hearts are characterized by diastolic pressure-volume curves that are shifted toward larger volumes (remodeling) but have a net chamber stiffness that is not different from normal. The ESPVR is shifted toward larger volumes and has a shallower slope (decreased chamber contractile state). Stress-strain analysis suggests that the average composite myocardial properties in the chronically remodeled heart are similar to those of normal hearts in this model of heart failure. The energetics of contraction are not significantly affected. These data serve as an important baseline characterization of the alterations in chamber contractile properties in this model of irreversible left ventricular dysfunction. Many differences between this model and the more commonly studied rapid pacing model of heart failure have been noted. This observation reveals that conclusions about ventricular properties in heart failure vary with the model and possibly the underlying severity of the heart failure.

**APPENDIX**

**Effect of Scar on Stress-Strain Relationship: A Theoretical Analysis**

The purpose of this analysis was to assess the effect of scar within the myocardial wall on stress-strain relationships in the chronic setting where both the ventricular chamber and the myocytes undergo structural remodeling. Assume that the stress-strain (σ-ε) relationship of normal myocardium is described by the following equation

\[ \sigma = a\epsilon^b + c \]  

(A1)

where \( a, b, \) and \( c \) describe material properties and the values of these parameters will be different during systole and diastole. By definition, strain is equal to

\[ \epsilon = \ln \left( \frac{L}{L_0} \right) - \ln \left( \frac{x}{L_0} + 1 \right) \]  

(A2)

where \( L \) is muscle length, \( L_0 \) is the reference (unstressed) muscle length, and \( x \) is amount of muscle extension beyond the unstressed length (\( x = L - L_0 \)). By substitution

\[ \epsilon = a(x/L_0 + 1)^b + c \]  

(A3)

For the case of infarct, there is loss of muscle mass which is replaced with scar. Over time, the surviving muscle hypertrophies and elongates (1, 13). The expected effects of these processes are a normalization of total myocardial mass (Table 1) and an increase in LV unstressed volume (Table 2). In accordance with these experimental observations, we make the following assumptions. 1) that the properties of the surviving muscle are normal (Eq. A1), 2) that the hypertrophic response exactly balances the loss of muscle mass due to infarction, and 3) that the scar is a rigid element. On the basis of these assumptions, the net effect on the composite myocardium (normal myocardium plus scar) is to increase \( L_0 \) by an amount related to the amount of myocardium that was infarcted; that is, \( L_0 \) for the chronic state (\( L_0 \)) will be increased to \( \alpha L_0 \), where \( \alpha \) is a scaling factor equal to the sum of one plus the percent of the myocardium that is scarred. In such a case, the relationship between myocardial stress and displacement (\( x \) in Eq. A2) would be the same as in normal muscle (since the scar is considered to be a rigid element). However, strain in this chronic setting (\( \epsilon_c \)) would now be calculated as follows

\[ \epsilon_c = \ln \left( \frac{L}{L_0} \right) = \ln \left( \frac{L}{\alpha L_0} \right) = \ln \left( \frac{x}{\alpha L_0} + 1 \right) \]  

(A4)

By substitution, this can be simplified to the following

\[ \sigma = a[\alpha(e^{\epsilon_c} - 1) + 1]^b + c \]  

(A5)

Figure 9 shows systolic (A) and diastolic (B) stress-strain relations using values for \( a, b, \) and \( c \) taken from a representative normal heart (solid lines) for both systole and diastole. To simulate a chronic state, \( \alpha \) was set at a value of 1.2 based on our and previous findings showing that, in the chronic state, a maximum 20% of the ventricular wall is composed of scar in this model (16). The predicted stress-strain relations for this case, shown by the dashed lines, revealed a rather small upward shift of both diastolic and systolic stress-strain relationships. The predicted change in the relationship is smaller than the interanimal variability normally observed in these measurements (Fig. 4). Furthermore, two factors suggest that the prediction provided by this analysis will overestimate the differences between normal and diseased state: 1) scar tissue has some elasticity and is not truly rigid, and 2) the percent of scar chosen for the simulation (20%) represents an upper bound on what has been observed in this model. Thus, subject to the assumptions of the analysis, the average stress-strain relationship of the chronically embolized, remodeled myocardium may not differ substantially from normal, despite the marked changes in composition of the ventricular wall.

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Address for reprint requests: K. Todaka, Div. of Circulatory Physiology, Columbia University, Milstein Hospital Bldg., Rm. 5–435, 111 Fort Washington Ave., New York, NY 10032.

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