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Endothelial function and exercise training: Evidence from studies using animal models

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Abstract

This review summarizes and examines the evidence from experiments using animal models to determine the effect of exercise training on endothelium-dependent dilation in the arterial circulation. The response of the endothelium to exercise training is complex and depends on a number of factors that include: the duration of the training program, the size of the artery/arteriole, the anatomical location of the artery/arteriole, and the health of the individual. In general, evidence supports the notion that exercise training causes greater increases in endothelium-dependent dilation in various disease states than in healthy individuals. There is little evidence for a generalized effect of training on arterial endothelium in all regions of the body. Available results indicate that training duration, artery size, and anatomical location interact in ways not fully understood at this time to determine whether and to what extent endothelium-dependent dilation will be enhanced by exercise training.

Keywords

endothelium; vasodilation; skeletal muscle; arteries; blood flow

Introduction: Blood flow adaptations to training

Exercise training elicits a number of physiological adaptations, including increased maximal oxygen consumption (VO_2max), increased cardiac output, and increased maximal oxygen extraction (26). Furthermore, training produces an increase in maximal skeletal muscle blood flow capacity in dogs, rats, and humans (26), increases skeletal muscle blood flow during high-intensity exercise in dogs (39), rats (26), and humans (26), but does not appear to alter total skeletal muscle blood flow under resting conditions or during submaximal exercise at similar absolute exercise intensities (26). However, despite similar total blood flow to skeletal muscle, the distribution of blood flow between different muscles and within specific regions of muscle during moderate intensity exercise is altered by training (1). Specifically, blood flow to regions

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composed primarily of highly oxidative muscle fibers is increased while blood flow to primarily glycolytic regions of muscle is reduced and flow to non-locomotory muscle is not altered (39). Thus exercise training causes blood flow (and oxygen delivery) to be increased to the fibers whose ATP generation is most dependent on oxygen and decreased to fibers that are less dependent on oxygen availability for ATP production.

One mechanism by which exercise training may alter blood flow is by changing either endothelial or smooth muscle control of vascular resistance. Furchgott and Zawadski (10) discovered more than two decades ago that the endothelium is an important regulator of vascular tone, and there has been much interest in the subject in years since. The endothelium is located in a strategic position, between the blood and the vascular smooth muscle, and it responds to changes in shear stress and a host of chemical signals by producing factors (nitric oxide (NO), prostacyclin (PGI_2), and/or one or more endothelium-derived hyperpolarizing factors (EDHF)) that act on the vascular smooth muscle to regulate vascular tone (26). Exercise training-induced alterations in any of these signaling pathways would lead to changes in endothelial control of blood flow.

Recently, Moyna and Thompson (37) concluded that cross-sectional and longitudinal studies in human subjects indicate that exercise training has little effect on endothelial function in conduit arteries of normal subjects but document improved endothelial function with exercise training in subjects who had blunted endothelial function prior to training. These conclusions, combined with our experience with similar studies in animals, stimulated the question: does current literature indicate a similar interactive effect of endothelial health and exercise in animals such that exercise training has a greater effect on endothelial function in conditions of abnormal endothelial function? Therefore, this review has three purposes: 1) To evaluate the hypothesis that exercise training enhances endothelial function in normal health and preserves or restores endothelial function in animal models of disease with endothelial dysfunction., 2) Compare the effects of short (1–4 weeks) term training vs. long term training on endothelial function in animal models, and 3) Evaluate the hypothesis that exercise training has a generalized, systemic effect on endothelial health in animal models.

Endothelial adaptations to training in normal (young) healthy animals

Conduit Arteries

The most common measure of endothelial function/health is a measurement of endothelium-dependent dilation/relaxation (EDD). In 1993, Delp et al. reported that relaxation to acetylcholine (ACh), an endothelium-dependent dilator, was enhanced by 12 weeks of exercise training (8). L-NAME, an arginine analog that competitively inhibits NO production, partially inhibited EDD in aortic rings from both sedentary and trained rats, but the inhibition was greater in rings from trained rats such that L-NAME abolished the difference between groups. Furthermore, aortic contractions caused by norepinephrine (NE) were decreased by training, but contraction was similar when α_2 adrenergic blockade was present in both sets of vessels, indicating that training caused an increase in endothelial cell α_2 mediated dilation. Training-induced alterations appeared to be specific to the aortic endothelium since endothelium-independent dilations (to sodium nitroprusside) were not altered by training.

Examination of the time-course of training-induced increases in aortic EDD revealed no change following a single exercise bout or after training durations of less than four weeks, but aortic EDD was increased following training programs of 4 weeks and 10 weeks (7). Subsequent studies using 8–10 weeks of training in rats (5,6,61) confirmed these results (see Table 1). Also, 16–19 weeks of training in pigs (45) produce changes in aortic endothelial gene expression consistent with enhanced EDD following long term training.

The effect of exercise training on EDD in other conduit arteries differs from the aorta (Table 2). Results of a study examining porcine femoral and brachial arteries indicate that short term training (7 days) elicits enhanced EDD in the brachial, but not the femoral artery (35). Relaxations to sodium nitroprusside (endothelium-independent) were not altered. In contrast, long term training of pigs (16–20 wks) had no effect on EDD in either the brachial or femoral arteries of male pigs (29). In female pigs, femoral artery responses were not altered with short or long term training (29,34) but EDD was improved in brachial arteries of female pigs trained for 20 weeks (29). Thus, results do not consistently reveal enhanced EDD of arteries providing blood to limb muscles of trained pigs. Indeed, in normal male and female pigs, exercise training has only moderate effects on EDD in conduit arteries, as the amount of increase in EDD is modest in normal female pigs even when statistically significantly increased. Finally, EDD in porcine renal, mesenteric, and hepatic arteries (34), and of porcine pulmonary arteries (20) is not altered by 16–20 weeks of exercise training. These data indicate that long term exercise training does not increase EDD throughout the porcine arterial tree, i.e. training does not have a generalized effect on endothelial function in conduit arteries of non-muscular vascular beds.

Skeletal Muscle Resistance Vessels

Short term training consistently causes endothelial adaptations in skeletal muscle resistance vessels (Table 3). Three to four weeks of daily exercise in rats increased EDD of gracilis muscle arterioles to acetylcholine and L-arginine (51) and to increased levels of perfusate flow (24). The augmented response to flow was partially abolished by blocking eNOS or cyclooxygenase, indicating that both NO and PGI_2 pathways were enhanced (24). Flow-induced dilation of arterioles from the plantaris muscle was also increased in rats by 3–4 weeks of exercise (49). Although, Massett et al. found that EDD in response to increased osmolarity in rat gracilis arterioles was not altered by four weeks of exercise training (32), available evidence generally indicates that short-term exercise training increases EDD in resistance arteries of skeletal muscle.

There have been only a few studies of the effects of long-term training on EDD in skeletal muscle resistance arteries (Table 3), and results are variable. For example, Lash and Bohlen (25) reported that 8 weeks of exercise training did not alter EDD in spinotrapezius muscle arteries of rats, but 16 weeks of training did elicit an increased dilation to ACh in first and second order arterioles from this muscle. However, they also reported an increased dilation to sodium nitroprusside in first order arterioles and feed arteries after 16 weeks, so it is difficult to know whether the increased dilation in first order branches was due to adaptations in the smooth muscle alone or if the endothelium also contributed. It should be noted that functional dilation (response to electrical stimulation) was increased at 8 weeks, but this augmentation was almost gone by 16 weeks of training. Thus the time course of adaptations in EDD was dissociated from the time course of adaptations in functional dilation. Although the oxidative capacity of the spinotrapezius (as measured by citrate synthase activity) was increased a small amount in this study, it should be noted that the spinotrapezius is not a primary locomotory muscle.

The soleus muscle is used extensively in posture maintenance and locomotion, and is a muscle whose blood flow is increased during exercise (1). Exercise training for 12 wks did not alter EDD in rat soleus muscle feed arteries (17). This observation may be the result of the fact that the soleus muscle is used constantly in the maintenance of posture in the standing rat. Due to this high level of recruitment, soleus muscle metabolic activity is high even in sedentary rats, as is the blood flow and shear stress through the soleus muscle feed arteries (16). Consistent with this interpretation are results of a study in which decreasing metabolic activity and blood flow of the soleus muscle via hindlimb unweighting produced a reduction in EDD (18). The conclusion of studies altering soleus activity with chronic training and chronic inactivity

indicate that EDD in soleus feed arteries can be reduced, but not enhanced, by chronic alterations in soleus muscle activity. This is probably the result of the high level of metabolism and blood flow to the soleus during normal daily activity in the rat, which is sufficient to maintain EDD near optimal levels, even in untrained rats.

Another study examining long-term training used a high-intensity, sprint training protocol for 10 weeks in rats (30). Sprint training increased the hindlimb response to ACh and increased EDD in second order arterioles of the white portion of the gastrocnemius, but not in gastrocnemius feed arteries, second order arterioles from red region of gastrocnemius, or third order arterioles from the white portion. In contrast, McAllister et al. found that moderate-intensity training for 8–12 weeks resulted in enhanced EDD and increased endothelial NOS levels in arterioles from the red, but not white portion of gastrocnemius (33). Together with the data from Lash and Bohlen described above (25), these data indicate that the pattern of skeletal muscle resistance artery endothelial adaptation to exercise training is very complex, and much work still needs to be done in order to define the manner in which these adaptations occur in the skeletal muscle arteriolar network.

Coronary Vascular Bed

In larger arteries of the heart, short-term exercise training consistently increases EDD (Table 2). Studies in dogs (47) and pigs (28) report increased EDD following 7–10 days of daily exercise. Furthermore, 10 days of training in dogs increases NO production and eNOS expression in large coronary arteries (54). Interestingly, 7 days of training did not alter EDD in porcine resistance arterioles (28), indicating that endothelial adaptations appear to be limited to larger coronary vessels when the training program is short in duration. In contrast, adaptations to longer term exercise training are not observed in larger coronary arteries and appear to be limited to smaller resistance vessels. Oltman et al. (42) found that 13–20 weeks of training had no effect on EDD in porcine coronary arteries. In contrast, when porcine resistance arterioles were studied, 16–20 weeks of training resulted in an enhancement of EDD (38). Thus it appears that the smaller coronary resistance arterioles have enhanced EDD after a long-term training protocol, but enhanced EDD is observed in the larger coronary conduit arteries only after short term training.

Vascular Beds in Non-contracting Tissue

It has been proposed that there would be no training-induced adaptation in arteries of tissues that do not increase activity during exercise because these tissues have neither increased metabolism nor increased blood flow (31). Additionally, alterations in blood flow have been shown to be greatest in the specific muscle regions that have the greatest relative increase in activity during exercise training bouts (26). However, there is evidence in humans (see Maiorana et al. review (31)) that leg cycle training can elicit enhanced EDD in the forearm, tissue that would not be active during the training bouts. These data suggest that in humans exercise training may bring about systemic adaptations in endothelial function.

McAllister et al. (34) examined the responses of the porcine mesenteric, renal, and hepatic conduit arteries of pigs following long-term training and found no endothelial adaptations to exercise in these vessels. As summarized in Table 2, these data indicate that long term training in pigs does not alter EDD of non-skeletal muscle conduit arteries. Additionally, short term training does not alter flow-induced dilation of rat mesenteric arterioles (49), supporting the notion that vascular endothelium in non-active regions does not undergo adaptations to training.

As mentioned above, short term training has been reported to increase EDD in rat gracilis arterioles (24,51) and longer training protocols increase EDD in the rat spinotrapezius muscle

(25). This is interesting because neither gracilis (1) nor spinotrapezius (40) have increased blood flow during exercise. Also, gracilis blood flow during exercise is not altered by training (1). Thus the fact that EDD is increased by training in these muscles suggests that training can induce adaptations in endothelial function in resistance vessels of skeletal muscle tissue that has little or no increase in activity or blood flow during training bouts. Furthermore, exercise training has been reported to enhance EDD in the rat carotid artery (23), suggesting that conduit arteries from inactive regions can also have training-induced endothelial augmentation. Thus while generalized adaptations in endothelial function do not occur in the pig model, most data from rat studies support results from human studies indicating that improved EDD can occur in resistance vessels in non-active regions of the body, and that exercise training has a non-specific, systemic effect on endothelial function. A potential explanation for improved EDD in arteries of tissue with no change or decreased blood flow during exercise is that vascular wall shear stress may increase in arteries perfusing these regions during exercise even if flow does not increase, due to decreased diameters of these arteries during exercise. During exercise there is a generalized increase in sympathetic nerve activity which causes vasoconstriction of arteries in many regions of the body. This vasoconstriction serves to shunt blood flow away from non-active regions toward the active regions that require increased oxygen and substrate delivery. It may be that vasoconstriction in non-active regions actually increases wall shear stress in the resistance vasculature of some non-active body regions, and that chronic exposure to this stimulus results in enhanced endothelial function in these regions. A second potential explanation is that some chemical mediator of enhanced endothelial function is produced in actively contracting muscle and carried via the vasculature to non-active regions.

Summary of Exercise Training in Normal Healthy Subjects

In summary, it appears that exercise training has non-uniform effects on arterial endothelium in normal healthy animals. The effects of training are determined by a number of known parameters including: the length of the training protocol, the branch order of the vasculature studied, and the specific tissue studied. Current results indicate that long term endurance exercise training induces enhanced EDD in the aorta and in resistance arteries of the heart. Short term, but not long term, training increases EDD in some other conduit arteries. Short term training also increases EDD in resistance arterioles of the gracilis and plantaris muscles. However, after long term training only modest increases in EDD are reported in the spinotrapezius and no changes are seen in soleus resistance arteries.

It may seem counterintuitive that short exposure to training causes adaptations in endothelial function while increasing the duration of exposure to the training stimulus causes a regression of these adaptations. It has been proposed that these observations reveal the sequence of adaptations in vascular control and structure throughout a training program (28,31). Increases in vascular wall shear stress produced during exercise hyperemia may be an important stimulus for augmentation of EDD (56) and subsequently for changes in vascular structure (43). Short term exercise training causes increases in shear stress, and the result is an increased expression of eNOS and possibly other proteins which help to increase EDD of arteries. As the duration of the training period increases, eNOS, vascular endothelial growth factor (VEGF), and other factors produced during exercise bouts elicit vascular remodeling, formation of new vessels and enlargement of existing vessels. These structural adaptations return vascular shear stress back to normal levels and EDD returns to normal. In support of this hypothesis, eNOS mRNA levels can be increased in as little as 2–4 hours by in vitro increases in flow (56), and increased eNOS protein expression can occur in 7–10 days (54). However, strong evidence regarding the nature and time course of structural adaptations in the arterial microcirculation is not currently available.

Endothelial Adaptations to Training in Conditions of Attenuated Endothelial Function

Aging

A number of studies have reported reduced EDD in both conduit and resistance vessels of older versus younger rats (Table 4). Sun et al. (50) found that gracilis arterioles of older rats had reduced sensitivity to wall shear stress and that an 18–20 wk treadmill training program increased sensitivity of these arterioles to shear stress. Responses to ACh were also increased by exercise training in the older rats, while responses to sodium nitroprusside were not altered. Spier et al. (48) compared EDD in first order arterioles of the soleus muscle (primarily slow-oxidative fibers) and of the white portion of the gastrocnemius muscle (primarily fast, glycolytic fibers). They found that aging reduced EDD to ACh in the arterioles of the soleus, but not the white gastrocnemius muscle, and that 12 weeks of low-intensity exercise training increased ACh-induced EDD in soleus arterioles from young and old rats and in white gastrocnemius arterioles from young, but not old rats. Both aging and exercise training effects were due to differences in NO production and training was found to increase both eNOS mRNA and eNOS protein levels in arterioles from both muscles in both age groups. Although treadmill running in old rats has been reported to reduce aortic sensitivity to lower doses of acetylcholine (10^{-7} M or less) (14,53) the preponderance of data, particularly in resistance vessels, indicate that exercise training in older subjects reverses the age-related decline in EDD.

Heart Disease

Griffin et al. (12) reported that 16 weeks of exercise training elicited increased EDD in coronary conduit arteries from both the collateral-dependent region and the normal region perfused by the left anterior descending artery (LAD) in a porcine model of chronic coronary occlusion. The enhanced EDD was the result of training-induced increases in production of NO and EDHF. Griffin et al. subsequently reported that coronary arterioles from the collateral-dependent region also exhibited training-induced increases in EDD and increased eNOS mRNA expression (13). Similarly, VEGF-induced EDD of coronary arterioles from the collateral-dependent region is enhanced by exercise training due to increased NO production (9). EDD of the pulmonary arteries from these coronary artery occluded pigs are also enhanced by 16 weeks of training (21), an adaptation to training that was not found in normal pigs (20). The increased pulmonary artery EDD appeared to result both from an increase in NO production and reduced production of a vasoconstrictor prostanoid. Thus in this group of studies using the coronary artery occlusion model, exercise training consistently enhances EDD in coronary and pulmonary arteries (Table 4).

There have also been some studies in which exercise training has been used in models of heart failure. In dogs with congestive heart failure induced by cardiac pacing, exercise training improved EDD (55,62). Wang et al. (55) reported that training preserved EDD of coronary arteries and increased eNOS protein expression. Yi et al. (62) reported that training preserved EDD of the left circumflex coronary artery to arachidonic acid, but that prostacyclin or nitroglycerin induced dilations were not altered by training. Thus training preserved EDD during the development of heart failure, but did not alter vascular smooth muscle function.

Hypercholesterolemia

A large number of studies have reported reduced EDD in hypercholesteremia (see Table 4) that is reversed or prevented by exercise training of mice (41,44), rabbits (19,59,60), and pigs (52,57,58). In a genetic model of mouse hypercholesterolemia, the apolipoprotein E knockout mouse, EDD of the thoracic aorta was decreased in relation to wild type mice and exercise training restored normal EDD (41). Expression of eNOS protein in the carotid artery of

apolipoprotein E knockout mice was reduced, but was also restored to normal levels by exercise training (44). In rabbit aorta, hypercholesterolemia decreased EDD to ACH and this was linked to reductions in endothelial production of both NO and EDHF (59,60). Treadmill exercise training increased production of NO and EDHF and restored ACh-induced EDD. At least part of the reduction in endothelial production of NO and EDHF may result from impaired calcium signaling in endothelial cells, because hypercholesterolemia decreased the ACh-mediated elevation in endothelial cell calcium levels in rabbit femoral arteries, an alteration that was also reversed by exercise training (19). Finally, data from studies using pigs demonstrate that hypercholesterolemia decreases NO-mediated signaling in coronary and brachial arteries (52, 57,58). Exercise training restored EDD of coronary arteries by increasing NO-mediated dilation and decreasing production of a prostanoid vasoconstrictor (57,58). Thus available results indicate that hypercholesterolemia reduces and exercise training restores NO-mediated EDD.

Hypertension

Studies using rings of aorta (3,4,11), carotid artery (2,4) and/or mesenteric artery (2) to examine the effects of exercise training in spontaneously hypertensive rats (SHR) have consistently shown that EDD is reduced by hypertension and that attenuated NO production is at least partially responsible (see Table 4). Exercise training improves EDD in these arteries from SHR, and NO production is increased by training in these arteries (2,4). Additionally, exercise training increases expression of eNOS in SHR, which would explain the findings of increased NO production (11). Graham and Rush (11) also examined levels of superoxide dismutase and catalase, two enzymatic scavengers of oxygen free radicals, and found no difference in trained versus sedentary SHRs. Interestingly, levels of the pro-oxidant enzyme, NAD(P)H oxidase, were reduced by exercise training, which may have a beneficial effect on the half-life of NO in the vascular wall. Thus the improvement in EDD with training of hypertensive animals appears to result from increased NO production and availability, and not from improved free radical scavenging by anti-oxidant enzymes or from increases in other endothelium-derived dilators (2).

Type II Diabetes Mellitus

Two studies have examined the effects of exercise training on EDD in Type II diabetes mellitus. Sakamoto et al. (46) found that diabetes reduced aortic EDD in rats and that exercise training improved EDD. Training also increased insulin sensitivity and reduced plasma levels of glucose and insulin. A subsequent study of diabetic rats by Minami et al. (36) found that thoracic aorta and mesenteric artery rings from diabetic rats had reduced responses to ACh, with endothelial production of both NO and EDHF attenuated. Exercise training increased relaxation to ACh and production of both NO and EDHF was increased.

Conclusion

The evidence reviewed in this paper indicates that the effects of exercise training on EDD in normal animals is dependent both on the location of the arteries and on the duration of the training program (see Figure 1). In normal, healthy animals, the aortic endothelium consistently demonstrates increased EDD by the fourth week of training and this enhanced EDD persists throughout longer training protocols. In conduit arteries feeding skeletal muscle or inactive tissue, neither short term (1–4 wks) nor long term training consistently elicit increases in EDD, while coronary arteries have increased EDD following short, but not long term training. Coronary resistance arteries have increased EDD only after long term training. Resistance arteries from inactive tissues do not exhibit consistent increases in EDD after either short or long term training. In conditions in which EDD is compromised such as: aging, heart disease, hypercholesterolemia, Type II diabetes, and hypertension, results indicate that exercise training

consistently preserves or restores EDD toward normal levels. The amount of increase in EDD is also greater than that seen in the few examples where EDD is improved by training in normal animals. It should be noted that almost all studies of exercise and endothelial function in pathological conditions have examined conduit arteries, so more work is needed to determine how exercise interacts with these various diseases in determining EDD and health. Finally, although some evidence indicates that exercise training can enhance EDD even in regions of the body that are not active during training bouts, evidence also indicates that some endothelial adaptations are specific to certain regions, as not all inactive body regions show this effect. Based on this body of evidence we conclude that long term exercise training does not significantly increase endothelial function of arteries in normal healthy animals, but exercise training can prevent or reverse the development of endothelial dysfunction that accompanies some diseases.

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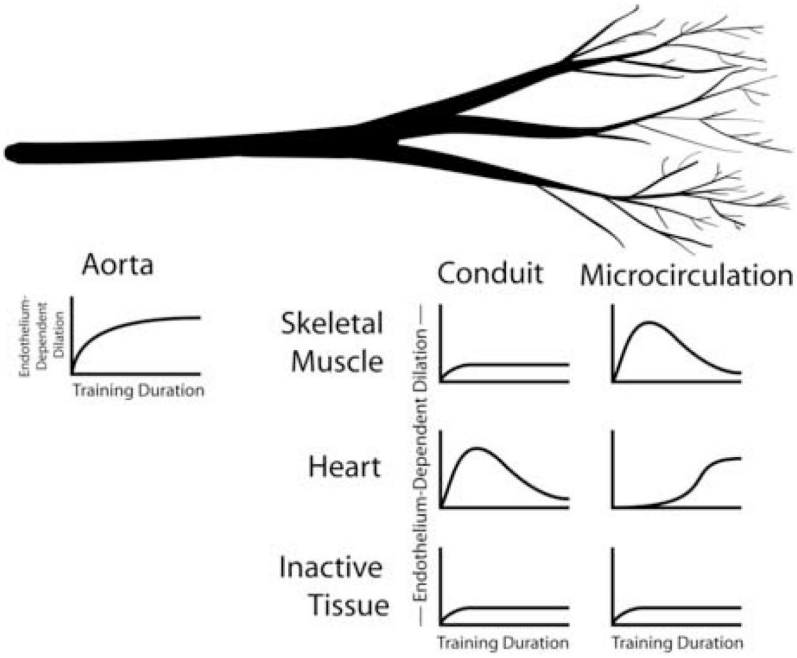

Figure 1.
Interaction between organ, vessel size, and training duration on the increase in endothelial-dependent dilation resulting from exercise training. A small deflection above baseline indicates small or inconsistent increases in endothelial function. A large deflection above baseline indicates larger and consistent increases in endothelial function.

Table 1

Effect of exercise training on endothelial function in normal, healthy animals: Aorta

Reference	Species	Method	Vessels	EDD	EID	Comments
Chen et al., 1996 (5)	WKY Rat	In vitro rings	Aorta	↑ due to BK-Ca channels		↑ blocked by L-NAME, TTX, and CTX 8 wk training
Chu et al., 2000 (6)	Wistar Rat	In vitro rings	Aorta	↑ Ca influx into endo cells		10 wk training
Delp & Laughlin, 1997 (7)	Rat	In vitro rings	Aorta	↑ in 4 & 10 wk, but not shorter protocols		↑ abolished by L-NAME eNOS also up at 4 & 10 weeks
Delp et al., 1993 (8)	Rat	In vitro rings	Aorta	↑ ACh; ↑ blocked by L-NAME	No change	10–12 wk training
Rush et al., 2003 (45)	Pig	Molecular	Aorta	↑ SOD-1 and Cu/Zn SOD		16–19 wk training; Overall ↓ in oxidative stress and ERK activation
Yang et al., 2002 (61)	Rat	Molecular	Aorta	↑ iNOS and eNOS ↓ PE constriction		10 wk training ↓ PE constriction reversed w/ aminoguanidine

TTX: tetrodotoxin, CTX: charybdotoxin, eNOS: endothelial nitric oxide synthase, iNOS: inducible NOS; SOD: superoxide dismutase.

Table 2

Effect of exercise training on endothelial function in normal, healthy animals: Conduit arteries

Reference	Species	Method	Vessels	EDD	EID	Comments
SHORT-TERM TRAINING						
Johnson et al. JAP 90:1102, 2001 (22)	Pig	In vitro rings	Pulmonary artery	↑ EDD and ↑ eNOS ↔ SOD-1	No change	7 day training
Laughlin et al., 2003 (28)	Pig	In vitro rings	Coronary conduit arteries	↑, but no ↑ in eNOS		7 day training Aorta eNOS was ↑ ed
McAllister & Laughlin, 1997 (35)	Pig	In vitro rings	Femoral & brachial	↑ in brachial, not fem Not NO or PG's	No change	7 day training
Sessa et al., 1994 (47)	Dog	Nitrite & molecular	Coronary arteries	↑ nitrite production & ↑ eNOS mRNA		10 day training
Wang et al., 1993 (54)	Dog	In vivo flow probe	Coronary arteries	↑ ACh dilation abolished by L-NNA		7 day training
LONG-TERM TRAINING						
Johnson & Laughlin, 2000 (20)	Pig	In vitro rings	Pulmonary artery	↔ ACh	No change	16 wk training
Kemi et al., 2004 (23)	Rat	In vitro rings	Carotid	↑ ACh	No change	10 wk training; ↑ EDD completely lost after 2 weeks detraining
Laughlin et al., 2001 (29)	Pig	In vitro rings	Femoral &	Male: ↔ Female: ↔	No change in either gender	Were other gender specific effects 16–20 wk training
			Brachial	Male: ↔ Female: ↑	No change in either gender	
Laughlin et al., 2001 (27)	Pig	Molecular	Coronary	↑ eNOS in arterioles and small arteries		16–20 wk training No change in eNOS in conduit arteries
McAllister et al., 1996 (34)	Pig	In vitro rings	Fem., brach., renal, mes., hepatic arteries	↔ ACh	No change	16–20 wk training
Oltman et al., 1995 (42)	Pig	In vitro rings	Coronary	No change	No change	13–20 wk training

EDD: endothelium-dependent dilation. See Table 1 for other abbreviations.

Table 3

Effect of exercise training on endothelial function in normal, healthy animals: Resistance arteries and arterioles

Reference	Species	Method	Vessels	EDD	EID	Comments
SHORT-TERM TRAINING						
Koller et al., 1995 (24)	Rat	In vitro cannulated	Gracilis arterioles	↑ Flow dilation; due to ↑ NO & ↑ PGI_2		3 wk training
Laughlin et al., 2003 (28)	Pig	In vitro cannulated	Coronary arterioles	no change		7 day training
Massett et al., 2000 (32)	Rat	In vitro cannulated	Gracilis arterioles	↔ dilation to ↑ osmolarity		4 wk training protocol; dilation to osmolarity was KOed by endothelium removal
Sun et al., 1994 (51)	Rat	In vitro cannulated	Gracilis arterioles	↑ ACh, L-Arg	No change or ↓	4 wk training
Sun et al., 1998 (49)	Rat	In vitro cannulated	Mesenteric arterioles	↔ Flow dilation		3–4 wks training
			Plantaris arterioles	↑ Flow dilation		
LONG-TERM TRAINING						
Jasperse & Laughlin, 1999 (17)	Rat	In vitro cannulated	Soleus feed artery	↔ ACh ↔ Flow dilation	No change	12 wk training
Lash & Bohlen, 1997 (25)	Rat	In situ microscopy	Spinotrapezius arterioles	↔ ACh @ 8 wks; ↑ ACh in 1A & 2A @ 16 wks	↑ SNP in FA @ 8 wks; ↑ in FA & 1A @ 16 wks	8 & 16 wk training ↑ functional dilation at 8 wks, but mostly gone at 16 wks
Laughlin et al., 2004 (30)	Rat	In situ, in vitro, and molecular	1-3A from red G and white G	↑ in WG 2A, ↔ in WG 3A ↔ in RG 2A	No change	Interval sprint training for 10 weeks ↑ eNOS in conduits, GFA, WG4A, RG5A ↑ SOD-1 in popliteal, WG4A
McAllister et al., 2005 (33)	Rat	In situ, in vitro, and molecular	Many orders of arterioles from RG and WG	↑ in some orders from RG;	↑ in some orders from RG	8–12 wk training ↑ eNOS in some orders from RG
Muller et al., 1994 (38)	Pig	In vitro cannulated	Coronary arterioles	↑ BK; ↑ abolished by L-NMMA	No change	16–20 wks training

G: gastrocnemius, R: red, W: white, FA: feed artery, SOD: superoxide dismutase; KO: knock out.

Table 4

Effect of exercise training on endothelial function in aging or pathology

Reference	Species	Method	Vessels	EDD	EID	Comments
AGING						
Hashimoto, 1990 (14)	Rat	In vitro rings	Aorta	↔ max to Ach ↓ sensitivity to ACh		12 wk treadmill training
Spier et al., 2004 (48)	Fischer Rat	In vitro cannulated	SOL 1A	↑ Ach & eNOS pro & mRNA in both O & Y	No effect of aging or ExTr	Aging ↓ Ach, NOS X abolished ExTr effect Aging ↑ eNOS, but not mRNA
			WG 1A	↑ Ach & eNOS in Y only, but ↑ mRNA in O & Y	No effect of aging or ExTr	Aging ↔ Ach; Aging ↔ eNOS & mRNA 12 wk ExTr at 15 m/min
Sun et al., 2002 (50)	Rat	In vitro cannulated	Gracilis arterioles	Aging ↓ and ExTr ↑ flow-induced dilation	No change	Young and adult rats 18–20 wk training
Tsutsumi et al., 2001 (53)	Rat	In vitro rings	Aorta	↓ at low doses ACh	No change	3 month treadmill training
CORONARY DISEASE MODELS						
Fogarty et al., 2004 (9)	Pig	In vitro cannulated	Coronary arterioles	↑ VEGF in collateral dep. Only; dilation ↓ by NOS blockade		14 wk training Ameroid occluder
Griffin et al., 1999 (12)	Pig (female)	In vitro rings	Coronary arteries	↑ in normal and collateral-dependent		16 wk training Ameroid occluder
Griffin et al., 2001 (13)	Pig (female)	In vitro cannulated	Coronary arterioles	Occlusion ↓ and ExTr ↑ BK dil. & eNOS	No change	16 wk training Ameroid occluder
Indolfi et al., 2002 (15)	Rat	Various	Carotid arteries	↑ eNOS & ↓ neointimal hyperplasia		Balloon angioplasty; Swim training 2 wks pre and 2 wks post injury
Johnson et al., 2000 (21)	Pig (female)	In vitro rings	Pulmonary artery in ameroid occluder pigs	↑ in NO dependent manner	No change	16 wk training
Yi et al., 2000 (62)	Dog	In vivo Doppler	LCX	AA dilation ↓ by CHF, ↑ by ExTr	No change to PGI2 or NTG	Pacing-induced CHF for 4 wks or pacing + 2 hrs/d of treadmill
HYPERCHOLESTEROLEMIA						
Jen et al., 2002 (19)	Rabbit	In vitro rings	Femoral	HF ↓ Ach dilation & Ca ExTr ↑ Ach & Ca	HF ↓ and ExTr ↑	Hypercholesterolemic 8 wk training
Niebauer et al., 1999 (41)	Mice	In vitro rings	Aorta	↓ by ApoE KO & ↑ by ExTr	↓ by ApoE KO, but ↔ to ExTr	Hypercholesterolemic (ApoE KO) Treadmill ExTr for 4 wks
Pynn et al., 2004 (44)	Mice	Various	Carotid artery injury in ApoE KO mice	↑ eNOS ↓ neointimal lesions		Hypercholesterolemic (ApoE KO); 3 wks running prior to injury & 3 wks after.

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Reference	Species	Method	Vessels	EDD	EID	Comments
AGING						
Thompson et al., 2004 (52)	Pig (male)	In vitro rings	Coronary arteries	↑ BK dilation and ↑ SOD -1 & 2; ↔ eNOS		Hypercholesterolemic 16–20 week training
Woodman et al., 2004 (57)	Pig (female)	In vitro rings	Coronary arteries	↑ BK dilation via ↑ NO activity	↑ in high fat and HF ExTr	Hypercholesterolemic 16–20 week training
Woodman et al., 2003 (58)	Pig (female)	In vitro rings	Brachial	↓ by HF due to NO, PGI ↑ by ExTr due to other	No change	Hyperlipidemia 16 week training
Yang & Chen, 2003 (59)	Rabbit	In vitro rings	Aorta	↑Ach dilation in normal, less ↑ in high chol.		Hypercholesterolemic 8 wks ExTr ↓ iNOS and adhesion molecule expression
Yang et al., 2003 (60)	Rabbit	In vitro rings	Aorta	↑ Ach dil. in high chol. Due to ↑ NO & ↑ EDHF		Hypercholesterolemic 2,4,6 wks ExTr; 4 & 6 wk ↓ adhesion molecule expression
HYPERTENSION						
Arvola et al., 1999 (2)	Zucker Rats	In vitro rings	Mesenteric	↑ ACh in Lean & Ob.	↑ SNP in Lean & Obese	Obesity/Hypertension; 22 wks training ExTr effect KOed by L-NAME, but not COX or EDHF block
			Carotid	↑ ACh only in Obese	↑ SNP in both	
Chen and Chiang, 1996 (3)	WKY & SHR Rats	In vitro rings	Aorta	↑ PE constriction		10 wk training ↓ PE abolished by L-NNA
Chen et al., 1996 (4)	WKY & SHR Rats	In vitro rings	Aorta Carotid	↑ Ach due to NO ↔ ACh	↔ SNP	10 week training
Graham & Rush, 2004 (11)	WKY & SHR Rats	In vitro rings Molecular	Aorta	↑ Ach dilation & eNOS, ↔ SOD, catalase	No change	Hypertension 6 wk low intensity exercise
TYPE II DIABETES MELLITUS						
Minami et al., 2002 (36)	OL-E Rat	In vitro rings	Aorta	D ↓ EDRF & EDHF		Diabetic Wheel running for 9 and 24 wks
			Mesenteric	ExTr ↑ EDRF & EDHF		
Sakamoto et al., 1998 (46)	OL-E Rat	In vitro rings	Aorta	D ↓ Histamine	No change	Diabetic Wheel running 16 wks
			Mesenteric	ExTr ↑ Histamine		

EDD: endothelium-dependent dilation, G: gastrocnemius, R: red, W: white, ExTr: exercise training, HF: high fat, D: diabetes, KO: knock out.