Hypertension-Induced Cardiac Hypertrophy
Oxygen Supply and Consumption With Pacing

Catherine M. Cimini and Harvey R. Weiss

The purpose of this study was to determine if hypertrophied myocardium was associated with diminished cardiac function, restricted oxygen supply, or oxygen consumption during tachycardia. Myocardial oxygen supply and oxygen consumption were determined during baseline and atrial pacing conditions 30 days after New Zealand White rabbits were prepared as one-kidney, one clip Goldblatt hypertensive or uninephrectomized sham control rabbits. Coronary blood flow and cardiac output, using radioactive microspheres, and small vessel oxygen saturations, using microspectrophotometry, were measured in hypertrophied and nonhypertrophied hearts. After 30 days, baseline blood pressure was significantly higher in the Goldblatt rabbits compared with sham controls, and hypertension was maintained during pacing. The myocardium was hypertrophied in the Goldblatt hypertensive rabbits compared with sham controls. Baseline heart rates were not different between animal groups (242 ± 32 and 244 ± 24 beats/min, respectively). Both groups were paced 35% above baseline heart rates; during pacing, cardiac output was similar to baseline values in the sham controls (304 ± 99 versus 321 ± 116 ml/min, respectively) but reduced in the hypertensive rabbits (248 ± 43 versus 325 ± 62 ml/min). Myocardial oxygen consumption increased twofold in both nonhypertrophied and hypertrophied ventricles during tachycardia. Oxygen extraction was significantly elevated, but coronary blood flow was not altered during pacing in either animal group. Therefore, at the pacing level chosen the diminished function in cardiac hypertrophy was not associated with reduced oxygen consumption. Conversely, reduced efficiency during pacing in the hypertrophied myocardium was suggested. (Hypertension 1990;16:35-42)

Systemic hypertension leads to myocardial hypertrophy, which is thought to be a beneficial, adaptive response. The oxygen supply in pressure-induced hypertrophied myocardium appears to be sufficient under baseline conditions.1,2 Resting myocardial oxygen consumption measured in hypertrophy may or may not be elevated.1,2 However, coronary flow reserves are generally diminished in hypertension-induced cardiac hypertrophy compared with the nonhypertrophied myocardium, and minimal coronary vascular resistance is elevated.2 Clinical and experimental evidence suggest that the hypertension-induced hypertrophied myocardium is especially vulnerable to ischemia during stress.3 These observations have led to the suggestion that restricted myocardial flow contributes to the increased vulnerability during increased work.

Increased coronary flow to all layers of the ventricle is generally observed with stress, such as tachycardia, imposed on the nonhypertrophied myocardium.4-7 Additionally, oxygen extraction may also increase.8 Cardiac output is maintained during pacing in the nonhypertrophied heart.6 Thus, the nonhypertrophied myocardium tolerates chronotropic stress well. Conversely, attenuated coronary blood flow response to exercise and pharmacologically stimulated tachycardia have been reported in experimental myocardial hypertrophy, although impaired coronary blood flow response has not always been observed.4,7,9 The concomitant oxygen extraction response to tachycardia in the hypertrophic myocardium has not been documented. Cardiac output may be diminished with imposed stress.10

The purpose of this study was to test the hypothesis that diminished cardiac function would be exhibited by the hypertrophied myocardium during tachycardia and that this would be associated with restricted oxygen supply. Previous experiments revealed diminished coronary flow reserves and normal myocardial oxygen extraction in one-kidney, one clip (1K1C)
Goldblatt rabbits compared with the sham-operated controls during baseline, unstressed conditions. Because this model appeared to be flow restricted, it was hypothesized that increased myocardial oxygen consumption ($\text{MVO}_2$) would be attenuated in the hypertrophied myocardium compared with the nonhypertrophied myocardium during pacing. Alternatively, $\text{MVO}_2$ might not be attenuated if the oxygen extraction reserve was used. Cardiac function was assessed by the measurement of cardiac output in 1K1C and sham rabbits. Coronary blood flow and microvascular oxygen saturation were measured in the subepicardium (EPI) and subendocardium (ENDO) of the hypertrophied and nonhypertrophied left ventricle during baseline and atrial pacing conditions.

Methods

The 1K1C Goldblatt model was used to induce hypertension and left ventricular hypertrophy. New Zealand White rabbits (2.5–3.5 kg) were prepared as 1K1C or sham controls under sterile, anesthetized conditions (30 mg/kg sodium pentobarbital i.v.). A Sterling silver clip (0.5 mm gap opening) was threaded around the left renal artery and folded over itself, securing it in place. The renal artery, vein, and ureter of the contralateral kidney were ligated and the kidney removed. Sham-operated controls were uninephrectomized. Postoperatively, all rabbits were given 250 mg tetracycline in the water daily for 3 weeks. Water and food were available ad libitum. Because of the nature of the measurements, four experimental groups of rabbits were used (n=7 per group). Two groups of rabbits were used to measure oxygen supply and consumption during baseline conditions, and two additional groups were used for the same measurements during pacing conditions. Three additional experimental groups were added to examine the coronary blood flow response during pacing.

Experiments were conducted 30 days after preparation with sodium pentobarbital–anesthetized, open-chest animals. The femoral artery and vein were catheterized with polyethylene tubing. The rabbits were intubated and ventilation controlled with a Harvard respirator (Harvard Apparatus Co., Inc., South Natick, Mass.). A left thoracotomy was performed at the fifth intercostal space, and the pericardium was resected to expose the heart. A catheter was placed in the left atrium for microsphere injection. Electrodes were fastened to the left atrial appendage in those rabbits used for the pacing series. After surgery was completed, arterial blood samples were anaerobically obtained and electrometrically analyzed for blood gases and pH (Radiometer BMS 3, Radiometer America, Inc., Cleveland, Ohio). Arterial blood gases were maintained within a prescribed range by adjusting the ventilatory rate and volume. Hemoglobin content was determined spectrophotometrically (Fisher Hemophotometer, Fisher Scientific Co., Pittsburgh, Penn.).

Arterial blood pressures and heart rates were recorded with a Beckman R-411 dynograph recorder (Beckman Instruments, Inc., Fullerton, Calif.). Baseline coronary blood flow and cardiac output were measured using approximately $9 \times 10^5$ microspheres (3 M Co., St. Paul, Minn.), 15±3 µm in diameter, labeled with $^{14}$Ce or $^{85}$Sr. Microspheres were agitated for 2 minutes, and a known weight of microspheres was injected as a 0.2 ml bolus into the left atrium. The catheter was then flushed with 0.5 ml saline. The reference sample method was used for the flow determination. A blood sample was withdrawn from the femoral artery at a constant rate of 1 ml/min for 3 minutes. Blood withdrawal began 30 seconds before radioactive microsphere injection.

Animals used for the baseline series of measurements were killed after baseline measurements were established. Those used for pacing were subsequently paced with a Grass SD9 stimulator (Grass Instruments Co., Quincy, Mass.) (voltage 1–10 V and 0.4 msec duration). The frequency was adjusted such that the heartbeat was approximately 35% above its baseline level. The rabbits were paced at this level for 15 minutes before hemodynamic, coronary blood flow, and cardiac output measurements were repeated. Two additional groups (n=5/group) of "true" control rabbits (renal system intact) were paced and coronary blood flow measured with the same methods as described above. The pacing levels used with these rabbits were either 20% or 35% above their baseline heart rates. Coronary blood flow was measured in one additional group (n=5) of 1K1C rabbits during baseline, 35% atrial pacing, and adenosine infusion (0.4 mg/kg/min) administered during pacing.

Rabbits were killed at the end of all experiments by quickly removing the heart. The myocardium was cut below the atrioventricular ring with a large pair of shears and submerged in liquid nitrogen. This technique ensured that freezing began simultaneously on both sides of the ventricular wall and that oxygen saturations were unaltered. Frozen hearts were cut on a band saw in $-20^\circ$ C to isolate the left ventricular free wall and section it into the apex and base. Two adjacent myocardial plugs were then cut from these sections for coronary blood flow and microspectrophotometric measurements.

Coronary blood flow and cardiac output were determined by the reference flow technique. The left ventricular tissue used for coronary blood flow measurements was sectioned, separating the EPI and ENDO regions of the left ventricular apex and base. Radioactivity in the tissue samples was measured in a Packard Model 5320 automatic gamma spectrometer (Packard Instrument Co., Inc., Downers Grove, Ill.). Radioactivity was also assessed at the same time in the reference blood sample and in a minute sample of the microspheres used. Corrections were made for radioactive overlap. The formulas to calculate the coronary blood flow and cardiac output were:

$$\text{coronary blood flow} = F_r(C_r/C_s)$$

and
were cut on a rotary microtome-cryostat (-35°C) in
where Fr represents the reference flow, Q equals the
venules (CvOj) was determined by the product of the
prechilled glass slides and covered with
degassed silicone oil and a cover glass. These slides
were placed on a Zeiss microspectrophotometer
(from frozen myocardial tissue, sections (25 μm)
were significantly higher compared with those of the
samples in each myocardial tissue sample was not less than 700
Coronary blood flow for the EPI and
endothelial surfaces were determined by the average
myocardial vascular resistance was calculated from the measurements of coronary blood flow and
arterial pressure. We did not attempt to account for
coronary venous pressure.
Myocardial tissue cut from either the apex or base
and adjacent to the pieces used for coronary blood
flow measurements was used to measure oxygen
saturations. Oxygen saturations of arterioles (SaOj)
and venules (SVOj) were determined by a threewavelength microspectrophotometric method previously described. Briefly, the procedure is as follows:
From frozen myocardial tissue, sections (25 μm)
cut on a rotary microtome-cryostat (-35°C) in
a nitrogen atmosphere. The sections were transferred to prechilled glass slides and covered with
degassed silicone oil and a cover glass. These slides
were placed on a Zeiss microspectrophotometer
(Karl Zeiss Inc., Thornwood, N.Y.), fitted with a
nitrogen flushed cold stage, and absorbance readings
at wavelengths 560, 568, and 503 nm were obtained.
The size of the measuring spot was 8 μm. Oxygen
measurements for each rabbit were determined in six
arterioles and 10 venules (20–100 μm diameter) in
the EPI and ENDO regions. All vessels were randomly selected. The accuracy of this measurement is
within 3% compared with the Van Slyke analysis.

The oxygen content of arterioles (CaOj)
and venules (CvOj) was determined by the product of the percent oxygen saturation and the hemoglobin
concentration multiplied by 1.36. Oxygen extraction was calculated from the difference CaOj − CvOj. Oxygen
consumption was calculated as the product of the oxygen extraction and coronary blood flow separately
for the EPI and ENDO regions within the myocardium. The oxygen supply/consumption ratio was calculated
by dividing local oxygen supply by local oxygen consumption,

\[
\text{CaO}_j^* \times \frac{Q}{Q^*} \times (\text{CaO}_j - \text{CvO}_j)
\]

which reduces to

\[
\text{SaO}_j^/(\text{SaO}_j - \text{SVO}_j)
\]

Analysis of variance was used to determine differences in heart and body weights, hemodynamic
parameters, coronary blood flow, and oxygen parameters for 1K1C and sham rabbits in the baseline or
pacing condition. Regional differences were also assessed within the myocardium. An α level of 0.05
was accepted as significant. Duncan's procedure was used as the post hoc test. Differences between base-
line and pacing in the true control rabbits was determined by a Student's t test. All values are
represented as the mean ± SD.

Results
The rabbits used in these experiments were ini-
tially matched for age and weight. Thirty days after the
Goldblatt preparation, there was no body weight difference between the groups or experimental series
(Table 1). The heart weights of the 1K1C rabbits
were significantly higher compared with those of the
sham controls, resulting in a 35% higher heart
weight-to-body weight ratio in the 1K1C rabbits in
both experimental series.
The hemodynamic and blood gas data for both the
baseline series and the pacing series during the
baseline and pacing periods are shown in Table 2.
Blood pressures were elevated in the 1K1C rabbits
compared with sham controls throughout all condi-
tions. Control blood pressures of the sham controls
were similar in the baseline and pacing series. Also,
baseline blood pressures were similar for the 1K1C
rabbits in both series. Pacing did not significantly
alter blood pressures in either the hypertensive or
normotensive rabbits. Heart rate was not different
between the baseline conditions of either experimen-
tal series. Pacing significantly elevated heart rates to
the same level in both 1K1C and sham rabbits. The
ventilation was controlled such that arterial oxygen
and carbon dioxide were held within a prescribed
range and were not different between groups in any
condition. The cardiac output was determined during
both the baseline and pacing conditions of the pacing
series only (Table 2). The cardiac output was not
different between 1K1C and sham rabbits in the
baseline condition. In the sham controls, the cardiac
output was unchanged during pacing compared with
baseline conditions. Conversely, the cardiac output
was significantly diminished during pacing in the
1K1C rabbits.
Table 2. Hemodynamic and Arterial Blood Gas Data for Sham Control and One-Kidney, One Clip Hypertensive Rabbits

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Sham</th>
<th>1K1C</th>
<th>Sham</th>
<th>1K1C</th>
<th>Sham</th>
<th>1K1C</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBP (mm Hg)</td>
<td>91±13</td>
<td>142±27*</td>
<td>89±10</td>
<td>146±21*</td>
<td>89±15</td>
<td>124±26*</td>
</tr>
<tr>
<td>DBP (mm Hg)</td>
<td>65±10</td>
<td>111±16*</td>
<td>65±8</td>
<td>109±18*</td>
<td>62±9</td>
<td>103±24*</td>
</tr>
<tr>
<td>MAP (mm Hg)</td>
<td>74±11</td>
<td>121±19*</td>
<td>73±8</td>
<td>121±18*</td>
<td>71±10</td>
<td>110±2*</td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td>250±45</td>
<td>256±18</td>
<td>242±32</td>
<td>244±24</td>
<td>321±34†</td>
<td>320±28†</td>
</tr>
<tr>
<td>CO (ml/min)</td>
<td>79±12</td>
<td>76±5</td>
<td>74±8</td>
<td>70±4</td>
<td>77±2</td>
<td>74±2</td>
</tr>
<tr>
<td>PO2 (mm Hg)</td>
<td>35±3</td>
<td>33±4</td>
<td>32±3</td>
<td>32±3</td>
<td>30±4</td>
<td>31±5</td>
</tr>
</tbody>
</table>

Values represent mean±SD. 1K1C, one-kidney, one clip Goldblatt hypertensive rabbits; SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean aortic pressure; HR, heart rate; CO, cardiac output; PO2, partial pressure of oxygen; PCO2, partial pressure of carbon dioxide.

*Indicates significant difference compared with sham controls (p<0.05).
†Indicates significant difference compared with baseline condition (p<0.05).

Oxygen saturations were determined in the EPI and ENDO regions in the baseline series and during the paced condition of the pacing series (Figure 1). SaO2 was not different between groups and unchanged with pacing compared with the baseline condition. SvO2 was not different between the 1K1C rabbits and sham controls during the baseline condition. SvO2 was significantly reduced in the EPI and ENDO regions of both the 1K1C and sham rabbits during pacing compared with the baseline conditions. Also, in the paced condition, the ENDO SvO2 values within both groups were significantly reduced compared with their respective EPI regions. The SvO2 measured in both the EPI and ENDO regions of the 1K1C rabbits were significantly lower than that measured in the sham controls.

Oxygen extraction in the EPI and ENDO regions was not different between 1K1C rabbits and sham controls under baseline conditions (Table 3). Oxygen extraction increased in both the 1K1C and sham rabbits with pacing. The oxygen extraction increase was significantly higher in the EPI region of both groups. The EPI oxygen extraction measured in the 1K1C rabbits during pacing, although 16% higher, was not significantly different compared with the EPI oxygen extraction measured in the sham controls. Similarly, the ENDO oxygen extraction of the 1K1C rabbits during pacing was 15% higher but not statistically different from the sham controls. Average oxygen extraction was significantly higher in the hypertrophied compared with the nonhypertrophied myocardium during pacing (10.3±1.8 and 8.9±2.1 ml oxygen/100 ml blood, respectively).

A nonsignificantly higher coronary blood flow (19% and 26% in the EPI and ENDO regions, respectively) was observed in the hypertrophied myocardium compared with the nonhypertrophied myocardium during baseline conditions. No significant coronary blood flow response was observed within either the sham control or 1K1C rabbits with pacing. Under baseline conditions, coronary vascular resistance was not significantly different between the 1K1C and sham control rabbits. There was a modest nonsignificant coronary vascular resistance decrease (12%) in both the EPI and ENDO of sham control rabbits during pacing. Conversely, there was a slight nonsignificant coronary vascular resistance increase in the EPI (8%) and ENDO (7%) of the 1K1C rabbits. The result was a significantly greater coronary vascular resistance in the 1K1C rabbits compared with the sham controls during pacing.

The average MVO2 was elevated in the 1K1C rabbits compared with the sham controls under baseline conditions. No regional MVO2 difference was observed within either the hypertrophied or nonhypertrophied myocardium. The MVO2 was elevated to similar levels in both the 1K1C and sham rabbits.
TABLE 3. Coronary Oxygen Supply Parameters and Myocardial Oxygen Consumption Measured During Baseline and Atrial Pacing Conditions in Control and Cardiac Hypertrophy

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Sham</th>
<th>1K1C</th>
<th>Sham</th>
<th>1K1C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coronary blood flow (ml/min/100 g)</td>
<td>172±27</td>
<td>204±30</td>
<td>193±45</td>
<td>169±26</td>
</tr>
<tr>
<td>EPI</td>
<td>175±37</td>
<td>220±35</td>
<td>187±34</td>
<td>189±57</td>
</tr>
<tr>
<td>Coronary vascular resistance (mm Hg/ml/min/100 g)</td>
<td>0.44±0.15</td>
<td>0.61±0.14</td>
<td>0.39±0.11</td>
<td>0.66±0.17*</td>
</tr>
<tr>
<td>EPI</td>
<td>0.45±0.15</td>
<td>0.57±0.16</td>
<td>0.40±0.12</td>
<td>0.61±0.16*</td>
</tr>
<tr>
<td>O2 extraction (ml O2/100 ml)</td>
<td>5.9±1.0</td>
<td>5.8±1.0</td>
<td>7.9±1.8†</td>
<td>9.2±1.6†</td>
</tr>
<tr>
<td>EPI</td>
<td>5.5±1.3</td>
<td>5.4±1.4</td>
<td>9.9±1.9†‡</td>
<td>11.5±1.3†‡</td>
</tr>
<tr>
<td>MVV02 (ml O2/min/100 g)</td>
<td>9.9±1.2</td>
<td>11.8±2.2*</td>
<td>14.7±2.9†</td>
<td>15.6±3.5†</td>
</tr>
<tr>
<td>EPI</td>
<td>9.8±3.9</td>
<td>11.6±2.2</td>
<td>18.4±4.2†</td>
<td>21.6±6.2†</td>
</tr>
<tr>
<td>O2 Supply/Consumption</td>
<td>1.98±0.19</td>
<td>2.05±0.39</td>
<td>1.87±0.30†</td>
<td>1.52±0.01†</td>
</tr>
<tr>
<td>EPI</td>
<td>2.22±0.43</td>
<td>2.32±0.62</td>
<td>1.55±0.20†</td>
<td>1.31±0.13†</td>
</tr>
</tbody>
</table>

Values represent mean±SD. 1K1C, one-kidney, one clip Goldblatt hypertensive rabbits; EPI, subepicardium; ENDO, subendocardium.

*Indicates significant difference compared with the sham controls under similar conditions (p<0.05).
†Indicates significant difference compared with the baseline value for the same region within animal groups (p<0.05).
‡Indicates significant difference compared with the EPI region for that condition within animal groups (p<0.05).

During pacing. The elevated MVV02 was balanced between the EPI and ENDO regions within both animal groups.

The oxygen supply/consumption ratio was similar in the EPI and ENDO regions under baseline conditions for both the sham controls and 1K1C rabbits. These baseline ratios were not different between groups. Pacing resulted in significantly reduced oxygen supply/consumption ratios in both groups; however, the reduction was greater in the 1K1C rabbits. The relation between EPI and ENDO oxygen supply/consumption ratios was unchanged during pacing in the sham controls. The oxygen supply/consumption ratio of the ENDO region was significantly reduced in comparison with the EPI region within the hypertrophied ventricle.

We subjected true control rabbits to one of two pacing levels, either 20% or 35% above their baseline heart rates (Table 4). The baseline blood pressure, heart rate, and coronary blood flow measured in the true controls were similar to the sham controls. Arterial blood gases were controlled within the prescribed range during all experiments. Mean arterial pressures were maintained and heart rates were significantly increased as compared with their respective baseline values during both the 20% and 35% atrial pacing. Coronary blood flow significantly increased during 20% pacing compared with the baseline values. Conversely, coronary blood flow did not change significantly during 35% atrial pacing compared with the respective baseline values.

TABLE 4. Comparison of Coronary Blood Flow Response to Low (20%) and High (35%) Atrial Pacing in “True” Control Animals

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Baseline</th>
<th>20% pacing</th>
<th>35% pacing</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAP (mm Hg)</td>
<td>88±11</td>
<td>76±16</td>
<td>90±15</td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td>271±31</td>
<td>325±36*</td>
<td>230±24</td>
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<tr>
<td>P02 (mm Hg)</td>
<td>70±7</td>
<td>73±12</td>
<td>67±7</td>
</tr>
<tr>
<td>PC02 (mm Hg)</td>
<td>34±5</td>
<td>35±3</td>
<td>37±1</td>
</tr>
<tr>
<td>Coronary blood flow (ml/min/100 g)</td>
<td>180±46</td>
<td>278±35*</td>
<td>237±73</td>
</tr>
<tr>
<td>EPI</td>
<td>202±64</td>
<td>275±69</td>
<td>236±48</td>
</tr>
</tbody>
</table>

Values represent mean±SD. MAP, mean aortic pressure; HR, heart rate; P02, partial pressure of oxygen; PC02, partial pressure of carbon dioxide; EPI, subepicardium; ENDO, subendocardium.

*Indicates significant difference from baseline value (p<0.05).
Adenosine infusion during 35% atrial pacing resulted in significant pressure or flow changes with the exception of a significantly reduced cardiac output. Adenosine infusion during 35% atrial pacing resulted in significantly reduced blood pressure, coronary vascular resistance, and increased coronary blood flow. Cardiac output, reduced during pacing, was not restored toward baseline levels with the infusion of adenosine.

**Discussion**

These experiments tested the hypothesis that, in the hypertrophied myocardium, impaired cardiac function would be associated with restricted oxygen supply and consumption during atrial pacing. Cardiac output was maintained during tachycardia in the sham control rabbits; conversely, it was reduced in the 1K1C rabbits. MVs2 was elevated to similar levels in the hypertrophied as in the nonhypertrophied myocardium subjected to the same level of pacing. Oxygen extraction increased and coronary blood flow did not change in either group in response to pacing. Thus, diminished cardiac function was evident in the hypertrophied myocardium during atrial pacing, but it was not associated with diminished oxygen consumption. Therefore, during tachycardia reduced efficiency (work/oxygen consumption) of the hypertrophied myocardium was suggested.

The Goldblatt model is a commonly used model of hypertension, and 1 month appears to be a sufficient time for sustained cardiac hypertrophy in small animals. We previously demonstrated that myocardial hypertrophy in this 1K1C Goldblatt rabbit model was associated with an elevated coronary blood flow and minimal coronary vascular resistance, as well as reduced flow reserve compared with the nonhypertrophied myocardium of the sham control during baseline, unstressed conditions. The oxygen extraction and coronary blood flow measured in the present baseline study were similar to that previously reported.

Additionally, a group of 30-day 1K1C rabbits were subjected to 35% atrial pacing and adenosine infusion. Baseline blood pressure, heart rate, coronary blood flow, coronary vascular resistance, and cardiac output were similar to baseline data from other 30-day 1K1C rabbits (Table 5). During pacing, no significant pressure or flow changes occurred with the exception of a significantly reduced cardiac output.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Baseline</th>
<th>Pacing</th>
<th>Pacing and adenosine</th>
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</thead>
<tbody>
<tr>
<td>MAP (mm Hg)</td>
<td>116±23</td>
<td>94±15</td>
<td>57±8*</td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td>268±28</td>
<td>348±38*</td>
<td>350±34*</td>
</tr>
<tr>
<td>Coronary blood flow (ml/min/100 g)</td>
<td>240±31</td>
<td>190±40</td>
<td>270±79†</td>
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<tr>
<td>Coronary vascular resistance (mm Hg/ml/min/100 g)</td>
<td>221±30</td>
<td>171±34</td>
<td>228±49*†</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Baseline</th>
<th>Pacing</th>
<th>Pacing and adenosine</th>
</tr>
</thead>
<tbody>
<tr>
<td>EPI</td>
<td>0.46±0.07</td>
<td>0.53±0.73</td>
<td>0.23±0.07†</td>
</tr>
<tr>
<td>ENDO</td>
<td>0.48±0.05</td>
<td>0.58±0.21</td>
<td>0.26±0.05†</td>
</tr>
<tr>
<td>CO (ml/min)</td>
<td>375±75</td>
<td>219±46*</td>
<td>223±83*</td>
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</table>

Values represent mean±SD. MAP, mean aortic pressure; HR, heart rate; CO, cardiac output.

Indicates significant difference compared with baseline condition (p<0.05).

Indicates significant difference compared with pacing condition (p<0.05).

The hearts were paced 35% above their baseline rate. Because there was no difference in baseline heart rates between groups, hearts were paced to the same level in both animal groups. Hypertension was maintained in the 1K1C rabbits during atrial pacing. The cardiac output was not different between groups during baseline conditions despite the elevated pressures in the 1K1C rabbits, indicating that the external work of the hypertrophied myocardium was higher than that of the nonhypertrophied myocardium under baseline conditions. Cardiac output was maintained in the sham control rabbits but was reduced in the 1K1C rabbits during atrial pacing. Thus, during pacing external work was maintained by the nonhypertrophied myocardium, whereas it was diminished in hypertrophied myocardium.

Additionally, a group of 30-day 1K1C rabbits were subjected to 35% atrial pacing and adenosine infusion. Baseline blood pressure, heart rate, coronary blood flow, coronary vascular resistance, and cardiac output were similar to baseline data from other 30-day 1K1C rabbits (Table 5). During pacing, no significant pressure or flow changes occurred with the exception of a significantly reduced cardiac output. Adenosine infusion during 35% atrial pacing resulted in significantly reduced blood pressure, coronary vascular resistance, and increased coronary blood flow. Cardiac output, reduced during pacing, was not restored toward baseline levels with the infusion of adenosine.

**Discussion**

These experiments tested the hypothesis that, in the hypertrophied myocardium, impaired cardiac function would be associated with restricted oxygen supply and consumption during atrial pacing. Cardiac output was maintained during tachycardia in the sham control rabbits; conversely, it was reduced in the 1K1C rabbits. MVs2 was elevated to similar levels in the hypertrophied as in the nonhypertrophied myocardium subjected to the same level of pacing. Oxygen extraction increased and coronary blood flow did not change in either group in response to pacing. Thus, diminished cardiac function was evident in the hypertrophied myocardium during atrial pacing, but it was not associated with diminished oxygen consumption. Therefore, during tachycardia reduced efficiency (work/oxygen consumption) of the hypertrophied myocardium was suggested.

The Goldblatt model is a commonly used model of hypertension, and 1 month appears to be a sufficient time for sustained cardiac hypertrophy in small animals. We previously demonstrated that myocardial hypertrophy in this 1K1C Goldblatt rabbit model was associated with an elevated coronary blood flow and minimal coronary vascular resistance, as well as reduced flow reserve compared with the nonhypertrophied myocardium of the sham control during baseline, unstressed conditions. The oxygen extraction and coronary blood flow measured in the present baseline study were similar to that previously reported.

The hearts were paced 35% above their baseline rate. Because there was no difference in baseline heart rates between groups, hearts were paced to the same level in both animal groups. Hypertension was maintained in the 1K1C rabbits during atrial pacing. The cardiac output was not different between groups during baseline conditions despite the elevated pressures in the 1K1C rabbits, indicating that the external work of the hypertrophied myocardium was higher than that of the nonhypertrophied myocardium under baseline conditions. Cardiac output was maintained in the sham control rabbits but was reduced in the 1K1C rabbits during atrial pacing. Thus, during pacing external work was maintained by the nonhypertrophied myocardium, whereas it was diminished in hypertrophied myocardium.

The inability of the hypertrophied myocardium to maintain cardiac output, and thus external work during stress, has been previously reported. Saragoca and Tarazi demonstrated a reduced contractile response to isoproterenol in cardiac hypertrophy that could not be completely explained by a diminished β-adrenergic receptor function. They suggested that the limitation could in part be influenced by metabolic imbalances and in part be due to a greater dependency on the Starling mechanism enhancing contractility. In our study, MVs2 was elevated to the same level with atrial pacing in the 1K1C and sham control groups. Therefore, the 1K1C rabbit hearts used the same amount of oxygen for a reduced level of external work, indicating a reduced level of efficiency.

Previous experiments with this model demonstrated a restricted flow reserve. We hypothesized that, during atrial pacing, the coronary blood flow reserve would be used in response to elevated oxygen demand, and as such, the hypertrophied myocardium would be limited. However, both groups primarily used the oxygen extraction reserve in response to tachycardia. An oxygen extraction response to increased oxygen consumption had been previously reported in rabbits. These experiments indicated a greater use of the oxygen extraction reserve in
cardiac hypertrophy. This suggests that tissue oxygenation may be lower in the hypertrophied myocyte.

The coronary blood flow response to imposed tachycardia was surprisingly absent in both animal groups. It is generally accepted that MVO2 and coronary blood flow are closely correlated and that oxygen extraction is used when flow is restricted. However, there have been experiments with exercise and hypoxia that demonstrated increased oxygen extraction in response to increased MVO2 despite unrestricted flow reserves.8,19 Nevertheless, atrial pacing is associated with an increased coronary blood flow in most dog models,4,5,7,14 and previous experiments with this rabbit model described a vasodilator potential.1

Reduced coronary reserve is associated with the hypertrophied myocardium; thus, we anticipated an attenuated flow response to tachycardia in hypertrophied myocardium. Our data suggest some limitation to the coronary flow reserve for the rabbit myocardium at this pacing level. Supporting this possibility, it was reported that the rabbit myocardium was unable to sustain high heart rates with exercise.17 Further, even in a dog model, a plateau phase is apparent in the flow response at high heart rates during stepwise coronary pacing experiments.20 Therefore, it seemed possible that some innate coronary dynamic alteration may have limited the blood flow response in these animals.

To examine the possibility that the pacing level chosen restricted the flow reserve, we subjected a small group of true control rabbits to a lower level of atrial pacing (20% above baseline) in addition to the level of atrial pacing used in this study. Coronary blood flow was significantly increased during 20% pacing; however, no change was measured during 35% atrial pacing. Thus, the flow response in the rabbit appears limited by the rate of atrial pacing chosen. A 35% pacing rate does not seem excessive for other models such as the dog. However, the rabbit heart maintains a higher heart rate and smaller stroke volume during unstressed conditions in comparison with the dog heart. Imposing a 35% rate elevation in the rabbit resulted in rates of approximately 320 beats/min. The lack of coronary flow response to 35% tachycardia may have been due in part to critically limited diastolic time or reduced stroke volume in these rabbits.

To more clearly determine if the hypertrophied heart could use the coronary blood flow reserve and if this increased oxygen supply would restore the cardiac performance, an additional group of 1K1C rabbits were first paced 35% above baseline and then infused with adenosine during tachycardia. The comparison may be drawn between this group and the previous 35% pacing 1K1C group as the baseline parameters, experimental conditions, and flow response to pacing were similar. Adenosine infusion dilated the coronary vasculature and slightly enhanced coronary flow but not to the extent previously measured in unpaced 1K1C animals with the same adenosine dose.1 These data support the idea of some coronary flow reserve in pacing despite shortened diastolic time.

Despite adenosine-induced vasodilation, cardiac output remained diminished during pacing. This supports the idea that metabolism was not a limitation, and factors other than oxygen delivery influenced the diminished performance of the hypertrophied myocardium during 35% tachycardia. These other influences are speculative but could include diminished internal Ca2+ binding21 or reduced β-adrenergic receptor responses within the hypertrophied myocyte.22 Perhaps, as was proposed by Saragoca and Tarazi,10 a greater influence of the Starling mechanism contributes to the contractility of the hypertrophied myocardium compared with the nonhypertrophied myocyte. This may be due to excessive fibrosis of the hypertrophied myocardium.23 Regardless of the mechanism, the oxygen consumed was similar between the hypertrophied and nonhypertrophied myocardium, yet the performance was reduced, and therefore oxygen use efficiency was reduced in the hypertrophied myocardium during tachycardia.

In summary, elevated blood pressures were maintained and cardiac output was reduced during tachycardia in this model of hypertension-induced cardiac hypertrophy. MVO2 was elevated to similar levels in the hypertrophied as in the nonhypertrophied myocardium; concomitantly, in both groups, oxygen extraction increased and coronary flow was unchanged. Together this indicated that diminished cardiac function in the hypertrophied myocardium during 35% atrial pacing was not associated with oxygen consumption restrictions. The data suggest that the efficiency of oxygen use is reduced in hypertrophied myocardium during tachycardia.

References


**KEY WORDS** • cardiac hypertrophy • cardiac function • tachycardia • oxygen consumption • rabbit studies
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C M Cimini and H R Weiss

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