The Coronary Circulation in Exercise Training

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ABSTRACT

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 due to 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 due to 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 due to 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 (NO) bioavailability due to changes in NO 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 progression of atherosclerotic lesions or even induce 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 regression of or slow 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 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.
INTRODUCTION

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 (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 increases slightly 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 prevention (10), (162) and in 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 prevention and treatment of CAD, it is apparent that additional mechanisms contribute because the beneficial effects of EX in CAD can not be fully explained by 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 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 due to 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 extravascular 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, due to 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),
due to increased conduit artery size (15, 62, 82, 99, 180). For example, 60 min of swimming/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 exercise trained dogs (180) and monkeys (15, 82). EX also appears to increase the size of human epicardial coronary arteries as echocardiographic and MRI measures (80, 81, 128, 185) indicate increases in cross-sectional area of proximal coronary arteries. These increases in artery size were proportional to increases in LV mass in elite athletes compared to healthy sedentary individuals (128, 185). Windecker et al. (177) reported that 5 months 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 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 (71) reported that nitroglycerin produced significantly greater dilation of the LAD in athletes than in sedentary men. Kozakova et al (80) also reported a 2 fold greater dipyridamole-induced dilation of the left main coronary artery in athletes than in control subjects. Thus, 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 mm² (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 (µm² arterioles per mm² of myocardium) of arterioles in the range of 20-120 µm increased significantly by 16 weeks of EX, with a greater increase in total area in arterioles of 20-40 µm (40-60%) than in arterioles of 40-120 µm (15-30%) (Fig. 1). Interestingly, in 20-40 µm arterioles the increase resulted primarily from an increase in the number of arterioles, whereas in 40-120 µm 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/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 months 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 (39) for detailed review).
Studies using dogs (94, 180, 181) and swine (20) also report no change in capillary/fiber ratio (20, 94) or capillary density (20, 94, 180, 181) following treadmill EX (Table 2 of (39)). Interestingly, endothelial cell division in pig coronary circulation was increased as was capillary sprouting at 1, 3 and 8 weeks of EX but were no longer different from control after 16 weeks of EX (Fig 1). Capillary growth exceeded myocyte growth at 3 wks, but by 8 wks 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 EX animals 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 pathologic 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 the 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 while α-adrenergic receptor density has been reported to be either increased (44) or decreased (176) in myocardium after EX.

**Conduit Coronary Arteries.** Bove and Dewey reported that EX blunted the vasoconstrictor response of the proximal coronary arteries to α₁-adrenergic receptor stimulation with phenylephrine, but not to serotonin in closed-chest sedated adult dogs (15). 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 concentrations (Ca_i) 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 Figure 4A, there appear to be a number of mechanisms for the altered vasoconstrictor responses due to remodeling of control of (Ca_i) in coronary vascular smooth muscle of conduit arteries. Conversely, endothelium-dependent vasodilation produced by α2-adrenergic receptor stimulation was not altered in coronary arteries from EX dogs (123). Finally, blunting of the β-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 4-5 wks of EX resulted in a blunted phentolamine-induced increase in diastolic CBF during exercise (101). Subsequent studies from the same laboratory found that α-adrenergic blockade with phentolamine resulted in significantly greater (53) or smaller (37) increases in mean CBF during submaximal exercise in EX dogs compared to sedentary animals. In open-chest dogs α₁-adrenoceptor blockade caused a slightly larger increase in mean CBF in EX than in sedentary animals (85). Thus, current literature suggests that, after EX, α-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 α₁-adrenergic stimulation after EX. The sustained α-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 non-selective adrenoceptor blockade (53, 102), β₁-selective adrenoceptor blockade (53, 102) or β₂-selective adrenoceptor blockade (37) during submaximal exercise. A maintained β-adrenergoc vasodilator influence in the presence of lower circulating catecholamines is consistent with the reported increase in β₂-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 maintained or slightly increased α-adrenergic and maintained β-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, α- and β-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 α- and β-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 hrs/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 inhibition of nitric oxide synthase (NOS) with NLA and 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 weeks) dogs(136), swine (124), or rats (127) whether EDD was stimulated in response to \(\alpha\)-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 eNOS expression normalize (86, 93), thereby allowing EDD responses to return towards baseline levels (86, 95, 124, 136).

*Endothelial Control of Microcirculation.* EX of dogs for 8 wks 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 \(\mu\)m in diameter) isolated from EX swine. Treatment of the arterioles with L-NMMA 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 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. Consistent with this interpretation, Laughlin et al (93) reported increased endothelial NO synthase content in the coronary arterioles of EX swine.

*Myogenic Tone and SM Responsiveness to Constrictors.* Although active changes in diameter of small coronary arteries (75-150 \(\mu\)m in diameter) in response to 10 mmHg increments of intraluminal pressure were similar in arteries 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 in produced by direct voltage-gated calcium channel activation by the L-type calcium channel agonist Bay K8644 or by K^+ were modified by EX (91). Results from coronary vascular smooth muscle of epicardial arteries from EX animals suggest that the adaptation may involve increased activity of K_v and K_Ca 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 regulation of CBF under conditions of normal arterial inflow (3, 72, 165), the maximal adenosine-induced increase CBF is reported to be greater after EX in both dogs *in vivo* (36, 85, 94), and miniature swine *in vivo* (92). Also, Von Restorff *et al.* (168) and Stone (155) reported a slight increase in myocardial oxygen extraction in EX dogs suggesting 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 K_v or K_Ca 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 K_v or K_Ca 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 intrinsic vasomotor properties of coronary resistance vessels. Arterioles exhibit 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 include a calcium-dependent PKC signaling mediated alteration in voltage-gated calcium channel activity in response to stretch. It is currently unclear whether metabolic control mechanisms, including adenosine and K^+ -channel activity, in coronary resistance vessels are altered by EX.

**INTEGRATED CORONARY VASCULAR ADAPTATIONS**

The significance of the functional or 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 discussed in detail previously (39, 84, 85, 87, 90, 92). In studies where maximal vasodilation was demonstrated under tightly controlled hemodynamic conditions and 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) (see Table 3 in (39) for details). There have also been a number of clinical studies that assessed CBF capacity using echo-Doppler or positron emission tomography (PET). 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 variables and documentation of training effectiveness make it difficult to evaluate the quality of the CBF capacity measurements 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, adenosine is not simply a coronary vasodilator but also has cardioprotective, algesic and anti-hypertrophy properties (70). 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 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 optimization of CBF distribution effectively increasing the capillary surface area so that the maximal capillary exchange capacity becomes available 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 increased CBF is associated with
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 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 Lowel Stone (155) in EX dogs, although Stone (155) reported there was no statistically significant difference in absolute a-v O₂ 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 coronary blood flow 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.

**EXERCISE TRAINING, CAD, AND THE CORONARY COLLATERAL CIRCULATION**

Although EX does not provide immunity to atherosclerosis (34, 113), EX has emerged as an intervention for primary and secondary prevention of coronary artery disease (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/vasculogenesis) (87, 106). For an overview of the effects of EX in patients with CAD and 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 on 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 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 regression, of atherosclerotic lesions in coronary arteries of animal models of disease including mice, rabbits, pigs, and non-human primates.

Okabe et al. (121) reported that 20 minutes of swimming exercise, three times/week for 8 and 16 wks in apo E-deficient mice fed a high-fat diet exhibited less fatty streak formation and lesser fibrofatty plaques in the root of the aorta than non-exercised mice. Using this same mouse model, this group (122, 150) also reported that the decreased lesion progression in swim EX mice due to increased antioxidant effects mediated through the NO system. In contrast, Young et al. (184) reported that swim training of apo 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 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 months. In contrast, recent results of experiments on pigs in early stage disease demonstrated that EX did not appear to retard 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 progression or reverse CAD as measured with angiographic measures of lesion area. While their results indicated that exercise did not inhibit 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 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 interpreted carefully as 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 % 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 results of angiographic studies and documented the ability of regular, leisure time exercise to retard progression of and/or reverse CAD. In the Hambrecht et al. study 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 (56). Thirty minutes of daily exercise was recommended for both groups but the intervention group also received two 60 minute 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 indices of cardiorespiratory fitness were decreased in patients in the control group. The exercise intervention group exhibited regression of CAD in 8 patients (28%), 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/week) as opposed to patients with no change (1,533 +/- 122 kcal/week) or regression of disease (2,204 +/- 237 kcal/week) (p < 0.005)(56). Thus, these seminal experiments suggested that if a CAD patient could sustain 2,204 kcal/week 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 1 year than the usual care group. Of interest, 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 1990's. 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 angiography 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 who performed 3 supervised exercise bouts (at 60 % peak oxygen consumption) and Control (mild normal activity of life). Follow-up studies were performed 6 months 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. While 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 recently reported that EX inhibits coronary artery lesion development and alters the extracellular matrix composition of the coronary neointimal formed following percutaneous transluminal coronary angioplasty in Yucatan miniswine (45). 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 (LCx) coronary artery. Total collagen was increased and fibronectin was decreased by EX in the neointima of both LAD and LCx 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 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, 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 beneficial effects of exercise in coronary arteries that have been treated with percutaneous transluminal coronary angioplasty and/or intravascular stents. If our conclusion 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) is correct, 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 cath lab 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: “...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 overall endothelial function in the coronary circulation.

Finally, exercise-induced alterations in atherosclerotic lesion composition represent a compelling potential mechanism for reduced CHD mortality in physically active individuals. Human clinical trials report reduction in CHD mortality as the most consistent effect of physical activity. Acute coronary syndromes (ACS) 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 activity and 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. Exercise training 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 (MPP-9) and increased tissue inhibitor of metalloproteinases (TIMP). Similar beneficial changes in lesion composition have also been shown in post-angioplasty restenosis in swine (45).

**EX May Alter Lesion Progression in Atherosclerosis by Changing CSM 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 intracellular calcium (Ca$_i$) (17-19, 171). Clearly these EX-induced changes in the control of Ca$_i$ would be expected to decrease the tendency for coronary vasospasm as well. Also, as summarized in Figure 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 eNOS (93, 95, 96, 115, 178) and increased expression of superoxide dismutase (SOD) (139, 140). Also Hambrecht et al. (57) reported that EX increased EDD of conduit and resistance coronary arteries of CAD patients (57). Further, 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 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 removal of a prostanoid vasoconstrictor but EX did not appear to alter the role of non-COX, non-NOS 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:** 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) provide 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 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, 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 subject 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 measurement of 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 8 wks of moderate EX increased collateral CBF. 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, ameroid constrictors have been applied on a coronary artery and as the ameroid material absorbs water it gradually occludes the coronary artery over a period of 3 to 5 weeks. 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 ameroid constrictor on a coronary artery. In contrast to these results in dogs, CBF was 50% of normal in the collateral-dependent region of pigs that were EX trained with an ameroid coronary occluder in place (13, 138).

**Vasomotor Control of Coronary Resistance Vessels in Collateral-Dependent Myocardium.** As discussed above, 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 ameroid occlusion model. For example, examination of the effects of EX on epicardial arteries within the collateral-dependent region of EX hearts revealed improved EDD (51) and improved adenosine-induced vasodilation (65) compared to sedentary pigs with ameroid occlusions. EX also improved bradykinin-induced EDD in arterioles isolated from the collateral-dependent myocardium (52) and vascular endothelial growth factor (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 non-occluded 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) which may be mediated by increased PKC-mediated CSM Ca^{2+}-sensitization (135). Further evidence of EX effects on coronary vascular smooth muscle cell in collateral-dependent arteries is provided by the report of augmented vasodilator responses through KV 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, current evidence does not firmly support the hypothesis that these beneficial effects of exercise result from blunted progression and/or 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, current evidence indicates that EX improves endothelial phenotype and function in coronary arteries of humans and animal models with CAD and that has beneficial effects on coronary vascular smooth muscle cell 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 ß-adrenergic blockade was administered to minimize the occurrence of myocardial ischemia during gradual coronary occlusion with an ameroid 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 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 (i) increased conduit artery diameters, (ii) increased arteriolar densities and diameters and (iii) 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 (i) an increased EDD (transient in conduit arteries; sustained in resistance vessels) that is principally NO-mediated, (ii) altered alpha-adrenergic influence (reduced in conduit vessels and increased in resistance vessels) and (iii) a change in local control of resistance vessels. Coronary arterioles exhibit increased myogenic tone after EX.

In models of disease 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, evidence indicates that EX increases EDD in conduit arteries and in the arterial tree. However, evidence that EX reverses or slows 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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Figure Legends

**Figure 1.** Graph showing the effects of EX in swine on DNA labeling in arterioles, (upper left panel; smooth muscle cells closed boxes and endothelial cells closed circles), arteriolar density (second upper panel; open circles = 20 – 30 µm diameter, open boxes = 31-40 µm diameter, open diamonds 41-70 µm diameter and open triangles = 71 – 120 µm diameter arterioles), arteriolar diameter (third upper panel; open circles = 20 – 30 µm diameter, open boxes = 31-40 µm diameter, open diamonds 41-70 µm diameter and open triangles = 71 – 120 µm diameter arterioles), total arteriolar cross-sectional area (CSA; fourth upper panel; open circles = 20 – 30 µm diameter, open boxes = 31-40 µm diameter, open diamonds 41-70 µm diameter and open triangles = 71 – 120 µm diameter arterioles), coronary blood flow (CBF; fifth upper panel) and DNA labeling of capillaries (lower left panel), sprouting of new capillaries (second lower panel), capillary diameter (third lower panel), capillary density (fourth lower panel), and coronary transport reserve (CTR; lower right panel). Data are from White et al. (173) presented as mean ± SE for 5 groups, with 6 animals in each group (0, 1, 3, 8 and 16 wks). *P<0.05 different from the 0 wk time point (sedentary swine). See text for further explanation. Modified from (39) with permission of the American Physiological Society.

**Figure 2.** Graph summarizing the structural and functional coronary microcirculatory adaptations to chronic EX in normal subjects. ACh = acetylcholine; M = muscarinic receptor; NE = norepinephrine; α₁ = α₁-adrenergic receptor; β₁ = β₁-adrenergic receptor; β₂ = β₂-adrenergic receptor; Kᵥ = voltage-dependent K channel; KᵥCa = Ca²⁺-dependent K channel. Modified from (39) with permission of the American Physiological Society.

**Figure 3.** Graph summarizing the structural and functional coronary adaptations to chronic EX in the collateral circulation. Abbreviations the same as in Figure 2. A = adenosine receptor; ET = Endothelin receptor. Modified from (39) with permission of the American Physiological Society.

**Figure 4A.** Model of EX-induced adaptations of coronary smooth muscle (CSM) in normal subjects (bold) indicates those elements altered by EX). The left center of the figure illustrates decreased intracellular calcium (Caᵢ) response to selective agonists (e.g. endothelin) which produces a reduced Ca²⁺-dependent activation of contraction. This decreased Caᵢ occurs despite an increased Ca²⁺-influx through L-type Ca²⁺ channels (Caᵥ₁.2) which is buffered by a non-sarcoplasmic reticulum (SR), non-Na⁺/Ca²⁺ exchanger mechanisms. Nuclear Ca²⁺ responses (Caₙ) are similarly reduced by EX, which may affect Ca²⁺-dependent transcription factors (CaTF, e.g. CREB, NFAT) and target gene expression. On the top right note that EX increases spontaneous, slow-Ca²⁺ release from the SR into the subsarcolemmal space (Caₛₛ) which may contribute to the increased activation of large conductance, Ca²⁺-activated (BK) potassium channels by EX. In addition, voltage-gated (Kᵥ) potassium
channels are also activated by EX. In arteriolar CSM, Ca^{2+}-dependent PKC (e.g. PKCα) signaling enhances Ca_{v}1.2 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.

**4B.** 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 CAD (gray = atherogenic effects). Pro-atherogenic factors (such as PDGF-BB, TNFα, leptin) upregulate intermediate conductance Ca^{2+}-activated K channels (K_{Ca3.1}, IK) and voltage-independent Ca^{2+} channels (e.g. TRP) while supressing Ca_{v}1.2 and BK (K_{Ca1.1}) channels. CAD also disrupts SR Ca^{2+} release and extrusion and increases Ca_{in}. 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 pro-inflammatory matrix composition and synthesis of proliferative genes (PLF). EX adaptations described in 3A produce a stable, non-inflammatory phenotype and increased expression of collagens III and IV (Col III, IV) producing a non-inflammatory matrix.

Note that there are a number of similarities and differences in the effects of EX on CSM in normal and diseased states.


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Functional Adaptations Epicardial Arteries

- Neurohumoral influences $\uparrow / \downarrow$
  - Sympathetic
  - Parasympathetic
- Endothelial influence $\uparrow$ (early) / $\leftrightarrow$ (late)

Structural Adaptations

- Epicardial artery diameter $\uparrow$

Structural Adaptations

- Arteriolar density $\uparrow$
- Arteriolar size $\uparrow$
- Capillary density $\uparrow$ (early) / $\leftrightarrow$ (late)

Functional Adaptations Coronary Resistance Vessels

- Neurohumoral influences $\uparrow / \uparrow$
  - Sympathetic
  - Parasympathetic
- Extravascular influences $\downarrow$
  - Heart rate $\downarrow$
  - Systolic compression $\downarrow$
- Metabolic influences $?$
- Endothelial influence $\uparrow$
- Myogenic Tone $\uparrow$

Endo-/Paracrine influences $?$
Fig 3

**Functional Adaptations Epicardial Arteries in Collateral-Dependent Myocardium**
- Endothelial influence (NO) ↑
- Adenosine-induced vasodilation ↑

**Functional Adaptations Remote Epicardial Arteries**
- Endothelial influence (NO) ↑
- Adenosine-induced vasodilation ↑

**Functional Adaptations Coronary Resistance Vessels in Collateral-Dependent Myocardium**
- Neurohumoral influences ? / ?
  - sympathetic
  - parasympathetic
  - NE ↓
  - ACh↑
- Metabolic influences ?
- Endo-/Paracrine influences ?
  - NO ↑
  - ET₂ ↑
- Myogenic Tone ↑
- Heart rate ↓
- Systolic compression ↓

**Functional Adaptations Coronary Resistance Vessels in Remote Myocardium**
- Neurohumoral influences ? / ?
  - sympathetic
  - parasympathetic
  - NE ↓
  - ACh↑
- Metabolic influences ?
- Endo-/Paracrine influences ?
  - NO ↔
  - ET₂ ↔
- Myogenic Tone ↔
- Heart rate ↓
- Systolic compression ↓