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Review

Understanding Exercise Capacity: From Elite Athlete to HFpEF

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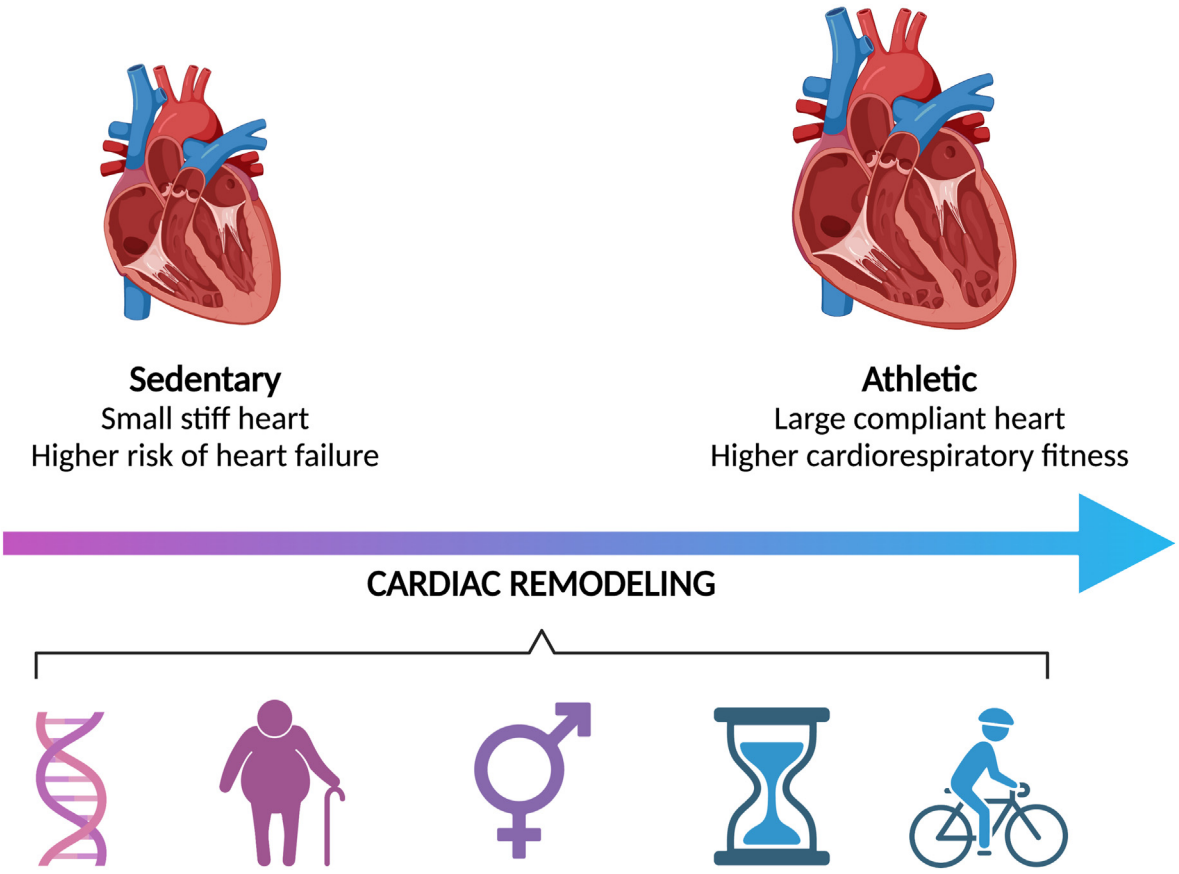

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ABSTRACT

Exercise capacity is a spectrum that reflects an individual's functional capacity and the dynamic nature of cardiac remodelling along with respiratory and skeletal muscle systems. The relationship of increasing physical activity, increased cardiac mass and volumes, and improved cardiorespiratory fitness (CRF) is well established in the endurance athlete. However, less emphasis has been placed on the other end of the spectrum, which includes individuals with a more sedentary lifestyle and small hearts who are at increased risk of functional disability and poor clinical outcomes. Reduced CRF is an independent predictor of all-cause mortality and cardiovascular events determined by multiple inter-related exogenous and endogenous factors. In this review, we explore the relationship of physical activity, cardiac remodelling, and CRF across the exercise spectrum, emphasising the critical role of cardiac size in determining exercise capacity. In contrast to the large compliant left ventricle of the endurance athlete, an individual with a lifetime of physical inactivity is likely to have a small, stiff heart with reduced cardiac reserve. We propose that this might contribute to the development of heart failure with preserved ejection fraction in certain individuals, and is key to understanding the link between low CRF and increased risk of heart failure.

RÉSUMÉ

La capacité à l'effort est un spectre qui reflète la capacité fonctionnelle d'une personne et la nature dynamique du remodelage cardiaque ainsi que des systèmes respiratoire et musculosquelettique. La relation entre l'augmentation de l'activité physique, l'accroissement de la masse et du volume du cœur et une meilleure fonction cardiorespiratoire est bien établie chez les athlètes d'endurance. Toutefois, ces effets n'ont pas été étudiés de façon aussi approfondie chez les personnes ayant un mode de vie plus sédentaire et un cœur moins développé, lesquelles présentent un risque accru d'incapacité fonctionnelle et de mauvais résultats cliniques. Une fonction cardiorespiratoire réduite est un facteur indépendant de prédiction de la mortalité toutes causes confondues et d'événements cardiovasculaires déterminés par différents facteurs exogènes et endogènes interreliés. Dans cette analyse, nous explorons la relation entre l'activité physique, le remodelage cardiaque et la fonction cardiorespiratoire en fonction du niveau d'activité physique, en mettant l'accent sur le rôle essentiel de la taille du cœur dans la capacité à l'effort. En comparaison de l'athlète d'endurance, qui a généralement un gros ventricule gauche distensible, une personne qui n'a jamais été réellement active est susceptible d'avoir un cœur peu distensible de petite dimension avec une réserve cardiaque réduite. Nous avançons que ce déficit peut, dans certains cas, contribuer à l'apparition de l'insuffisance cardiaque avec fraction d'éjection préservée et qu'il joue un rôle central dans la compréhension du lien entre une faible fonction cardiorespiratoire et un risque accru d'insuffisance cardiaque.

Exercise capacity is a spectrum determined by a complex interplay of multiple body systems, environmental exposure (eg, physical activity), and our underlying genetic signature. From the endurance athlete to the individual with shortness of breath while carrying groceries, there is wide phenotypic variation when it comes to functional ability. Exercise intolerance and dyspnea are cardinal features of heart failure (HF), with traditional definitions describing a condition in which "the heart cannot pump enough blood to meet the body's needs."[1] However, all individuals will eventually reach this physiological limit when exercising, but not all have the same risk of adverse clinical events and functional disability. Our current understanding of HF and its pathophysiology has changed, and contemporary definitions are more complex in an attempt to improve diagnosis and risk prediction.[2] With the current prevalence of HF frequently estimated at 1%-3% of adults and expected to increase with the aging population, there is a need to identify individuals at risk or affected at an early age.[3,4]

The distribution of left ventricular (LV) ejection fraction (EF) at the time of HF diagnosis shows a bimodal distribution with up to 50% of patients having preserved EF.[5,6] HF with preserved EF (HFpEF) is a clinical syndrome with significant heterogeneity in etiology, pathophysiology, and remodelling phenotype.[7-9] This heterogeneity makes it challenging to create a unified prevention and treatment strategy and is pivotal to finding effective interventions. Although there is clinical utility in categorizing HF according to EF, particularly in relation to therapy response, this can also oversimplify the complexity of the HF continuum. Furthermore, individuals with normal EF who have impaired cardiac reserve and poor cardiorespiratory fitness (CRF) but who fail to meet the strict definition of HF might not be diagnosed with HFpEF, despite being at risk of significant morbidity and mortality.

Exercise capacity is inversely associated with the risk of HF independent of traditional risk factors.[10] The mechanism of this relationship is poorly understood, however, cardiac structural remodelling, as opposed to resting cardiac function, might be a key factor. In a study of close to 3000 individuals, low CRF was associated with smaller heart size and nearly twice the prevalence of concentric remodelling compared with high CRF individuals (38% vs 21%; $P < 0.0001$).[11] Importantly, there was no association of CRF and resting LV systolic function. Our knowledge from endurance athletes informs us of the strong relationship of cardiac remodelling, physical activity, and improved CRF. Conversely, we propose that physical inactivity and low CRF is associated with a lack of this physiological remodelling, and even cardiac atrophy.

In this review, we explore the relationship of exercise capacity, physical activity, and cardiac remodelling across the exercise spectrum. We argue that the corollary of the large, compliant heart portending excellent exercise capacity in athletes is the small, stiff heart associated with sedentary behaviour. We assert that this is associated with reduced exercise capacity, increased clinical events, and is a risk factor for

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See page S330 for disclosure information.

the development of HFpEF. As opposed to HF with reduced EF, it is likely that "bigger" is actually better for individuals with an EF > 50%, and that the development of HFpEF in a subset of the population is related to exercise deficiency and a subsequent small and stiff heart.

Exercise Capacity: An Underappreciated Predictor of Morbidity and Mortality

CRF reflects the functional capacity of an individual and is a strong predictor of disability, cardiovascular, and all-cause mortality.[12-14] Usually considered synonymous with exercise capacity, the concept of CRF encompasses the cohesive interaction of respiratory and cardiac function in transporting oxygen to skeletal muscle mitochondria for the aerobic energy production required for physical activity. Physical activity refers to any bodily movement produced by skeletal muscles that results in energy expenditure, whereas exercise/physical training is considered a subset of this, which is planned, structured, and repetitive with the final objective of altering fitness.[15] In the periphery, the extraction and utilization of oxygen by skeletal muscle as well as anaerobic energy production and buffering capacity, is also vital. There is variability in the degree to which a given individual's exercise limitation is caused by deficits in the transport (central factors) compared with the peripheral extraction and metabolism of oxygen.[16,17] Expressed as maximal oxygen consumption (VO_2max), CRF can be measured directly during cardiopulmonary exercise testing or estimated from peak work rate achieved during exercise testing on a treadmill or cycle ergometer.[14] Similarly, peak oxygen consumption (VO_2peak) reflects CRF, however, it refers to the highest oxygen consumption (VO_2) attained during testing irrespective of the subject's effort. The body's response to exercise depends on a complex multiorgan interaction of cardiovascular, respiratory, neural, and cellular pathways. Augmentation of cardiac output (CO) with exercise is a critical determinant of CRF defined according to the Fick equation as $VO_2 = CO \times a\text{-}vO_2diff$; (where $a\text{-}vO_2diff$ is arteriovenous oxygen difference). It is likely that there is some concordance in the factors that regulate central oxygen delivery and peripheral oxygen extraction. Regular physical training promotes improvements in CO and mitochondrial respiration in the muscle,[18,19] and it is likely that the corollary is also true; that sedentary behaviour attenuates the function of central and peripheral factors such as muscle oxidative capacity. CO, determined by heart rate and stroke volume (SV), can increase up to eightfold during exercise[19-23] and regular exercise training also promotes favourable changes in skeletal morphology and function (ie, increased myosin heavy chain type 1, skeletal muscle capillarity, and mitochondrial content[18,19]), increased total plasma volume with associated reduced blood viscosity,[19] and reduced peripheral resistance.[24] Although central and peripheral factors influence exercise capacity, CO is an important determinant and the degree to which cardiac morphology affects this is still poorly defined.

In the past 4 decades, CRF (particularly CRF in midlife) has been recognized as a strong and independent predictor of functional independence,[13] HF hospitalization,[25-27] and mortality.[12,28,29] Greater midlife fitness is protective against future risk of HF hospitalization (hazard ratio, 0.82 [95% confidence interval, 0.76-0.87] per metabolic equivalent of task) independent of comorbidities.[27] Low rates of CRF and physical activity in middle age is a strong predictor of HF hospitalization in older age[25,27]—yet CRF still remains underappreciated as a risk factor in the clinical setting.[14] Large population studies have consistently shown that low rates of CRF carries a comparable, if not greater, risk of all-cause mortality than traditional cardiovascular risk factors such as hypertension, type 2 diabetes mellitus, smoking, and dyslipidemia.[30,31] A meta-analysis of 33 epidemiological studies that assessed CRF and clinical outcomes across age and sex identified that for every 1 metabolic equivalent of task improvement in CRF, there is an associated 13% and 15% reduction in risk of all-cause mortality and cardiovascular disease, respectively.[12] In individuals with coronary heart disease, an improvement in VO_2 by 1 $mL/kg^{-1}/min^{-1}$ during cardiac rehabilitation was associated with a 10% reduction in all-cause mortality, highlighting the role of exercise in improving outcomes in high-risk individuals in addition to medical therapy.[32] Despite this knowledge, the most recent global estimates show that 27.5% of the world's adult population do not meet the recommended level of physical activity of at least 150 minutes of moderate-intensity, or 75 minutes of vigorous-intensity physical activity per week and this estimate has not changed in the past 2 decades.[33,34] Importantly, the dose-response relationship of CRF and mortality is curvilinear, meaning even small improvements in exercise capacity can have a prognostic effect and that the greatest relative benefit is seen in individuals who are the most sedentary.[14,35] This is still seen in very old adults (mean age, 87.7 years[36]), emphasizing the contribution of CRF deconditioning to the morbidity and mortality associated with older age. At the extreme end of endurance exercise, the dose-response relationship might differ with evidence of increased myocardial fibrosis and coronary atherosclerosis.[37,38] Mainstream resting cardiac measures used to predict exercise capacity such as resting EF and LV filling pressure estimates have limited prognostic value in individuals with normal EF[39] and they have failed to show a meaningful relationship to CRF.[11,40] The lack of robust predictors of CRF have made the clinical use of CRF more challenging and alternative imaging predictors need to be identified to identify patients at risk of poor outcome.

Cardiac Size Matters—A Key Determinant of VO_2max

Traditional thinking about cardiac size and outcomes originates from our knowledge of HF with reduced EF where LV dilation is a strong predictor of HF hospitalization and mortality.[41,42] Conversely, LV dilation in the elite endurance athlete is associated with enhanced CRF and favourable longevity.[43-47] Resting cardiac magnetic resonance imaging (MRI) measures of cardiac volumes and mass account for 50%-75% of the variance of VO_2peak whereas there is no significant relationship between resting LV EF and CRF.[43,48] This suggests that a change in cardiac geometry, as opposed to changes in resting cardiac function, can be used to predict exercise capacity. Because maximal heart rate does not increase with endurance training,[49] the fundamental mechanism for increased CO with exercise is on the basis of the ability to

increase SV. Exercise-induced cardiac remodelling resulting in balanced left and right ventricular dilation facilitates this,[50,51] resulting in enhanced cardiac reserve and the ability to sustain high workloads.

It is not only athletes but potentially all individuals with normal EF, in whom a strong positive relationship between LV size and CRF might be observed. This is arguably of greatest clinical relevance to those at the other end of the spectrum to athletes. That is, people with a more sedentary lifestyle and smaller hearts. In a cohort of 137 individuals with normal resting LV EF who underwent stress echocardiogram, LV cavity size was reported to be 34% smaller in individuals with poor exercise capacity compared with those with excellent exercise capacity.[52] Interestingly, 60% of the patients with poor CRF had a test indication for unexplained dyspnea compared with only 5% of individuals with excellent exercise capacity.[52] The pathophysiology linking small cardiac dimensions to reduced exercise capacity remains unclear, however, recently Foulkes et al.[53] identified a possible explanation when they examined 185 healthy women using exercise cardiac MRI and cardiopulmonary exercise testing. VO_2peak was strongly associated with resting measures of LV end diastolic volume (LVEDV)—in which a 14-mL decrement in LVEDV was associated with a 10% decrement in absolute VO_2peak. During exercise cardiac MRI, individuals with an LVEDV in the lowest quartile (Q) showed the smallest augmentation in LV SV (Q1: +11 mL vs Q4: +20 mL) and CO (Q1: +6.6 L/min vs Q4: +10.3 L/min). This describes a possible mechanism whereby a small ventricle has lesser resting SVs but also a diminished ability to augment SV during exercise. Because female sex is associated with smaller ventricular size,[54] this might partially explain why women generally have a VO_2max 70%-75% that of men[19] and are more likely to develop low CRF.[55] Guidelines for LV chamber quantification report normal LVEDV values (men: 62-150 mL; women: 46-106 mL) and values for LV dilation, however a cutoff for abnormally small is not provided.[56] Identifying gender-specific values for the small ventricle that are relative to anthropometric measures is imperative to incorporating the concept into guidelines. Irrespective of sex, a small heart with small LV end diastolic and end systolic volumes at rest has a reduced ability to decrease LV end systolic volume further with exercise (Fig. 1). This results in a diminished ability to increase SV with exercise despite having a preserved or supranormal EF. This concept provides a plausible link between small ventricular size and low CRF and suggests that a small ventricle might predispose individuals to exertional dyspnea and impaired functional capacity.

Exercise deficiency and cardiac atrophy: evidence of the sedentary, small heart

The concept of cardiac plasticity and remodelling stems from the idea that the heart has a remarkable ability to adapt to environmental demands. The changes characterized by exercise-induced cardiac remodelling in athletes can also regress when the training stimulus is removed. Small studies of detraining in athletes show the dynamic nature of adaptive remodelling with a regression of LV wall thickness and LV diameter within 3 months of training cessation.[57] This regression is often discussed in the context of differentiating "athlete's heart" from pathological cardiomyopathies. However, it is also vital when considering the relationship of sedentary individuals with low CRF and small ventricular size. In the nonathlete, exercise deficiency and sedentary behaviour will result in a lack of physiologic remodelling and possibly even cardiac atrophy.[58-60] The relationship of physical inactivity, cardiac atrophy, and CRF is best evidenced by the Dallas Bed Rest Study in 1968 and its subsequent reports.[61] In the initial study, 5 subjects completed 3 weeks of bed rest followed by 8 weeks of endurance training. The key findings were that VO_2max declined by 26% after bed rest, and subsequently increased by 45% with training, that was largely attributable to changes in SV and CO. Although there were no significant changes in maximal a-vO_2diff, impairment of skeletal muscle oxidative function has also been identified after bed rest, highlighting the effect of inactivity on multiple physiological systems.[62] Repeat assessment of these same 5 individuals 40 years later showed that the decline in VO_2max after 40 years of life was equivalent to that experienced after 3 weeks of bed rest at the age of 20 years.[63] Supporting these findings, Perhonen et al. examined morphological changes in response to physical inactivity using cardiac MRI in 5 individuals who underwent strict bed rest.[64] After 2 weeks of bed rest, there was a 14% reduction in LVEDV and after 6 weeks of bed rest LV mass decreased by 8%. Although bed rest studies are an extreme example of sedentarism, they provide compelling evidence of a possible causal link between a lack of exercise and cardiac atrophy. Further longitudinal studies are needed to understand the causal relationship of physical inactivity, small cardiac size, and low CRF.

LV compliance and the exercise spectrum: the consequences of a small heart

Morphological cardiac changes that occur in response to exercise training or a lack of exercise have implications on LV compliance (absolute change in volume per unit increase in pressure, inverse of LV stiffness) and distensibility (relative change in volume per unit increase in pressure). Ventricular chamber stiffness relates to the extent to which LV filling pressures increase in response to an additional volume load as described by the pressure-volume relationship. Exercise results in an acute volume load to the heart and therefore adaptations that result in improved compliance allow for a more efficient use of the Frank-Starling mechanism, leading to a greater change in SV for any given cardiac filling pressure. Chamber stiffness is determined by cardiac volume, mass, the stiffness of myocardium itself, and external constraints.[65,66] The influence of ventricular size on LV compliance and distensibility forms the basis of the idea that a small heart is a stiff heart and a large heart is compliant. Levine et al. characterized this relationship in 7 athletes and 6 control participants using invasive cardiac assessments with saline volume challenge.[67] They showed that for any given filling pressure, athletes had a greater SV and that for any given LVEDV, athletes had a lower LV end diastolic pressure compared with control participants. Athletes had larger absolute and relative changes in LVEDV induced by saline-loading. Overall, the athletes improved chamber compliance and distensibility without any evidence of change in overall systolic function. At the other end of the spectrum, Markus et al. assessed echocardiographic

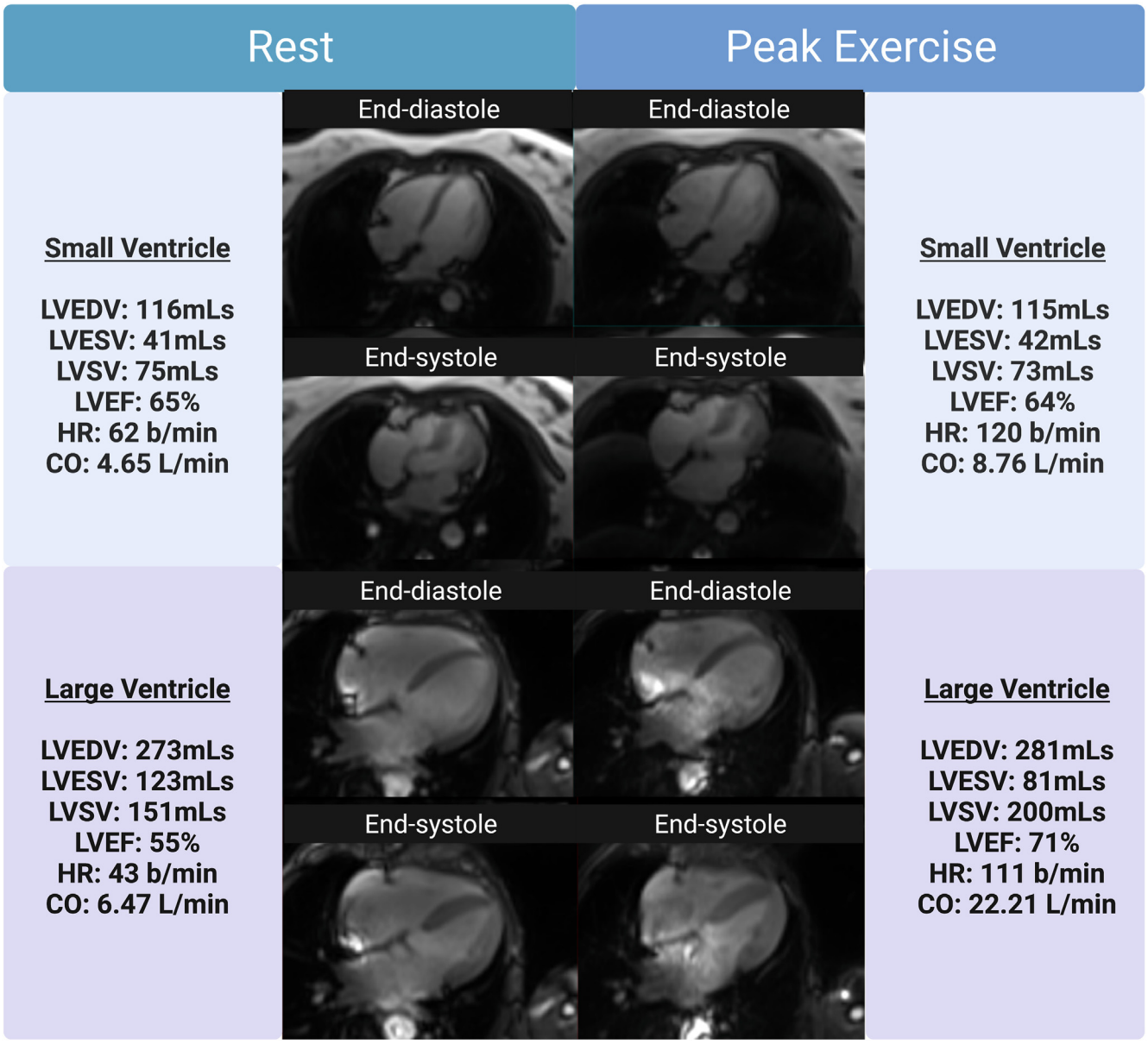

Figure 1. The effect of cardiac size on cardiac reserve. Exercise cardiac magnetic resonance imaging (supine cycling) imaging from 2 individuals (nonathlete with a small left ventricle and endurance athlete with a large left ventricle) at rest and at peak exercise. The small ventricle has a small left ventricular end-diastolic and end-systolic volume at rest with a limited ability to augment stroke volume and cardiac output at peak exercise despite a normal ejection fraction. In contrast, the large ventricle has significantly larger resting cardiac volumes, which allows for a significant reduction in end-systolic volume and augmentation of stroke volume and cardiac output at peak exercise. As expected with supine exercise, there is minimal difference between left ventricular end-diastolic volume (LVEDV) at rest or with exercise. Created with BioRender (BioRender.com). b/min, beats per minute; CO, cardiac output; HR, heart rate; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume; LVSV, left ventricular stroke volume.

parameters and VO_2peak in > 2800 individuals with a focus on low CRF.[58] Termed the "sedentary's heart," they reported that low CRF was associated with small LV chamber dimensions and mass, and higher LV end diastolic elastance (an echocardiographic marker of ventricular stiffness). Irrespective of intrinsic myocardial stiffness, the same volume load will have a different effect on a small heart compared with a large heart because of the relative pressure increase. Recent studies using invasive and noninvasive measures have observed that individuals with HFpEF and higher EF (> 60%-65%) have smaller hearts and increased LV stiffness compared with those with HFpEF and low normal LV EF.[68,69] Considering the link between low CRF and HF, it might be true that small cardiac size and the associated increased ventricular stiffness could be a substrate or mechanism for developing HFpEF. In addition, there is significant phenotypic overlap of individuals with low CRF and HFpEF with regard to cardiovascular comorbidities, such as diabetes and hypertension,[70] and

peripheral maladaptation including increased arterial stiffness.[71,72] The close relationship of CRF and risk of HF[10,73] is yet to be explained, but phenotypic and physiologic similarities of low CRF and HFpEF suggest that reduced exercise capacity could be a marker or potential precursor to the development of HFpEF.

Exercise Training, CRF, and Cardiac Remodelling

The response to exercise training—are we all the same?

The health benefits of exercise training are clear—increased physical activity is associated with a lower risk of mortality, cardiovascular events, and HF.[25,74] Along with improving CRF, regular exercise can improve traditional cardiovascular risk factors which often coexist.[75] As previously outlined, the spectrum of exercise capacity correlates with a spectrum of cardiac remodelling, which is determined according to multiple factors (Fig. 2)—the additional question is understanding the degree to which increases in cardiac dimensions underlie improvements in exercise capacity. Longitudinal studies have been critical in assessing the causal relationship between exercise training and alterations in cardiac geometry. Baggish et al. showed this by evaluating cardiac structure in 64 athletes who completed a 90-day training period in either endurance training or strength training activities.[50] After the training period, there were distinct training-specific structural profiles identified, with both groups experiencing a significant increase in LV mass, but only sustained aerobic exercise being associated with both LV and right ventricular dilation. However, the volume of training undertaken by athletes is not necessarily feasible in the general population and there is significant intersubject variability, suggesting that not all individuals will respond the same. Kohrt et al. illustrated this variability in a group of 110 healthy, sedentary subjects who completed at least 9 months of endurance exercise training at 80% ± 5% of maximal heart rate determined from pretraining cardiopulmonary exercise testing.[76] After training, there was a mean improvement in VO_2max by 24%, however there was a significant variation in response, ranging from 0% up to 58% improvement,[76] which might reflect inadequate training stimulus because of the use of fixed-percentage parameters for exercise prescription.[77] However, multiple exogenous factors contribute to the training response including exercise volume and intensity, as well as biological factors such as an individual's genetic profile, which also need to be considered.[78-80] Overall, most individuals when given sufficient stimulus appear to have a physiological response to training,[79] with high-intensity 3- to 5-minute intervals resulting in the greatest increase in VO_2max[78]—although its comparative effect on cardiac remodelling is less clear.

The existence of nonresponders to exercise training is controversial,[79,81] however, hereditary factors likely play a significant role in determining CRF and even cardiac adaptation to exercise. The angiotensin-converting enzyme gene is the most frequently investigated genetic marker in the context of athletic performance with the insertion/deletion polymorphism being associated with improvements in exercise duration, as well as implicated in LV growth response to training.[82] However, the key studies advancing our understanding of the complex interplay of genotype, phenotype, and environment come from Bouchard et al. and the **He**alth, **Ri**sk Factors, Exercise **T**raining **a**nd **Ge**netics (HERITAGE) family study.[80,83,84] This series of studies showed that approximately 50% of the variance in VO_2max training response could be explained by genetics and that this could be predicted with a panel of 21 single-nucleotide polymorphisms. By constructing a predictor score using these single-nucleotide polymorphisms, they were able to identify low and high responders to regular exercise. Although larger cohort studies are required and little is known about the exact function of these genomic markers, it provides an early insight into the possibility of personalized preventive medicine related to exercise and CRF. The relationship of genetic variations and the magnitude of cardiac remodelling with exercise training is also ill defined and should be the focus of future research.

Exercise capacity and aging: can it be too late to change?

The ability to maintain functional independence with aging relies on adequate exercise capacity as well as peripheral factors such as muscle strength, endurance, and power. VO_2peak < 18 mL/kg^{-1}/min^{-1} is considered a threshold at which an individual is likely to lose the ability to independently perform activities of daily living.[13] With aging, it is estimated that there is a decline in peak VO_2 of approximately 10% per decade,[85-87] with longitudinal studies suggesting this might be accelerated beyond the age of 70 years.[88] This age-related VO_2 decline is predominantly explained by lower SV and CO at maximal exercise in older individuals, but also attributable to sarcopenia and changes in oxygen extraction in skeletal muscle.[87,89] The natural trajectory of CRF over the lifetime highlights the importance of fitness in younger age. Compared with a sedentary individual with a VO_2max measuring 25 mL/kg^{-1}/min^{-1}, an elite endurance athlete with VO_2max of 75 mL/kg^{-1}/min^{-1} will have decades longer before they reach a level of CRF associated with functional disability. Similarly, because the average VO_2max in women is less than that in men of the equivalent age,[90] the age-related decline in CRF might partially explain why low rates of fitness in adulthood is more prevalent in women and why women are more predisposed to disability and frailty in older age.[55,91]

Changes in cardiac compliance and distensibility with sedentary aging likely contribute to the decline in CRF, and lifelong exercise might delay these changes. Arbab-Zadeh et al. assessed invasive hemodynamic measures in 12 sedentary seniors (mean age, 69.8 years), 12 Masters athletes (mean age, 67.8 years), and 14 young sedentary control participants (mean age, 28.9 years) to elucidate the relationship of LV compliance, age, and exercise.[92] Sedentary seniors had greater LV stiffness and less distensibility compared with sedentary young control participants indicated by a leftward shift and steeper slope of the pressure-volume curve. This decrease in cardiac compliance with aging appeared to be eradicated by prolonged endurance exercise because Masters athletes had larger, more compliant ventricles that were similar to that in the young sedentary control participants. These results are supported the evaluation of 102 healthy seniors (age > 64 years) who were recruited from populations of varying self-reported lifelong patterns of exercise training by Bhella et al.[93] Compared with athletes, sedentary individuals and

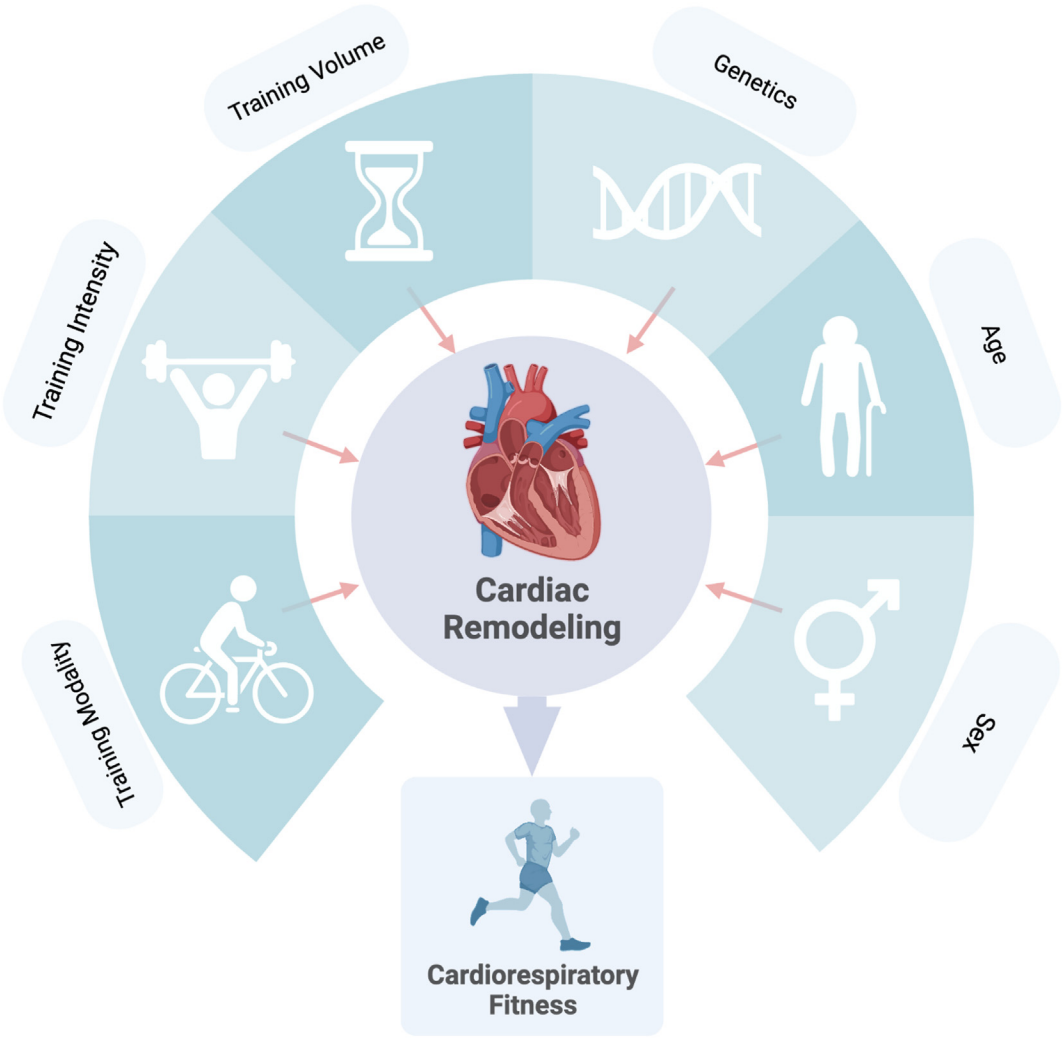

Figure 2. Key factors that influence cardiac remodelling. Multiple factors determine the degree of cardiac remodelling in response to exercise and play a role in changes in cardiorespiratory fitness. These factors include exogenous factors (training modality, intensity, and volume) and endogenous factors (genetics, age, sex). Created with BioRender (BioRender.com).

casual exercisers (2-3 sessions per week) exhibited smaller cardiac sizes (LVEDV indexed 75.4 ± 13.7 mL/m^2 in athletes compared with 56.5 ± 11.3 mL/m^2 in sedentary subjects). This was associated with diminished SV and stiffer ventricles. There was a graded increase in these measures with increasing amounts of exercise. Lifelong exercise of at least 30 minutes at moderate-intensity > 3 days per week appeared to attenuate age-expected decreases in LV volumes and LV compliance with Masters athletes displaying the largest LV mass and LVEDV associated with superior CRF. The reduction in LV compliance and distensibility with sedentary aging is similarly seen in individuals with HFpEF.[94,95] One might extrapolate from these observations to suggest that lifelong exercise might be an approach to prevent the future development HFpEF.

If lifelong endurance exercise can mitigate age-related changes in cardiovascular stiffness, then exercise training started later in life might also alter the cardiac effects of lifelong sedentary behaviour. Fujimoto et al. investigated this by comparing 12 Masters athletes to 12 sedentary seniors (age > 65 years) who underwent 1 year of vigourous exercise training.[96] A year of training for the sedentary seniors increased VO_2max by 19%, attributable to an increase in SV and CO at peak exercise (by 13% and 11%, respectively) as opposed to change in their peak a-vO_2diff. Despite evidence of physiological remodelling, there was no alteration in LV compliance after exercise training. A possible explanation for this was later described by the study group when they identified that the process of age-associated LV stiffening appears to manifest between the ages of 50 and 64 years, and beyond 65 years there was a decrease in LVEDV at baseline but also at all filling pressures, indicating a decrease in LV distensibility.[97] This signifies that exercise started later in life in sedentary seniors might have less effect on cardiac remodelling and compliance. Importantly, exercise training initiated a decade earlier in middle age can still result in improved LV compliance, representing a window to intervene to prevent age-related cardiac

stiffening.[98] Although cardiac plasticity appears to be attenuated with older age, regular physical activity can still improve CRF and prognosis at more advanced ages.

Exercise as therapy: the only successful intervention for HFpEF?

As outlined, there is a strong association of physical inactivity, cardiac size and stiffness, and reduced exercise capacity. There is also considerable overlap with these factors and the pathophysiology of HFpEF, suggesting that exercise training might be a useful intervention. Most HFpEF trials of medical therapies have failed to show clinical or prognostic improvement.[99] This is particularly true in higher and supranormal EF groups who, in addition to having smaller and stiffer hearts, appear less responsive to sodium-glucose co-transporter 2 inhibitor and neurohormonal therapy compared with individuals at the lower end of the LV EF spectrum in HFpEF.[100,101] In contrast, an increasing number of prospective trials have shown that exercise training at an appropriate dose can consistently improve exercise capacity[102-104] and might improve quality of life measures.[102,104,105] A recent meta-analysis of 8 randomized controlled trials highlights the importance of supervised exercise training in patients with HFpEF.[106] The results indicated that supervised exercise training significantly improved VO_2peak by 14% compared with a 2% decline seen in control participants. The effect of exercise on resting diastolic parameters and quality of life were less consistent, which might represent trial variation in inclusion criteria and training duration, as well as the underlying heterogeneity of HFpEF. Another key challenge associated with exercise programs is long-term adherence in a population with multimorbidity, particularly with home-based programs, however, this might improve with ongoing community support.[107] Most HFpEF exercise trials have used supervised programs, however when home-based programs are used adherence declines.[105] Successful implementation of exercise programs in the community will rely on larger studies with longer follow-up periods to better understand patient safety and barriers to continued engagement. Raising awareness of the evidence and benefits of exercise training in patients with HFpEF is also vital to encourage exercise prescription and referral to community groups.

In contrast to the athlete—in whom CRF is increased as a result of cardiac and noncardiac adaptations—the improvement in CRF in HFpEF with exercise training is predominantly attributable to improved O_2 transport and utilization in skeletal muscle.[103,108] Indeed, randomized trials of exercise training in HFpEF patients have shown that it fails to induce the physiological cardiac remodelling normally seen with endurance training, and does not appear to result in alterations of LV stiffness like it does in young, healthy individuals.[103,109] This likely reflects diminished cardiac plasticity with advancing age as previously discussed, and also possibly sex differences in exercise-induced cardiac remodelling. Women are overrepresented in the HFpEF population[110] and there is a suggestion that they might have a reduced degree of remodelling in response to exercise compared with men.[111] Importantly, the pleiotropic effects of exercise spread beyond the cardiovascular system with substantial benefits in associated conditions such as glycemic control[112] and hypertension.[113] Whether the benefits of exercise training in individuals with HFpEF will translate to reduced HF hospitalization or mortality remains unclear and long-term studies powered to assess these outcomes are still needed. The benefits of exercise training in individuals with HFpEF should not be understated, however, the lack of additional therapeutic options available means that the focus of future research also needs to be on prevention. By midlife, sedentary behaviours are embedded in an individual's lifestyle and the ability to prevent age-associated LV stiffness and cardiac atrophy is diminished. With low CRF being seen as an early-stage marker of individuals at risk of HFpEF,[114] early intervention to improve CRF is likely to be critical to reducing the burden of HF.

Conclusion

An individual's exercise capacity is dependent on a number of inter-related modifiable and nonmodifiable factors. Increasing physical activity is associated with improved CRF because of skeletal changes as well as physiological cardiac remodelling resulting in increased cardiac volumes and cardiac reserve. At the other end of the spectrum, this review highlights that exercise deficiency and sedentary behaviour is associated with cardiac atrophy, reduced cardiac compliance, and blunted augmentation of CO with exercise, resulting in low CRF. The consequence of this includes functional impairment, exertional dyspnea, and a possible substrate for the development of HFpEF later in life. We conclude that there is a strong association of physical activity, cardiac size, and CRF, and that regular exercise when younger or middle-aged can delay age-related cardiac changes that contribute to functional disability and risk of clinical events when older. One-quarter of the world's population do not meet current physical activity guidelines despite low CRF being a strong and independent predictor of all-cause mortality and cardiovascular events.[14,33] This represents a significant proportion of individuals at risk. Identifying these individuals and providing early intervention is key to preventing the consequences of low CRF and the potential risk of HFpEF.

Ethics Statement

The research reported has adhered to the relevant ethical guidelines.

Patient Consent

The authors confirm that patient consent is not applicable because this is a review article.

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