Effect of Age on Coronary Circulation After Imposition of Pressure-Overload in Rats

Shogen Isoyama, Fumitoshi Sato, and Tamotsu Takishima

We examined the effects of pressure overload on coronary circulation in young adult (7 months old) and old rats (18 months old). Four weeks after the ascending aorta was banded, in vivo left ventricular pressure was measured to estimate the degree of pressure load. In the two age groups, similar increases in peak left ventricular pressure were observed (113±7 mm Hg in sham-operated rats versus 160±11 mm Hg in banded rats of the young adult group; 103±7 mm Hg in sham-operated rats versus 156±11 mm Hg in banded rats of the old group). After isolating the hearts, they were perfused with Tyrode’s solution containing bovine red blood cells and albumin. Resting coronary perfusion pressure–flow relations and reactive hyperemic response after a 40-second ischemia were obtained under beating but nonworking conditions.

In young adult banded rats, significant myocardial hypertrophy was observed at the organ level (124% of controls in left ventricular dry weight/body weight ratio; 119% in left ventricular dry weight/tibial length ratio) and at the cell level. Minimal coronary vascular resistance obtained by the perfusion pressure–peak flow relation during reactive hyperemia increased to 150% of controls, and coronary flow reserve decreased significantly. In contrast, myocardial hypertrophy was not observed at the organ or cell level in old banded rats. However, minimal coronary vascular resistance increased, and flow reserve decreased significantly. Thus, pressure overload with coronary arterial hypertension caused abnormalities of the coronary circulation in old subjects even in the absence of myocardial hypertrophy. These coronary vascular changes as well as diminished hypertrophic response may explain the high incidence of heart failure or ischemic episodes during chronic hemodynamic stress in aged patients. (Hypertension 1991;17:369-377)

Physiological aging after maturation causes structural and functional changes in coronary vasculature. Morphometrically, age-related decrease in capillary density and capillary surface area because of myocyte hypertrophy occurs.1-4 Functionally, decreased coronary flow/unit myocardial mass,5,6 decreased flow reserve in response to reactive hyperemia, adenosine, or sodium nitroprusside administration,6-8 increased coronary vascular resistance/unit muscle mass, and lower perfusion in the endocardium9 occur. At the same time, aging causes myocardial hypertrophy at organ4,10,11 and cellular levels4,10,12 and cell loss.12 Functionally, age-related decreases in the rate of tension rise and increases in duration of contraction force or decreases in shortening velocity have been reported at organ and muscle levels.4,13-17 Furthermore, the capacity for myocardial hypertrophy to develop in response to chronic pressure- or volume-overload is diminished in aged subjects compared with younger adults.10,11,18,19 At present, however, there is no information concerning the coronary vascular response to stress from chronic pressure overload in aged subjects.

Abnormalities of the coronary circulation in pressure-overloaded hearts are caused by hypertensive vascular changes20,21 as well as by the presence of myocardial hypertrophy.22-24 Therefore, even if a similar pressure-overload stress is applied to young adult and old subjects, the stress may produce different effects on coronary circulation between young and old subjects directly through underlying age-related changes in coronary vasculature or indirectly through the diminished myocardial hypertrophic response. To test this hypothesis, we examined the effects of pressure overload on the degree of myocardial hypertrophy and coronary circulation in young adult and old rats. We performed ascending aortic banding to produce the same increase in left
ventricular pressure (i.e., coronary arterial hypertension and pressure load to the left ventricle) in young adult and old rats. After the same duration of pressure overload, we estimated coronary hemodynamics in an experimental model of isolated, blood-perfused, nonworking hearts and compared coronary perfusion pressure–flow relations during resting conditions and maximal vasodilatation after brief ischemia in the two age groups.

Methods

We used male Wistar rats of two age groups: young adult (7 months old, n=21) and old rats (18 months old, n=21). After opening the chest, we banded the ascending aorta. Four weeks after banding in vivo left ventricular and aortic pressures were measured. After isolating the hearts, we studied coronary hemodynamics in an experimental model of beating but nonworking, retrograde, blood-perfused hearts and compared the coronary perfusion pressure–flow relations between the sham-operated and banded rats in each age group.

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 intubated endotracheally. The thorax was opened at the third intercostal space under artificial ventilation with room air (model 141, Princeton Medical Instruments Inc., Natick, Mass.). The ascending aorta was dissected free, and a surgical thread (3-0) was drawn under the ascending aorta. A rigid tube (1.6 mm o.d.) was placed alongside the ascending aorta. The tube and the ascending aorta were tightly tied together with the thread, and the tube was removed rapidly. 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 Vivo Pressure Measurements

In 19 of 21 young adult rats and 14 of 21 old rats, we measured in vivo left ventricular and aortic pressures immediately before isolation of the hearts to estimate the degree of pressure overload in the two age groups. Each rat was anesthetized (pentobarbital sodium, 50 mg/kg i.p.) and tracheal intubation was performed after tracheotomy. Under controlled ventilation with room air, 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 measure aortic pressure. 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). The damping coefficient and undamped natural frequency of the pressure measurement system were 0.86 and 49 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. The coronary arteries were perfused with modified Tyrode's solution containing oxygenated bovine red blood cells and 15 g/l bovine serum albumin (Sigma Chemical Co., St. Louis, Mo.). The time between isolation of the heart and initiation of coronary perfusion was 15 seconds or less. The composition of the modified Tyrode's solution was as follows (mM): NaCl 106, KCl 6.0, CaCl2 2.5, NaH2PO4 0.435, MgCl2 1.0, NaHCO3 36, and glucose 11. Fresh bovine blood was collected at a local slaughterhouse in polyethylene bottles with sufficient sodium heparin for anticoagulation and stored in polyvinyl chloride bags containing sufficient ACD solution (citrate, dextrose). The stored blood was used within 3 days. The blood was centrifuged at 4°C for 20 minutes at 2,600g. 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 sufficient amount of the modified Tyrode's solution before use. The perfusate was equilibrated with a 20% O2, 3% CO2, and 77% N2 gas mixture by bubbling. The perfusate pH, PO2, PCO2, and hematocrit were measured and ranged from 7.32 to 7.45, from 114 to 149 mm Hg, from 20 to 42 mm Hg, and from 31% to 34%, respectively. We prepared approximately 1,000 ml perfusate for use on the same day and studied one or two pairs of hearts of sham-operated and banded rats in each age group as far as possible, using the same perfusate to eliminate the effects of slight variation in pH, PO2, PCO2, and hematocrit on coronary circulation. The perfusate was not recirculated. A drainage cannula was inserted into the left ventricular cavity through a left atrial incision to vent the Thebesian flow and keep the left ventricular cavity empty. The temperature of the perfusate was maintained at 37°C with a water-jacketed reservoir and bubble trap. Heart rate was kept constant at 300 beats/min by right ventricular pacing with an electrical stimulator (Elec-
trical Stimulator SEN 7103, Nihon Kohden Co., Ltd., Tokyo).

Coronary perfusion pressure was regulated with a pressurized gas tank and a pressure regulator (Pressure Regulator Type 70, Bellofram, Burlington, Mass.) and measured from the side arm of the perfusion line. Zero pressure reference was taken at the midlevel of the heart. Mean coronary flow rate was measured using an extracorporeal-type probe (model FF-010T, Nihon Kohden, Tokyo) of 1 mm internal diameter, and an electromagnetic flowmeter (model MFV-3100, Nihon Kohden). The time constant of the electrical circuit to obtain mean flow was 1.0 second. Calibration was performed by timed sampling of volume in each heart with the same solution to perfuse the heart.

Protocol Used 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. We elevated coronary perfusion pressure to 150 mm Hg and measured coronary flow rate at a new steady state. Then, the coronary perfusion pressure was reduced successively to 125, 112, 100, 87, 75, 62, and to 50 mm Hg. At each level of coronary perfusion pressure, mean coronary flow rate 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 a 40-second period of 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 flow rates at 100 and 25 mm Hg of coronary perfusion pressure were obtained as described above. At the conclusion of the experiment we measured coronary flow rate at 25 mm Hg of coronary perfusion pressure to avoid irreversible myocardial damage by ischemia. Initial and final coronary flow rates at 100 mm Hg of coronary perfusion pressure were as follows: 1.92±0.17 and 2.29±0.28 ml/min/g in hearts of the young adult, sham-operated control group; 2.53±0.38 and 2.59±0.43 ml/min/g in hearts of the young adult, banded rats; 2.25±0.42 and 1.94±0.29 ml/min/g in hearts of the old, sham-operated control group; 2.11±0.28 and 2.22±0.29 ml/min/g in hearts of the old, banded rats.

The wet weights of the left ventricle, including the septum and the right ventricular free wall, were measured. The left and right ventricles were divided into two portions: septal and free wall portions in the left ventricle and two free wall portions in the right ventricle, respectively. The septal portion and one of the right ventricular free wall portions were weighed and dried to a constant weight at 70°C for 3 days. The dry weight/wet weight ratio in each ventricle was obtained, and the total left and right ventricular dry weights were calculated from the wet weight and the dry weight/wet weight ratio, respectively. For estimation of hypertrophy at the cell level, the other portion of each ventricle was fixed with 10% neutral buffered formalin and stored in this solution until histological examination.

Coronary flow rate was expressed as the ratio of coronary flow rate per ventricular wet weight (left and right ventricular weights) (ml/min/g). The degree of left ventricular hypertrophy at the organ level was estimated by the dry weight/body weight ratio when the rats were killed and dry weight/tibial length ratio, because the surgery for aortic banding altered body weights.10,11 Minimal coronary vascular resistance was calculated from the linear relation between the coronary perfusion pressure and peak flow rate during reactive hyperemia. Coronary flow reserve was defined as an increase in flow from the resting condition to peak during reactive hyperemia.

Histological Examination

Transmural myocardial sections of the left ventricular free wall were cut in a transverse plane perpendicular to the apex-to-base axis. Sections were processed conventionally for histological examination (dehydrated in graded alcohols and embedded in paraffin), cut in 5-μm sections, and stained with hematoxylin-eosin. For each section, a mean myocyte width was determined by measurement of transmural widths of random, longitudinally oriented myocytes in the circular midwall bundles with a calibrated microscope eyepiece reticle (10 cells for each sample) on random fields at a magnification of ×400.10 In the right ventricle, myocardial sections were cut in planes perpendicular and parallel to the apex-to-base axis. A mean myocyte width was obtained in those samples as was done in the left ventricle. All measurements and histological observations were made by a single observer.

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 banded rats was assessed by the unpaired Student’s t test. Linear regression analysis of peak coronary flow during reactive hyperemia at the three levels of perfusion pressure was performed with the least-square method in each heart. The mean values of the slope and x intercept in hearts of the sham-operated and banded rats were statistically analyzed with Student’s t test.

Results

Table 1 summarizes in vivo hemodynamic changes in the groups of sham-operated and banded rats of the two age groups. In the banded rats of both age groups, the peak systolic left ventricular pressure and
TABLE 1. In Vivo Left Ventricular and Aortic Pressures and Heart Rate in the Sham-Operated and Banded Rats of the Two Age Groups

<table>
<thead>
<tr>
<th>Hemodynamic measurements</th>
<th>Young adult</th>
<th>Old</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Sham (n=10)</td>
<td>Banded (n=9)</td>
</tr>
<tr>
<td>Systolic LVP (mm Hg)</td>
<td>113±7</td>
<td>160±11*</td>
</tr>
<tr>
<td>LVEDP (mm Hg)</td>
<td>4±0.5</td>
<td>6±0.5</td>
</tr>
<tr>
<td>Systolic AoP (mm Hg)</td>
<td>110±6</td>
<td>124±10</td>
</tr>
<tr>
<td>Diastolic AoP (mm Hg)</td>
<td>85±6</td>
<td>96±8</td>
</tr>
<tr>
<td>Mean AoP (mm Hg)</td>
<td>94±6</td>
<td>104±9</td>
</tr>
<tr>
<td>ΔP (mm Hg)</td>
<td>4±1</td>
<td>36±6*</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>366±18</td>
<td>395±18</td>
</tr>
</tbody>
</table>

Values are mean±SEM. Sham, sham-operated control group of rats; banded, banded group of rats; LVP, left ventricular pressure; LVEDP, left ventricular end-diastolic pressure; AoP, aortic pressure; ΔP, peak-to-peak difference between the LVP and the AoP.

*p<0.01, p<0.05, significant difference between sham-operated and banded rats in each age group.

peak-to-peak pressure difference between the left ventricle and the aorta significantly increased to similar levels. There were no significant differences in left ventricular end-diastolic pressure, systolic, diastolic, and mean aortic pressures or heart rate between the sham-operated and banded rats in either age group.

As summarized in Table 2, there was no significant difference in initial and final body weights or tibial length between the sham-operated and banded rats in each age group. In the young adult banded rats, the left ventricular dry weight, the left ventricular dry weight/final body weight ratio, and left ventricular dry weight/tibial length ratio were significantly increased compared with those of the sham-operated rats. Myocyte width in the left ventricle significantly increased compared with the value in the sham-operated rats. In contrast, in the old banded rats no significant myocardial hypertrophy was observed in terms of left ventricular wet and dry weights or the left ventricular dry weight/final body weight ratio and left ventricular dry weight/tibial length ratio. Nor did aortic banding produce a significant increase in the myocyte width. In the right ventricle, there was no significant difference in ventricular weight, the dry weight/final body weight ratio, the dry weight/tibial length ratio, or the myocyte width between the sham-operated and banded rats in each age group.

Figure 1 shows typical tracings of mean coronary flow rate during reactive hyperemia after a 40-second period of ischemia at 100 mm Hg of perfusion pressure in hearts of the sham-operated and banded rats of the two age groups. In a heart from the young adult, sham-operated group, a pronounced reactive hyperemic response was observed, and the peak flow rate increased to threefold of the resting flow. In a heart of the young adult, banded group, reactive hyperemic response was smaller, and the peak flow

TABLE 2. Body Weight, Heart Weight, and Myocyte Widths in the Sham-Operated and Banded Rats of the Two Age Groups

<table>
<thead>
<tr>
<th>Measurements</th>
<th>Young adult</th>
<th>Old</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sham (n=11)</td>
<td>Banded (n=10)</td>
</tr>
<tr>
<td>Initial body wt (g)</td>
<td>624±18</td>
<td>603±22</td>
</tr>
<tr>
<td>Final body wt (g)</td>
<td>589±17</td>
<td>554±23</td>
</tr>
<tr>
<td>Tibial L (cm)</td>
<td>4.58±0.03</td>
<td>4.54±0.04</td>
</tr>
<tr>
<td>LV wet wt (mg)</td>
<td>1,242±43</td>
<td>1,423±87</td>
</tr>
<tr>
<td>RV wet wt (mg)</td>
<td>346±18</td>
<td>343±15</td>
</tr>
<tr>
<td>LV dry wt (mg)</td>
<td>223±7</td>
<td>262±14*</td>
</tr>
<tr>
<td>RV dry wt (mg)</td>
<td>61±5</td>
<td>57±3</td>
</tr>
<tr>
<td>LV dry wt/final body wt</td>
<td>0.383±0.010</td>
<td>0.476±0.022*</td>
</tr>
<tr>
<td>RV dry wt/final body wt</td>
<td>0.105±0.009</td>
<td>0.104±0.009</td>
</tr>
<tr>
<td>LV dry wt/tibial L</td>
<td>48.3±1.5</td>
<td>57.6±2.9†</td>
</tr>
<tr>
<td>RV dry wt/tibial L</td>
<td>13.1±0.9</td>
<td>12.5±0.8</td>
</tr>
<tr>
<td>LV myocyte widths (μm)</td>
<td>19.4±0.5</td>
<td>24.0±0.8*</td>
</tr>
<tr>
<td>RV myocyte widths (μm)</td>
<td>16.0±0.8</td>
<td>16.1±0.6</td>
</tr>
</tbody>
</table>

Values are mean±SEM. Sham, sham-operated control group of rats; banded, banded group of rats; initial and final body wt, body weight at the beginning of the experiment and when the rats were killed, respectively; L, length; LV, left ventricle; RV, right ventricle.

*p<0.01; †p<0.05 significant difference between sham-operated and banded rats in each age group.
Isoyama et al. Effect of Age on Coronary Circulation

Figure 1. Typical tracings of mean coronary flow rate during reactive hyperemia after a 40-second period of ischemia at a coronary perfusion pressure of 100 mm Hg in hearts of sham-operated and banded rats of the two age groups.

rate was approximately twofold of the resting flow. In a heart from the old, sham-operated group, the reactive hyperemic response was slightly smaller compared with the heart in the young adult, sham-operated group. After aortic banding, the response decreased further in a heart of the old group.

Figure 2 shows the relation between coronary perfusion pressure and flow rate/unit mass ratio in the sham-operated and banded rats of the two age groups. During resting conditions, the coronary flow rate/unit mass ratio was slightly higher in the young adult, banded rats and slightly lower in the old, banded rats when compared with the sham-operated control rats. During reactive hyperemia, the relations between coronary perfusion pressure and peak flow rate/unit mass were rectilinear. After aortic banding, peak coronary flow rate at higher levels of perfusion pressure was significantly smaller when compared with the sham-operated controls (p<0.05 at 100 mm Hg of coronary perfusion pressure and p<0.01 at 150 mm Hg in the young adult rats; p<0.01 at 50 mm Hg, p<0.01 at 100 mm Hg, and p<0.01 at 150 mm Hg in the old rats).

Discussion

In this study, we examined abnormalities of the coronary circulation and degree of myocardial hypertrophy in response to the same duration and degree of pressure overload (i.e., same degree of coronary arterial hypertension and pressure load to the left ventricle in young adult and old rats). Our data demonstrate that minimal coronary vascular resistance in the sham-operated and banded rats of the two age groups. Minimal resistance was significantly greater in the young adult, banded rats than in the sham-operated rats (150% of that of the control group). In the old, banded rats the vascular resistance increased to 129% of that of the control group.

Figure 4 shows changes in coronary flow reserve in the sham-operated and banded rats of the two age groups. In both age groups, coronary flow reserve significantly decreased after aortic banding (p<0.01 at 100 mm Hg of coronary perfusion pressure and p<0.01 at 150 mm Hg in the young adult rats; p<0.01 at 50 mm Hg, p<0.01 at 100 mm Hg, and p<0.01 at 150 mm Hg in the old rats).

Table 3. Relations Between Coronary Perfusion Pressure (x) and Peak Flow Rate (y) During Reactive Hyperemia in the Sham-Operated and Banded Rats of the Two Age Groups

<table>
<thead>
<tr>
<th>Group</th>
<th>Slope (ml/min/mg/mm Hg)</th>
<th>x intercept (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Young adult, sham (n=11)</td>
<td>0.071±0.007</td>
<td>17±3</td>
</tr>
<tr>
<td>Old, sham (n=11)</td>
<td>0.060±0.004</td>
<td>16±5</td>
</tr>
<tr>
<td>Young adult, banded (n=10)</td>
<td>0.049±0.005</td>
<td>13±4</td>
</tr>
<tr>
<td>Old, banded (n=10)</td>
<td>0.048±0.003</td>
<td>15±6</td>
</tr>
</tbody>
</table>

NS, not significant.
Coronary vascular resistance increased and coronary flow reserve decreased in the absence of myocardial hypertrophy in old rats and in the presence of significant myocardial hypertrophy in young adult rats.

Bache et al. studied abnormalities of the coronary circulation in hypertrophied hearts produced by banding of the ascending aorta in premature and young adult dogs and showed that left ventricular hypertrophy beginning at 7 weeks of age and continuing during the subsequent period of normal body growth resulted in impairment of minimal coronary vascular resistance similar to that seen when hypertrophy begins after the animals have reached adulthood. Rakusan et al. also found that terminal vascular capacity of the coronary vascular bed estimated with radiolabeled albumin remained a constant fraction of left ventricular weight when hypertrophy was produced by aortic banding in rabbits 7–9 weeks of age, whereas terminal vascular capacity failed to increase when hypertrophy occurred in adult rabbits. On the other hand, in the studies of Tomanek and Hovance and Peters et al., significant decrements in coronary vascular reserve and capillary density during developing (3 or 4 months of age) and peak left ventricular hypertrophy (7 months of age) disappeared during stabilized hypertrophy (12 or 15 months of age) in the spontaneously hypertensive rat (SHR). However, biological significance in the present study is quite different from that in the studies described above for the following reasons. First, when a similar hemodynamic stress is given among the subjects of different ages, the capacity for myocardial hypertrophy in response to the stress diminishes with age after maturation. Also, underlying age-related changes in coronary vascular trees, vascular wall, or coronary circulation may differ among premature, mature, and aged rats.6–8,33–35 Second, the differing ages in the SHR always mean differing durations and severity of pressure overload. Third, in a genetic model such as the SHR, factors other than pressure load may modulate coronary vascular abnormalities and myocardial hypertrophy. Therefore, it is not appropriate to extrapolate the data from premature phase subjects or young adults to aged subjects regarding the responses of coronary vasculature to pressure overload. At present, there are no data on coronary hemodynamics after imposition of pressure overload in aged subjects.

To examine the coronary hemodynamics in the present study, we used an experimental model of isolated, beating but nonworking hearts perfused with crystalloid solution containing bovine red blood cells and serum albumin for the following reasons. First, it is difficult to estimate relatively pure characteristics of coronary vasculature per se after imposition of pressure overload in an in vivo preparation because aortic or left ventricular pressure would modify the coronary perfusion pressure-flow relations and reactive hyperemic response through the higher coronary perfusion pressure, greater extravascular compression forces, or higher metabolic demand of the myocardium. Therefore, in isolated, nonworking hearts we estimated coronary perfusion pressure-flow relations under resting conditions and reactive hyperemia and then compared pressure-overloaded and sham-operated hearts at the same levels of perfusion pressure over a wide range of perfusion pressure levels. Second, the characteristics of the perfusate modify the coronary hemodynamics measured in isolated hearts. Coronary flow rate under resting conditions was approximately fivefold greater in hearts perfused with crystalloid solution containing bovine red blood cells and albumin than in hearts perfused with crystalloid solution containing bovine red blood cells and albumin. In addition, reactive hyperemic response was smaller in hearts perfused with crystalloid solution compared with the value measured.
in an in vivo study, or in our previous ex vivo hearts perfused with crystalloid solution containing red blood cells and albumin (less than 2.0 versus near 3.0 of peak/resting flow in control group young hearts described in our previous study). Therefore, in this study we added bovine red blood cells and serum albumin to estimate coronary perfusion pressure–flow relations under resting conditions and during maximal vasodilation in pressure-overloaded and sham-operated control hearts. The coronary hemodynamics estimated in the present study show the relatively pure characteristics of the coronary vasculature per se.

Diminished capacity for myocardial hypertrophy in response to hemodynamic overload in aged subjects is consistent with previous data from our laboratory and from others. In the previous studies of Isoyama et al and Walford et al, aging decreased the capacity for myocardial hypertrophy in the left and right ventricles in response to pressure and volume overload. In the present study, the 4-week duration and severity of the 40–50 mm Hg increase in pressure load caused significant myocardial hypertrophy in young adult rats. In contrast, the same degree and duration of pressure overload caused no significant myocardial hypertrophy at the organ or cell level in aged subjects. However, the degree of hypertrophy in young adult rats was not remarkable compared with the values obtained in the developmental phase of rats. In the present study, the purpose was to examine the effects of pressure overload on abnormalities of the coronary circulation and myocardial hypertrophy in young adult and aged rats. It was impossible to examine the response of the myocardium and coronary vasculature to more severe pressure overload because more severe loading might have produced an extremely high mortality in old rats, as mentioned in the previous study of Isoyama et al. The data in this study show myocardial hypertrophic response and coronary hemodynamic response to relatively mild pressure overload in the two age groups. We should emphasize that even mild pressure overload caused abnormalities of the coronary circulation in the absence of significant myocardial hypertrophy in the aged group.

In the present study, the coronary perfusion pressure–flow relations were rectilinear at peak reactive hyperemia but curvilinear under resting conditions. In addition, the values of x intercept in the relations (zero flow pressure) were not zero. Therefore, the peak flow/resting flow ratio or minimal vascular resistance calculated at one point of perfusion pressure may not always reveal the real characteristics of the coronary vasculature. We estimated vasodilator capacity using indexes of minimal coronary vascular resistance calculated from the rectilinear pressure–flow relations and flow reserve.

Minimal coronary vascular resistance and flow reserve tended to increase and decrease, respectively, with aging alone. These age-related changes are consistent with the data of Peters et al, Toma et al, and Hachamovitch et al. After imposition of aortic banding, peak flow rate during reactive hyperemia and flow reserve decreased in young adult banded rats as in the study of Jeremy et al in our previous studies and as suggested by Hoffman. The increased minimal coronary vascular resistance and decreased flow reserve in young adult rats are the result of coronary arterial hypertension and myocardial hypertrophy. It is not clear how and which factors mainly contributed to the abnormalities of the coronary circulation. In old rats, however, the decreased capacity for vasodilation during reactive hyperemia was observed in coronary circulation in the absence of myocardial hypertrophy. Therefore, changes in coronary vasculature would be mainly responsible for the abnormalities of the coronary circulation in old rats.

In the study of Hachamovitch et al, age-related changes in coronary circulation (increased coronary vascular resistance per unit myocardial mass during maximal vasodilation and more depressed perfusion in the endocardium than in the epicardium) were similar to the abnormalities of the coronary circulation in pressure-overloaded hypertrophy in premature and young adult rats. In the present study, changes in coronary circulation produced by aging alone were similar to those in young adult, banded rats in terms of increased minimal coronary vascular resistance and decreased coronary flow reserve. In the systemic arterial trees, it has been reported that aging causes intimal and medial thickening and an increase of collagen relative to elastin content in the arterial wall. This relative increase in collagen reduces distensibility of cerebral arterioles. In addition, aging per se reduces endothelium-dependent relaxation in cerebral arterioles and promotes endothelium-dependent contraction in the aorta. Furthermore, the intimal thickening may cause uncoupling between the endothelium and smooth muscles. Chronic hypertension also causes morphological and functional changes in the systemic arteries or arterioles qualitatively similar to those in aged systemic arterial trees: intimal and medial thickening, decreased endothelium-dependent relaxation, promoted endothelium-dependent contraction, changes in smooth muscle length-tension characteristics, and impaired coupling between the endothelium and smooth muscles by intimal thickening. If in the coronary vasculature aging per se and chronic hypertension cause the same arteriolar wall changes as in the systemic arterial trees, it is possible that coronary arterial hypertension accelerates age-related changes after imposition of aortic banding in old rats. At present, it is not clear whether hypertension produces endothelial dysfunction and changes in smooth muscle characteristics in the aged coronary vasculature similar to those in younger rats. If the endothelium has effects on controlling coronary flow under resting conditions and during vasodilation by reactive hyperemia, it is also possible...
that endothelium-dependent relaxation or constriction in the coronary microvessels contributed to the different peak coronary flow rates during reactive hyperemia between young adult and old rats and the differences before and after imposition of pressure overload in each age group.

In conclusion, we studied the effects of age on coronary pressure–flow relations during resting conditions and maximal vasodilation after imposition of chronic pressure overload with coronary arterial hypertension. The imposition of the pressure overload in old rats increased minimal coronary vascular resistance and decreased flow reserve in the absence of myocardial hypertrophy. Not only did the hypertrophic response but also increased minimal coronary vascular resistance and decreased flow reserve may explain the higher incidence of heart failure or increased vulnerability of the myocardium to ischemic episodes in old patients compared with younger subjects.

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