Load-sensitive measures may overestimate global systolic function in the presence of left ventricular hypertrophy: a comparison with load-insensitive measures

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Connelly, K. A., D. L. Prior, D. J. Kelly, M. P. Feneley, H. Krum, and R. E. Gilbert. Load-sensitive measures may overestimate global systolic function in the presence of left ventricular (LV) hypertrophy: a comparison with load-insensitive measures. Am J Physiol Heart Circ Physiol 290: H1699–H1705, 2006. First published November 4, 2005; doi:10.1152/ajpheart.00577.2005.—Transgenic animal models have provided a vital insight into the pathogenesis of cardiovascular disease, but functional cardiac assessment is often limited by high heart rates and small heart size. We hypothesized that in the presence of concentric left ventricular (LV) hypertrophy (LVH), load-sensitive measures of contractility may be misinterpreted as overstating global cardiac function, because the normal function of excess sarcomeres may displace a greater volume of blood during contraction. Conductance catheter technology was used to evaluate pressure-volume (P–V) relationships as a load-insensitive method of assessing cardiac function in vivo in 18-wk-old heterozygous (mRen-2)27 transgenic rats (a model of LVH), compared with age-matched Sprague-Dawley (SD) controls. Anesthetized animals underwent echocardiography followed by P-V loop analysis. Blood pressure, body weight, and heart rate were higher in the Ren-2 rats (P < 0.05).

Load-sensitive measures of systolic function, including fractional area change, fractional shortening, ejection fraction, and positive peak rate of LV pressure development, were greater in the Ren-2 than control animals (P < 0.05). Load-insensitive measures of systolic function, including the preload recruitable stroke work relationship and the end-systolic P–V relationship, were not different between Ren-2 and SD rats. Regional wall motion assessed by circumferential shortening velocity suggested enhanced circumferential fiber contractility in the Ren-2 rats (P = 0.02), but tissue Doppler imaging, used to assess longitudinal function, was not different between groups. Although conventional measures suggested enhanced systolic function in the Ren-2 rat, load-insensitive measures of contractility were not different between Ren-2 and SD animals. These findings suggest that the normal range of values for load-sensitive indexes of contractility needs to be altered according to the degree of LVH. To accurately identify changes in systolic function, we suggest that a combination of echocardiography with assessment of load-insensitive measures be used routinely.

hypertension; conductance catheter; echocardiography; transgenic rat

TRADITIONAL ASSESSMENT of left ventricular (LV) systolic function relies on load-sensitive measurements performed with echocardiography, nuclear studies, MRI, or ventriculography. These measurements of cardiac function and the therapeutic effects of pharmacological or surgical interventions are often limited by the complex interdependency of cardiac properties, vascular loading, and other factors. Over the last two decades, pressure-volume (P–V) relationship analysis has evolved as the preferred method to elucidate changes in intrinsic cardiac function, independent of alterations in loading conditions (16). Although there are no truly load-insensitive measurements, the measurement of multiple P–V loops over a wide range of loading conditions can provide valuable insight and is better able to separate chamber function into primary systolic, diastolic, and ventricular loading properties (2).

Recent advances in conductance catheter technology have enabled the relatively simple acquisition of P–V data, with micromanometers allowing P–V analysis from a single catheter in a closed-chest model, in species ranging from human to mouse (35). Real-time analysis of indexes of contractility, diastolic function, and vascular coupling is now possible. Despite some limitations of the technology and assumptions made during interpretation of P–V data, conductance volumetry has evolved as the predominant method for P–V loop construction (2).

LV hypertrophy (LVH) represents the commonest condition whereby load-sensitive measures of contractility can be misinterpreted (4). The contraction of excess sarcomeres may mask subnormal function of cardiomyocytes in the presence of LVH by maintaining normal wall shortening and thickening values. Furthermore, radial and circumferential fiber contractility is preserved in LVH, but longitudinal fiber function may be impaired, possibly due to the effects of subendocardial ischemia (1). We hypothesized that load-sensitive methods of assessing cardiac contractility, which rely on circumferential or radial fiber function, such as the ejection fraction (EF), fractional shortening (FS), fractional area change (FAC), and the myocardial velocity of LV circumferential shortening (Vcf), may overestimate cardiac contractility in the presence of LVH and that load-insensitive contractility indexes derived from P–V loop analysis would better reflect cardiac contractility at the cardiomyocyte level. The hypertensive model used was the heterozygous (mRen-2)27 transgenic rat (Ren-2), a monogenic model with overactive local angiotensin II production at sites of normal physiological expression (24).

METHODS

Animals and Procedures

Male Sprague-Dawley (SD) and Ren-2 rats were studied. SD rats were obtained from the Animal Resource Centre (Murdoch, Western Australia).
Australia). The Ren-2 rats were bred from an existing colony based at St. Vincent’s Hospital Animal Resource Centre. All animals were approved for use by the St. Vincent’s Hospital Animal Ethics Committee in accordance with the National Health and Medical Research Council guidelines. Animals were housed and maintained at a constant room temperature (21 ± 1°C) and 12:12-h light-dark cycle. They were fed standard rat chow and given water ad libitum. Blood pressure was assessed at 6 wk by using the tail-cuff method (27) and every 4 wk thereafter until age 18 wk. At age 18 wk, after hypertension was well established, animals were anesthetized (60 mg/kg ip pentobarbital sodium), the abdomen, neck, and chest were then shaved, and echocardiography was performed. In the same eight SD control and nine Ren-2 animals, echocardiography was followed by in vivo cardiac P-V loop acquisition. After the P-V loop acquisition, animals were euthanized with subsequent excision of the heart and lungs.

Echocardiography

Echocardiography, including Doppler examination, was performed by using a Vivid 7 (GE Vingmed, Horten, Norway) with a 10-MHz phased-array probe. ECG was acquired simultaneously. End diastole was defined as the peak of the R wave, and end systole was defined as the end of the T wave.

All animals underwent echocardiographic interrogation while lying in a left recumbent position. Parasternal short-axis and apical long-axis views were obtained. M-mode echocardiography was performed by using a parasternal short-axis view at the level of the papillary muscles. LV posterior and anterior wall thicknesses were obtained during diastole(d) and systole(s), as were the LV internal diameter at end diastole (LVIDd) and end systole (LVIDs). FS and FAC were calculated according to the formulas FS = [(LVIDd – LVIDs)/LVIDd] × 100; and FAC = [(end-diastolic area – end-systolic area)/end-diastolic area] × 100, respectively. Vcf was calculated as Vcf = [(LVIDd – LVIDs)/LVIDd/ejection time (32)]. LV ejection time was calculated from pulsed-wave Doppler tracings of LV outflow obtained from the apical five-chamber view by measuring the interval from the beginning of acceleration to the end of deceleration (6).

The Tei index was calculated as the total isovolumic (contraction and relaxation) time divided by ejection time (33). The time from cessation of the mitral valve A wave to the onset of the mitral valve E wave of the next cardiac cycle (a) is equal to the total isovolumic time plus the ejection time (b). The Tei index was calculated therefore by the formula (a – b)/b. This was obtained from the apical five-chamber view, with pulsed-wave Doppler measured at the level of the LV outflow tract by using a sample volume of 2 mm.

The apical four-chamber view was used to assess early and late transmural peak diastolic flow velocity (E and A waves) by using pulsed-wave Doppler with a sample volume of 2 mm placed at the tips of the mitral valve leaflets. All Doppler spectra were recorded for 10 cardiac cycles at a sweep speed of 200 mm/s. Tissue Doppler imaging was performed in the apical four-chamber view and was used to assess peak systolic as well as early and late (E’ and A’), diastolic tissue annular velocities. S’ and relaxation velocity; A’, peak atrial contraction velocity. Note the A’ after the P wave seen on electocardiograph.

In Vivo P-V Loops

Animals were placed on a warming pad (37°C) and intubated with the use of 14-gauge catheter. The animals were then ventilated by using positive pressure with a tidal volume of 8–10% body wt at 70 breaths/min using room air. Animals were secured in a recumbent position on a heat pad, and the right jugular vein was cannulated with 0.9% NaCl infused at 100 μl/h. Pressure was calibrated after the catheter was warmed in 0.9% NaCl at 37°C for 30 min. The right internal carotid was identified and ligated cranially. A 2-Fr miniaturized, combined catheter-micromanometer (model SPR-838; Millar Instruments, Houston, TX) was advanced into the carotid artery to obtain a peripheral blood pressure estimation and then advanced into the left ventricle until stable P-V loops were obtained (11). The abdomen was then opened, and the inferior vena cava and portal vein were identified. Elastic bands were placed around these vessels to allow rapid reduction in cardiac preload. All loops were obtained with the ventilator turned off for 5–10 s and the animal anepnic. After data were recorded under steady-state conditions and during preload reduction, parallel conductance values were obtained by the injection of ~200 μl of 10% NaCl into the right atrium (10, 13).

Calibration from relative volume unit conductance signal to absolute volumes (in μl) was undertaken by using a previously described method. In brief, whole rat blood was placed in six 1-cm wells, ranging 4–9 mm in diameter. In this calibration, the linear volume-conductance regression of the absolute volume in each cylinder versus the raw signal acquired by the conductance catheter was used as the volume calibration formula (26).

In an additional six SD animals, the in vivo PV loops described above were obtained before and immediately after a single 4 μg/kg intravenous bolus of dobutamine was given to assess the ability of the catheter-derived indexes to assess changes in contractility. The sensitivity of these indexes to assess a change in contractility was calculated by dividing the maximal value by the baseline value, multiplied by 100. The addition of dobutamine to Ren-2 rats resulted in a hyperdynamic ventricle with a small end-systolic volume (ESV), causing malposition of the catheter with the pressure manometer coming into contact with the endocardial surface. This resulted in a characteristic spike in the upper left corner of the P-V loop, preventing analysis of load-insensitive indexes of cardiac contractility.

The following validated parameters were assessed by using Millar conductance data acquisition and analysis software PVAN3.2: end-diastolic volume (EDV), ESV, end-diastolic pressure (EDP), end-systolic pressure (ESP), EF, stroke volume (SV), the slope of the end-systolic P-V relationship (ESPVR) (29), the slope of the end-diastolic P-V relationship (EDPVR), diastolic chamber stiffness [chamber stiffness is calculated by fitting the end-diastolic points by using an exponential fit, EDP = k2 × exp(k1 × EDV)], where k2 is a constant and k1 is diastolic chamber stiffness], maximum and min-
Statistical Analysis

Results are expressed as means ± SE. Differences between groups were determined by unpaired Student’s t-test. A value of P < 0.05 was considered statistically significant. In analyzing load-insensitive contractility indexes, both the slope and intercept of each relationship were considered. Because no difference was found between the volume axis intercept of the Ren-2 and SD rats for any of the indexes, differences were sought between the slopes of the relationships in the two groups by using univariate analysis. This accounts for the phenomenon of parallel shift of the P-V loops to the right, indicating reduced contractility but equivalent slope.

RESULTS

Animal Data

The Ren-2 rats had higher heart rate, systolic blood pressure, LV weight, and body weight (Table 1).

Echocardiography

Systolic function. Echocardiography demonstrated marked differences between SD and Ren-2 rats. The posterior and anterior walls were significantly thicker in the Ren-2 rats (Table 2). The LV radius-to-wall thickness ratio was reduced by 28% in the Ren-2 rat, indicating concentric LVH. FAC and FS are significantly higher in the Ren-2 rat than in the SD rats. The Tei, or myocardial performance index, an index of global contractility, was higher in the Ren-2 rats than in the SD rats. Septal mitral annular systolic shortening velocity, a measure of longitudinal function, demonstrated no difference between SD and Ren-2 rats.

Regional cardiac systolic function was assessed. Vcf was higher in the Ren-2 rats than in the SD rats. Septal mitral annular systolic shortening velocity, a measure of longitudinal function, demonstrated no difference between Ren-2 and SD rats.

Diastolic function. Diastolic function was assessed by using tissue Doppler imaging and mitral inflow. However, assessment of physiological heart rates in rodents resulted in fusion of E and A waves, preventing analysis of this parameter in all the indexes. Differences were sought between the slopes of the relationships in the two groups by using univariate analysis. This accounts for the phenomenon of parallel shift of the P-V loops to the right, indicating reduced contractility but equivalent slope.

P-V Relationships

Steady state. Steady-state characteristics are shown (Table 3). Steady-state data demonstrated higher EF and maximal rise of LV pressure (+dP/dt) in the Ren-2 rats. Representative steady-state loops are shown (Fig. 2).

Preload Reduction

Preload reduction allowed relative load-insensitive measures of systolic and diastolic function to be assessed. We measured time-varying elastance and the slopes of ESPVR, PRSW, and dP/dr-EDV. To indicate a true difference in systolic function, we felt a number of parameters needed to be significantly different. Table 4 lists the parameters measured, and an example of P-V loops obtained during preload reduction is shown in Fig. 3. There were no significant differences in the slopes of load-insensitive measures between Ren-2 rats and controls (Table 4).

The Ren-2 rats demonstrated a nonsignificant trend to improved, early active relaxation with a reduced τ when compared with SD rats.

Despite the ventricular hypertrophy, the Ren-2 rats did not demonstrate impaired passive relaxation, with both diastolic chamber stiffness and the EDPVR showing no difference between groups. LVEDP was also not different.

Table 2. Echocardiographic parameters assessed in SD and Ren-2 rats

<table>
<thead>
<tr>
<th>Parameter</th>
<th>SD</th>
<th>n</th>
<th>Ren-2</th>
<th>n</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVAWd, mm</td>
<td>1.9±0.7</td>
<td>8</td>
<td>2.6±0.8</td>
<td>18</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>LVPWd, mm</td>
<td>1.7±0.06</td>
<td>8</td>
<td>2.3±0.07</td>
<td>18</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>LVId, mm</td>
<td>7.6±0.18</td>
<td>8</td>
<td>8.2±0.19</td>
<td>18</td>
<td>0.2</td>
</tr>
<tr>
<td>FAC, %</td>
<td>4.6±0.23</td>
<td>8</td>
<td>4.1±0.18</td>
<td>18</td>
<td>0.1</td>
</tr>
<tr>
<td>FS, % (M-mode)</td>
<td>39.2±2.4</td>
<td>8</td>
<td>48.7±1.59</td>
<td>18</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Vcf, cm/s</td>
<td>0.59±0.02</td>
<td>8</td>
<td>0.76±0.05</td>
<td>13</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Peak E, cm/s</td>
<td>75.9±3.3</td>
<td>6</td>
<td>80.3±2.4</td>
<td>2</td>
<td>0.5</td>
</tr>
<tr>
<td>Peak A, cm/s</td>
<td>46.5±3</td>
<td>6</td>
<td>72.5±0.8</td>
<td>2</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>E/A ratio</td>
<td>1.66±0.11</td>
<td>6</td>
<td>1.11±0.04</td>
<td>2</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>MPI</td>
<td>0.61±0.06</td>
<td>8</td>
<td>0.67±0.02</td>
<td>7</td>
<td>0.22</td>
</tr>
<tr>
<td>Sep S', cm/s</td>
<td>2.97±0.02</td>
<td>7</td>
<td>3.28±0.01</td>
<td>10</td>
<td>0.25</td>
</tr>
<tr>
<td>Sep E', cm/s</td>
<td>3.64±0.02</td>
<td>7</td>
<td>3.09±0.01</td>
<td>11</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

Values are means ± SE. n, no. of rats. LVAWd, diastolic anterior wall thickness; LVPWd, LV diastolic posterior wall thickness; LVId, LV diastolic internal diameter; LVId, LV systolic internal diameter; FAC, fractional area change; FS, fractional shortening; Vcf, myocardial velocity of LV circumferential fiber shortening; E, peak early velocity of transmitral flow; A, peak atrial contraction velocity of transmitral flow; MPI, myocardial performance index; Sep S', peak systolic mitral annular velocity; Sep E', peak early mitral annular relaxation velocity.

Table 3. Steady-state parameters of SD and Ren-2 rats obtained with invasive P-V loop analysis

<table>
<thead>
<tr>
<th>Parameter</th>
<th>SD</th>
<th>Ren-2</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>End-diastolic volume, μl</td>
<td>440±53</td>
<td>400±41</td>
<td>0.31</td>
</tr>
<tr>
<td>End-systolic pressure, mmHg</td>
<td>125±7</td>
<td>163±9</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>End-diastolic pressure, mmHg</td>
<td>8.9±1.6</td>
<td>8.8±1</td>
<td>0.42</td>
</tr>
<tr>
<td>Stroke volume, μl</td>
<td>217±21</td>
<td>244±21</td>
<td>0.38</td>
</tr>
<tr>
<td>Ejection fraction, %</td>
<td>55±7</td>
<td>75±5</td>
<td>0.03</td>
</tr>
<tr>
<td>dp/dmax, mmHg/s</td>
<td>7,429±600</td>
<td>12,410±624</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>dp/dmin, mmHg/s</td>
<td>-7,870±815</td>
<td>-10,235±440</td>
<td>0.03</td>
</tr>
<tr>
<td>Ratio dp/dmax/dp/dmin</td>
<td>0.944</td>
<td>1.16</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Tau, ms</td>
<td>12.24±0.7</td>
<td>11.28±0.7</td>
<td>0.4</td>
</tr>
</tbody>
</table>

Values are means ± SE. P-V, pressure-volume; dp/dmax and dp/dmin, positive and negative peak rate of pressure development.
To ensure that P-V-derived indexes are sensitive to alterations in cardiac contractility, we assessed the response of ESPVR, PRSW, and dP/dt-EDV as well as EF and +dP/dt to a dobutamine bolus in SD rats. ESPVR, PRSW, +dP/dt-EDV, and +dP/dt increased significantly with dobutamine (P < 0.05), whereas EF did not (Table 5). ESPVR and +dP/dt-EDV demonstrated the greatest percentage increase with dobutamine, but further analysis did not demonstrate superiority of any one measure. This confirmed that the conductance catheter was able to assess changes in contractility to a similar degree as routine load-sensitive measures (Fig. 4).

DISCUSSION

Load-sensitive measures of contractility have been assessed against a range of load-insensitive measures in this model of LVH, which confirms our hypothesis that these measures...
overestimate cardiac function. Also, dobutamine infusion confirmed that the conductance catheter is as sensitive as routine measurements in the assessment of cardiac contractility.

Concentric LVH is the most common condition in which load-sensitive measures of contractility are misinterpreted (4). EF, FS, +dP/dt, and FAC are highly load sensitive (20) and may be maintained by subnormal function of excess sarcomeres laid down in parallel (32), with subnormal shortening of extra parallel sarcomeres leading to the same thickening and displacement of blood as would normal shortening of fewer sarcomeres. Hence, normal values of these indexes in the presence of concentric hypertrophy may indicate substantial dysfunction (8). Alternatively, as was the case in the present study, the increase in load-sensitive indexes in the presence of hypertrophy indicated normal cardiomyocyte function. This has implications in human cardiac physiology, particularly when defining diastolic heart failure. LVH is frequently observed in this patient group, which defines normal systolic function (10). The software used to assess the myocardial backscatter (21, 23) appear to be promising. They allow as- 
sessing regional wall motion analysis such as strain, strain rate, and cyclic variability of integrated backscatter (21, 23) appear to be promising. They allow assessing of regional wall motion and appear to be relatively load independent (12). The echocardiography derivation of strain and strain rate is technically demanding in rodents and is rarely performed, although it would aid greatly in the interpretation of regional myocardial contractility. Overall, we believe that echocardiography is invaluable in the assessment of myocardial contractility in small animals, provided that the limitations of those indexes derived are taken into consideration.

Given the difficulties of measuring “absolute” contractility, we felt that a number of load-insensitive measures were necessary to identify a true change in cardiac function. The load-insensitive measures used are not without problems. The ESPVR is curvilinear (29) and is dependent on heart size and mass. Kass et al. (17) have demonstrated that, where possible, the slopes should be measured over similar ESP ranges to reduce nonlinearity of the ESPVR curve, which clearly introduces a different set of problems in a rat model such as this. The PRSW relationship is independent of chamber size and mass and has been demonstrated to be sensitive to changes in in the Ren-2 rat, as evidenced by the increased circumferential fiber shortening. Longitudinal fiber function was assessed by using tissue Doppler imaging. Tissue Doppler imaging assessment of the myocardial velocity gradient has been assessed in pressure overload rat models and found to be relatively load insensitive (7). The software used to assess the myocardial velocity gradient is not widely available; hence we assessed longitudinal systolic shortening velocity (septal S’) and found no difference between Ren-2 and SD rats. Previous studies have demonstrated a significant correlation between S’ and the slope of the ESPVR (12), suggesting this may be a load-insensitive index. The present study did not formally assess the response of septal S’ to alterations in preload, afterload, and inotropy; hence whereas it appears as a promising load-insensitive index, further study is required to validate its use in rodents.

Newer methods of cardiac regional wall motion analysis such as strain, strain rate, and cyclic variability of integrated backscatter (21, 23) appear to be promising. They allow assessment of regional wall motion and appear to be relatively load independent (12). The echocardiography derivation of strain and strain rate is technically demanding in rodents and is rarely performed, although it would aid greatly in the interpretation of regional myocardial contractility. Overall, we believe that echocardiography is invaluable in the assessment of myocardial contractility in small animals, provided that the limitations of those indexes derived are taken into consideration.

Table 5. Steady-state data and preload reduction data: SD control rats postdobutamine bolus

<table>
<thead>
<tr>
<th>Parameter</th>
<th>SD Baseline</th>
<th>Postdobutamine</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate, beats/min</td>
<td>342 ± 17</td>
<td>427 ± 21</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>End-systolic pressure, mmHg</td>
<td>107 ± 7</td>
<td>132 ± 11</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Ejection fraction, %</td>
<td>40 ± 6</td>
<td>62 ± 7</td>
<td>0.08</td>
</tr>
<tr>
<td>Cardiac output, μl/min</td>
<td>34,895 ± 5,700</td>
<td>76,925 ± 8,650</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Stroke work, mmHg/ml</td>
<td>9,500 ± 1994</td>
<td>19,650 ± 2,862</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Arterial elastance, mmHg/μl</td>
<td>1.2 ± 0.22</td>
<td>0.78 ± 0.12</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>dP/dtmax, mmHg/s</td>
<td>6,571 ± 661</td>
<td>14,160 ± 1592</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>dP/dtmax, mmHg/s</td>
<td>–7,556 ± 698</td>
<td>–10,777 ± 1,440</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>ESPVR, mmHg/μl</td>
<td>0.58 ± 0.13</td>
<td>1.17 ± 0.28</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>dP/dt-EDV, mmHg/s-μl^-1</td>
<td>32 ± 3</td>
<td>56 ± 10</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>PRSW, mmHg</td>
<td>63 ± 21</td>
<td>115 ± 12</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>EDPVR, mmHg/μl</td>
<td>0.04 ± 0.014</td>
<td>0.035 ± 0.006</td>
<td>0.35</td>
</tr>
</tbody>
</table>

Values are means ± SE. Dobutamine dose was 4 μg/kg.
cardiac contractility (15). We also measured the dP/dt-EDV relationship because positive peak rate of pressure development is a sensitive marker of cardiac contractility but is highly dependent on preload. The single bolus of dobutamine resulted in marked increases in ESPVR, PRSW, and dP/dt-EDV as well as EF and dP/dt, whereas \( \tau \) shortened and EDPV remained stable. These results confirmed enhanced cardiac contractility and active relaxation but no change in passive relaxation with dobutamine. We assessed the sensitivity of P-V relationships to detect changes in systolic function, and the P-V-derived data demonstrated a similar sensitivity to routine, load-sensitive measures. We were unable to assess this in the transgenic animals because the dobutamine bolus resulted in a hyperdynamic LV with small ESV, which displaced the catheter, causing interference between the pressure manometer and the endocardial surface. This caused a spike in the upper left corner of the P-V loop, preventing interpretation of the results.

Despite the advantages that P-V loop analysis offers in the assessment of load-insensitive measures of cardiac contractility, there are limitations such as the invasive nature of the technique. P-V loop analysis is a terminal procedure, and thus serial assessment is not possible. Another possible limitation is the choice of anesthetic agent and mechanical ventilation. In this study, the barbiturate pentobarbitone was used because it offers several advantages including sustained deep anesthesia with limited effect on heart rate and systolic blood pressure. Agents such as ketamine and xylazine profoundly depress heart rate and cardiac function (19).

There was a discrepancy between systolic blood pressure generated by the tail-cuff method and invasive end-systolic blood pressure in the Ren-2 rats that was not observed in SD controls. There are several possible explanations, which include greater effect of the anesthetic agent on systolic blood pressure in hypertensive animals or possibly overestimation of tail-cuff blood pressure due to altered arterial compliance. There is a paucity of data regarding the effects of anesthetic agents on cardiac function in rodent models of LVH. Previous studies (5) have used barbiturates without significant effect on cardiac function in the spontaneously hypertensive rat, another model of LVH. In the present study, load-sensitive indexes were significantly increased in the Ren-2 rat, whereas load-insensitive measures were not. These findings suggest that the anesthetic agent did not reduce cardiac function enough to explain the lack of difference in load-insensitive measures.

In conclusion, whereas the availability of transgenic species has enabled the effects of single gene alterations on cardiac function to be studied, the present study suggests there are substantial limitations of routine echocardiography indexes in the assessment of cardiac contractility. We have confirmed that P-V loops are able to demonstrate enhanced cardiac contractility in vivo in SD rats. We have shown that in the Ren-2 hypertensive animal model, load-insensitive measures of contractility were not different, although conventional load-sensitive measures indicated enhanced systolic function. This suggests that the difference seen with conventional methods appears to reflect loading conditions and alterations in regional wall motion rather than a true difference in global myocardial systolic function. To accurately identify changes in systolic function, we suggest that an assessment of load-insensitive measures be routinely used, ideally, P-V relationships and echocardiography. This has broader implications in the assessment of diastolic heart failure and hypertensive heart disease, not only in transgenic species but in the assessment of cardiac function in humans with LVH and normal values of cardiac contractility.

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GRANTS

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