Exercise training improves femoral artery blood flow responses to endothelium-dependent dilators in hypercholesterolemic pigs

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Submitted 27 September 2005; accepted in final form 4 January 2006

Woodman, Christopher R., David Ingram, John Bonagura, and M. Harold Laughlin. Exercise training improves femoral artery blood flow responses to endothelium-dependent dilators in hypercholesterolemic pigs. Am J Physiol Heart Circ Physiol 290: H2362–H2368, 2006. First published January 6, 2006; doi:10.1152/ajpheart.01026.2005.—We tested two hypotheses: 1) that the effects of hypercholesterolemia on endothelial function in femoral arteries exceed those reported in brachial arteries and 2) that exercise (Ex) training enhances endothelium-dependent dilation and improves femoral artery blood flow (FABF) in hypercholesterolemic pigs. Adult male pigs were fed a normal fat (NF) or high-fat/cholesterol (HF) diet for 20 wk. Four weeks after the diet was initiated, pigs were Ex trained or remained sedentary (Sed) for 16 wk, thus yielding four groups: NF-Sed, NF-Ex, HF-Sed, and HF-Ex. Endothelium-dependent vasodilator responses were assessed in vivo by measuring changes in FABF after intraarterial injections of ADP and bradykinin (BK). Endothelium-dependent and -independent relaxation was assessed in vitro by measuring relaxation responses to BK and sodium nitroprusside (SNP). FABF increased in response to ADP and BK in all groups. FABF responses to ADP and BK were not impaired by HF but were improved by Ex in HF pigs. BK- and SNP-induced relaxation of femoral artery rings was not altered by HF or Ex. To determine whether the mechanism(s) for vasorelaxation of femoral arteries was altered by HF or Ex, BK-induced relaxation was assessed in vitro in the absence or presence of L5-nitro-l-arginine methyl ester [L-NAME; to inhibit nitric oxide synthase (NOS)], indomethacin (Indo; to inhibit cyclooxygenase), or Indo.BK-induced relaxation was inhibited by L-NAME and L-NAME + Indo in all groups of femoral arteries. Ex increased the NOS-dependent component of endothelium-dependent relaxation in NF (not HF) arteries. Indo did not inhibit BK-induced relaxation. Collectively, these results indicate that hypercholesterolemia does not alter endothelial function in femoral arteries and that Ex training improves FABF responses to ADP and BK; however, the improvement cannot be attributed to enhanced endothelial function in HF femoral arteries. These data suggest that Ex-induced improvements in FABF in HF arteries are mediated by vascular adaptations in arteries/arterioles downstream from the femoral artery.

endothelium-dependent dilation; nitric oxide; prostacyclin; endothelium-derived hyperpolarizing factor; Doppler ultrasonography

HYPERCHOLESTEROLEMIA IS ASSOCIATED with a decline in endothelial function in coronary and peripheral arteries (1–3, 7, 8, 17, 18, 27). Results from previous studies (24, 29–31) indicate that the primary effects of hypercholesterolemia, as well as the mechanisms accounting for endothelial dysfunction, are not uniformly expressed throughout the arterial tree. For example, previous studies (30, 31), using arteries from adult female pigs, revealed that hypercholesterolemia induces endothelial dysfunction in coronary and brachial arteries, whereas subsequent results from male pigs revealed endothelial dysfunction only in coronary arteries (24, 29). In addition, previously published results from our laboratory (25) indicate that consumption of a diet high in fat and cholesterol is associated with foam cell accumulation and increased intima-media thickness in porcine femoral arteries but not in brachial arteries.

In young healthy human subjects, femoral arteries exhibit blunted vasodilator responsiveness to endothelium-dependent dilators relative to brachial arteries (12), suggesting fundamental differences between femoral and brachial arteries. In addition, it is well established that conduit arteries of the legs are more prone to atherosclerosis than are brachial arteries of humans (20). If the distribution of atherosclerosis in the arterial tree is similar in pigs and humans, the effects of hypercholesterolemia on endothelial function in femoral arteries may be expected to exceed those reported in brachial arteries of male pigs (29). Given these observations, the purpose of the present study was to test the hypothesis that the effects of hypercholesterolemia on endothelial function in femoral arteries exceed those reported in brachial arteries (29).

Endurance exercise training improves endothelial function in some, but not all, vascular beds of healthy humans and animals (9–11, 13, 15, 21, 22, 26). In addition, exercise training attenuates or reverses the detrimental effects of hypercholesterolemia on endothelial function in porcine brachial arteries (29, 31). Given the differences between femoral and brachial arteries outlined above, it is conceivable that endothelial adaptations to exercise training in femoral arteries differ from those reported in brachial arteries (29). Therefore, an additional aim of this study was to test the hypothesis that endurance exercise training enhances endothelium-dependent vasodilator responses and improves femoral arterial blood flow in hypercholesterolemic adult male pigs. In addition, endothelium-dependent and -independent vasorelaxation of femoral arteries was examined in vitro.

METHODS

Experimental Animals

Before this study was initiated, approval was received from the Animal Care and Use Committee at the University of Missouri. The experimental animals were adult male Yucatan miniature swine (n = 32) that were purchased from a commercial breeder (Sinclair Research Farm, Columbia, MO). The pigs were 8–12 mo of age and weighed 25–40 kg. All of the pigs were housed in the animal care facility in the Department of Biomedical Sciences in a room maintained at 20–23°C with a 12-h:12-h light-dark cycle. Some of the pigs...
(n = 16) were provided a normal fat (NF) diet (Purina Lab Mini-pig Chow) in which 8% of daily caloric intake was derived from fat. The remaining pigs (n = 16) were provided a high-fat (HF) diet, consisting of pig chow supplemented with cholesterol (2.0%), coconut oil (17.1%), corn oil (2.3%), and sodium cholate (0.7%), such that 46% of daily caloric intake was derived from fat (4). Four weeks after the diet was initiated, pigs were exercise trained (Ex) or remained sedentary (Sed) for 16 wk. During this 16-wk time period, pigs continued to consume the HF or NF diet. The resulting experimental design consisted of four groups of pigs: 1) NF-Sed (n = 8), 2) NF-Ex (n = 8), 3) HF-Sed (n = 8), and 4) HF-Ex (n = 8). Plasma lipid and arterial function data from the pigs used in the present study have been reported elsewhere (23, 24, 29). The results indicated that the HF diet significantly elevated plasma levels of cholesterol, triglycerides, and LDL cholesterol (LDL-C) (23). In addition, endothelium-dependent relaxation was impaired in coronary arteries of HF-Sed pigs (24).

Training Program

All pigs were familiarized with running on a motorized treadmill and randomly assigned to Ex or Sed groups for 16 wk. The Ex group completed a 16-wk endurance training program as described previously (11, 23, 31). The training bouts were controlled such that the intensity of exercise was about 75% of maximal exercise capacity. Pigs assigned to the Sed group were restricted to their enclosures (2-4 m-pens) and did not exercise. The training program resulted in significant increases in run time to exhaustion, heart weight-to-body weight ratio, and citrate synthase activity measured in the deltoid muscle. These data have been published previously (23).

Duplex Doppler Studies of In Vivo Femoral Artery Blood Flow

At the end of the 16-wk training program, pigs were anesthetized, and femoral artery diameter and blood flow were measured by duplex Doppler ultrasonography using previously described methods (5). Pigs were sedated with an intramuscular injection of 35 mg/kg ketamine (Ketaset, Fort Dodge Animal Health) and 2.25 mg/kg xylazine (Rompun, Bayer). Isoflurane (4–5% in 100% oxygen) was delivered by face mask to allow endotracheal intubation. General anesthesia was maintained with 1–2% isoflurane in oxygen. Intravenous 0.9% NaCl solution at a rate of 10 ml·kg⁻¹·h⁻¹ was administered via an ear vein catheter during the study. Heart rate was monitored by electrocardiography using standard limb leads. The anesthetized pig was placed in dorsal recumbency. The hindlimbs were extended caudally and maintained in a fixed degree of extension throughout the study. The right femoral artery was accessed by surgical cutdown to allow placement of a 6-Fr catheter introducer sheath (Cook Veterinary Products). The tip of the catheter was advanced until it was located in the terminal aorta near the origin of the external iliac arteries. Position was verified by ultrasound identification of microbubbles in the left femoral artery after the injection of sterile saline solution into the catheter sheath. The catheter was secured and used for injection of drugs. The side port of the catheter introducer was attached to a pressure recording system (Marquette Systems, GE) to monitor arterial blood pressure.

Femoral artery blood flow velocity and vessel diameter were recorded immediately before and at least 2 min after injection of drugs into the terminal aorta. Blood flow measurements were made after injections of saline (baseline), xylazine (0.5 mg/kg), ADP (0.2, 1.0, 5.0, and 10 ng/kg), and bradykinin (BK; 0.0025, 0.005, and 0.01 μg/kg). All agents were administered in 1-ml injection volumes. Xylazine was used to preconstrict the arteries. ADP and BK were used to assess endothelium-dependent dilation. Injection of each drug was followed by immediate equi-volume flushes of sterile saline to clear any residual drug solution from the sheath. Intraarterial injections were evident as microbubbles traversing the femoral artery on the two-dimentional (2-D) image and by transient distortion of the Doppler velocity spectrum. Heart rate and arterial blood pressure were allowed to stabilize between injections of different drugs or drug concentrations.

Blood flow in the left femoral artery was measured noninvasively using clinical 2-D and Doppler ultrasonographic methods (Duplex Doppler) as described previously (5). A commercial ultrasound imaging system (Asonics Impact, Universal Medical Systems, Bedford Hills, NY), equipped with a duplex linear array transducer, was used at an operating frequency of 10 MHz and recording depth of 2 cm. The handheld transducer was coupled to the skin using ultrasonic coupling gel. The transducer was oriented parallel to the common femoral artery and angled to allow imaging of the femoral artery and the more distal saphenous branch. Special care was taken to ensure that the probe position was stable and consistent throughout the study and that the artery was not compressed by external manual pressure.

The pulsed-wave Doppler mode was activated by using a lateral crystal in the transducer array, and a 1-mm sample volume was steered to the center of the vessel. This sample volume was chosen because it allowed precise placement within the lumen, and previous pilot studies in our laboratory had indicated that a larger sample volume (one filling the vessel lumen) did not produce different velocity results in pigs. The sample volume was centered ~1 cm cranial to the origin of the saphenous branch of the femoral artery. This position was chosen to provide a repeatable and standardized location and to minimize turbulence from flow into branch vessels. Two-dimensional images of the femoral artery and Doppler spectra were recorded at 100 mm/s and recorded on S-VHS videotape for subsequent off-line analysis.

Internal femoral artery diameter was measured in three individual, 2-D image frames immediately after the maximal peak effect of every drug. Within each 2-D frame, the diameter was measured in the center of the sample volume. These measurements were then averaged to estimate femoral artery diameter (d) across the cardiac cycle. Cross-sectional area (CSA) of the femoral artery was calculated as follows: CSA = π(d/2)². Three cardiac cycles were measured and averaged to obtain the instantaneous maximal peak velocity, mean velocity, and flow velocity integral (FVI). To eliminate the effect of heart rate differences between pigs, femoral arterial blood flow per cardiac cycle was calculated by the formula: Flow/cardiac cycle (in cm³) = CSA (in cm²) × FVI (in cm). Femoral artery diameter and blood flow measures were successfully obtained on 25 of the 32 pigs, distributed among the four groups as follows: NF-Sed (n = 5), NF-Ex (n = 8), HF-Sed (n = 6), and HF-Ex (n = 6) pigs.

In Vitro Assessment of Vasorelaxation

Vascular ring preparation. Segments of the femoral artery were removed and trimmed of connective tissue and fat. Vessel segments were taken from the same sites in all pigs. A Filar-calibrated micrometer eyepiece was used to measure axial length, inside diameter (ID), and outside diameter (OD) of each femoral ring. Vasomotor reactivity was examined with the rings stretched to the length that produced maximal active tension (Lmax), as described previously (30, 31).

Relaxation responses of arterial rings. Procedures used to assess vasoactive responses of femoral artery rings have been published previously in detail (31). Before dose-response curves were initiated, all arterial rings were preconstricted with PGE₁ (30 μM). Endothelium-dependent vasorelaxation was assessed by using BK (10⁻¹¹, 10⁻⁸ M). Endothelium-independent relaxation was assessed with sodium nitroprusside (SNP; 10⁻¹⁰, 10⁻⁴ M). A total of four femoral rings were studied in parallel from each pig. In arterial ring 1, vasorelaxation to agonist alone was measured by adding cumulatively increasing doses of the selected drug to the organ bath while measuring changes in force. In arterial ring 2, the role of nitric oxide (NO) in vasoactive responses was assessed in the presence of N²-nitro-L-
arginine methyl ester (l-NAME; 300 μM) to block NO synthase (NOS). In arterial ring 3, the importance of prostacyclin (PGI2) in vasoactive responses was assessed in the presence of indomethacin (Indo; 5 μM) to block cyclooxygenase (COX). In arterial ring 4, double blockade with l-NAME + Indo was used to assess the importance of NOS- and COX-independent mechanisms of relaxation. The experimental protocol was designed such that BK was always the first agonist administered, followed by SNP. At the end of each dose-response protocol, bicarbonate buffer solution was replaced to wash out the drug, and the arterial segments were allowed 1 h to stabilize before initiation of the next protocol.

**Solutions and Drugs**

Krebs bicarbonate buffer solution contained (in mM) 131.5 NaCl, 5.0 KCl, 1.2 NaH2PO4, 1.2 MgCl2, 2.5 CaCl2, 11.2 glucose, 20.8 NaHCO3, 0.003 propranolol, and 0.025 EDTA. Solutions were aerated with 95% O2-5% CO2 (pH 7.4) and maintained at 37°C. All drugs and chemicals were purchased from Sigma Chemical.

**Statistical Analysis**

All values are means ± SE. Between-group differences in femoral artery ring characteristics were determined by using one-way ANOVA. Concentration-response curves were analyzed by two-way ANOVA with repeated measures on one factor (dose). When a significant F value was obtained, post hoc analyses were performed using Tukey-Kramer’s multiple comparison test. Statistical significance was set at the P ≤ 0.05 probability level.

**RESULTS**

**In Vivo Vasodilator Responses**

Femoral artery blood flow before drug injections (baseline) was not significantly different in NF-Sed, NF-Ex, HF-Sed, and HF-Ex pigs (Fig. 1). Femoral artery blood flow increased in response to ADP and BK in all groups (Fig. 1). The increase in blood flow induced by ADP and BK was not significantly blunted in HF pigs (Fig. 1); however, blood flow responses were improved by exercise training in HF arteries, such that femoral artery blood flow per cardiac cycle was significantly greater in HF-Ex than in HF-Sed and NF-Sed pigs (Fig. 1). No significant increase in femoral artery diameter could be identified across the four treatment groups (P = 0.996) or between different dosages of vasodilating drugs (P = 0.534; data not shown). Furthermore, the percent change in vessel diameter before and after injection of vasodilating drugs was never >1.2% for any treatment group for any level of drug treatment.

**Vascular ring characteristics.** Femoral artery ring characteristics are presented in Table 1. One-way ANOVA revealed that OD, ID, wall thickness, and axial length were similar in all groups of femoral arteries.

**BK responses.** BK elicited a concentration-dependent relaxation of femoral artery rings from all groups of pigs (Fig. 2). Relaxation to BK was not impaired by the HF diet or improved by exercise training. BK-induced relaxation was inhibited by l-NAME in all groups of arteries (Fig. 3). In the presence of l-NAME, BK-induced relaxation was significantly greater in NF-Sed than in NF-Ex arteries (Fig. 3A), whereas BK-induced relaxation in the presence of l-NAME was similar in HF-Sed and HF-Ex arteries (Fig. 3B). Indo did not significantly alter BK-induced relaxation in any group of arteries (Fig. 4). In the absence of l-NAME + Indo, BK-induced relaxation was inhibited (not abolished) in all groups of arteries (Fig. 5). Importantly, BK-induced relaxation in the presence of l-NAME + Indo was similar in all groups of arteries (Fig. 5C). Thus, endothelium-derived hyperpolarizing factor (EDHF) appears to mediate a major component of BK-induced relaxation in NF and HF arteries.

**SNP Responses**

SNP elicited a concentration-dependent relaxation in femoral artery rings from all groups of pigs (Fig. 6). Direct smooth muscle relaxation induced by SNP was similar in NF-Sed, NF-Ex, HF-Sed, and HF-Ex arteries.

**DISCUSSION**

The purpose of this study was to test the hypothesis that the effects of hypercholesterolemia on endothelial function in femoral arteries exceed those reported in brachial arteries. In addition, we tested the hypothesis that endurance exercise training enhances endothelium-dependent dilation and improves femoral artery blood flow in hypercholesterolemic pigs. The primary findings of the study were as follows. First, femoral artery blood flow at rest was not significantly different in NF and HF pigs. Second, femoral artery blood flow increased in response to intra-arterial injections of ADP and BK in NF and HF pigs. Third, the increase in blood flow in response to ADP and BK was improved by exercise in HF pigs, such that blood flow/cardiac cycle was significantly greater in HF-Ex than in HF-Sed pigs. Significantly different from *NF-Sed and #HF-Sed (P ≤ 0.05).

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![Graph](https://via.placeholder.com/150)  
**Fig. 1.** Femoral artery blood flow responses to intra-arterial injections of ADP and bradykinin (BK). Blood flow was measured with Duplex Doppler Ultrasound. Values are means ± SE; n = 5–8 pigs/group. NF, normal fat; HF, high fat; Sed, sedentary; Ex, exercise trained; Xyl, xylazine. Two-way repeated measures ANOVA revealed a significant main effect of drug infusion, indicating that femoral artery blood flow increased in response to ADP and BK. Exercise training improved blood flow response to ADP and BK in HF pigs, such that femoral artery blood flow per cardiac cycle was significantly greater in HF-Ex than in HF-Sed pigs. Significantly different from *NF-Sed and #HF-Sed (P ≤ 0.05).
Finally, in the presence of L-NAME or L-NAME + Indo, BK-induced relaxation was inhibited in NF and HF arteries, whereas Indo alone did not inhibit BK-induced relaxation in arteries of any group. Collectively, these results indicate that exercise training improves femoral artery blood flow responses to ADP and BK in HF male pigs; however, the improvement in femoral artery blood flow is not the result of enhanced endothelial function in the common femoral artery, because BK-induced relaxation of femoral artery rings was not altered by the HF diet or exercise training.

Influence of Hypercholesterolemia and Exercise on Endothelium-Dependent Relaxation

Hypercholesterolemia-induced endothelial dysfunction has been reported previously in coronary and brachial arteries of adult pigs (24, 30, 31). In addition, endurance exercise training improves endothelial function in coronary and brachial arteries from hypercholesterolemic adult pigs (24, 29–31). Results of the present study reveal that femoral artery blood flow increased in response to intra-arterial injections of ADP and BK in all groups of pigs (Fig. 1). Although femoral artery blood flow per cardiac cycle tended to be lower in HF-Sed than in NF-Sed arteries across all drug treatments (Fig. 1), the difference was not statistically significant. Thus these results indicate that hypercholesterolemia does not impair endothelium-dependent vasodilation in femoral arteries in adult male pigs. Previous results from the hypercholesterolemic male pigs

Table 1. Characteristics of femoral arteries

<table>
<thead>
<tr>
<th>Variable</th>
<th>NF-Sed</th>
<th>NF-Ex</th>
<th>HF-Sed</th>
<th>HF-Ex</th>
</tr>
</thead>
<tbody>
<tr>
<td>Outer diameter, mm</td>
<td>3.25±0.08</td>
<td>3.49±0.13</td>
<td>3.39±0.15</td>
<td>3.44±0.14</td>
</tr>
<tr>
<td>Inner diameter, mm</td>
<td>2.17±0.09</td>
<td>2.38±0.10</td>
<td>2.15±0.17</td>
<td>2.30±0.13</td>
</tr>
<tr>
<td>Wall thickness, mm</td>
<td>0.54±0.01</td>
<td>0.56±0.03</td>
<td>0.62±0.03</td>
<td>0.57±0.02</td>
</tr>
<tr>
<td>Axial length, mm</td>
<td>3.55±0.39</td>
<td>3.82±0.27</td>
<td>3.66±0.29</td>
<td>3.73±0.21</td>
</tr>
</tbody>
</table>

Values are means ± SE; n, number of pigs. All data were analyzed by one-way ANOVA. NF, normal fat; Ex, exercise trained; HF, high fat; Sed, sedentary. ANOVA revealed no significant between-group differences.

Fig. 2. BK-induced relaxation in femoral artery rings. Values are means ± SE; n = 6–7 pigs/group. Percent relaxation was calculated as percent reduction in force from prostaglandin F\(_2\alpha\) (30 \(\mu\)m)-induced tension. ANOVA revealed no significant between-group differences.

Fig. 3. BK-induced relaxation in femoral artery rings in the absence or presence of \(N^\alpha\)-nitro-L-arginine methyl ester (L-NAME; 0.3 mM) to inhibit nitric oxide synthase. A: NF pigs. B: HF pigs. C: all groups. Values are means ± SE; n = 6–7 pigs/group. Percent relaxation was calculated as percent reduction in force from prostaglandin F\(_2\alpha\) (30 \(\mu\)m)-induced tension. Significantly different from 1NF-Sed, 2NF-Ex, 3NF-Sed + L-NAME, 5HF-Sed, and 6HF-Ex (P ≤ 0.05).
used in the present study also revealed preserved endothelial function in brachial arteries (29), whereas endothelium-dependent relaxation in coronary arteries was impaired (24). Thus the effects of hypercholesterolemia on vascular function are not uniform in all vascular beds of male pigs.

In accord with our hypothesis, blood flow responses to intra-arterial injections of ADP and BK were significantly improved by Ex in HF femoral arteries, such that blood flow was significantly greater in HF-Ex than in HF-Sed pigs (Fig. 1). Thus endurance exercise training improved blood flow responses in the femoral vascular bed despite the lack of HF-induced endothelial dysfunction. Exercise also tended to improve blood flow in the NF pigs compared with their Sed controls (Fig. 1).

Based on results indicating that exercise training enhanced blood flow responses to ADP and BK (Fig. 1), it could be argued that exercise training induces vascular adaptations resulting in enhanced endothelial cell function in HF femoral arteries. It is important to note, however, that femoral artery diameters were not different among groups under basal conditions or during injections of ADP and BK.
Importantly, BK-induced relaxation in the presence of L-NAME was greater in Sed (27%) than in Ex (47%) arteries (Fig. 3). ANOVA revealed no significant between-group differences.

unweighting are associated with impaired vasodilation, and chronic reductions in physical activity induced by hindlimb unweighting are associated with impaired vasodilation, and previous that exercise training enhances endothelium-dependent dilation of arterioles perfusing soleus and gastrocnemius muscles of young adult rats. Conversely, dent vasodilator responses in arterioles perfusing soleus and HF-Ex arteries. Thus exercise training enhanced the role of NO in arterioles downstream from the femoral artery. Indeed, previous studies indicate that the level of muscle function, SNP-induced relaxation should have been greater in femoral arteries from Ex pigs.

It is unlikely that exercise training improved femoral artery blood flow via enhanced vascular smooth responsiveness, because SNP-induced relaxation of femoral artery rings in vitro was not altered by exercise (Fig. 2).

To determine whether the relative contributions of known endothelium-derived vasodilator substances were altered by exercise training in HF femoral arteries, BK-induced relaxation was assessed in the absence or presence of L-NAME, Indo, and L-NAME + Indo. Results revealed that in HF arteries, BK-induced relaxation was inhibited (not abolished) in the presence of L-NAME and L-NAME + Indo (Figs. 3 and 5). Importantly, in the presence of these inhibitors, BK-induced relaxation was similar in HF-Sed and HF-Ex arteries. Thus, whereas NO and EDHF appear to be the major mediators of BK-induced relaxation in HF femoral arteries, the relative roles of NO and EDHF were not altered by the HF diet or exercise training. In HF arteries, L-NAME produced less inhibition of BK-induced relaxation in Sed (27%) than in Ex (47%) arteries (Fig. 3).

Importantly, BK-induced relaxation in the presence of L-NAME was significantly greater in HF-Sed than in HF-Ex arteries. Thus exercise training enhanced the role of NO in BK-induced relaxation of NF (not HF) femoral arteries (Fig. 3).

It is unlikely that exercise training improved femoral artery blood flow via enhanced vascular smooth responsiveness, because SNP-induced relaxation of femoral artery rings was not enhanced by exercise training (Fig. 6). SNP is a NO donor that acts directly on vascular smooth muscle to cause vasorelaxation. Thus, if exercise training had enhanced vascular smooth muscle function, SNP-induced relaxation should have been greater in femoral arteries from Ex pigs.

It is possible that enhanced blood flow responses were due, in part, to enhanced vasodilator responses and/or the size and number of arteries/arterioles downstream from the femoral artery. Indeed, previous studies indicate that the level of physical activity can influence endothelial function in skeletal muscle arterioles. For example, Spier et al. (19) reported previously that exercise training enhances endothelium-dependent vasodilator responses in arterioles perfusing soleus and gastrocnemius muscles of young adult rats. Conversely, chronic reductions in physical activity induced by hindlimb unweighting are associated with impaired vasodilation, and blunted blood flow responses, to endothelium-dependent agonists (6, 16, 28).

In the coronary arterial tree of pigs, Muller et al. (11) reported that exercise improved endothelium-dependent dilation of arterioles, whereas Oltman et al. (14) reported no effect of exercise on endothelium-dependent relaxation of conduit coronary arteries. In the present study, it is conceivable that a similar pattern of adaptation occurred in the femoral vascular tree because it appears that exercise increased endothelial function in the small resistance arteries of the HF pigs, but no change was observed in the conduit femoral artery. Future work is required to test this hypothesis.

Study Limitations

In the present study, no statistically significant changes in femoral artery diameter were detected after injections of ADP and BK. It is important to note that pigs were sedated with ketamine and anesthetized with isoflurane during measurement of femoral artery blood flow and common femoral artery diameters. As a result, it is possible that the anesthetics influenced vasomotor tone and caused us to find no statistically significant changes in common femoral artery diameter during infusion of ADP and/or BK during our experiments. Indeed, BK and ADP may have produced significant increases in artery diameter if measurements had been made in conscious animals. Anesthetics may also have influenced our measures of the ability of BK and ADP to increase blood flow. We previously observed that pretreatment with vasoconstrictor agents, such as xylazine (an α2 agonist), improved resolution of the vasodilator actions of BK (5).

In conclusion, we tested the hypothesis that exercise training enhances endothelium-dependent vasodilation and improves femoral artery blood flow responses in hypercholesterolemic male pigs. Results of this study indicate that endurance exercise training improves femoral artery blood flow responses to intra-arterial injections of ADP and BK; however, the improvement in femoral artery blood flow does not appear to be the result of enhanced endothelial function in common femoral arteries, because ADP- and BK-induced relaxation of femoral artery rings in vitro was not improved by exercise. In addition, present results indicate that hypercholesterolemia and exercise have similar effects on vasomotor responses of femoral arteries and brachial arteries (31) in pigs. Further study is needed to determine whether exercise-induced improvements in femoral artery blood flow in response to ADP and BK are mediated by enhanced endothelium-dependent dilation of arteries/arterioles downstream from the femoral artery and/or increased number and size of arteries/arterioles downstream of the common femoral artery.

ACKNOWLEDGMENTS

The authors gratefully acknowledge the expert technical assistance of Pam Thorne, Denise Holiman, Daniel Hatfield, and Tammy Strawn. Present address of C. R. Woodman: Dept. of Health and Kinesiology, Texas A&M Univ., College Station, TX 77843-4243.

GRANTS

This work was supported by National Heart, Lung, and Blood Institute Grants HL-52490 and HL-36088 (to M. H. Laughlin) and National Institute on Aging Grant AG-00988 (to C. R. Woodman).
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AJP-Heart Circ Physiol • VOL 290 • JUNE 2006 • www.ajpheart.org