Morphometry of Exercise-Induced Right Ventricular Hypertrophy in the Rat

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SUMMARY. In our morphometric study of the effects of exercise on the heart, male Wistar-Kyoto rats at 5 weeks of age were subjected daily to a moderate treadmill running program that lasted for 7 weeks. The heart responded to physical conditioning by different magnitudes of tissue growth of the right (22%) and left (7%) ventricular myocardium, the latter change not statistically significant. The increase in right ventricular volume was associated with a 25% enlargement of ventricular area, a 26% average lengthening of the myocytes, and no change in sarcomere length and in ventricular midwall thickness. Exercise produced significant alterations in the quantitative parameters of the microvasculature of the right ventricle, but no appreciable changes in the left ventricle. Right ventricular hypertrophy was characterized by an absolute 44% growth of the endothelial luminal surface brought about through a 16% increase in capillary numerical density, and a 41% augmentation of the total length of the capillary network. Maximum diffusion distance from the capillary wall to the mitochondria of myocytes decreased 10% as a result of capillary proliferation and the lack of lateral expansion of myocyte cross-sectional area. Evaluation of the subcellular constituents of myocytes showed no change in the mitochondria: myofibrils volume ratio, indicating a growth of these components proportional to each other and to the growth of the myocyte population as a whole. It was concluded that, as a result of running exercise, right ventricular growth is analogous to eccentric hypertrophy in which the structural adaptations of the capillary bed can be expected to improve the diffusion and transport of oxygen within the tissue. (Circ Res 52: 57–64, 1983)

NUMEROUS studies in recent years have been concerned with the ways that exercise may improve the performance and increase the reserve capacity of the cardiovascular system and the myocardium in particular (Clausen, 1977; Scheuer and Tipton, 1977). Beneficial effects of chronic exercise are evident in the enhanced ability of hearts from conditioned animals to withstand a variety of stresses (Scheuer and Stezosky, 1972; Dowell et al., 1976a; McElroy et al., 1978). This may be due to the fact that physical training has been found to be associated with a greater coronary blood flow potential (Spear et al., 1978), probably based on structural augmentation of the microcirculation in the myocardium (Bloor and Leon, 1970; Tomanek, 1970; Ljungqvist and Unge, 1972; McElroy et al., 1978).

There are three fundamental structural properties of the capillary network that are relevant to tissue oxygenation (Weibel, 1979; Hoppeler et al., 1981b), and may be involved in the compensatory adaptation of the myocardium during exercise: (1) capillary luminal volume density, which is related to the volume of capillary blood available for gas exchange within the tissue; (2) capillary luminal surface density, which represents the capillary area available for oxygen transport from the blood to the tissue; and (3) the average diffusion distance from the capillary wall to the mitochondria of myocytes, where oxygen is predominantly consumed in generating ATP through the process of oxidative phosphorylation.

Adaptation to exercise is specific for a given model of physical activity (Keul et al., 1981) and events requiring dynamic exercise and endurance training are accompanied by an increased preload of the heart (Keul et al., 1981), a functional condition that progresses into biventricular hypertrophy (Lin et al., 1977). However, it is yet to be demonstrated whether exercise-induced volume overload provokes a compensatory response of the heart of equal magnitude in both ventricles. The present study has been undertaken to assess the growth response of the left and right ventricular myocardium following a moderate exercise regime. The structural changes in the ventricles have been analyzed morphometrically by measuring the component structures implicated in tissue oxygenation, and the cytoplasmic structures of the myocytes responsible for oxygen consumption and ATP synthesis (i.e., the mitochondria) and for ATP utilization (i.e., the contractile proteins assembled in the myofibrils). The significance of evaluating these morphological parameters lies in the estimation of the tissue and cellular properties that should characterize the potential beneficial effect of exercise.

Methods

A total of 18 five-week-old male Wistar-Kyoto rats (Charles River, Breeding Labs) were obtained for this study. Nine animals weighing an average of 80 g were trained to run 1 hour/day, 5 days/week, at 13.4 m/min on a Quinton model 42-15 treadmill (Quinton Instruments Co.). The treadmill was maintained on a 7.5% slope. There was an initial training period of 10 days, during which the speed...
and duration of the exercise was progressively increased to this level. The total training period lasted for 7 weeks. Nine rats, used as controls, were placed daily for 10 minutes on the stationary treadmill in order to provide an equivalent amount of handling. All animals were killed at 12 weeks of age. Each rat was anesthetized with Nembutal (sodium pentobarbital, Abbott Laboratories, 3 mg/100 g of body weight, intraperitoneally) and the abdominal aorta cannulated with a catheter connected to a perfusion apparatus (Anversa et al., 1980). The heart was arrested in diastole by intravenous injection of KCl, the right atrium opened, and the myocardium perfused for 3 minutes with 0.1 M phosphate buffer (pH 7.2) containing 100 IU of heparin/ml. Subsequently, each heart was perfused for 15 minutes with a glutaraldehyde-paraformaldehyde mixture diluted 1:1 with phosphate buffer. All perfusions were done at a pressure of 80 mm Hg, approximately equal to the average diastolic pressure in adult anesthetized rats (Lais et al., 1977).

The heart was excised rapidly and the weights of the carefully dissected right ventricle and left ventricle, including the septum, determined. The mid-zone of the free wall of each ventricle was then sliced transversely into several thin arcs from which 15 blocks extending from the endocardial to epicardial surface were obtained. The blocks were fixed an additional 2-3 hours, washed overnight in buffer, postfixed in 1% OsO4, dehydrated with acetone, and embedded in Araldite, using flat embedding molds.

Five tissue blocks were chosen at random from each ventricle and sections, 0.5 μm thick, that included the entire thickness of the wall were cut, stained with a 1% aqueous solution of toluidine blue, and viewed with a microscope having an ocular micrometer accurate to 0.01 mm. Microscopic determinations of the thickness of the ventricular wall were made by measuring its width in four uniformly spaced sites along the length of each section.

A total of 72 tissue blocks with myofibers oriented transversely were examined by electron microscopy for the description of tissue, cellular, and subcellular composition: four from each of 18 rats, representing an equally distributed sampling of the subendocardial and subepicardial regions of left and right ventricular myocardium. Seven micrographs of randomly selected cross-sectional fields of myocardium were taken from each block at 1,800X and printed at 4,700X with a standard morphometric grid consisting of 130 sampling points and 13 line segments each 194 mm long (Anversa et al., 1978). An additional sampling of 10 random fields representative of myocyte cytoplasm were collected from each block and similarly examined at final magnification of 40,000X. Magnification calibrations were checked periodically with a diffraction grating replica (E.F. Fullam, Inc., Schenectady, New York).

Stereological measurements were made on both low and high magnification micrographs. The volume fraction of myocardial components was measured in 504 low power micrographs by counting the sampling points overlying myocytes, myocyte nuclei, and three compartments within the interstitium: capillary lumen, endothelial cells, and all other interstitial structures. The surface density of two membrane elements of the myocardium was evaluated by counting intersections of their profiles with the sampling line: myocyte cell surface (sarcolemma and intercalated disc only) and capillary luminal surface. The luminal surface area of endothelium was related to the myocytes to minimize possible variations of the interstitial space (Eisenberg et al., 1974; Hoppeler et al., 1981b). Finally, the number of profiles of myocytes and capillary lumina in the sampled areas of tissue cross-sections was collected. The number of profiles of myocytes and capillaries was determined following the criteria described by Gundersen (Gundersen, 1977), to measure their numerical densities, average cross-sectional areas, and lengths per unit volume. Mean sarcomere length in myofibrils was determined in each animal from 100 measurements made at a magnification of 15,000X in longitudinally oriented sections of left and right ventricular myocardium. Assuming a tissue density of 1.06 (Mendez and Keys, 1960), the volume of the right ventricular free wall was calculated from its measured weight. The absolute component volumes, surface areas, and lengths could then be evaluated from the product of the total ventricular myocardial volume and their respective values per unit volume.

Similar point counts were made in 720 higher power electron micrographs to determine the volume fraction of three cytoplasmic components within ventricular myocytes: myofibrils, mitochondria, and matrix. The matrix compartment included glycogen, ribosomes, lipid, Golgi apparatus, smooth endoplasmic reticulum, rough endoplasmic reticulum, and amorphous regions.

Standard morphometric relationships and compression correction factors, previously described in detail (Anversa et al., 1979), were used for surface area and number measurements. Wall thickness determinations were also corrected for the effect of compression artifact. The maximum diffusion distance for oxygen represented by the maximum distance from the capillary wall to the mitochondria of myocytes was calculated from the capillary profile density in transverse myocardial sections (Weibel, 1979; Hoppeler et al., 1981b). Since mitochondria are uniformly distributed in the interfibrillar compartment of the cell, this diffusion distance can be approximately measured by the radius of a cylinder of muscle tissue supplied by the average capillary, based on the Krogh's cylinder model for gas exchange in tissue (Weibel, 1979) minus the mean radius of the capillary.

Morphometric determinations presented in the tables show the mean ± SD computed from the average of measurements obtained from each rat. Significance levels for comparisons between different measurements have been evaluated using Student's t-test. Statistical significance in multiple comparisons among independent groups of data, in which analysis of variance and the F-test indicated the presence of significant differences, was determined by the Bonferroni method (Wallenstein et al., 1980). Values of P less than 0.05 were considered to be significant.

**Results**

Table 1 shows that the ratios of the weights of the heart, right ventricular free wall, and the left ventricle including the septum-to-body weight, increased 17%, 31%, and 13%, respectively, following the moderate exercise regime employed here. The mean weight of the heart and left ventricle did not change significantly, but the weight of the free wall of the right ventricle was found to be increased by 22%. However, no significant alteration in right ventricular wall thickness was observed despite the augmentation in tissue mass. Right ventricular wall volume, assuming a tissue density of 1.06, divided by mean wall thickness yields a measure of the mean area of the right ventricular free wall, shown last in Table 1. This calculation assumes that the ventricular wall may be treated as a thin sheet. The 25% increase in wall area implies a
TABLE 1
Gross Cardiac Changes following Moderate Exercise

<table>
<thead>
<tr>
<th>No. of rats</th>
<th>Sedentary rats</th>
<th>Exercised rats</th>
<th>% Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body wt (g)</td>
<td>259 ± 26</td>
<td>243 ± 24</td>
<td>−6</td>
</tr>
<tr>
<td>Heart wt (mg)</td>
<td>864 ± 88</td>
<td>950 ± 122</td>
<td>10</td>
</tr>
<tr>
<td>Right ventricle</td>
<td>185 ± 27</td>
<td>226 ± 44</td>
<td>22*</td>
</tr>
<tr>
<td>Left ventricle</td>
<td>679 ± 75</td>
<td>724 ± 101</td>
<td>7</td>
</tr>
<tr>
<td>Heart weight:body weight</td>
<td>3.35 ± 0.24</td>
<td>3.92 ± 0.43</td>
<td>17*</td>
</tr>
<tr>
<td>Right ventricular weight/body weight</td>
<td>0.717 ± 0.101</td>
<td>0.940 ± 0.207</td>
<td>31*</td>
</tr>
<tr>
<td>Left ventricular weight/body weight</td>
<td>2.63 ± 0.22</td>
<td>2.97 ± 0.28</td>
<td>13*</td>
</tr>
<tr>
<td>Wall thickness (μm)</td>
<td>790 ± 88</td>
<td>769 ± 104</td>
<td>−3</td>
</tr>
<tr>
<td>Right ventricle</td>
<td>2,280 ± 347</td>
<td>2,344 ± 439</td>
<td>3</td>
</tr>
<tr>
<td>Left ventricle</td>
<td>2,380 ± 347</td>
<td>2,220 ± 104</td>
<td></td>
</tr>
<tr>
<td>Mean area (mm²) of right ventricular free wall</td>
<td>222 ± 29</td>
<td>277 ± 38</td>
<td>25*</td>
</tr>
</tbody>
</table>

Results are expressed as mean ± SD. * Indicates a percent change that is statistically significant.

The larger chamber volume. The same calculation was not possible for the left ventricle since the weight of the free wall was not separately determined.

Morphometric data from low power electron micrographs are shown in Tables 2 and 3. Table 2 demonstrates that exercise produced practically no change in the volume percentage of the major components of the right and left ventricular myocardium. In addition, no significant difference was observed in the composition of the two ventricles in either the control or experimental groups. The data listed in the first column of Table 3 indicate that several differences exist between the structural properties of the capillary network of the right and left ventricular myocardium in sedentary rats. The mean area of capillary lumen was found to be significantly smaller (−23%) in the left ventricle. On the other hand, the 42% greater capillary density resulted in a 36% and a 41% higher capillary-to-myocyte ratio and luminal surface area per mm² of myocytes. Furthermore, the maximum distance from the capillary wall to the mitochondria of myocytes was 18% less in the left ventricle. Table 3 also shows that the exercise regime employed here yielded significant changes in the quantitative morphological parameters of the capillary bed of the right ventricle, whereas no appreciable difference was observed in the left ventricle.

Analysis of the results obtained in the right ventri-
cle demonstrates that exercise produced no effect on the luminal cross-sectional area of myocardial capillaries. The number of capillary profiles per mm² of tissue, on the other hand, increased 16%. The adaptation of the contractile component of the ventricle was evaluated by measuring the mean cross-sectional area of myocytes and their numerical density per unit area of myocardium, shown next in Table 3. These two morphometric parameters were found to be unchanged as a result of exercise, an observation that is consistent with the fact that wall thickness (Table 1) and the volume percentage of myocytes (Table 2) were almost identical in the right ventricle of both sedentary and exercised rats. A further consequence of the maintenance of myocyte density is the 14% increase of the numerical ratio of capillary-to-myocyte profiles in the experimental animals that agrees with the 16% greater number of capillaries per mm² of myocardial tissue. Such data demonstrate that capillary proliferation does occur during exercise, whereas there was no indication of either hyperplasia or loss of ventricular myocytes. The proliferation of myocardial capillaries with respect to myocytes produced a significant increase (17%) of the capillary luminal surface per unit volume of myocytes and an approximately identical increase of endothelial surface per myocyte cell surface, since the sarcolemmal area of myocytes remained constant in exercise. Finally, the average maximum distance from the capillary wall to the mitochondria of myocytes was smaller in conditioned animals (−10%) because of the greater concentration of capillaries and no change in myocyte cross-sectional area or diameter.

Comparison of the data listed in the second column of Table 3 indicates that an effect of exercise was to reduce some of the differences normally present between the two ventricles. However, capillary density, the ratio of capillary profiles to myocyte profiles, and capillary luminal surface per unit volume of myocytes were still 27, 20, and 16% greater in left ventricular myocardium.

The results in Tables 2 and 3 reflect only the effects of exercise on the structural characteristics of the myocardium on a per unit volume or per unit area basis. To obtain an overall view of the growth of the myocardium in the right ventricle, the total volume change of the ventricular free wall is shown at the top of Table 4 and is combined with the preceding morphometric data to summarize the overall growth adaptation that has occurred in the capillaries, myocytes, myocytes.
and interstitium during the 7-week period of physical conditioning. It is apparent, from the data listed in Table 4, that the absolute percent increase in capillary lumen, endothelium, myocytes, and other interstitial structures is essentially equal to the total volume gain of the ventricle. In contrast, overall capillary growth exceeded ventricular growth (22%) with respect to its luminal surface (44%), and length (41%). Absolute changes in myocyte length and surface were found to be 26% and 19%, respectively. Assuming no change in the total number of myocytes in the ventricle, the 26% increase in total length corresponds to a 26% increase in length and a 23% increase in volume of the average myocyte. This lengthening of the myocyte population occurred without alteration in mean sarcomere length.

Table 5 shows that the volume fraction of myofibrils, mitochondria, and matrix of myocyte cytoplasm in the right ventricle remained nearly identical in both animal groups. It can be concluded, therefore, that these subcellular organelles have grown in proportion to the myocyte population. Although no significant differences were found in comparing the subcellular constituents of left ventricular myocytes between sedentary and conditioned rats, the concentration of myofibrils was consistently greater (8%, P < 0.05) in the left ventricle than in the right ventricle.

**Discussion**

The results of the present study indicate that, following a moderate exercise regime, the heart responds by different magnitudes of tissue growth of the right and left ventricular myocardium: 22% and 7%, respectively. The change in mass of the left ventricle was not statistically significant. The differential growth rate between the ventricles was unexpected and surprising. It is well known, in fact, that endurance training results in an increased volume load of the heart (Keul et al., 1981), a condition in which an identical additional work demand is applied to both ventricles. When the primary stimulus is volume overload, however, the elevation in diastolic wall stress should be relatively greater per unit volume of tissue in the right ventricle because of its smaller total number of myocytes, less ventricular mass, and thinner wall. In contrast with the present findings in Wistar Kyoto rats, an approximately similar amount of hypertrophic growth in the right and left ventricular myocardium has been shown in albino rats subjected to the same kind of physical conditioning (Van Liere et al., 1965). On the other hand, both female and male Sprague-Dawley rats on a more moderate treadmill running program did not develop hypertrophy of either ventricle (Dowell et al., 1976a, 1976b). Strain

<table>
<thead>
<tr>
<th>Volume (mm$^3$):</th>
<th>Sedentary rats</th>
<th>Exercised rats</th>
<th>% Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ventricular wall</td>
<td>174 ± 25</td>
<td>213 ± 42</td>
<td>22*</td>
</tr>
<tr>
<td>Capillary lumen</td>
<td>14.47 ± 3.01</td>
<td>18.03 ± 4.39</td>
<td>25</td>
</tr>
<tr>
<td>Endothelium</td>
<td>4.34 ± 1.47</td>
<td>5.25 ± 1.34</td>
<td>21</td>
</tr>
<tr>
<td>Myocytes</td>
<td>142 ± 22</td>
<td>174 ± 37</td>
<td>22</td>
</tr>
<tr>
<td>Other interstitium</td>
<td>13.39 ± 3.18</td>
<td>16.04 ± 5.22</td>
<td>20</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Length (m)</th>
<th>Capillaries</th>
<th>Myocytes</th>
<th>Sarcomere length (μm)</th>
<th>Surface area (mm$^2$)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>484 ± 97</td>
<td>684 ± 147</td>
<td>1.898 ± 0.071</td>
<td>8,653 ± 1,935</td>
</tr>
<tr>
<td></td>
<td>722 ± 84</td>
<td>909 ± 186</td>
<td>1.897 ± 0.082</td>
<td>40,278 ± 7,968</td>
</tr>
</tbody>
</table>

Results are expressed as mean ± SD. * Indicates a percent change that is statistically significant.

**Table 5**

<table>
<thead>
<tr>
<th>Volume Composition of Myocyte Cytoplasm in Right and Left Ventricular Myocardium</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sedentary rats</td>
</tr>
<tr>
<td>----------------</td>
</tr>
<tr>
<td>Myofibrils RV</td>
</tr>
<tr>
<td>LV</td>
</tr>
<tr>
<td>Mitochondria RV</td>
</tr>
<tr>
<td>LV</td>
</tr>
<tr>
<td>Matrix RV</td>
</tr>
<tr>
<td>LV</td>
</tr>
</tbody>
</table>

Results are expressed as mean ± SD. The percent changes are not statistically significant.
density and capillary luminal surface are 42% and quantitatively distinct in the two ventricles. Capillary structural properties of the microvasculature of the heart are functionally relevant to tissue oxygenation. Thus these structural factors are implicated in the process of capillary proliferation, since myocyte hyperplasia should not take place at this age in the rat (Claycomb, 1975). On the other hand, the increase in absolute length of capillaries may reflect an overestimation of capillary proliferation because the mean length of a capillary unit in the myocardium of normal and conditioned rats is at present unknown. It is evident that compensatory lengthening of the microvasculature can occur by two mechanisms, namely, by increasing the number and/or length of individual capillaries. How these structural factors are implicated in the process of capillary proliferation remains to be determined. In contrast to rats subjected to an exercise regime, capillary proliferation does not occur in pressure overload hypertrophy of adult myocardium (Anversa et al., 1978, 1980). In this case, capillary-to-myocyte ratio and the total length of capillaries do not change significantly, implying that the number of capillaries in the myocardium stays essentially constant (Anversa et al., 1978, 1980).

The quantitative results presented in Table 2 on a per unit volume basis and in Table 4 in terms of absolute changes indicate that exercise-induced compensatory hypertrophy of the right ventricle produced little alteration in the volume percentage of capillary lumen in the myocardium resulting in a total increase of capillary luminal volume that is proportional to the

and sex differences, age of the animals at the beginning of training, type and duration of exercise, all are significant factors modulating the effects of exercise on the heart.

Increasing volume load in the adult heart induces eccentric hypertrophy which in ventricular chamber volume enlarges without a relative increase in its wall thickness (Lin et al., 1977). The observation in this study of a 22% ventricular growth without a significant change in wall thickness has resulted in a 25% expansion of the mean area of the right ventricular free wall, consistent with eccentric hypertrophic growth of the right ventricle in treadmill exercise. The increase in heart volume with dynamic training, which affects mainly its cavities (Dowell et al., 1976b; Ritzer et al., 1980), has been explained as an interrelated functional-anatomical adaptation necessary to maintain greater stroke volume and cardiac output (Gleeson and Baldwin, 1981; Keul et al., 1981) required during heavy exercise. Chamber enlargement appears to be brought about through lengthening of myocytes by replication of sarcomeres in series (Grossman et al., 1975), as strongly suggested by the average 26% increase in length of these cells with no change in their mean transverse cross-sectional area and mean sarcomere length. In contrast, when the primary stimulus is pressure overload, ventricular hypertrophy typically results in wall thickening proportional to the increase in mean cross-sectional diameter of the myocytes (Anversa et al., 1978, 1980) brought about by parallel replication of sarcomeres (Grossman et al., 1975) without a lengthening of the cells (Anversa et al., 1980).

As outlined in the introduction, measurements of capillary luminal volume density, capillary luminal surface density, and diffusion distance from the capillary wall to the mitochondria of myocytes were undertaken to determine the effectiveness of physical exercise programs on improving the principal structural variables of the microvasculature of the heart that are functionally relevant to tissue oxygenation (Weibel, 1979; Hoppeler et al., 1981b). During the hypertrophic growth of the right ventricle with treadmill exercise, myocardial capillaries exhibited a 17% increase in endothelial luminal surface per unit volume of myocytes, and a 10% decrease in the mean distance for oxygen diffusion, but no change was found in the relative volume of capillary lumen. The relative (17%) and absolute (44%) increases in capillary surface indicate that oxygen transport to the myocytes may be facilitated by the greater availability of endothelial luminal area. The reduction in maximum diffusion distance implies a smaller path length required for molecular transport to the cells.

The present investigation also demonstrates that the structural properties of the capillary network are quantitatively distinct in the two ventricles. Capillary density and capillary luminal surface are 42% and 41% greater in the left than in the right ventricle of sedentary rats. Moreover, an 18% smaller distance from the capillary wall to the mitochondria of myocytes was calculated in the left myocardium. The implication of these morphometric results is that the tissue parameters controlling oxygen distribution and consumption are intrinsically better in the left ventricle. This is consistent with the greater work load sustained by this ventricle in adult life and may possibly explain its capacity to withstand the additional work demand imposed by exercise without significant tissue growth.

The changes in the quantitative characteristics of the capillary bed in the right ventricular myocardium are the result of the greater concentration of capillary profiles per unit area of tissue. Such changes do not occur in the left ventricle, since its capillary numerical density was not affected by the relatively moderate exercise regime utilized here. On the other hand, there have been repeated reports (Bloor and Leon, 1970; Tomanek, 1970; Ljungqvist and Unge, 1972) of increased capillary density in the left ventricle following endurance training in rats. This apparent discrepancy with our data may be due to the fact that different strains of rats, older animals, and more severe exercise programs were employed in the studies mentioned above.

The morphometric results obtained in the right ventricle demonstrate increases in capillary density (16%), in capillary-to-myocyte ratio (14%) and in the total length of capillaries (41%), all indices that capillary proliferation does occur with exercise. However, none of these quantitative structural parameters describes the proliferation of capillaries in terms of an increase in the number of individual capillary units (Olivetti et al., 1980). The elevation of capillary-to-myocyte ratio can be considered a minimal index of capillary proliferation, since myocyte hyperplasia should not take place at this age in the rat. The changes in absolute length of capillaries may reflect an overestimation of capillary proliferation because the mean length of a capillary unit in the myocardium of normal and conditioned rats is at present unknown. It is evident that compensatory lengthening of the microvasculature can occur by two mechanisms, namely, by increasing the number and/or length of individual capillaries. How these structural factors are implicated in the process of capillary proliferation remains to be determined. In contrast to rats subjected to an exercise regime, capillary proliferation does not occur in pressure overload hypertrophy of adult myocardium (Anversa et al., 1978, 1980). In this case, capillary-to-myocyte ratio and the total length of capillaries do not change significantly, implying that the number of capillaries in the myocardium stays essentially constant (Anversa et al., 1978, 1980).

The quantitative results presented in Table 2 on a per unit volume basis and in Table 4 in terms of absolute changes indicate that exercise-induced compensatory hypertrophy of the right ventricle produced little alteration in the volume percentage of capillary lumen in the myocardium resulting in a total increase of capillary luminal volume that is proportional to the
growth of the right ventricular mass. These data are suggestive of a greater total coronary blood flow in the whole ventricle, whereas blood flow per unit mass of myocardium should remain constant. In this regard, it has been recently demonstrated that coronary blood flow per gram of tissue is not affected by a moderate exercise regime either during control states or under different stresses, like hypoxia and volume loading (Yipintsoi et al., 1980).

At the subcellular level, the composition of myocyte cytoplasm in the right ventricle is not modified by exercise hypertrophy and the volume fractions of mitochondria and myofibrils are approximately 33% and 50%, respectively. As a consequence, the mitochondria-to-myofibril volume ratio remains constant, indicating a growth of these components proportional to each other and to the cell volume as a whole. Since the enzyme system involved in the process of oxidative phosphorylation is associated with the inner mitochondrial membranes (Lehninger, 1975), the measurements of the surface density of mitochondrial cristae per unit volume of these organelles would provide a more direct estimate of the structure functionally related to the oxidative capacity of the mitochondria. It has been discussed recently that this morphometric measurement is affected by several systematic methodological errors that cannot be predicted with reasonable accuracy (Hoppeler et al., 1981a). However, available information indicated that the concentration of inner membranes in mitochondria of cardiac and skeletal muscle fibers is not significantly altered under a variety of stresses (Page and McCallister, 1973; Anversa et al., 1980; Hoppeler et al., 1981a). On this basis, the quantitative analysis of the volume density of mitochondria, as a measure of the oxidative capacity of muscle tissue, has been previously employed and justified (Hoppeler et al., 1981a). Therefore, the unchanged mitochondrial : myofibril volume ratio in myocytes following treadmill exercise demonstrates a well-balanced compensatory response of the component structures involved in energy production and energy utilization. Similar results have been reported in other experimental models of volume overload hypertrophy (Vitali-Mazza and Anversa, 1972). In contrast, progressive hypertrophy of heart muscle cells induced by pressure overload does not produce an increase in the volume of mitochondria commensurate with the increase in the amount of contractile substance (Page and McCallister, 1973; Anversa et al., 1978, 1980). Such a phenomenon may be highly significant in determining the energy supply of the hypertrophied myocytes and may be an important factor limiting the functional compensatory capacity of hypertrophied cardiac muscle cells.

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