Left ventricular diastolic function of remodeled myocardium in dogs with pacing-induced heart failure

STEVEN B. SOLOMON,1,2 SRDJAN D. NIKOLIC,3 STANTON A. GLANTZ,2 AND EDWARD L. YELLIN1
1Departments of Cardiothoracic Surgery and Biophysics and Physiology, Albert Einstein College of Medicine, Bronx, New York 10461; 2Cardiovascular Research Institute and Department of Medicine, University of California, San Francisco 94143; and 3Department of Cardiovascular and Thoracic Surgery, Research Institute of the Palo Alto Medical Foundation, Stanford University School of Medicine, Palo Alto, California 94306

Solomon, Steven B., Srdjan D. Nikolic, Stanton A. Glantz, and Edward L. Yellin. Left ventricular diastolic function of remodeled myocardium in dogs with pacing-induced heart failure. Am. J. Physiol. 274 (Heart Circ. Physiol. 43): H945–H954, 1998.—In patients with heart failure, decreased contractility resulting in high end-diastolic pressures and a restrictive pattern of left ventricular filling produces a decrease in early diastolic filling, suggesting a stiff ventricle. This study investigated the elastic properties of the myocardium and left ventricular chamber and the ability of the heart to utilize elastic recoil to facilitate filling during pacing-induced heart failure in the anesthetized dog. Elastic properties of the myocardium were determined by analyzing the myocardial stress-strain relation. Left ventricular chamber properties were determined by analyzing the pressure-volume relation using a logarithmic approach. Elastic recoil was characterized using a computer-controlled mitral valve occluder to prevent transmitial flow during diastole. We conclude that, during heart failure, the high end-diastolic pressures suggestive of a stiff ventricle are due not to stiffer myocardium but to a ventricle whose chamber compliance characteristics are changed due to geometric remodeling of the myocardium. The restrictive filling pattern is a result of the ventricle being forced to operate on the stiff portion of the diastolic pressure-volume relation to maintain cardiac output. Slowed relaxation and decreased contractility result in an inability of the heart to contract to an end-systolic volume below its diastolic equilibrium volume. Thus the left ventricle cannot utilize elastic recoil to facilitate filling during heart failure.

cardiac mechanics; restrictive pattern of filling; elastic recoil

In patients with heart failure, the heart undergoes considerable remodeling, which produces changes in diastolic properties and function. These diastolic properties, combined with atrial function, determine the atrioventricular pressure gradient, the driving force for left ventricular filling. During heart failure, a restrictive left ventricular filling pattern is observed. The restrictive pattern of left ventricular filling is composed of an early filling wave that is narrowed with an increased peak velocity and a late filling wave that is also narrowed with a decreased peak velocity (1, 21). It is not clear what changes in diastolic properties, left ventricular relaxation or myocardial or chamber stiffness, are responsible for the restrictive pattern of left ventricular filling.

The restrictive pattern of left ventricular filling during heart failure suggests an increase in chamber stiffness. This increase in chamber stiffness is consistent with the findings of Ohno et al. (22), who found an increase in the chamber stiffness (dP/dV) during heart failure. Whether this increase in chamber stiffness is due to an increase in myocardial stiffness or simply a reflection of changed geometry has not been determined. Some investigators have assumed that myocardial stiffness is increased, as reflected by an increase in end-diastolic pressure (P_{es}), and is responsible for abnormalities in diastolic function (16). This conclusion is partially supported by Kajstura et al. (15), who investigated the cellular and structural changes in the remodeled heart and showed a moderate increase in fibrosis and myocyte death. In contrast, Spinale et al. (26, 27) showed a decrease in fibrosis and myocyte death. These changes in the myocardium shown by Spinale et al. (26, 27) would be inconsistent with an increase in myocardial stiffness. Thus it is unclear whether the myocardium is stiffer during heart failure.

Several researchers have shown that left ventricular filling is facilitated by negative pressures produced in the normal left ventricle (11, 20, 33). The development of negative pressures in the left ventricle has been characterized as demonstrating elastic recoil (diastolic suction) (20, 30). The presence of elastic recoil depends on the ability of the myocardium to contract to an end-systolic volume below the equilibrium volume (V_{0}), the volume at zero transmural pressure. During left ventricular relaxation, the internal elastic forces restore the chamber to its initial shape, resulting in a negative transmural pressure. Thus elastic recoil is dependent on the contractile function of the myocardium and the extent of left ventricular relaxation (20). Damiano et al. (8) showed that a decrease in contractility is the first functional change to occur as the heart fails. This decrease in contractility leads to dilation and chamber remodeling, which leads to increases in ventricular dimension and slowed left ventricular relaxation. Thus, during heart failure, contractile function and left ventricular relaxation are impaired, suggesting that the ability of the heart to utilize elastic recoil to facilitate early diastolic filling is impaired.

This study was designed to test the hypothesis that the increase in chamber stiffness during pacing-induced heart failure is not due to an increase in myocardial stiffness but to left ventricular dilation. We also hypothesized that if the myocardium was not stiffer, the restrictive pattern of left ventricular filling...
is due to the left ventricle operating on the stiff portion of the diastolic pressure-volume relation to maintain cardiac output. In addition, we hypothesized that impaired contractility and left ventricular relaxation during pacing-induced heart failure results in the inability of the ventricle to contract to an end-systolic volume below \( V_0 \), resulting in the absence of elastic recoil to facilitate filling.

**METHODS**

Two protocols were performed to investigate the effects of pacing-induced heart failure on the hemodynamic measurements, myocardial and chamber properties, and filling patterns of the left ventricle. Protocol 1 examined the hemodynamic, echocardiographic, and morphological changes that occur at baseline, 1 wk, and 6 wk of left ventricular pacing. Protocol 2 investigated changes in left ventricular relaxation, elastic recoil and myocardial and chamber stiffness. Left ventricular relaxation and elastic recoil were determined independently of the effects of mitral filling by implanting a computer-controlled mitral valve (25) and preventing flow into the left ventricle during diastole. Myocardial and chamber stiffness were calculated from the left ventricular diastolic pressure-volume curve in control dogs and in another set of dogs after 4 wk of left ventricular pacing.

In all dogs, a pacemaker was implanted and was left off until the animals recovered from surgery. In protocol 1, a baseline study (hemodynamic and echocardiographic measurements) was performed, and the pacemakers were turned on. After 6 wk of pacing, the pacemaker was turned off, and the baseline study was repeated. Echocardiographic measurements were performed each week. In protocol 2, the dogs were divided into two groups, control and heart failure. In the control group, the pacemakers were not turned on, and after 4 wk, a study was performed. In the heart-failure group, the pacemakers were turned on for 4 wk. After 4 wk of left ventricular pacing, the pacemakers were turned off, and a study was performed. The duration of pacing in the two protocols was of different lengths because, after 6 wk of pacing, the dogs were too ill to tolerate the surgery necessary to implant the computer-controlled mitral valve needed for protocol 2. All the dogs were in heart failure by 4 wk.

**Pacemaker Implantation**

Adult mongrel dogs were anesthetized with thiopental sodium (15 mg/kg) followed by intubation and mechanical ventilation. Halothane (1–1.5%) was then administered via the endotracheal tube for the duration of the procedure. A right thoracotomy at the fourth intercostal space was made under sterile conditions, the pericardium was opened, and the left ventricular apex was exposed. A pacing lead was attached to the apex of the left ventricle and tunneled back into a subcutaneous pocket that was made below the rib cage. A programmable pacemaker (Medtronic 5984LP, Minneapolis, MN) was attached to the pacing lead and secured in the pocket. The pericardium was left open and the thoracotomy was closed. In both protocols, the pacemaker was implanted in the same position. Postoperatively, the dogs were given oxymorphone hydrochloride (1.5 mg) immediately with additional analgesia as needed. Gentamicin sulfate (40 mg) and cefazolin, sodium salt (Kezol, 2 g) were administered for 7 days. Temperature, heart rate, respiration rate, and stool were monitored daily. After a 7- to 10-day recovery period and the absence of sepsis, the pacemaker was activated at a rate of 240 beats/min, and the dogs were paced continuously for 6 wk in protocol 1 and 4 wk in the heart-failure group in protocol 2. The final results for protocol 1 include seven pacing-induced heart-failure dogs (22–30 kg) each used as its own control. The results for protocol 2 include five pacing-induced heart-failure dogs and five control dogs (23–32 kg). These numbers do not include 4 dogs in protocol 1 and 10 dogs in protocol 2 that were lost due to sepsis, sudden death, or arrhythmia.

**Protocol 1. Hemodynamic and Echocardiographic Study**

Under sterile conditions at the time of pacemaker implantation, the dogs were instrumented as follows. They were anesthetized with thiopental sodium (15 mg/kg), intubated, mechanically ventilated, and administered fentanyl (5–10 µg/kg) every 30 min via the femoral vein. After a midline sternotomy, the heart was supported in a pericardial cradle. Left atrial and left ventricular pressures were measured with micromanometers (Millar Instruments, Houston, TX) inserted via the pulmonary vein and the carotid artery. A fluid-filled catheter positioned at the level of the heart was used to establish the reference zero level. The left atrial and left ventricular pressure traces were carefully matched during diastole (13). A Swan-Ganz catheter was inserted into the left external jugular vein and positioned in the pulmonary artery. Mean arterial pressure, the first time derivative of left ventricular pressure (dP/dt), and electrocardiograms (ECG) were also recorded. All pressures were calibrated, zeroed, and recorded on a photographic recorder (VR-12, Electronics For Medicine, White Plains, NY) at a speed of 100 mm/s. The data were also recorded on CODAS (Dataq Instruments, Akron, OH), a computer-based real-time data acquisition system, at 200 samples/s. All studies were performed after the pacemaker was deactivated, a steady-state was achieved, and the respirator was turned off. All measurements were made with a heart rate below 100 beats/min, obtained by infusion of ULSF-49, a bradycardic agent that directly affects the sino-atrial node without any other hemodynamic effects (14). The heart rates were decreased below 100 beats/min because, at faster rates, it is difficult to interpret mitral filling patterns using Doppler echocardiography (HP Sonos 100, Andover, MA). Hemodynamic measurements in each dog were made at baseline and after 6 wk of left ventricular pacing. A typical run in the hemodynamic study consisted of recording 10–15 control beats after hemodynamic steady-state conditions were reached. Pressures and flow were synchronized by a marker (voltage shift) on the video and photographic records. Echocardiography was performed at baseline and at weekly intervals. Each week the dogs were anesthetized with thiopental sodium (15 mg/kg), intubated, mechanically ventilated, and administered fentanyl (5–10 µg/kg) intravenously every 30 min. ULSF-49 was administered to maintain a heart rate below 100 beats/min. Pulsed Doppler mitral flow velocity was measured at the tip of the mitral leaflets, and left ventricular M-mode short-axis dimensions were measured below the level of the papillary muscles and were recorded on video tape for later playback and analysis.

**Protocol 2. Mitral Valve Occlusion**

Left ventricular pressure and volume were measured to determine the diastolic pressure-volume relation. A micromanometer was placed in the left ventricle via an apical stick. Volume was measured with a 7-Fr eight-electrode conductance catheter (Cordis Europa NV, Roden, The Netherlands) inserted into the left ventricle via the right carotid artery and connected to electronics (Leuem-Sigma 5, Leiden, The Netherlands) that convert the conductance signal into a volume.
The tip of the conductance catheter was placed at the apex of the ventricle, positioned to avoid contact with the walls of the chamber. A standard calibration function was used to correct left ventricular volume by adjusting for the parallel conductance volume and slope (2, 3). Parallel conductance was found by bolus injection of 10 ml of hypertonic saline (5%) into the pulmonary artery (2, 3).

Data analysis

A modified prosthetic mitral valve that allowed for independent control of ventricular filling (25) was implanted after 4 wk of left ventricular pacing. The prosthetic mitral valve is a Bjork-Shiley pivoting disk valve. This valve was modified with a control cable that moves through the center of the valve ring perpendicular to the direction of flow through the valve. The cable allows the valve to function in two modes, closed and neutral. The cable is attached to two opposing solenoids. For the closed position, the control cable is moved forward by the solenoids, forcing the disk to close the mitral orifice. For the neutral position, the control cable is retracted, and the valve moves under normal physiological pressures and flows. Activation of the valve is controlled by a computer in accordance with a delay after the ECG QRS and duration of the occlusion set by the investigator. To implant the mitral valve, a right thoracotomy was performed in the fourth intercostal space, and the pericardium was opened to expose the right atrium. The right atrium was opened, and the mitral leaflets and chordae were excised. The valve was implanted, and the control cable was guided through the left atrial appendage. The left atrium was closed, and the heart was returned to sinus rhythm by defibrillation. After return to a steady-state rhythm, the dog was weaned from bypass.

Data analysis

Hemodynamic measurements. Hemodynamic variables were measured from the left atrial and left ventricular pressure waveforms. Left ventricular end-diastolic pressure (LVEDP) was taken at the peak of the R wave on the ECG. Left atrial pressure crossover (Pco), and the times of first and second atrioventricular pressure crossover after Pco (t1, t2) were determined from the matched left atrial and left ventricular pressure traces. An index of the driving atrioventricular pressure gradient was calculated as the left atrial pressure at the onset of mitral flow minus the minimal left ventricular pressure, Pco – LVPmin. The time constant of isovolumic relaxation, t, was determined by fitting the left ventricular pressure between the times of dP/dtmin and left atrial Pco to the function P = P0 · e⁻⁰ᵗ, where P0 is the pressure at dP/dtmin and a decay to zero pressure is assumed (31, 33).

Echocardiographic measurements. The echocardiographic studies of the transmitral flow velocity patterns and M mode were performed using a Hewlett-Packard ultrasound system (Sonos 100) equipped with 2.5/3.5- and 5.0-MHz transducers. Diastolic filling time was determined echocardiographically as the duration of mitral flow. Acceleration (Ea) and deceleration (Ed) times were measured from the onset of the E wave (early filling wave) to E wave peak and from the E wave peak to E wave termination, respectively. The mean acceleration (Ea) and deceleration (Ed) rates were calculated as peak velocity divided by the respective acceleration and deceleration intervals, Ea and Ed. The flow areas Ea and Ed were calculated as one-half of the total duration of the respective waveform (Ea or Ed) multiplied by the wave's peak velocity.

Ventricular wall mass was calculated from the M-mode echocardiographic data according to

\[ M_{LV} = (4\pi/3)(r_i^2 - r_o^3) \]

where M_{LV} is the left ventricular wall mass, r_i is the inner radius, and r_o is the outer radius. Measurements were made at end diastole. Because this is based on a spherical construct, M_{LV} will become more accurate as the normally elliptical heart becomes more spherical with the onset of heart failure.

Characterization of passive diastolic pressure-volume relation. The diastolic pressure-volume relation is characterized using Nikolic et al.'s approach (20)

\[ P = -S_o \ln [(V_m - V)/V_m - V_{on}]] \]

where S_o is a parameter that describes the curvature of the pressure-volume relation, V_{on} is the equilibrium volume, and V_m is the maximal attainable volume of the ventricular chamber.

Characterization of passive myocardial stress-strain relation. To estimate the myocardial stress-strain relation, we used the ventricular pressure-volume relation based on a thick-walled version of the Laplace relation and the exponential stress-strain relation for the myocardium (10). The passive diastolic stress-strain relation that describes the myocardium's nonlinear elasticity is (10)

\[ \sigma = (a \epsilon^2 - 1) \]

where \( \sigma \) is stress (force/area in the myocardial wall); \( \epsilon \) is Lagrangian strain, (1 - l_0/l_0), where l is the increase in length, relative to the equilibrium length, l_0, which reflects the amount of sarcomere stretch (fractional extension from rest length); and a and b are parameters that describe muscle stiffness. a, b, and the equilibrium volume of the left ventricle, V_{eq}, are calculated directly from the diastolic pressure-volume relation using (10)

\[ P = \alpha(2 + \eta)(\exp [\beta(2 + \eta)(3\pi^2/32)^{1/3} - x_0] - 1) \]

where

\[ \eta = h(4\pi/3V)^{1/3} \]

\[ x_0 = n[(3\pi^2/4)^{1/3} + h/2] \]

To characterize the changes in the passive elastic properties of the myocardium, this equation was used to fit the end-diastolic pressure-volume data points from the passive with-
drawal of volume into the cardiopulmonary bypass reservoir performed in protocol 2.

Systolic pressure-volume relation. The slope of the end-systolic pressure-volume relation, $E_{es}$, an index of contractility, was determined by linear regression analysis of the end-systolic pressure ($P_{es}$) and volume ($V_{es}$) data obtained during passive withdrawal of volume into the cardiopulmonary bypass reservoir combined with mitral occlusions using

$$P_{es} = E_{es}(V_{es} - V_0)$$

where $E_{es}$ is the slope and dead volume, $V_0$, is the volume-axis intercept of the end-systolic pressure-volume relation (29). The end-systolic pressure-volume data points were calculated from the maximal pressure-volume ratio normalized to $V_d$, $P/(V - V_d)$, using Kono et al.’s method (17).

Statistical Methods

To estimate the parameters in the Nikolic et al. (20) and Glantz and Kernoff (10) equations, we used a nonlinear regression using the Marquardt-Levenberg algorithm to find the parameters of the independent variables that give the best fit between the equation and the data. The ln($a$) was used as the parameter to estimate in the Glantz and Kernoff equation to provide a better conditioned nonlinear parameter estimation problem. The nonlinear regression algorithm seeks the values of the parameters that minimize the sum of the squared differences between the values of the observed and predicted values of the dependent variable. The fitting process is stopped when the difference of the square root of the sum of the squares of the residuals for two consecutive fits was < 0.0001.

Values are presented as means ± SD. Differences between serial measurements in protocol 1 were analyzed using repeated-measures analysis of variance followed by Student-Newman-Keuls for multiple comparison testing. Differences between measurements in control and dogs with heart failure in protocol 2 were compared by unpaired Student’s t-test. Computations were done with SigmaStat (version 2.0., Jandel Scientific, San Rafael, CA). We considered differences significant at P < 0.05.

$V_0$ calculated by the Nikolic et al. (20) and Glantz and Kernoff (10) methods, $V_{0N}$ and $V_{0G}$, were compared using the Bland-Altman method. The Bland-Altman method showed that these two estimates of $V_0$ were similar (see RESULTS); so we computed a single estimate of equilibrium volume as $V_0 = (V_{0N} + V_{0G})/2$. As presented in RESULTS, we found that $V_0$ and $V_d$ increased with heart failure. To determine whether the increase in $V_d$ simply reflected an increase in heart size (as reflected by $V_0$), we examined the linear relationship between $V_d$ and $V_0$ in the control and dogs with heart failure and then compared this relationship with an overall test of coincidence.

RESULTS

All the dogs in protocols 1 and 2 developed congestive heart failure, showing signs of lethargy, shortness of breath, and ascites. None of the dogs used for data collection showed any signs of sepsis.

Protocol 1. Hemodynamic and Echocardiographic Study

Hemodynamic data. Typical oscillographic records of pressure and flow in normal and heart-failure dogs are illustrated in Fig. 1. After 6 wk of pacing, minimal left ventricular pressure increased from $0.1 ± 0.6$ to $12.4 ± 3.0$ mmHg and LVEDP increased from $6.7 ± 3.2$ to $35 ± 16$ mmHg (Table 1). The pressure crossover (pressure at time of mitral valve opening) also increased markedly ($7.5 ± 6.0$ vs. $32.5 ± 12.0$ mmHg, P < 0.0001). These changes represent a fivefold increase in LVEDP and a fourfold increase in pressure crossover after 6 wk of ventricular tachycardia. Time to $t_1$ and $t_2$, the first and second pressure reversals after pressure crossover, decreased significantly (P < 0.01) compared with controls ($99 ± 18$, $191 ± 20$ vs. $73 ± 10$ ms, $134 ± 16$ ms, respectively). $P_{co} - P_{min}$, the atrioventricular pressure difference, increased from $6.1 ± 3.3$ at baseline to $24 ± 7$ mmHg after 6 wk of pacing (P < 0.0001). The increase in filling pressures ($P_{ed}$, $P_{co}$, $P_{min}$), atrioventricular pressure gradient, and decreased time until pressure reversal ($t_1$ and $t_2$) suggest that the ventricular chamber is stiffer. Peak systolic pressure ($P_{max}$) was unchanged. $t_1$ increased ($37 ± 12$ vs. $49 ± 5$ ms, P < 0.05) reflecting an impaired left ventricular relaxation. Cardiac output (CO) was unchanged after 6 wk of pacing compared with control (P = 0.71).
and total time (Eat wave (early filling), velocity, area, acceleration time, and E wave deceleration; A, peak velocity during late filling; Aarea, area of late filling. *Significantly different from baseline; †significantly different from 1 wk of pacing.

Values are means ± SD; n = 7 dogs. E, peak velocity during early filling; Earea, area of early filling; Eacc, E wave acceleration time; Edec, E wave deceleration time; Emax, total E wave time; Eacc, E wave acceleration; Edec, E wave deceleration; A, peak velocity during late filling; Aarea, area of late filling. *Significantly different from baseline; †significantly different from 1 wk of pacing.

although Eacc and Edec decreased between 1 and 6 wk of pacing (503 vs. 667 cm/s, respectively), after 6 wk of pacing, they more than doubled from baseline values (1,372 ± 334 vs. 670 ± 385 and 1,649 ± 1,094 vs. 667 ± 234 cm/s², respectively). These changes in the early filling wave resulted in an increased velocity and decreased duration after 6 wk of pacing.

The A wave (late filling) velocity (41 ± 24 cm/s) and area (2.3 ± 1.1 cm) showed no change from baseline after 1 wk of pacing but decreased after 6 wk of pacing (23 ± 7 cm/s, 1.0 ± 0.4 cm, P < 0.001, respectively). These changes are summarized in Fig. 2 using the average values (without presenting SD for clarity). These results show an overall decrease in the amount of filling volume after the onset of heart failure. The increase in E wave velocity and decrease in E wave duration after 6 wk of pacing and the decreased A wave velocity and duration reflect a restrictive pattern of filling and suggest a stiff ventricular chamber.

M-mode echocardiographic short-axis dimension. The M-mode echocardiographic short-axis dimension was measured each week from baseline through 6 wk of pacing in protocol 1 (Fig. 3A). The end-diastolic dimension increased gradually and consistently from a baseline value of 4.26 ± 0.49 to 5.29 ± 0.67 cm after 6 wk of pacing. End-systolic dimension significantly increased in parallel to those found in the end-diastolic dimension from 2.92 ± 0.52 cm at baseline to 4.39 ± 0.63 cm at 6 wk.

Fractional shortening [(end-diastolic diameter − end-systolic diameter)/end-diastolic diameter], an ejection phase index of ventricular contractile performance, decreased significantly after 1 wk of pacing, 17 ± 3 vs. 10 ± 2.7 cm, respectively, after 1 wk of pacing.
32 ± 4%, and did not change significantly thereafter (Fig. 3B).

MLV was calculated from the difference between the left ventricular interior and exterior volumes at end diastole. The calculations were made serially from baseline to 6 wk of pacing. The calculated left ventricular wall mass increased each week from a baseline of 102 ± 6 to 199 ± 23 g (P < 0.0001) at 6 wk of pacing (Fig. 3C), coinciding with an increase in left ventricular wall thickness from 10 ± 2 to 15 ± 2 mm (Fig. 3D).

Protocol 2. Mitral Valve Occlusion Study

Hemodynamics. The Ped (10 ± 6 vs. 26 ± 4 mmHg, P < 0.0001) and Ved (55 ± 9 vs. 159 ± 31 ml, P < 0.0001) increased in heart failure compared with control (Table 3).

Table 3. Protocol 2. End-diastolic and end-systolic pressure and volume data: control vs. heart failure-mitral valve occlusion

<table>
<thead>
<tr>
<th>Dog No.</th>
<th>Ped, mmHg</th>
<th>Ved, ml</th>
<th>Pes, mmHg</th>
<th>Ves, ml</th>
<th>Pmin, mmHg</th>
<th>dP/dV at Ped, mmHg/ml</th>
<th>Ees, mmHg/ml</th>
<th>Vd, ml</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>6</td>
<td>60</td>
<td>96</td>
<td>40</td>
<td>−7.2</td>
<td>0.35</td>
<td>4.6</td>
<td>21</td>
</tr>
<tr>
<td>2</td>
<td>6</td>
<td>57</td>
<td>69</td>
<td>28</td>
<td>−4.6</td>
<td>0.46</td>
<td>2.1</td>
<td>30</td>
</tr>
<tr>
<td>3</td>
<td>10</td>
<td>51</td>
<td>95</td>
<td>32</td>
<td>−2.1</td>
<td>0.51</td>
<td>2.7</td>
<td>7</td>
</tr>
<tr>
<td>4</td>
<td>12</td>
<td>42</td>
<td>110</td>
<td>21</td>
<td>−3.6</td>
<td>0.50</td>
<td>2.4</td>
<td>26</td>
</tr>
<tr>
<td>5</td>
<td>14</td>
<td>65</td>
<td>82</td>
<td>38</td>
<td>−0.5</td>
<td>0.64</td>
<td>5.4</td>
<td>61</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>10 ± 4</td>
<td>55 ± 9</td>
<td>90 ± 16</td>
<td>32 ± 8</td>
<td>−3.6 ± 2.5</td>
<td>0.49 ± 0.10</td>
<td>3.4 ± 1.5</td>
<td>27 ± 16</td>
</tr>
<tr>
<td>Heart failure</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>20</td>
<td>114</td>
<td>111</td>
<td>101</td>
<td>0.5</td>
<td>1.2</td>
<td>2.4</td>
<td>104</td>
</tr>
<tr>
<td>7</td>
<td>25</td>
<td>171</td>
<td>119</td>
<td>144</td>
<td>2.3</td>
<td>1.5</td>
<td>1.4</td>
<td>108</td>
</tr>
<tr>
<td>8</td>
<td>27</td>
<td>142</td>
<td>107</td>
<td>126</td>
<td>6.7</td>
<td>1.3</td>
<td>1.2</td>
<td>99</td>
</tr>
<tr>
<td>9</td>
<td>31</td>
<td>179</td>
<td>101</td>
<td>146</td>
<td>1.9</td>
<td>0.96</td>
<td>1.4</td>
<td>78</td>
</tr>
<tr>
<td>10</td>
<td>26</td>
<td>189</td>
<td>122</td>
<td>169</td>
<td>3.5</td>
<td>1.6</td>
<td>1.6</td>
<td>123</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>26 ± 4</td>
<td>159 ± 31</td>
<td>112 ± 9</td>
<td>137 ± 25</td>
<td>3.0 ± 2.4</td>
<td>1.3 ± 0.25</td>
<td>1.6 ± 0.5</td>
<td>102 ± 16</td>
</tr>
<tr>
<td>P</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>&lt;0.03</td>
<td>&lt;0.0001</td>
<td>&lt;0.003</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Ved, end-diastolic volume; Ped, end-systolic pressure; Ved, end-systolic volume; Pmin, minimum pressure after an end-systolic occlusion; dP/dV at Ped, an index of chamber stiffness at end-diastolic pressure; Ees, end-systolic elastance; Vd, dead volume.
dP/dV at Ped, an index of chamber stiffness, increased heart failure compared with the control. The minimal pressure after mitral valve occlusions fit to the Glantz and Kernoff (10) equation; V0, average equilibrium volume. (20) equation to fit the end-diastolic pressure-volume data points in Fig. 4A shows a typical series of end-diastolic pressure-volume data points fitted by Nikolic et al.’s equation (20) during mitral valve occlusions. These results show that chamber stiffness did not change and that the hearts are severely dilated after 4 wk of pacing.

We examined the relationship between left ventricular equilibrium volume estimated using the Nikolic et al. (20) equation, V0N, and the Glantz and Kernoff (10) equation, V0G, in control and heart-failure dogs by comparing the linear regression lines fit to the two groups of dogs with an overall test of coincidence. This test showed no difference between the relationship of V0N and V0G in controls or heart failure (P = 0.56), i.e., they fell on the same straight line (Fig. 5A). The Bland-Altman method was then applied and showed that the two measures of equilibrium volume yielded similar results [mean difference = 3.4 ± 9.0 ml (SD); Fig. 5A, inset]. We therefore calculated an average equilibrium volume, \( V_0 = (V_{0N} + V_{0G})/2 \), and used it throughout the remainder of the study. \( V_0 \) was bigger in heart failure than controls (103 ± 14 vs. 38 ± 17 ml, P < 0.01).

### Table 4. Protocol 2. Diastolic properties of left ventricle control vs. heart failure mitral valve occlusion

<table>
<thead>
<tr>
<th>Dog No.</th>
<th>( S_p ) mmHg</th>
<th>( V_m, ) ml</th>
<th>( V_{0N}, ) ml</th>
<th>( V_m-V_{0N}, ) ml</th>
<th>( r^2 )</th>
<th>ln(( \alpha ))</th>
<th>( \alpha, ) mmHg</th>
<th>( \beta, ) ml</th>
<th>( V_{0G}, ) ml</th>
<th>( V_0, ) ml</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>18.2</td>
<td>110</td>
<td>36</td>
<td>74</td>
<td>0.96</td>
<td>−28.4</td>
<td>5 × 10^{-13}</td>
<td>29.4</td>
<td>25</td>
<td>0.98</td>
</tr>
<tr>
<td>2</td>
<td>4.9</td>
<td>91</td>
<td>55</td>
<td>46</td>
<td>0.97</td>
<td>−26.0</td>
<td>5 × 10^{-12}</td>
<td>26.9</td>
<td>48</td>
<td>0.98</td>
</tr>
<tr>
<td>3</td>
<td>12.7</td>
<td>62</td>
<td>11</td>
<td>51</td>
<td>0.91</td>
<td>−26.3</td>
<td>4 × 10^{-12}</td>
<td>28.6</td>
<td>8</td>
<td>0.96</td>
</tr>
<tr>
<td>4</td>
<td>17.5</td>
<td>85</td>
<td>46</td>
<td>38</td>
<td>0.92</td>
<td>−23.8</td>
<td>5 × 10^{-11}</td>
<td>23.4</td>
<td>55</td>
<td>0.99</td>
</tr>
<tr>
<td>5</td>
<td>9.4</td>
<td>86</td>
<td>51</td>
<td>34</td>
<td>0.90</td>
<td>−21.2</td>
<td>6 × 10^{-10}</td>
<td>21.2</td>
<td>48</td>
<td>0.99</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>12.5 ± 5.6</td>
<td>87 ± 17</td>
<td>40 ± 18</td>
<td>49 ± 16</td>
<td>0.93 ± 0.03</td>
<td>−25.1 ± 2.7</td>
<td>1 ± 3 × 10^{-10}</td>
<td>25.9 ± 3.5</td>
<td>37 ± 20</td>
<td>0.98 ± 0.01</td>
</tr>
</tbody>
</table>

Heart failure

<table>
<thead>
<tr>
<th>No.</th>
<th>Sp, coefficient of chamber stiffness; Vm, maximal volume; V0N, equilibrium volume as calculated by Nikolic et al. (20) method; Vm–V0, operating range; r2, goodness of fit from nonlinear regression; α, β, parameters of muscle elasticity; V0G, equilibrium volume as calculated by Glantz and Kernoff (10) method; V0, average equilibrium volume.</th>
<th>Sp, mmHg</th>
<th>Vm, ml</th>
<th>V0N, ml</th>
<th>Vm–V0, ml</th>
<th>r2</th>
<th>ln(α)</th>
<th>α, mmHg</th>
<th>β, ml</th>
<th>V0G, ml</th>
<th>V0, ml</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>14.5</td>
<td>139</td>
<td>101</td>
<td>37</td>
<td>0.97</td>
<td>−9.4</td>
<td>8 × 10^{-5}</td>
<td>27.5</td>
<td>113</td>
<td>0.97</td>
<td>106</td>
</tr>
<tr>
<td>7</td>
<td>8.5</td>
<td>227</td>
<td>118</td>
<td>101</td>
<td>0.98</td>
<td>−24.6</td>
<td>2 × 10^{-11}</td>
<td>15.7</td>
<td>104</td>
<td>0.96</td>
<td>113</td>
</tr>
<tr>
<td>8</td>
<td>16.3</td>
<td>179</td>
<td>123</td>
<td>62</td>
<td>0.96</td>
<td>−11.7</td>
<td>8 × 10^{-8}</td>
<td>18.5</td>
<td>114</td>
<td>0.94</td>
<td>116</td>
</tr>
<tr>
<td>9</td>
<td>16.3</td>
<td>162</td>
<td>88</td>
<td>83</td>
<td>0.95</td>
<td>−28.1</td>
<td>2 × 10^{-13}</td>
<td>21.2</td>
<td>78</td>
<td>0.95</td>
<td>82</td>
</tr>
<tr>
<td>10</td>
<td>12.6</td>
<td>166</td>
<td>95</td>
<td>67</td>
<td>0.96</td>
<td>−20.6</td>
<td>1 × 10^{-9}</td>
<td>27.1</td>
<td>100</td>
<td>0.99</td>
<td>99</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>11.3 ± 4.8</td>
<td>175 ± 33</td>
<td>105 ± 15</td>
<td>70 ± 24</td>
<td>0.96 ± 0.01</td>
<td>−19.1 ± 8.4</td>
<td>5 × 10^{-4}</td>
<td>22 ± 5.2</td>
<td>102 ± 15</td>
<td>0.96 ± 0.02</td>
<td>103 ± 14</td>
</tr>
<tr>
<td>P</td>
<td>&lt;0.73</td>
<td>&lt;0.0001</td>
<td>&lt;0.13</td>
<td>&lt;0.063</td>
<td>0.17</td>
<td>&lt;0.11</td>
<td>&lt;0.20</td>
<td>&lt;0.0001</td>
<td>&lt;0.08</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
</tbody>
</table>
Vd and V0 and found a single linear relationship for both the control and heart-failure dogs (P < 0.0001; Fig. 5B). The slope was not significantly different from 1.09 ± 0.13 (SE), P < 0.92, and the intercept was not significantly different from 0 [-12.3 ± 10.3 (SE) ml, P < 0.56]. Therefore the increase in Vd seems to reflect an increase in left ventricular size as measured by V0.

DISCUSSION

In this study, pacing-induced heart failure produced a decrease in chamber contractility, resulting in an increase in chamber pressures and volumes and simultaneously increasing chamber size, producing a restrictive pattern of mitral flow. This restrictive pattern of filling is not due to a stiffer left ventricle because myocardial passive elastic properties do not change during heart failure compared with control. The rightward shift in the diastolic pressure-volume curve that occurs during heart failure is due to the fact that the equilibrium volume of the left ventricle increases. Thus the restrictive pattern of filling during heart failure is due to the left ventricle operating on a stiffer portion of the passive diastolic pressure-volume curve, quantified as an increase in dP/dV at end-diastolic pressure.

We also found that by preventing the ventricle from filling at end systole, we could separate the effects of passive filling from active relaxation. During heart failure, the nonfilling hearts could not actively relax to a negative pressure below the equilibrium volume compared with the baseline end-systolic occlusions (Fig. 4A). This inability of the myocardium to relax to a negative pressure prevented these failure hearts from utilizing the stored energy of elastic recoil to facilitate filling. During heart failure, when a restrictive pattern of filling exists, the myocardium cannot employ this ultrastructural mechanism for creating the internal restoring forces necessary for elastic recoil.

Pacing-induced tachycardia was first used to produce an experimental canine preparation of heart failure by...
Coleman et al. (7). These investigators and others (6, 8, 19, 32) demonstrated that rapid ventricular pacing for 2–8 wk increased LVEDP, produced biventricular dilation, and ascites. These observations showed that the pacing-induced model of heart failure produces both hemodynamic and ultrastructural changes similar to heart failure seen in humans (4, 23, 24). Results of the present study show that ventricular pacing at 240 beats/min for 4 or 6 wk produces increases in the determinants of diastolic filling, end-diastolic pressure, left atrial pressure crossover, and t.

The increase in t shows that ventricular relaxation, a component of the atrioventricular pressure gradient, is impaired. Our results show that there is no change in total diastolic filling time between control and heart-failure dogs despite the slowed relaxation. Ishida et al. (13) showed that increases in left atrial pressure can overcome slowing in the rate of left ventricular relaxation (5, 9). This result is consistent with our findings that although relaxation was slowed, a large increase in the atrioventricular pressure gradient maintained and even increased E wave velocity to maintain cardiac output, which did not change (2.3 ± 0.4 vs. 2.2 ± 0.5 l/min, P = 0.71). This result can be explained by an increase in left atrial pressure crossover, which initiates filling earlier and so maintains diastolic filling time. In addition to an increase in t, t1, and t2, the first and second reversals of atrioventricular pressure occurred earlier. The increase in left atrial pressure crossover and decrease in the times to pressure reversal suggest the failure heart is functioning on a stiffer portion of the pressure-volume curve compared with control. This conclusion is supported by our findings that dP/dVat end-diastolic pressure, an index of chamber stiffness, is significantly increased during heart failure compared with controls. These results show impaired relaxation can be compensated for by increasing left atrial pressure and, in a normal heart, increase contractile performance to maintain end-diastolic volume and pressure. In the failure heart, impaired relaxation coupled with diminished contractile function leads to an increase in end-diastolic volume and pressure, resulting in a heart that is forced to function on a stiffer portion of the pressure-volume curve.

These changes in t and the atrioventricular pressure gradient produce a change in the mitral flow pattern consistent with previous studies (12, 22). Peak velocity of early filling increased by 32%, with increases in acceleration and deceleration rates to twice the baseline values. The duration of early filling decreased by 40%, and the flow area was reduced by 25%. The increased amplitude of the E wave is due to the increase in atrioventricular pressure gradient. In late diastolic filling, both amplitude and duration of the A wave are reduced with the atrial contribution to total flow falling from 28 to 18%. The total diastolic flow velocity integral decreased by 33%. This diastolic filling pattern of a high peak E wave of short duration with high acceleration and deceleration and minimal A wave contribution describes a restrictive pattern of diastolic filling, which suggests an increase in left ventricular chamber stiffness (28). These results are consistent with the early filling patterns in dogs with increased chamber stiffness in response to phenylephrine (18). In patients, Spirito et al. (28) and Appleton et al. (1) described a similar restrictive pattern of diastolic filling. However, Appleton et al. (1) did not find any change in peak early filling velocity. When the left ventricle functions on a stiff portion of the pressure-volume relation, a small increase in ventricular volume produces a large increase in pressure. The restrictive pattern results from a large atrioventricular pressure gradient, which, at the time of mitral valve opening, sees a stiffer ventricle. The large pressure gradient in this study produces the high inflow velocity. In the ventricular chamber during heart failure, the increased stiffness at the operating volume causes a small amount of volume to increase pressure more rapidly than in controls. This increase results in an earlier reversal of atrioventricular pressure (illustrated by decrease in t1 and t2), and the more rapid reversals of pressure create a pattern of filling whose components, i.e., E and A waves, are of shortened duration compared with that of control ventricles. The restrictive pattern of filling during heart failure is a result of an increase in filling pressures and, inasmuch as our data show an increase in chamber size, due to geometric remodeling of the myocardium and not an increase in myocardial stiffness. The increase in equilibrium volume reflects the fact that the left ventricle is dilated during heart failure.

The time course and extent of remodeling during the development of heart failure was measured by serial M-mode echocardiography. Our results show increases in end-diastolic and end-systolic dimensions after 1 wk of pacing. Fractional shortening decreases by 50% after 1 wk of pacing with no additional changes for the remainder of the study. This result shows that the myocardium responds quickly to early impaired contractility by dilating. Similar echocardiographic changes have been reported to show a large increase in ventricular dimension after 1 wk of pacing and a gradual increase thereafter (12). Damiano et al. (8) also reported that rapid pacing resulted in significant left ventricular chamber dilation and reduced fractional shortening. We also found that left ventricular wall mass, due to an increase in wall thickness, or wall or chamber volume, calculated from M-mode echocardiographic data, increased significantly during heart failure. The extent of the increase in wall thickness found during heart failure was at the high end of increased wall thickness found in previous studies but was not inconsistent with those studies. The increase in wall thickness appears to be in response to the increase in systemic pressure. A possible source of error in the measurements of wall thickness may be due to the plane of measurement being close to the papillary muscles.

The restrictive pattern of filling reflects a ventricular chamber that functions at high end-diastolic pressure and volume on a stiff portion of the diastolic pressure-volume curve necessary to maintain cardiac output.
This filling pattern is a result of a decrease in contractility beginning after 1 wk of pacing tachycardia continuing throughout heart failure. The decrease in contractile function in conjunction with an impaired active relaxation during heart failure prevented these failure hearts from utilizing the stored energy of elastic recoil to facilitate filling. The change in the diastolic pressure-volume relation is due to the increase chamber size and not to a change in the myocardial elastic properties.

Address for reprint requests: S. Solomon, University of California, San Francisco, 505 Parnassus Ave., Box 0124, San Francisco, CA 94143-0124.

Received 30 April 1997; accepted in final form 13 November 1997.

REFERENCES


