Normalization of Impaired Coronary Circulation in Hypertrophied Rat Hearts

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We tested the hypothesis that impaired coronary autoregulation, decreased flow reserve, and diminished reactive hyperemic response in hypertrophied hearts with coronary arterial hypertension may be reversible after relief of pressure overload. In 4-week ascending aortic banded rats, in vivo peak systolic left ventricular pressure increased to 178±8 mm Hg (103±6 mm Hg in sham-operated control group). This increased pressure produced myocardial hypertrophy, and the left ventricular weight/body weight ratio was 46% above that of the control group. After the rats were killed, the coronary perfusion pressure–flow relations were obtained during resting conditions and maximal vasodilation after a 40-second period of ischemia in beating but nonworking isolated hearts perfused with Tyrode's solution with bovine red blood cells and albumin. In hearts from control rats, coronary autoregulation (i.e., a slight decrease in flow with reduction of pressure) was observed in the range of 50-100 mm Hg of perfusion pressure. A pronounced reactive hyperemic response was observed: a peak flow/resting flow ratio of 2.9±0.1 and a repayment ratio of 1.7±0.2 at 100 mm Hg of perfusion pressure. In hearts of banded rats the resting pressure–flow relation was rectilinear in the range of 25-175 mm Hg of perfusion pressure. Flow reserve and the time of reactive hyperemia to one half peak flow decreased at 50, 100, and 150 mm Hg of perfusion pressure compared with values in control rat hearts. Four weeks after debanding, peak systolic left ventricular pressure and cardiac hypertrophy had normalized. The impaired autoregulation, decreased flow reserve, and diminished reactive hyperemic response had completely reversed. Thus, impaired autoregulation and vasodilator capacity in cardiac hypertrophy are highly reversible after relief of pressure overload. (Hypertension 1990;16:26-34)

In normal hearts, coronary blood flow decreases only slightly with reduction of perfusion pressure in the autoregulatory range.1 In the subendocardium of hypertrophied hearts with hypertension, autoregulation is impaired in the lower range of coronary perfusion pressure.2 Furthermore, coronary flow reserve estimated with adenosine, dipyridamole, or flow increases during stress or after ischemia is also decreased in hypertrophied hearts.3-23 In previous studies,24,25 we reported that the maximal coronary flow rate during reactive hyperemia decreased in cardiac hypertrophy, but the decreased flow normalized after relief of pressure overload. Also, Anderson et al26 reported that decreased flow reserve and coronary vascular structural changes in the spontaneously hypertensive rat were reversible after antihypertensive drug administration. However, there is no information concerning the reversibility of impaired coronary autoregulation in hypertrophied hearts. In the present study, we tested the hypothesis that the impaired coronary autoregulation and diminished hyperemic response to brief ischemia may reverse after relief of pressure overload. For this purpose, we used an experimental model consisting of ascending aortic banding and debanding in the rat. After isolation of the heart, we studied coronary hemodynamics in beating but nonworking hearts perfused with Tyrode's solution with bovine red blood cells and albumin because coronary autoregulation depends on myocardial metabolism.1 Moreover, because coronary flow reserve depends on coronary perfusion pressure,1,18 we attempted to determine coronary flow reserve from coronary pressure–flow relations during resting conditions and during maximal vasodilation after brief ischemia.

Methods
We used male Wistar rats 6–8 weeks old. After opening the chest, we banded the ascending aorta. Four weeks after banding, we operated on the rats again for the purpose of debanding some of them. We studied coronary hemodynamics in the following

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weeks after debanding in the debanded rats, the heart was isolated. Coronary hemodynamic measurements were estimated in beating but nonworking hearts perfused with Tyrode’s solution with bovine red blood cells and albumin.

**Surgical Procedures**

Details of the ascending aortic banding procedures have been described elsewhere. Each rat was anesthetized with pentobarbital sodium (50 mg/kg i.p.) and endotracheal intubation was performed with direct visualization. The thorax was opened at the third intercostal space to expose the ascending aorta under artificial ventilation with room air (model 141, Princeton Medical Instruments Inc., Natick, Mass.). The ascending aorta was dissected free and a surgical nylon thread (3-0) was drawn under the ascending aorta. A rigid tube (1.4 mm o.d.) was placed alongside the ascending aorta. The tube and the ascending aorta were tightly tied together with the thread. The tube was removed rapidly, leaving the ascending aorta constricted to a diameter of 1.4 mm. The lung was inflated with a positive end-expiratory pressure of approximately 10 cm H2O, and the chest was closed with a silk thread. The tracheal tube was removed, and the rats were fed with standard rat chow and water ad libitum for 4 weeks. In sham-operated rats, the same procedures were repeated except for aortic banding.

In some of the banded rats, 4 weeks after aortic banding, the left thorax was opened again under artificial ventilation with room air after intraperitoneal anesthesia and tracheal intubation as described above. Fibrotic tissue around the nylon thread that had been used for aortic banding in the first operation was removed, and the nylon thread was taken off. The chest was closed after removal of the endotracheal tube in the same manner as described above. Sham-operation was performed in the rats serving as the respective controls.

**In Vivo Pressure Measurements**

Each rat was anesthetized intraperitoneally and tracheal intubation was performed after tracheotomy. Under controlled ventilation with room air, the neck region was opened and the right carotid artery was approached as in previous studies. To measure aortic pressure, a polyethylene cannula (polyethylene tubing, SP-31, 0.50 mm i.d., 0.80 mm o.d., Natsume Instrument Co., Ltd., Tokyo) was inserted into the right carotid artery. To estimate left ventricular peak systolic and end-diastolic pressures and peak-to-peak pressure difference between the left ventricle and the aorta, the left thorax was opened at the fourth intercostal space. The left ventricular cavity was approached from the left ventricular base with a 21-gauge needle, through which the left ventricular pressure was measured with a strain gauge pressure transducer (model TP-300T, Nihon Kohden Co., Ltd., Tokyo). Zero pressure reference was taken at the midlevel of the heart. Recordings of phasic and mean pressures were continuously displayed on a multichannel recorder (Type 8S, Rectigraph, San-ei Instrument Co., Ltd., Tokyo). Frequency response of the pressure measurement system was estimated by the pop method. The damping coefficient and the undamped natural frequency were 0.56 and 41 Hz, respectively.

**Perfusion Technique**

After in vivo pressure measurements, the pericardium was opened and the heart was quickly isolated. A perfusion cannula was inserted into the ascending aorta (at the proximal portion of the thread that had been used for aortic banding in the groups of banded rats) and was positioned immediately above the aortic valve. The heart was mounted on a perfusion apparatus as shown in previous studies. Each rat was perfused with modified Tyrode’s solution containing 30% oxygenated bovine red blood cells and 15 g/l bovine serum albumin (No. A-4503, Sigma Chemical Co., St. Louis, Mo.). The time between isolation of the heart and initiation of coronary perfusion was within 15 seconds. The composition of the modified Tyrode’s solution was as follows (mM): NaCl 106.0, KCl 6.0, CaCl2 2.5, NaH2PO4 0.435, MgCl2 1.0, NaHCO3 36.0, and glucose 11.0. Fresh bovine blood was collected at a local slaughterhouse in polyethyl- ene bottles with sufficient sodium heparin to prevent coagulation and stored in polyvinyl chloride bags containing sufficient ACD solution (citrate, dextrose). The stored blood was used within 5 days. The blood was centrifuged at 4°C for 20 minutes at 2,600 rpm. After aspirating the plasma and buffy coat, the cells were washed with the modified Tyrode’s solution. The red blood cells were added to the modified Tyrode’s solution containing bovine albumin, which had been filtered through a 0.8 μm membrane filter (Advantec, Toyo Roshi Kaisha, Ltd., Tokyo) with a 21-gauge needle, through which the left ventricular pressure was measured with a strain gauge pressure transducer (model TP-300T, Nihon Kohden Co., Ltd., Tokyo). Zero pressure reference was taken at the midlevel of the heart. Recordings of phasic and mean pressures were continuously displayed on a multichannel recorder (Type 8S, Rectigraph, San-ei Instrument Co., Ltd., Tokyo). Frequency response of the pressure measurement system was estimated by the pop method. The damping coefficient and the undamped natural frequency were 0.56 and 41 Hz, respectively.
Heart rate was kept constant at 300 beats/min by right ventricular pacing with an electrical stimulator (electrical stimulator SEN 7103, Nihon Kohden). Coronary perfusion pressure was regulated with a pressure regulator and measured from the side arm of the perfusion line. Zero pressure reference was taken at the midlevel of the heart. Mean coronary flow was measured using an extracorporeal-type probe (model FF-010T, Nihon Kohden) of 1 mm i.d., and an electromagnetic flowmeter (model MFV-3100, Nihon Kohden). The time constant of the electrical circuit used to obtain mean flow values was 1.0 second. Calibration was performed by timed volume sampling.

Protocol to Estimate Coronary Hemodynamics

Coronary hemodynamic data were obtained after coronary flow had reached a steady state at 100 mm Hg of coronary perfusion pressure. In the hearts of the sham-operated and debanded groups, we could observe a steady state of coronary flow at 100 mm Hg of coronary perfusion pressure approximately 15 minutes after initiation of coronary perfusion. In the hearts of the banded group, the time was slightly shorter. We elevated coronary perfusion pressure to 150 mm Hg and measured coronary flow at a new steady state. Then, the coronary perfusion pressure was reduced successively to 125, 112, 100, 87, 75, and 50 mm Hg. At each level of coronary perfusion pressure, mean coronary flow was measured in the steady state. At 50 mm Hg of coronary perfusion pressure, coronary flow was reduced to zero in a stepwise fashion. After 40-second ischemia, coronary perfusion pressure was returned to 50 mm Hg to obtain the reactive hyperemic response. After the coronary flow increased by ischemia was returned to the baseline value, the same procedures were repeated at coronary perfusion pressures of 100 and 150 mm Hg. Next, resting coronary flows at 100, 175, and 25 mm Hg of coronary perfusion pressure were obtained as described above. Because we attempted to avoid myocardial tissue edema at 175 mm Hg of coronary perfusion pressure in control hearts and irreversible myocardial damage by ischemia at 25 mm Hg of coronary perfusion pressure, we measured coronary flows at 175 and 25 mm Hg of coronary perfusion pressure at the conclusion of the experiment. Initial and final coronary flows at 100 mm Hg of coronary perfusion pressure were as follows: 2.6 ±0.1 and 2.7 ±0.2 ml/min/g in the sham-operated controls for the banded group, 2.9 ±0.2 and 3.0 ±0.3 ml/min/g in the banded group, 2.4 ±0.3 and 2.4 ±0.4 ml/min/g in the sham-operated controls for the debanded group, and 2.1 ±0.4 and 2.4 ±0.4 ml/min/g in the debanded group. The weights of the left ventricle including the septum and the right ventricular free wall were measured. Coronary flow was expressed as the ratio of coronary flow per left ventricular weight (ml/min/g). Autoregulation gain was calculated by the following equation: Gain = 1 - [(flow change/initial flow)/(pressure change/initial pressure)]. The reactive hyperemic response was estimated by the ratios of peak flow/resting flow, repayment flow/debt flow, and the times from the onset of reactive hyperemia to the points of peak flow and one half peak flow.

Statistical Analysis

Variables measured are expressed as mean±SEM. The statistical significance of differences in mean values between the two groups of sham-operated and experimental rats was assessed by the unpaired Student’s t test.

Results

Table 1 summarizes in vivo hemodynamic changes in the groups of sham-operated, banded, and debanded rats. Peak systolic left ventricular pressure and peak-to-peak pressure difference between the left ventricle and the aorta in the group of banded rats increased significantly compared with the sham-operated control rats. After debanding, the elevated peak systolic left ventricular pressure and the pressure difference decreased to levels similar to those in the sham-operated controls. There were no significant differences in left ventricular end-diastolic pressure, systolic, diastolic, and mean aortic pressures or...
TABLE 2. Body Weight and Heart Weight in the Sham-Operated, Banded, and Debanded Groups of Rats

<table>
<thead>
<tr>
<th>Variables</th>
<th>Sham-B</th>
<th>B</th>
<th>p</th>
<th>Sham-DB</th>
<th>DB</th>
<th>p</th>
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<tbody>
<tr>
<td>n</td>
<td>7</td>
<td>7</td>
<td></td>
<td>6</td>
<td>6</td>
<td></td>
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<tr>
<td>Body wt (g)</td>
<td>305±18</td>
<td>314±11</td>
<td>NS</td>
<td>262±7</td>
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<td>NS</td>
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<td>LV wt (mg)</td>
<td>773±45</td>
<td>1107±78</td>
<td>&lt;0.01</td>
<td>622±22</td>
<td>723±21</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>RV wt (mg)</td>
<td>191±13</td>
<td>227±27</td>
<td>NS</td>
<td>159±7</td>
<td>154±8</td>
<td>NS</td>
</tr>
<tr>
<td>LV wt/body wt</td>
<td>2.41±0.05</td>
<td>3.51±0.16</td>
<td>&lt;0.01</td>
<td>2.37±0.06</td>
<td>2.73±0.05</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>RV wt/body wt</td>
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<td>0.71±0.06</td>
<td>NS</td>
<td>0.61±0.02</td>
<td>0.58±0.02</td>
<td>NS</td>
</tr>
</tbody>
</table>

Values are mean±SEM. LV, left ventricle; RV, right ventricle; Sham-B, sham-operated controls for banded group of rats; B, banded group of rats; Sham-DB, sham-operated controls for debanded groups of rats; DB, debanded group of rats.

As summarized in Table 2, there was no significant difference in body weight between the sham-operated control and experimental groups. Left ventricular weight and the ratio of left ventricular weight/body weight in the group of banded rats increased significantly (43% and 46%, respectively) compared with those of the sham-operated control rats. Four weeks after debanding, the weight and the ratio decreased significantly ($p<0.01$) but were still higher (16% and 15%, respectively) than those in the group of sham-operated rats. There was no significant difference in right ventricular weight or the ratio of right ventricular weight/body weight between the sham-operated control and experimental groups.

Figure 1 shows tracings of coronary perfusion pressure and mean flow in hearts of sham-operated, banded, and debanded groups of rats. In a heart of the sham-operated group, coronary flow decreased slightly with a reduction of perfusion pressure between 50 and 100 mm Hg. In a heart of the banded group, coronary flow decreased linearly with reduction of perfusion pressure over the whole range. After debanding, the changes in coronary flow with reduction of perfusion pressure were similar to those in the heart of the sham-operated group.

Figure 2 shows typical tracings of mean coronary flow during reactive hyperemia at 100 mm Hg of perfusion pressure in hearts of the sham-operated, banded, and debanded groups. In a heart of the sham-operated group, resting coronary flow was 2.1 ml/min and increased to 5.5 ml/min at peak response after a 40-second period of ischemia. The time from the onset of reactive hyperemia to the point of one half peak flow was 30 seconds. In a heart of the banded group, reactive hyperemic response was diminished compared with that in the heart of the sham-operated group: a moderate increase in peak coronary flow, a smaller ratio of peak flow/resting flow and shorter duration of reactive hyperemia. In hearts of the debanded group, the response was similar to that in the hearts of the sham-operated group with a similar increase in peak flow and ratio of peak/resting flow and duration of reactive hyperemia.

Figure 3 shows changes in coronary flow in the range of perfusion pressure between 25 and 175 mm Hg in the groups of sham-operated, banded, and debanded rats. The pressure–flow relation during resting conditions in the group of sham-operated rats was curvilinear and revealed that coronary flow decreased slightly with reduction of perfusion pressure between 50 and 100 mm Hg. In contrast, the resting pressure–flow relation in the group of banded rats was rectilinear. After debanding, the relation during resting conditions was similar to that in the sham-operated group. The relation during maximal vasodilation was rectilinear in all groups of rats. In the banded group, the relation during maximal vasodilation shifted downward compared with the group of sham-operated control rats (Sham-B). After debanding, the relation during maximal vasodilation...
was similar to that in the group of sham-operated control rats (Sham-DB).

In the banded group, absolute values of resting coronary flow tended to be greater compared with those in the sham-operated control rats (1.1±0.1, 3.0±0.4, and 5.3±0.7 ml/min at 50, 100, and 150 mm Hg of perfusion pressure, respectively, in the banded group; 1.2±0.2, 1.9±0.2, and 3.7±0.3 ml/min in the sham-operated control group). On the other hand, absolute values of peak coronary flow during hyperemia did not differ between the banded and sham-operated groups of rats (2.0±0.2, 5.8±0.6, and 9.7±1.1 ml/min at 50, 100, and 150 mm Hg of perfusion pressure, respectively, in the banded group; 2.9±0.4, 5.4±0.4, and 8.9±0.5 ml/min in the sham-operated control group). In the debanded group, absolute values of resting and peak coronary flow were similar to those in the sham-operated control group.

Figure 4 shows coronary autoregulation gain in the groups of sham-operated, banded, and debanded rats. The gain values in the banded group were significantly lower at coronary perfusion pressures between 50 and 100 mm Hg compared with those in the group of sham-operated control rats (Figure 4A). After debanding, there was no significant difference in values between the groups of debanded and sham-operated rats (Figure 4B).

Figure 5 shows changes in coronary flow reserve in the groups of sham-operated, banded, and debanded rats. Coronary flow reserve depended on the level of perfusion pressure. In the banded group, flow reserve...
Figure 4. Line graphs showing autoregulation gains in sham-operated, banded (panel A) and debanded (panel B) groups. Values are mean±SEM. Sham-B, sham-operated control group for the banded group; Sham-DB, sham-operated control group for the debanded group; CPP, coronary perfusion pressure. *p<0.05; **p<0.01 compared between sham-operated and experimental groups.

decreased significantly at any level of coronary perfusion pressure compared with the sham-operated control group (Figure 5A). In the debanded group, no significant difference in flow reserve was observed at any level of coronary perfusion pressure compared with the group of sham-operated control rats (Figure 5B).

Figure 5 shows changes in hyperemic response in the groups of sham-operated, banded, and debanded rats. The response in the banded group was significantly smaller than that in the sham-operated control group: smaller peak flow/resting flow ratio (Figure 6A), smaller repayment flow/debt flow ratio (Figure 6B), and shorter duration of reactive hyperemia estimated by the times from the onset to the point of peak flow and to the point of one half peak flow (Figure 6C and 6D). In the debanded group, no significant difference was observed in hyperemic response compared with the sham-operated control group (Figure 6A–6D).

Discussion

In this study, we obtained coronary perfusion pressure–flow relations during resting conditions and during maximal vasodilation after brief ischemia in hearts of ascending aortic banded and debanded rats perfused with Tyrode's solution with bovine red blood cells and albumin and examined reversibilities of impaired coronary autoregulation, decreased flow reserve, and diminished reactive hyperemic response in hypertrophied hearts. Our major new findings are as follows: after relief of pressure overload, 1) impaired coronary autoregulation in hypertrophied hearts with coronary hypertension was reversible; 2) decreased coronary flow reserve increased toward normal; 3) dimin-
ished coronary hyperemic response normalized in terms of peak flow/resting flow ratio, repayment flow/debt flow ratio, and duration of hyperemia. This is the first report showing that both impaired coronary autoregulation and diminished hyperemic response to brief ischemia in cardiac hypertrophy produced by pressure overload are highly reversible.

We used an experimental model consisting of mechanical constriction of the ascending aorta rather than a model of renal hypertension or spontaneously hypertensive rats. In this experimental model, we were able to choose the precise duration of pressure overload and the time after relief of pressure overload. In addition, we estimated the severity of pressure overload in banded rats and were able to observe normalization of elevated left ventricular systolic pressure and pressure difference between the left ventricle and the aorta in debanded rats.

In small laboratory animals such as mice, rats, and guinea pigs, reactive hyperemic responses are moderate compared with larger animals or humans. In our experimental model of isolated hearts, reactive hyperemic response after a 40-second period of ischemia showed that changes in the peak flow/resting flow ratio and repayment flow/debt flow ratio were near 3.0 and 2.0, respectively, in sham-operated control rat hearts. This responsiveness of coronary vasculature to brief ischemia in our present study was greater than the values in in vivo or ex vivo measurements that have been reported from other laboratories. Gain values of coronary autoregulation in sham-operated control rats in our study were slightly smaller than the values in in situ working hearts or isolated, blood-perfused, empty beating hearts of larger animals such as dogs. At present, however, no data concerning the pressure-flow relation in blood-perfused hearts of small animals are available to compare with our data. Differences between the values in the present study and those of previous experiments may derive from the difference between small and larger animals.

In our present study, coronary autoregulation in hypertrophied hearts was impaired in the whole range of perfusion pressure. On the other hand, Strandgaard et al and Jones et al have reported that the autoregulation of cerebral circulation in hypertensive patients and baboons was not impaired but shifted to the right. The difference between our observation in the coronary circulation and their observation in the cerebral circulation might derive from the different situations in the surrounding tissues. In the heart with hypertension, elevated pressure causes cardiac muscle hypertrophy and the hypertrophied muscle per se may affect the coronary circulation.

It is suggested that, in hypertrophied hearts, decreased maximal coronary flow or increased minimal coronary vascular resistance after administration of adenosine or dipyridamole may be correlated with the decreased number of arterioles or capillaries measured by morphological techniques. However, the impaired coronary autoregulation in hypertrophied hearts may not be explained by those changes, even if the number of arterioles or capillaries was decreased. Because increased myocardial work shifts the resting pressure-flow relation to the right and upward in nonhypertrophied, working hearts, we determined the coronary pressure-flow relation in nonworking hearts to minimize myocardial oxygen demand. Therefore, it is unlikely that the myocardial oxygen demand, which may be only slightly elevated by increased myocardial mass, produced the rectilinear relation observed during resting conditions. In addition, the decreased number of arterioles and capillaries per se will not produce changes in the characteristics of the pressure-flow relation during resting conditions: rectilinear relation in hypertrophied hearts and curvilinear relation in control hearts. In our opinion, the impaired coronary autoregulation might mainly be caused by the changes in the pressure-flow relation in each arteriole rather than by morphological changes such as a decrease in the number of arterioles. These physiological changes in each arteriole might produce changes in hyperemic response (time from onset to one half peak reactive flow) as well as the pressure-flow relation during resting conditions. Furthermore, these physiological changes in coronary vasculature may explain the changeable coronary circulation abnormalities in cardiac hypertrophy to given new conditions.

In our present study, coronary autoregulation was impaired in the whole range of perfusion pressure. The impairment of coronary autoregulation was accompanied by diminished reactive hyperemic response in terms of peak flow/unit myocardial mass ratio of peak flow/resting flow, and duration of reactive hyperemia. Furthermore, at 4 weeks after relief of pressure overload impaired autoregulation, decreased flow reserve and diminished reactive hyperemic response had completely reversed. Namely, impaired autoregulation and diminished reactive hyperemic response were coexistent in the progression process and normalized together in the regression process. From these results, we speculate that regulation sites of the coronary arterial trees at the microvascular levels for coronary autoregulation and for reactive hyperemia may be the same or that the principal mechanisms may also be the same in coronary autoregulation and reactive hyperemia due to ischemia.

In our experimental model, pressure overload to the myocardium and coronary arterial hypertension coexist in the clinical situation of systemic hypertension. Therefore, coronary circulation abnormalities might be caused by myocardial hypertrophy, coronary arterial hypertension, or both. In addition, coronary circulation abnormalities in the SHR regressed without changes in myocardial hypertrophy after administration of an antihypertensive drug for 12 weeks in the study of Anderson et al. However, in our previous study diminished vasodilation
capacity after brief ischemia in hypertrophied hearts produced by long-term (10 weeks) pressure overload (aortic banding) did not regress in spite of regression of myocardial hypertrophy. Thus, in the progression and regression processes of myocardial hypertrophy, coronary arterial hypertension and myocardial hypertrophy affect the coronary circulation in hypertrophied hearts produced by pressure overload with coronary arterial hypertension. In this study, it is not clear whether the reversible abnormalities of coronary autoregulation and reactive hyperemia are related to the vascular changes associated with myocardial hypertrophy or to hypertensive coronary vascular changes.

In conclusion, we obtained coronary pressure-flow relations during rest and during maximal vasodilation produced by brief ischemia in control, banded, and debanded hearts and estimated the reversibilities in impaired coronary autoregulation and diminished reactive hyperemic response after relief of pressure overload. The impaired autoregulation and decreased flow reserve in hypertrophied hearts with coronary hypertension were completely reversible. The coronary hyperemic response estimated by the peak flow/resting flow ratio, repayment flow/debt flow ratio, and duration of hyperemia also normalized completely. These findings indicate that coronary vascular abnormalities in relatively short-term cardiac hypertrophy with coronary arterial hypertension may be functional and are highly reversible.

References


**KEY WORDS** • coronary circulation • coarctation hypertension • hypertrophy • autoregulation • hyperemia
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