Hypertrophy represents an adaptive response of the myocardium to an increased work load. Studies of experimental pressure overload have largely examined relatively short-term models of compensated hypertrophy, in which mechanical or pharmacological interventions impose a relatively abrupt load on the heart (e.g., see References 3–5). There are relatively few studies of long-term stable hypertrophy, which then progresses to heart failure. The spontaneously hypertensive rat (SHR) provides a laboratory model of chronic hypertension. Hemodynamic studies in the SHR demonstrate a compensated state of hypertension up to 12 months of age and evidence of impaired hemodynamic performance at 18 months. In our studies of the aging male SHR, we have observed that between the ages of 18 and 24 months, many animals exhibit evidence of heart failure, including progressive tachypnea and labored respiration. At the time of death, a number of these animals were found to have pleural or pericardial effusions or both, left atrial thrombi, and right ventricular hypertrophy. Isolated muscle studies demonstrate depression of active muscle properties and increased passive stiffness. Previous studies have demonstrated altered energy metabolism in models of hypertrophy, and it has been considered that alterations in energy supply/demand relations may be responsible for impairment of cardiac function. The present study was carried out to evaluate the relation between myocardial stress development and oxygen consumption in the SHR during the transition from compensated hypertrophy to failure. It was hypothesized that myocardial hypoxia may be a factor contributing to the impaired function of failing myocardium and that decreasing oxygen availability may render hypertrophied and failing myocardium more vulnerable to hypoxic stress. Although the oxygen cost of stress development was found to be increased in...
hypertrophied and failing hearts, sensitivity to hypoxia is not increased, and there is no evidence of hypoxia in the baseline state to explain impaired contractile function in the failing heart.

Methods

Animal Model

Male SHRs and normotensive Wistar-Kyoto (WKY) rats were purchased as retired breeders at 6–9 months of age (Taconic Farms, Inc., Germantown, N.Y.) and were boarded at the animal facility at the Boston Veterans Administration Medical Center until the time of age (18–21 months of age). All rats were housed under identical conditions and had free access to food and water. Systolic arterial blood pressure was measured weekly using the indirect tail-cuff technique.14

All animals were studied between 18 and 21 months of age. After 18 months of age, animals were observed daily and studied if tachypnea and labored respiration were noted. On the basis of pathological findings made at the time the rats were killed, a group of SHRs with evidence of heart failure (SHR-F; n=8) was defined. The presence of right ventricular hypertrophy (right ventricular-to-body weight ratio >0.80 mg/g) in association with either left atrial thrombi or effusions was used as criteria for inclusion of SHRs in the SHR-F group. Findings on pathological examination included pleural or pericardial effusions or both (n=7), left atrial thrombi (n=8), and right ventricular hypertrophy (n=8). Age-matched SHRs without heart failure (SHR-NF; n=8) and nonhypertensive WKY control animals (n=13) were studied for comparison.

Preparation

An isolated isovolumically contracting rat heart preparation was used. After rats were killed, hearts were quickly removed and placed in oxygenated Krebs-Henseleit solution16 containing heparin at 28°C. The ascending aorta was cannulated, and hearts were perfused, using the Langendorff technique, in a retrograde manner, with oxygenated Krebs-Henseleit solution at 37°C with a constant perfusion pressure of 100 mm Hg. Heart weight was determined, and after 24 hours of drying for determination of wet-to-dry weight ratio, a group of SHRs without heart failure (SHR-NF; n=8) and nonhypertensive WKY control animals (n=13) were studied for comparison.

Baseline Pressure–Volume Determinations

Baseline measurements were obtained when the preparation achieved a steady state after instrumentation (approximately 15 minutes). After this equilibration period, a baseline pressure–volume relation was determined for every heart; left ventricular peak systolic and end-diastolic pressures were measured in the oxygenated control state 20–30 seconds after 0.02-ml increments in balloon volume until an end-diastolic pressure of approximately 20 mm Hg was achieved.

Hemodynamic and Metabolic Parameters

Hemodynamic and metabolic measurements were carried out at a reference volume, which was determined for each animal based on body weight (0.025 ml per 100 g body weight). Because the WKY rats were larger (Table 1), the reference volume was slightly larger in these rats. It was felt most appropriate to select a common volume, rather than a volume at a common filling pressure, because a common volume is more likely to result in comparable fiber lengths. In addition, volume was constrained, rather than end-diastolic pressure, because changes in left ventricular wall thickness and compliance may alter left ventricular end-diastolic pressure–volume relations in cardiac hypertrophy.

After final adjustment of balloon volume, hearts were allowed to contract isovolumically for an additional 5-minute period before measurements were obtained. Coronary flow was determined by collecting coronary effluent for 60 seconds. Perfusion PO2 was determined with a blood gas analyzer (model 213, Instrumentation Laboratories, Lexington, Mass.); arteriovenous oxygen difference was calculated from the difference in PO2 between the aortic perfusate and coronary venous effluent, assuming a solubility of 0.023 ml O2 per milliliter of perfusate at 760 mm Hg, and was expressed as micromoles per milliliter. Myocardial oxygen consumption (MV02) was calculated as the product of arteriovenous oxygen difference and coronary flow (milliliters per minute per gram dry left ventricle) and expressed as micromoles per minute per gram dry left ventricle.
TABLE 1. Body Weight, Raw and Normalized Cardiac Chamber Weights, and Tissue Wet-to-Dry Ratios

<table>
<thead>
<tr>
<th>Group</th>
<th>Body wt (g, wet)</th>
<th>LV wt (g, wet)</th>
<th>RV wt (g, wet)</th>
<th>Atrial wt (g, wet)</th>
<th>LV/BW (x10^3)</th>
<th>RV/BW (x10^3)</th>
<th>LV W/D</th>
<th>RV W/D</th>
<th>Lung W/D</th>
<th>Liver W/D</th>
</tr>
</thead>
<tbody>
<tr>
<td>WKY (n=13)</td>
<td>609±65</td>
<td>1.30±0.18</td>
<td>0.34±0.05</td>
<td>0.13±0.02</td>
<td>2.14±0.31</td>
<td>0.56±0.09</td>
<td>5.05±0.26</td>
<td>5.11±0.25</td>
<td>5.23±0.92</td>
<td>3.31±0.58</td>
</tr>
<tr>
<td>SHR (n=16)</td>
<td>397±31</td>
<td>1.62±0.29</td>
<td>0.36±0.13</td>
<td>0.20±0.12</td>
<td>4.08±0.62</td>
<td>0.91±0.31</td>
<td>5.20±0.43</td>
<td>5.14±0.46</td>
<td>5.41±0.40</td>
<td>3.43±0.20</td>
</tr>
<tr>
<td>SHR-NF (n=8)</td>
<td>391±27</td>
<td>1.43±0.24</td>
<td>0.25±0.05</td>
<td>0.12±0.06</td>
<td>3.66±0.53</td>
<td>0.64±0.12</td>
<td>4.99±0.42</td>
<td>5.10±0.57</td>
<td>5.49±0.51</td>
<td>3.27±0.26</td>
</tr>
<tr>
<td>SHR-F (n=8)</td>
<td>403±35</td>
<td>1.81±0.20</td>
<td>0.47±0.06</td>
<td>0.30±0.09</td>
<td>4.50±0.38</td>
<td>1.18±0.15</td>
<td>5.41±0.35</td>
<td>5.18±0.35</td>
<td>5.33±0.26</td>
<td>3.58±0.1</td>
</tr>
</tbody>
</table>

LV, left ventricle; RV, right ventricle; BW, body weight; W/D, ratio of wet weight to dry weight; WKY, Wistar-Kyoto rat; SHR, spontaneously hypertensive rat; NF, nonfailing (no evidence of heart failure); F, failing (evidence of heart failure). Values are mean±SD.

* p<0.01, † p<0.05.

Coronary venous samples were collected and analyzed for lactate concentration by the lactate dehydrogenase procedure (Sigma Chemical Co., St. Louis, Mo.) using a standard spectrophotometric technique. Samples were collected and stored on ice before subsequent analysis. Lactate production was expressed as micromoles per minute per gram dry left ventricle.

After measurements in the baseline state (95% O2-5% CO2 at 100 mm Hg perfusion pressure), measurements were repeated with perfusion pressure increased to 130 mm Hg for a 5-minute period (with unchanged balloon volume), followed by a return to control coronary perfusion pressure (100 mm Hg). This sequence was then repeated with progressive hypoxia (50%, 25%, and 0% oxygen) followed by reoxygenation (95% oxygen). Pressure measurements were made, and arterial and coronary venous samples were collected during the last 3–5 minutes of each 5-minute intervention period. Thus, hemodynamic and metabolic parameters were determined at two perfusion pressures (100 and 130 mm Hg) for each successive stage of hypoxia and reoxygenation (95%, 50%, 25%, 0%, and 95% oxygen).

Peak systolic circumferential stress (σ) was derived from ventricular pressure measurements, balloon volume, and ventricular weight. A spherical model was assumed, in which the left ventricular cavity is of radius Ri, and the balloon volume (Vb) is assumed to be equal to the left ventricular chamber volume. Thus,

\[ V_b = \frac{4}{3} \pi R_i^3 \]

and

\[ R_i = \left( \frac{V_b}{(4/3 \pi)} \right)^{1/3} \]

The total heart volume is equal to the sum of \( V_b \) and \( V_{wall} \) where \( V_{wall} \) is the volume of the left ventricular wall (Vwall=left ventricular weight/1.05, the specific gravity of myocardium). This volume is contained in a sphere of radius \( R_i + h \), where \( R_i \) is chamber radius and \( h \) is wall thickness. Therefore,

\[ V_b + V_{wall} = \frac{4}{3} \pi (R_i + h)^3 \]

and

\[ R_i + h = \left( \frac{V_b + V_{wall}}{(4/3 \pi)} \right)^{1/3} \]

Left ventricular circumferential wall stress is then derived from the relation described by Mirsky17:

\[ \sigma = \frac{pR_i^2}{(2R_i + h)} \]

Statistical Methods

Results are expressed as mean±SD. Initially, analysis of differences between strains (SHR versus WKY) was performed using a one-way analysis of variance and the unpaired t test. Based on criteria noted above (see "Animal Model"), the SHR group was then subdivided into a group with evidence of heart failure (SHR-F) and without heart failure (SHR-NF). A one-way analysis of variance and Newman-Keuls multiple-sample comparison test18 were then used to test for differences among groups (WKY, SHR-NF, SHR-F). A two-way analysis of variance with replications was used to test for effects of \( P_02 \) and perfusion pressure. The Newman-Keuls multiple-sample comparison test was used to localize differences where significant effects were identified by analysis of variance; a blocked analysis was used where appropriate (for comparison of perfusion pressures and levels of hypoxia).

Results

Animal Data

Table 1 presents gross and normalized (for animal weight) cardiac chamber weight data and tissue wet-to-dry weight ratio data. Part A of Table 1 presents a comparison of normotensive WKY rats and all age-matched SHRs. Significant differences in body weight, left ventricular weight, left ventricular-to-body weight ratio and right ventricular-to-body weight ratio between strains were present. Part B of Table 1 compares data among WKY rats and nonfailing (SHR-NF) and failing (SHR-F) SHRs. Left ventricular weight in the SHR-F group was greater than in both the WKY and SHR-NF groups (p<0.01; part B of Table 1). Left ventricular weight normalized by body weight (LV/BW) was greater in both SHR groups than in the WKY group (p<0.01) and slightly greater in the SHR-F group than in the SHR-NF group (p<0.01), despite lower body weight in both SHR groups as compared with the WKY group. Normalized right ventricular weight was greater in the SHR-F group as compared with both the SHR-NF and WKY groups (p<0.01). Left ventricular wet-to-dry weight ratio was significantly greater in the SHR-F group as compared with both WKY and SHR-NF groups (p<0.05); nonetheless, the dry left ventricular...
weight of the SHR-F group was still significantly greater than the other two groups (p<0.01). There was no significant difference in wet-to-dry weight ratio of the right ventricle, lung, or liver among the WKY or SHR groups. Tail-cuff blood pressure in both SHR groups was significantly greater than in the age-matched WKY group (WKY, 120±4; SHR-NF, 185±21; SHR-F, 181±17 mm Hg; p<0.01).

Baseline Hemodynamic and Metabolic Data

Figure 1 presents baseline pressure-volume relations in the oxygenated control state. At any volume, SHR-NF hearts develop a greater pressure than WKY hearts. Both of these groups develop a greater pressure than the SHR-F group.

Baseline hemodynamic data were obtained at a reference ventricular volume of 0.025 ml per 100 g body weight. At this volume, mean systolic pressures were WKY, 174±19; SHR-NF, 211±23; and SHR-F, 120±24 mm Hg (see Table 2 for statistical comparisons); corresponding diastolic pressures were WKY, 0±2; SHR-NF, 0±2; and SHR-F, 1±4 mm Hg (no significant difference in diastolic pressure among groups). Part A of Table 2 presents a comparison of baseline hemodynamic data between normotensive WKY rats and all age-matched SHRs. At reference ventricular volume (based on animal weight; see "Methods"), significant differences in midwall stress and MVo2/stress were present between strains. Differences among WKY, SHR-NF, and SHR-F groups are presented in part B of Table 2. Peak developed pressure was greater in the SHR-NF than in the WKY group (p<0.01), which was, in turn, greater than in the SHR-F group (p<0.01, part B of Table 2). However, because of differences in wall thickness among groups, peak midwall systolic stress was greatest in the WKY group, whereas it was lowest in the SHR-F group.

Coronary flow, normalized for dry left ventricular weight, and arteriovenous oxygen difference did not differ significantly among groups, although both appeared to be lower in the SHR-F group. MVo2 was reduced in the SHR-F group compared with both WKY and SHR-NF groups (p<0.01). Despite differences in stress development between WKY and SHR-NF, MVo2 did not differ between these two groups. Myocardial oxygen cost of stress development (MVo2/stress, Table 2) was least in the WKY group, greater in the SHR-NF group, and greatest in the SHR-F group.

In the baseline state, under oxygenated conditions, a few hearts in each group did produce small but detectable amounts of lactate; there was no significant difference in lactate production among the three groups.

Effects of Perfusion Pressure on Midwall Stress and Metabolic Data

Table 3 and Figure 2 present the effects of increasing perfusion pressure. Left ventricular midwall stress increased significantly when perfusion pressure was increased from 100 to 130 mm Hg in the baseline state (95% O2-5% CO2) in all groups (Figure 2A). Coronary blood flow increased significantly in all groups, and arteriovenous oxygen difference narrowed. MVo2 increased significantly in the WKY and SHR-NF groups but not in the SHR-F group (Figure 2B). Despite increasing perfusion pressure from 100 to 130 mm Hg, developed stress and MVo2 remained markedly lower in the SHR-F group than in the WKY or SHR-NF groups. As described above,

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### Table 2. Baseline Hemodynamic and Metabolic Data

<table>
<thead>
<tr>
<th>Group</th>
<th>LV pressure (mm Hg)</th>
<th>LV chamber radius (R) (mm)</th>
<th>LV wall thickness (h) (mm)</th>
<th>Systolic stress (kdyne/cm²)</th>
<th>A-V O₂ (ml/min/g dry LV)</th>
<th>CBF (ml/min/g dry LV)</th>
<th>MVo2 (µM/min/g dry LV)</th>
<th>Lactate (µM/min/g dry LV)</th>
<th>MVo2/stress</th>
</tr>
</thead>
<tbody>
<tr>
<td>WKY (n=13)</td>
<td>174±19</td>
<td>0.33±0.01</td>
<td>0.30±0.02</td>
<td>89±14</td>
<td>0.37±0.04</td>
<td>81±17</td>
<td>30.0±4.6</td>
<td>1.1±2.1</td>
<td>0.34±0.06</td>
</tr>
<tr>
<td>SHR-NF (n=8)</td>
<td>165±52</td>
<td>0.29±0.01</td>
<td>0.38±0.03</td>
<td>52±19</td>
<td>0.36±0.06</td>
<td>77±15</td>
<td>27.1±5.3</td>
<td>1.47±3.0</td>
<td>0.57±0.20</td>
</tr>
<tr>
<td>SHR-F (n=8)</td>
<td>211±23</td>
<td>0.28±0.01</td>
<td>0.36±0.02</td>
<td>69±8</td>
<td>0.37±0.04</td>
<td>88±31</td>
<td>30.8±4.6</td>
<td>2.2±5.2</td>
<td>0.45±0.06</td>
</tr>
</tbody>
</table>

LV, left ventricle; Systolic stress, peak systolic midwall stress; A-V O₂, arteriovenous oxygen difference; CBF, coronary blood flow; MVo2, myocardial oxygen consumption; WKY, Wistar-Kyoto rat; SHR, spontaneously hypertensive rat; NF, nonfailing (no evidence of heart failure); F, failing (evidence of heart failure). Peak systolic pressure (LV pressure) determined at corrected volume (see text); LV chamber radius and wall thickness determined from balloon volume and heart rate (see text). Perfusion pressure was 100 mm Hg. Values are mean±SD.

*p<0.01.
TABLE 3. Effect of Graded Hypoxia and Reoxygenation and Perfusion Pressure on Hemodynamic and Metabolic Parameters

<table>
<thead>
<tr>
<th>% Oxygen</th>
<th>Systolic stress (kdyne/cm²)</th>
<th>CBF (ml/min/g)</th>
<th>A-V O₂ (mm Hg)</th>
<th>MVO₂ (µM/min/g dry LV)</th>
<th>Lactate (µM/min/g dry LV)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>100 mm Hg</td>
<td>130 mm Hg</td>
<td>100 mm Hg</td>
<td>130 mm Hg</td>
<td>100 mm Hg</td>
</tr>
<tr>
<td>95% O₂</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WKY</td>
<td>89±14 * 93±15</td>
<td>81±17 * 103±17</td>
<td>276±33 * 239±41</td>
<td>30.0±4.6 * 32.5±5.2</td>
<td>1.1±2.1 * 0.5±1.6</td>
</tr>
<tr>
<td>SHR-NF</td>
<td>69±8 * 74±10</td>
<td>88±31 * 110±28</td>
<td>276±59 * 244±60</td>
<td>30.8±4.6 * 34.8±6.4</td>
<td>2.2±5.2 * 0.9±1.9</td>
</tr>
<tr>
<td>SHR-F</td>
<td>35±9 * 40±11</td>
<td>66±12 * 78±20</td>
<td>261±36 * 227±45</td>
<td>23.3±2.3 * 23.0±2.6</td>
<td>0.8±1.7 * 1.4±2.0</td>
</tr>
<tr>
<td>50% O₂</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WKY</td>
<td>82±15 * 87±18</td>
<td>113±19 * 133±18</td>
<td>154±21 * 138±19</td>
<td>23.5±5.1 * 24.8±4.7</td>
<td>15.5±10.6 * 4.9±7.5</td>
</tr>
<tr>
<td>SHR-NF</td>
<td>48±6 * 62±9</td>
<td>102±28 * 135±35</td>
<td>138±44 * 142±50</td>
<td>17.4±3.0 * 21.1±3.2</td>
<td>38.4±19.6 * 16.6±15.8</td>
</tr>
<tr>
<td>SHR-F</td>
<td>34±8 * 39±7</td>
<td>82±18 * 105±30</td>
<td>150±31 * 131±27</td>
<td>16.8±1.3 * 18.5±1.7</td>
<td>21.1±12.1 * 6.1±8.4</td>
</tr>
<tr>
<td>25% O₂</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WKY</td>
<td>61±15 * 64±18</td>
<td>129±21 * 168±25</td>
<td>80±15 * 80±10</td>
<td>13.9±3.6 * 18.5±3.7</td>
<td>56±20 * 36±17</td>
</tr>
<tr>
<td>SHR-NF</td>
<td>37±7 * 42±9</td>
<td>130±35 * 162±47</td>
<td>65±21 * 62±24</td>
<td>10.6±1.7 * 12.2±2.6</td>
<td>73±29 * 58±17</td>
</tr>
<tr>
<td>SHR-F</td>
<td>28±6 * 31±5</td>
<td>101±26 * 135±18</td>
<td>77±22 * 75±13</td>
<td>10.0±2.7 * 14.9±3.0</td>
<td>52±18 * 36±17</td>
</tr>
<tr>
<td>0% O₂</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WKY</td>
<td>34±9 * 20±8</td>
<td>111±25 * 155±26</td>
<td>0 * 0 * 0 * 0</td>
<td>0</td>
<td>91±52 * 133±49</td>
</tr>
<tr>
<td>SHR-NF</td>
<td>22±5 * 15±4</td>
<td>120±43 * 168±59</td>
<td>0 * 0 * 0 * 0</td>
<td>119±47 * 161±45</td>
<td></td>
</tr>
<tr>
<td>SHR-F</td>
<td>15±3 * 9±2</td>
<td>86±16 * 120±28</td>
<td>0</td>
<td>0</td>
<td>85±30 * 129±41</td>
</tr>
<tr>
<td>95% O₂ (REOX)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WKY</td>
<td>59±20 * 64±20</td>
<td>115±21 * 137±28</td>
<td>224±32 * 223±66</td>
<td>32.5±7.4 * 38.1±7.7</td>
<td>6.3±2.1 * 5.6±2.0</td>
</tr>
<tr>
<td>SHR-NF</td>
<td>51±12 * 59±10</td>
<td>112±37 * 127±44</td>
<td>240±59 * 232±57</td>
<td>33.9±5.7 * 36.7±3.8</td>
<td>3.9±2.6 * 1.1±1.0</td>
</tr>
<tr>
<td>SHR-F</td>
<td>28±4 * 33±6</td>
<td>88±12 * 106±15</td>
<td>235±26 * 215±32</td>
<td>26.9±2.7 * 28.9±2.6</td>
<td>5.5±2.5 * 1.2±1.2</td>
</tr>
</tbody>
</table>

Systolic stress, peak systolic midwall stress; CBF, coronary blood flow; A-V O₂, arteriovenous oxygen difference; MVO₂, myocardial oxygen consumption; LV, left ventricle; WKY, Wistar-Kyoto rat; SHR, spontaneously hypertensive rat; NF, nonfailing (no evidence of heart failure); F, failing (evidence of heart failure); REOXY, reoxygenation. Values are mean±SD; n=13 WKY, n=8 SHR-NF, n=8 SHR-F.

* p<0.01, ** p<0.05 (130 vs. 100 mm Hg perfusion pressure).

Despite significant differences in stress development between the WKY and SHR-NF groups in the baseline state, MVO₂ was similar in these two groups. Increasing perfusion pressure significantly increased midwall stress values in all groups, but the small increase in stress development did not correct baseline differences.

Effect of Graded Hypoxia on Midwall Stress and Metabolic Data

Figure 3A and Table 3 show the effect of graded hypoxia on midwall stress (at constant perfusion pressure and ventricular volume). With 50% oxygen (a PO₂ decline from approximately 450-460 to 230-240...
mm Hg), peak stress fell in the WKY and SHR-NF groups. The relative decline in peak stress in the SHR-NF group was more prominent than in the WKY and SHR-F groups. Further reduction in perfusate PO$_2$, however, demonstrated a nearly proportional decrease in peak stress in all groups.

Mean coronary flow increased in all groups in response to hypoxia. Maximal coronary flow was seen at 25% oxygen or perfusate PO$_2$ of approximately 130 mm Hg. Coronary arteriovenous oxygen difference narrowed progressively as the oxygen in the perfusate was reduced and then increased to near baseline values after reoxygenation with 95% oxygen. There were no significant differences in arteriovenous oxygen difference among the three groups at any of the perfusate oxygen states. MVO$_2$ decreased in all groups in response to graded hypoxia. With 50% oxygen, MVO$_2$ was significantly greater in the WKY than both SHR groups. As with 50% oxygen, MVO$_2$ was higher in the WKY group with 25% perfusate oxygen as compared with the other two groups. Thus, although MVO$_2$ was significantly depressed in SHR-F relative to the other groups in the oxygenated baseline state (p<0.01), both SHR groups continued to demonstrate significant depression of MVO$_2$ relative to the WKY group during hypoxia.

Significant lactate production was seen in all groups with 50% oxygen and was greater in the SHR-NF than SHR-F and WKY groups. Lactate production rose progressively with increasing severity of hypoxia. Lactate production appeared to be highest in the SHR-NF group, but there were no statistically significant differences among groups.

After 5 minutes of reoxygenation, peak stress returned toward baseline values in all hearts studied, although recovery in all groups was incomplete. Despite incomplete recovery of peak stress, MVO$_2$ recovered in all groups to levels greater than prehypoxia baseline. Mean coronary flow decreased from peak hypoxic flow rates but remained elevated in comparison to prehypoxia values in all groups. Lactate production fell to near baseline values but was still detectable in a few hearts.

**Effects of Perfusion Pressure During Hypoxia on Midwall Stress and Metabolic Data**

Changing the perfusate gas mixture from 95% to 50% oxygen resulted in an increase in coronary flow, a decrease in arteriovenous oxygen difference, a decline in MVO$_2$, an increase in lactate production, and a fall in midwall stress in all groups, as described above. Increasing perfusion pressure to 130 mm Hg resulted in increases in coronary flow in all groups. Oxygen extraction fell significantly in the WKY and SHR-F groups but not in the SHR-NF group. As a result, MVO$_2$ increased significantly in the SHR-NF (p<0.01) but not in the other two groups. Nonetheless, MVO$_2$ remained significantly greater in the WKY group relative to the two SHR groups. Lactate production fell significantly with the increase in perfusion pressure in the WKY and SHR-F groups; an apparent fall in the SHR-NF group was of borderline statistical significance. Peak midwall stress increased significantly in all groups, with the largest improvement found in the SHR-NF group.

With 25% oxygen, increasing perfusion pressure to 130 mm Hg resulted in a further significant increase in coronary flow in all groups (p<0.01). Although coronary oxygen extraction fell with the change from 50% to 25% oxygen, there was no further change in arteriovenous oxygen difference with increasing perfusion pressure. MVO$_2$ increased significantly in all groups, and lactate production fell. After perfusion pressure was increased, MVO$_2$ remained significantly greater in the WKY relative to the SHR groups, whereas lactate production was greatest in the SHR-NF group. Peak stress appeared to increase slightly in all groups with the increase in perfusion pressure; however, this change achieved statistical significance only in the SHR groups. At a perfusion pressure of 130 mm Hg, peak stress remained significantly greater in the WKY group relative to both SHR groups.

There was no further increase in coronary flow with 0% oxygen; increasing perfusion pressure to 130 mm Hg did result in a significant increase in coronary flow in all groups. Lactate production, which increased with progressive hypoxia, increased significantly further with the increase in perfusion pressure, although there were no significant differences among groups. Peak stress fell significantly in all groups (p<0.01) after perfusion pressure was raised to 130 mm Hg (in contrast to an increase seen with 95%, 50%, and 25% oxygen).

After reoxygenation with 95% oxygen, increasing perfusion pressure to 130 mm Hg increased coronary flow in all groups, but there were no statistically significant differences among groups. LV, left ventricle; WKY, Wistar-Kyoto group; SHR-NF, nonfailing spontaneously hypertensive rat group; SHR-F, failing spontaneously hypertensive rat group; REOX, reoxygenation.
flow significantly in all groups. Arteriovenous oxygen difference narrowed slightly in the SHR-F group (p<0.05) but did not change significantly in the other two groups. MV\textsubscript{O\textsubscript{2}} increased in the WKY and SHR-F groups (p<0.05), but there was no significant change in the SHR-NF group. As at a perfusion pressure of 100 mm Hg, MV\textsubscript{O\textsubscript{2}} was significantly greater in the WKY and SHR-NF groups than the SHR-F group. Minimal lactate was produced in this state, and there was no change after perfusion pressure was raised. Peak midwall stress increased significantly in all groups after perfusion pressure was raised. Again, as at 100 mm Hg perfusion pressure, peak stress was significantly greater in both the WKY and SHR-NF groups in comparison to the SHR-F group.

Discussion

It has been hypothesized that chronic pressure overload results in a state of stable hypertension that is followed by decompensation and the development of heart failure.\textsuperscript{19} Although many studies of experimental pressure overload hypertrophy have been carried out, relatively few have examined long-term stable hypertension and the transition to heart failure. Studies of the SHR have demonstrated normal cardiac function in mature animals with evidence of reduced function in older animals.\textsuperscript{7,14,20,21} The present studies, using the isolated perfused heart preparation with a balloon in the left ventricle, permit an assessment of cardiac function under experimental conditions in which cardiac load and perfusion pressures are directly controlled. Findings demonstrate impairment of left ventricular midwall stress development during the transition to heart failure in the aging SHR. As suggested by Miersky et al,\textsuperscript{20} depressed myocardial contractility appears to underlie impaired pumping ability seen in the aging SHR. These observations and those of our previous report of depressed isolated muscle function in the SHR with findings suggestive of heart failure\textsuperscript{a} are all consistent with the concept that an abnormality of left ventricular myocardium forms the basis for impaired hemodynamic function.

An important finding of this study is that depressed left ventricular midwall stress development is demonstrated in a group of animals with clinical and pathological findings suggestive of heart failure. It might be argued that clinical and pathological findings, although suggestive of left ventricular decompensation, may conceivably have a noncardiac basis or may reflect cardiac pathology other than left ventricular disease. For example, right ventricular hypertrophy has been found in WKY rats in association with biventricular hypertrophy in the absence of evidence for heart failure.\textsuperscript{22} A direct demonstration of depressed left ventricular midwall stress development strongly suggests that left ventricular failure is responsible for the clinicopathological observations in these animals.

The relation between myocardial function and oxygen consumption has been the subject of investigations of both normal hearts and hearts subjected to interventions and pathological states. The importance of wall stress as a major determinant of oxygen consumption has been reviewed by Gibbs and Chapman.\textsuperscript{23} A number of other functional parameters, e.g., contractile element work,\textsuperscript{24} have been studied in relation to changes in

![Figure 4. Line graph shows relation between peak myocardial oxygen consumption and developed midwall stress at 95% (baseline), 50%, 25%, and 0% perfusate oxygen.](http://link+hypertension.ahajournals.org/article-pdf/21/1/62/32225208/32225208)

MV\textsubscript{O\textsubscript{2}}. The use of pressure-volume area\textsuperscript{25,26} in particular may have conceptual advantages over other performance parameters.\textsuperscript{27}

Figure 4 summarizes the relation between oxygen consumption and developed midwall stress at the differing oxygen concentrations. At any given level of MV\textsubscript{O\textsubscript{2}}, including the oxygenated baseline state, SHR-NF and in particular SHR-F hearts develop less systolic stress. Thus, the oxygen cost of stress development is increased in hypertrophied and, particularly, failing hearts. The finding of an increase in oxygen consumption per unit stress developed by hypertrophied myocardium has been reported in humans with pressure overload hypertrophy due to aortic valve disease.\textsuperscript{28} In other studies of human hearts,\textsuperscript{29} the relation between oxygen consumption and pressure-volume area was found to be relatively independent of inotropic state in hearts with normal to mildly impaired systolic function. On the other hand, a reduction in mechanical efficiency with ejection fractions <40% has been reported.\textsuperscript{30,31} In studies of the pulmonary artery banded cat, Cooper et al\textsuperscript{10} and Gunning and Coleman\textsuperscript{11} observed an increase in the oxygen cost of stress development. In a subsequent study of the cat with chronic pulmonary artery banding, parallel depression of function and MV\textsubscript{O\textsubscript{2}} was observed, and it was suggested that the changes described in the earlier studies may be related to injury associated with more abrupt pulmonary artery constriction.\textsuperscript{32}

Studies of myocardial energetics in pressure overloaded hypertrophied, but not failing, myocardium (using myothermal measurement techniques) have demonstrated a decreased ratio of heat production to tension time integral, suggesting increased "economy" with respect to myocardial energetics.\textsuperscript{12,23,34} The mechanism for the increased oxygen cost of stress development, which seems paradoxical to myothermal data demonstrating an increase in "economy," is conjectural at this point. Cooper et al\textsuperscript{10} have presented data suggesting that the increase in MV\textsubscript{O\textsubscript{2}} in hypertrophied myocardium is related to nonphosphorylating mitochondrial respiration. If increased myothermal "economy" is found to be present in animals with heart failure, uncoupling of
respiration and oxidative phosphorylation might explain the apparent dissociation between MVO₂ and myothermal data; in this case, ATP utilization may be proportional to myocardial stress development, whereas oxygen consumption would be increased.

It has been suggested that the connective tissue response in cardiac hypertrophy may play a role in altered function seen with cardiac hypertrophy and failure. Mechanical and histological evidence of progressive fibrosis is observed in SHR myocardium during the transition to heart failure. One might speculate that the increased oxygen cost of stress development in hypertrophied and failing hearts might be explained by the tethering or entrapment of myocytes by the fibrotic process, such that contractile activity is not efficiently translated into stress development. Thus, the connective tissue response may contribute to impaired left ventricular stress development, particularly in the later stages of the disease process when the increase in fibrosis appears particularly prominent.

Although the oxygen cost of stress development is increased in both SHR groups relative to the WKY group, there is no evidence for anaerobic metabolic activity under oxygenated conditions (based on lactate production data). The studies of hypoxia, on the other hand, demonstrate that myocardium from all three groups is capable of lactate production with a 50% or greater reduction in perfusate oxygen. A shift from fatty acid to glucose utilization has been reported in hearts from rats with hypertension, suggesting that a change in the preferred substrate might occur in the SHR as well. Nevertheless, the present data suggest that aerobic metabolic activity is able to meet the energetic demands of these hypertrophied and failing perfused hearts in the baseline state.

Increasing perfusion pressure results in a small increase in MVO₂ and stress development in all study groups. Augmenting perfusion by raising perfusion pressure did reduce lactate production in all groups during hypoxia (except for 0% oxygen) but did little to correct the marked depression of isovolumic stress development present in the SHR-F group. Thus, improving flow and tissue oxygenation by increasing perfusion pressure either in the baseline state or during hypoxia does little to correct the marked impairment of stress development in the SHR-F group.

In summary, the present studies document a decline in midwall stress development in the SHR with chronic left ventricular hypertrophy and failure. Because the decline in stress development is associated with a lesser decline in oxygen consumption, the oxygen cost of stress development is progressively increased in hypertrophied and failing myocardium. Despite the increased oxygen cost of stress development, evidence for tissue hypoxia (lactate production) is absent in the baseline state where midwall stress development is depressed in failing hearts. Thus, there is no evidence of tissue hypoxia to explain depression of contractile function in the isolated failing heart in the baseline state. The increased oxygen cost of stress development, however, may be a factor contributing to the development of progressive myocardial dysfunction associated with the transition from hypertrophy to failure.

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