What can we learn about treating heart failure from the heart’s response to acute exercise? Focus on the coronary microcirculation

Ilkka Heinonen,1,2 Oana Sorop,1 Vincent J. de Beer,1 Dirk J. Duncker,1 and Daphne Merkus1
1Division of Experimental Cardiology, Thoraxcenter, Erasmus MC, University Medical Center Rotterdam, Rotterdam, the Netherlands; and 2Turku PET Centre, University of Turku and Turku University Hospital, Turku, Finland

Heinonen I, Sorop O, de Beer VJ, Duncker DJ, Merkus D. What can we learn about treating heart failure from the heart’s response to acute exercise? Focus on the coronary microcirculation. J Appl Physiol 119: 934–943, 2015. First published June 5, 2015; doi:10.1152/japplphysiol.00053.2015.—Coronary microvascular function and cardiac function are closely related in that proper cardiac function requires adequate oxygen delivery through the coronary microvasculature. Because of the close proximity of cardiomyocytes and coronary microvascular endothelium, cardiomyocytes not only communicate their metabolic needs to the coronary microvasculature, but endothelium-derived factors also directly modulate cardiac function. This review summarizes evidence that the myocardial oxygen balance is disturbed in the failing heart because of increased extravascular compressive forces and coronary microvascular dysfunction. The perturbations in myocardial oxygen balance are exaggerated during exercise and are due to alterations in neurohumoral influences, endothelial function, and oxidative stress. Although there is some evidence from animal studies that the myocardial oxygen balance can partly be restored by exercise training, it is largely unknown to what extent the beneficial effects of exercise training include improvements in endothelial function and/or oxidative stress in the coronary microvasculature and how these improvements are impacted by risk factors such as diabetes, obesity, and hypercholesterolemia.

CORONARY MICROVASCULAR FUNCTION and cardiac function are closely related in that proper cardiac function requires adequate oxygen delivery through the coronary microcirculation, which is accomplished by an intricate interplay of neurohumoral, metabolic, and endothelium-derived factors (50). Moreover, because of the close proximity of cardiomyocytes and coronary microvascular endothelium, cardiomyocytes not only communicate their metabolic needs to the coronary microvasculature (20, 50), but endothelium-derived factors also directly modulate cardiac function (66, 90).

In this brief review, we summarize evidence that regulation of the coronary microvasculature is altered in conditions associated with left ventricular (LV) dysfunction. Because alterations in microvascular and cardiac function are first revealed during increased physical activity, exercise testing provides a valuable tool to interrogate coronary microvascular function, and abnormal responses may provide targets for therapeutic interventions. After summarizing general physiological responses to acute exercise in health and in the presence of LV dysfunction, we will focus on three modulators of coronary microvascular function and perfusion that are altered by exercise as well as LV dysfunction: 1) extravascular compressive forces, 2) neurohumoral activity, and 3) oxidative stress. Finally, the potential of exercise training to correct microvascular, as well as LV, dysfunction is briefly reviewed.

GENERAL CARDIOVASCULAR RESPONSES TO ACUTE STRESS

The cardiovascular system is of vital importance to maintain function of all tissues in the body under a wide range of internal and external challenges. Thus the cardiovascular system is tightly regulated to ensure adequate delivery of oxygen and nutrients to, and removal of carbon-dioxide and waste products from, the body (50). To guarantee adequate blood supply to each tissue at any given time, communication of these tissues with the cardiovascular system is required. This is accomplished by an intricate interplay of local vasomotor control mechanisms with various neurohumoral systems (50).
The classic stress response of the body is the fight, flight, or freeze (FFF) response to an acute threat, which is an evolutionary adaptation to cope with potentially harmful or dangerous situations, such as predators (37). Initially, activation of the sympathetic nervous system leads to the release of acute phase stress hormones adrenaline and noradrenaline, resulting in an increase in heart rate and myocardial contractility to increase cardiac output and oxygen delivery, and in peripheral vasoconstriction to maintain or increase blood pressure and enhance venous return, whereas perfusion of the heart and active skeletal muscle is promoted by recruitment of local vasodilator mechanisms (50). In the recovery phase after the acute attack by and presumably successful escape from the predator, blood loss was compensated by initial restoration of the fluid balance through activation of the renin-angiotensin-aldosterone system (RAAS) and fluid retention by the kidneys, whereas production of erythropoietin by the interstitial fibroblasts in the kidney ensured activation of erythropoiesis in the bone marrow (37). To cope with the increase in reactive oxygen species that occurs as a consequence of the neurohumoral activation, antioxidative defense mechanisms are upregulated in the subsequent recovery phase (45).

Western society has become increasingly sedentary, and voluntary physical exercise is the physiological form of stress that has the closest resemblance to the FFF response. Hence, during exercise, the body responds with activation of the sympathetic nervous system, and the stress reaction of the cardiovascular system ensures adequate perfusion of exercising skeletal muscle (50). Thus, although in the current Western society the threat from predators has substantially decreased, the FFF response is still the evolutionary basis of how the body deals with any form of stress, either physiological or pathological (37).

GENERAL CARDIOVASCULAR RESPONSES OF HEART FAILURE WITH REDUCED OR PRESERVED EJECTION FRACTION

Acute myocardial infarction (MI) results in the loss of viable contracting myocardium, leading to a decrease in stroke volume. The consequent reduction in cardiac output initiates a strong stress response of the body (37). The initial response of sympathetic activation is similar to that described above but is particularly pronounced in the heart (71), which serves to increase heart rate and contractility and is followed by sodium and fluid retention by the kidneys through activation of the RAAS. However, in contrast to the transient nature of an attack by a predator, persistent LV dysfunction results in sustained and exaggerated activation of the different neurohumoral systems (37), which is accompanied by an increase in oxidative stress in the myocardium (81). Although the neurohumoral changes are initially beneficial as they restore cardiac function and result in formation of a stable scar, LV function often deteriorates over time, particularly in patients with a large MI, resulting in heart failure with reduced ejection fraction (HFrEF) (37).

In HFrEF patients the impaired contraction of the LV leads to a reduced stroke volume. In contrast, in patients with predominantly diastolic LV dysfunction [heart failure with preserved ejection fraction (HFpEF)], stroke volume is reduced by impaired filling of the left ventricle, which results from LV hypertrophy and increased LV stiffness (6). Changes in cardiomyocyte function, along with oxidative stress, inflammation, and increased stiffness of the extracellular matrix, are thought to play a key role in the development and progression of HFpEF (99). Pathological activation of the renin-angiotensin-aldosterone system, natriuretic peptides, and the sympathetic nervous system are characteristic of both HFrEF and HFpEF but have been studied much more extensively in HFrEF. (6, 7, 99). Also, low-grade inflammation and endothelial dysfunction are present in both HFrEF and HFpEF and are associated with oxidative stress in the myocardium (66, 99).

The mechanisms that contribute to the transition of LV dysfunction toward overt heart failure remain incompletely understood. Because adequate oxygen delivery by myocardial perfusion is crucial for proper cardiac function, crosstalk between cardiomyocytes and the coronary microvasculature plays an essential role in matching myocardial oxygen supply to myocardial oxygen demand. In addition, the close proximity and interplay of cardiomyocytes and microvascular endothelial cells not only allows paracrine modulation of microvascular function by cardiomyocytes but also paracrine modulation of cardiomyocyte function by endothelial and vascular smooth muscle cells (77). In this context, it was recently proposed that, particularly in patients with diastolic dysfunction, there is a prominent role for microvascular dysfunction on cardiomyocyte dysfunction (66). These paracrine effects of the coronary microvasculature on the surrounding myocardium are mediated, at least in part, via reactive oxygen species and nitric oxide (NO), which influence contractile function, cardiomyocyte growth, hypertrophy, and fibrosis (97). A new paradigm has therefore been proposed that endothelial dysfunction, characterized by reduced NO bioavailability, enhanced reactive oxygen species, and/or increased endothelin (ET) production, plays a direct role in adverse cardiac remodeling (50, 55, 66). Consequently, we propose that the coronary microvasculature plays a key role in the progression of LV dysfunction. Because alterations in microvascular as well as cardiac function are first revealed during increased physical activity, exercise testing provides a valuable method to investigate coronary microvascular function and abnormal responses may provide potential targets for novel therapies.

CORONARY MICROVASCULAR PERFUSION IN RESPONSE TO ACUTE EXERCISE

The increase in heart rate, wall stress, and contractility during any stress reaction results in an increase in myocardial oxygen consumption. Because the heart already uses 60–80% of the oxygen delivered through the coronary vasculature, increases in myocardial oxygen consumption must principally be met by increases in myocardial oxygen supply (20, 21, 50). Although splenic contraction and hemoconcentration result in modest increases in circulating erythrocytes and thereby arterial oxygen content, the increase in myocardial oxygen demand is principally achieved through an increase in coronary blood flow. This increase in coronary blood flow is accomplished by vasodilation of the coronary arterioles, resulting in a decrease in coronary vascular resistance (50). In swine, the increase in myocardial oxygen supply matches the increase in oxygen consumption, so that myocardial oxygen extraction and hence coronary venous O2 tension remain largely constant.
Review

Coronary Microcirculation during Exercise in LV Dysfunction • Heinonen I et al.

(22, 24, 30, 33), whereas in dogs, there is a small decrease in coronary venous O₂ tension, suggesting that the increase in myocardial oxygen demand slightly exceeds the increase in myocardial oxygen supply (88).

After MI, there is an increase in myocardial oxygen demand of the remote, noninfarcted myocardium, as a result of the increase in heart rate in combination with hypertrophy of the remote myocardium, which compensates for the loss of viable LV myocardium. The increase in myocardial oxygen demand is met by an increase in coronary blood flow, although a small increase in myocardial oxygen extraction is observed under resting conditions, which is further exacerbated during exercise (21, 36). These data obtained in our porcine animal model with features of HFpEF are in accordance with studies in humans showing a decrease in coronary flow reserve in patients with HFpEF compared with healthy controls (51, 86). The decrease in flow reserve is most likely the result of flow reserve recruitment to sustain myocardial perfusion under basal resting conditions in the face of increased extravascular compression and decreased capillary density, which hamper perfusion and decrease maximal flow (96). Moreover, the decrease in flow reserve is accompanied by alterations in control of coronary vasomotor tone (21, 55).

In a swine model with features of HFpEF, 6 mo of aortic banding resulted in LV hypertrophy that was accompanied by diastolic dysfunction (53). Coronary blood flow normalized per gram of tissue and myocardial oxygen extraction were not altered under resting conditions, but with increased myocardial work load under anesthesia, myocardial oxygen extraction was higher in the swine with LV dysfunction compared with control swine, indicating that the increase in myocardial oxygen supply did not completely match the increase in myocardial oxygen demand (53).

Chronic rapid pacing of an initially normal heart results in development of congestive heart failure resembling dilated cardiomyopathy within 3–5 wk (95). Coronary blood is reduced under basal resting conditions (11, 80), but coronary venous Po₂ is unaltered (11). Although there is no evidence for anaerobic metabolism in this model and coronary blood flow can still increase during exercise, this increase is blunted compared with healthy control animals, whereas myocardial oxygen extraction is simultaneously increased compared with control (10, 11, 85).

In summary, in animal models of HFrEF, HFpEF, and dilated cardiomyopathy, there is evidence of a mismatch between myocardial oxygen supply and myocardial oxygen demand particularly when heart rate increases, as occurs during exercise.

EXTRAVASCULAR COMPRESSIVE FORCES

Because the coronary vasculature is embedded in the myocardium, there is an obvious physical interaction as the coronary vasculature is compressed during systole (90). Myocardial perfusion therefore occurs mostly during diastole, particularly in the LV subendocardium, and diastolic duration is an important determinant of subendocardial perfusion. However, it should be noted that even during diastole, the coronary vasculature is compressed. The magnitude of this compression depends on diastolic LV pressure that is transmitted across the myocardium. LV diastolic pressures are elevated in animal models after myocardial infarction (15, 36), in animals with LV hypertrophy induced by pressure overload of the LV (23, 42), and in animals with pacing induced heart failure (78), resulting in an increased extravascular compression that contributes to reduced flow reserve, particularly of the subendocardium (23, 42). Exercise exacerbates the increase in diastolic LV pressure, which together with the increased systolic compression due to the increase in heart rate, results in a further decrease in maximal subendocardial perfusion (23, 36, 42, 78). Also in humans, elevated diastolic LV pressures correlate with decreased subendocardial flow reserve as measured with positron emission tomography (PET) in patients both with ischemic heart disease (86) and with hypertension with LV hypertrophy (72). Moreover, the decrease in peak oxygen uptake of the myocardium during exercise in HFpEF patients is associated with a reduced cardiac energetic reserve and contributes to the cardiac dysfunction (67). These observations are consistent with the concept that the heart enters a vicious cycle in which left ventricular dysfunction produces an increase in end diastolic pressure, which compromises flow reserve and reduces peak maximal oxygen uptake, thereby reducing contractile reserve and further contributing to LV dysfunction (Fig. 1).

NEUROHUMORAL CONTROL OF CORONARY BLOOD FLOW

Neurohumoral activation during stress impacts bodily functions beyond the effects on cardiac function. Receptors for neurohumoral factors such as for (nor)adrenaline, angiotensin II (ANG II), endothelin (ET, particularly ET-1) are also present on the coronary microvasculature and serve to optimize coronary blood flow distribution during stress (20, 50) (Fig. 1). β-Adrenergic receptor activation results in coronary vasodilatation, whereas activation of the α-adrenergic receptor, the AT₁ receptor, and the ETA and ETB receptors on coronary vascular smooth muscle results in coronary vasoconstriction (21). ET-induced vasoconstriction is blunted slightly by activation of the ETB receptors on the endothelium, which results in vasodilatation (57). The initial stress response consists of withdrawal of the parasympathetic nervous system and sympathetic activation, as evidenced by increases of (nor)adrenaline (22). Activation of both β₁- and β₂-receptors contributes to coronary vasodilatation, resulting in an increase in myocardial oxygen delivery that serves to feed the myocardium during periods of increased work (30). After β-blockade, both myocardial oxygen demand and myocardial oxygen supply are reduced. However, the reduction in stress-induced vasodilatation is larger than the β-blockade-induced reduction in myocardial work, which underlines the importance of feed-forward β-adrenergic vasodilation in the response to physical stress (22, 24, 30, 33).

Activation of the RAAS, as well as the ET system, occurs during more prolonged exercise. In contrast to the vasodilatation induced by activation of the β-adrenergic receptors, the RAAS and the ET system exert a vasoconstrictor effect on the healthy coronary vasculature (15, 21). It might seem counterproductive to increase circulating levels of these vasoconstrictors when the body has an increased oxygen demand, such as during exercise. However, it should be noted that these vasoconstrictors exert their influence predominantly in the tissues and tissue regions that are metabolically less active, thus contributing to the redistribution of flow toward exercising tissue and tissue regions that have the highest demand of oxygen and nutrients.
to hydrogen peroxide (H2O2) by superoxide dismutase (SOD), but when produced in excess is likely to result in vasoconstriction. Importantly, impaired crosstalk between microvasculature and cardiomyocytes (arrows) may further contribute to deterioration of both contractile function and microvascular function. Impaired NO production and increased superoxide production impair myofilament contractility, whereas increased diastolic extravascular compressive forces further impair myocardial perfusion particularly in the subendocardium.

Fig. 1. A schematic summary of coronary microvasculature and major alterations in its control in left ventricular (LV) dysfunction. Nitric oxide (NO) production that exerts a direct vasodilator effect on the coronary microvasculature and blunts endothelin (ET)-mediated vasoconstriction is further blunted because of prostanoids. Phosphodiesterase 5 (PDE) expression is reduced, potentially to preserve NO-cGMP-mediated vasodilation. There is also increased production of O2· in the failing myocardium, most likely because of increased activation of NADPH oxidases (NOX) in combination with uncoupled eNOS. O2· is normally converted to hydrogen peroxide (H2O2) by superoxide dismutase (SOD), but when produced in excess is likely to result in vasoconstriction. Importantly, impaired crosstalk between microvasculature and cardiomyocytes (arrows) may further contribute to deterioration of both contractile function and microvascular function. Impaired NO production and increased superoxide production impair myofilament contractility, whereas increased diastolic extravascular compressive forces further impair myocardial perfusion particularly in the subendocardium.

(52). Indeed, the heart manages to escape from the increased vasoconstrictor influence of the activated ET system. During exercise, the coronary vasoconstrictor influence of endogenous ET decreases (57) as cardiac ET production from its precursor big ET by endothelin converting enzyme decreases (14). Nitric oxide (NO) and prostanoids play a pivotal role in this suppression of ET-mediated vasoconstriction during exercise (59).

In swine with LV dysfunction early after MI, neurohumoral activation is modest at rest, with resting catecholamine as well as ANG II levels still in the normal range, whereas plasma ET levels are slightly increased. However, activation of all three neurohumoral systems is increased during graded treadmill exercise (22, 36). The exaggerated increase in catecholamines serves to maintain the chronotropic and inotropic responses to acute exercise, because LV myocardial β-adrenoceptor responsiveness is reduced. The total β-adrenergic vasodilator influence on the coronary circulation is similar in swine with MI compared with control swine despite the higher levels of catecholamine levels during exercise, suggesting a diminished β-adrenergic vasodilator responsiveness of the coronary resistance vessels after MI (22). Despite increased plasma levels of ANG II and ET-1, particularly during exercise, blockade of their respective receptors has no vasodilator effect on the coronary microvasculature (56, 58). Similar to acute exercise, the heart “protects” its perfusion by interfering with these vasoconstrictor influences. The loss of ET-mediated vasoconstriction in the remote myocardium is principally mediated by prostanoids (16). In contrast to these findings in MI animals with a relatively mild LV dysfunction, in animals with pacing induced heart failure, blockade of AT1 (13) and ETA (43) receptors did result in an enhanced increase in myocardial blood flow compared with normal animals. It is possible that with severe LV dysfunction, which is accompanied by more pronounced neurohumoral activation, blockade of AT1 or ETA receptor alone is sufficient to induce vasodilation. Because both AT1 and ETA receptors activate NADPH oxidase and thereby increase oxidative stress in the coronary vasculature and the myocardium, blockade of these receptors may also alleviate oxidative stress to such an extent that it does result in changes in coronary microvascular tone and cardiac function. Indeed, although the acute effects of AT1 receptor blockade on oxidative stress in the vasculature and myocardium are unknown, chronic AT1 receptor blockade has been shown to decrease oxidative stress in the vasculature (76) as well as the myocardium (63) in rats with a large myocardial infarction and thereby improve LV function.

Interestingly, combined blockade of AT1 and ETA receptors does result in coronary vasodilation in swine with MI, suggesting crosstalk between these two vasoconstrictor systems in control of coronary vasomotor tone (15), which may be mediated by oxidative stress. Thus, in animals with mild LV dysfunction and neurohumoral activation, blockade of these two vasoconstrictors together may be required to alleviate oxidative stress to such an extent that it improves myocardial perfusion as well as cardiac function.

Standard therapy of patients with LV dysfunction after MI consists of β-blockers in combination with ACE inhibitors and/or angiotensin receptor blockers (2). This therapy, which interferes with the effects of neurohumoral activation, is principally targeted at the myocardium, and is aimed at reducing heart rate and limiting adverse remodeling and fibrosis (48). However, the potential effects of this therapy on the coronary microvasculature are often overlooked. Particularly the effect of β-blockade on coronary flow reserve has been shown to yield contradictory results during stress. Thus it has been found that, during cold-pressor tests, a decrease in flow reserve in the...
presence of β-blockade most likely occurs because of unopposed α-adrenergic constriction (29). In contrast, β-blockade enhances adenosine-induced vasodilation, because the β-blockade-induced decrease in heart rate not only lowers resting blood flow but may also enhance maximal blood flow due to the reduction in systolic extravascular compression (29).

Sympathetic activation in patients with HFrEF is similar or slightly less pronounced compared with patients with HFpEF (7). Nevertheless, conventional heart failure therapy with β-blockade does not benefit patients with HFpEF (6). Although there are currently no studies that have investigated the coronary microvascular responses in animal models of LV diastolic dysfunction or HFpEF to acute exercise, and the role therein of neurohumoral activation, a decrease in heart rate induced by β-blockade will increase diastolic perfusion time, and is therefore likely to benefit myocardial perfusion. The extent to which an increase in diastolic perfusion time benefits myocardial perfusion is dependent on diastolic LV pressures, and thereby diastolic extravascular compression, regardless of the underlying cause of heart failure.

Inhibition of the RAAS mainly aims to target fibrosis, and ANG II levels are generally higher in patients with LV diastolic dysfunction (6, 7, 99). Moreover, NADPH oxidase is increased in the myocardium of rats with LV diastolic dysfunction (28) as well as in dogs with pacing-induced heart failure (98). Because one of the activators of NADPH oxidase is the AT1 receptor, it is possible that AT1 blockade reduces activation of NADPH oxidase, thereby alleviating oxidative stress in the coronary microvasculature and improving microvascular function. However, clinical trials in HFpEF with ACE inhibitors or AT1 blockers have not shown any benefit of the treatment, whereas combined blockade of the AT1 receptor with inhibition of the neutral endopeptidase has shown some beneficial effects (31).

In summary, although neurohumoral activation occurs to a similar extent in patients with HFpEF and HFrEF, it is currently unknown why therapies interfering with neurohumoral pathways work well in HFrEF but less in HFpEF. Moreover, in contrast to the wealth of data in animal models of HFrEF there is a paucity of data (and hence a need for future studies) pertaining to neurohumoral control mechanisms of coronary microvascular function at rest and during exercise studies in (animal models of) HFpEF.

REDOX SIGNALING IN CONTROL OF CORONARY BLOOD FLOW

The nitroso-redox balance, i.e., the balance between NO and reactive oxygen species, plays a key role in regulating coronary microvascular tone (35, 81) (Fig. 1). NO is produced by endothelial nitric oxide synthase (eNOS) in response to shear stress or a variety of agonists and is a potent vasodilator. NO acts through activation of soluble guanylyl cyclase in vascular smooth muscle cells, resulting in formation of cGMP, activation of PKG, a reduction in intracellular calcium, and relaxation of the smooth muscle cells (50). In addition to this direct vasodilator action, NO scavenges superoxide (27), resulting in the formation of (ONOO−), thereby reducing the deleterious effects of superoxide (O2·−). O2·− in the coronary microvasculature is derived from different sources, including the mitochondrial respiratory chain, NADPH oxidase, and uncoupled eNOS (35, 81). O2·− can oxidize various K+ channels in vascular smooth muscle cells, thereby depolarizing the membrane and resulting in vasoconstriction (35, 81).

In the healthy microcirculation, O2·− levels are tightly controlled by superoxide dismutase (SOD) (81). SOD catalyzes the reaction of O2·− into H2O2 and O2. H2O2, a potent vasodilator (73, 75), is more stable and diffusible than O2·− and, under normal physiological conditions, can affect vascular tone (81). The net effect of ROS on vascular tone therefore depends on the relative quantities of O2·− and H2O2.

Administration of a SOD mimetic has no effect on coronary vasomotor tone in awake dogs either at rest or during exercise (10), indicating optimal efficiency of endogenous SOD in converting superoxide to H2O2. Importantly, enhancing H2O2 breakdown with catalase significantly limited stress-induced coronary vasodilation in dogs, further underlining the efficient conversion of superoxide to H2O2 (75). However, in the porcine coronary circulation, free radical scavenging did have a small but significant vasodilator effect both at rest and during exercise. These findings indicate that the O2·− that is generated in the coronary microvasculature may not be (completely) converted to H2O2 and exerts a net vasoconstrictor effect on the coronary vasculature (82).

The nitroso-redox balance is shifted after MI, resulting in oxidative stress in the myocardium, not only in the infarcted area but also in the remote myocardium (5). This increase in superoxide not only occurs in the cardiomyocytes but also in the remote coronary arteries of rats with MI (4) and in monocytes/macrophages within the intima, media, and adventitia in vessels with coronary artery disease (9). In animal models of LV dysfunction, NADPH oxidase (98) and uncoupled eNOS (82) become the most prominent sources of superoxide in the coronary microvasculature. Interestingly, PDE5 expression is reduced in the coronary vasculature of dogs with pacing-induced heart failure (11) as well as in the remote coronary microvasculature after MI (60), suggesting that PDE5 is downregulated in an attempt to preserve the NO-cGMP mediated vasodilation.

The decrease in eNOS expression in combination with an increase in eNOS uncoupling and an increase in superoxide production in the remote coronary vasculature after MI and in pacing-induced heart failure results in a shift of the nitroso-redox balance toward oxidative stress (10, 32, 82) and a reduction in NO bioavailability (32). Similarly, oxidative stress and the concomitant decrease in bioavailability of NO in patients with HFpEF has been proposed to play a key role in microvascular dysfunction in HFpEF patients (66). Thus a shift in the nitroso-redox balance in HFrEF and HFpEF likely results in vasoconstriction in the coronary microvasculature and may contribute to the perturbations in myocardial oxygen balance.

The nitroso-redox balance is not only important for vascular function but also plays a critical role in structural coronary adaptations. Thus both NO and ROS are important for coronary collateral formation (34, 54). Particularly the amount of ROS appears to be critical in this process, because impaired coronary collateral formation due to excess ROS in obese Zucker rats can be restored by antioxidant treatment (12, 70).

Finally, given the close proximity of cardiomyocytes to capillary endothelial cells, this shift in the nitroso-redox balance may result in oxidative modifications of contractile pro-
teins. These modification, by affecting myofibrillar function, likely further contribute to cardiomyocyte dysfunction (65, 97).

**POTENTIAL OF EXERCISE TRAINING TO CORRECT A FAILING HEART**

Given the prevalence and progressive nature of heart failure there is an urgent need for effective drugs and/or lifestyle interventions to decrease morbidity and mortality. Although heart failure is, by definition, a disease of the heart, it is increasingly recognized that other organs also contribute to the impairment of exercise capacity in both HFrEF and HFP EF patients. Heart failure should therefore be considered a disease of the whole body (69).

Habitual physical activity and especially exercise training are capable of inducing physiological adaptations in all organs of the body, including the heart (39). In the heart, exercise training induces a moderate hypertrophy, as well as changes in the coronary microvasculature. The latter has been recently reviewed (49) and consists of both structural and functional changes, resulting in an increased capillary exchange capacity (40) as well as an improved endothelial function and decreased oxidative stress (49).

Regular physical activity not only decreases the incidence of MI but also improves survival after MI (61). Some caution is warranted, however, as a recent study reported higher mortality in vigorously exercise-trained heart attack survivors (91). Mechanisms of exercise training benefits include, but are not limited to, direct improvement of cardiac function, ventilatory and vascular adaptations, and changes in skeletal muscles (1, 62). There are currently not enough data available to make comprehensive comparisons between the two types of heart failure of the mechanisms of training-induced benefits. Nevertheless, there is some evidence that peripheral vascular function does not improve in HFP EF (46), whereas endothelial function but not endothelium-independent vascular function is consistently found to be improved in HFrEF (89). The latter appears to be exercise intensity dependent, as high-intensity aerobic interval training showed greater improvements than continuous moderate intensity training in terms of peripheral endothelial function in HFrEF patients (92).

With respect to the heart, animal studies have elucidated that although survival or infarct size are not necessarily favorably affected, early exercise training improves LV fractional shortening and attenuates the MI-induced decrease of myocyte maximal force developing capacity (17, 18, 25). Interestingly, these beneficial effects that are mainly due to improved myofilament function, because calcium handling of myocyte remains largely unchanged (18), require full eNOS expression (19). An exercise training-induced decrease in heart rate together with improved compliance of the left ventricle will enhance subendocardial perfusion by increasing the diastolic perfusion time. Indeed, in swine with diastolic dysfunction, exercise training restored the myocardial oxygen balance toward control levels (53), suggesting improved microvascular perfusion. Moreover, exercise training is capable of inducing structural adaptations of the coronary vasculature such as capillary as well as collateral growth (38, 84). Studies in humans suggest that maximal myocardial blood flow or flow reserve, noninvasive surrogates for capillarization, are negatively affected by the degree of myocardial hypertrophy in exercise-trained athletes (47) and are not improved even in highly trained athletes (41), whereas a recent observation in swine shows that capillary density is not altered by exercise training in swine with LV hypertrophy due to aortic banding (26). The current thinking thus is that there is a commensurate increase but not an excess in capillarity with cardiac growth produced by exercise training (49).

It is generally assumed that a more favorable balance between ROS and antioxidant mechanisms plays a role in the beneficial effects of physical activity (8). Indeed, physical activity results in an upregulation of antioxidant mechanisms such as NO and SOD in healthy individuals (74). Similarly, eNOS is upregulated in non-collateral-dependent myocardium of exercise-trained swine with an ameroid constrictor (94). In addition, there was an increased contribution of H2O2 to bradykinin-induced vasodilation, likely due to an increased production of superoxide by the NADPH-oxidase subunit p67phox, which was subsequently converted by SOD to H2O2 (94). These findings are consistent with observations that...
exercise training reduces oxidative stress in MI-induced heart failure in mice (19) and rats (3, 68).

Although the benefits of exercise training in heart failure patients with particularly systolic dysfunction are well-establish and adopted within the guidelines of HFrEF therapy (44), the effects of exercise training on vascular oxidative stress are not that well established. Because of a shift in antioxidant defense mechanisms, vascular oxidative stress in patients with HFrEF (93) as well as HFP EF (87) at rest is higher compared with healthy controls. Animal models suggest that the effect of exercise training on oxidative stress may be different in subjects with or without comorbidities and/or dependent on the duration of metabolic derangement. Similar to healthy animals, SOD expression was increased and oxidative stress was reduced in exercise-trained rats on a high-fat diet after myocardial infarction (3). Also, exercise training increased eNOS and SOD expression and thereby improved endothelium-dependent vasodilation in the coronary microvasculature of swine that were fed a high-fat diet (83). However, a recent study showed that exercise training failed to improve endothelium-dependent vasodilation in the coronary microvasculature of swine with familial hypercholesterolemia, which is in accordance with a lack of change in expression of eNOS and SOD in that model (79). Thus physical activity may also impact oxidative stress differently in healthy individuals compared with heart failure patients. These observations emphasize the need to investigate how acute exercise as well as exercise training impact the coronary microvasculature of subjects with long-term presence of comorbidities that promote oxidative stress including diabetes, hypertension, and hypercholesterolemia. These studies may also be able to elucidate why systolic or diastolic function is not improved in heart failure patients with preserved ejection fraction despite improvements in cardiorespiratory fitness and quality of life (64).

SUMMARY AND CONCLUSIONS

Acute exercise induces a strong stress reaction of the whole body, which is exaggerated in LV dysfunction after MI. The increases in heart rate and myocardial mass result in an enhanced oxygen demand of the surviving remote myocardial region(s). The cardiac microvasculature responds to the increase in oxygen demand by vasodilation, resulting in an increase in coronary blood flow. However, oxygen delivery is hampered, particularly in the subendocardium region, because of elevated LV diastolic pressures in both systolic and diastolic LV dysfunction. The increased oxygen demand combined with the impaired oxygen delivery compromises flow reserve and forces the myocardium to increase its oxygen extraction, especially during exercise. Neurohumoral activation and endothelial dysfunction contribute to an increase in oxidative stress and alter coronary microvascular control (Fig. 1). Exercise training has the potential to ameliorate heart failure by beneficially influencing cardiac, ventilatory, and vascular function, as well as affecting changes in skeletal muscle properties. The exercise training-induced decrease in heart rate together with improved compliance of the LV enhances subendocardial perfusion by increasing the diastolic perfusion time, leading to partial restoration of the myocardial oxygen balance and contractile function (Fig. 2). eNOS and vascular antioxidant mechanisms are upregulated by exercise training in healthy individuals, but the effects of exercise training on coronary microvascular and myocardial oxidative stress in patients with chronic heart failure is currently unknown. Although similar improvements may occur in these patients (Fig. 2), there is clearly a need to further investigate the influences of exercise training on coronary microvascular structure and function in subjects with heart failure and comorbidities that are known to be associated with elevations in oxidative stress such as diabetes, hypertension, and hypercholesterolemia.

ACKNOWLEDGMENTS

Present address of I. Heinonen: School of Sport Science, Exercise and Health, University Of Western Australia, Crawley, Western Australia, Australia.

GRANTS

This study was supported by European Commission FP7-Health-2010 Grant MEDIA-261409 (to D. J. Duncker and D. Merkus), the Netherlands CardioVascular Research Initiative: the Dutch Heart Foundation, Dutch Federation of University Medical Centers, The Netherlands Organisation for Health Research and Development and the Royal Netherlands Academy of Sciences CVON2014-11 RECONNECT (to D. J. Duncker and D. Merkus) and CVON2012-08 PHAEDRA (to D. Merkus), and The Academy of Finland 251272, Finnish Diabetes Research Foundation, and Finnish Foundation for Cardiovascular Research (to I. Heinonen).

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

AUTHOR CONTRIBUTIONS

Author contributions: I.H. and D.M. drafted manuscript; I.H., O.E.S., V.J.d.B., D.J.D., and D.M. edited and revised manuscript; I.H., O.E.S., V.J.d.B., D.J.D., and D.M. approved final version of manuscript.

REFERENCES


44. Kitzman DW, Brubaker PH, Herrington DM, Morgan TM, Stewart KP, Hundle WY, Abdelhammed A, Haykovsky MJ. Effect of endur-
Coronary Microrcirculation during Exercise in LV Dysfunction • Heinonen I et al.


68. Rimoldi O, Rosen SD, Camici PG. The blunting of coronary flow reserve in hypertension with left ventricular hypertrophy is transmural and correlates with systolic blood pressure. J Hypertens 32: 2465–2471, 2014.


80. van den Heuvel AF, Bax JJ, Blankens PA, Vaalburg W, Crijns HJ, van Veldhuisen DJ. Abnormalities in myocardial contractility, metabo-


