The coronary circulation in exercise training

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Laughlin MH, Bowles DK, Duncker DJ. The coronary circulation in exercise training. Am J Physiol Heart Circ Physiol 302: H10–H23, 2012. First published October 7, 2011; doi:10.1152/ajpheart.00574.2011.—Exercise training (EX) induces increases in coronary transport capacity through adaptations in the coronary microcirculation including increased arteriolar diameters and/or densities and changes in the vasomotor reactivity of coronary resistance arteries. In large animals, EX increases capillary exchange capacity through angiogenesis of new capillaries at a rate matched to EX-induced cardiac hypertrophy so that capillary density remains normal. However, after EX coronary capillary exchange area is greater (i.e., capillary permeability surface area product is greater) at any given blood flow because of altered coronary vascular resistance and matching of exchange surface area and blood flow distribution. The improved coronary capillary blood flow distribution appears to be the result of structural changes in the coronary tree and alterations in vasoreactivity of coronary resistance arteries. EX also alters vasomotor reactivity of conduit coronary arteries in that after EX, α-adrenergic receptor responsiveness is blunted. Of interest, α- and β-adrenergic tone appears to be maintained in the coronary microcirculation in the presence of lower circulating catecholamine levels because of increased receptor responsiveness to adrenergic stimulation. EX also alters other vasomotor control processes of coronary resistance vessels. For example, coronary arterioles exhibit increased myogenic tone after EX, likely because of a calcium-dependent PKC signaling-mediated alteration in voltage-gated calcium channel activity in response to stretch. Conversely, EX augments endothelium-dependent vasodilation throughout the coronary arteriolar network and in the conduit arteries in coronary artery disease (CAD). The enhanced endothelium-dependent dilation appears to result from increased nitric oxide bioavailability because of changes in nitric oxide synthase expression/activity and decreased oxidant stress. EX also decreases extravascular compressive forces in the myocardium at rest and at comparable levels of exercise, mainly because of decreases in heart rate and duration of systole. EX does not stimulate growth of coronary collateral vessels in the normal heart. However, if exercise produces ischemia, which would be absent or minimal under resting conditions, there is evidence that collateral growth can be enhanced. While there is evidence that EX can decrease the progression of atherosclerotic lesions or even induce the regression of atherosclerotic lesions in humans, the evidence of this is not strong due to the fact that most prospective trials conducted to date have included other lifestyle changes and treatment strategies by necessity. The literature from large animal models of CAD also presents a cloudy picture concerning whether EX can induce the regression of or slow the progression of atherosclerotic lesions. Thus, while evidence from research using humans with CAD and animal models of CAD indicates that EX increases endothelium-dependent dilation throughout the coronary vascular tree, evidence that EX reverses or slows the progression of lesion development in CAD is not conclusive at this time. This suggests that the beneficial effects of EX in CAD may not be the result of direct effects on the coronary artery wall. If this suggestion is true, it is important to determine the mechanisms involved in these beneficial effects.

atherosclerosis; coronary blood flow; endothelium; physical activity; smooth muscle

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Although there is no evidence that coronary blood flow (CBF) capacity limits aerobic metabolism in the normal heart, dynamic exercise training (EX) in normal subjects increases coronary transport capacity through increases in CBF capacity and capillary exchange capacity. Training-induced coronary
vascular adaptations can be divided into functional (alterations in vasomotor control) and structural adaptations (angiogenesis and vascular remodeling) (21, 84, 85, 87). Functional adaptations in normal subjects include changes in neurohumoral control of vascular resistance and changes in vasomotor reactivity of coronary resistance arteries. Although EX does not increase the oxygen carrying capacity of blood (28), myocardial oxygen extraction slightly increases following EX (155, 168). Much of the interest in the effects of EX on the coronary circulation results from the well-established effectiveness of physical activity/EX in the prevention (10, 162) and in the treatment of coronary artery disease (CAD) (161). While the mechanisms involved in EX-induced adaptations in the normal coronary circulation likely contribute to adaptations responsible for the effectiveness of EX in the prevention and treatment of CAD, it is apparent that additional mechanisms contribute because the beneficial effects of EX in CAD cannot be fully explained by the effects seen in normal subjects. The purpose of this review is to summarize and discuss what is known about the effects of EX on the coronary circulation in health and disease. We begin by discussing vascular adaptations seen in normal subjects and animals and then extend the discussion to the effects seen in the presence of atherosclerosis and CAD.

It is important to keep in mind that EX also increases maximal cardiac output, which is the result of cardiac adaptations in left ventricular (LV) mass and diameter produced by eccentric myocardial hypertrophy. Also, EX decreases myocardial oxygen demand because of decreases in heart rate and LV work. CBF per gram of myocardium is decreased in EX subjects because heart rate is decreased (5, 29, 68, 110, 168) and myocardial contractility, LV systolic wall stress, and ventricular work per gram of myocardium are minimally affected at rest and at a given level of submaximal exercise (24, 43, 109, 120, 141, 145, 174). These cardiac adaptations can also influence CBF capacity through a decrease in the extrascular compressive forces acting on the intramural coronary microvessels. Thus bradycardia contributes to the increased CBF capacity after EX because the bradycardia-mediated reduction in systolic time decreases impedance to CBF produced by systolic compression of the intramural coronary vessels (40). While these cardiac adaptations to EX are important, because of space limitations our primary focus in this discussion will be on coronary vascular adaptations induced by EX.

### Structural Vascular Adaptations in the Normal Heart

**Epicardial arteries.** Results from early experiments using corrosion casts of the coronary vasculature of young rodents indicated that EX induces an increase in the volume of the coronary vasculature (154, 157) because of increased conduit artery size (15, 62, 82, 99, 180). For example, 60 min of swimming per day increased coronary artery luminal area in young male rats with cardiac hypertrophy, but rats that exercised only twice each week and did not develop cardiac hypertrophy did not exhibit this adaptation (99). Increases in coronary artery size related to cardiac hypertrophy have also been reported in EX dogs (180) and monkeys (82). EX also appears to increase the size of human epicardial coronary arteries since echocardiographic and MRI measures (80, 81, 128, 185) indicate increases in the cross-sectional area of proximal coronary arteries. These increases in artery size were proportional to increases in LV mass in elite athletes compared with healthy sedentary individuals (128, 185). Windecker et al. (177) reported that 5 mo of EX resulted in a 28% increase in LV mass and a 23% increase in combined cross-sectional area of the left main and right coronary arteries measured with quantitative angiography. In contrast, Haskell et al. (62) reported no difference in angiographically measured cross-sectional areas of right coronary artery, left main, and left anterior descending coronary artery (LAD) of ultra-distance runners and sedentary subjects under basal resting conditions. However, nitroglycerin-induced increases in coronary cross-sectional area were positively correlated with aerobic exercise capacity. Hildick-Smith et al. (71) reported that nitroglycerin produced significantly greater dilation of the LAD in athletes than in sedentary men. Kozakova et al. (80) also reported a twofold greater dipyridamole-induced dilation of the left main coronary artery in athletes than in control subjects. Thus the results indicate that EX causes growth of epicardial arteries in proportion to the degree of exercise-induced cardiac hypertrophy. Simultaneously, conduit coronary artery tone during basal resting conditions is greater in EX individuals, so that conduit artery vasodilator capacity is greater in EX humans (62, 71, 177).

**Resistance vessels.** The number of coronary arterioles per square millimeters (numerical density) was reported to be 40–60% greater in treadmill EX than in sedentary swine (20, 174). White et al. (173) measured EX-induced adaptations of arterioles and found that total cross-sectional area ($\mu m^2$ arterioles per mm$^2$ of myocardium) of arterioles in the diameter range of 20–120 $\mu m$ significantly increased by 16 wk of EX, with a greater increase in total area in arterioles of 20–40 $\mu m$ in diameter (40–60%) than in arterioles of 40–120 $\mu m$ in diameter (15–30%) (Fig. 1). Interestingly, in 20–40-$\mu m$-diameter arterioles, the increase primarily resulted from an increase in the number of arterioles, whereas in 40–120-$\mu m$-diameter arterioles, an increase in arteriolar diameter was the major cause of increased total cross-sectional area (173).

**Capillary numerical density.** Early studies suggested an increase in capillary numerical density in young guinea pigs (130, 131) and dogs (163) following treadmill EX. Also, capillary density was found to be greater in wild than in domesticated rabbits (169, 170). In contrast, capillary-to-fiber ratio did not increase in young guinea pigs subjected to running (55) or in adult guinea pigs subjected to swimming (47). Rats from 3 to 18 mo of age, trained by either treadmill exercise or swimming, exhibit increased capillary densities with training (1, 9, 12, 26, 73, 98, 99, 107, 112, 158, 164, 167). However, in older rats angiogenesis is matched to cardiac hypertrophy so that EX does not alter capillary density (12, 73, 164) [see detailed review (39)].

Studies using dogs (94, 180, 181) and swine (20) also report no change in capillary-to-fiber ratio (20, 94) or capillary density (20, 94, 180, 181) following treadmill EX [see Table 2 in (39)]. Interestingly, endothelial cell division in pig coronary circulation was increased as was capillary sprouting at 1, 3, and 8 wk of EX but were no longer different from control after 16 wk of EX (Fig. 1). Capillary growth exceeded myocyte growth at 3 wk, but by 8 wk of EX, capillary density had returned to control (173). Thus, during the training program capillary angiogenesis occurred and temporarily exceeded the increase...
in LV mass, but with prolonged EX, angiogenesis was matched to LV hypertrophy.

Summary. EX increases epicardial coronary artery diameter and arteriolar densities and/or diameters, providing a morphometric basis for increased CBF capacity in EX animals (Fig. 1). Although there is evidence that EX increases myocardial capillary density in young rats, larger animals subjected to EX exhibit capillary density matched to cardiac hypertrophy; i.e., capillary density is maintained in the normal range. This matching of capillary angiogenesis to the degree of myocardial hypertrophy is in contrast to pathological forms of myocardial hypertrophy (due to hypertension or aortic stenosis) where capillary rarefaction often occurs (2).

Adaptations of Neurohumoral Control

Altered neurohumoral control of the coronary vascular resistance can result from changes in the following: 1) central autonomic activity, 2) the number and/or affinity of vascular receptors, or 3) receptor/second messenger signaling in vascular cells (186) (Figs. 2 and 3). EX increases resting parasympathetic tone to the heart, but myocardial muscarinic receptor density and sensitivity appear to be unchanged (4, 44) or slightly decreased (14, 176) after EX. Also, circulating levels of catecholamines are lower in EX humans and animals (11, 133, 146), particularly when comparing similar absolute levels of submaximal exercise. These combined results suggest that EX results in increased parasympathetic and decreased sympathetic activity to the heart (11, 133, 146). Although there is little information concerning the effects of EX on adrenergic or muscarinic receptor density/sensitivity in coronary vasculature, myocardial β-adrenergic receptor density and sensitivity are reported to be unchanged (58, 137, 176) or slightly decreased (4) after EX, whereas α-adrenergic receptor density has been reported to be either increased (44) or decreased (176) in the myocardium after EX.

Conduit coronary arteries. Bove and Dewey (15) reported that EX blunted the vasoconstrictor response of the proximal coronary arteries to β1-receptor stimulation with phenylephrine but not to serotonin in closed-chest, sedated adult dogs. Similarly, vasoconstrictor responses to norepinephrine and phenylephrine were blunted in conduit coronary arteries of EX dogs (136) and swine (123). Stehno-Bittel et al. (152, 153) proposed that the decreased vasoconstrictor reactivity is the result of EX-induced decreases of intracellular calcium (Cai^{2+}) in coronary vascular smooth muscle. Interestingly, vasoconstrictor responses of proximal coronary arteries to KCl or prostaglandin F_2α are not altered by EX (123, 136). As summarized in Fig. 4A, there appear to be a number of...
mechanisms for the altered vasoconstrictor responses due to remodeling of control of Ca\(^{2+}\) in coronary vascular smooth muscle of conduit arteries. Conversely, endothelium-dependent vasodilation produced by \(\alpha_2\)-adrenergic receptor stimulation was not altered in coronary arteries from EX dogs (123). Finally, blunting of the \(\beta\)-adrenergic vasodilator response to isoproterenol was observed in coronary arteries of EX dogs (136) but not in EX swine (123).

**Coronary resistance vessels.** Important evidence that EX may alter adrenergically mediated vasomotor function in coronary resistance arteries came from experiments that demonstrated that 4 to 5 wk of EX resulted in a blunted phenolamine-induced increase in diastolic CBF during exercise (101). Subsequent studies from the same laboratory found that \(\alpha\)-adrenergic blockade with phenolamine resulted in significantly greater (53), smaller (37), or, in the presence of \(\beta\)-blockade, similar (37) increases in mean CBF during submaximal exercise in EX dogs compared with sedentary animals. In open-chest dogs, \(\alpha_1\)-adrenoceptor blockade caused a slightly larger increase in mean CBF in EX than in sedentary animals (85). Thus current literature suggests that after EX, \(\alpha\)-adrenergic tone is maintained or slightly increased in coronary resistance vessels. These findings are consistent with an interpretation of increased adrenergic sensitivity after EX in the presence of lower circulating levels of catecholamines (11, 133, 146). This interpretation is supported by observations that both peripheral (97, 108) and coronary (36, 53) resistance vessels exhibit greater constriction in response to \(\alpha_1\)-adrenergic stimulation after EX. The sustained \(\alpha\)-adrenergic tone may contribute to enhanced myocardial oxygen extraction after EX (155, 168).

There are reports that EX and sedentary dogs exhibit similar decreases in CBF in response to nonselective \(\beta\)-adrenoceptor blockade (53, 102), \(\beta_1\)-selective adrenoceptor blockade (53, 102), or \(\beta_2\)-selective adrenoceptor blockade (37) during submaximal exercise. A maintained \(\beta\)-adrenergic vasodilator influence in the presence of lower circulating catecholamines is consistent with the reported increase in \(\beta_2\)-adrenergic receptor responsiveness of coronary resistance vessels following EX (36, 60).

There is no evidence for altered parasympathetic control of coronary resistance vessel tone after EX. Muscarinic receptor blockade did not change CBF in exercising dogs before or after EX (53).

**Summary.** Available data indicate that in the coronary microcirculation of EX subjects, there is a maintained or slightly increased \(\alpha\)-adrenergic and maintained \(\beta\)-adrenergic tone during submaximal exercise. Maintenance of adrenergic tone in the presence of lower circulating catecholamine levels is consistent with the observed increased receptor responsiveness to adrenergic stimulation. Conversely, \(\alpha\)- and \(\beta\)-adrenergic responsiveness seems to be reduced in large conduit coronary arteries of EX animals, which together with the lower catecholamine levels circulating in the blood, likely translates into lower \(\alpha\)- and \(\beta\)-adrenergic influences in EX subjects. Finally, there is no evidence for altered parasympathetic control of coronary conduit and resistance vessel tone after EX.

**Intrinsic Coronary Vascular Control**

**Endothelial control of conduit arteries.** Wang et al. (172) reported enhanced conduit coronary artery vasodilation in response to acetylcholine and reactive hyperemia in chronically instrumented dogs after 2 h/day of treadmill EX for only 7 days. This training had no effect on LV mass, heart rate, or CBF either at rest or during exercise. The enhanced dilation was abolished by the inhibition of nitric oxide (NO) synthase with nitro-L-arginine, and the dilation induced by nitroglycerine was not affected by EX. In contrast, endothelium-dependent relaxation (EDD) of proximal arteries was not increased following longer periods of EX (>10 wk) in dogs (136), swine (124), or rats (127) irrespective of whether EDD was stimulated in response to \(\alpha_2\)-adrenergic stimulation, substance P, vasoactive intestinal peptide, bradykinin, or acetylcholine. EX had little (123) to no (124) effect on the vasodilator response of the proximal coronary arteries to the endothelium-independent vasodilator nitroprusside in swine. Taken together, these observations suggest that during chronic EX, progressive outward remodeling of the epicardial arteries occurs so that shear stress levels and hence endothelial NO synthase expression normal-
ize (86, 93), thereby allowing EDD responses to return toward baseline levels (86, 95, 124, 136).

Endothelial control of microcirculation. EX of dogs for 8 wk was reported to enhance serotonin-induced increases in CBF measured in closed-chest anesthetized dogs, suggesting augmented EDD (15). Similarly, Muller et al. (115) reported enhanced bradykinin-induced EDD in coronary arterioles (64–157 μm in diameter) isolated from EX swine. The treatment of the arterioles with Nω-monomethyl-L-arginine inhibited bradykinin-induced vasodilation to a greater extent in the EX group and eliminated the difference between the two groups, suggesting that EX enhances NO production (115). The observation that cytosolic copper/zinc superoxide dismutase (SOD-1) was upregulated (139) suggests that the increased EDD responses were, at least in part, the result of a decreased quenching of NO by superoxide. The vasodilator response to sodium nitroprusside was not different between sedentary and EX swine (115), suggesting that EX principally increased NO production.

Myogenic tone and smooth muscle responsiveness to constrictors. Although active changes in diameter of coronary arterioles (75–150 μm in diameter) in response to 10-mmHg increments of intraluminal pressure were similar in arterioles from EX and sedentary swine, enhanced constriction was observed in coronary arterioles of EX swine for pressures above 40 mmHg (115). Subsequent work revealed that the enhanced tone was due to altered calcium-dependent PKC signaling in the coronary vascular smooth muscle cells (79) and enhanced voltage-gated calcium currents in large arterioles through L-type calcium channels (Fig. 4) (17). This increase of basal myogenic tone in arterioles appears to be specific for stretch-mediated contractions because neither the receptor-mediated vasoconstriction in response to endothelin-1 or acetylcholine nor the vasoconstriction produced by direct voltage-gated calcium channel activation by the L-type calcium channel agonist Bay K 8644 or by K^+ were modified by EX (91). The results from coronary vascular smooth muscle in epicardial arteries from EX animals suggest that the adaptation may involve increased activity of voltage-gated K^+ (Kv) and calcium-activated K^+ (KCa) channels or adaptations at the level of the sarcoplasmic reticulum (19, 63, 87). However, it is uncertain whether mechanisms involved in coronary vascular smooth muscle of epicardial arteries also occur in coronary vascular smooth muscle of coronary arterioles.

Metabolic control. Although adenosine does not play an essential role in the regulation of CBF under conditions of normal arterial inflow (3, 72, 165), the maximal adenosine-induced increase in CBF is reported to be greater after EX in both dogs (36, 85, 94) and miniature swine (92) in vivo. Also, von Restorff et al. (168) and Stone (155) reported a slight increase in myocardial oxygen extraction in EX dogs, suggesting an altered local control of CBF. EX has also been reported to result in slightly lower values of CBF per gram of myocardium both at rest and during submaximal exercise (68, 168). However, CBF at similar levels of cardiac work is not changed by EX (53, 68, 101, 155, 168), suggesting that EX has a minimal effect on the coupling between myocardial metabolism and CBF.

Heaps et al. (64) found that Kv or KCa channel function in arterioles from remote, normally perfused myocardium in hearts with a chronic coronary artery occlusion were not altered following EX. In contrast, EX enhanced Kv or KCa channel activity in porcine large conductance arteries, which could serve to facilitate downstream metabolic vasodilation (Fig. 4) (18). The effects of EX on arteriolar K^+ channel function in the normal heart remain to be determined.

Summary. EX produces a sustained augmentation of EDD in normal coronary microcirculation but apparently only transiently in conduit coronary arteries. This enhanced endothelium responsiveness appears to be principally due to increased NO bioavailability. Available data also indicate that EX alters the intrinsic vasomotor properties of coronary resistance vessels. Arterioles exhibit an increased myogenic tone, which appears specific for stretch-induced contractions, as vasoconstrictor responses to various agonists are unchanged. The mechanisms underlying the increased myogenic tone likely involve increased activity of voltage-gated K^+ (Kv) and calcium-activated K^+ (KCa) channels.
Signalings enhance Cav1.2, leading to activation of contractile filaments and also activated by EX. In arteriolar CSM, Ca²⁺ increases [Ca²⁺], protein-1. smooth muscle-specific gene expression; Myo, myocardin; AP1, activator states. RyR, ryanodine receptor; ROK, Rho-associated protein kinase; SMX, larities and differences in the effects of EX on CSM in normal and diseased producing a noninflammatory matrix. Note that there are a number of simi-

phenotype and increased expression of collagens III and IV (Col III, IV), a more proinflammatory matrix composition and synthesis of proliferative enhancing CSM synthesis of fibronectin (FN) and collagen I (Col I), leading to

[Ca²⁺] ss), which may contribute to the increased activation of large-conduc-

classical Ca²⁺/H²⁺ exchange mechanisms. Nuclear Ca²⁺ responses ([Ca²⁺]), which are similarly re-
duced by EX, which may affect Ca²⁺ -dependent transcription factors (CaTF, e.g., cAMP response element-binding protein and nuclear factor of activated T cell) and target gene expression. On the top right note that EX increases spontaneous, slow-Ca²⁺ release from the SR into the subsarcolemmal space ([Ca²⁺], which may contribute to the increased activation of large-conduc-
tance Ca²⁺-activated BK K⁺ channels by EX. In addition, K⁺ channels are also activated by EX. In arteriolar CSM, Ca²⁺-dependent PKC (e.g., PKCs) signaling enhances Ca₁.2, leading to activation of contractile filaments and enhanced myogenic tone. Together, these changes result in an increase in the gain of the vasomotor contractile system and a more stable mature CSM phenotype. B: proposed model illustrating the manner in which EX may interact with proatherogenic factors, thereby decreasing lesion progression and/or stimulating lesion regression of atherosclerosis through regulation of CSM phenotype in coronary artery disease (CAD; gray, atherogenic effects). Proatherogenic factors (such as PDGF-BB, TNF-α, leptin) upregulate intermediate conductance Ca²⁺-activated K⁺ channels (K⁺), voltage-independent Ca²⁺ channels (e.g., TRP) while suppressing Ca₁.2 and BK (K⁺) channels. CAD also disrupts SR Ca²⁺ release and extrusion and increases [Ca²⁺]. As shown on the right, this ion channel profile switch enhances CSM synthesis of fibronectin (FN) and collagen I (Col I), leading to a more proinflammatory matrix composition and synthesis of proliferative genes (PLF). EX adaptations described in A produce a stable, noninflammatory phenotype and increased expression of collagens III and IV (Col III, IV), producing a noninflammatory matrix. Note that there are a number of simi-

larities and differences in the effects of EX on CSM in normal and diseased states. RyR, ryanodine receptor; ROK, Rho-associated protein kinase; SMX, smooth muscle-specific gene expression; Myo, myocardin; AP1, activator protein-1.

Integrated Coronary Vascular Adaptations

The significance of the structural and functional adaptations of the various segments within the coronary vascular tree is demonstrated in the improved myocardial oxygen transport capacity apparent after EX. Current literature indicates that maximal CBF and capillary diffusion capacity are both increased by EX.

**Maximum CBF.** Experiments designed to determine the effects of EX on CBF capacity have reported either no change (5, 16, 20, 25, 30, 100, 143, 155, 183) or an increase in CBF capacity after EX (6, 23, 36, 85, 89, 92, 94, 103, 129, 151, 173). Differing results may be caused by several factors including differences in species, age, and sex of the experimental animals and the duration, intensity, and type of the EX. Based on our review of the literature, we consider the most important factor to be the method used to assess CBF capacity as previously discussed in detail (39, 84, 85, 87, 90, 92). In studies where maximal vasodilation was demonstrated under tightly controlled hemodynamic conditions and where the efficacy of the training program was documented, CBF capacity was consistently reported to be increased following EX in swine (92, 173), dogs (85, 94), and rats (23) [for details, see Table 3 in (39)]. There have also been a number of clinical studies that assessed CBF capacity using echo-Doppler or positron emission tomography. These clinical studies also provide a mixed view of effects of EX on CBF capacity, with some reporting increases (54, 71, 80, 81, 177) and others no change (59, 67, 76, 132). Similar to the animal studies, assurance of maximal vasodilation, control of hemodynamic vari-

cables and documentation of training effectiveness make it difficult to evaluate the quality of the CBF capacity measure-
ments in these clinical studies. Importantly, it is common to use standard doses of adenosine with cut-off values below normal values in clinical studies to estimate what is referred to as coronary reserve (70). However, as summarized by Heusch (70), adenosine is not simply a coronary vasodilator but also has cardioprotective, algesic, and antihippertrophy properties. Thus, in these clinical studies of coronary vasodilator reserve, maximal adenosine vasodilation is generally not demonstrated, so that while these measures provide valuable prognostic information, they may not rigorously estimate true coronary flow reserve. The weight of the currently available evidence suggests that EX increases maximal CBF per gram of myocardium when 1) CBF capacity is measured rigorously and 2) when the exercise program is of sufficient intensity to produce a training effect.

**Capillary diffusion capacity.** Capillary exchange capacity, measured as the permeability surface area product, is determined by capillary permeability and total capillary surface area available for exchange. Although capillary numerical density is not increased by EX, increased capillary permeability surface area product could still result from the optimization of CBF distribution, effectively increasing the capillary surface area so that the maximal capillary exchange capacity becomes avail-

![Fig. 4. A: model of EX-induced adaptations of coronary smooth muscle (CSM) in normal subjects (boldface indicates those elements altered by EX). The left center illustrates decreased intracellular calcium concentration ([Ca²⁺]) response to selective agonists (e.g., endothelin), which produces a reduced Ca²⁺-dependent activation of contraction. This decreased [Ca²⁺] occurs despite an increased Ca²⁺-influx through L-type Ca²⁺ channels (Ca₁.2), which is buffered by a non-sarcoplasmic reticulum (SR), non-Na⁺/Ca²⁺ exchanger mechanisms. Nuclear Ca²⁺ responses ([Ca²⁺]), which are similarly reduced by EX, which may affect Ca²⁺-dependent transcription factors (CaTF, e.g., cAMP response element-binding protein and nuclear factor of activated T cell) and target gene expression. On the top right note that EX increases spontaneous, slow-Ca²⁺ release from the SR into the subsarcolemmal space ([Ca²⁺]), which may contribute to the increased activation of large-conductance Ca²⁺-activated BK K⁺ channels by EX. In addition, K⁺ channels are also activated by EX. In arteriolar CSM, Ca²⁺-dependent PKC (e.g., PKCs) signaling enhances Ca₁.2, leading to activation of contractile filaments and enhanced myogenic tone. Together, these changes result in an increase in the gain of the vasomotor contractile system and a more stable mature CSM phenotype. B: proposed model illustrating the manner in which EX may interact with proatherogenic factors, thereby decreasing lesion progression and/or stimulating lesion regression of atherosclerosis through regulation of CSM phenotype in coronary artery disease (CAD; gray, atherogenic effects). Proatherogenic factors (such as PDGF-BB, TNF-α, leptin) upregulate intermediate conductance Ca²⁺-activated K⁺ channels (K⁺), voltage-independent Ca²⁺ channels (e.g., TRP) while suppressing Ca₁.2 and BK (K⁺) channels. CAD also disrupts SR Ca²⁺ release and extrusion and increases [Ca²⁺]. As shown on the right, this ion channel profile switch enhances CSM synthesis of fibronectin (FN) and collagen I (Col I), leading to a more proinflammatory matrix composition and synthesis of proliferative genes (PLF). EX adaptations described in A produce a stable, noninflammatory phenotype and increased expression of collagens III and IV (Col III, IV), producing a noninflammatory matrix. Note that there are a number of simi-

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able for exchange. Laughlin and associates reported that EX caused an increase in coronary capillary permeability surface area product in dogs (85, 88, 94) and miniature swine (92).

When morphometric measurements of capillarization and capillary permeability surface area product were examined in the same hearts, EX was found to increase coronary capillary permeability surface area product with no change in capillary density (92, 94). In the maximally vasodilated bed, capillary permeability surface area product is a function of blood flow, possibly because the increased CBF is associated with the recruitment of more capillary exchange area (92, 94). White et al. (174) also demonstrated that EX increased CBF capacity and capillary permeability surface area product with no net change in capillary density. However, as summarized in Fig. 1, White et al. reported increases in capillary diameters and increases in arteriolar densities, two adaptations that could decrease capillary transit time and improve matching of capillary blood flow and exchange capacity. Although a higher capillary permeability surface area product in trained animals could be due to the higher maximal flow rates, this is unlikely because a higher capillary permeability surface area product was also observed when sedentary and EX animals were compared at similar flow rates (92, 94, 126). Thus EX changes the coronary vascular resistance distribution, thereby increasing the effective capillary surface area and capillary permeability surface area product without a change in coronary capillary numerical density.

These effects of EX on capillary exchange may contribute to the decreased coronary sinus oxygen content and increased percent oxygen extraction reported by von Restorff et al. (168) and Stone (155) in EX dogs, although Stone (155) reported there was no statistically significant difference in absolute arteriovenous oxygen content difference after training. These studies reveal that after EX at any given myocardial oxygen consumption rate, oxygen extraction was greater and coronary sinus oxygen content was less, demonstrating that the coronary circulation was providing the required oxygen with less blood flow after training (155, 168). It is likely that these EX-induced changes are, in part, the result of changes in the distribution of CBF through the coronary capillary bed, resulting in improved oxygen extraction.

Summary. Available evidence indicates that both an increase in maximum CBF and an increase in coronary capillary permeability surface area product contribute to the enhanced capacity and reserve to deliver oxygen to the myocardium in EX subjects.

EX, CAD, and the Coronary Collateral Circulation

Although EX does not provide immunity to atherosclerosis (34, 113), EX has emerged as an intervention for the primary and secondary prevention of CAD (49, 50, 87, 106, 160–162). The mechanisms proposed to contribute to the beneficial effects of EX include regression of atherosclerosis, improvement of endothelial function, formation of collaterals (arteriogenesis), and development of new vessels (angiogenesis/vasculo-genesis) (87, 106). For an overview of the effects of EX in patients with CAD and the potential mechanisms, the reader is referred to several review articles (49, 50, 106, 134). Here we briefly summarize evidence concerning the effects of EX on coronary lesion progression/regression, endothelial and coronary vascular smooth muscle cell function in CAD, and the collateral circulation and coronary microcirculation within collateral-dependent myocardium.

Effects of exercise on coronary plaque/lesion progression/regression in CAD. It is well established that EX stimulates the enlargement of conduit coronary arteries in normal humans and animals (80, 81, 90, 128, 180, 185). There is also evidence that EX reduces the development, and/or causes the regression, of atherosclerotic lesions in coronary arteries of animal models of disease including mice, rabbits, pigs, and nonhuman primates. Okabe et al. (121) reported that 20 min of swimming exercise 3 times/wk for 8 and 16 wk in apolipoprotein E-deficient mice fed a high-fat diet exhibited less fatty streak formation and lesser fibrofatty plaques in the root of the aorta than nonexercised mice. Using this same mouse model, this group (122, 150) also reported that the decreased lesion progression in swim EX mice was due to increased antioxidant effects mediated through the NO system. In contrast, Young et al. (184) reported that swim training of apolipoprotein E-deficient mice did not alter atherosclerotic lesion development (Oil Red O staining) or oxidant load in the aorta. Consistent with the results from the Okabe group, Yang et al. (182) reported that treadmill exercise blunted the development of lipid deposition and expression of inflammatory mediators in the endothelium of the aorta of rabbits on a high-fat diet without modifying blood lipid contents. Endothelium-dependent relaxation of the atherosclerotic aortas was also improved by EX in these rabbits (182).

Link et al. (104) reported less CAD in left coronary arteries and fewer total atheromas in the arterial tree of male and female pigs trained for 22 mo. In contrast, recent results of experiments on pigs in early stage disease demonstrated that EX did not appear to retard the progression or reverse coronary atherosclerosis (166). Kramsch et al. (82) reported that exercise decreased CAD in monkeys, but a recent study by Williams et al. (175) found that wheel running in adult male monkeys did not appear to retard the progression or reverse CAD as measured with angiographic measures of lesion area. While their results indicated that exercise did not inhibit the progression of CAD or improve vascular lesions, their results also indicated that exercise improved measures of cardiovascular health (175). We and others have demonstrated in a number of porcine models of CAD that EX has beneficial effects on endothelial function/phenotype, as reflected in an increased EDD and altered expression of endothelial genes toward a more atheroprotective phenotype (159, 171, 179).

The current literature contains several randomized human trials, which angiographically evaluated the effects of exercise on coronary lesion progression/regression in CAD (56, 61, 125, 147). While these trials provide important insight into whether or not exercise has a direct effect on lesion size in CAD, these data must be carefully interpreted since the studies included exercise as one component of lifestyle and/or medical intervention. Ornish et al. (125) included exercise in combination with low-fat diet as part of the lifestyle interventions in the Lifestyle Heart Trial and found that the percent stenosis decreased (regressed) in the coronary arteries of the treatment group but increased (progressed) in the control group. The Heidelberg Regression Study (56, 147) reported the results of angiographic studies and documented the ability of regular, leisure time exercise to retard the progression of and/or reverse
CAD. In the Hambrecht et al. study (56), CAD patients were prospectively randomized either to an intervention group that participated in regular exercise (n = 29) or to a control group (n = 33) receiving usual care and no supervised exercise. Thirty minutes of daily exercise was recommended for both groups, but the intervention group also received two 60-min supervised exercise sessions each week. Energy expenditure in leisure-time physical activity was estimated from standardized questionnaires and from participation in group exercise sessions. After one year of participation, repeat coronary angiography was performed and coronary lesions were measured by digital image processing. Patients in the exercise intervention group exhibited an increase in oxygen uptake of 7% (P < 0.001) at ventilatory threshold and of 14% at peak exercise (P < 0.05). Both indexes of cardiorespiratory fitness were decreased in patients in the control group. The exercise intervention group exhibited regression of CAD in 8 patients (28%), the progression of disease in 3 patients (10%), and no change in coronary morphology in 18 patients (62%), whereas in the control group progression was observed in 45%, no change in 49%, and regression of disease in 6%. When the patient groups were combined into groups according to progression/no change/regression of CAD, the lowest level of leisure time physical activity was noted in patients with progression of disease (1,022 ± 142 kcal/wk) as opposed to patients with no change (1,533 ± 122 kcal/wk) or regression of disease (2,204 ± 237 kcal/wk) (P < 0.005) (56). Thus these seminal experiments suggested that if a CAD patient could sustain 2,204 kcal/wk in leisure-time physical activity for one year, they would induce regression of CAD lesions (56). Similar results were obtained from the Stanford Coronary Risk Intervention Project (61) in which patients were assigned to a risk reduction group or usual care group. The risk reduction group exhibited 47% less lesion progression after one year than the usual care group. Of interest, the results indicated that the change in treadmill exercise performance was the best predictor of the change in coronary stenosis in this data set (61). It does not appear that the question of whether or not EX can cause regression or slower growth of coronary atherosclerotic lesions has been addressed in human subjects since the mid-1990s. Indeed, in a recent review article on this topic, Gielen et al. (49) state that “Surprisingly, not a single study has addressed exercise-mediated changes in plaque volume by intravascular ultrasound thus far...”

There is evidence that EX may have a greater effect on CAD lesion progression/regression following treatment with percutaneous transluminal coronary angioplasty and/or placement of intravascular stents. Belardinelli et al. (8) divided 118 patients who received percutaneous transluminal coronary angioplasty and/or stent treatments into two groups: EX patients, who performed three supervised exercise bouts (at 60% peak oxygen consumption), and control patients (mild normal activity of life). Follow-up studies were performed 6 mo after group assignment. They found that the EX patients exhibited improved functional capacity and quality of life relative to controls with fewer coronary events and lower hospital readmissions. Whereas the number of patients exhibiting restenosis was not affected by EX, the extent of restenosis was lower in the EX patients in both the balloon-dilated and stented segments. In three EX patients, regression of CAD was seen and no control subjects exhibited regression of CAD. Furthermore, the number of new lesions in epicardial coronary arteries not undergoing angioplasty was lower in the EX patients. In related experiments, Fleenor and Bowles (45) recently reported that EX inhibits coronary artery lesion development and alters the extracellular matrix composition of the coronary neointima formed following percutaneous transluminal coronary angioplasty in Yucatan miniswine. EX significantly decreased lesion size and neointima proliferation in the LAD and attenuated type I collagen expression. These beneficial effects of EX were not observed in the left circumflex coronary artery. Total collagen was increased and fibronectin was decreased by EX in the neointima of both LAD and left circumflex coronary arteries. The authors concluded that EX following percutaneous transluminal coronary angioplasty may increase event-free survival rates by decreasing coronary lesion size and altering the composition of the extracellular matrix of the wall of the coronary arteries (45). EX also appeared to reduce vascular disease in the peri-stent and non-stent regions of coronary arteries treated with percutaneous transluminal coronary angioplasty and stents in Ossabaw pigs, a model of type 2 diabetes (42).

In summary, the current literature paints a mixed picture concerning whether or not EX limits progression or produces regression of atherosclerotic lesions. Most data in large mammals do not indicate that exercise alters lesion progression/regression, but there is evidence of the beneficial effects of EX in coronary arteries that have been treated with percutaneous transluminal coronary angioplasty and/or intravascular stents. If our conclusion is correct that the current literature suggests that EX does not limit lesion development or lead to CAD plaque regression except following interventional procedures (percutaneous transluminal coronary angioplasty or stent placement), it is not clear why this is the case. It is possible that coronary hemodynamics are altered by percutaneous transluminal coronary angioplasty and/or stenting and related catheter laboratory procedures so that exercise bouts generate more beneficial mechanical signals in the walls of these arteries. If this is true, the mechanisms await discovery. Perhaps the most compelling evidence of a beneficial effect of exercise on lesion regression, in the absence of interventional procedures, is from human subjects. However, the reported changes in percent stenosis in these studies are quite small and therefore likely of little functional significance (56, 61, 125, 147). In this regard, Linke et al. (106) concluded that “the almost negligible amount of regression is unlikely to account for the tremendous relief in symptoms of CAD and the improvement of myocardial perfusion in patients undergoing exercise training.” Linke et al. (106) went on to conclude that the beneficial effects of EX may be largely attributed to EX-induced improvement in EDD and/or the overall endothelial function in the coronary circulation.

Finally, exercise-induced alterations in atherosclerotic lesion composition represent a compelling potential mechanism for reduced coronary heart disease mortality in physically active individuals. Human clinical trials report a reduction in coronary heart disease mortality as the most consistent effect of physical activity. Acute coronary syndromes and sudden death are most often associated with rupture of complex, vulnerable plaques that are otherwise clinically benign, i.e., <70% luminal stenosis, and asymptomatic (27). Lakka et al. (83) demonstrated an inverse relationship between chronic physical activ-
ity and the incidence of first acute myocardial infarction, even in individuals with normal stress EKGs consistent with the concept that physical activity may shift a “vulnerable” thin-cap atheroma to a more stable lesion less prone to rupture. Experimental evidence in animal models provides some support for this concept. EX in mice (75, 116) has been shown to reduce plaque rupture and increase cap thickness and collagen content, the latter likely due to lower matrix metalloproteinase (MMP-9) and increased tissue inhibitor of metalloproteinases. Similar beneficial changes in lesion composition have also been shown in postangioplasty restenosis in swine (45).

EX may alter lesion progression in atherosclerosis by changing coronary smooth muscle phenotype. Smooth muscle plays an important role in both the initiation and progression of atherosclerotic lesions (148, 149). There is also growing evidence that EX can modify coronary vascular smooth muscle cell phenotypic modulation in atherosclerosis through altered ion channel regulation of Ca$^{2+}$ (17–19, 171). Clearly these EX-induced changes in the control of Ca$^{2+}$ would be expected to decrease the tendency for coronary vasospasm as well. Also, as summarized in Fig. 4B, there is evidence that EX interacts with proatherogenic factors, thereby decreasing lesion progression and/or regression through its effects on shear stress stimulated release of NO, alterations in transmural pressure and/or altered circulating factors. It is clear that more work is needed to fully understand the effects or EX on coronary vascular smooth muscle cell and its role in atherogenesis.

EX increases EDD in hyperlipidemia, atherosclerosis, and CAD. EX has been shown to improve endothelial function in normal coronary (115, 172) and peripheral arteries (35, 74, 111), which is, at least in part, due to increased NO production through endothelial NO synthase (93, 95, 96, 115, 178) and increased expression of SOD (139, 140). Also, Hambrecht et al. (57) reported that EX increased EDD of conduit and resistance coronary arteries of CAD patients (57). Furthermore, EX appears to preserve EDD of coronary arteries of female (179) and male hypercholesterolemic pigs (159) in early stage CAD. Indeed, the endothelial dysfunction produced by a high-fat diet as well as the effects of EX in preserving endothelial function in coronary arteries are generally similar in male and female pigs (159, 179). EX attenuated the deleterious effects of hypercholesterolemia on endothelial function in coronary arteries, in part, by increased NO bioavailability (perhaps due to increased SOD content) and by the removal of a prostanoid vasoconstrictor, but EX did not appear to alter the role of non-cyclooxygenase, non-NO synthase factors such as endothelium-derived hyperpolarizing factor (159, 179). Thus most available information indicates that in animal models of CAD and in patients with CAD, EX increases EDD in the conduit arteries and in arterioles (49, 87, 105, 106, 134).

Effects of EX on collateral arteries. A comparison of collateral CBF between sedentary and EX animals where collateral CBF is measured as retrograde flow from a cannulated collateral dependent coronary artery (22, 33, 143) or with radioactive microspheres (32, 38, 77, 78, 142, 144) provides exclusively negative results; i.e., collateral flow in EX animals is the same as sedentary values. Knight and Stone (77) measured collateral CBF in the same chronically instrumented dogs before and after EX and found that collateral CBF was increased by EX. An advantage of this study (77) was that measuring collateral CBF before and after EX allowed an adjustment for interanimal differences in the native collateral bed of the dogs. Cohen (32) also observed an increase in collateral CBF in chronically instrumented dogs following EX. Importantly, Cohen (32) found that the chronic instrumentation procedure stimulated the growth of coronary collaterals independent of EX, as he reported a similar increase in collateral CBF in sedentary animals maintained sedentary while the EX dogs trained. Thus the available literature indicates that EX does not enhance native collateral blood flow in the normal heart.

Effects of EX on collateral arteries: coronary stenosis or occlusion. A pivotal study by Eckstein (41) reported that EX of dogs with a chronic coronary artery stenosis increased collateral formation. Eckstein (41) measured retrograde blood flow from the cannulated collateral-dependent artery and found that EX produced the greatest increase in this measure of collateral CBF when imposed on a dog with a mild stenosis, which resulted in minimal collateral formation in the sedentary animals. These results suggested that if exercise bouts produce myocardial ischemia, it is more effective in stimulating collateral vessel growth. However, many angiographic studies of collateralization in CAD patients have reported that EX did not improve angiographically detectable collateralization (48, 119). Angiographic measures of collateralization are limited to the measurement of the size of relatively large coronary collaterals and do not assess collateral blood flow. Circumventing this limitation of angiography, Belardinelli et al. (7) used thallium uptake to measure collateral-dependent myocardial perfusion in patients with ischemic cardiomyopathy and reported that 8 wk of moderate EX increased collateral CBF. The current literature indicates that EX does not appear to stimulate collateral formation in the coronary circulation of normal hearts, whereas evidence exists to suggest that if exercise bouts produce or aggravate myocardial ischemia in a region of myocardium distal to a coronary lesion (stenosis), then EX is effective in stimulating collateral vessel growth.

Another model of coronary disease that has been used to explore the hypothesis that EX can increase growth of coronary collaterals is the gradual coronary artery occlusion model. Most commonly, amiodor constrictors have been applied on a coronary artery, and as the amiodor material absorbs water, it gradually occludes the coronary artery over a period of 3 to 5 wk. Use of this model of CAD has also yielded equivocal results relative to the effects of EX on collateralization. Heaton et al. (66) and Neill and Oxendine (118) examined the effects of EX on collateral CBF in dogs and reported no effects of EX on collateral CBF 6–8 wk after placement of an amiodor constrictor on a coronary artery. In contrast to these results in dogs, CBF was ~70% of normal in the collateral-dependent region of pigs that were EX, compared with ~55% in sedentary pigs with an amiodor coronary occluder in place (13, 138).

Vasomotor control of coronary resistance vessels in collateral-dependent myocardium. As discussed in Effects of EX on collateral arteries: coronary stenosis or occlusion, the literature does not consistently indicate that EX results in enhanced growth of collateral arteries in models of CAD or in patients with CAD. The literature is more consistent in reference to the question of whether or not EX has beneficial effects on the vasomotor reactivity of collateral arteries and/or vasomotor control of resistance in collateral-dependent myocardium. The majority of experiments relating to this question have used the chronic amiodor occlusion model. For example, examination of the effects of EX on epicar-
dial arteries within the collateral-dependent region of EX hearts revealed improved EDD (51) and improved adenosine-induced vasodilation (65) compared with sedentary pigs with atherosclerotic occlusions. EX also improved bradykinin-induced EDD in arterioles isolated from the collateral-dependent myocardium (52), and VEGF165-induced EDD was reported to be enhanced in collateral-dependent arterioles (46). Fogarty et al. (46) also reported that the enhanced VEGF-induced EDD was mediated principally via increased NO bioavailability. Another important observation of these studies was that EX did not improve bradykinin-induced EDD of arterioles isolated from the normally perfused region of collateralized hearts (52) in contrast to results from coronary arterioles isolated from normal EX pigs (115). Griffin et al. (51) proposed that the effects of EX on coronary arteriolar vasomotor reactivity are modified in the nonoccluded arterial beds of chronically coronary occluded hearts (52). Thus the coronary arteries located in the nonoccluded zones of hearts cannot be assumed to be “control” vessels.

It is interesting that EX appears to increase myogenic tone in arterioles isolated from collateral-dependent zones of this model of CAD (64) in a manner similar to that reported for arterioles from normal EX hearts (114). EX is also reported to enhance endothelin-1-mediated contractile responses in collateral-dependent resistance arteries (∼150 μm) that may be mediated by increased PKC-mediated coronary smooth muscle calcium sensitization (135). Further evidence of EX effects on coronary vascular smooth muscle in collateral-dependent arteries is provided by the report of augmented vasodilator responses through K⁺ channel activity (64).

Summary. There is no doubt that epidemiologic studies consistently indicate that there is an inverse relationship between CAD and regular physical activity and/or cardiorespiratory fitness (49, 106, 161). However, the current evidence does not firmly support the hypothesis that these beneficial effects of exercise result from a blunted progression and/or an increased regression of coronary lesions. The strongest evidence supporting this hypothesis is from human studies, but these results may reflect the overall effects of lifestyle changes, of which exercise was but one component. In general, the current evidence indicates that EX improves endothelial phenotype and function in coronary arteries of humans and animal models with CAD, and that EX has beneficial effects on coronary vascular smooth muscle in diseased coronary arteries.

Coronary collateral growth does not appear to be increased by EX in normal subjects. However, there is evidence that collateral growth can be enhanced by EX if exercise produces or increases myocardial ischemia. Nevertheless, the concept that exercise-induced ischemia stimulates collateral vessel growth is not supported by studies in which β-adrenergic blockade was administered to minimize the occurrence of myocardial ischemia during gradual coronary occlusion with an atherosclerotic constrictor. Thus propranolol had no effect on the rate of collateral formation in either swine (156) or dogs (31, 117), suggesting that other factors such as the pressure gradient between vascular beds, which determines the shear stress on the collateral vessel endothelium, may actually be more important than ischemia in EX-induced stimulation of growth of collateral vessels.

Resistance arteries isolated from the collateral-dependent region of hearts from EX pigs exhibit increased basal tone and increased vasodilator influences, increased NO production, and increased K⁺ channel activity (Fig. 3). Coronary resistance arteries isolated from the hearts of pigs with atherosclerotic CAD exhibit similar adaptations to EX (69). It seems reasonable to propose that these arteriolar adaptations to EX may provide a greater capacity of the coronary microcirculation to sustain CBF to myocardium at risk of ischemia. Indeed, Linke et al. (103) proposed that the effects of EX on endothelium and EDD may be greater in importance than any other known effect of EX on the coronary circulation.

Conclusions and Future Perspectives

In the normal heart, EX produces a variety of structural adaptations in the coronary circulation, including 1) increased conduit artery diameters, 2) increased arteriolar densities and diameters, and 3) maintained coronary capillary numerical density commensurate with the degree of cardiac hypertrophy. These changes likely underlie the increased CBF per gram of myocardium and increased diffusion capacity in EX hearts.

EX also induces functional adaptations in coronary circulation, including 1) an increased EDD (transient in conduit arteries, sustained in resistance vessels) that is principally NO mediated, 2) altered α-adrenergic influence (reduced in conduit vessels and increased in resistance vessels), and 3) a change in local control of resistance vessels. Coronary arterioles exhibit increased myogenic tone after EX.

In animal models of coronary artery obstruction and CAD patients, if exercise bouts produce or increase ischemia, there is evidence that collateral growth can be enhanced. In CAD patients and animal models of CAD, the evidence indicates that EX increases EDD in conduit arteries and in the arterial tree. However, the evidence that EX reverses or slows the progression of lesion development in CAD is not conclusive.

Notwithstanding these major advances in our understanding of coronary vascular adaptation to EX in health and CAD, several research questions remain outstanding. For example, the molecular mechanisms underlying the structural and functional adaptations to EX in the coronary vascular tree of the normal heart remain incompletely understood and await further elucidation. Also, the mechanism by which EX induces/enhances collateral formation in hearts with a coronary artery stenosis remains incompletely understood. Moreover, there seems to be no explanation for the lack of effect of EX on atherosclerosis progression/regression, despite the apparent beneficial effects of EX on endothelial function in animal models of CAD. Finally, we do not fully understand the mechanism underlying the clinical benefit of EX in patients with CAD. Answering these questions will be a major challenge in years to come.

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AUTHOR CONTRIBUTIONS

M.H.L., D.K.B., and D.J.D. conception and design of research; M.H.L. and D.J.D. performed experiments; M.H.L. drafted manuscript; M.H.L., D.K.B., and D.J.D. edited and revised manuscript; M.H.L., D.K.B., and D.J.D. approved final version of manuscript; D.K.B. interpreted results of experiments; D.J.D. analyzed data.
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