Regional Changes in Hemodynamics and Cardiac Myocyte Size in Rats With Aortocaval Fistulas

1. Developing and Established Hypertrophy

Zhi Liu, Don R. Hilbelink, William B. Crockett, and A. Martin Gerdes

The effects of a large arteriovenous fistula on left and right ventricular hemodynamics and cardiac myocyte size were examined in adult rats at 1 week and 1 month after surgery. Cardiac output, left ventricular function, and right ventricular function were evaluated before obtaining isolated myocytes for cell size measurements. Average heart weight increased 35% at 1 week and 86% at 1 month in rats with fistulas. In general, myocyte hypertrophy was due to a proportional increase in length and width (length/width ratio remained constant). This change was more evident in the large hearts from rats with 1-month fistulas. At both the 1-week and 1-month intervals, the hypotrophic response of right ventricular myocytes was slightly greater than that observed in the left ventricle or interventricular septum. Left ventricular systolic pressure and dP/dt_{max} were significantly reduced at 1 week but returned to normal after 1 month of overloading. Left ventricular end-diastolic pressure was increased approximately fivefold and twofold at 1 week and 1 month, respectively. Right ventricular systolic pressure and dP/dt_{max} were increased at both intervals examined. We conclude that severe volume overloading from a large aortocaval fistula in the rat is characterized by 1) depressed left ventricular function at 1 week followed by a large compensatory hypertrophy and near normal function at 1 month, 2) right ventricular pressure overload, and 3) changes in myocyte shape that resemble normal physiological growth. (*Circulation Research* 1991;69:52–58)

Volume-overload–induced cardiac hypertrophy occurs in response to stimuli such as aortic insufficiency, arteriovenous fistula, mitral regurgitation, and heart block.1–10 A proportional increase in circumference and wall thickness typically occurs in these disorders.1,2 The length and diameter of cardiac myocytes are believed to increase proportionally, reflecting the observed gross anatomic changes.1,2,4 However, left and right ventricular changes in cardiac myocyte dimensions (volume, length, cross-sectional area, and diameter) from animals with a large degree of volume-overload–induced hypertrophy have not been adequately documented. A major goal of this study was to determine the specific changes in myocyte dimensions that are associated with developing and established cardiac hypertrophy in rats with large arteriovenous shunts.

Volume overloading often produces a twofold or threefold increase in cardiac mass in humans.3,4 The degree of cardiomegaly observed in hearts from animals with a similar degree of overloading, however, is usually much less. For instance, aortocaval fistulas of 1 month or longer typically result in only a 10–30% increase in cardiac mass in dogs,6,7,9–11 although a recent report12 has indicated that a much larger degree of cardiac enlargement may be attained in this species (79% increase in one group of dogs with aortocaval fistulas). Aortocaval fistulas in the rat have also resulted in considerable variability in the extent of cardiac hypertrophy.13–17 A goal of these experiments was to produce a model of volume overloading in the rat that would result in a very large but consistent degree of cardiac hypertrophy.

Flaim and coworkers15,18 have examined hemodynamic changes in rats at 1 day and at 2 months after aortocaval fistula surgery. However, heart weight increased only 20% in their model after 2 months of overloading. The hemodynamic response of the rat to an arteriovenous fistula that produces a large cardiac hypertrophy is not known.

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In the present experiments, severe volume overloading was induced in the rat to examine cardiac hypertrophy as it developed (at 1 week after surgery) and after it was more established (at 1 month after surgery). Changes in hemodynamics and myocyte dimensions from both the right and left ventricles were assessed for potential differences in the regional response of the heart. Additionally, direct measurements of myocyte length at the two stages of overloading provided new information about the rate of induced sarcomereogenesis.

Materials and Methods

Aortocaval Fistula Model

Female Sprague-Dawley rats weighing 270–300 g were obtained from Holtzman Laboratory Animals, Madison, Wis. The rats were pretreated with ketamine hydrochloride (10 mg i.p. per rat) and subsequently anesthetized using isoflurane (5% for the first minute followed by 2–3% during the remainder of the surgery). The skin was sterilized with povidone-iodine solution before making a midline celiotomy. The intestines were displaced laterally using sterile sponges. The aorta and the inferior vena cava were isolated, and the left and right iliolombar arteries and veins were ligated and clamped. Microvascular clamps were applied to the aorta and vena cava, both proximal and distal to the site of anastomosis. Heparin (10 units) was administered intravenously. An end-to-side anastomosis was produced between the distal end of the left iliomobar vein and the side of the aorta. The arteriotomy and shunt diameter were both ~1.25 mm. Various pieces of polyethylene tubing ranging from 1.22 to 1.50 mm were used to estimate arteriotomy size. Rats with shunts larger than 1.5 mm in diameter usually died within a few days. Patency of the fistula was visually confirmed. The aorta and vena cava were clamped for 30 minutes but were not anastomosed in sham-operated rats.

Hemodynamics

Rats were anesthetized with an intraperitoneal injection of thiopental sodium (60 mg/kg) and placed on a 37°C heating pad (Deltaplex Isothermal Pad, model 39 DP, Braintree Scientific, Inc., Braintree, Mass.) before hemodynamic measurements at 1 week and 1 month after surgery. After the rats were fully sedated, a tracheal tube was inserted, and the left ventricle was catheterized with an ultraminiature catheter pressure transducer (model SPR-407, Millar Instruments, Inc., Houston) via the right common carotid artery. Left ventricular systolic pressure, diastolic pressure, end-diastolic pressure, and dP/dt max were assessed using a recorder (model 3400, Gould, Cleveland, Ohio). The catheter was subsequently withdrawn a few millimeters to measure aortic pressure. Cardiac output was obtained with a computer (Cardiotherm 500, Columbus Instruments, Columbus, Ohio) using the thermodilution method. Right ventricular hemodynamics were obtained with a specially designed curved ultraminiature catheter (model SPR-407 curved, Millar Instruments), which was inserted into the right jugular vein. The hemodynamic methods have been described in detail by Zimmer and colleagues.19,20

Cell Isolation and Morphometry

Hearts of anesthetized rats were quickly removed, trimmed of excess tissue, blotted, and weighed after hemodynamic measurements. The procedure for isolating and fixing cardiac myocytes for morphological examination has been described previously.21 Briefly, hearts were perfused in a retrograde manner on a Langendorff apparatus with Joklik media followed by collagenase. Cells were collected from the left ventricular free wall, septum, and right ventricular free wall.

Cell volume of isolated myocytes was determined using a Coulter Channelizer (model C256, Coulter Corp., Hialeah, Fla.) interfaced to a Coulter Counter (model ZBI). The Coulter system determines cell volume by measuring the change in electrical resistance across an aperture resulting from the displacement of electrolytes as cells move through the aperture.21,22 Based on the work of Hurley,23 a shape factor of 1.05, representing a cell length/width ratio of ~7, was used.

Cell length, defined as the longest length parallel to the longitudinal axis of the myocyte, was measured directly with a microscope. Myocyte cross-sectional area was calculated from cell volume/cell length. A minimum of 40 myocytes from each heart region of each rat was measured. The isolation procedure typically produces cells with a mean sarcomere length of 1.90 μm.16,21 The consistency of sarcomere lengths was confirmed again in preliminary experiments by measuring sarcomere lengths of six samples from each rat group (200 sarcomeres per sample).

Fresh tissue samples of lung, liver, and kidney were collected from each rat to determine if there were any changes in percent dry weight. Statistical analyses were done using analysis of variance (ANOVA). Sheffe's test was used to make individual comparisons between groups when a significant change was observed with the ANOVA.

Results

Values for heart weight, body weight, and the heart weight/body weight ratio are given in Table 1. Heart weight increased 35% and 86% at 1 week and at 1 month after fistula surgery, respectively. There was no significant change in the body weight of rats 1 week after aortocaval fistula surgery (1-week fistula rats weighed 287±6 g when killed and 291±16 g before surgery). However, the mean body weight of 1-week sham-operated rats was slightly (8%), though significantly, greater than that of 1-week fistula rats (Table 1). Total mortality rate was ~47% for the 1-week and 1-month fistula groups combined. In the majority of failures, the time of death was ~24–48 hours after surgery. Loss of body mass was usually a reliable predictor of mortality.
Percent dry weight of liver, lung, and kidney were not altered in the experimental rats at either 1 week or 1 month after surgery (data not shown).

**Hemodynamic Alterations**

Mean values for various hemodynamic parameters from sham-operated controls and experimental rats are shown in Tables 1 and 2. Left ventricular function was depressed in rats with fistulas of 1-week duration as evidenced by significant reductions in dP/dt\(_{\text{max}}\), end-diastolic pressure and a decrease in end-diastolic pressure. Left ventricular dP/dt\(_{\text{max}}\) and systolic pressure returned to normal after 1 month of overloading. Left ventricular end-diastolic pressure returned toward normal values but remained significantly elevated at 1 month. Systolic aortic pressure was the same as left ventricular systolic pressure in each rat group. Diastolic aortic pressure was significantly depressed at both 1 week and 1 month after surgery, although the change was not as dramatic at 1 month.

In contrast to the changes in the left ventricle, right ventricular dP/dt\(_{\text{max}}\) and systolic pressure were significantly increased at both intervals examined. Right ventricular end-diastolic pressure was increased at 1 week and 1 month.

Cardiac output index was ~2.7 times that of controls at both 1 week and 1 month after surgery. Increased stroke volume accounted for virtually all of the increase in cardiac output, since heart rate was not changed in either experimental group. Total peripheral resistance index (shunt inclusive) was significantly reduced at both 1 week and 1 month.

**Cell Size Changes**

Regional changes in myocyte volume, length, and cross-sectional area are illustrated in Figures 1, 2, and 3, respectively. In general, myocyte volume increased ~22% at 1 week and 73% at 1 month after surgery (mean change in right ventricle, left ventricle, and septum). At both intervals examined, approxi-

### Table 1. Heart Weight, Body Weight, and Hemodynamic Changes in Rats

<table>
<thead>
<tr>
<th>Rat group</th>
<th>BW (g)</th>
<th>HW (mg)</th>
<th>HW/BW (mg/g)</th>
<th>HR (beats/min)</th>
<th>CO (ml/min)</th>
<th>COI (ml/min·kg)</th>
<th>SV (ml/beat)</th>
<th>TPRI</th>
</tr>
</thead>
<tbody>
<tr>
<td>After 1 week</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WF (n=9)</td>
<td>287±6</td>
<td>1,317±47</td>
<td>4.60±0.21</td>
<td>400±13</td>
<td>237±51</td>
<td>823±219</td>
<td>0.58±0.11</td>
<td>0.15±0.02</td>
</tr>
<tr>
<td>WS (n=7)</td>
<td>313±5</td>
<td>975±32</td>
<td>3.12±0.10</td>
<td>418±9</td>
<td>95±8</td>
<td>306±28</td>
<td>0.23±0.02</td>
<td>0.50±0.06</td>
</tr>
<tr>
<td>Change (%)</td>
<td>↓ 8</td>
<td>↑ 35</td>
<td>↑ 47</td>
<td>↓ 4</td>
<td>↑ 149</td>
<td>↑ 169</td>
<td>↑ 152</td>
<td>↓ 70</td>
</tr>
</tbody>
</table>

**Values are mean±SEM. BW, body weight; HW, heart weight; HR, heart rate; CO, cardiac output; COI, cardiac output index; SV, stroke volume; TPRI, total peripheral resistance index (mm Hg·min·kg⁻¹); WF, 1 week after fistula surgery; WS, 1 week after sham operation; Change, percent change after fistula surgery; MF, 1 month after fistula surgery; MS, 1 month after sham operation; ANOVA, analysis of variance; Yes, significantly different among the groups (p<0.05); No, not significantly different among the groups.**

### Table 2. Hemodynamic Changes in Rats

<table>
<thead>
<tr>
<th>Rat group</th>
<th>LVdP/dt(_{\text{max}}) (mm Hg/sec)</th>
<th>LVSP (mm Hg)</th>
<th>LVDP (mm Hg)</th>
<th>LVEDP (mm Hg)</th>
<th>SAP (mm Hg)</th>
<th>DAP (mm Hg)</th>
<th>RVdP/dt(_{\text{max}}) (mm Hg/sec)</th>
<th>RVSP (mm Hg)</th>
<th>RVDP (mm Hg)</th>
<th>RVEDP (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>After 1 week</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WF (n=9)</td>
<td>8,372±612</td>
<td>114±5</td>
<td>1.1±0.7</td>
<td>14.0±2.0</td>
<td>112±6</td>
<td>68±6</td>
<td>3,337±191</td>
<td>45±2</td>
<td>2.3±0.9</td>
<td>8.4±0.9</td>
</tr>
<tr>
<td>WS (n=7)</td>
<td>10,697±514</td>
<td>158±6</td>
<td>0.9±0.3</td>
<td>2.6±0.5</td>
<td>158±6</td>
<td>128±5</td>
<td>1,880±151</td>
<td>34±1</td>
<td>0.9±0.4</td>
<td>2.5±0.5</td>
</tr>
<tr>
<td>Change (%)</td>
<td>↓ 22</td>
<td>↓ 28</td>
<td>↑ 22</td>
<td>↑ 439</td>
<td>↓ 29</td>
<td>↓ 47</td>
<td>↑ 78</td>
<td>↑ 32</td>
<td>↑ 156</td>
<td>↑ 236</td>
</tr>
</tbody>
</table>

**Values are mean±SEM. LV, left ventricular; SP, systolic pressure; dP/dt\(_{\text{max}}\), maximal rate of rise of ventricular pressure; DP, diastolic pressure; EDP, end-diastolic pressure; SAP, systolic aortic pressure; DAP, diastolic aortic pressure; RV, right ventricular; WF, 1 week after fistula surgery; WS, 1 week after sham operation; Change, percent change after fistula surgery; MF, 1 month after fistula surgery; MS, 1 month after sham operation; ANOVA, analysis of variance; Yes, significantly different among the groups (p<0.05); No, not significantly different among the groups.**
imately one third of the hypertrophy was due to an increase in cell length and two thirds was due to an increase in myocyte cross-sectional area. This was true of each heart region, although right ventricular myocytes displayed the greatest increase in volume, length, and cross-sectional area.

Changes in the length, width (width = 2 × radius as calculated from cross-sectional area using the formula for the area of a circle), and length/width ratios are shown in Table 3. Length/width ratio was not altered significantly in any region of experimental rats.

Discussion

Experimental Model

Volume overloading was produced in adult rats by connecting the severed end of an iliacom, tributary of the inferior vena cava to the side of the abdominal aorta. The hypertrophic response at 1 month (86%) was similar to that observed by Dart and Holloszy and Hatt et al in rats with chronic aortocaval fistulas. A much smaller cardiac hypertrophy resulted from the aortocaval shunt procedure used by Flaim et al in adult rats. Michel et al reported increases in cardiac mass of 56%, 32%, and 43% in rats with aortocaval fistulas of 1, 3, and 6 months, respectively. Mercadier et al observed up to a 99% increase in heart mass in rats with aortocaval fistulas. In their model, a hole was cut between the medial walls of the aorta and inferior vena cava. Containment of blood within the vascular system was dependent on the surrounding common sheath of connective tissue. Previously, we have looked at several types of side-to-side aortocaval fistula procedures similar to those used by others (authors’ unpublished data). Data have been reported from rats with aortocaval shunts of restricted size and rats with femoral arteriovenous fistulas. Only a moderate hypertrophy was obtained with these models. In these experiments, the objectives were to produce a model of volume-overload-induced hypertrophy in the rat with the following features: 1) a large degree of cardiac hypertrophy similar to that observed frequently in humans, 2) a consistent degree of cardiac hypertrophy, and 3) a shunt that could be closed relatively easily (we plan to study the reversal of volume-overload-induced hypertrophy in future experiments). Results indicate that a large and consistent hypertrophy resulted from
TABLE 3. Cell Length to Cell Width Ratio

<table>
<thead>
<tr>
<th>Rat group</th>
<th>RV</th>
<th></th>
<th>LV</th>
<th></th>
<th>SEPT</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CL</td>
<td>CW</td>
<td>CL/W</td>
<td>CL</td>
<td>CW</td>
<td>CL/W</td>
</tr>
<tr>
<td>After 1 week</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WF (n=9)</td>
<td>131±7</td>
<td>15.0±0.9</td>
<td>8.8±0.8</td>
<td>141±9</td>
<td>16.4±1.4</td>
<td>8.6±1.0</td>
</tr>
<tr>
<td>WS (n=7)</td>
<td>118±6</td>
<td>13.7±0.9</td>
<td>8.7±0.9</td>
<td>129±8</td>
<td>15.6±1.3</td>
<td>8.3±0.8</td>
</tr>
<tr>
<td>Change (%)</td>
<td>↑11</td>
<td>↑9</td>
<td>↑1</td>
<td>↑9</td>
<td>↑5</td>
<td>↑4</td>
</tr>
<tr>
<td>After 1 month</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MF (n=9)</td>
<td>154±14</td>
<td>17.2±1.5</td>
<td>9.0±0.9</td>
<td>166±11</td>
<td>18.4±1.5</td>
<td>9.1±0.9</td>
</tr>
<tr>
<td>MS (n=8)</td>
<td>127±9</td>
<td>13.4±1.2</td>
<td>9.5±0.9</td>
<td>140±9</td>
<td>15.7±1.0</td>
<td>8.9±0.7</td>
</tr>
<tr>
<td>Change (%)</td>
<td>↑21</td>
<td>↑28</td>
<td>↓5</td>
<td>↑19</td>
<td>↑17</td>
<td>↑2</td>
</tr>
<tr>
<td>ANOVA</td>
<td>MF&gt;WF&gt;MS</td>
<td>MF&gt;WF&gt;</td>
<td>No</td>
<td>MF&gt;MS = WF&gt;WS</td>
<td>MF&gt;WF = MS</td>
<td>WF=MS</td>
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<tr>
<td>Scheffe's test</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>

Values are mean±SEM. RV, right ventricle; LV, left ventricle; SEPT, septum; CL, cell length; CW, cell width; WF, 1 week after fistula surgery; WS, 1 week after sham operation; Change, percent change after fistula surgery; MF, 1 month after fistula surgery; MS, 1 month after sham operation; ANOVA, analysis of variance; Yes, significantly different among the groups (p<0.05); No, not significantly different among the groups.

With acute or chronic fistulas, although the magnitude of the response is often quite variable, Flaim et al have reported no change in heart rate after 1 day18 and a reduction in heart rate after 2 months15 in rats with aortocaval fistulas. Heart rate was not changed at either 1 week or 1 month after induction of the overload in our experiments. It appears that tachycardia is not a significant compensatory response to large (our present study) or small15,18 degrees of arteriovenous shunting in this species.

Cardiac output in rats with aortocaval fistulas was ~2.7 times that of sham-operated controls at both 1 week and 1 month after surgery. At both intervals, increased stroke volume accounted for the elevated cardiac output, since heart rate was not significantly altered. Left ventricular function was depressed 1 week after creation of an aortocaval fistula, as evidenced by an increase in end-diastolic pressure and a reduction in systolic pressure, diastolic pressure, and dP/dtmax. Left ventricular systolic pressure and dP/dtmax returned to normal after 1 month of overloading. It is likely that a mismatch occurred between left ventricular pumping ability and load at 1 week (e.g., inadequate hypertrophy). Unfortunately, it is not possible to determine in vivo end-diastolic sarcomere lengths from isolated myocytes. Consequently, the contribution of the Frank-Starling length–tension curve after 1 week and 1 month of overloading cannot be determined at this time. Additional experiments using whole tissue will be necessary to determine the contributions of sarcomere length and perhaps myocyte slippage to the ventricular dilation that occurs in this model.

Volume-overload–induced hypertrophy is believed to develop in response to an increase in end-diastolic wall stress.1 The resulting increase in chamber volume and wall thickness in response to volume overloading returns wall stress toward normal. In our experiments, left ventricular end-diastolic pressure

Functional Changes

Acute and chronic changes in hemodynamics from volume overloading due to various types of arteriovenous shunts have been examined extensively.8–12,15,17,18,25–37 Most of the experimental work has been conducted in dogs. There is general agreement that arteriovenous shunts lead to an increase in cardiac output, stroke volume, and systemic peripheral resistance (excluding shunt). Heart rate is usually increased in dogs and humans

this surgical procedure. Although closure of the shunt has not been attempted, this model appears more promising than the side-to-side models, since the inferior vena cava is not damaged or constricted during the surgical procedure and a single ligature around the iliofemoral vein will close the fistula.

The percent dry weight of lung, liver, and kidney tissue was not changed in either experimental rat group. Additionally, percent dry weight of lung, liver, and kidney was not altered in the five rats that were examined 1 day after creating a large aortocaval shunt (data not shown). Aside from the absence of evidence for pulmonary, renal, and hepatic congestion, ascites was not observed in any of the overloaded rats in our study. Flaim et al18 observed an increase in lung water 1 day after creating a smaller aortocaval shunt in rats. Lung water returned to normal 2 months after induction of the overload.15 At the same time, water content of the kidney and spleen had declined slightly by 2 months after surgery. It is not clear why the overload produced by Flaim’s procedure led to changes in organ water content, whereas our procedure, which produced a much larger overload, did not. It should be noted, however, that the changes in water content observed by Flaim and coworkers were very small. In general, it appears that rats may tolerate volume overloading better than dogs, since symptoms of congestive heart failure are more typical of canine models.8,11,12,25–29

Values are mean±SEM. RV, right ventricle; LV, left ventricle; SEPT, septum; CL, cell length; CW, cell width; WF, 1 week after fistula surgery; WS, 1 week after sham operation; Change, percent change after fistula surgery; MF, 1 month after fistula surgery; MS, 1 month after sham operation; ANOVA, analysis of variance; Yes, significantly different among the groups (p<0.05); No, not significantly different among the groups.
and presumably end-diastolic wall stress were markedly elevated in rats with aortocaval fistulas of 1 week. End-diastolic pressure returned toward normal after 1 month of overloading. These data support the idea that volume overloading leads to an increase in end-diastolic wall stress, with the resulting hypertrophy occurring as a response to this stimulus. Recent data from volume-overloaded rats with aortic insufficiency also support this concept.42

Right ventricular dP/dt max and peak systolic pressure were significantly increased in rats with aortocaval fistulas of both 1 week and 1 month. It is likely that the greater degree of myocyte hypertrophy observed in the right ventricle at both intervals is related to the combined pressure and volume overloading of that ventricle. Pulmonary hypertension has long been recognized as a consequence of aortocaval fistulas in dogs and humans.30,33,35,43 The mechanism of pulmonary hypertension may be similar to that observed in hyperthyroid rats, in which increased cardiac output coupled with minimal changes in pulmonary resistance led to elevated pressure.44 Since pulmonary blood pressure was not measured directly in our experiments, this theory was not confirmed.

Cellular Changes

Approximately two thirds of the myocyte hypertrophy was due to an increase in cross-sectional area at both 1 week and 1 month after surgery. Increased cell length accounted for the remainder of the myocyte enlargement. Perhaps related to the combined volume and pressure overloading, cellular hypertrophy was slightly greater in the right ventricle. The relative contributions of cell length and cross-sectional area to myocyte enlargement were identical to the pattern observed during normal physiological growth.45 After converting cross-sectional area to mean cell diameter by using the formula for a circle, there was an equal increase in cell diameter and cell length in rats with aortocaval fistulas. Korecky and Rakusan46 have noted previously that cell length and diameter increase proportionally during normal physiological growth. In agreement with our findings, Hatt et al14 also concluded that the relative increase in cell diameter and cell length were the same in rats with large aortocaval fistulas; they were able to reach this conclusion despite the recognized difficulty in obtaining cell length measurements using whole sectioned tissue.14,47

The eccentrically hypertrophied heart has been described as “magnified in all gross dimensions” with a normal wall thickness/radius ratio.1,2 Consequently, Ford2 has suggested that pure volume overload “should produce cell growth that is equal in all dimensions.” This is precisely the conclusion reached in these experiments and by Hatt et al.14 In both experiments, cardiac mass was almost doubled. Smaller degrees of pure volume overloading, however, may produce a somewhat different change in myocyte shape. Increased length, rather than cross-sectional area accounted for most of the myocyte hypertrophy in rats with small (15% cardiac hypertrophy in 10 weeks) and medium (41% hypertrophy in 10 weeks) size arteriovenous shunts.16 Thomas et al7 found that left ventricular weight increased 28% while myocyte cross-sectional area increased only 7% in dogs with volume-overload–induced hypertrophy. They concluded that increased myocyte length was responsible for most of the hypertrophy. It is possible that the severity of overloading may be responsible for the observed differences in the pattern of myocyte remodeling with volume overloading (e.g., severe overloading conditions, which cause depression of cardiac function, versus modest overloads, which do not).

The relative increase in myocyte volume was slightly less than the increase in cardiac mass in rats with aortocaval fistulas at both intervals examined. It is possible that some degree of tissue edema or increase in the nonmyocyte tissue compartment (e.g., increased vascularization) took place in experimental rats. Additional experiments using whole-sectioned tissue will be necessary to determine if such changes occurred in our model.

Compared with sham-operated controls, the length of cardiac myocytes from overloaded hearts increased an average of 10.6 µm at 1 week and 24.7 µm at 1 month after surgery. The mean sarcomere length of isolated myocytes in each rat group was constant at 1.90 µm. Therefore, new sarcomeres were added at the rate of ~0.8/day during the first week of overloading. The overall rate of new sarcomere formation was 0.45/day in the 1-month fistula group. The faster rate of cell lengthening during the first week suggests that it would be more fruitful to study the process of induced sarcomere genesis during the early stage of the hypertrophic process. Since the mechanism and location of induced sarcomere formation in adult hearts is poorly understood, this experimental model should prove useful in future experiments where this process is examined in more detail.

In summary, left ventricular systolic pressure and dP/dt max were depressed after 1 week of severe volume overloading in the rat but returned to normal within 1 month. The normalization of these left ventricular functional parameters after 1 month of overloading may be related to the much larger degree of cardiac hypertrophy observed at that time. In contrast, right ventricular dP/dt max and pressure were significantly increased at both 1 week and 1 month after surgery. Myocyte hypertrophy was greater in the right ventricle, perhaps reflecting the combined pressure and volume overloading of that chamber. Growth of cardiac myocyte dimensions in volume-overloaded rats resembled that of normal physiological hypertrophy.

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References


**KEY WORDS** • cardiac hypertrophy • isolated myocytes • volume overload • pulmonary hypertension • cardiac pathophysiology
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