INVITED REVIEW

TITLE: Basic Science behind the Cardiovascular Benefits of Exercise

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ABSTRACT

Cardiorespiratory fitness is a strong predictor of cardiovascular (CV) disease and all-cause mortality, with increases in cardiorespiratory fitness associated with corresponding decreases in CV disease risk. The effects of exercise upon the myocardium and vascular system are dependent upon the frequency, intensity and duration of the exercise itself. Following a prolonged period (≥ 6 months) of regular intensive exercise in previously untrained individuals, resting and sub-maximal exercising heart rates are typically 5-20 beats lower, with an increase in stroke volume of ~ 20% and enhanced myocardial contractility. Structurally, all four heart chambers increase in volume with mild increases in wall thickness's, resulting in greater cardiac mass due to increased myocardial cell size. With this in mind, the present paper aims to review the basic science behind the CV benefits of exercise. Attention will be will be paid to understanding 1) the relationship between exercise and cardiac remodelling, 2) the cardiac cellular and molecular adaptations in response to exercise, including the examination of molecular mechanisms of physiological cardiac growth and applying these mechanisms to identify new therapeutic targets to prevent or reverse pathological remodelling and heart failure and 3) vascular adaptations in response to exercise. Finally, this review will briefly examine how to optimise the CV benefits of exercise, by considering how much and how intense exercise should be.

INTRODUCTION

The cardiovascular (CV) benefits of regular physical exercise are well documented. Cardiorespiratory fitness is a strong predictor of CV disease and all-cause mortality [1, 2], with increases in cardiorespiratory fitness associated with corresponding decreases in CV disease risk [3]. Indeed, a 41% reduction in mortality was reported in 786 former Tour de France cyclists compared to the general French male population [4]. The effects of exercise upon the myocardium and vascular system are dependent upon the frequency, intensity and duration of the exercise itself. Following a prolonged period (≥ 6 months) of regular intensive exercise in previously untrained individuals, resting and sub-maximal exercising heart rates are typically 5-20 beats lower, with an increase in stroke volume of ~ 20% and enhanced myocardial contractility [5]. Structurally, all four heart chambers increase in volume with mild increases in wall thicknesses, resulting in greater cardiac mass due to increased myocardial cell size.

With this in mind, the present paper aims to review the basic science behind the CV benefits of exercise. Attention will be will be paid to understanding 1) the relationship between exercise and cardiac remodelling, 2) the cardiac cellular and molecular adaptations in response to exercise, including the examination of molecular mechanisms of physiological cardiac growth and applying these mechanisms to identify new therapeutic targets to prevent or reverse pathological remodelling and heart failure and 3) vascular adaptions in response to exercise. Finally, this review will briefly examine how to optimise the CV benefits of exercise, by considering how much and how intense exercise should be.

Cardiac structure and functional adaptations in response to exercise

Exercise and cardiac remodelling

The term ‘Athlete’s Heart’ refers to a constellation of adaptations that affect the structure, electrical conduction and function of the heart that facilitate appropriate increases in cardiac output during exercise. There is a plethora of studies demonstrating dilatation of all 4 cardiac chambers and an increase in the maximal wall thickness in trained individuals compared to sedentary controls. Whilst CV adaptation depends on the modality, intensity and volume of conditioning, even in previously sedentary individuals, intensive and prolonged endurance training leads to cardiac remodelling mimicking parameters commonly observed in athletes [6].

Athlete’s heart dogma suggests that endurance athletes present with eccentric hypertrophy, whilst athletes whose training is predominately resistance based present concentric hypertrophy. A recent meta-analysis of 92 prospective echocardiographic or CMR studies involving elite male athletes however, demonstrated that whilst both endurance and resistance-trained athletes demonstrate larger LV structures than sedentary controls (with greater volumes observed in endurance athletes), LV wall thicknesses were similar between both groups thwarting support for concentric hypertrophy in resistance only athletes (Table 3) [7]. Limited echocardiographic data are available on the right cardiac chambers, though data from cardiac magnetic resonance (CMR) studies suggest a balanced structural adaptation between LV and RV chambers in both young and veteran athletes [8, 9].

Cardiac remodelling in life-long exercisers

Ageing is associated with changes to the CV system that underpin a reduced functional capacity, although regular endurance exercise training may slow this progressive decline in CV function. Using CMR, our group observed that male veteran endurance athletes (56 ± 6 years) involved in lifelong (43 ± 6 years) exercise had smaller LV and RV end-diastolic and end-systolic volumes, with matched wall thicknesses and LV mass compared to younger male endurance athletes (31 ± 5 years) [9] (Table 2). Yet compared to age-matched controls (60 ± 5 years), veteran athletes had larger absolute and indexed LV and RV end-diastolic and systolic volumes, wall thicknesses and LV and RV stroke volumes. Despite known age related reductions in cardiomyocyte numbers, this data supports findings of maintained LV mass and cardiac compliance in trained veterans, likely through hypertrophy of the remaining cells and an increase in interstitial tissue.

Upper limits of cardiac remodelling in athletes

Whilst the majority of athlete's exhibit structural and electrical changes that are considered physiological, there are however, an extremely small proportion of athletes who develop pronounced morphological changes which overlap with phenotypic expressions of cardiac pathology associated with sudden cardiac death; namely hypertrophic cardiomyopathy, dilated cardiomyopathy and arrhythmogenic RV cardiomyopathy. From four large echocardiographic studies examining 5,053 elite, predominately male athletes [10-13], 134 (2.7%) demonstrated a maximal wall thickness ≥12mm, of which 27 athletes (0.5%) presented ≥13 mm. In absolute terms and regardless of an athlete's body surface area, the upper limit of physiological hypertrophy in athletes is considered ≥13 mm for maximal wall thickness and ≥65 mm for LV

internal diameter in diastole. Values above these should be viewed with suspicion; heightened if the athlete also presents with personal symptoms suggestive of an underlying cardiac condition, a family history of sudden cardiac death and/or an abnormal ECG. In conclusion, whilst there is no upper threshold where the CV health benefits observed with regular exercise are diminished, there does however, appear to be an upper limit to physiological cardiac remodelling.

Cardiac cellular and molecular adaptations in response to exercise

Cellular cardiac adaptations – hypertrophy, death and renewal

Cardiac growth has been generally defined as either physiological or pathological. Exercise-induced cardiac growth as a prototype of physiological heart growth is associated with normal cardiac structure, cell hypertrophy [14, 15], no cell death or fibrosis [16-18], activation of resident cardiac stem cells and cardiomyocyte renewal [15, 19, 20], angiogenesis [15, 21, 22] and normal or improved cardiac function [15, 16]. Pathological cardiac remodelling is typically associated with death of cardiomyocytes, fibrotic replacement, cardiac dysfunction, and increased risk of heart failure and sudden death (Figure 1) [23, 24].

Although very low, the human heart has the capacity to self-renew cardiomyocytes over a lifespan [25]. The adult heart harbours a pool of resident endogenous cardiac stem and progenitor cells (eCSCs). These small primitive cells, positive for stem cell surface receptor markers (i.e. c-kit, Sca-1) and negative for markers of the hematopoietic lineage (i.e. CD45) and mast cells (i.e. tryptase), exhibit properties of stem cells; being clonogenic, self-renewing and

multipotent, both in vitro and in vivo [26, 27]. We have recently shown that intensity-controlled treadmill exercise in adult rats produces improved cardiac function and increased myocardial mass through cardiomyocyte hypertrophy, and new cardiomyocyte and capillary formation (Figure 2). The latter is due to the activation and ensuing differentiation of the eCSCs (Figure 3) [15]. Moreover, endurance swim training in mice induced cardiomyocyte hypertrophy and renewal, which was dependent on a reduction in the expression of the transcription factor C/EBPb [19].

Molecular mechanisms of physiological cardiac growth

The molecular mechanisms and signalling cascades underpinning cardiac adaptations with exercise are shown in Table 1. The best characterized signalling cascade responsible for mediating physiological cardiac growth is the IGF-1-PI3K(p110α)-Akt pathway. Indeed, increased cardiac IGF-1 expression and activation of the PI3K (p110α) pathway has been implicated in increased cardiomyocyte hypertrophy with endurance exercise in athletes [28]. Furthermore, over-expression of the IGF-1 receptor (IGF-1R) in cardiomyocytes increases myocyte size, with absence of myocyte death or disarray, and enhanced systolic function, and PI3K and ensuing Akt phosphorylation were increased in the hearts of IGF-1R transgenic mice [29]. On the other hand, mice lacking the p85 subunit of PI3K showed attenuation of exercise-induced cardiac hypertrophy [30] and in mice with ablation of the IGF-1R gene in cardiomyocytes, the hypertrophic response to swim exercise training was blunted [31]. Importantly, PI3K(p110α) is critical for physiological exercise-induced growth of the heart but not for pathological growth. dn-PI3K mice showed significant hypertrophy in response to

pressure overload, but a blunted hypertrophic response to swim training, when compared to non-transgenic mice [32]. Additionally, hearts of double transgenic mice over-expressing both the IGF-1R and dnPI3K were not significantly different in size to those from dnPI3K mice alone [29].

Akt, a serine/threonine kinase (also known as protein kinase B), is a well characterized target of PI3K activity. Recent studies on Akt knockout mice suggest that Akt1 is required for physiological rather than pathological heart growth. Akt1 knockout mice (showing normal cardiac phenotype under basal conditions) showed a blunted hypertrophic response to swim training but not to pressure overload [33]. On the other hand, overexpression of nuclear-targeted Akt does not directly induce cardiac hypertrophy; however, transgenic hearts are protected from ischemia-reperfusion injury [34].

We have identified the up-regulation of the growth factors, neuroregulin, BMP-10, IGF-1, and TGF-β1 in the cardiomyocytes following high intensity treadmill exercise training. IGF-1 and neuroregulin increase eCSC proliferation, with the activation of their respective receptors and physiologic molecular signalling targets, Akt and STAT-3, respectively [15]. Furthermore, over-expression of myocardial IGF-1 increases the survival and number of eCSCs and prevents myocyte attrition during ageing fostering myocyte renewal, which is governed by the PI3K-Akt signalling pathway [35]. Intriguingly, cardiac-specific expression of nuclear-targeted Akt in transgenic mice prolongs postnatal cardiomyocyte cycling and promotes the expansion of the c-kitpos-Nkx-2.5pos cardiac progenitor cell population. However, cardiac progenitor cells

genetically modified to overexpress nuclear-localized Akt exhibit increased proliferation but have inhibited capacity for cardiomyocyte lineage commitment [36]. On the other hand, BMP-10 and TGF-β1 stimulated differentiation of the eCSCs into the three main cardiac lineages; cardiomyocytes, vascular smooth muscle and endothelial cells [15].

Utilising the cellular and molecular mechanisms of exercise to identify new therapeutic targets

By identifying the cellular and molecular mechanisms associated with physiological cardiac remodelling we can identify new therapeutic targets that could prevent or reverse pathological remodelling and heart failure. Exercise increases the production and secretion of key growth factors, e.g. IGF-1, HGF, neuregulin1, VEGF, BMP-10, nitric oxide, periostin, TGF-β1, PDGF, and their associated signalling pathways [28, 37-41]. Intracoronary injections of IGF-1 and HGF, following myocardial infarction in a pig heart promotes cardiomyocyte survival and contractility, induces eCSC migration, proliferation and cardiomyogenic differentiation, leading to physiologically significant myocardial repair and regeneration [42]. Moreover, Santini et al. [43] found that in post-infarcted mice, which express the transgene of the locally acting IGF-1 in the myocardium (mIGF-1), had improved myocardial repair and function, attributable in part to an increase in the number of newly-formed cardiomyocytes. The origin of these replenished myocytes was not determined, but in light of recent findings it is likely they are the product of eCSC myogenic differentiation.

Finally, by identifying the specific profile of cardiac up-regulated and down-regulated miRNAs in exercise trained physiological hypertrophic hearts, as opposed to pathological hypertrophy; it

will be possible to test the relative miRNA-mimics and/or miRNA antagonists/inhibitors as a specific therapy for CV disorders. This work is currently on-going.

Vascular structure and functional adaptions in response to exercise

Exercise, the endothelium and nitric oxide

The endothelium is a single layer of cells that lines the entire CV system and plays a key role in the vascular adaptations seen with exercise training. The endothelium produces a number of vasoactive hormones that alter the tone of conduit and resistance vessels. Principle amongst these is nitric oxide (NO), which, in addition to causing smooth muscle cell relaxation and vasodilation, has antiatherogenic and antithrombotic properties [44]. Indeed, the endothelium and the release of NO has been postulated as the vehicle for exercise-induced improvement in CV risk profile, given that modification of traditional risk factors explain only of 50% of risk reduction in patients performing exercise [45].

In response to an increase in blood flow and shear rate, endothelial NO is released and over time (and exercise stimulus) repeated episodic increases in shear stress provoke vascular adaptation and remodeling of the artery. The integrity of blood vessels function can be assessed using the technique of flow-mediated dilatation (FMD) which uses an ischemic challenge to induce changes in shear stress that stimulates vasodilation that is NO dependent [46]. Acute exercise causes a biphasic FMD response. Immediately post-exercise (5-30 minutes), FMD is reduced, with enhanced FMD 1-24 hours post-exercise, and a normalisation back to baseline between 24-

48 hours. The post exercise reduction in FMD is dependent on exercise intensity and mode, with higher intensities causing a greater reduction in FMD. The mechanisms responsible for reduced FMD relate to an increase in oxidative stress [47], and/or a decline in endothelial (arginine) substrate utilization to cleave NO [48]. Additionally, high intensity exercise may cause more oscillatory or retrograde flow patterns that inhibit the NO production pathways than the more laminar antegrade flow patterns promoted at lower intensities [49].

Exercise-induced adaptations of the endothelium and the blood vessels have been reviewed extensively [50]. Briefly, studies undertaken in symptomatic CHD patients report that exercise enhances endothelial function both locally (in the popliteal artery following leg exercise) and systemically (in the brachial artery following leg exercise) [51]. This pattern of response is less clearly evident in healthy asymptomatic individuals and may be intensity-related, with low to moderate intensity exercise enhancing endothelial function whereas high intensities do not [52]. Tinken et al. [53] qualified this by measuring FMD every 2 weeks across 8 weeks of training and observed that following an initial up-regulation, FMD returned to baseline after 4 weeks; suggesting that studies which measure FMD merely pre and post, would likely miss training-induced changes.

Longitudinal training studies report enlarged diameter of conduit arteries and indeed, when assessed by peak vasodilator capacity, Tinken et al. [53] reported the same change from weeks 4 to 8 of training. Taken together, FMD and vasodilator capacity data signify that with training, endothelial function improves prior to a structural modification of the vessel, and that the latter

occurs to normalise shear rate and thereby return FMD to baseline levels. These observations may also help explain the paradox that in athletic population's endothelial function is similar to sedentary individuals. Rowley et al. [54] reported larger vessel diameters in the dominant versus non-dominant arms of squash players, and that both diameters were larger than sedentary controls. In addition, wall thickness was less in squash players and consequently wall to lumen ratios was reduced in athletes. Therefore the structural modification that enhances lumen size in the athlete operates to normalise shear rate and explains the observed "normal" FMD in elite athletes.

The mechanisms responsible for the up regulation of endothelial function and the structural diameter changes appear to relate to shear stress during exercise. Tinken et al. [55] repeated the 8-week exercise training study reported previously, with the exception that blood flow and shear rate were reduced by the inflation of a pneumatic cuff in one arm during each training session. In the un-cuffed arm the usual pattern of increased FMD followed by structural modification was observed, whereas in the cuffed arm these adaptations were abolished (Figure 4). This data strongly suggests that shear stress is obligatory for training-induced changes in vascular structure and function. The changes in wall thickness were independent of shear rate modification, suggesting that a systemic rather than localized mechanism exists, with the most likely candidate being changes in transmural pressure [56].

The vasculature is the target for both functional and structural change in response to exercise. The degree of change detected is dependent on the individual's health and fitness status, as well

as exercise intensity. What is clear is that the phenotype for an athlete's artery is different from sedentary individuals (Figure 5). The athlete's artery is characterized by a large lumen with a thin wall and relatively normal endothelial function. Such structural modification conveys performance and health benefits, although the exact mechanism responsible for these modifications requires further investigation.

Optimising the CV benefits of exercise

How much exercise?

In 2008, the U.S. Department of Health and Human Services released 'physical activity guidelines for Americans' [57]; being 150-300 minutes per week of moderate intensity aerobic exercise or 75 minutes per week of vigorous intensity exercise. Whilst all exercise programmes must consider intensity, duration and frequency; it is total volume of exercise that appears to be the most consistently related to the size of reduction in CV disease or functional improvement [58]. Whilst no optimal exercise volume or 'dose' has been established, low doses of casual lifelong exercise (2-3 sessions per week) do not prevent the decreased cardiac compliance and distensibility observed in healthy yet sedentary ageing. Bhella et al. [59] observed stiffer ventricles in casual exercisers (2-3 sessions per week) than committed (4-5 exercise sessions per week), with LV distensability similar between casual exercisers and sedentary individuals. Since LV stiffening is associated with the pathophysiology of many CV conditions, the 'dose' of exercise is clearly an important consideration in the prevention of CV disease.

How intense should exercise be?

Exercise intensity, specifically vigorous (>6 METS) or high intensity interval training [HIIT; >85% $\dot{V}O_{2peak}$ or >90% HR $_{peak}$, separated by 2-3 minutes of active recovery], and its impact upon CV health and cardiorespiratory fitness vs. moderate-intensity continuous training (MICT) has recently received significant attention. A meta-analysis of patients with cardiometabolic diseases (i.e. coronary artery disease, heart failure, hypertension, metabolic syndrome and obesity) observed significantly greater increases in $\dot{V}O_{2peak}$ following HIIT compared to MICT, equivalent to 9%, meaning that HIIT improved cardiorespiratory fitness by almost double [60]. It appears that HIIT improves cardiorespiratory fitness more than MICT across a broad range of populations, including healthy sedentary [61] and heart failure patients with preserved ejection fractions [62]. Possessing good aerobic capacity is important, as $\dot{V}O_{2max}$ is a prognostic marker of CV disease more so than any other established risk factor [63]. It should be noted however, that 6 METS is often used as a definition of 'vigorous' activity, equating to just 21 $ml.kg^{-1}.min^{-1}$. Thus MET use for prescribing high-intensity exercise is mediocre at best, as it does not consider an individual's exercise capacity. 6 METS in relatively fit individual is likely to be far from >85% $\dot{V}O_{2peak}$ or >90% HR $_{peak}$.

The vast majority of evidence suggests that regular (≥4 times per week), sustained (≥45 minutes) and intensive exercise throughout life is the most advantageous to optimise CV health. However, considering that physical activity rates in adolescents and adults are reducing year on year, a balance must be struck considering 1) there is no lower exercise threshold for CV benefits to be

seen, and 2) CV disease risk reduction is greatest in the un-fittest individuals who start exercising, signifying that ‘some exercise is better than none’.

CONCLUSION

In conclusion, exercise is a potent stimulator activating numerous downstream cascades at a molecular and cellular level, that if sustained and intensive enough enables gross anatomical remodelling capable of enhancing functional capacity in both healthy and diseased populations. Since aerobic capacity is a prognostic marker of CV disease and mortality more than any other established risk factor, clinicians should promote the expansive benefits of exercise in all spectrums of society, be it the casual exerciser, the sedentary individual or those with established CV disease.

References

1. Blair SN, Kohl HW, 3rd, Paffenbarger RS, Jr., et al. Physical fitness and all-cause mortality. A prospective study of healthy men and women. *JAMA* 1989;262(17):2395-401.
2. Kodama S, Saito K, Tanaka S, et al. Cardiorespiratory fitness as a quantitative predictor of all-cause mortality and cardiovascular events in healthy men and women: a meta-analysis. *JAMA* 2009;301(19):2024-35.
3. Lee DC, Sui X, Artero EG, et al. Long-term effects of changes in cardiorespiratory fitness and body mass index on all-cause and cardiovascular disease mortality in men: the Aerobics Center Longitudinal Study. *Circulation* 2011;124(23):2483-90.
4. Marijon E, Tafflet M, Antero-Jacquemin J, et al. Mortality of French participants in the Tour de France (1947-2012). *Eur Heart J* 2013;34(40):3145-50.
5. Swedish National Institute of Public Health. *Physical Activity in the Prevention and Treatment of Disease*. 2010. Sweden. **http://www.fyss.se/wp-content/uploads/2011/02/fyss_2010_english.pdf**
6. Arbab-Zadeh A, Perhonen M, Howden E, et al. Cardiac Remodeling in Response to 1 Year of Intensive Endurance Training. *Circulation* 2014.
7. Utomi V, Oxborough D, Whyte GP, et al. Systematic review and meta-analysis of training mode, imaging modality and body size influences on the morphology and function of the male athlete's heart. *Heart* 2013;99(23):1727-33.
8. Scharhag J, Thunenkotter T, Urhausen A, et al. Echocardiography of the right ventricle in athlete's heart and hearts of normal size compared to magnetic resonance imaging: which measurements should be applied in athletes? *Int J Sports Med* 2010;31(1):58-64.
9. Wilson M, O'Hanlon R, Prasad S, et al. Diverse patterns of myocardial fibrosis in lifelong, veteran endurance athletes. *J Appl Physiol* 2011;110(6):1622-6.
10. Pelliccia A, Maron BJ, Spataro A, et al. The upper limit of physiologic cardiac hypertrophy in highly trained elite athletes. *N Engl J Med* 1991;324(5):295-301.
11. Whyte GP, George K, Sharma S, et al. The upper limit of physiological cardiac hypertrophy in elite male and female athletes: the British experience. *Eur J Appl Physiol* 2004;92(4-5):592-7.
12. Basavarajaiah S, Boraita A, Whyte G, et al. Ethnic differences in left ventricular remodeling in highly-trained athletes relevance to differentiating physiologic left ventricular hypertrophy from hypertrophic cardiomyopathy. *J Am Coll Cardiol* 2008;51(23):2256-62.
13. Basavarajaiah S, Wilson M, Whyte G, et al. Prevalence of hypertrophic cardiomyopathy in highly trained athletes: relevance to pre-participation screening. *J Am Coll Cardiol* 2008;51(10):1033-9.
14. Kemi OJ, Loennechen JP, Wisloff U, et al. Intensity-controlled treadmill running in mice: cardiac and skeletal muscle hypertrophy. *J Appl Physiol (1985)* 2002;93(4):1301-9.
15. Waring CD, Vicinanza C, Papalamprou A, et al. The adult heart responds to increased workload with physiologic hypertrophy, cardiac stem cell activation, and new myocyte formation. *Eur Heart J* 2014;35(39):2722-31.
16. Jin H, Yang R, Li W, et al. Effects of exercise training on cardiac function, gene expression, and apoptosis in rats. *Am J Physiol Heart Circ Physiol* 2000;279(6):H2994-3002.

17. Kwak HB, Song W, and Lawler JM. Exercise training attenuates age-induced elevation in Bax/Bcl-2 ratio, apoptosis, and remodeling in the rat heart. *FASEB J* 2006;20(6):791-3.
18. Siu PM, Bryner RW, Martyn JK, et al. Apoptotic adaptations from exercise training in skeletal and cardiac muscles. *FASEB J* 2004;18(10):1150-2.
19. Bostrom P, Mann N, Wu J, et al. C/EBPbeta controls exercise-induced cardiac growth and protects against pathological cardiac remodeling. *Cell* 2010;143(7):1072-83.
20. Ellison GM, Waring CD, Vicinanza C, et al. Physiological cardiac remodelling in response to endurance exercise training: cellular and molecular mechanisms. *Heart* 2012;98(1):5-10.
21. White FC, Bloor CM, McKirnan MD, et al. Exercise training in swine promotes growth of arteriolar bed and capillary angiogenesis in heart. *J Appl Physiol (1985)* 1998;85(3):1160-8.
22. Thijssen DH, Torella D, Hopman MT, et al. The role of endothelial progenitor and cardiac stem cells in the cardiovascular adaptations to age and exercise. *Front Biosci (Landmark Ed)* 2009;14:4685-702.
23. Weeks KL and McMullen JR. The athlete's heart vs. the failing heart: can signaling explain the two distinct outcomes? *Physiology (Bethesda)* 2011;26(2):97-105.
24. Opie LH, Commerford PJ, Gersh BJ, et al. Controversies in ventricular remodelling. *Lancet* 2006;367(9507):356-67.
25. Bergmann O, Bhardwaj RD, Bernard S, et al. Evidence for cardiomyocyte renewal in humans. *Science* 2009;324(5923):98-102.
26. Beltrami AP, Barlucchi L, Torella D, et al. Adult cardiac stem cells are multipotent and support myocardial regeneration. *Cell* 2003;114(6):763-76.
27. Ellison GM, Vicinanza C, Smith AJ, et al. Adult c-kit(pos) cardiac stem cells are necessary and sufficient for functional cardiac regeneration and repair. *Cell* 2013;154(4):827-42.
28. Neri Serneri GG, Boddi M, Modesti PA, et al. Increased cardiac sympathetic activity and insulin-like growth factor-I formation are associated with physiological hypertrophy in athletes. *Circ Res* 2001;89(11):977-82.
29. McMullen JR, Shioi T, Huang WY, et al. The insulin-like growth factor 1 receptor induces physiological heart growth via the phosphoinositide 3-kinase(p110alpha) pathway. *J Biol Chem* 2004;279(6):4782-93.
30. Luo J, McMullen JR, Sobkiw CL, et al. Class IA phosphoinositide 3-kinase regulates heart size and physiological cardiac hypertrophy. *Mol Cell Biol* 2005;25(21):9491-502.
31. Kim J, Wende AR, Sena S, et al. Insulin-like growth factor I receptor signaling is required for exercise-induced cardiac hypertrophy. *Mol Endocrinol* 2008;22(11):2531-43.
32. McMullen JR, Amirahmadi F, Woodcock EA, et al. Protective effects of exercise and phosphoinositide 3-kinase(p110alpha) signaling in dilated and hypertrophic cardiomyopathy. *Proc Natl Acad Sci U S A* 2007;104(2):612-7.
33. DeBosch B, Treskov I, Lupu TS, et al. Akt1 is required for physiological cardiac growth. *Circulation* 2006;113(17):2097-104.
34. Shiraishi I, Melendez J, Ahn Y, et al. Nuclear targeting of Akt enhances kinase activity and survival of cardiomyocytes. *Circ Res* 2004;94(7):884-91.
35. Torella D, Rota M, Nurzynska D, et al. Cardiac stem cell and myocyte aging, heart failure, and insulin-like growth factor-1 overexpression. *Circ Res* 2004;94(4):514-24.

36. Fischer KM, Din S, Gude N, et al. Cardiac progenitor cell commitment is inhibited by nuclear Akt expression. *Circ Res* 2011;108(8):960-70.
37. Yasuda S, Goto Y, Takaki H, et al. Exercise-induced hepatocyte growth factor production in patients after acute myocardial infarction: its relationship to exercise capacity and brain natriuretic peptide levels. *Circ J* 2004;68(4):304-7.
38. Laufs U, Werner N, Link A, et al. Physical training increases endothelial progenitor cells, inhibits neointima formation, and enhances angiogenesis. *Circulation* 2004;109(2):220-6.
39. Gustafsson T, Rundqvist H, Norrbom J, et al. The influence of physical training on the angiopoietin and VEGF-A systems in human skeletal muscle. *J Appl Physiol (1985)* 2007;103(3):1012-20.
40. Czarkowska-Paczek B, Bartlomiejczyk I, and Przybylski J. The serum levels of growth factors: PDGF, TGF-beta and VEGF are increased after strenuous physical exercise. *J Physiol Pharmacol* 2006;57(2):189-97.
41. Rastaldo R, Pagliaro P, Cappello S, et al. Nitric oxide and cardiac function. *Life Sci* 2007;81(10):779-93.
42. Ellison GM, Torella D, Dellegrottaglie S, et al. Endogenous cardiac stem cell activation by insulin-like growth factor-1/hepatocyte growth factor intracoronary injection fosters survival and regeneration of the infarcted pig heart. *J Am Coll Cardiol* 2011;58(9):977-86.
43. Santini MP, Tsao L, Monassier L, et al. Enhancing repair of the mammalian heart. *Circ Res* 2007;100(12):1732-40.
44. Jin RC and Loscalzo J. Vascular Nitric Oxide: Formation and Function. *J Blood Med* 2010;2010(1):147-162.
45. Green DJ, O'Driscoll G, Joyner MJ, et al. Exercise and cardiovascular risk reduction: time to update the rationale for exercise? *J Appl Physiol (1985)* 2008;105(2):766-8.
46. Doshi SN, Naka KK, Payne N, et al. Flow-mediated dilatation following wrist and upper arm occlusion in humans: the contribution of nitric oxide. *Clin Sci (Lond)* 2001;101(6):629-35.
47. Goto C, Higashi Y, Kimura M, et al. Effect of different intensities of exercise on endothelium-dependent vasodilation in humans: role of endothelium-dependent nitric oxide and oxidative stress. *Circulation* 2003;108(5):530-5.
48. Ohara Y, Peterson TE, and Harrison DG. Hypercholesterolemia increases endothelial superoxide anion production. *J Clin Invest* 1993;91(6):2546-51.
49. Birk GK, Dawson EA, Atkinson C, et al. Brachial artery adaptation to lower limb exercise training: role of shear stress. *J Appl Physiol (1985)* 2012;112(10):1653-8.
50. Green DJ, Spence A, Halliwill JR, et al. Exercise and vascular adaptation in asymptomatic humans. *Exp Physiol* 2011;96(2):57-70.
51. Thijssen DH, Maiorana AJ, O'Driscoll G, et al. Impact of inactivity and exercise on the vasculature in humans. *Eur J Appl Physiol* 2010;108(5):845-75.
52. Dawson EA, Whyte GP, Black MA, et al. Changes in vascular and cardiac function after prolonged strenuous exercise in humans. *J Appl Physiol (1985)* 2008;105(5):1562-8.
53. Tinken TM, Thijssen DH, Black MA, et al. Time course of change in vasodilator function and capacity in response to exercise training in humans. *J Physiol* 2008;586(Pt 20):5003-12.
54. Rowley NJ, Dawson EA, Birk GK, et al. Exercise and arterial adaptation in humans: uncoupling localized and systemic effects. *J Appl Physiol (1985)* 2011;110(5):1190-5.

55. Tinken TM, Thijssen DH, Hopkins N, et al. Shear stress mediates endothelial adaptations to exercise training in humans. *Hypertension* 2010;55(2):312-8.
56. Newcomer SC, Thijssen DH, and Green DJ. Effects of exercise on endothelium and endothelium/smooth muscle cross talk: role of exercise-induced hemodynamics. *J Appl Physiol (1985)* 2011;111(1):311-20.
57. Phys. Act. Guidel. Advis. Comm. *Physical Activity Guidelines Advisory Committee Report: 2008*. Washington, DC: US Dept. Health Hum. Serv. **http://www.health.gov/paguidelines/Report/pdf/CommitteeReport.pdf**
58. Powell KE, Paluch AE, and Blair SN. Physical activity for health: What kind? How much? How intense? On top of what? *Annu Rev Public Health* 2011;32:349-65.
59. Bhella PS, Hastings JL, Fujimoto N, et al. Impact of lifelong exercise "dose" on left ventricular compliance and distensibility. *J Am Coll Cardiol* 2014;64(12):1257-66.
60. Weston KS, Wisloff U, and Coombes JS. High-intensity interval training in patients with lifestyle-induced cardiometabolic disease: a systematic review and meta-analysis. *Br J Sports Med* 2014;48(16):1227-34.
61. Weston M, Taylor KL, Batterham AM, et al. Effects of low-volume high-intensity interval training (HIT) on fitness in adults: a meta-analysis of controlled and non-controlled trials. *Sports Med* 2014;44(7):1005-17.
62. Angadi SS, Mookadam F, Lee CD, et al. High-intensity interval training vs. moderate-intensity continuous exercise training in heart failure with preserved ejection fraction: A pilot study. *J Appl Physiol (1985)* 2014:jap 00518 2014.
63. Lee DC, Artero EG, Sui X, et al. Mortality trends in the general population: the importance of cardiorespiratory fitness. *J Psychopharmacol* 2010;24(4 Suppl):27-35.
64. Green DJ, Spence A, Rowley N, et al. Vascular adaptation in athletes: is there an 'athlete's artery'? *Exp Physiol* 2012;97(3):295-304.
65. Bernardo BC, Weeks KL, Pretorius L, et al. Molecular distinction between physiological and pathological cardiac hypertrophy: experimental findings and therapeutic strategies. *Pharmacol Ther* 2010;128(1):191-227.

Figure legends

Figure 1: Cellular cardiac adaptations with physiological and pathological remodelling

The question mark after irreversible signifies whether by identifying cellular and molecular mechanisms, new therapeutic targets could be devised to reverse pathological remodelling. These cellular and molecular mechanisms could be identified from what occurs with physiological remodelling and as a result of exercise training.

Figure 2: Intensity controlled treadmill running exercise in rats induces cardiac myogenesis and angiogenesis

A, A small newly formed $BrdU^{pos}$ (green) cardiomyocyte (α-sarcomeric actin; red) in the LV of a high intensity exercising animal. (Inset is x2 zoom of boxed area). Nuclei detected by DAPI in blue. B, The % number of $BrdU^{pos}$ cardiomyocytes formed was dependent on exercise duration and intensity. C, A newly formed $BrdU^{pos}$ (green) capillary (vWF; red) from the LV of a high intensity exercising animal (Inset is x2 zoom). D, Capillary density in the LV of exercising animals was dependent on exercise intensity. (Data are Mean ± SEM, *P<0.05 vs. CTRL, **P<0.05 vs. LI, †P<0.05 vs. 1 (B) & 2 (B & D) weeks; n=6 for All). Adapted from Waring et al. [15]

Figure 3: Activation and proliferation of c-kit^{pos} eCSCs in hearts of exercising animals

A, c-kit^{pos} eCSC number in the LV of CTRL and following 2 or 4 weeks of high intensity exercise training. B, c-kit^{pos} (green), $Ki67^{pos}$ (white) eCSCs from the LV (α-sarcomeric actin; red) of a high intensity exercise trained animal. Nuclei detected by DAPI in blue. (Data are Mean ± SEM, *P<0.05 vs. CTRL; n=6 for All). Panel A is adapted from Waring et al. [15]

Figure 4: Relative change in brachial artery flow mediated dilation (FMD) from baseline (FMD%) across the 8-week handgrip exercise training in healthy young men.

FMD (an index of endothelial function) adapts rapidly to training and then returns towards baseline levels. These adaptations may be superseded by other functional changes or structural arterial remodelling. When the shear stress response to each bout of exercise was ameliorated by inflation of a proximal pressure cuff, functional adaptations were not apparent. These studies suggest that repeated increases in shear stress are obligatory for adaptation of conduit arterial function in response to exercise training. Figure from [50].

Figure 5: An athlete's artery relative to an artery from a healthy non-athletic control subject.

A figure representing an 'athlete's artery' comprising of a larger lumen dimension with a decreased wall thickness, relative to an artery from a healthy non-athletic control individual. Two key points to consider; 1) this conclusion is draw from endurance athlete data as little is

known about the systematic effects of resistance or power athleticism on arterial size or function, and 2) it is not always apparent that athletes' arteries are larger based on resting lumen dimensions; this is due to the possible compensatory increase in basal constrictor tone in larger arteries. Figure from [64].

Table 1: Molecular Features of Physiological and Pathological Cardiac Remodelling

PHYIOLOGICAL	**PATHOLOGICAL**
↑ autocrine and paracrine humoral factors such as IGF-1, neuroregulin, periostin, BMP-10, TGFβ, cardiotrophin 1 (CT-1).	↑ autocrine and paracrine humoral factors (AngII, ET-1, noradrenaline, TGFβ, TNFα, serum response factor)
↑ Heat shock proteins 20, 27 and 70	↑ expression of fetal genes (ANP, BNP, β-MHC, α-actin)
↑ S6K1, eNOS	↑ Ca^{2+} handling proteins (SERCA2A)
↑ Rates of fatty acid and glucose oxidation	↑ S6K1, RhoA,
Microarray – cell survival, fatty acid oxidation, insulin signalling, EGF signalling and HSF1 gene clusters	Microarray – inflammation, apoptotic, cardiac fetal gene and oxidative stress gene clusters
miRNA-1, -133, -29c	miRNA-1, -133
Signalling Pathways	**Signalling Pathways**
- **IGF-1-PI3K(p110α)-Akt pathway**	**GPCR-Gαq signalling**
- *Gp130/JAK/STAT pathway*	- PI3K(110γ)
- *Thyroid Hormone signalling*	- MAPKs (ERKs, JNKs, p38-MAPKs)
- HSF1 pathway	- Protein kinases C (PKC) and D (PKD)
	- Calcineurin and calmodulin (CAMKII)
	- GTPases - Ras and Rho

HSF1; Heat Shock Transcription Factor 1. S6K1; Ribosomal S6 kinase 1. EGF; Epidermal growth factor. TGFβ; transforming growth factor beta. BMP-10; Bone morphogenetic protein-10. IGF-1; Insulin-like Growth factor-1. ET-1; Endothelin-1. TNFα; Tumor necrosis factor alpha. ANP; Atrial natriuretic peptide. BNP; Brain natriuretic peptide. β–MHC; beta-myosin heavy chain. SERCA2A; sarcoplasmic reticulum Ca2+ ATPase. ERKs; Extracellular signal-regulated kinases. JNKs; c-Jun N-terminal kinases. MAPKs; Mitogen-activated protein kinases. CAMKII; Ca2+ /calmodulin-dependent protein kinase II. *Written in Italics* – Not directly shown to be activated by exercise but have been shown to have a protective role in the heart and with physiological heart growth. Data taken from Bernardo et al. [65] and Waring et al. [15]

Table 2: CMR data indices of LA, LV and RV volumes, mass and systolic function. Values are expressed as mean ± SD and (range).

	Veteran Athletes (VA)		**Age-Matched Controls (C)**		**Young Athletes (YA)**			
	Absolute	**Absolute ^BSA**	**Absolute**	**Absolute ^BSA**	**Absolute**	**Absolute ^BSA**	***P value (VA vs. C)***	***P value (VA vs. YA)***
LAEDV (ml)	70 ± 13 (52 – 92)	25.7 ± 5.6 (24.6 – 34)	78 ± 12 (54 – 101)	26.6 ± 3.5 (18 – 32)	72 ± 21 (43 – 117)	25.5 ± 6.8 (22.6 – 35.3)	*0.567*	*1.000*
LVEDV (ml)	182 ± 28 (142 – 232)	66.8 ± 11.3 (52 – 81)	143 ± 18 (100 – 170)	52.8 ± 6.6 (36 – 65)	211 ± 35 (162 – 272)	74.7 ± 9.6 (57 – 88)	*P<0.001*	*0.018*
LVESV (ml)	63 ± 16 (42 – 90)	23 ± 6.4 (16 – 35)	42 ± 9 (25 - 61)	15.5 ± 3.4 (19 – 23)	76 ± 18 (47 - 111)	26.8 ± 5.6 (16 – 39)	*P<0.001*	*0.049*
IVSd (mm)	11 ± 1 (9 – 13)	7.8 ± 0.9 (6.6 – 9.5)	10 ± 2 (7 – 13)	6.9 ± 1.0 (5.1 – 9.4)	10 ± 1 (9 – 12)	7.4 ± 0.5 (6.6 – 8.5)	*0.049*	*1.000*
PWd (mm)	10 ± 1 (8 – 11)	6.9 ± 0.9 (5.8 – 8.2)	8 ± 1 (7 – 10)	5.9 ± 0.6 (7 – 7)	10 ± 1 (9 – 12)	7.3 ± 0.5 (6.5 – 8.5)	*P<0.001*	*0.113*
LV Length (mm)	88 ± 6 (78 – 97)	63 ± 4.5 (56.8 – 70)	93 ± 6 (84 – 102)	96.0 ± 5.8 (85 – 104)	97 ± 7 (89 – 112)	69.1 ± 3.1 (62.4 – 73.9)	*0.088*	*P<0.001*
LV mass (g)	148 ± 16 (120 – 167)	54.6 ± 6.7 (45 – 66)	147 ± 23 (108 – 180)	54.2 ± 7.1 (44 – 71)	151 ± 23 (119 – 210)	53.3 ± 5.2 (43 – 64)	*1.000*	*1.000*
RVEDV (ml)	181 ± 24 (150 – 227)	66.6 ± 9.4 (56 – 88)	146 ± 19 (113 – 187)	54.2 ± 7.2 (41 - 66)	215 ± 37 (143 – 276)	72.1 ± 21.5 (58 – 92)	*0.003*	*0.008*
RVESV (ml)	63 ± 15 (45 – 96)	23 ± 6.4 (18 – 37)	42 ± 13 (25 – 69)	15.8 ± 4.7 (8 – 25)	82 ± 22 (41 – 114)	26.8 ± 5.6 (18 – 42)	*0.005*	*0.011*
LVSV (ml)	119 ± 18 (101 – 163)	43.8 ± 6.9 (36 – 56)	101 ± 11 (75 – 1115)	37.3 ± 4.1 (27 – 46)	136 ± 21 (104 – 183)	47.9 ± 5.4 (36 – 55)	*0.014*	*0.036*
RVSV (ml)	119 ± 16 (102 – 174)	43.7 ± 6.4 (36 – 54)	104 ± 12 (77 – 124)	38.4 ± 4.0 (28 – 48)	133 ± 21 (97 – 154)	44.5 ± 12.6 (36 – 45)	*0.047*	*0.093*
LVEF (%)	66 ± 5 (55 – 71)	-	71 ± 4 (64 – 78)	-	65 ± 4 (56 – 74)	-	*0.008*	*1.000*

RVEF (%)	66 ± 5 (58 – 75)	-	72 ± 6 (63 – 82)	-	62 ± 6 (53 – 73)	-	*0.03*	*0.22*

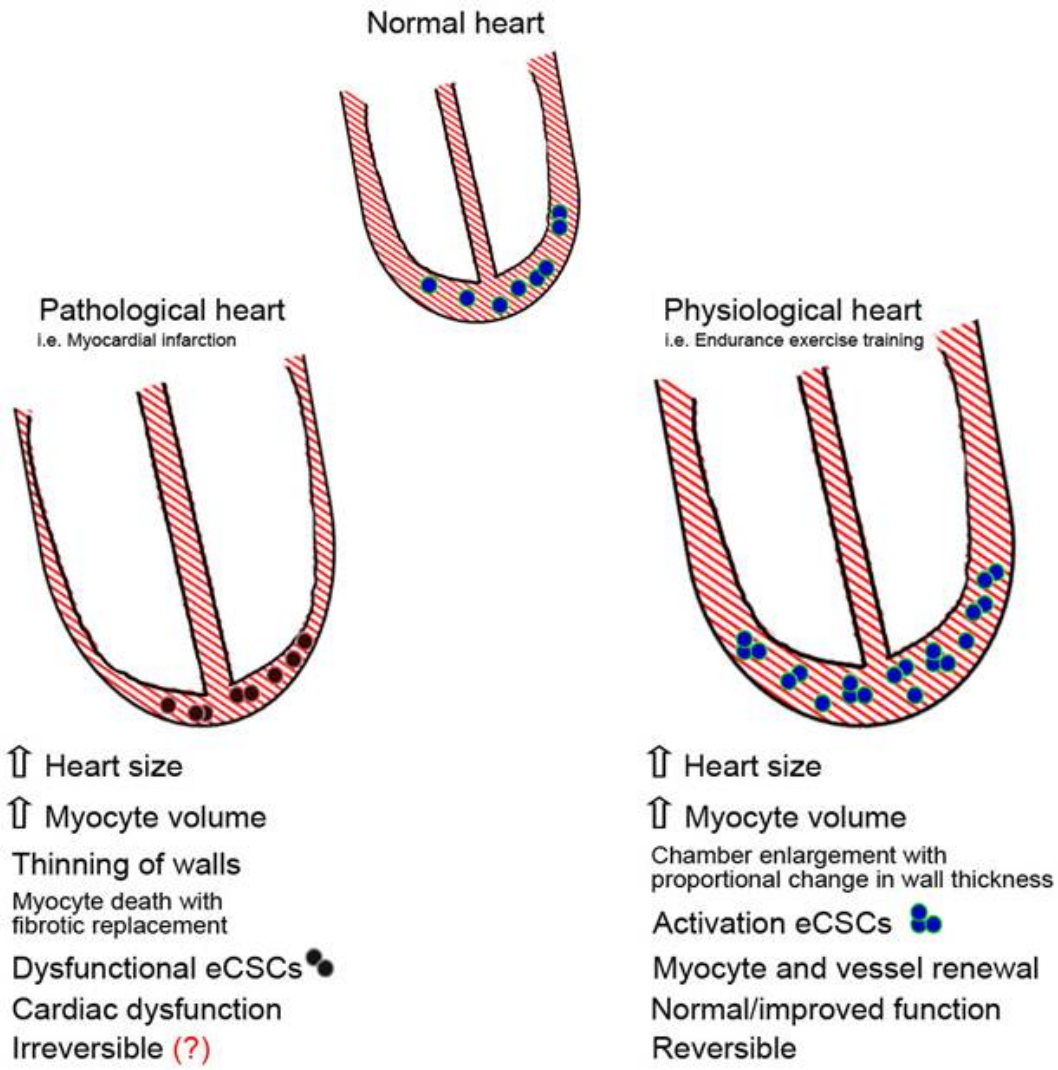
LAEDV, left atrium end diastolic volume; LVEDV, left ventricular end diastolic volume; LVESV, left ventricular end systolic volume; IVSd, intra-ventricular septum during diastole; PWd, posterior wall thickness during diastole; LV length, left ventricular length; LVmass, left ventricular mass; RVEDV, right ventricular end diastolic volume; RVESV, right ventricular end systolic volume; LVSV, left ventricular stroke volume; RVSV, right ventricular stroke volume; LVEF, left ventricular ejection fraction; RVEF, right ventricular ejection fraction. **Data from [9]**

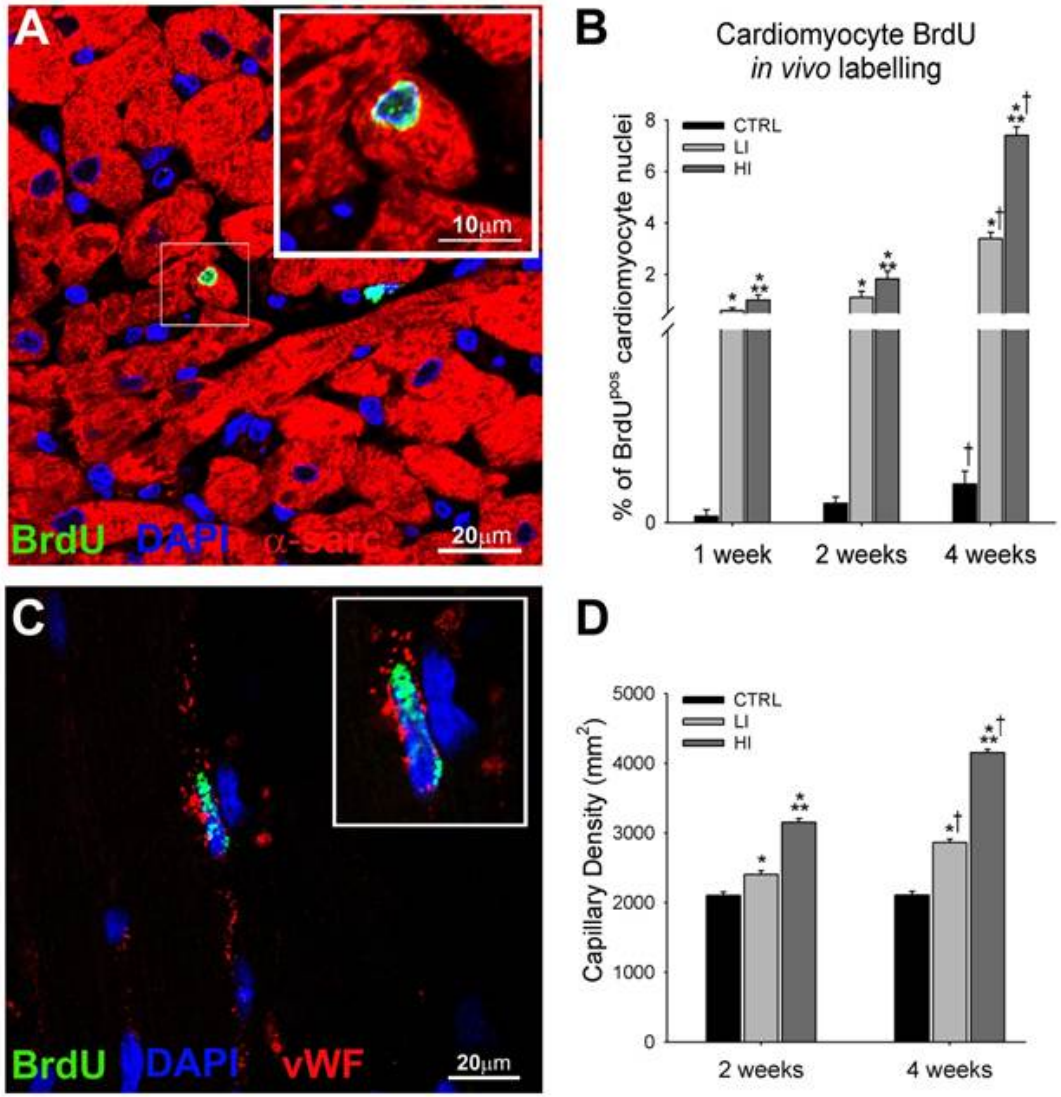
Table 3: Left ventricular structural and functional data in male endurance-trained, resistance-trained and sedentary control subjects. Data are mean, (95% confidence intervals), [number of studies; number of participants].

Parameter	**Endurance-Trained (ET)**	**Resistance-Trained (RT)**	**Sedentary Controls (CT)**	**P-value (All groups)**	**Post-hoc significant differences**	**Heterogeneity test**		
						Hetero-geneity	I squared (%)	P value
LV mass (g)	232 (200-260) [n=64; 1099]	220 (205-234) [n=25; 510]	166 (145-186) [n=59; 1239]	P<0.001	ET,RT>CT	21	99.8%	<0.001
IVSWT (mm)	11.0 (10.8-11.3) [n=68; 1802]	11.0 (10.3-11.8) [n=19; 408]	9.2 (8.9-9.5) [n=63; 1352]	P<0.001	ET,RT>CT	98	99.2%	<0.001
PWT (mm)	10.6 (10.3-10.9) [n=57; 1928]	10.4 (9.8-10.9) [n=14; 370]	8.8 (8.6-9.1) [n=53; 1433]	P<0.001	ET,RT>CT	87	99.2%	<0.001
LVEDD (mm)	54.8 (54.1-55.6) [n=61; 1548]	52.4 (51.2-53.6) [n=17; 384]	50.1 (49.5-50.7) [n=56; 1174]	P<0.001	ET>RT,CT RT>CT	95	99.1%	<0.001
LVEDV (ml)	171 (157-185) [n=34; 493]	131 (120-142) [n=14; 189]	135 (125-145) [n=34; 539]	P<0.001	ET>RT,CT	23	99.2%	<0.001
LV SV (ml)	106 (97-116) [n=28; 479]	86 (77-95) [n=9; 125]	83 (77-90) [n=27; 590]	P<0.001	ET>RT,CT	16	98.7%	<0.001
LV EF (%)	63 (61-64) [n=42; 1330]	66 (62-70) [n=7; 85]	64 (62-65) [n=37; 878]	P=0.365	NA	2.0	97.7%	<0.001
LV E/A	2.0 (1.9-2.1) [n=34; 844]	1.9 (1.7-2.0) [n=8; 214]	1.8 (1.7-1.9) [n=34; 868]	P=0.014		8.5	98.8%	<0.001
LV E'	13.6	*	11.0	P=0.014		18	98.6%	<0.001

	(12.3-14.9) [n=7; 204]		(9.4-12.6) [n=4; 183]					

LV-left ventricle, IVSWT-inter ventricular septal wall thickness, PWT-posterior wall thickness, EDD-end-diastolic dimension, EDV-end-diastolic volume, SV-stroke volume, EF-ejection fraction, E/A-peak early to atrial Doppler trans-mitral flow velocities, E' peak septal early diastole longitudinal tissue velocity, *-insufficient data, NA – not applicable as main effect not significant ($p>0.05$). **Data from [7]**


Normal heart
Pathological heart
i.e. Myocardial infarction
Physiological heart
i.e. Endurance exercise training
⇧ Heart size
⇧ Myocyte volume
Thinning of walls
Myocyte death with
fibrotic replacement
Dysfunctional eCSCs
Cardiac dysfunction
Irreversible (?)
⇧ Heart size
⇧ Myocyte volume
Chamber enlargement with
proportional change in wall thickness
Activation eCSCs
Myocyte and vessel renewal
Normal/improved function
Reversible


A
10μm
BrdU DAPI α-Sarc
20μm
B
Cardiomyocyte BrdU
in vivo labelling
% of BrdU^pos cardiomyocyte nuclei
CTRL
LI
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1 week
2 weeks
4 weeks
C
BrdU DAPI vWF
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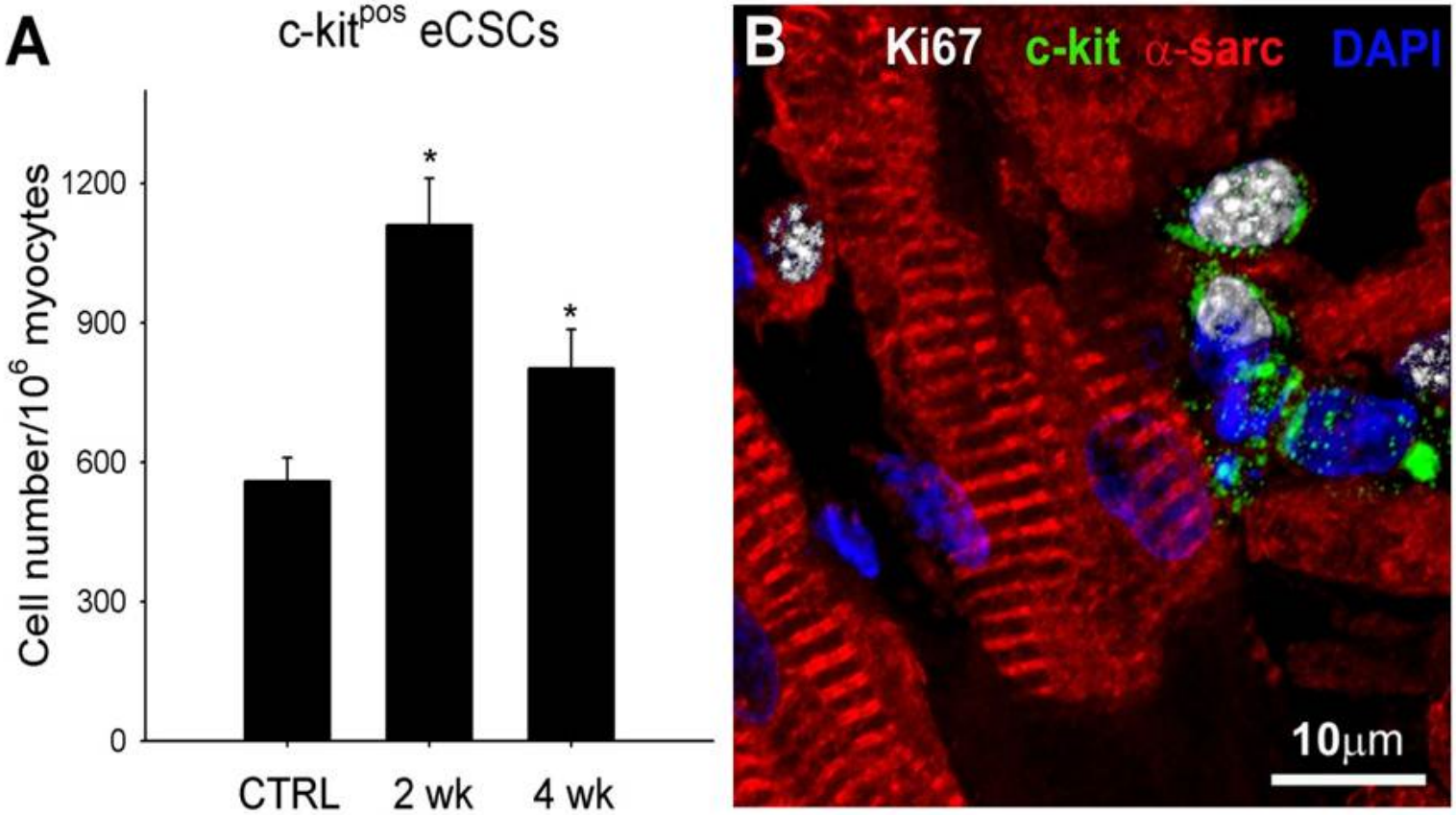
D
Capillary Density (mm^2)
CTRL
LI
HI
2 weeks
4 weeks


A
c-kit^pos eCSCs
Cell number/10^6 myocytes
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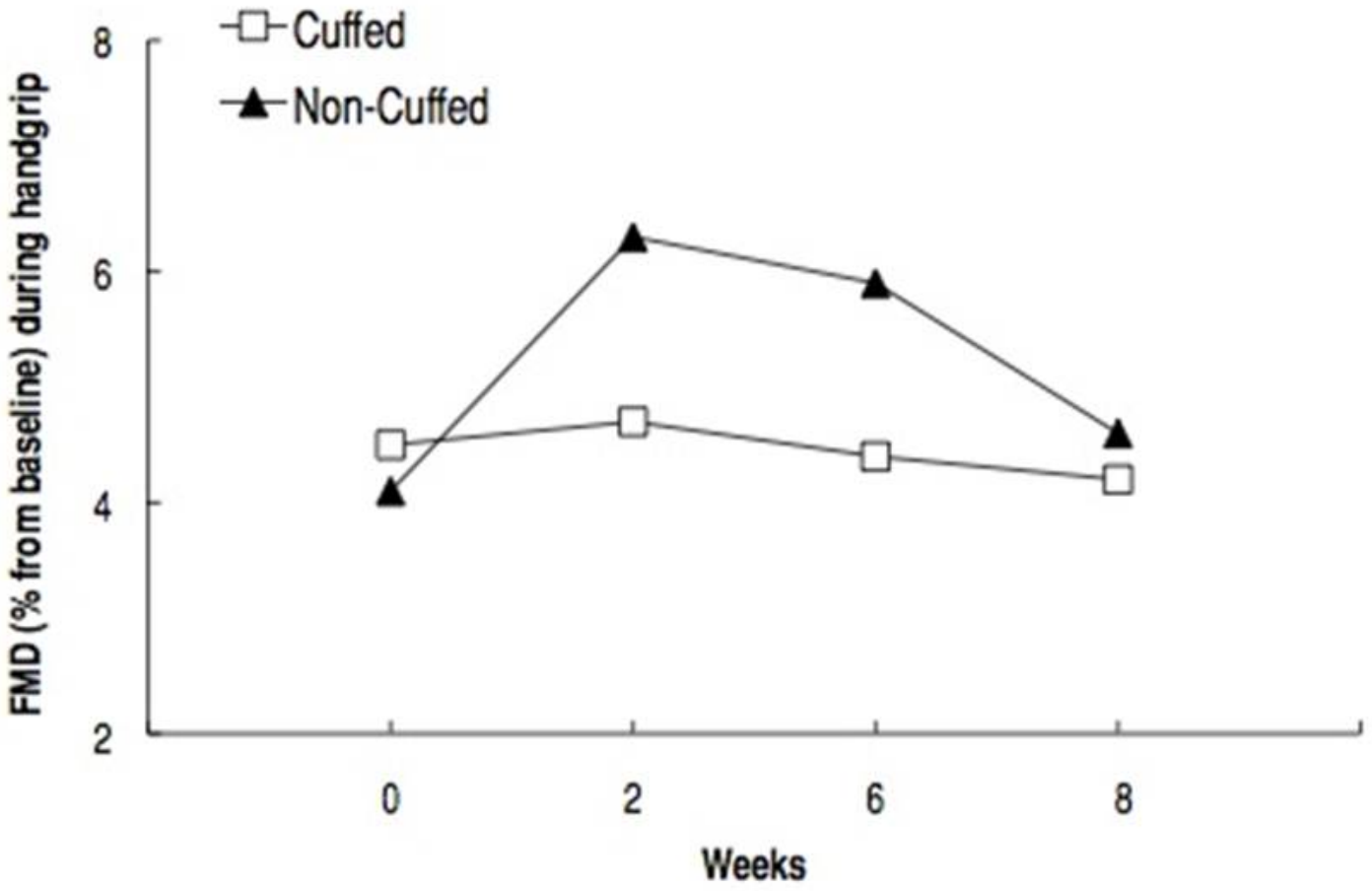
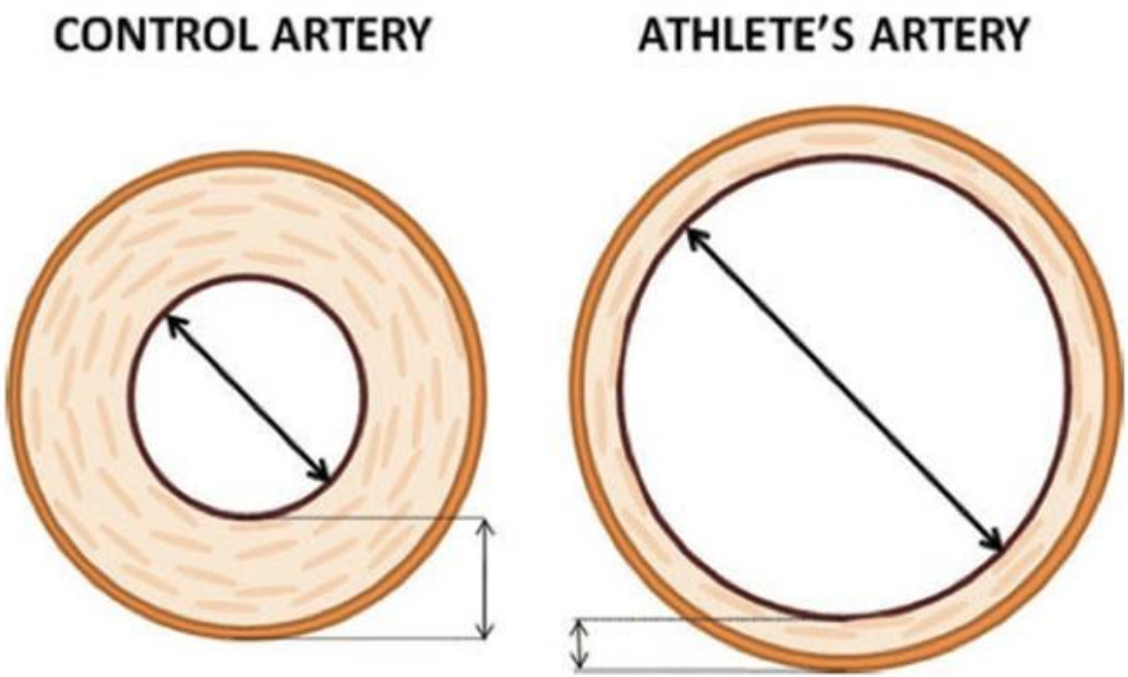
900
600
300
0
*
*
CTRL
2 wk
4 wk
B
Ki67
c-kit
α-sarc
DAPI
10μm


Cuffed
Non-Cuffed
FMD (% from baseline) during handgrip
8
6
4
2
0
2
6
8
Weeks


CONTROL ARTERY
ATHLETE'S ARTERY