Aging Effects on Myocardial Hypertrophic Response and Coronary Circulation in Pressure-Overload

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We examined the effect of age on capacity for myocardial hypertrophy, pressure-generating ability and coronary circulation after imposition of pressure-overload. Marked right ventricular and cellular hypertrophy was observed 1 week after pulmonary artery constriction in the developmental phase of rats (2 months of age) and after 3 weeks in the young-adult rats (7 months). In old rats (18 months) similar increases in peak right ventricular pressure did not produce significant hypertrophy even after 3 weeks. The right ventricular hypertrophy at the organ and cell levels in response to pressure-overload decreased with age. In vivo pressure-generating ability, which was determined by maximum isovolumic pressure during pulmonary artery occlusion, correlated with the degree of myocardial hypertrophy in each age group.

During the ascending aortic constriction experiment the age-associated diminution in hypertrophic response was also observed in the left ventricle. Coronary dilator capacity, which was determined after brief ischemia in an isolated, blood-perfused, beating but nonworking heart model, was decreased in the presence of myocardial hypertrophy in young-adult rats (7 months) and in the absence of significant myocardial hypertrophy in old rats (18 months).

The age-associated diminution in capacity for myocardial hypertrophy, pressure-generating ability and maladaptation in the coronary circulation may explain the higher incidence of heart failure or increased vulnerability of the myocardium to ischemic episodes during hemodynamic stress in aged patients. (Jpn Circ J 1992; 56: 482—488)

Heart failure occurs more frequently in aged than in young subjects. Also, relatively mild hemodynamic stress may cause heart failure or ischemic episodes in aged patients. The higher incidence of heart failure and increased vulnerability of the myocardium to ischemic episodes in elderly subjects may be due to diminished capacity for adaptation to hemodynamic stress and/or maladaptation in the myocardium and in the coronary vasculature. We examined the effects of age on myocardial hypertrophic response, pressure-generating ability and the coronary circulation after imposition of pressure-overload in rats.

Experiment I: Myocardial Hypertrophic Response and Pressure-Generating Ability

Key words:
Age
Cardiac hypertrophy
Coronary dilator reserve
Pulmonary artery constriction
Ascending aortic constriction
Right ventricle
Left ventricle
Rat

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Japanese Circulation Journal Vol. 56, May 1992
TABLE 1  BODY WEIGHT AND HEART WEIGHT IN THE THREE AGE GROUPS OF RATS

<table>
<thead>
<tr>
<th>Age (months)</th>
<th>2 months</th>
<th>7 months</th>
<th>18 months</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control</td>
<td>PAC-1w</td>
<td>PAC-3w</td>
</tr>
<tr>
<td>n</td>
<td>6</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>BW (g)</td>
<td>21±2</td>
<td>22±1</td>
<td>22±1</td>
</tr>
<tr>
<td>RRVW (mg)</td>
<td>13±8</td>
<td>13±8</td>
<td>13±8</td>
</tr>
<tr>
<td>LW (mg)</td>
<td>471±16</td>
<td>471±16</td>
<td>471±16</td>
</tr>
<tr>
<td>RWLVW</td>
<td>0.28±0.01</td>
<td>0.28±0.01</td>
<td>0.28±0.01</td>
</tr>
</tbody>
</table>

Values are mean ± SEM. Abbreviations: BW=body weight, RRVW and LW=right and left ventricular muscle weight. *p<0.01, experimental vs. control rats in each age group.

Fig. 1. Isovolumic systolic right ventricular pressure in the 3 age groups of rats. Abbreviations: RVP=right ventricular pressure; C=control; 1 w or 3 w=1 week or 3 weeks after pulmonary artery constriction; M=months. *p<0.05, **p<0.01, vs controls in each age group.

METHODS

We used male Wistar rats of 3 age groups: 2, 7 and 18 months. Details of the methods have been described elsewhere! Under general anesthesia and artificial ventilation through an endotracheal tube, right ventricular pressure was measured through a cannula which was inserted into the right ventricle via the right jugular vein. After opening the chest, the pulmonary artery was constricted to 1.4 mm internal diameter in the 2-month-old rats, 2.0 mm in the 7-month-old rats and 2.2 mm in the 18-month-old rats. The procedure of pulmonary artery constriction produced the same pressure increase among the 3 age groups of rats (an increase in peak right ventricular pressure by 15 mmHg). After closing the chest, the rats were fed with standard rat pellet chow.

At 0, 1 or 3 weeks after pulmonary artery constriction, the rats were anesthetized again and artificially ventilated. A cannula was inserted into the right ventricle through the left jugular vein. After opening the chest, we occluded the pulmonary artery for 5 or 6 sec with a thread which had been used for pulmonary artery constriction at the first operation, and measured isovolumic right ventricular pressure to estimate the pressure-generating ability. The rats were sacrificed thereafter. The degree of right ventricular hypertrophic response at the organ level was
TABLE II  CORONARY DILATOR CAPACITY AT A PERFUSION PRESSURE OF 100 mmHg IN THE TWO AGE GROUPS

<table>
<thead>
<tr>
<th></th>
<th>Young-adult (7 months)</th>
<th>Old (18 months)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sham-operated</td>
<td>AoC</td>
</tr>
<tr>
<td><strong>n</strong></td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td><strong>LVW/BW (mg/g)</strong></td>
<td>0.382 ± 0.016</td>
<td>0.476 ± 0.032*</td>
</tr>
<tr>
<td><strong>LVW/TL (mg/cm)</strong></td>
<td>49.0 ± 2.1</td>
<td>59.2 ± 3.9*</td>
</tr>
<tr>
<td><strong>Flow Reserve (ml/min)</strong></td>
<td>3.94 ± 0.67</td>
<td>2.34 ± 0.59*</td>
</tr>
<tr>
<td><strong>Peak Flow/Resting Flow</strong></td>
<td>2.60 ± 0.25</td>
<td>1.84 ± 0.19*</td>
</tr>
</tbody>
</table>

Values are mean ± SEM.
Abbreviations: AoC=ascending aortic constriction; LVP=left ventricular pressure; LVW=LV weight; BW=body weight; TL=tibial length.
*p < 0.05, Sham-operated vs. banded rats in each age group.

estimated by the ratios of the right ventricular weight/body weight, the weight/left ventricular weight and the weight/tibial length. Protein content in the right ventricular free wall was also measured. The degree of the cellular hypertrophic responses was estimated by histological measurements of myocyte width.

RESULTS AND DISCUSSION

As summarized in Table I, the ratio of right ventricular weight/left ventricular weight increased to 175% of the control group value 1 week after pulmonary artery constriction in the 2-month-old rats. After 3 week constriction the ratio increased further to 211%. In the 7-month-old rats, the hearts had responded to the pulmonary artery constriction with significant but moderate hypertrophy at 3 weeks (146%). In the 18-month-old rats, no significant myocardial hypertrophic response was observed even at 3 weeks after pulmonary artery constriction. (The ratios of the right ventricular weight/body weight and the weight/tibial length are not shown here. See Reference 1 for details.) Thus, marked and rapid hypertrophic response was observed in the developmental phase of rats, but no response in the old rats. This age-associated hypertrophic response at the organ level was similar to that at the cell level estimated by changes in myocyte widths! The age-associated response was also confirmed by protein measurement in the myocardial tissue!

As shown in Fig. 1, pressure-generating ability in the right ventricle estimated by maximum isovolumic peak systolic pressure increased parallel with the degree of hypertrophy. A decrease in isovolumic pressure after imposition of pulmonary artery constriction was not observed even in the old rats. In the study of Boluyt et al, age-associated diminution in myocardial hypertrophy was not observed, but isovolumic systolic pressure and maximum dp/dt, which was measured in an isolated Langendorff preparation, was decreased 7 days after pressure-overload in aged left ventricles, compared with those in sham-operated, age-matched control rats. Isoyama et al reported that pressure- or wall stress-generating ability was decreased 4 weeks after induction of volume-overload in aged left ventricles. In the present study, however, maximum isovolumic pressure increased parallel with the degree of myocardial hypertrophy and was not decreased after pressure-overload even in old rats. From the results in the present study, it does not seem that chronic hemodynamic stress causes maladaptation in pressure-generating ability in the aged right ventricle.

To determine hypertrophic response in the right ventricle, we did not directly measure the wall stress. However, the diminished hypertrophic response in older subjects was not caused by the different degree of stimulus. In the left ventricle, similarly increased wall stress by volume-overload caused differing hypertrophic responses between young-adult and old rats. The age-associated diminution in hypertrophic response observed in the pressure-overloaded right
ventricles is consistent with the observations in pressure$^4$ and volume-overloaded left ventricles$^3$ and volume-overloaded hearts$^5$. Aging means changes in extracardiac factors as well as aging of hearts or myocytes per se. Therefore, it is not clear whether the age-associated diminution is caused by the characteristics of aged hearts or myocytes per se, or how extracardiac factors such as thyroid hormone, testosterone, insulin and norepinephrine modify the hypertrophic response in aging process. Hypertrophic response to treatment with thyroid hormone in aged mice or rats was not diminished compared with younger subjects$^6,7$. Additionally, it is known that T$_3$, T$_4$ and thyroid stimulating hormone levels are lower in aged subjects. Therefore, it is important to determine whether the age-associated hypertrophic response is caused by the characteristics of aged hearts or myocytes, or by extracardiac factors. In vitro studies are needed to answer this question. If the age-associated diminution in hypertrophic response is caused by the characteristics of hearts or myocytes per se, underlying molecular and biochemical mechanism (s) for the age-associated diminution should be also clarified.

**EXPERIMENT II: Effects of Age on Coronary Circulation in Pressure-Overload**

**METHODS**

Details of the methods have been described elsewhere.$^8,9,10,11$ Two age groups of Wistar rats were used: 7 and 18 months. The chest was opened, and the ascending aorta was constricted to 1.6 mm internal diameter under anesthesia and artificial ventilation as described above. The procedure increased peak systolic left ventricular pressure to $150\pm10$ mmHg in the 7-month-old rats ($p<0.05$ vs $108\pm10$ mmHg in the sham-operated controls) and to $146\pm17$ mmHg in the 18-month-old rats ($p<0.05$ vs $101\pm16$ mmHg in the sham-operated controls). Four weeks after aortic constriction, the rats were sacrificed. The heart was isolated and perfused with modified Tyrode's solution with bovine red blood cells (hematocrit=30%) and serum albumin (15 g/L). The perfusate was oxygenated with a gas mixture of 20% O$_2$, 3% CO$_2$ and 77% N$_2$. Coronary perfusion pressure was controlled with a pressurized reservoir and a pressure regulator$^{12}$. The left ventricle was maintained empty with an apical drain to minimize the effect of extravascular forces. Coronary flow rates at 100 mmHg of perfusion pressure were measured under resting conditions and during reactive hyperemia after a 40 sec ischemia. Coronary dilator capacity was estimated by flow reserve (peak flow minus resting flow) and the ratio of peak flow/resting flow during reactive hyperemia.

**RESULTS AND DISCUSSION**

The same degree of pressure-overload produced significant myocardial hypertrophy in young-adult rats, but did not do so in old rats. The age-associated diminution in left ventricular hypertrophic response was also observed at the cellular level.

As summarized in Table II, coronary dilator capacity decreased with age (young-adult, sham-operated vs old, sham-operated controls). (See Reference 8 for details.) After imposition of pressure-overload, vasodilator capacity decreased in young-adult rats probably through myocardial hypertrophy, vascular changes induced by coronary arterial hypertension or both. In old rats, dilator capacity decreased in spite of the absence of significant myocardial hypertrophy.

The age-related changes in coronary dilator capacity have been reported from our laboratory$^{12}$ and from others$^8,13,14$. Coronary flow under resting conditions is higher in the early phase after birth (4 weeks of age in guinea pigs) and maintained constant throughout the phase of development and maturation$^{13}$. Even at the aged phase (18 months of age in rats) resting coronary flow does not decrease at the coronary perfusion pressure of in vivo operating levels$^{12,13}$. Coronary autoregulatory and dilator capacity, however, is maintained during the matured phase, but diminishes at the aged phase (18 months of age in guinea pigs and rats)$^{12}$. The following mechanisms responsible for the age-related changes in coronary circulation should be considered: (1) morphological vascular wall changes such as intimal thickening and increased extracellular protein, especially collagen$^{15,16}$ (2)
decreased distensibility of the vascular wall, (3) dysfunction of the endothelium, i.e., decreased endothelium-dependent relaxation\textsuperscript{17} and promoted endothelium-dependent constriction, and (4) impaired coupling between the endothelium and smooth muscles by intimal thickening. It is likely that extracellular protein such as collagen in the coronary vascular wall decreases the distensibility of the wall and that perivascular collagen limits the vasodilator capacity. It is also possible that endothelium-dependent relaxation and constriction play an important role in regulation of coronary flow during reactive hyperemia. However, to date, it is not clear how the endothelium-dependent relaxation and constriction modulate coronary flow during reactive hyperemia. Another possible mechanism is that in aged subjects, sensitivity of the smooth muscle cells to vasoactive substances (which are released from the myocytes or endothelial cells) or the functional characteristics of the smooth muscle cells differ from that in young subjects.

After imposition of left ventricular pressure-overload with coronary arterial hypertension, coronary flow reserve was decreased in the presence of significant myocardial hypertrophy at the organ and cell levels in young-adult rats. A number of investigators have reported the diminished capacity for vasodilation in hypertrophied hearts produced by pressure-overload. Our observations in young-adult rats are in agreement with those reported from other laboratories. The diminished capacity is caused by myocardial hypertrophy\textsuperscript{19} hypertensive coronary vascular changes\textsuperscript{20} or both. In a previous study, myocardial hypertrophy \textit{per se} diminished the vasodilator capacity in an experimental model of aortic valvular stenosis\textsuperscript{19}. On the other hand, in the spontaneously hypertensive rat vasodilator capacity is diminished in the right ventricle with coronary arterial hypertension and without significant myocardial hypertrophy\textsuperscript{20}. In the present study, in old subjects coronary dilator capacity decreased in the absence of significant myocardial hypertrophy at the organ or cell level after imposition of pressure-overload with coronary arterial hypertension. Our study indicates that pressure-overload with coronary hypertension affects the left ventricular myocardium and coronary arterial trees in a different manner between young-adult and old subjects.

Vascular changes caused by chronic hypertension in the systemic and coronary arterial trees are qualitatively similar to those caused by aging alone, namely, rarefaction of arterioles\textsuperscript{21} intimal and medial thickening\textsuperscript{22–24} increased deposition of collagen in the vascular wall\textsuperscript{22} decreased distensibility of the vascular wall\textsuperscript{25} decreased endothelium-dependent vasodilation\textsuperscript{21,25–29,30} and promoted endothelium-dependent vasoconstriction\textsuperscript{31,32} and impaired coupling between the endothelium and smooth muscles by intimal thickening\textsuperscript{33}. In the study of Haudenshild et al\textsuperscript{34} blood pressure lowering diminished the age-related changes in the rat aortic intima. If we can extrapolate the observations in the systemic arterial trees to changes in the coronary arterial trees, imposition of chronic hypertension in old subjects may accelerate the vascular changes caused by aging alone. Also, it should be clarified whether the locally activated renin-angiotensin system has a role in controlling coronary perfusion in hypertrophied hearts and in aged hearts.

In conclusion, aging diminished capacity for myocardial hypertrophy in response to pressure-overload in both the right and left ventricles at the organ and cell levels. Pressure-generating ability was parallel with the degree of myocardial hypertrophy in the right ventricle in all age groups. After imposition of pressure-overload, coronary dilator reserve decreased in the presence of significant myocardial hypertrophy in young-adult subjects and in the absence of myocardial hypertrophy in the old subjects. This diminished hypertrophic response with less pressure-generating ability and decreased coronary dilator capacity may explain the higher incidence of heart failure or increased vulnerability of the myocardium to ischemic episodes during stress in aged patients.

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