Chronic exercise training does not alter pulmonary vasorelaxation in normal pigs

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Exercise training. Mature, female Yucatan miniature swine were divided into sedentary (Sed) and exercise trained (Ex) groups. Exercise trained pigs were acclimated to a low-speed motorized treadmill (Quinton) and performed an exercise training protocol of progressive intensity adapted from a treadmill training program formulated by Tipton et al. (20) for use in dogs. During the first week of training, swine ran on the treadmill at 3 miles/h (mph), 0% grade, for 20–30 min, followed by a 15-min sprint at 5 mph. Length of training and treadmill speed were increased over 15 wk in accordance with the tolerance of individual pigs. From the fourth week of training, pigs exercised for 85 min, with a 5-min warm-up at 2.5 mph, a 15-min sprint at 5–8 mph, a 60-min endurance run at 4–5 mph, and a 5-min cooldown run at 2 mph. Sed pigs were caged over the same time period to serve as controls. All animal relaxation was theorized to represent a favorable adaptation to exercise training that might improve gas exchange and cardiac efficiency. However, pulmonary artery diameters have not been measured during exercise, and, therefore, the impact of these hemodynamic changes on shear stress in the pulmonary circulation is unknown. Chronically increased pulmonary blood flow in the absence of pulmonary hypertension resulted in impaired endothelium-dependent (ACH-induced) and endothelium-independent [sodium nitroprusside (SNP)-induced] vasorelaxation in pulmonary arteries of adult dogs with arteriovenous shunts (5). Chen and Li (3) reported enhanced ACH-induced relaxation in pulmonary arteries of exercise-trained rabbits, although Mitali et al. (11) found that exercise-trained rats did not exhibit changes in vasomotor responsiveness of pulmonary arteries after chronic training.

Our laboratory has previously observed that pigs with experimentally induced coronary occlusion exhibit enhanced relaxation to ACH in conduit-sized pulmonary vessels from a single site within the pulmonary circulation after chronic exercise training (8). This augmentation of relaxation was mediated by changes in at least two signaling pathways within endothelial cells (8). The purpose of this study was to test the hypothesis that exercise training increases endothelium-dependent vasomotor responses in healthy pigs. We used inhibition of ecNOS to investigate the role of nitric oxide in pulmonary responses to exercise and inhibition of cyclooxygenase (COX) to examine the role of prostaglandin metabolites. Contrary to the findings in pulmonary arteries from pigs with experimentally induced coronary occlusion, healthy exercise-trained pigs exhibited no change in pulmonary vasorelaxation.

METHODS
protocols were approved by the Animal Care and Use Committee of the University of Missouri.

The efficacy of training was assessed by comparing heart-to-body weight ratios and skeletal muscle oxidative capacity of Sed and Ex pigs (8, 9, 12, 21). Muscle samples were taken from the triceps brachii and deltoid, frozen in liquid nitrogen, and stored at −70°C until processed for citrate synthase activity as described by Srere (19). Spectrophotometric analysis confirmed increased muscle citrate synthase activity in Ex pigs.

Isolation and preparation of pulmonary arteries. Pigs were sedated with ketamine (25 mg/kg im) and xylazine (2 mg/kg im), anesthetized with thiopental sodium (30 mg/kg iv), and administered heparin (2,000 U/kg iv). The heart was removed by transection of the great vessels, and lungs were immediately placed in ice-cold K rebs solution containing (in mM) 131.5 NaCl, 5.0 KCl, 1.2 MgCl₂·6H₂O, 2.5 CaCl₂·2H₂O, 1.2 NaH₂PO₄·H₂O, 11.2 glucose, and 20.8 NaHCO₃ for vessel isolation.

Pulmonary arteries (2- to 3-mm OD) were located by their position medial to the bronchi. The lobar pulmonary artery to the right caudal lung lobe was identified, and the first ventrally oriented artery was carefully isolated and deamed of surrounding adventitial tissue. Pulmonary arteries were cut into four ring segments, each 2–3 mm in length. Vessel area was calculated from internal and outer diameter and ring length, recorded in millimeters for each vascular ring.

Pulmonary artery rings were mounted between two stainless steel wires connected to a force transducer (ETH-200/400 series, CB Science, Dover, NH) to measure developed tension and to a micrometer micrometric allowing stretch of the vessel by known increments. Vessel rings were stretched to a passive tension of 1.0 g for 1 h in individual 20-ml baths containing Krebs solution equilibrated at 37°C and continuously bubbled with 95% O₂-5% CO₂. Krebs solution contained propranolol (3 x 10⁻⁶ M) to oppose β₂-adrenergic-receptor-mediated vasorelaxation. Isometric tension (in g) was continuously recorded by a computer acquisition system (MacLab, CB Sciences, Milford, MA). Individual length-tension curves were generated for each arterial ring to determine optimal ring length. Vessels were progressively stretched by 10% of the outer diameter and exposed to 30 mM KCl for successive tension determinations. The optimal length for a given artery (L_max) was defined as the length at which contractile force evoked by KCl failed to increase by >10% of the previous measurement. Vessels were stabilized at L_max for 30 min before experimentation.

Contractile and relaxation responses. Overall, arteries from 12 Sed and 13 Ex pigs were evaluated. When more than one arterial ring was present within a treatment group, responses were averaged such that n is number of pigs studied in each analysis. Contraction to 80 mM KCl was measured to assess activation of voltage-gated calcium channels. Arteries were washed to resting tension, and then response to norepinephrine (NE; 10⁻⁶ to 10⁻⁴ M, in half-log doses) was examined by cumulative addition of stock solutions to vessel baths. Response to contractile agonists was expressed as the developed change in tension (in g) from resting tension. A concentration-response curve was constructed by plotting developed tension against log NE concentration, and the concentration that resulted in half-maximal contraction (EC₅₀) was determined.

Arteries were washed to resting tension and then contracted with the predetermined EC₅₀ of NE (5.75 x 10⁻⁷ M) and stabilized for 20 min. Preliminary experiments indicated that NE resulted in stable contraction for >150 min in these arteries. The presence of endothelium was confirmed by observing >60% relaxation to a single dose of bradykinin (10⁻⁶ M) after NE precontraction. Arterial rings that did not exhibit >60% relaxation to bradykinin were discarded.

The role of different endothelium-derived mediators was evaluated by using pharmacological inhibition of ecNOS with Nω-nitro-L-arginine methyl ester (L-NAME; 300 µM) and inhibition of COX with indomethacin (10 µM). Arterial rings were reconstituted with 5.75 x 10⁻⁷ M NE, and response to 6 M bradykinin was reassessed in the presence of pharmacological inhibition of ecNOS or COX to determine the contribution of nitric oxide and prostaglandin metabolites to single-dose bradykinin-induced relaxation. In rings from some pigs, endothelial denudation was performed by gently rubbing the internal surface of each ring with the edge of stainless steel forceps. Denudation was considered successful when <5% relaxation was observed after reexposure to 10⁻⁶ M bradykinin and was confirmed by histological examination.

After the second bradykinin response, arterial rings were washed to resting tension, and then 5.75 x 10⁻⁷ M NE and inhibitors were added to appropriate vessel baths. Endothelium-dependent relaxation was determined through cumulative addition of ACh (10⁻¹⁰ to 10⁻⁴ M, in half-log doses) stock solutions to the vessel bath. Percent relaxation was determined as percent reduction in NE-induced tension. Arterial rings were washed to resting tension, and then 5.75 x 10⁻⁷ M NE and appropriate inhibitors were added to each vessel bath. Tension was stabilized for 20 min, and relaxation to SNP (10⁻¹⁰ to 10⁻⁴ M, in half-log doses) was determined to assess endothelium-independent relaxation. Maximal relaxation was identified through incubation in zero-calcium Krebs solution containing 2 mM EGTA for 30–60 min.

Control experiments were performed in the presence of 300 µM Nω-nitro-L-arginine methyl ester (L-NAME), the inactive isomer of L-NAME, to confirm that inhibition of ecNOS was responsible for the observed effects. In some pigs, control experiments were performed in the presence of 0.07% ethanol to confirm that responses were related to pharmacological inhibition of COX by indomethacin.

Solutions. All chemicals were obtained from Sigma Chemical (St. Louis, MO) unless otherwise noted. Krebs solution was made fresh daily, equilibrated at 37°C, bubbled with 95% O₂-5% CO₂ for 20 min, and adjusted to pH 7.4 before use. Solutions of bradykinin (Bachem California, Torrance, CA), ACh, and NE dissolved in distilled, deionized water were made in a single batch and stored at −20°C until use. Dilutions used in experiments were made fresh daily by using Krebs solution as a diluent. NE was kept covered and on ice throughout the experiment to prevent oxidative degradation. SNP was made fresh daily in Krebs solution and was kept in the dark immediately before addition to the bath. L-NAME or L-NAME was dissolved in distilled, deionized water and stored as a stock solution of 300 mM at −20°C. Indomethacin was prepared in 70% ethanol as a stock solution of 10⁻² M and stored at −20°C before use.

Data analysis. Data are presented as means ± SE. If more than one arterial ring was present in a treatment group, responses were averaged before inclusion in the data set, and n is number of pigs in each analysis. Contractile tension was calculated by subtracting resting tension from tension measured after each addition of drug. A concentration-response curve was constructed by plotting log M NE concentration vs. developed tension. The EC₅₀ was determined from the semilog curve by using a linear regression computer program (Basica IC₅₀).

Relaxation was expressed as percent reduction from precontracted tension induced by 5.75 x 10⁻⁷ M NE (EC₅₀) at each dose added. IC₅₀ was defined as the drug concentration resulting in half-maximal relaxation. These values were
generated by a linear regression computer program (Basica IC50). Cumulative concentration-response curves for ACh and SNP were analyzed by using repeated-measures analysis of variance (SuperANOVA, Abacus Concepts). Comparisons between Sed and Ex were made for ACh and SNP concentration-response curves in the presence and absence of indomethacin, L-NAME, and endothelial denudation. When indicated by a significant F-test, planned post hoc tests were performed to detect differences between individual means.

Maximal responses, EC50, and IC50 concentrations were compared between Sed and Ex pigs by using the Student’s t-test. For all analyses, significance was set at P < 0.05.

RESULTS

Indexes of exercise training. Ex pigs had a significantly greater heart-to-body weight ratio (5.32 ± 0.19) than did Sed pigs (4.66 ± 0.11; P < 0.05). Exercise training resulted in significant increases in citrate synthase activity in the medial head of the triceps (Sed = 14.8 ± 0.6 and Ex = 19.6 ± 1.9 µmol·min⁻¹·g⁻¹) and in the deltoid muscle (Sed = 15.3 ± 0.8 and Ex = 18.5 ± 0.8 µmol·min⁻¹·g⁻¹; P < 0.05).

Characteristics of pulmonary arteries. Arterial rings from Sed and Ex pigs did not differ in passive characteristics, physical dimensions, or percent stretch required to reach Lmax (Table 1). Passive tension necessary to attain Lmax was also similar in arteries of Sed and Ex pigs.

Constrictive responses. Response to 80 mM KCl was greater in arteries from Ex (3.89 ± 0.28 g) than from Sed (3.06 ± 0.18 g) pigs (P < 0.05). Developed tension corrected for vessel area was also greater in arteries from Ex (1.63 ± 0.12 g/cm²) than from Sed (1.24 ± 0.08 g/cm²) pigs (P < 0.05). In contrast, the concentration-response relationship to NE did not differ between arteries from Sed and Ex pigs (Fig. 1). Tension developed in response to EC50 levels of NE also did not differ between Sed and Ex groups in the presence or absence of inhibition of nitric oxide or with endothelial denudation.

Relaxation responses. The concentration-response relationship to ACh was similar in arteries from Sed and Ex pigs, and L-NAME suppressed ACh-mediated relaxation significantly but equally in Sed and Ex arteries (Fig. 2). These data indicate that pulmonary arteries of both Sed and Ex pigs rely on nitric oxide for ~36% of ACh-mediated relaxation. Inhibition of COX resulted in enhanced relaxation in arteries from Sed and Ex pigs (Fig. 3, A and B), but there were no significant differences between groups. ACh-mediated relaxation was endothelium-dependent, because relaxation to ACh was <10% in both groups after endothelial denudation.

Endothelium-mediated relaxation to 10⁻⁶ M bradykinin did not differ between arteries from Sed (82.3 ± 1.4%) and Ex (82.2 ± 2.5%) pigs. L-NAME inhibited bradykinin-mediated relaxation equally in arteries from Sed (41.1 ± 2.2%) and Ex (40.1 ± 2.1%) pigs, and

Table 1. Physical characteristics of pulmonary arterial rings from sedentary and exercise-trained pigs

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Sed Arteries</th>
<th>Ex Arteries</th>
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<tbody>
<tr>
<td>Outer diameter, mm</td>
<td>2.71 ± 0.06</td>
<td>2.84 ± 0.06</td>
</tr>
<tr>
<td>Inner diameter, mm</td>
<td>2.20 ± 0.05</td>
<td>2.35 ± 0.06</td>
</tr>
<tr>
<td>Wall thickness, mm</td>
<td>0.26 ± 0.01</td>
<td>0.25 ± 0.01</td>
</tr>
<tr>
<td>Length, mm</td>
<td>2.40 ± 0.08</td>
<td>2.49 ± 0.06</td>
</tr>
<tr>
<td>%Stretch to reach Lmax</td>
<td>154 ± 3</td>
<td>155 ± 3</td>
</tr>
<tr>
<td>Resting tension at Lmax, g</td>
<td>1.40 ± 0.18</td>
<td>1.52 ± 0.14</td>
</tr>
</tbody>
</table>

Values are means ± SE from 12 sedentary (Sed) and 13 exercise-trained (Ex) pigs. Lmax, apex of length-tension relationship. There were no significant differences between Sed and Ex pigs for any of these parameters.
treatment with indomethacin did not reveal differences between groups.

Arteries from Sed and Ex pigs exhibited similar responses to the endothelium-independent vasodilator SNP in the presence and absence of ecNOS inhibition (Fig. 4). Pulmonary arteries displayed increased sensitivity to SNP in the presence of ecNOS inhibition (Sed: \( P < 0.05 \), Ex: \( P = 0.06 \)), as indicated by smaller IC\(_{50}\) concentrations (Table 2). After incubation in zero-calcium Krebs solution, pulmonary arteries from both Sed and Ex pigs (\( n = 12 \)) exhibited similar degrees of relaxation (Sed = 115.9 ± 7.2 and Ex = 117.0 ± 3.9%; \( P = 0.89 \)).

**DISCUSSION**

The goal of this study was to test the hypothesis that exercise training resulted in enhanced endothelium-mediated pulmonary vasomotor responses in a conduit-type artery of normal pigs. We surmised that augmented pulmonary vasorelaxation would represent a favorable response to exercise training, possibly allowing optimization of gas exchange and improved cardiac efficiency. Previous work in our laboratory had demonstrated that chronic exercise training enhanced endothelium-dependent relaxation in a conduit pulmonary artery of pigs with experimentally induced coronary occlusion (8), and we hypothesized that exercise would also result in endothelial adaptations in this same conduit pulmonary artery of normal pigs. However, in the present study, normal pigs did not develop enhanced endothelium-dependent relaxation after 16 wk of treadmill training but maintained ACh-mediated relaxation equal to that found in sedentary pigs.

It is important to note that training effects were evaluated in arteries taken from a single site within the pulmonary circulation. This represents both a strength and a weakness of isolated ring studies. Our laboratory has previously observed that pulmonary arteries in the pig exhibit striking lateralizing differences in endothelium-dependent relaxation (7). Comparison of responses in Sed and Ex pigs in an artery taken from the same location in all pigs ensured that any differences observed between Sed and Ex would be the result of exercise training and not the result of comparing different arteries in the two groups. Others have also noted that pulmonary artery position plays a role in vasomotor responses. Pelletier et al. (15) reported greater ACh-induced relaxation in dorsocaudal arteries compared with arteries taken from a ventral position within the equine lung. This difference was mediated...
Relaxation response to sodium nitroprusside in pulmonary arteries of sedentary and exercise-trained pigs

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<thead>
<tr>
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<th>Sed</th>
<th>Ex</th>
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<tbody>
<tr>
<td></td>
<td>Maximal relaxation, %</td>
<td>SNP IC50 IC50, M</td>
</tr>
<tr>
<td>Control</td>
<td>100.9 ± 2.7 (n = 10)</td>
<td>6.26 ± 0.58 × 10⁻⁶ (n = 10) IS</td>
</tr>
<tr>
<td>Denuded</td>
<td>109.7 ± 5.0 (n = 6)</td>
<td>4.79 ± 1.0 × 10⁻⁸ (n = 6)</td>
</tr>
<tr>
<td>L-NAME</td>
<td>105.4 ± 1.4 (n = 11)</td>
<td>4.02 ± 0.54 × 10⁻⁸ * (n = 11)</td>
</tr>
<tr>
<td>Indomethacin</td>
<td>106.5 ± 4.2 (n = 11)</td>
<td>7.76 ± 1.58 × 10⁻⁶ (n = 11)</td>
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<tr>
<td></td>
<td>103.2 ± 3.8 (n = 12)</td>
<td>8.36 ± 1.30 × 10⁻⁸ (n = 12)</td>
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<td></td>
<td>108.8 ± 4.5 (n = 5)</td>
<td>5.75 ± 1.11 × 10⁻⁸ (n = 5)</td>
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<td></td>
<td>110.9 ± 2.8 (n = 12)</td>
<td>5.22 ± 0.91 × 10⁻⁸ (n = 12)</td>
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<tr>
<td></td>
<td>103.8 ± 1.8 (n = 11)</td>
<td>9.48 ± 1.49 × 10⁻⁸ (n = 11)</td>
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Values are means ± SE; n, no. of experimental animals. IC50, concentration of vasoactive drug resulting in half-maximal relaxation from norepinephrine-induced tension. L-NAME, N-nitro-L-arginine methyl ester. SNP, sodium nitroprusside. *P < 0.05 for control vs. treatment effect. There were no significant differences between Sed and Ex groups.

by nitric oxide. In addition, pulmonary artery size influences endothelium-mediated relaxation because small (2- to 3-mm-OD) pulmonary arteries of the pig exhibit greater relaxation than do larger (5- to 6-mm-OD) pulmonary arteries (22). Our studies were performed on arteries from the same section of the circulation to avoid confounding experimental variability, and they indicated that exercise did not alter endothelium-dependent relaxation in arteries from this site. However, Mitani et al. (11) examined the effects of exercise training on both extra- and intrapulmonary arteries of the rat and found no exercise-induced adaptation in arteries taken from either site. Further studies are needed to determine whether pulmonary arteries of different sizes or branch orders in the pig exhibit a response to chronic exercise training, because it is possible that shear stress has differential effects along the heterogeneous pulmonary circulation.

Importantly, our studies document that relaxation to endothelium-independent mediators in the pulmonary circulation was also unaltered by exercise training, ensuring that no decrement in vasorelaxation developed after chronic training. Because vascular smooth muscle relaxation did not differ between groups, the response to ACh could be used to compare the role of endothelium-derived mediators between Sed and Ex pigs, and chronic training clearly had no effect on ACh-mediated relaxation in these pulmonary arteries from normal pigs. This is in striking contrast to the previously published report from our laboratory, where training enhanced endothelium-dependent relaxation of pulmonary arteries from pigs with coronary occlusion (8). In fact, the relative importance of diverse results in the two models is difficult to resolve; however, each raises important issues regarding effects of exercise on cardiopulmonary physiology. The following observations arise from this study.

Contractile responses after exercise training. Unexpected finding in this study was enhanced smooth muscle contraction to KCl stimulation in pulmonary arteries of Ex pigs. Increased contraction in Ex arteries could result from a greater amount of vascular smooth muscle, increased numbers of voltage-gated calcium channels, or increased open probability of calcium channels after exercise training. Developed tension corrected for vessel area was also greater in Ex pigs, indicating that the result was not likely an effect of increased smooth muscle within the arteries of Ex pigs. Also consistent with the notion that the amount of vascular smooth muscle is not altered by exercise, NE-induced contractions were similar between Sed and Ex pigs. It is possible that increased pressure within the artery during exercise bouts signals an increase in voltage-gated calcium channels. Bowles et al. (2) demonstrated that exercise training increased voltage-gated calcium current density in smooth muscle of coronary arteries in the pig. In normal pigs, exercise training may produce increased numbers of calcium channels or greater calcium channel activity in conduit-sized pulmonary arteries in a similar manner, resulting in increased response to KCl; however, the present study was not designed to test this hypothesis. It is unclear why this adaptation was not seen in the previous study of occluded pigs (8). Thus further studies are required to determine the reason for the increased KCl response noted in normal pigs studied here and the absence of this adaptation in the previous study (8).

Receptor-mediated activation of smooth muscle contraction with NE did not differ in arteries from Sed and Ex-trained pigs (Fig. 1). These results are consistent with other reports examining effects of exercise on vasomotor reactivity of pulmonary arteries. In a rat model of exercise training, pulmonary contractile responses to prostaglandin F2α were similar in sedentary and exercise-trained animals (11). Our results suggest that adrenergic signaling cascades within vascular smooth muscle cells of this pulmonary artery are not altered by exercise training.

Relaxation responses after exercise training. Contrary to our hypothesis, chronic exercise training did not alter endothelium-dependent pulmonary vasorelaxation in this model. ACh-mediated relaxation was similar in pulmonary arteries from normal Sed and Ex pigs, and groups exhibited equal reliance on nitric oxide for relaxation (Fig. 2). In contrast, our laboratory previously reported that pigs with coronary occlusion have increased reliance on nitric oxide for ACh-
mediated relaxation after exercise training (8). In the present study, indomethacin resulted in enhanced ACh-induced relaxation in arteries from both Sed and Ex pigs, whereas, in pigs with coronary occlusion, only arteries from Sed pigs demonstrated enhanced relaxation when indomethacin was added, suggesting that exercise training may have downregulated production of a prostanooid constrictor in pigs with coronary occlusion (8). It is clear that normal pigs and pigs with coronary occlusion have striking differences in the role of endothelium-derived mediators in ACh-induced relaxation and that pulmonary arteries were differentially affected by exercise training in the two models. In normal pigs, exercise training did not alter endothelial-mediated relaxation of these pulmonary arteries. However, we cannot rule out the possibility that exercise-induced adaptations occur at a different site within the pulmonary circulation in normal pigs. Given the complexity of branching and the known heterogeneity of responses in pulmonary arteries, it is likely that changes in shear stress or hemodynamics have varying effects at different sites within the circulation that were not addressed here.

Maximal response to endothelium-independent vasodilation with SNP and sensitivity to this direct donor of nitric oxide were also similar in arteries from Sed and Ex pigs (Fig. 4). This could be considered an important finding because chronic increases in pulmonary blood flow can lead to diminished vasorelaxation, even in the absence of pulmonary hypertension (5). Thus chronic exercise training did not alter pulmonary arterial vasorelaxation in conduit-type arteries of the pigs studied here.

Role of experimental animals. The fact that our results in normal pigs differed from those found in a coronary occlusion model raises intriguing questions regarding the effects of exercise training on the pulmonary circulation. Differences are not likely due to variations in the training protocol because all pigs were handled similarly and performed equivalent training programs. Indexes of exercise training in the group studied here were similar to others generated in our laboratory (8, 9, 12, 21), indicating successful training adaptations.

We believe that the different results found in normal and occluded pigs are most likely the result of hemodynamic effects resulting from chronic coronary occlusion and the surgical procedure used to produce coronary occlusion in a previous study from our laboratory (8). In that model, training resulted in enhanced ACh-mediated vasorelaxation in the same conduit pulmonary arteries used here. Pharmacological studies suggested that pulmonary arteries from exercise-trained pigs had greater reliance on the endothelium-derived mediator nitric oxide and reduced production of a prostanooid constrictor (8). Doppler echocardiography has revealed that human patients with ischemic heart disease exhibit abnormal pulmonary velocity profiles, leading to asymmetrical flow within the pulmonary artery and increased retrograde flow (18). Pulmonary flow profiles have not been assessed in pigs with coronary occlusion; however, if similar changes were present, exercise could accentuate effects of abnormal blood flow or shear stress on pulmonary endothelial cells. Increases in shear stress or blood flow are known to upregulate ecNOS gene expression (13, 14) and could lead to the observed physiological alterations in pulmonary vasorelaxation in pigs with coronary occlusion. Thus it is possible that cardiopulmonary hemodynamics in the normal pigs studied here were not altered during exercise bouts in the same manner as in occluded pigs, and, therefore, endothelium-dependent relaxation was not enhanced.

Some investigators believe that increased left atrial pressure is a key determinant of the acute drop in pulmonary vascular resistance that occurs during exercise (16), although the role of left atrial pressure elevations in chronic training adaptations is unknown. If coronary occlusion resulted in increased left atrial and pulmonary venous pressure, changes in shear stress sensed by pulmonary artery endothelial cells could be accentuated by greater radial stretch. Pulmonary arteries from occluded pigs might then experience a greater stimulus for endothelial adaptation. Hemodynamic studies of normal exercising pigs indicate that pulmonary wedge pressure, an estimate of left atrial pressure, increases from 4 to 13 mmHg at an exercise level of 85% maximal O2 uptake (6). In contrast, Roth et al. (17) found that miniature swine with ameroid-induced coronary occlusion have an increase in left atrial pressure during exercise from 8 to 20 mmHg. Therefore, it is possible that pigs with coronary occlusion studied previously had regional myocardial dysfunction and increased left atrial pressure that augmented the hemodynamic response to exercise in the pulmonary circulation. Because our experiments were not designed to test this hypothesis, left ventricular function and left atrial pressure were not performed in these studies. However, Sed and Ex pigs with coronary occlusion have greater heart weights than do normal pigs, suggesting myocardial hypertrophy or fibrosis unrelated to exercise training. Therefore, differences in left atrial pressure during exercise might explain the diverse results obtained in our two porcine models of exercise training.

The previous study from our laboratory showed that thoracotomy to place the ameroid occluder resulted in adhesion formation in the region of the left cranial lung lobe, thereby decreasing functional lung volume in pigs with coronary occlusion (8). Presumably, loss of ventilated lung volume from adhesion formation would cause redistribution of blood flow to other lung lobes. Normally, the pulmonary circulation tolerates large changes in blood flow with only small changes in vascular resistance; however, in occluded pigs, redistributed blood flow during exercise training bouts might have resulted in greater shear stress within pulmonary arteries. Thus it is possible that endothelial cells in the pulmonary arteries of occluded pigs experienced an increased shear stress signal that augmented production of nitric oxide and increased relaxation to ACh and that this added stimulus was lacking in the normal pigs studied here.
Conclusion. The effects of chronic exercise training on endothelial function within the pulmonary circulation are complex and may be influenced by multiple factors. Our results indicate that long-term exercise training did not alter endothelium-dependent vasorelaxation responses of conduit-type pulmonary arteries in normal pigs. In small mammals, ACh-induced relaxation has been augmented (3) or unchanged by short-term training (11). In large mammals, it is possible that conduit-sized pulmonary arteries are optimally vasoactive in normal animals and, therefore, do not respond to chronic exercise training with enhanced endothelial function. Alternatively, the length of training or the location of the artery within the pulmonary circulation might impact the development of exercise-induced adaptations. Responses in large pulmonary arteries may not reflect vasoreactivity in the pulmonary microcirculation. Increased blood flow associated with chronic exercise training may alter endothelium-dependent relaxation in pulmonary arteries of the pigs studied here.

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