Effects of Chronic Exercise on the Coronary Circulation in Conscious Rats with Renovascular Hypertension

PIERRE WICKER, MARVAN ABDUL-SAMAD, KAREL RAKUSAN, ROBERT C. TARAZI, AND BERNADINE HEALY

SUMMARY Since various studies suggest that chronic physical conditioning promotes myocardial vascularity, we investigated whether it could prevent the coronary reserve abnormalities of hypertensive cardiac hypertrophy. One week after operation, female Sprague-Dawley rats with two-kidney, one clip Goldblatt hypertension were either subjected to a moderate exercise program by swimming (n = 21) or kept sedentary (n = 16) for 9 weeks. Sedentary (n = 16) and exercised (n = 15) sham-operated rats served as controls. Maximal coronary blood flow and minimal coronary resistance, either per unit mass or for the entire left ventricle, an index of the functional cross-sectional area of the coronary resistance vessels, were determined in conscious, unrestrained rats by left atrial microsphere injection following maximal vasodilation with carbochrome (12 mg/kg). Following exercise, left ventricular mass was moderately (+5–10%) but significantly increased in normotensive rats, whereas left ventricular hypertrophy was significantly accentuated in the hypertensive rats. Minimal coronary resistance for the entire left ventricle was significantly decreased (~24%) in normotensive rats but did not change significantly in hypertensive rats. Minimal coronary resistance per unit mass (the coronary vasodilator reserve) tended to decrease in normotensive rats (~17%), whereas it tended to be further augmented in hypertensive rats (+13%). However, these differences were marginally significant and were not associated with any changes in maximal coronary blood flow per unit mass (the coronary flow reserve). Thus, in normal rats, exercise promoted myocardial arterial vascularity in parallel with the development of cardiac hypertrophy. However, when superimposed on hypertensive hypertrophy, exercise did not stimulate vascular growth, and the limitation in coronary vasodilator reserve characteristic of hypertensive cardiac hypertrophy was not prevented. (Hypertension 10: 74–81, 1987)

Key Words • coronary reserve • cardiac hypertrophy • physical exercise • renovascular hypertension

VARIOUS lines of evidence suggest that physical training, whether or not it results in physiological cardiac hypertrophy, may be associated with beneficiary changes in the coronary circulation, such as an improvement in the coronary vasodilator reserve. In contrast, coronary vasodilator reserve has consistently been found to be depressed in pressure overload left ventricular and right ventricular hypertrophy secondary to hypertension or other pathological states. These observations raised the possibility that physical training could beneficially influence coronary reserve in hypertensive cardiac hypertrophy. This question was recently addressed by Buttrick et al., who reported that the coronary reserve abnormalities of hypertensive cardiac hypertrophy were not prevented by a swimming program in renal hypertensive rats. However, they performed flow measurements in isolated hearts, and the applicability of these findings to in vivo situations remained unclear. Also, the effects of exercise on the left and right ventricular coronary circulation or on the transmural flow distribution between the left ventricular subendocardial and subepicardial lay-

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ers were not assessed. These questions assume particular importance in view of studies indicating that the response of the right ventricular coronary circulation to physical training may be different from that of the left ventricle or studies showing that the depression of coronary reserve in pressure overload hypertrophy is often more prominent in the subendocardial layers.3,4

The present study therefore was designed to test whether physical training could prevent the coronary reserve limitations of hypertensive cardiac hypertrophy. To this end, coronary reserve was measured in conscious rats with renovascular hypertension with and without a swimming program, the latter initiated before the onset of hypertension and before the development of cardiac hypertrophy.

Materials and Methods

Female Sprague-Dawley rats (age, 40–45 days; weight, 150–175 g; Hilltop Lab Animals, Scottsdale, PA, USA) were housed two to three a cage and fed a standard rat chow (Purina Chow; St. Louis, MO, USA). All surgical procedures and handling of the animals were performed in accordance with our institutional guidelines on animal use in research.

Preparation of Two-Kidney, One Clip Goldblatt Hypertension

Two-kidney, one clip Goldblatt hypertension was induced in female Sprague-Dawley rats by placing a silver clip (0.2 mm) on the left renal artery under ether anesthesia; the right kidney was left untouched. Rats subjected to a sham operation served as controls.

Training Program

Rats were submitted to a regular exercise (swimming) program according to the protocol developed by Ostman-Smith.9 This program consists of two phases: 1) an acclimation period of 4 weeks, during which the rats were made to swim for increasingly longer durations, from 15 minutes the first day to 120 minutes per day; and 2) a stable training period of 5 to 6 weeks, during which the rats swam 2 hours a day, 5 days a week. The rats were exercised in groups of six to eight in a 70 × 44 × 53-cm Plexiglas tank. Water temperature was maintained at 36 ± 1°C.

Coronary Blood Flow Measurements

Coronary blood flow was determined in conscious, unrestrained rats using left atrial injections of radioactive microspheres. This method has been previously reported in detail and validated in our laboratory.10,11 Briefly, a PE-10 catheter was positioned in the left atrium, with the rat under pentobarbital anesthesia (30 mg/kg i.p.), and exteriorized at the back of the neck. After this surgical procedure, the rats were allowed to recover for 3 to 5 days. On the day of flow measurements, another catheter (PE-50) was placed into the abdominal aorta through the right femoral artery under ether anesthesia and advanced to just below the level of the renal arteries. The catheter was tunneled subcutaneously and exteriorized at the back of the neck. Immediately after placement, 80 to 100 USP units of heparin was given subcutaneously to prevent clotting of the aortic catheter. Approximately 2 to 3 hours after aortic catheter insertion, the rats were placed in small plastic cages, where they sat quietly, so that subsequent measurements were made in conscious unrestrained rats. The femoral artery catheter was connected to an MP 15 transducer (Micron Instruments, Los Angeles, CA, USA) for blood pressure recording; the first injection of microspheres was given 1 hour later, after blood pressure and heart rate had stabilized.

Radioactive microsphere, 15 μm in diameter, labeled with either strontium-85 or cerium-141 (3M Company, St. Paul, MN, USA), were suspended in a 70% glucose solution with 0.05% polysorbate 80 (Tween 80). After mechanical and ultrasonic agitation for 10 to 15 minutes, approximately 300,000 microspheres were withdrawn in a PE-50 tubing for injection. This number of microspheres ensured that each myocardial sample received more than 2000 microspheres and the reference blood sample received more than 500 microspheres, so that variability related to random distribution of the particles was minimal.12,13 We and others14 have shown that this number of microspheres in the rat does not significantly affect cardiovascular hemodynamics and regional flow distribution.

The microspheres were injected into the left atrium over a 10-second period, and the tubing was flushed with 0.25 ml of saline solution over 10 to 15 seconds. Starting 10 seconds before the injection, blood was withdrawn for 90 seconds from the aortic catheter at a constant rate of 0.51 ml/min. with a Harvard pump (Model 940; South Natick, MA, USA). After the reference sample was taken, the rats were given 0.75 ml of blood from a sex-matched and strain-matched donor to replace the amount withdrawn.

After the first set of microspheres was injected, carbochrome was infused at a constant rate of 0.136 mg/min to a total dose of 12 mg/kg. Within 6 to 8 minutes after the end of the infusion, the second set of microspheres was injected. The dose and rate of infusion of carbochrome (Hoechst-Roussel Pharmaceuticals, Somerville, NJ, USA) and the timing of microsphere injection were selected to achieve and detect maximal coronary dilatation on the basis of our initial studies15 and additional unpublished experience with carbochrome.

At the end of the experiment the rats were killed with pentobarbital. The heart was removed and cleaned of fat and fibrous tissue. The proper location of the left atrial catheter was confirmed. The atria were removed, and the right ventricular free wall was cut away from the left ventricle. The left ventricle was divided into septum and the subendocardial and subepicardial halves of the free wall. The three pieces of left ventricle and the right ventricle were each weighed and counted for 10 minutes in a gamma well counter (Model 5010; Packard Instruments, Downers Grove, IL, USA) at the same time as the arterial blood was...
withdrawn from the aortic catheter (reference sample). Coronary blood flow and resistance were computed as previously described using a specifically designed program correcting for background, decay, and spill-over.

Experimental Protocols

One week after placement of the left renal artery clip or the sham procedure, the rats were allocated to one of the two experimental groups (i.e., swimming or cage confined). Blood pressure was measured at weekly intervals with an indirect tail-cuff method. Only rats with a systolic blood pressure consistently greater than 150 mm Hg (approximately 40% in both the swimming and sedentary groups) were included in this study. After the 9- to 10-week swimming program or confinement, coronary blood flow and resistance were measured as already described.

Statistical Analysis

Values reported are means ± SD. Statistical analysis was conducted according to recent recommendations. A two-way analysis of variance (ANOVA) with two grouping factors, the blood pressure level (i.e., hypertensive sham-operated groups) and conditioning status (i.e., swimming vs sedentary groups), was performed. When a significant interaction between the two grouping factors was found, the ANOVA was followed by a modified t test to determine if the effects of hypertension or exercise were present only in the trained or hypertensive animals, respectively. Therefore, four pairwise comparisons were performed, two in normotensive and hypertensive groups between trained and untrained animals and two in untrained and trained groups between normotensive and hypertensive animals. Changes in pressure, flow, and resistance before and after carbochrome were statistically assessed using a paired t test. All calculations were performed on the PROPHET computer system using the PROPHET or BMDP statistical packages.

Results

Blood Pressure and Heart Weight

As noted in Table 1, mean arterial pressure before the first injection of microspheres was significantly elevated in the renovascular hypertensive rats as compared with sham-operated animals and no significant differences were present between sedentary and trained rats. Weekly systolic blood pressure measurements also did not reveal any difference between cage-confined and exercised rats.

Left ventricular mass was increased by 40% in the hypertensive groups as compared with the normotensive animals (p < 0.001). Exercise caused a small (+5–10%) but statistically significant (p < 0.05) increase in left ventricular mass in both normotensive and hypertensive animals as compared with their sedentary controls. Thus, exercise superimposed on hypertension accentuated hypertrophy. These differences were similar whether left ventricular weight was expressed in absolute terms or normalized for body and brain weights (see Table 1). The latter index of hypertrophy was included because brain weight is said to be less affected by the health or nutrition and physical status of the animals than is body weight, as was the case in the present study, where brain weight was virtually the same in all groups (see Table 1).

Right ventricular weight, when normalized for body weight, was modestly increased in hypertensive animals (p < 0.05). However, when expressed in absolute terms or normalized for brain weight, no differences in right ventricular mass between normotensive and hypertensive groups were found. In contrast to the left ventricle, no significant increase in right ventricular mass was observed following training.

Heart rate, measured from the intra-arterial blood pressure recordings before the first microsphere injection, was similar in all groups.

Coronary Hemodynamics

Left Ventricle

Left ventricular coronary hemodynamics, as determined by microspheres, are shown in Table 2. In agreement with our previous studies, resting left ventricular coronary blood flow was increased significantly in rats with short-term renovascular hypertension (10–11 weeks; p < 0.01), particularly in the sedentary group (p < 0.01). Following carbochrome infusion, there was a fourfold to fivefold increase in coronary blood flow and decrease in coronary resistance (p < 0.01) in all groups. Coronary perfusion pressure, as judged from the mean arterial pressure, decreased slightly but significantly (p < 0.01) in hypertensive groups. Left ventricular coronary blood flow after carbochrome (coronary flow reserve) was similar in all four groups. The postcarbochrome endocardial/epicardial ratio, an index of the transmural coronary flow reserve, was significantly decreased in hypertensive groups. Left ventricular coronary blood flow after carbochrome was similar in all four groups. The postcarbochrome endocardial/epicardial ratio, an index of the transmural coronary flow reserve, was significantly decreased in hypertensive rats (p < 0.01). However, this change was related to a higher subepicardial flow reserve in the hypertensive animals rather than to any reduction in subendocardial flow reserve, and when subendocardial or subepicardial flow reserve was analyzed separately, no significant differences were found among the four groups.

Postcarbochrome minimal left ventricular coronary resistance per unit mass (the coronary vasodilator reserve) was significantly (p < 0.01) higher in hypertensive as compared with normotensive rats. A significant (p < 0.05) interaction between the two grouping factors (blood pressure and conditioning status) was found for this parameter. Thus, exercise caused directionally opposite changes in coronary vasodilator reserve, which tended to improve in the normotensive rats, whereas it tended to be further depressed in hypertensive animals. However, the differences in the coronary vasodilator reserve between normotensive trained and untrained rats on the one hand, and be-
TABLE 1. Blood Pressure and Heart Weight in Trained and Untrained Renovascular Hypertensive Rats

<table>
<thead>
<tr>
<th>Group</th>
<th>Normotensive</th>
<th>Hypertensive</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sedentary (n = 16)</td>
<td>Exercised (n = 15)</td>
<td>Sedentary (n = 16)</td>
<td>Exercised (n = 21)</td>
</tr>
<tr>
<td>Mean arterial pressure (mm Hg)</td>
<td>110 ± 9</td>
<td>109 ± 12</td>
<td>184 ± 29*</td>
<td>191 ± 20*</td>
</tr>
<tr>
<td>Body weight (g)</td>
<td>235 ± 17</td>
<td>233 ± 13</td>
<td>217 ± 19*</td>
<td>212 ± 32*</td>
</tr>
<tr>
<td>Brain weight (g)</td>
<td>1.78 ± 0.08</td>
<td>1.80 ± 0.08</td>
<td>1.82 ± 0.16</td>
<td>1.80 ± 0.10</td>
</tr>
<tr>
<td>Left ventricular weight (mg)</td>
<td>559 ± 48</td>
<td>601 ± 96†</td>
<td>771 ± 83*</td>
<td>812 ± 121*†</td>
</tr>
<tr>
<td>Weight/body weight (mg/g)</td>
<td>2.34 ± 0.17</td>
<td>2.61 ± 0.35†</td>
<td>3.57 ± 0.45*</td>
<td>3.88 ± 0.63*†</td>
</tr>
<tr>
<td>Weight/brain weight (g/g x 10)</td>
<td>3.11 ± 0.30</td>
<td>3.37 ± 0.44†</td>
<td>4.28 ± 0.51*</td>
<td>4.51 ± 0.53*†</td>
</tr>
<tr>
<td>Right ventricular weight (mg)</td>
<td>185 ± 31</td>
<td>193 ± 34</td>
<td>189 ± 42</td>
<td>200 ± 36</td>
</tr>
<tr>
<td>Weight/body weight (mg/g)</td>
<td>0.78 ± 0.11</td>
<td>0.83 ± 0.13</td>
<td>0.86 ± 0.18§</td>
<td>0.96 ± 0.21‡</td>
</tr>
<tr>
<td>Weight/brain weight (g/g x 10)</td>
<td>1.06 ± 0.19</td>
<td>1.07 ± 0.16</td>
<td>1.02 ± 0.19</td>
<td>1.11 ± 0.18</td>
</tr>
</tbody>
</table>

Values are means ± SD. *p < 0.01, †p < 0.05, compared with values in normotensive rats (two-way ANOVA). §p < 0.05, compared with sedentary values (two-way ANOVA).

TABLE 2. Left Ventricular Coronary Hemodynamics in Trained and Untrained Renovascular Hypertensive Rats

<table>
<thead>
<tr>
<th>Group</th>
<th>Normotensive</th>
<th>Hypertensive</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sedentary (n = 16)</td>
<td>Exercised (n = 15)</td>
<td>Sedentary (n = 16)</td>
<td>Exercised (n = 21)</td>
</tr>
<tr>
<td>Mean arterial pressure (mm Hg)</td>
<td>111 ± 2</td>
<td>104 ± 9</td>
<td>181 ± 23*</td>
<td>170 ± 22</td>
</tr>
<tr>
<td>Coronary blood flow (ml/min/100 g)</td>
<td>350 ± 92</td>
<td>403 ± 107</td>
<td>520 ± 123*†</td>
<td>439 ± 121*</td>
</tr>
<tr>
<td>Carbochrome</td>
<td>1857 ± 479</td>
<td>2134 ± 764</td>
<td>2010 ± 322</td>
<td>1884 ± 490</td>
</tr>
<tr>
<td>Subendocardial flow (ml/min/100 g)</td>
<td>367 ± 90</td>
<td>449 ± 151</td>
<td>575 ± 168*‡</td>
<td>456 ± 128*</td>
</tr>
<tr>
<td>Rest†</td>
<td>1824 ± 519</td>
<td>2209 ± 929</td>
<td>1799 ± 402</td>
<td>1852 ± 532</td>
</tr>
<tr>
<td>Carbochrome</td>
<td>1989 ± 632</td>
<td>2333 ± 905</td>
<td>2393 ± 369</td>
<td>2170 ± 671</td>
</tr>
<tr>
<td>Subepicardial flow (ml/min/100 g)</td>
<td>358 ± 93</td>
<td>428 ± 192</td>
<td>537 ± 166*‡</td>
<td>449 ± 138*</td>
</tr>
<tr>
<td>Rest†</td>
<td>1989 ± 632</td>
<td>2333 ± 905</td>
<td>2393 ± 369</td>
<td>2170 ± 671</td>
</tr>
<tr>
<td>Carbochrome</td>
<td>1824 ± 519</td>
<td>2209 ± 929</td>
<td>1799 ± 402</td>
<td>1852 ± 532</td>
</tr>
<tr>
<td>Endo/epi ratio</td>
<td>1.06 ± 0.25</td>
<td>1.12 ± 0.33</td>
<td>1.11 ± 0.29</td>
<td>1.04 ± 0.16</td>
</tr>
<tr>
<td>Coronary resistance (mm Hg/ml/min/100 g)</td>
<td>0.93 ± 0.15</td>
<td>0.95 ± 0.13</td>
<td>0.75 ± 0.14*</td>
<td>0.86 ± 0.12*</td>
</tr>
<tr>
<td>Rest†</td>
<td>0.34 ± 0.11</td>
<td>0.29 ± 0.08</td>
<td>0.37 ± 0.09*</td>
<td>0.48 ± 0.16*§</td>
</tr>
<tr>
<td>Carbochrome†</td>
<td>0.064 ± 0.018</td>
<td>0.053 ± 0.018</td>
<td>0.085 ± 0.014*§</td>
<td>0.096 ± 0.024*</td>
</tr>
<tr>
<td>Total coronary resistance (mm Hg/ml/min)</td>
<td>11.5 ± 3.3</td>
<td>8.7 ± 1.8‡</td>
<td>11.2 ± 1.8</td>
<td>11.9 ± 2.8</td>
</tr>
</tbody>
</table>

Values are means ± SD. All differences between resting and postcarbochrome determinations were significant (p < 0.01) within each group except for the mean arterial pressure and the endocardial/epicardial (endo/epi) ratio in the normotensive groups. *p < 0.01, †p < 0.05, compared with normotensive values (two-way ANOVA). §p < 0.05, significant interaction between hypertension and exercise for this parameter (two-way ANOVA). #p < 0.01, compared with normotensive sedentary; ‡p < 0.01, compared with normotensive exercised and p < 0.05, compared with hypertensive sedentary; and || p < 0.01 compared with normotensive exercised rats (all, modified t test following a significant interaction by two-way ANOVA).

between hypertensive trained and untrained rats on the other hand, were not statistically significant, as assessed by a modified t test. Similarly, a significant interaction between the two grouping factors was found for postcarbochrome total left ventricular coronary resistance, an index of the total functional coronary cross-sectional area of the coronary resistance vessels available for blood transport. This parameter was significantly decreased in exercised normotensive animals as compared with their sedentary normotensive controls (p < 0.05). In contrast, however, postcarbochrome total left ventricular coronary resistance was not significantly altered by exercise in hypertensive rats.
Table 3. Right Ventricular Coronary Hemodynamics in Trained and Untrained Renovascular Hypertensive Rats

<table>
<thead>
<tr>
<th>Group</th>
<th>Normotensive</th>
<th>Hypertensive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coronary blood flow (ml/min/100 g)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rest*</td>
<td>203 ± 50</td>
<td>289 ± 154</td>
</tr>
<tr>
<td>Carbochrome*</td>
<td>1628 ± 690</td>
<td>1715 ± 426</td>
</tr>
<tr>
<td>Coronary resistance (mm Hg/ml/min/100 g)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rest*</td>
<td>0.58 ± 0.13</td>
<td>0.46 ± 0.24</td>
</tr>
<tr>
<td>Carbochrome*</td>
<td>0.083 ± 0.04</td>
<td>0.064 ± 0.014</td>
</tr>
<tr>
<td>Total coronary resistance (mm Hg/ml/min)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rest*</td>
<td>325 ± 111</td>
<td>236 ± 102</td>
</tr>
<tr>
<td>Carbochrome*</td>
<td>46 ± 26</td>
<td>34 ± 7</td>
</tr>
</tbody>
</table>

Values are means ± SD. All differences between resting and postcarbochrome determinations were significant (p<0.01).

* p<0.05, significant interaction between hypertension and exercise for this parameter (two-way ANOVA).

tp<0.05, ||p<0.01, compared with normotensive values (two-way ANOVA).

§p<0.01, compared with normotensive sedentary, and §p < 0.01, compared with normotensive exercised rats (modified t test following a significant interaction by two-way ANOVA).

Right Ventricle

Data from the right ventricle are shown in Table 3. As with left ventricular coronary blood flow, resting right ventricular coronary blood flow per unit mass tended to be higher in hypertensive rats as compared with their normotensive controls, particularly in the hypertensive sedentary rats (p<0.01) as compared with their normotensive sedentary controls. Changes in minimal right ventricular coronary resistance per unit mass or for the whole ventricle were similar to those found in the left ventricle. The right ventricular coronary vasodilator reserve was significantly (p<0.01) reduced in hypertensive rats, an observation that we6 and others5 have previously reported. Exercise induced directionally opposite changes in this parameter, as evidenced by a significant (p<0.05) interaction between blood pressure and exercise. However, the differences in the normotensive and hypertensive groups between untrained and trained animals did not reach statistical significance. As seen in the left ventricle, the right ventricle total coronary resistance tended to decrease — although not significantly — by 26% in normotensive rats as compared with their sedentary normotensive controls following exercise training, whereas no changes were observed in hypertensive animals.

Discussion

This study is the first, to our knowledge, to examine the effects of chronic exercise on the coronary circulation of conscious rats with hypertensive cardiac hypertrophy. Our main objective was to determine whether physical training begun before the onset of hypertension and the development of cardiac hypertrophy could prevent the abnormalities in coronary reserve found in hypertensive cardiac hypertrophy. The main findings of this investigation were twofold. First, chronic physical conditioning by swimming increased the functional coronary arterial vascular space in normotensive rats, as shown by a decrease in the total left ventricular minimal coronary resistance. This expansion in myocardial arterial vascularity was greater than the increase in left ventricular mass (24% vs 5–10%), and the minimal coronary resistance per unit mass (i.e., the coronary vasodilator reserve) tended to improve, although marginally. Second, in contrast to normotensive rats, no vascular growth occurred in hypertensive rats. Exercise exaggerated hypertrophy in the hypertensive animals; hence, minimal coronary resistance per unit mass was unchanged or even tended to be higher in trained hypertensive rats as compared with their untrained controls. Thus, exercise did not prevent the reduction in coronary vasodilator reserve characteristic of hypertensive cardiac hypertrophy.

Effects of Exercise on Total Coronary Flow and Vasodilator Reserve

Various studies have shown that physical training results in an improvement in the coronary flow or vasodilator reserve in normal animals. Buttrick et al. reported that in normotensive female Sprague-Dawley rats an 8- to 10-week swimming program causes an 18% increase in heart weight and a significant increment in vasodilator coronary flow reserve measured in isolated hearts after maximal dilation with adenosine or anoxia. Coronary vasodilator reserve was not reported in this study; however, since all hearts were perfused at similar pressures, one would assume by this result that coronary vasodilator reserve was also improved. Buttrick et al. also demonstrated in isolated hearts from swimming-conditioned rats an increment in the capacity of the coronary resistance vessels to dilate as early as 10 days after the onset of exercise, at a time when little cardiac hypertrophy was present. This finding suggests that the effects of training on the coronary circulation may be independent of the hypertrophic process itself. In another study, maximal coronary conductance per unit mass measured after hypoxia-induced coronary dilation was found to be larger in rats trained by running than in their sedentary controls. Finally, Laughlin and colleagues reported...
that chronic treadmill exercise in dogs improves coronary flow and vasodilator reserve measured after maximal coronary dilation induced either by adenosine or by ischemia produced by transient coronary occlusion. In contrast to these studies, however, others found no improvement in coronary reserve after training. In rats conditioned by swimming, Yipintsoi et al. reported that coronary reserve measured after hypoxia-induced dilation was similar to that found in sedentary controls. Similarly, other studies in dogs trained by running could not demonstrate any significant change in coronary flow or vasodilator reserve measured after adenosine-induced coronary dilation. In our study, the total functional coronary cross-sectional area was significantly enlarged in normotensive exercised rats; however, coronary flow reserve remained unchanged, and coronary vasodilator reserve was marginally improved. Reasons for differences in these observations probably are related to differences in the severity and type of exercise or in the methodology used to induce coronary dilation or to measure coronary reserve. Even when present, however, changes in coronary flow or vasodilator reserve following exercise training are usually of a small magnitude, as found in this and other studies, and their physiological significance remains unclear.

As previously mentioned, one other study concerned with the effects of chronic exercise on the coronary reserve of rats with hypertensive cardiac hypertrophy has been recently reported by Buttrick et al. This study suggests that in renal hypertensive rats the alterations in coronary flow reserve (or equivalently in coronary vasodilator reserve) cannot be prevented by a swimming program. Our study confirms these results and extends them to the intact heart in a conscious, unrestrained animal. Our study also suggests that exercise may further diminish coronary vasodilator reserve. Although the differences between the hypertensive or normotensive sedentary and exercised rats were not significant, exercise induced directionally opposite changes in coronary vasodilator reserve in normotensive and hypertensive rats, as shown by a statistically significant interaction between the conditioning status of the animal and the blood pressure. That exercise may adversely affect the coronary circulation in hypertensive cardiac hypertrophy is not a totally new observation. Recently, Marcus and Tipton demonstrated that subendocardial capillary density declined in rats with severe renal hypertension and cardiac hypertrophy following a moderate exercise program by running. However, in the same study, myocardial capillarity was not affected by exercise in rats with moderate hypertension and cardiac hypertrophy, indicating that the magnitude of blood pressure elevation and the degree of cardiac hypertrophy may be important modulating factors. In contrast to these observations, Crisman et al. reported that myocardial capillary density returned to normal in young spontaneously hypertensive rats following physical training by running. Further studies are necessary 1) to confirm the observations that the additional stimulus of exercise may be more detrimental than beneficial to the coronary circulation in hearts with pathological hypertrophy, at least under some experimental conditions; 2) to identify the factors modulating these effects of exercise, such as the age of the animal, the experimental models, the severity of hypertension and cardiac hypertrophy, and the type or intensity of the exercise program; and 3) to assess the physiological significance of these findings.

Analysis of the data from our studies and those of Buttrick et al. provides some insight into the mechanisms involved in the effects of exercise on the coronary circulation. Theoretically, the reduction in the vasodilator capacity of the coronary resistance vessels observed in hypertensive hypertrophy can be ascribed to either structural or functional factors or a combination of both. Various observations point toward the role of alterations in structural properties of the resistance vessels, such as an increase in the wall thickness. The role of a functional component, for instance, an activation of the sympathetic nervous or the renin-angiotensin systems, has never been adequately investigated and remains unknown. In isolated hearts, only structural coronary alterations are presumably operative to limit coronary dilation. Thus, in normotensive rats the similarity between our in vivo results and those obtained in vitro suggest that exercise can expand the arterial vascular space by influencing mostly its structural properties. In isolated hearts from hypertensive rats, coronary flow reserve (and, equivalently, coronary vasodilator reserve) was found to be unchanged after exercise. In the present study, coronary vasodilator reserve, measured in conscious rats, tended to be slightly more depressed in hypertensive trained animals as compared with their sedentary controls. If confirmed, these composite results suggest that exercise may activate some functional vasoconstrictor factors in the conscious state and further limit the ability of the coronary vessels to maximally dilate. However, these hypotheses need to be tested more directly by studies correlating flow measurements with a histometric analysis of the coronary resistance vasculature in the same animal.

**Effects of Exercise on Left Ventricular Coronary Transmural Flow Reserve**

Only a few studies are available regarding the effects of physical training on transmural coronary flow reserve. One recent investigation reported a reduction in the endocardial/epicardial ratio at maximal dilation in normal pigs trained by treadmill running. However, this reduction in the transmural flow reserve was related more to an increase in subepicardial blood flow than to a reduction in subendocardial blood flow, which remained unchanged. Thus, there was no evidence of subendocardial underperfusion following training in this study. In support of this conclusion, other studies have reported identical endocardial/epicardial ratio, or indices of subendocardial resistance in normotensive dogs conditioned by running and in their sedentary controls. Similarly, in the
present study subendocardial and subepicardial flows, as well as the endocardial/epicardial ratio, were not significantly altered by exercise in normotensive rats. In addition, our study shows that regional distribution of myocardial blood flow was also unaffected by exercise in hypertensive rats.

Effects on Exercise on Right Ventricular Coronary Circulation

Changes in the right ventricular coronary circulation with hypertension and exercise (see Table 3) were strikingly similar to those noted in the left ventricle (see Table 2). In hypertensive rats, this resemblance in response suggests that the anatomical or functional factors responsible for the limitation of coronary vasodilator reserve in hypertensive cardiac hypertrophy are probably similar in the left and right ventricles and that these factors are equally unaffected by exercise. The similarity in the effects of exercise on the left ventricular and right ventricular coronary resistance vessels of normal rats contrasts with the variable response of the capillary bed noted by Anversa et al.3 These investigators found that a moderate running program promotes capillary growth in the right ventricle, but not in the left ventricle, and reasons for these different effects on the two ventricular chambers or on the coronary arteriolar and capillary bed are not known. To resolve these uncertainties we must gain more knowledge of the factors determining the structural and functional properties of the coronary vessels as well as the various ways physical training can affect them.

Methodological Considerations

Three methodological considerations should be addressed: 1) the use of left atrial injections of microspheres to measure coronary blood flow, 2) the extent of coronary dilation achieved with carbochrome, and 3) the adequacy of swimming as the exercise conditioning stimulus.

A major advantage of this study is the use of left atrial injection of microspheres to measure coronary flow in the conscious, unrestrained rat. This route of administration yields more precise coronary blood flow determinations than left ventricular injections.10,33 Hence, we should be more likely to detect small differences between experimental groups.

Another important methodological consideration in studies dealing with coronary reserve is whether maximal coronary dilation was actually reached. Wangler et al.34 conducted a systematic study of the effects of various doses (2 to 8 mg/kg/min i.v.) of dipyridamole, another potent coronary vasodilator, in Wistar-Kyoto rats. Minimal left ventricular coronary resistance per unit mass after dipyridamole ranged from 0.07 to 0.10 mm Hg/ml/min/100 g, and the coronary bed was considered to have been maximally dilated because peak reactive hyperemia following transient coronary occlusion was abolished. In the present study, minimal left ventricular coronary resistance per gram was lower by 10 to 50% than that measured after dipyridamole either by Wangler et al.34 or by ourselves (unpublished observations, 1986). These comparative observations therefore suggest that carbochrome induced maximal or near maximal coronary dilation in this study.

The adequacy of swimming as a means of exercise conditioning is debated. Rats spent a notable fraction of time under water,15 an observation that has led some investigators to suggest that cardiovascular modifications following swimming may actually represent the effects of submergence, of a diving reflex, or of intermittent periods of hypoxia rather than of physical training alone.35 Others have also suggested that a psychological stress may be involved (see review in Reference 36). However, rats have a natural tendency to swim and can do so for many hours after a training period, as long as the water temperature is maintained near thermoneutrality.36 In addition, three lines of evidence indicate that exercise represents a major component of the cardiovascular changes seen in rats subjected to swimming. First, the oxygen consumption measured during swimming rises to 50 to 70% of the maximal oxygen consumption achieved in rats trained by running.37,38 The oxygen consumption of rats swimming in groups is likely to be even higher because of interaction between the animals.3 Second, studies by Scheuer and his group,2 as summarized in their recent review, have demonstrated that swimming conditioning results in changes in cardiac function or in the contractile machinery similar to those observed after running. Third, swimming is associated with a modest but significant increment in cardiac mass, as confirmed in our study. Although the development of cardiac hypertrophy alone cannot be regarded as a criterion on which to assess the adequacy of the exercise program, this finding and the previous considerations suggest that the program used in this study was adequate to cause a training effect. However, we cannot exclude the possibility that physical conditioning by another form of exercise, such as running, or a longer and more severe swimming program would have yielded different results.

In summary, this study indicates that a moderate swimming program initiated early before the onset of hypertension and the development of cardiac hypertrophy does not prevent the reduction in the coronary vasodilator reserve characteristic of hypertensive cardiac hypertrophy. Furthermore, chronic exercise superimposed on a hypertensive stimulus may cause a further depression in coronary vasodilator reserve. However, this abnormality was marginally significant and was not associated with any change in coronary flow reserve, suggesting that if physical training did not improve the coronary circulation abnormalities of hypertensive cardiac hypertrophy, it also did not lead to any deterioration in the potential for myocardial tissue oxygenation.

References
CORONARY RESERVE IN EXERCISED RENOVASCULAR HYPERTENSIVE RATS/Wicker et al. 81


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