Contrasting effect of exercise and angiotensin II hypertension on in vivo and in vitro cardiac angiogenesis in rats

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Cardiac vessel density (β-actin immunolabeling) and angiogenic capacity of coronary artery explants (culture in collagen gel) was determined in hypertrophied heart obtained by exercise training (10 wk) or ANG II infusion for 10 days. A group of rats received ANG II the last 10 days of training. The heart weight index was similarly elevated after exercise, and ANG II-hypertension compared with controls (3.16 ± 0.09 and 3.11 ± 0.11 vs. 2.68 ± 0.08 mg/g, respectively), whereas tail cuff pressure (TCP) increased only in sedentary rats infused with ANG II. Vessel density was increased by 36% in trained rats and reduced by 30% in ANG II-infused rats. The number of sprouts generated by coronary rings was reduced by 50% in ANG II-infused rats and increased by 50% in exercise trained rats compared with controls (35 ± 4 and 113 ± 5 vs. 71 ± 1 sprouts per ring, respectively). Exercise-training partly prevented the hypertensive effect of ANG II (TCP of 141 ± 5 mmHg), whereas heart weight index (3.66 ± 0.06 mg/g body wt) was not lowered. Myocardial vessel density was normalized, and sprouting from coronary rings increased by 50% in trained rats infused with ANG II compared with sedentary normotensive rats. Cardiac VEGF (Western blot analysis) was higher in hypertensive rats and not affected by exercise. Facing a similar increase in cardiac mass, intense training, but not ANG II hypertension, is accompanied by an increase in vascular density of the heart. The effect of training is unlikely related to changes in resting VEGF and may represent enhanced angiogenic capacity of the coronary vascular bed.

coronary artery; left ventricular vessel density; three-dimensional tissue culture; VEGF

Exercise-induced left ventricular hypertrophy corresponds to physiological growth of cardiomyocytes similar to that observed during fetal development (24). Chronic endurance training induces functional adaptation of coronary vessels including structural adaptation in size and number of blood vessels as well as modification in the systemic, neurohumoral, and local control of skeletal and myocardial vascular bed (1). By contrast, the chronic phase of arterial hypertension is associated with an increase in cardiac mass characterized by a marked capillary rarefaction particularly in endomyocardium (11, 26), which may, in turn, participate in the increase in vascular resistance and hypertension.

The hypothesis tested in the present study was that variations in cardiac capillary density in response to cardiac hypertrophy associated with repetitive exercise or hypertension is accompanied by changes in in vitro angiogenic capacity of vessels. In addition, influence of prior exercise training on angiogenesis response to ANG II hypertension was evaluated. Therefore, we investigated in vitro angiogenesis of aortic and coronary rings as well as vessel density of left ventricle isolated from sedentary or trained normotensive and hypertensive rats.

METHODS

The present animal experiments complied with European and French laws and conform to the Guide for the Care and Use of Laboratory Animals published by the NIH (No. 85-23, revised 1996). All experiments were carried out in accordance with the European Communities Council Directive (86/609/EEC) and approved by the local Animal Ethics Committee (Agreement of the French Ministry of Agriculture No. B-3417225).

Forty male, 6-wk-old Sprague-Dawley rats (Charles River) were divided into four groups of 10 animals each. Exercise-trained rats were subjected to an exercise-training program. This consisted of 30 min/day, 5 days/week. The intensity was progressively increased (12.5 m/min) for up to 60 min/day, 5 days/week. The intensity was progressively increased during the first 3 wk to achieve 30 m/min for 1 h/day during the seven following weeks as previously described (11, 12, 34).

The fourth group was selected from among the trained rats, and animals were infused with ANG II for the last 10 days of training. The training program is associated with cardiac hypertrophy as well as increase aerobic enzyme activity in locomotor muscles (1, 28).
Before (week 8) and at the end (week 10) the infusion of ANG II or its vehicle, tail cuff pressure (TCP; PE-300; Narco Biosystems) and in vivo myocardial function and morphology (echocardiography) were measured. Rats were anesthetized with ketamine-HCl (50–75 mg/kg) and xylazine (10–15 mg/kg ip) (25), and transthoracic echocardiography was performed using an echocardiograph HDI 3000 and 5–8 MHz transducer (ATL; Philips, Bothell, WA). Left ventricular dimensions, wall thickness, and cavity volume were obtained. Left ventricular mass was calculated using the formula: left ventricular mass = 1.04 × [(diastolic end diameter + diastolic anterior wall thickness + diastolic posterior wall thickness)\(^3\) − (diastolic end diameter)\(^3\)] (6).

**Hemodynamic measurements.** Two to three days after echocardiography measurements, rats were anesthetized (60 mg/kg pentobarbital sodium), and a catheter (PE50; Merck-Bristol) was inserted into the right carotid artery, and systemic blood pressures, pulse pressure, and heart rate were recorded for 10 min. Finally, the heart and kidneys were removed and weighed.

**Cardiac and vascular morphology.** In addition to echocardiographic measurements, heart weight, as well as left and right ventricle indexes, were calculated as tissue weight-to-body weight ratio. In all rats undergoing hemodynamic measurement, the left carotid artery was fixed in formalin (10\%) at a constant pressure of 120 mmHg and cross-sectional area (CSA; mm\(^2\)) was measured on Sirius Red-colored slices of 5-μm thickness.

The left ventricle was paraffin embedded, and 5-μm-thick sections were used for immunohistochemistry analysis. Identification of endothelial cells was performed using a monoclonal anti-β-actin [mouse IgG2a isotype, Clone AC-74, as reported previously (9)], and detected with a peroxidase-3-amin-9-ethyl carbazole (AEC) kit (DAKO, Carpinteria, CA). Capillaries were counted (×20 objective) on eight different microscopic fields per rat (4 animals/group), and vessel density was expressed as number of vessels per millimeter squared.

**Immunoblot.** VEGF protein in myocardium was determined by Western blot analysis as previously described (2). Samples (60–80 mg) of left ventricles were homogenized in buffer containing (in mM): 300 sucrose, 20 HEPES, 1 sodium azide, with 0.5 trypsin inhibitor U/sample, pH 7.4. Protein concentration was determined by Bradford assay and 15 μg of total proteins were then separated by electrophoresis on a 10% SDS-PAGE gel. A standardized amount of protein (15 μg) prepared from left ventricular extract was deposited on each gel to act as an internal standard for comparison across blots. The gels were transferred overnight to a nitrocellulose membrane (Hybond C-extra; Amersham) to detect the immunoreactive signal by chemiluminescence, and membranes were then exposed to X-ray film (hyperfilm ECL RPN 3103K; Amersham) to detect the immunoreactive signal by chemiluminescence, and membranes were then exposed to X-ray film (hyperfilm ECL RPN 3103K; Amersham) for 4 min. The relative VEGF expression was determined by the VEGF band intensity-to-internal standard band intensity ratio.

**Angiogenesis.** In all rats of the four groups, aorta and septal coronary arteries were removed and cut into 1-mm-long rings for the in vitro angiogenesis assay derived from Nicosia’s technique (22, 23, 32). At least 15 and 5 rings/rat were made from the aorta and coronary artery, respectively. Arterial rings were centered in the well of 24-well plates precoated with 0.5 ml of rat type-I collagen lattice (4). Wells were then filled with 0.5 ml of a fresh rat type-I collagen lattice and cultured for 12 days.

The culture medium was composed of a standard medium consisting of 1 part of Ham’s F-12 medium and 3 parts of DMEM, supplemented with 10% fetal calf serum, penicillin (100 IU/ml), streptomycin (100 μg/ml), and fungizone (0.25 μg/ml). To obtain a maximal growth (number of sprouts/string 74 ± 4, n = 12), epidermal growth factor (10 ng/ml), insulin (5 μg/ml), and endothelial cell growth supplement (15 mg/ml) were added to the medium. All reagents were purchased from Invitrogen (Breda, The Netherlands) except for epidermal growth factor, insulin, and endothelial cell growth supplement, which were obtained from Sigma.

To characterize the phenotype of cells forming the sprouts, three-dimensional cultures were fixed overnight with formalin 4\% (Accustain; Sigma), permeabilized with 0.1% Triton X-100 in PBS (Sigma). Cultures were exposed overnight at 4°C to a monoclonal antibody (7) that recognizes the rat endothelial cell antigen (RECA-1) (dilution 1:40; clone HIS52, ref. MCA970R; Serotec, Oxford, UK). Cultures were further processed for immunoperoxidase staining with ChemMate detection Kit (peroxidase/AEC, rabbit/mouse, model K5003; DAKO). The cells that formed the sprouts stained positive, showing red peroxidase deposits. Negative controls were realized by omission of the primary antibody.

Angiogenesis was quantified in a blind fashion as the number of capillary sprouts growing throughout the collagen lattice, using a TM300 microscope equipped with a digital imaging system (model DXM1200; Nikon).

For the culture medium we used, it was observed that capillary growth plateaued by day 8 or 9 and thus, the angiogenic capacity was determined on day 10.

**Statistical analysis.** Data (means ± SE) were analyzed by one-way ANOVA or two-way ANOVA for repeated measures when required. Between-group differences were determined using the Fisher’s protected least significant difference test for multiple comparisons. Within-group differences were determined with Student’s t-test for paired values. The level of significant difference was set for P < 0.05.

### Table 1. Final blood pressure and cardiac parameters in sedentary and trained rats infused or not with ANG II

<table>
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<th>Exercise-ANG II</th>
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<td>Tail cuff pressure, mmHg</td>
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<td>127 ± 2</td>
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<td>Systolic arterial pressure, mmHg</td>
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<td>134 ± 3</td>
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<td>30 ± 3</td>
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<td>Final body weight, g</td>
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<td>444 ± 15</td>
<td>456 ± 17</td>
<td>414 ± 13*†</td>
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<td>Heart weight, g</td>
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<td>1.44 ± 0.05*</td>
<td>1.51 ± 0.03*</td>
</tr>
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<td>LV weight, g</td>
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<td>1.03 ± 0.03*</td>
<td>1.03 ± 0.01*</td>
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<tr>
<td>LV mass, g</td>
<td>0.622 ± 0.024</td>
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<td>0.835 ± 0.011*</td>
<td>0.852 ± 0.011*</td>
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<td>LV anterior wall, cm</td>
<td>0.11 ± 0.01</td>
<td>0.13 ± 0.01*</td>
<td>0.15 ± 0.01*</td>
<td>0.14 ± 0.01*</td>
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<tr>
<td>LV posterior wall, cm</td>
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<td>0.15 ± 0.01*</td>
<td>0.15 ± 0.01*</td>
<td>0.15 ± 0.01*</td>
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<tr>
<td>LV end-diastolic diameter, cm</td>
<td>0.77 ± 0.01</td>
<td>0.82 ± 0.01*</td>
<td>0.81 ± 0.01*</td>
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<td>Relative LV wall thickness, %</td>
<td>33 ± 1</td>
<td>36 ± 1*</td>
<td>37 ± 1*</td>
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</table>

Values are means ± SE. LV, left ventricle. *P < 0.05 compared with vehicle-infused sedentary (control) group; †P < 0.05 compared with sedentary rats infused with ANG II.
with the control and hypertensive sedentary groups (336 lower in trained groups infused or not with ANG II compared respective controls (Table 1). Heart rate was significantly higher in rats infused with ANG II compared with their pulse pressure measured in anesthetized rats, was significantly with ANG II. Similarly, systolic arterial pressure, as well as significantly lower from that achieved in sedentary rats infused ANG II, TCP increased significantly and reached a final value in sedentary rats infused with ANG II. In trained rats receiving exercised and sedentary rats, whereas TCP markedly increased compared with sedentary hypertensive animals. Of note, left ventricle weight and left ventricular mass evaluated by echocardiography were both higher than in the sedentary control group in the three other groups. Relative wall thickness was higher in ANG II-infused rats and no significant difference was observed between sedentary and trained rats with ANG II hypertension (Table 1).

The CSA of the carotid artery was similar in control and trained rats. In rats infused with ANG II, media thickness, wall-to-lumen ratio, and CSA of the carotid artery were larger than in control and trained normotensive rats. ANG II infusion in trained rats was associated with a higher CSA and lumen diameter compared with sedentary hypertensive animals (Fig. 1, Table 2).

### RESULTS

#### Hemodynamic changes

No change in TCP was observed in exercised and sedentary rats, whereas TCP markedly increased in sedentary rats infused with ANG II. In trained rats receiving ANG II, TCP increased significantly and reached a final value significantly lower from that achieved in sedentary rats infused with ANG II. Similarly, systolic arterial pressure, as well as pulse pressure measured in anesthetized rats, was significantly higher in rats infused with ANG II compared with their respective controls (Table 1). Heart rate was significantly lower in trained groups infused or not with ANG II compared with the control and hypertensive sedentary groups (336 ± 11 and 298 ± 8 vs. 367 ± 10 and 351 ± 10 beats/min, respectively). On the opposite, cardiac output was significantly enhanced in vehicle- and ANG II-infused trained rats compared with their respective sedentary control rats (88 ± 4 and 87 ± 5 vs. 68 ± 3 and 64 ± 7 ml/min, respectively).

#### Cardiac and vascular morphometric changes

Heart weight (Table 1) and heart weight index (Fig. 1) were similarly and significantly higher in trained and sedentary hypertensive as well as trained hypertensive rats compared with sedentary normotensive animals. Of note, left ventricle weight and left ventricular mass evaluated by echocardiography were both higher than in the sedentary control group in the three other groups. Relative wall thickness was higher in ANG II-infused rats and no significant difference was observed between sedentary and trained rats with ANG II hypertension (Table 1).

The CSA of the carotid artery was similar in control and trained rats. In rats infused with ANG II, media thickness, wall-to-lumen ratio, and CSA of the carotid artery were larger than in control and trained normotensive rats. ANG II infusion in trained rats was associated with a higher CSA and lumen diameter compared with sedentary hypertensive animals (Fig. 1, Table 2).

#### Angiogenesis

As presented in Fig. 2, histologic evaluation with β-actin of left ventricular transverse sections revealed a significant increase (by 36%) in vessel density in trained rats compared with controls. Vessel density was 30% less than controls in ANG II-infused rats. By contrast, vascular density was comparable in trained rats infused with ANG II and sedentary control group. In vitro angiogenic capacity of aorta and coronary artery rings is presented in Fig. 3. As illustrated, tube organization following cell proliferation and migration was observed after 9 days of culture of control aortic onto collagen lattice (Fig. 3A). The tubes were positively stained with RECA-1 (Fig. 3B). Sprouting from aorta rings was not affected by training and was significantly and similarly reduced in rats with ANG II hypertension (80 ± 1, 91 ± 1, 55 ± 1, 63 ± 1 sprouts/ring in control, trained, ANG II-infused, and trained ANG II-infused rats, respectively). The number of capillary sprouts generated by coronary rings was also reduced in ANG II-infused rats. However, training was associated with a 50% increase in the sprouting of both normotensive and hypertensive rats (71 ± 1, 113 ± 5, 35 ± 4, and 70 ± 1 sprouts/ring in control, trained, ANG II-infused, and trained ANG II-infused rats, respectively).

As presented in Fig. 4, the relative VEGF band intensity was not affected in trained normotensive rats compared with control sedentary rats, (VEGF-to-internal standard band intensity ratio of 42 ± 8 vs. 52 ± 9%). Infusion of ANG II was associated with a similar increase of this ratio in sedentary and trained groups (81 ± 7 and 69 ± 8%, respectively).

### Morphological parameters of the carotid artery

<table>
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<th>Control</th>
<th>Exercise</th>
<th>ANG II</th>
<th>Exercise-ANG II</th>
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<tbody>
<tr>
<td>Cross-sectional area</td>
<td>0.097±0.004</td>
<td>0.096±0.004</td>
<td>0.133±0.005*</td>
<td>0.165±0.004*</td>
</tr>
<tr>
<td>Media thickness, μm</td>
<td>44±3</td>
<td>41±2</td>
<td>55±2*</td>
<td>51±3*</td>
</tr>
<tr>
<td>Lumen diameter, μm</td>
<td>829±11</td>
<td>926±13*</td>
<td>737±16</td>
<td>883±10*</td>
</tr>
<tr>
<td>Wall-to-lumen ratio</td>
<td>51±3</td>
<td>44±2</td>
<td>71±4*</td>
<td>71±4*</td>
</tr>
</tbody>
</table>

Values are means ± SE. The carotid artery was perfused fixed at the standard pressure of 120 mmHg. *P < 0.05 compared with vehicle-infused sedentary (control) group; †P < 0.05 compared with sedentary rats infused with ANG II.
DISCUSSION

The present results confirm that training is associated with an increase in angiogenesis of the coronary vascular bed, whereas capillarogenesis is reduced in sedentary rats infused with ANG II. Interestingly, training partly prevented the effect of ANG II mainly on the coronary vascular bed. In addition, it is demonstrated that in vitro angiogenic capacity of coronary vessel parallels changes in cardiac capillary density associated with cardiac hypertrophy of various origins.

According to several in vivo studies, chronic administration of ANG II was associated with an increased cardiac mass (3, 11, 18). To obtain a cardiac hypertrophy independently of arterial hypertension, rats were submitted to high-intensity endurance training. As expected, a similar increase in heart weight index was achieved in trained normotensive rats and in ANG II-infused rats. The cardiac hypertrophy was confirmed by echocardiography, and it was associated with an increase in arterial pressure only in ANG II-infused rats. In contrast, high-intensity endurance training had no influence on resting arterial pressure in the present study as previously reported in normotensive Wistar Kyoto and Sprague-Dawley rats (1, 34). Together with the development of cardiac hypertrophy, CSA of aorta increased in ANG II-infused rats but not in normotensive trained rats. As previously described in ANG II hypertension (10, 17, 18, 20), large vessel hypertrophy was accompanied by an increase in media thickness and a decrease in inner diameter. In addition, resting pulse pressure was higher in hypertensive rats, thus probably indicating an increase in both arterial resistance and stiffness (13).

Fig. 2. Vessel density of the left ventricle at the end of training protocol and ANG II infusion. Top: example of myocardial vessels with endothelium identified by monoclonal anti-β-actin and detected with peroxidase/AEC kit (bar = 100 μm). Bottom: left ventricular vessel density determined on 8 different microscopic fields per rat (4 animals per group), and expressed as number of vessels/mm². *P < 0.05 compared with control sedentary rats.
The main goal of the present study was to evaluate the changes in microcirculation especially in hypertrophied hearts using in vivo and in vitro approaches. In vivo, cardiac vessels were labeled with an antibody that specifically detected β-actin, a component of the cytoskeletal compartment of cardiac capillary endothelial cells not present in cardiac myocytes (9). In our study, myocardial vessel density was slightly reduced in sedentary hypertensive rats. Although it was not determined in the present study, the reduction in the density of cardiac vessels was probably due to a decrease in capillary density as previously reported in the hypertrophied myocardium of rats receiving ANG II (26). Whether the myocardial rarefaction was the consequence of pressor mechanisms, increased size of the left ventricle with preserved number of vessels or direct involvement of the peptide cannot be distinguished in the present experiments. Microvascular rarefaction is probably a late adaptive process that transfers functional mechanisms into structural alteration of a vascular bed (12, 16). On the opposite, training was associated with a marked increase in myocardial vessel density in normotensive rats as observed in trained Wistar Kyoto rats (1, 19). It is therefore suggested that exercise training promotes capillarogenesis in the heart as described in swine (33). These findings were confirmed by the determination of the angiogenic capacity of vascular rings determined using an in vitro angiogenesis assay derived from that previously described (23). When a vascular ring is cultured within a three-dimensional rat collagen type-I lattice, cells proliferate, migrate, and organize in tubes. Endothelial cells, as confirmed with the positive staining of the tubes by the specific rat endothelial cell antigen RECA-1, formed the vascular sprouts. The monoclonal antibody RECA-1 was reported to recognize a cell surface antigen localized along the endothelium lining of the vasculature (7). Aortic and coronary explants cultured in collagen gel generated microvascular outgrowths that grow in number and length until a plateau is reached by day 8 or 9 as previously reported, even under serum-free conditions (32). In our experimental conditions, the angiogenic capacity of aortic rings was not affected in trained animals and was reduced in rats with ANG II hypertension. The contrasting effect of exercise and hypertension was more clearly observed in the coronary vascular bed. Sprouting was similarly inhibited by ANG II hypertension in both vessels, whereas a marked and significant enhancement of sprouting by exercise was only observed in rings isolated from the coronary artery.

Together with the vessel density of the left ventricle, these findings are in favor of the effective and opposite role of training and ANG II hypertension on vascular growth in vivo and in vitro. The increase in angiogenic capacity after training was specific of the coronary vascular bed and very likely of skeletal muscle bed (1), thus suggesting a local regulation of capillarogenesis in working muscles. In contrast, angiogenic capacity was reduced by ANG II hypertension in the two vascular beds observed. It is suggested that inhibition of

Fig. 3. Light microscopy views of capillary outgrowth and angiogenic capacity of aortic and coronary artery rings. Top: capillary outgrowth of a control aortic ring after 9 days of culture into collagen lattice alone (A; bar = 200 μm), and the positive (B) and negative (C) staining of sprouts with the rat endothelial cell antigen (RECA-1) antibody (bars = 50 μm). Bottom: number of sprouts per vascular rings cultured into rat type-I collagen lattice after 9 days of culture. *P < 0.05 compared with the control sedentary group.
microvascular angiogenesis is a generalized phenomenon, even affecting the working heart and despite the increase in cardiac mass. In the sedentary rats infused with ANG II, sprouting capacity of the vascular rings may be affected by the increase in media thickness. If such an effect cannot be ruled out for the aorta, it probably did not apply to coronary rings where the sprouting was enhanced in trained rats with ANG II hypertension despite comparable changes in vessels morphology. The difference in angiogenic capacity is hardly related to VEGF since it was increased in the myocardium of rats infused with ANG II and not affected at the end of the training protocol. Of note, the present culture medium was not supplemented with exogenous VEGF. Yet, VEGF does not seem to have a major role in the beneficial effect of prior exercise training in ANG II hypertension. The concomitant blunting of hypertension, very likely through a reduction in peripheral vascular resistance, and the increase in inner diameter of the carotid artery without change in wall-to-lumen ratio suggest that repetitive activity even at high intensity improves vascular morphology and function, which in turn may have a beneficial effect of angiogenesis. A blood pressure reduction was also reported in spontaneously hypertensive rats (SHR) submitted to low- (1, 19, 29) but not high-intensity exercise training (30, 31). Reduction of arteriolar wall-to-lumen ratio with increased inner and outer diameters was reported in skeletal muscle and myocardium of SHR submitted to a moderate exercise training (19). Discrepancies with the present results may reflect differences in the rat strain, model of hypertension (primary or secondary), or the time when exercise training was commenced, prior to hypertension in the present study and in established hypertension in SHR (1, 19, 30). Of note, the same exercise training failed to reverse the decrement in myocardial capillary density in old SHR (30) but stimulated capillary growth in young SHR (5).

In conclusion, it is demonstrated that facing a similar cardiac hypertrophy, high-intensity exercise training and ANG II hypertension in Sprague-Dawley rats have the contrasting influence of myocardial capillarogenesis. In addition, prior exercise training appears to have a beneficial effect on arterial pressure and vascular morphology as well as on the myocardial angiogenesis, probably through enhanced angiogenic capacity of the coronary vascular bed.

**Perspectives and Significance**

In the present study, we demonstrated that exercise normalized cardiac capillary density in ANG II hypertension. Yet, ANG II and/or high blood pressure seems to exert an antangiogenic influence on cardiac vessels, even in exercise-trained rats. Therefore, it would be interesting to evaluate whether or not regular exercise training proposed in established ANG II hypertension can reverse cardiac rarefaction and protect the heart from additional damages of arterial hypertension. Besides constriction and remodeling of the vessel, cardiac capillary density through angiogenesis and rarefaction may represent another target of arterial hypertension damage. The reduction in capillary density observed in hypertension may impair oxygen supply to cardiomyocytes and reduce the coronary flow reserve during prolonged enhanced ventricular work. One could speculate on functional consequences of such changes in
cardiac morphology and vascular density and their deleterious (hypertension) or beneficial (exercise) effect on cardiac function during aging.

REFERENCES


