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STATE-OF-THE-ART REVIEW

Intrinsic and Extrinsic Contributors to the Cardiac Benefits of Exercise

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HIGHLIGHTS

- **This review discusses systemic and cardiac adaptations contributing to the benefits of exercise, including changes in cardiomyocyte function, growth and proliferation, coronary microvasculature and lymphatics, cardiac fibrosis, systemic and cardiac metabolism and inflammation, and effects related to the gut microbiome.**
- **Insights from mechanistic and preclinical studies of exercise adaptation highlight the value of exercise as a platform for discovering potential therapeutic targets.**

SUMMARY

Among its many cardiovascular benefits, exercise training improves heart function and protects the heart against age-related decline, pathological stress, and injury. Here, we focus on cardiac benefits with an emphasis on more recent updates to our understanding. While the cardiomyocyte continues to play a central role as both a target and effector of exercise's benefits, there is a growing recognition of the important roles of other, noncardiomyocyte lineages and pathways, including some that lie outside the heart itself. We review what is known about mediators of exercise's benefits—both those intrinsic to the heart (at the level of cardiomyocytes, fibroblasts, or vascular cells) and those that are systemic (including metabolism, inflammation, the microbiome, and aging)—highlighting what is known about the molecular mechanisms responsible. (J Am Coll Cardiol Basic Trans Science 2023;■:■–■) © 2023 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

The importance of exercise in cardiovascular disease prevention and mitigation has long been recognized. While evidence of the cardiovascular benefits of exercise has come primarily from observational studies, it is further supported by some randomized trials,[1,2] meta-analyses,[3,4] and animal studies. As a result, physical activity guidelines codified by American College of Cardiology and the American Heart Association suggest moderate-intensity cardiorespiratory exercise training for at

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ABBREVIATIONS AND ACRONYMS

FMT = fecal microbiota transplantation

MI = myocardial infarction

TAC = transverse aortic constriction

least 30 minutes per day, 5 days per week for healthy adults.[5] In addition to reducing the risk of cardiovascular disease, exercise improves functional capacity and quality of life in populations with cardiovascular diseases such as heart failure and may improve clinical outcomes, although the latter has been difficult to establish unequivocally.[1,6,7]

Despite widespread acceptance of the cardiovascular benefits of exercise, many questions remain. In part, these reflect inherent limitations of studying lifestyle interventions. Bias and confounding limit observational studies and variability in adherence can undermine interventional trials. The optimal type, intensity, and duration of physical activity and how to optimize benefits for individuals remain unclear. In this context, animal studies can be particularly helpful. Not only can confounders be rigorously excluded, but also relevant tissues not available clinically can be accessed. Such studies can enhance understanding and identify new therapeutic targets. Although it is unlikely that any medicine will recapitulate all the benefits of exercise, it may be possible to manipulate specific downstream mediators to mimic some of the salutary effects. While those who can exercise should, exercise-mimetic therapeutics may be particularly helpful for patients who cannot exercise adequately. Another important practical goal is to identify biomarkers that correlate with exercise's benefits to guide individualized exercise recommendations. If exercise can be considered medicine, we currently have no way to judge appropriate dosage or to know that we have moved the needle toward clinical benefit. Here, too, mechanistic understanding and animal models are important supplements to clinical studies.

In this review, we discuss cardiac benefits of exercise (**Central Illustration**). Exercise-induced changes in cardiomyocyte growth, proliferation, and function are central to many of the cardiac effects of exercise. However, there is a growing recognition of key roles for noncardiomyocyte lineages in the heart, including fibroblasts and vascular cells, which we discuss in the context of fibrosis, coronary microcirculation, and lymphatics. In addition, pathways and processes primarily outside the heart are increasingly appreciated as contributors to disease—and exercise benefits. We discuss effects on metabolism, intestinal microbiome, inflammation, and briefly, aging, which is likely an extrinsic and intrinsic contributor to cardiac effects. Where possible, we highlight molecular mechanisms and possible translational applications.

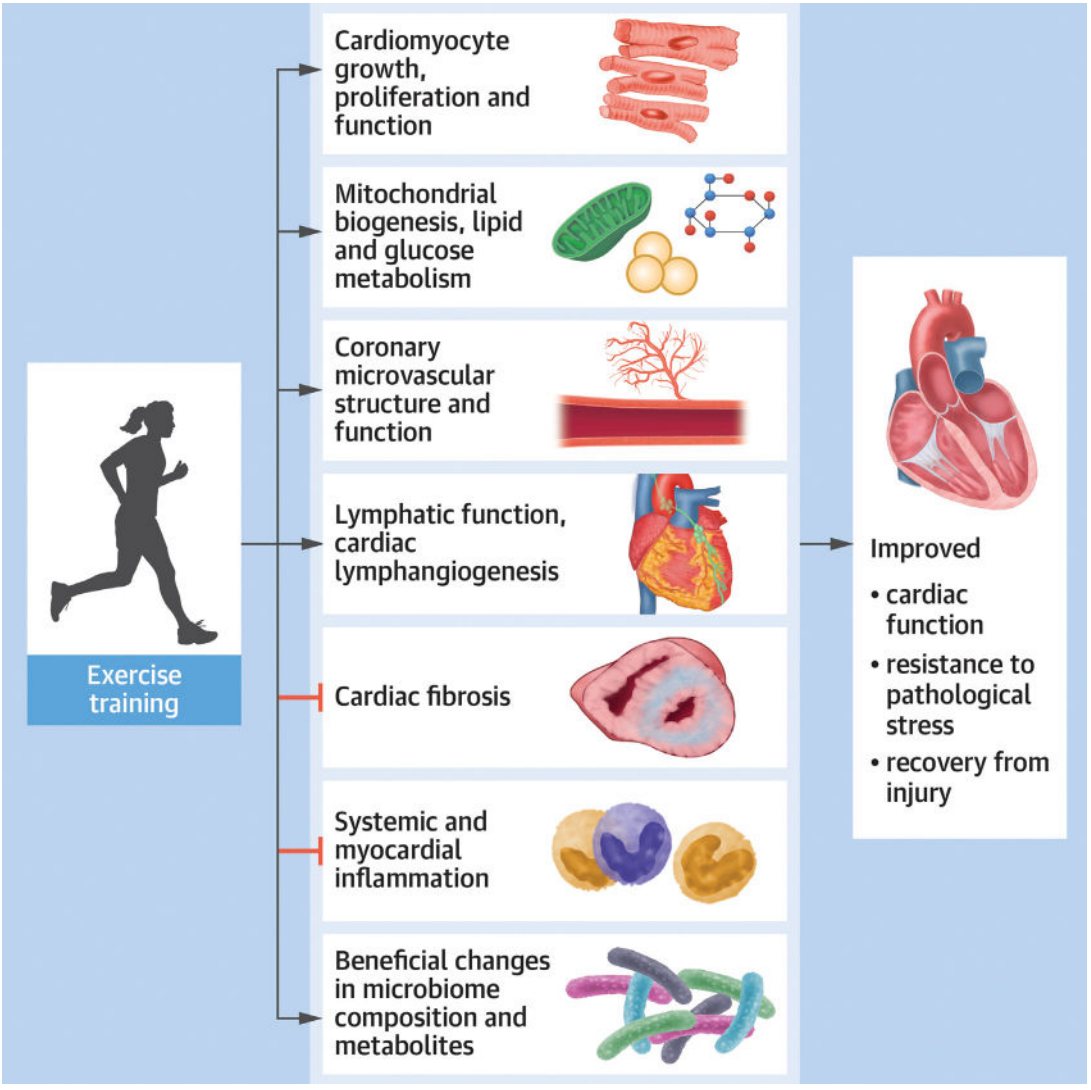
INTRINSIC CARDIAC EFFECTS

Understandably, cardiomyocytes have garnered much attention in the heart's response to exercise. The cardiomyocyte is responsible for some of the most salient exercise phenotypes, including cardiac growth (hypertrophy) and alterations in function. The evolving understanding of these processes and their potential therapeutic relevance is discussed subsequently, followed by consideration of the role of fibrosis, the microvasculature, and lymphatics. These rely principally on other cell types, often influenced by crosstalk with cardiomyocytes and systemic factors. The potential therapeutic value of targeting some of these other cell types and processes is an area of active investigation.

CARDIOMYOCYTE GROWTH AND PROLIFERATION IN PHYSIOLOGICAL CARDIAC HYPERTROPHY. Cardiomyocytes represent only ~30% to 40% of the heart's cells but account for ~70% to 85% of its volume, and endurance training leads to cardiac enlargement (hypertrophy), due primarily to an increase in cardiomyocyte size.[8] Despite appearing similar superficially to pathological cardiac growth that accompanies cardiovascular disease and often precedes heart failure,[9] exercise-induced physiological hypertrophy[10] differs in that it is reversible and, rather than dysfunction, is associated with protection from pathological stress.[11] It also involves a distinct transcriptional profile[10] without induction of pathological markers such as atrial natriuretic peptide or B-type natriuretic peptide.[12] Exercise also increases cardiomyocyte length and width proportionately, while pathological hypertrophy disproportionately increases cardiomyocyte length.[13] Notably, aerobic exercise training protects against[11] and even reverses[14] pathological hypertrophy in rodent models, supporting fundamental differences and dynamic tension between the two. Consistent with this, the underlying mechanisms also appear distinct, as detailed subsequently.

Physiological hypertrophy is associated with an increase in the adult mammalian heart's limited capacity to form new cardiomyocytes. Swim training increases proliferation markers in cardiomyocytes.[10] Because these markers do not unequivocally establish that new cardiomyocytes are formed, survive, and integrate into the myocardium, we used multi-isotope imaging mass spectrometry to demonstrate unambiguously that 8 weeks voluntary wheel running induced a 4.6-fold increase in cardiomyogenesis in adult mice.[15] Furthermore, we found that exercise training restored declining rates of

CENTRAL ILLUSTRATION **Systemic and Intrinsic Mechanisms Contribute to the Cardiac Benefits of Exercise**



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Mechanisms contributing to the benefits of exercise include effects on cardiomyocyte function, growth and proliferation, coronary microvasculature and cardiac lymphatics, cardiac fibrosis, systemic and cardiac metabolism and inflammation, and effects related to the gut microbiome. Created with BioRender.com.

cardiomyogenesis in aging mice to levels comparable to sedentary young adult animals.[15,16] Fewer new cardiomyocytes were induced than in young exercised animals, although this may be due to older animals running less.[16] Others reported a lasting increase in the proportion of mononucleated cardiomyocytes, thought to be the cardiomyocytes that proliferate, in juvenile rats following treadmill training, although the effect was diminished in adolescence and not detected in the adult.[17]

Thus, cardiomyogenesis may contribute to the clinical benefits of exercise in part by counteracting cardiomyocyte loss thought to contribute to heart failure in multiple settings.[18] However, it will be important to rigorously evaluate the functional implications of exercise-induced cardiomyogenesis

given the low absolute number of cardiomyocytes formed.[19,20] Treatment with antineoplastic agent 5-fluorouracil before swim training did not affect development of hypertrophy in mice but did reduce protection against subsequent ischemia reperfusion.[21] This suggested an essential role for proliferation in exercise-induced cardioprotection, if not growth, although inhibition of proliferation in non-cardiomyocytes may have contributed as 5-fluorouracil's effects are not cell type specific. As discussed next, the protective effects of exercise can be mimicked with genetic or pharmacological interventions, and measures of cardiomyogenesis are increased by many of these. However, as with exercise, it is not clear whether this proliferation contributes to the protective effects.

Pathways functionally important in the heart's hypertrophic response to exercise also counteract pathological stress and injury. Many pathways functionally important in the cardiac exercise response protect the heart against pathological stress when exercise-related changes are mimicked experimentally. Most extensively studied is the insulin-like growth factor (IGF)-1/PI3K/Akt pathway. Plasma IGF-1 is higher in elite athletes than control subjects[22] and cardiomyocyte-specific IGF-1 receptor knockout,[23] dominant negative PI3K,[24] or Akt1 knockout[23,25] in mice disrupts exercise-induced cardiomyocyte growth, while activation of this pathway induces heart growth.[26,27] Importantly, Akt activation reduces cardiomyocyte apoptosis,[28] myocardial injury, and cardiac dysfunction after ischemic injury.[29] Similarly, cardiac PI3K overexpression mitigates pathological remodeling and dysfunction after transverse aortic constriction (TAC).[30]

Similar results are seen with transcriptional pathways. The transcription factor CCAAT/enhancer-binding protein β (C/EBPβ) is down-regulated in hearts from exercised mice[10] and heterozygous C/EBPβ knockout mice, which have cardiac C/EBPβ messenger RNA levels comparable to exercised mice, show signs of physiological cardiomyocyte hypertrophy and proliferation[10] as well as improved heart function and survival after TAC.[10] The transcriptional regulator CITED4 increases in exercised hearts, mediating some of the effects of the decrease in C/EBPβ,[10] and its cardiomyocyte-specific deletion exacerbates TAC-induced dysfunction and pathological remodeling.[31] These mice also have an altered, pathological response to exercise training, including modest cardiac dysfunction and dilation[31] and impaired microstructural cardiac remodeling.[32] Like C/EBPβ heterozygotes, cardiomyocyte-specific CITED4 overexpression recapitulates key features of physiological cardiac growth and reduced adverse remodeling and dysfunction after ischemia reperfusion.[33]

Noncoding RNAs regulate physiological and pathological cardiac growth. Cardiac microRNA miR-222 is increased by exercise and is necessary for exercise-induced hypertrophy[34] and cardiomyogenesis.[15] Cardiomyocyte-specific miR-222 overexpression reduces pathological remodeling and dysfunction after ischemic injury.[34] We recently identified lncExACT1 as a long noncoding RNA up-regulated in pathological hypertrophy and down-regulated in physiological hypertrophy.[12] Surprisingly, both overexpression and inhibition of lncExACT1 lead to cardiac hypertrophy but with pathological and physiological features, respectively, suggesting a critical role in toggling the heart between physiological and pathological growth. lncExACT1 inhibition also induced signs of cardiomyocyte proliferation and protected against TAC- or ischemia-reperfusion-induced cardiac dysfunction.[12] Of note, the locked nucleic acid-antisense oligonucleotides used to inhibit miR-222 and lncExACT1 in these studies are not cardiomyocyte specific, and thus inhibition in other cell types may also contribute to effects observed.[12,34] Recently, Gao et al[35] identified another long noncoding RNA, cardiac physiological hypertrophy-associated regulator (CPhar), as up-regulated in exercised hearts but decreased in pathological hypertrophy. CPhar knockdown blocked swimming-induced cardiomyocyte hypertrophy and markers of cardiomyocyte proliferation, while overexpression protected against ischemia-reperfusion injury.[35]

These findings illustrate the value of animal exercise models for identifying therapeutic candidates, particularly as emerging technologies open new paths to translation. Of note, antisense inhibitors similar to those used to inhibit lncExACT1 are Food and Drug Administration approved for other indications.[36] Viral vector-based gene delivery is improving, which may facilitate translation, particularly when systemic manipulation is problematic, such as for the IGF-1/PI3K/Akt pathway, given known roles in tumor development and metastasis.[37]

CARDIOMYOCYTE FUNCTION. Some exercise benefits reflect changes in cardiomyocyte function. Exercise training increases cardiac systolic and diastolic function in both health and disease, with important implications for quality of life.[38] Although altered preload and afterload contribute to the improved cardiac function, changes in the heart's chronotropic, inotropic, and lusitropic properties also contribute.[38]

Animal studies have confirmed that aerobic training can increase cardiomyocyte fractional shortening by up to 40% to 50%, contraction and relaxation rates by up to 20% to 40%, and maximal power output by up to 60%.[39] These effects depend on exercise intensity and quickly regress with detraining.[40,41]

Mechanisms underlying improved cardiomyocyte function with exercise. Decades of animal studies have revealed exercise effects on nearly every component of the cardiomyocyte contractile machinery.[41,42] Rodent studies have shown exercise training not only increases myofilament calcium (Ca^{2+}) sensitivity, but also accelerates Ca^{2+} flux in the cardiomyocyte.[42,43] The latter is likely due to more effective coupling of L-type Ca^{2+} channels and ryanodine receptors, increased SERCA2a or sodium-calcium exchanger expression, enhanced SERCA2a activity, and/or more efficient organization of T-tubules.[39,41,44-47]

In a novel intersection between Ca^{2+} handling, epigenetic, and metabolic mechanisms, Lehmann et al[48] recently showed that HDAC4-NT, a proteolytic fragment of HDAC4, is up-regulated in mouse hearts by exercise but down-regulated in failing hearts, and its myocardial overexpression mimics the protective effects of exercise. In contrast, cardiomyocyte HDAC4 deletion impairs exercise capacity. Mechanistic studies suggest that HDAC4-NT enhances cardiac function by reducing expression of nuclear orphan receptor NR4A1, a negative regulator of cardiomyocyte contraction, through a pathway that includes both the hexosamine biosynthetic pathway and the calcium sensor STIM1.[48]

Cardiomyocyte hypertrophy may itself contribute to enhanced mechanical function, in part through an increase in sarcomere functional units.[49] Physiological hypertrophy is also associated with functionally favorable shifts in sarcomeric protein isoforms, such as an increased α- to β-myosin heavy chain ratio.[50,51]

Effects of exercise on cardiomyocyte function in disease and aging. Endogenous exercise-regulated pathways may provide therapeutic targets, not only for heart disease, but also for the decline in cardiac function that occurs in normal aging.[52-54] Exercise can reverse left ventricular stiffness in sedentary aging[53] and in middle-aged individuals with left ventricular hypertrophy at risk for heart failure.[54] Furthermore, we demonstrated reversal by exercise of many—though not all—hallmark features of heart failure with preserved ejection fraction in an aging mouse model, including improved exercise capacity, diastolic function, and contractile reserves.[55]

Molecular mediators of cardiomyocyte functional adaptation to exercise in healthy animals also appear to contribute to exercise benefits in heart failure and aging. In ischemic and nonischemic heart failure models, exercise training improves systolic and diastolic function by modulating expression or activity of key regulators of cardiomyocyte contractility including SERCA2a, ryanodine receptors, phospholamban, and CaMKII.[14,42,44,56] Many of these same mechanisms are implicated in exercise adaptation in aged cardiomyocytes, although there are distinctions including differing effects on cardiomyocyte β-adrenergic sensitivity,[57] SERCA2a activity, Ca^{2+} cycling,[58] and hypertrophic signaling.[16,46,55,59] Notably, exercise modulates expression and/or activity of proteins in the activin/myostatin family, important regulators of skeletal muscle mass that are also implicated in age-related cardiac dysfunction[60,61] through their effects on phospholamban and SERCA2a.[60,61] A deeper understanding of this and other intersections between exercise-regulated pathways and those driving cardiac dysfunction in aging and disease may yield therapeutic insights.

Directly manipulating exercise-related targets, such as SERCA2a[62] and activin/myostatin,[61] improves cardiac function in models of heart failure and aging, suggesting that these may be valuable therapeutic targets. While clinical trials testing AAV1-mediated SERCA2a gene therapy for heart failure were not successful, this may relate to technical limitations that could be overcome as gene delivery technology advances (NCT01643330).[63] Inhibitors of activin/myostatin signaling have also been evaluated in clinical trials for other indications, including a recent phase 3 trial in which a soluble ligand trap inhibitor of activin signaling (Sotatercept) increased exercise capacity relative to placebo in patients with pulmonary hypertension (NCT04576988).[64] Further delineation of mechanisms by which exercise affects heart function will likely suggest new therapeutic strategies in heart failure and age-related heart disease.

CARDIAC FIBROSIS. While pathological hypertrophy and age-related cardiac dysfunction are associated with interstitial fibrosis,[55,65] physiological hypertrophy generally is not.[66] Exercise-trained animals develop less fibrosis than sedentary control animals in response to cardiac injury or pathological stress including hypertension, anthracycline-induced cardiotoxicity, pressure overload, and ischemic injury, among others.[67,68] Although the roles of fibroblasts are multifaceted and include important structural, mechanical, and repair functions, these observations suggest that, in addition to the favorable effects on cardiomyocytes discussed previously, exercise may reduce adverse cardiac remodeling in part by limiting fibrosis.

Mechanisms by which exercise suppresses fibrosis in pathological models. Mechanistic studies further support a role for fibroblasts and cardiomyocyte-fibroblast crosstalk in the benefits of exercise. Transcriptional profiling of non-cardiomyocytes after exercise training, pressure overload, or myocardial infarction (MI) demonstrated activation of myofibroblast transformation gene programs in disease models but not in exercise.[67] Some pathways were regulated inversely in exercise and pathological stress. For example, NRF2-dependent antioxidant genes, including metallothioneins Mt1 and Mt2, were up-regulated with exercise but suppressed in disease states by transforming growth factor (TGF)-β signaling.[67] Interestingly, conditioned media from Mt1-overexpressing fibroblasts protected cardiomyocytes from oxidative injury and apoptosis, suggesting that, in addition to limiting fibrosis, exercise induced fibroblast-cardiomyocyte crosstalk to promote cardiomyocyte survival.[67]

Similarly, important crosstalk occurs downstream of exercise-induced transcriptional coactivator CITED4.[33] As mentioned, cardiomyocyte-specific CITED4 knockdown resulted in a pathological response to exercise as well as injury.[31] This included fibrosis and profibrotic gene expression (eg, collagens, CTGF, TGF-β2).[31] CITED4 deletion also reduced cardiomyocyte miR30d expression and secretion via extracellular vesicles.[31] Conditioned media from CITED4-deleted cardiomyocytes was sufficient to induce profibrotic gene programs in fibroblasts, an effect that was lost when cardiomyocyte miR30d expression was restored with miR-mimics.[31]

Mimicking exercised-related changes in noncoding RNA expression, including miR-222 and lncExACT1, also protects against fibrosis under pathological conditions.[12,34] Interestingly, lncExACT1 acts through regulation of miR-222, calcineurin, and Hippo/Yap.[12] Again highlighting the importance of cardiomyocyte-fibroblast crosstalk, manipulation of miR-222 in these studies was cardiomyocyte specific. Similarly, another exercise-induced microRNA, miR-29c, was inversely regulated with the fibrotic gene program, and its deletion in a murine pressure overload model also attenuated cardiac fibrosis.[69]

Across multiple preclinical models, suppression of cardiac fibrosis by exercise training has been linked to reduced inflammation and oxidative stress. For example, treadmill or swim training reduce fibrosis, oxidative stress, and inflammation in doxorubicin cardiotoxicity.[68,70] Similarly, exercise reduces fibrosis when initiated 1 week after MI in rats, as well as in hypertensive rats, and is associated with reduced inflammatory and fibrotic gene expression (TGF-β, p-Smad2/3, CTGF, matrix metalloproteinase 9, and collagen I).[71,72] Swim training mitigates isoproterenol-induced cardiac fibrosis in an adenosine monophosphate-activated protein kinase (AMPK)-dependent manner, consistent with an oxidative stress-related mechanism.[73] Chronic exercise also reduces oxidative stress as well as profibrotic signaling (TGFβ, pSmad2/3, matrix metalloproteinase 2, CTGF) and fibrosis in rats with diet-induced type 2 diabetes and cardiac dysfunction.[74] As oxidative stress and inflammation play important roles in the pathogenesis of fibrosis, these changes likely contribute to reduction of fibrosis by exercise.

Exercise likely influences fibrosis through multiple mechanisms in the aged heart. Treadmill exercise in aged rats reduced fibrosis and advanced glycation end-product accumulation that are associated with both aging and diabetes.[75] In a recent study, 8 weeks of voluntary wheel running increased the number of fibroblasts without changing overall fibrosis in the hearts of aged mice.[16] The relevance of fibroblast hyperplasia in this setting is unclear.

Possible benefits and risks of reducing fibrosis in disease and aging. Although fibrosis is a hallmark of adverse cardiac remodeling in the elderly,[55] it remains challenging to define the contribution of fibrosis per se to these conditions. Excessive fibrosis can impair cardiac systolic and diastolic function as well as lead to arrhythmia, but fibroblasts likely also play important roles in homeostasis, generating the extracellular matrix that serves as the scaffold of the heart,[76,77] contributing to the heart's response to mechanical stress,[78] replacing lost cardiomyocytes, and mediating scar formation after injury.[79,80] Thus, benefits and risks of targeting fibrosis likely vary in different contexts, with concerns about potential rupture, especially after infarction. Interestingly, the Tallquist laboratory recently demonstrated that genetic ablation of substantial numbers of cardiac fibroblasts was remarkably well tolerated, and fibroblast-ablated mice even showed improved cardiac function under pathological conditions (angiotensin II/phenylephrine infusion).[81] Thus, either fibroblasts are not as critical as generally thought or the system can compensate for considerable fibroblast loss. Further preclinical studies will be critical for evaluating risks and benefits of targeting fibrosis.

Of note, focal myocardial fibrosis has been reported in longtime athletes in some[82,83] but not all studies,[84,85] suggesting that exercise can promote fibrosis under some conditions, although causality is uncertain given confounders inherent in

observational studies.[86,87] These observations underscore the importance of reliable biomarkers to gauge exercise benefit.

CARDIAC VASCULATURE. Clinically, considerable attention is devoted to the epicardial vessels because of their role in acute coronary syndromes as well as myocardial ischemia and infarction. While exercise has important effects at this level, there is growing recognition of the importance of other vascular components, notably coronary microcirculation and cardiac lymphatics, which we discuss here.

Coronary microcirculation. The coronary microcirculation comprises an uninterrupted network of cardiac blood vessels with diameters decreasing in size from prearterioles (500-100 μm in diameter) to arterioles (<100 μm diameter) and capillaries. This microvasculature regulates myocardial perfusion to match blood supply with oxygen consumption.[88] On short time scales, such as during acute exercise, rapid adjustments in blood flow are achieved primarily by changes in diameter of prearterioles and arterioles. However, the coronary microvasculature also undergoes long-term structural and functional adaptations to chronic exercise.[89,90] Exercise training enhances both smooth muscle-dependent, pressure-induced myogenic constriction and endothelium-dependent/shear stress-induced dilation in coronary arterioles.[90] Arteriole diameter and density as well as capillary surface area and permeability are increased.[90-94] Exercise training decreases elastic modulus and increases wall thickness, wall stress, and distensibility and in rat coronary arterioles.[95] In contrast to pathological hypertrophy, in which muscle growth can outpace angiogenesis, likely contributing to heart failure,[96] exercise training induces capillary angiogenesis proportionate to cardiac growth.[91,93] Exercise also may protect the coronary microcirculation indirectly by mitigating inflammation, platelet activation, autonomic dysfunction, and hemodynamic forces.[90,97]

Molecular mechanisms of exercise-induced coronary microcirculation adaptions. Exercise training promotes endothelium-dependent vascular relaxation as well as angiogenesis in part by increasing nitric oxide (NO) signaling. Endothelial nitric oxide synthase (eNOS) messenger RNA and protein expression are increased in arterioles after exercise training and contribute to enhanced endothelium-dependent dilation.[98,99] Increased eNOS expression may be triggered by exercise-related flow and shear stress.[100] Expression of Cu/Zn superoxide dismutase is also flow dependent,[100] and superoxide dismutase activity is increased with exercise training in the mouse heart[101] and rat ventricular myocardium,[102] suggesting that it may also contribute to increased NO bioavailability, as well as to reducing oxidative stress. β3-adrenergic receptor-dependent modulation of eNOS phosphorylation also contributes to increased cardiac eNOS activity with exercise training.[101]

Ion channels also contribute to coronary microvascular adaptations during exercise training. Exercise training increases calcium currents through voltage-gated Ca^{2+} channels in smooth muscle from conduit arteries, small arteries, and large arterioles, likely contributing to enhanced myogenic constriction.[103] In cultured endothelial cells, shear stress altered the distribution of transient receptor potential channel TRPV4,[104] a Ca^{2+}-permeable cation channel involved in endothelium-dependent dilation,[105] consistent with possible modulation by exercise training.

Although still poorly understood, microvascular adaptation also involves a complex interplay of many vasodilators and vasoconstrictors, including neurohormones and endothelial and myocardial influences. Further investigation is needed to define fully how exercise regulates coronary microvascular structure and function.

Exercise-induced coronary microcirculation adaptations in aging and disease. Regular exercise benefits patients with diseases involving dysregulation of coronary microcirculation, including heart failure and coronary artery disease, among others.[4,106] Supporting a role for microvascular changes in the clinical benefits of exercise, 12-week aerobic interval training increased coronary flow reserve in coronary artery disease patients.[106] Aging is also associated with coronary microvascular dysfunction,[107,108] and microvascular changes may also contribute to exercise benefits in aging. Moderate exercise improved leg microvascular function in older adults,[109] and in rats, treadmill training reversed age-related aortic stiffness as well as impaired coronary blood flow responses, endothelium-dependent vasodilatation, and early to atrial filling velocity ratio.[110]

The clinical benefits of exercise have been linked to many of the molecular mediators described previously. The protective effects of exercise against myocardial ischemia-reperfusion injury were lost in mice deficient in eNOS or the β3-adrenergic receptor, although reduced exercise in these mice may be a confounder.[101] Adrenergic modulation was also associated with exercise benefits in patients with microvascular angina and syndrome X.[111,112] In

porcine models, treadmill training reversed impaired NO-mediated dilation of arterioles distal to coronary artery occlusion, and this was dependent on enhanced H_2O_2 and NO production.[113] Consistent with a possible role for TRPV4, exercise training reversed age-related decline in TRPV4-dependent, endothelium-derived hyperpolarizing factor-mediated dilation in rat aortic arteries.[114] Molecular mechanisms underlying exercise benefits may also differ in the context of age or disease, for example, exercise training reduced vessel wall collagen-to-elastin ratio in coronary arterioles of old but not young rats.[93,94] These observations suggest exercise-inspired therapeutics targeting the microvasculature could benefit cardiovascular diseases and cardiac aging.

Cardiac lymphatics. Recent findings suggest a role for cardiac lymphatics in the benefits of exercise. Lymphatic vessels play essential and dynamic roles in maintaining interstitial pressure, lipid transport, and clearance of antigens and immune cells, as well as organ-specific adaptation to the local microenvironment.[115-117] Regular exercise improves impaired lymphatic function both in animal studies and in randomized controlled trials with human patients.[118] Vascular endothelial growth factor C and D are the main drivers of lymphangiogenesis via the receptor vascular endothelial growth factor receptor 3 (VEGFR3), and all of these were elevated in mouse hearts after swim training.[119] Lymphatic markers podoplanin and LYVE-1 were also increased in swim trained animals in a VEGFR3-dependent manner, as was the density of LYVE-1-positive vessels.[119] Importantly, VEGFR3 inhibition attenuated exercise-induced cardiac and cardiomyocyte growth, suggesting a role of lymphangiogenesis in physiological cardiac hypertrophy.[119] This role likely involves crosstalk between lymphatic endothelial cells and cardiomyocytes, as VEGFR3-dependent hypertrophy and proliferation was also induced in cultured neonatal rat cardiomyocytes treated with conditioned medium from lymphatic endothelial cells.[119]

The role of cardiac lymphatics in the therapeutic effects of exercise has not been directly examined; however, dysregulation of cardiac lymphatics in disease has been long recognized,[120] and has been documented in hypertension,[121] atherosclerosis and dyslipidemia,[122,123] MI, and heart failure.[124] Moreover, growing evidence supports cardiac lymphatic growth and remodeling as potential therapeutic targets.[125,126] Vascular endothelial growth factor C gene delivery by adeno-associated virus or injection of protein reduced cardiac inflammation, infarct thinning, and cardiac dysfunction after MI.[127,128] These benefits may in part reflect the role of cardiac lymphatics in transport of immune cells to and from the injury site after MI.[129] Recently, analysis of the lymphatic endothelial cell secretome uncovered RELN as a lymphoangiocrine protein directing cardiomyocyte proliferation and survival during MI.[130] Notably, RELN and IGF-1 were increased in mouse hearts by swim training.[119] Further work is needed to define exercise-regulated lymphangiogenic pathways and crosstalk with cardiomyocytes and investigate their potential therapeutic relevance.

SYSTEMIC EFFECTS WITH IMPORTANT CARDIAC CONSEQUENCES

METABOLISM. Exercise training, and physical activity more generally, induces systemic metabolic changes that reduce cardiovascular disease risk factors such as obesity and diabetes. In part, this may reflect changes in energy homeostasis although this effect is generally modest. Likely more important are improved insulin sensitivity and glucose uptake by skeletal muscle and other tissues, due in part to increased expression of the glucose transporter GLUT4[131,132] and AMPK,[133,134] a key kinase regulating glucose uptake. Another key systemic adaptation related to metabolic disease is skeletal muscle induction of transcriptional coactivator PGC-1α,[135] important in mitochondrial biogenesis and oxidative metabolism.

In the myocardium, either increased substrate or more efficient energy utilization is necessary to support augmented cardiomyocyte size and function in response to exercise training, particularly as SERCA2a and other ion pumps involved in cardiomyocyte function account for the bulk of the heart's adenosine triphosphate needs. Exercise training up-regulates metabolic modulatory enzymes in the heart including Akt1,[136] NAD(+)-dependent deacetylases, SIRT-1[137] and SIRT-3,[138] eNOS,[139] and the energy sensor, AMPK.[139] Through targets including PGC-1α[139,140] and transcription factors, FoxO1[141] and FoxO3a,[138] these interconnected signaling pathways activate transcriptional networks that increase measures of mitochondrial mass and function,[139] improve cardiac fatty acid and glucose handling,[139,142] and protect against oxidative stress.[138,141]

Exercise-mediated changes in metabolism in disease and aging. Exercise also directly counteracts metabolic changes seen in aging and diseased hearts. Pathological hypertrophy and cardiac aging are associated with impaired mitochondrial

respiratory capacity, decreased mitochondrial biogenesis, a shift in substrate utilization from fatty acids to glucose, and excessive production of mitochondrial reactive oxygen species.[143,144] These changes reduce metabolic reserve.[145] In contrast, physiological cardiac remodeling is not associated with a shift from fatty acid metabolism to glycolysis and is associated with increased mitochondrial biogenesis and antioxidant mechanisms.[146]

Exercise training enhances cardiac metabolism in rodent heart failure models through more efficient fatty acid metabolism, restoration of autophagic flux, and increased mitochondrial biogenesis, essentially reprogramming the bioenergetic profile of the failing heart to improve function.[147,148] The cardiac metabolic benefits of exercise also extend to aged subjects, but appear greater in young individuals,[145] and this tracks with changes in the metabolic response to training. For example, exercise-induced muscle expression of PGC-1α is lower in older subjects.[149]

Pathways that modulate cardiac metabolic adaptation to exercise are also necessary and/or sufficient to protect the heart against pathological stress, injury, and aging. Cardiac-specific SIRT1 deletion exacerbated while overexpression protected against ischemia-reperfusion injury.[141] SIRT3 overexpression in the heart blocked angiotensin II-induced pathological hypertrophy.[138] Exercise training also ameliorated cardiac metabolic impairments in a diabetic cardiomyopathy model by increasing PGC-1α and Akt activation[150] and reduced the age-related increase in mitochondrial reactive oxygen species production.[144]

These preclinical findings point to exercise-modulated metabolic regulators as clinically relevant targets. Notably, metformin, which activates AMPK, has been widely used for treatment of type 2 diabetes and may have protective effects on the cardiovascular system,[151] and supplements such as resveratrol that have been reported to activate sirtuin, PGC-1α, and AMPK signaling are being investigated in clinical trials in the context of cardiovascular as well as metabolic disease.[152] New pharmacological approaches targeting these pathways warrant further investigation.

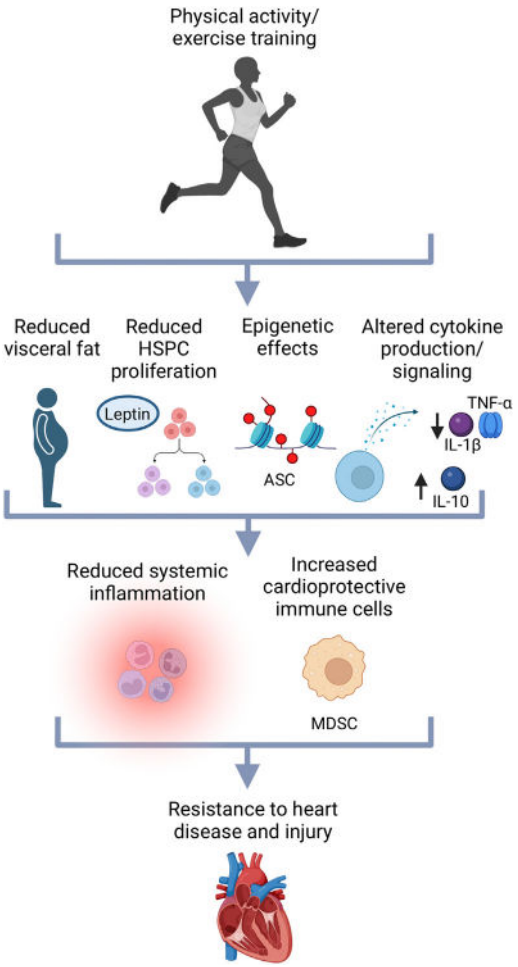
INFLAMMATION AND IMMUNE CELLS. As mentioned previously, inflammation is important in the pathogenesis of many cardiovascular diseases,[153] and the anti-inflammatory effects of exercise are important in its cardiovascular benefits (**Figure 1**). Controlled experiments in humans and animal models demonstrate an association between exercise benefits and a reduction in inflammatory markers systemically and in the heart, both during aging and in a range of pathological conditions including heart failure, MI, and atherosclerosis.[68,71,72,154-156] Underscoring again the need for biomarkers of exercise benefit, strenuous acute exercise has been linked to increased inflammation, suggesting that the relationship between training and inflammation may change at high intensities.[157]

The systemic anti-inflammatory benefits of exercise are likely due in part to reduced accumulation of visceral fat, which is associated with proinflammatory immune cell infiltration.[158,159] However, exercise also appears to directly modulate the immune system.[160] For example, in a mouse isoproterenol-induced heart failure model, exercise-induced cardioprotection was associated with increased serum and cardiac interleukin (IL)-10 and cardiac myeloid-derived suppressor cells, and protection was lost in myeloid-derived suppressor cell-depleted or IL-10 knockout mice.[161]

A recent study[162] suggested that physical activity improved cardiac function in part through changes in the bone marrow microenvironment that reduced hematopoiesis. In mice, 6-week voluntary exercise triggered a 34% reduction in proliferation of hematopoietic stem and progenitor cells, which give rise to leukocytes, including lymphocytes, and macrophages. This in turn decreased circulating inflammatory leukocytes. Bone marrow mononuclear cells in exercise-trained mice were less able to differentiate into granulocytes, macrophages, and B cells. These effects were traced to decreased leptin signaling in bone marrow stromal cells, resulting from reduced leptin secretion from visceral adipose tissue. The reduction in circulating leukocytes and hematopoietic stem and progenitor cell proliferation was blocked by increasing leptin to sedentary levels, or mimicked by deleting the leptin receptor in bone marrow stromal cells. Decreased circulating leptin and leukocytes were also observed with exercise in atherosclerosis, both in humans and mice, and exercise benefits were mimicked in atherosclerotic mice lacking the bone marrow stromal cell leptin receptor. Mice lacking the leptin receptor also showed improved cardiac function and reduced cardiac and circulating leukocyte numbers after MI.

Other mechanisms of immune modulation have been indirectly implicated in the cardiovascular benefits of exercise. For example, one study reported that physical activity diminished cytokine production capacity of peripheral blood mononuclear cells in individuals at risk for cardiovascular disease.[156] Other work pointed to epigenetic regulation of the gene encoding ASC, an adaptor protein that mediates

FIGURE 1 Possible Inflammatory and Immune Mechanisms Underlying Exercise Effects on the Heart



Reduced systemic inflammation and expansion of cardioprotective immune cells, including myeloid derived suppressor cells (MDSCs), likely contribute to the cardiac benefits of exercise. Underlying mechanisms include reduced visceral fat, reduced hematopoietic stem and progenitor cell (HSPC) proliferation, epigenetic changes, and altered cytokine production/signaling. Created with BioRender.com.
IL = interleukin; TNF = tumor necrosis factor.

proinflammatory signaling. Exercise increased methylation and decreased expression of ASC in peripheral blood from older individuals[163] and heart failure patients.[164] ASC methylation was associated with reduced plasma IL-1β and better performance on a 6-minute walk test in the heart failure patients. In contrast, aging[163] and poor heart failure outcomes[165] have been associated with decreased ASC methylation.

Systemic inflammation increases with aging and obesity and, due to increasing population age and obesity, represents a growing problem. Understanding the anti-inflammatory effects of exercise may provide new therapeutic targets for combatting these trends.

THE MICROBIOME. The intestinal microbiome is increasingly recognized as a possible contributor to exercise effects, including effects on inflammation and metabolism. In recent work from the Xiao laboratory, antibiotics abolished the protective effects of running in mice after MI, and fecal microbiota transplantation (FMT) from mice exercised post-MI attenuated postinfarction cardiac remodeling and improved heart function.[166] Exercise was reported to increase microbial diversity, enrich beneficial bacterial genera, and reduce hypertension in spontaneously hypertensive rats.[167] Indicating a causal role for the microbiome, FMT from exercised rats was also sufficient to decrease systolic blood pressure.[167] The microbiome is also implicated in exercise benefits for prevention of diabetes, a cardiovascular risk factor, in humans. Prediabetics who derived glycemic benefits from exercise training could be discriminated from those who did not based on changes in their microbiome and associated metabolites,[168] and FMT from responders but not nonresponders reproduced the glycemic benefits in obese mice.[168] These observations suggest that microbiome changes may contribute to the cardiovascular benefits of exercise (Figure 2).

Potential mechanisms of microbiome-mediated exercise benefits. The effects of exercise likely reflect changes in microbiome diversity, composition, and metabolites. Increases and decreases in a range of fecal and serum metabolites are observed after acute exercise in amateur runners,[169,170] with evidence of metabolite exchange between serum and fecal compartments.[170] Regular exercise altered the gut microbiome in animals and humans, with effects on the most prevalent gut microbial phyla, Bacteroidetes and Firmicutes,[171,172] although no consistent pattern has emerged at the genus level (Table 1). Some, but not all, reports suggest that physical activity also increases gut microbiome diversity.[173]

Although few studies have directly addressed mechanisms by which the microbiome mediates exercise effects on the heart, some microbiota-associated metabolites that are modulated by exercise training also impact cardiovascular disease phenotypes (Table 2). Fecal short-chain fatty acids (SCFAs) are increased in athletes,[174] and SCFAs are associated with diverse, often protective roles in cardiovascular diseases, including atherosclerosis, hypertension, and heart failure.[175,176] These effects

may be related to SCFA modulation of inflammatory and immune phenotypes, including tumor necrosis factor and nuclear factor κB signaling, which SCFAs modulate through interaction with G protein-coupled receptors[175] and by acting as histone deacetylase inhibitors, highlighting again the likely role of epigenetic mechanisms in the benefits of exercise training.[177] Consistent with immune effects, SCFAs restore myeloid cell, macrophage, and neutrophil levels, as well as survival and favorable remodeling after MI in mice with depleted gut microbiota.[178] Evidence supporting SCFAs as a link between exercise, microbiota, and cardiovascular risk comes from the observation that insulin resistance in obese mice was improved by FMT from prediabetic exercise responders but not nonresponders, and SCFA supplementation partially restored the beneficial effects in mice transplanted with "nonresponder" microbiota. In contrast, branched-chain amino acid supplementation decreased the beneficial effects in mice transplanted with "responder" microbiota.[168]

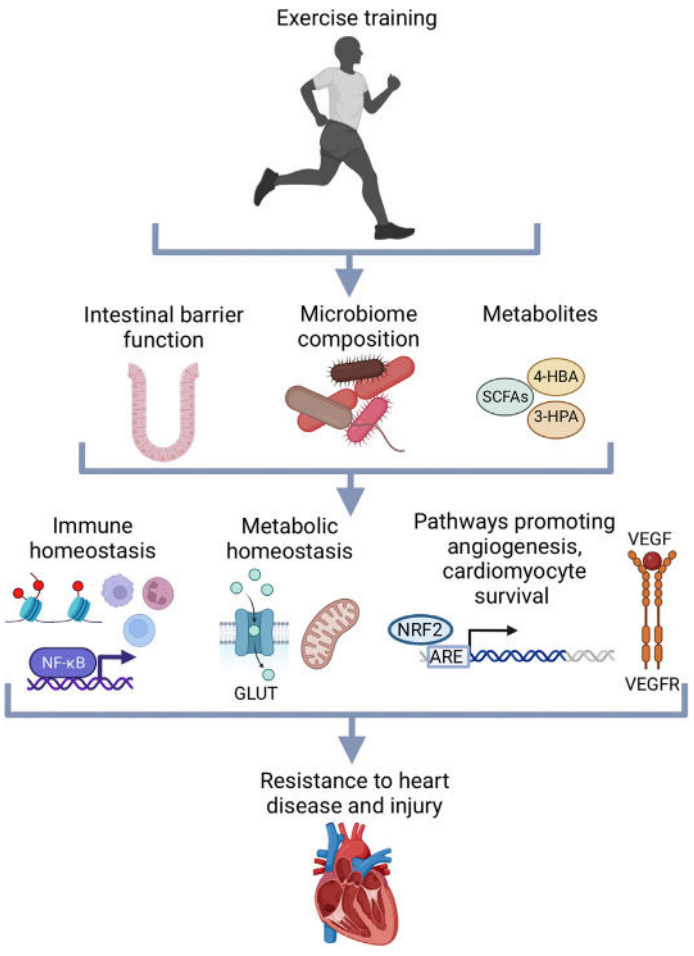
Recently, metabolomic profiling of fecal samples identified 3-HPA and 4-HBA as candidate mediators of the protective effects of exercise in mice post-MI, and supplementation improved cardiac function and protected against cardiac dysfunction after MI.[166] Mechanistically, 3-HPA and 4-HBA reduced cardiomyocyte apoptosis by activating NRF2,[166] a new target of microbiota-derived metabolites.

Another microbiota-derived metabolite linked to both cardiovascular disease and exercise is trimethylamine. Trimethylamine is further metabolized to TMAO, which increased risk of atherosclerosis,[179] cardiovascular events such as ischemic stroke,[180] and heart failure.[181] Interestingly exercise reversed the aggravation of cognitive dysfunction by TMAO in an Alzheimer's mouse model.[182]

These data are consistent with the hypothesis that exercise contributes to cardiac benefits by increasing advantageous metabolites and/or reversing pathological metabolic changes. Supporting the latter possibility, cardiovascular diseases were associated with altered enterotypes,[183] and FMT and microbiome-depletion experiments suggest causal roles for gut microbiota in cardiovascular diseases including hypertension and MI.[178,183]

Finally, effects on gut permeability may also contribute to the cardiovascular benefits of exercise. The intestinal mucosa serves as a selectively permeable barrier for nutrient absorption while preventing pathogen entry that could increase systemic inflammation, a driver of cardiovascular disease.[184] While intense, acute exercise increases measures of intestinal permeability in humans,[185] chronic exercise increased intestinal integrity and selective barrier function, possibly through changes in gut microbiota.[186-188] In a recent study, lipopolysaccharide (LPS) and D-lactate, products of gut bacterial translocation, were increased in plasma after MI in patients and gut permeability was increased after MI in mice due to suppression of tight junction proteins and intestinal mucosal injury.[189] The antibiotic polymyxin B inhibited gut microbial translocation and reduced cardiomyocyte injury.[189] Interestingly, while voluntary wheel running alleviates symptoms and

FIGURE 2 Mechanisms by Which Gut Microbiota May Mediate the Effects of Exercise Training on the Heart



Exercise may reduce systemic inflammation, maintain metabolic homeostasis, and activate angiogenic and cardioprotective pathways in part through its effects on intestinal permeability, microbiota composition, and microbial metabolites. These processes could potentially be targeted through antibiotic treatment, fecal microbiota transplantation, or metabolite supplementation as therapeutic approaches for cardiovascular disease. Created with BioRender.com. NF-κB = nuclear factor-κB; SCFA = short-chain fatty acid; VEGF = vascular endothelial growth factor; VEGFR = vascular endothelial growth factor receptor.

TABLE 1 Summary of Studies Demonstrating Exercise Training Effects on the Composition of the Microbiome

Model	Exercise Training	Effects of Exercise	Ref. #
Human: 32 previously sedentary women (n = 20) and men (n = 12) based on a lean or obese body mass index	2 wk of baseline testing + 6 wk endurance-based exercise intervention + 6-wk washout period	Butyrate producers (*Clostridiales* spp., *Lachnospira* spp., *Roseburia* spp. f_*Lachnospiraceae* unclass, and *Faecalibacterium* spp.) increased.	197
Human: sedentary overweight women (n = 19) aged 36.8 ± 3.9 y	6 wk of endurance training (40-60 min)	*Dorea*, *Anaerofilum*, and *Akkermansia* increased while unidentified Porphyromonadaceae, *Odoribacter*, unidentified Desulfovibrionaceae, and unidentified Enterobacteriaceae decreased.	198
Rat: male Sprague Dawley rats (5 wk old)	6 d running wheels	*Bifidobacterium* and *Lactobacillus* increased; *Bacteroides*, *Prevotella*, *Enterococcus*, and *Clostridium* decreased.	199
Mouse: male type 2 diabetic db/db mice (6 wk old)	6 wk of low-intensity treadmill running (5 d/wk)	*Bifidobacterium* spp. and *Methanobrevibacter* spp. decreased; *Lactobacillus* spp. and *Clostridium leptum* increased.	200
Mouse: 8-wek-old male mice fed with HFD	6 wk of treadmill running (1 h each day; 17-22 m/min)	*Lactococcus* was decreased 1 h after acute exercise, but change did not persist 1 wk after acute exercise.	201
Mouse: male C57BL/6 mice post-MI (8-10 wk old)	8 wk of treadmill running (15 m/min)	*Alistipes*, *Ruminococcus*, *Allobaculum*, and Oscillospiraceae UCG-005 increased; *Lachnospiraceae_UCG-001* decreased.	166

HFD = high-fat diet; MI = myocardial infarction.

reduces inflammation in a mouse model of colitis, in an inflammatory disease involving increased gut permeability, forced treadmill running exacerbates it, possibly reflecting differences in intensity or stress in these exercise models.[190]

Metabolites and microbiota are readily manipulated, suggesting that interventions targeting the microbiome may be particularly amenable to translation. SCFAs in particular are already being investigated as a possible therapeutic for hypertension in clinical trials.[191] While experiments in animal models will be essential for identifying therapeutic candidates, further work is also needed to characterize changes in the microbiome with exercise in patients with and without cardiovascular disease.

EXERCISE AND AGING. Advanced age is one of the strongest risk factors for cardiovascular disease in general and heart failure in particular,[192] although precisely how aging contributes to the development of cardiovascular disease and whether it is possible to intervene in this process remain unclear. In part this reflects our still incomplete understanding of aging itself. While a detailed discussion of these issues is beyond the scope of this review, the interested reader is referred to a recent update cataloguing the phenotypic and molecular hallmarks of aging[193] as

TABLE 2 Cardiovascular Benefits and Mechanisms Associated With Exercise-Regulated Microbiome Metabolites

Metabolite		Disease or Model	Mechanisms	Ref. #
Short-chain fatty acids	Propionate	Hypertensive	Propionate affected immune homeostasis and beneficially modulated effector T cells.	202
		Akt2 knockout-induced cardiac contractile and mitochondrial dysfunction	Propionate attenuated the decrease in G protein-coupled receptor GPR41 in this model.	203
		Myocardial infarction	Propionate promoted macrophages reduction and inhibited JNK/P38/NFκB.	204
	Butyrate	Diabetic cardiomyopathy mice (streptozotocin)	Butyrate inhibited HDAC4 and increased GLUT1 and GLUT4, as well as GLUT1 acetylation in the myocardium.	205
		Diabetic rats (HFD and low dose streptozotocin)	Sodium butyrate and exercise increased VEGF-A and VEGFR2.	206
		Doxorubicin-induced cardiotoxicity	Butyrate derivative phenylalanine-butyramide inhibited oxidative and nitrosative stress and counteracted mitochondrial dysfunction.	207
3-HPA 4-HBA		Myocardial infarction	3-HPA and 4-HBA increased the expression of NRF2 in oxygen glucose deprivation/reoxygenation-induced neonatal rat cardiomyocytes.	166

HFD = high-fat diet; VEGF = vascular endothelial growth factor; VEGFR = vascular endothelial growth factor receptor.

well as recent reviews on targeting these pathways in heart disease and the role of exercise in this context.[46,194] The same processes driving aging of the organism occur within the heart itself, so aging represents both a systemic and intrinsic contributor to heart disease. Interestingly, exercise counteracts many of these aging pathways. Consistent with this conceptual framework, exercise is one of the few interventions that appears effective in reducing age-related cardiac functional decline. On the other hand, in general, aged animals exercise at lower intensities than young animals, reducing the potential benefits of exercise. As noted previously, we found that forced treadmill exercise reversed many—but not all—of the phenotypes seen in age-related heart failure with preserved ejection fraction.[55] Moreover, while voluntary wheel running induced cardiomyogenesis in both young adult and aged mice,[15,16] the older mice ran less and only restored cardiomyogenesis to levels seen in sedentary younger mice. This illustrates one of the challenges of working with older animals because it is impossible to infer whether the lower rates of cardiomyogenesis reflect the lower activity level, a dampened response to exercise, or some combination.

With advanced age, hearts become hypertrophied with increases in cardiomyocyte size. However, the effect of exercise on age-related cardiac hypertrophy is controversial. Swim training for 8 weeks in 23-month-old mice was reported to increase capillary density without impacting cardiomyocyte size.[195] In contrast, others have found that both short-term (10 weeks) and long-term (12 months) treadmill training increased heart weight and cardiomyocyte size in 24-month-old mice.[196] Other reports demonstrated that 12 weeks of swim training reversed cardiac hypertrophy in 18-month-old mice.[137] These inconsistencies may result from differences in age, exercise protocols, or animal strains used, but they also raise the possibility that exercise may be less effective in aged animals. While we have attempted to highlight what is known about the impact of exercise not only in young adults, but also in the context of advanced age, in many cases, our understanding remains incomplete.

CONCLUSIONS

A wealth of clinical and preclinical data have contributed to our appreciation of the cardiac benefits of exercise and physical activity. Yet, our insights into the responsible mechanisms and identification of reliable reporters of response remain limited. Here, we have reviewed our current understanding of the mediators of exercise benefits, including mechanisms intrinsic to the heart, involving cardiomyocytes and noncardiomyocyte, and those systemic processes that have important implications for cardiac biology. Efforts continue to better understand these contributions, notably including the Molecular Transducers of Physical Activity Consortium initiative, supported by the National Institutes of Health Common Fund. This large-scale, multidisciplinary consortium aims to comprehensively characterize the molecular changes induced by exercise across tissues in humans and preclinical models. In addition to identifying new mechanisms, the Molecular Transducers of Physical Activity Consortium's publicly available multiomics dataset will be a hypothesis-generating resource of unprecedented scope. Improved understanding and identification of molecular mediators as well as markers of benefit could lead to new therapeutic strategies, inspired by exercise, and ways to personalize general recommendations for physical activity. In the meantime, those who can should incorporate physical activity into their daily lives wherever possible as a route to preventing and mitigating disease as well as improving quality of life.

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