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Towards a personalized approach in exercise-based cardiovascular rehabilitation: How can translational research help?

A 'call to action' from the Section on Secondary Prevention and Cardiac Rehabilitation of the European Association of Preventive Cardiology

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Abstract

The benefit of regular physical activity and exercise training for the prevention of cardiovascular and metabolic diseases is undisputed. Many molecular mechanisms mediating exercise effects have been deciphered. Personalized exercise prescription can help patients in achieving their individual greatest benefit from an exercise-based ~~cardiac~~cardiovascular rehabilitation programme. Yet, we still struggle to provide truly personalized exercise prescriptions to our patients.

In this position paper, we address novel basic and translational research concepts that can help us understand the principles underlying the inter-individual differences in the response to exercise, and identify early on who would most likely benefit from which exercise intervention. This includes hereditary, non-hereditary and sex-specific concepts. Recent insights have helped us to take on a more holistic view, integrating exercise-mediated molecular mechanisms with those influenced by metabolism and immunity. Unfortunately, while the outline is recognizable, many details are still lacking to turn the understanding of a concept into a roadmap ready to be used in clinical routine. This position paper therefore also investigates perspectives on how the advent of 'big data' and the use of animal models could help unravel inter-individual responses to exercise parameters and thus influence hypothesis building for translational research in exercise-based ~~cardiac~~cardiovascular rehabilitation.

Abstract word count: 198

Keywords: ~~cardiac~~cardiovascular rehabilitation, exercise, personalized medicine, responders/non-responders, immune system, machine learning, big data, animal models

1. Introduction

Epidemiological and interventional studies have demonstrated a benefit of regular physical activity and exercise for the prevention of cardiovascular and metabolic diseases.[1–6] Exercise acts in a pleiotropic manner, addressing cardiac contractile and diastolic properties, muscle anabolic and catabolic pathways, substrate metabolism, and regulatory processes governing tissue perfusion and energy storage.[7,8]

While physiological research of the past decades allowed us to understand these principal interactions, crucial questions remain on how to effectively implement exercise interventions in clinical therapy. Access and compliance to cardiovascular rehabilitation (CR) programmes remains a critical factor in the success of an exercise intervention, which requires a highly motivated multi-disciplinary team.[9] But basic and translational research can also help, addressing questions regarding the personalization of exercise prescription, in order to improve efficacy of exercise interventions ~~throughout the cardio/vascular/metabolic continuum~~. Why do some patients not respond to exercise-based ~~cardiac rehabilitation (~~CR~~)~~, and how can we identify them early on? What drives the difference in response to CR in men and women? How is the response to exercise influenced by metabolism, immunity and their interaction?

In addition to that, research methodology is rapidly advancing, bringing different views on translation of biochemical findings into the clinics. How will the advent of 'big data' influence hypothesis building for translational research in CR? What is the sense and nonsense of using animal models in modern CR research? In this position paper, we aim to address these future challenges for basic and translational research in exercise-based CR. We critically review recent studies dealing with the most important yet unanswered questions in the field, both in preclinical and clinical research. Finally, we pinpoint gaps in current evidence that deserve intensified attention in future research.

2. Future targets and open questions in translational ~~cardiac~~cardiovascular rehabilitation research

While exercise-based intervention programmes are recommended in ~~primary and secondary~~ cardiovascular prevention,[10,11] it has also become clear that exercise parameters – type, intensity, duration, frequency – differentially address cardio-vascular and metabolic endpoints, and that the quality and quantity of the response may differ ~~s significantly~~ between participants.[~~10~~] In addition to improving implementation, it is the personalization of exercise interventions that is an important focus of current and future research. Personalization of therapy includes taking account of patient-specific parameters with potential impact on the mechanism of disease and therapy effect, including age, gender and co-morbidities. In addition, personalization also means that target parameters need to be chosen according to the clinical need of the patient, based on their underlying morbidities and risk profile.

2.1 What factors contribute to the large variability in individual response to cardiovascular rehabilitation?~~Why do some patients not respond?~~

The improvement in maximal aerobic capacity (peak oxygen uptake, VO_2peak) following exercise-based CR is related to survival in a wide range of cardiovascular diseases, independent of other important risk factors.[12–14] Even small increments in VO_2peak result in substantially lower risk for all-cause and cause-specific mortality.[3] Although trials that investigated the effects of exercise-based CR on exercise capacity have consistently shown favourable and clinically significant changes,[15,16] a large variability is seen in the individual training response (relative change in VO_2peak following training, ΔVO_2peak). This variability exists both in healthy subjects and in patients with established cardiovascular disease, when exposed to similar exercise programs.[14,17,18] Recent studies have shown that up to 33% of patients fail to demonstrate a meaningful increase in VO_2peak in response to CR, despite adequate compliance to training. These 'non-responders' show a decrease in VO_2peak, or an increase within the test-retest variability of VO_2peak measurement (generally accepted to be

±6%).[18–20] The mechanisms driving this variability in ΔVO_2peak are not well understood, nor do we have good predictors for the response to exercise intervention. Possible contributing factors are summarized in **Figure 1**. We introduce some of the most important contributors below. Interested readers can further explore the

Among the factors influencing the individual response to CR, exercise parameters have been studied intensely recently. Williams et al. combined data from different laboratories that had compared training volumes ranging between high and moderate intensities, in populations of both healthy subjects and patients with established cardiovascular disease.[24] When exercise was performed with great amounts and high intensities, the likelihood of subjects increasing their exercise capacity was significantly greater. Similarly, Montero et al. showed that healthy non-responders to an exercise training intervention did increase their VO_2peak when subjected to greater training volumes.[25] Yet, the evidence regarding the additional beneficial effects of higher exercise intensities is still conflicting.[26] Total energy expenditure may be more relevant for improvements in exercise capacity than exercise intensity in these subjects. More comparative exercise intervention studies are needed to determine the inter-individual variability in exercise capacity caused by different variables of exercise programs (**Figure 3**).

It still remains to be elucidated which phenotypic and genotypic characteristics predict the response of a patient to these specific exercise interventions.[23] Previous studies already suggested that in addition to exercise training characteristics (e.g. intensity, volume, type), common personal characteristics like age, sex, body mass index, and baseline physical fitness predict between 15-21% of variability in ΔVO_2peak.[15,17,19,24] Moreover, an additional physiological factor that may influence ΔVO_2peak in patients with chronic heart failure (HF) is the circulatory response to acute exercise.[27,28] Considering the relatively low predictability of these factors, other more important factors that affect ΔVO_2peak likely still need to be discovered.

Heritability explains more than 50% of the inter-individual differences in cross-sectionally measured VO_2peak.[29,30] In addition, the Heritage Family study demonstrated that the change in VO_2peak to exercise training intervention is also largely (47%) determined by heritable factors (i.e. genetic, epigenetic or familial environmental factors).[31] Heritability of training-induced changes in haemodynamic response and skeletal muscle characteristics are also relatively high.[32,33] Most importantly, the heritability of ΔVO_2peak was independent of baseline VO_2peak.[34] This implies that even subjects with a low aerobic capacity may still substantially benefit from exercise training during CR.

Single gene diagnostics can help to improve our understanding of the genetics underlying the variability in VO_2peak and ΔVO_2peak. 'The human gene map for performance and health-related fitness phenotypes' has identified more than 200 autosomal gene variants and quantitative trait loci.[35] However, as data was mainly derived from underpowered sample sizes, this study did not provide compelling evidence that DNA sequence variants in a given gene are associated with human variation in fitness and performance

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traits.[35] Interaction between gene variants and disease modifying factors add to the complexity. For example, a single nucleotide polymorphism (SNP) in the *FTO* gene is associated with higher risk for adiposity, but this interaction term was weaker in physically active people.[36]

A means to overcome the focus on a single gene or locus could be transcriptome wide RNA expression profiling studies. Timmons et al. identified 11 SNPs in skeletal muscle, which were responsible for nearly 50% of the heritability of ΔVO_2peak in healthy subjects.[37] Genome-wide association studies could also provide unbiased insight into the genetics underlying baseline VO_2peak as well as ΔVO_2peak. Bouchard et al. discovered a total of 39 SNPs significantly associated with ΔVO_2peak.[38] Unfortunately, there was no overlap between the genes identified by Timmons et al. and those reported by Bouchard et al.[39] Another large genome-wide association study compared SNPs in 1520 elite athletes with SNPs in 2760 non-athletes, and identified only a single SNP (in the *GALNTL6* gene) that was more common in athletes.[40] Hence, while previous studies have started to use hypothesis-free methods to improve our understanding of the genetics underlying VO_2peak and ΔVO_2peak, there is still a long way to go.

~~Post-translational~~Epigenetic ~~modifications~~regulation ~~-~~may also influence protein function. This includes DNA methylation, histone modification, and post-translational modifications by non-coding RNAs, and each of these mechanisms has been described to contribute to the response to exercise training.~~Indeed, several non-coding RNA species have been linked to VO_2peak or ΔVO_2peak.~~
Both acute bouts of exercise and repeated training influence promoter DNA methylation.[41–43] Acute exercise-induced expression of key signalling pathways, including AMPK/PGC-1α, was paired with a hypomethylation of the respective promoter sequence.[42] Importantly, the magnitude of the effect on DNA methylation was dependent on exercise dose, suggesting a role of DNA methylation in the individual response to training.[42]
Deacetylation of histones and ~~, but also~~ other proteins~~,~~ by sirtuins, is known ~~for a while~~ to mediate adaptation to repeated exercise.[44]~~Exercise-induced histone modifications, including acetylation and methylation, have also been reported.[44–46]~~
failure depending on which metabolic pathway is switched on when the heart is put under stress.[45] [PMID: 29227474] In addition, histone deacetylase 3 ~~(HDAC3)~~ plays a major role in skeletal muscle by regulating fuel metabolism.[46] [PMID: 30428023] These findings are especially interesting with regards to ~~the~~ insulin resistance in patients with metabolic ~~disease~~syndrome. Whether or not pharmaceutical interventions targeting ~~HDAC3~~histone deacetylases add an additive effect to exercise based CR alone, remains to be determined ~~by future research~~.

Finally~~In healthy subjects~~, microRNAs are released into the circulation ~~even~~ after acute exercise, and exercise training induces long-term changes in their expression.[47,48] In a rat model of HF, Souza et al. identified a set of 14 cardiac microRNAs of which expression was influenced by exercise training.[49] Other studies have identified additional exercise-responsive microRNAs in animal models of different cardiovascular diseases.[48] To date, only two small studies have assessed the effect of exercise training on microRNA expression in human patients with established cardiovascular disease.[50,51] Taurino et al. showed that *miR-92a* and *miR-92b* were upregulated after exercise-based CR in patients with coronary artery disease, coinciding with a downregulation of their gene targets.[50] Xu et al. identified 3 microRNA dysregulated by acute exercise in HF patients, but a clear correlation with VO_2peak was not found.[51]
None of these epigenetic mechanisms has yet been linked to ΔVO_2peak. ~~More~~ Exercise epigenetics is a highly active research area, and more extensive studies, including larger numbers of patients, ~~and screening for more miRNA,~~ are still needed before reliable conclusions can be drawn.

While For for most studies, improvement of VO_2peak is the main target parameter of an exercise intervention. Yet, depending on the Personalization of therapy demand that target parameters could be chosen according to the clinical need of the patient and based on their underlying morbidities and risk profile, other parameters such as . This is not necessarily always VO_2peak, but can be improved submaximal exercise parameters, increased cardiac function, better glucose handling, reduced inflammation, or improved vascular stiffness might be more relevant too.[5,52–55] Of note, target parameters of the exercise intervention might even change over time in each patient.

- *To summarize, the change in VO_2peak to exercise training shows large inter-individual variability. Understanding how such inter-individual differences emerge is important, as a lower response is linked to poorer outcomes.[12–14] ΔVO_2peak seems to be regulated by the interaction between heritable factors and lifestyle – including exercise parameters, SNPs, and non-coding RNAs – but individual targets have yet to be confirmed. We need controlled randomized studies using multi-omics techniques (transcriptomics, genomics, proteomics and metabolomics) to identify potential pathways in a 'systems biology' approach. The complex interaction between lifestyle and heritable factors likely explains a large part of the individual response to exercise training, and future studies should aim to improve our understanding of this interaction.*

2.2 The potential role of sex differences in response to CR

In general, VO_2peak is ~15% lower in women compared to men.[56] Intriguingly, however, women seem to experience better clinical outcomes following exercise training, despite similar improvements in exercise capacity.[57,58] While sex-specific effects thus likely play a key role in the clinical benefits associated with exercise interventions, the mechanisms responsible for these benefits remain poorly are not completely understood.

Cardiac Cardiovascular physiology as well as pathophysiology are markedly different between men and women, as has been reviewed extensively elsewhere. The main differences are summarized in Table 1. For a more extensive overview, we refer the reader to existing reviews.[59]

Sex-specific hormones may explain part of these differences. In pre vs. postmenopausal women of similar age, blood pressure is lower, and left ventricular end-systolic volume, ejection fraction and filling rate are larger.[62] The vasodilating properties of oestrogen may play a role.[63] Also, RNA sequencing in cardiomyocytes revealed more than 600 genes with sexually dimorphic expression patterns.[64] This adds to genetic differences due to male specific Y-chromosomal gene expression and differences in epigenetics (histone and DNA modifications, non-coding RNA expression).[60]

Thus, in addition to the obvious endocrine differences between men and women, a variety of anatomical, genetic al and molecular differences exists within the heart. These may influence not just cardiovascular disease progression, but also affect secondary prevention strategies.[61]

While central hemodynamic differences likely explain some of the sex-specific effects in response to CR,[61] other factors are also involved. It is well established that cardiac cardiovascular disorders induce secondary impairments to the periphery, including endothelial and skeletal muscle dysfunction, which are closely linked to symptoms of exercise intolerance and prognosis.[65] Surprisingly, it is still largely unclear how sex modulates the crosstalk of mechanisms governing the loss of endothelial, skeletal and cardiac function. A few studies have revealed that in patients with HF, mitochondrial enzymes in skeletal muscle show either no major changes or more pronounced deficits in men compared to women, with a greater shift towards glycolytic enzymes and type IIX fatigable fibres in men.[66,67] In response to an aerobic endurance training intervention, evidence has revealed minor differences in terms of skeletal muscle biochemistry, with reports suggesting men with HF can increase the content of the slow myosin heavy chain isoform towards similar levels to that

observed at baseline in women.[68] Thus, women may experience a greater preservation of muscle oxidative function compared to men with HF, which could help to explain why women demonstrate greater clinical benefits after CR.[57] The mechanisms underpinning the sex-specific differences in muscle physiology and effects of exercise intervention remain unclear. Hormonal effects of oestrogen regulation on mitochondrial dynamics and/or a preferential shift towards fatty acid oxidation in women may play a role, [69,70] but more extensive measures of muscle function and physiology and higher sample sizes are still required to confirm this.

In addition to skeletal muscle alterations, endothelial dysfunction also develops in HF patients, both in men and women.[71] Yet, little data is available to clearly demonstrate whether any sex-specific alterations are present following CR in patients. Recent evidence from animal~~s~~ models of HF have shown that high-intensity interval training can attenuate endothelial dysfunction in both female and male rats, which seems to act via mechanisms specifically lowering oxidative stress in males and increasing endothelial nitric oxide synthase expression in females.[72,73] Whether these molecular benefits are paralleled in male and female patients with HF remains unclear. Furthermore, sex-specific substrate utilisation could play a key role in the exercise response in women and may fill the above-mentioned gap in the literature with regards to the effectiveness of exercise-based CR. One example is that women rely on carbohydrates to a lesser extent but have a higher content of intramyocellular lipids.[74]

While CR programs clearly reduce the risk of all-cause and cardiac-related mortality and improve quality of life, directly extrapolating these findings from men to women remains fraught with complexities since women have consistently been under-represented in previous trials.[75] In large meta-analyses and randomized controlled trials, the amount of women recruited was 11-28%.[61] Given that women are also ~40 % less likely to enrol in CR and have a significantly lower adherence to the interventions compared to men, [76,77] the need to better understand sex-specific mechanisms in response to exercise training will first require rapid improvement in CR recruitment and adherence of women. Identification of sex-specific targets is likely to substantially improve outcomes following CR programmes by optimising training regimes. Nonetheless, women seem to benefit at least as much from exercise-based CR as men.[57,78,79] The most recent Cochrane reviews which assessed the benefits of exercise-based CR concluded that exercise improves cardiovascular mortality and hospitalization (in patients with coronary artery disease) and improves health-related quality of life (in patients with coronary artery disease or HF).[80,81] The authors also clearly state that evidence for benefits of exercise-based CR in women is currently insufficient. Given the above mentioned physiological and pathophysiological differences between men and women, we cannot assume that exercise regimes which worked for men will also be effective for women.

- *To summarize, important differences exist in the response to CR in men and women. Besides obvious differences in cardiovascular and skeletal muscle structure, function and physiology, the underlying hormonal and molecular mechanisms are still understudied. Identification of sex-specific targets might further improve outcomes after CR. Further, in order to put the physiological differences between ~~man~~men and women into a larger perspective, novel 'omics' techniques, ~~omics approaches~~ which enable a systems biology approach, should be used to determine which differences contribute to the response to exercise based CR.*

2.3 Immune-metabolism interactions and inflammation

Both enhanced activation and impaired resolution of inflammation are major underlying principles of cardiovascular and metabolic pathologies.[82] Regular exercise training has been shown to lower systemic and vascular inflammatory load within a few weeks ~~of intervention~~.[55] This has been partly attributed to active

secretion of anti-inflammatory myokines from skeletal muscle.[83] While biochemical interactions of some myokines have been deciphered, it remains a major task to chart the network of biochemical interactions between energy demand by skeletal muscle contractile activity (affected by exercise parameters, such as duration, type and frequency) and the fine-tuning of inflammatory mechanisms. The recent years have brought a refinement in our understanding of inflammation in atherosclerosis, including the appreciation of resolution of inflammation as an active process, distinct from inhibition of inflammation, as well as the tight interactions between immune cell activation and their energy metabolism. ~~Only a fraction of these newly understood mechanisms has been exploited in the context of the cardiovascular effects of regular exercise training.~~ Those initial in vitro data have not yet been translated into ~~therapy~~therapeutic strategies. Unanswered questions include to which extent immunometabolic observations made in mouse macrophages can be translated to the human and to which extent in vitro differentiated macrophage phenotypes resemble in vivo macrophages, regarding both~~,~~ immunologic function and energy metabolic profile.

Resolution of inflammation versus anti-inflammation: The termination of an acute inflammatory response is normally governed by both the decay of pro-inflammatory signals, as well as the active production of pro-resolving factors.[84] The inability to resolve an ongoing inflammatory process is a hallmark of inflammatory degenerative ~~processes~~diseases, including atherosclerosis.[85] On the one hand, innate immune-activating signals - ligands of pattern-recognition receptors, such as modified lipids - do not disappear in atherosclerosis, as it would happen in a 'normal' injury. On the other hand, the production of pro-resolving mediators appears to be dysregulated. Anti-inflammatory therapies have been employed more or less successfully in secondary cardiovascular prevention.[86,87] However, therapeutic success appears to depend on the inflammatory signalling mechanism targeted, likely interleukin-1β and interleukin-6 signalling, and may be flawed by increased incidence of lethal infections.[86,87] In addition, blocking inflammation also appears to block resolving mechanisms, the removal of apoptotic particles and cell debris as well as the induction of regenerative processes.[85]

~~The termination of an acute inflammatory response is normally governed by both the decay of pro-inflammatory signals, as well as the active production of pro-resolving factors.[88]~~ A number of studies support the ability of exercise - ranging from a single session of high-intensity interval exercise to a 3-month multicomponent exercise programme – to reduce cellular responsiveness to toll-like receptor -mediated signalling, induced by damage-associated molecular patterns.[88–90]

Dietary interventions targeting synthesis of specialized resolving mediators (SPM) have been tested for some time now and it becomes evident that both~~,~~ the dosage and the formulation might be relevant to their success in cardiovascular prevention.[91] In contrast, only few studies have systematically addressed the effects of exercise intervention on the release of SPMs – resolvins, lipoxins, protectins and maresins – but the existing literature indicates an increase in SPM release by regular exercise.[92–94] This might be attributed to acute and chronic effects: strain and acute release of pro-inflammatory mediators are associated with SPM release in acute high-intensity exertion, while chronic effects of exercise intervention might be connected to the exercise-mediated shift in macrophage polarization towards the M2-like phenotype.[92,94,95] M2-like macrophages are better suited to perform efferocytosis than the M1-like phenotype and it is during efferocytosis that SPMs are released.[96] Thus, we know that regular exercise is associated with a shift towards the more pro-resolving macrophage spectrum, as well as higher levels of pro-resolving mediators, but we do not know which exercise parameters (e.g. intensity, volume, type) could be used to boost this effect, nor whether a combination with dietary approaches to supplement SPMs could potentiate the effects of exercise intervention on cardiovascular inflammation (**Figure 2**).

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Energy metabolism and inflammation: From tumour biology, we know that increased glycolysis and glutaminolysis provide energy flexibility to the cell and generate intermediates that feed into anabolic processes - probably the reason why glycolysis is preferred over oxidative phosphorylation by proliferating tumour cells.[97–99] In a similar manner, glycolysis is preferred by activated and proliferating myeloid and lymphoid cells[100] and stimulating glycolysis can activate macrophages.[101] In addition, M1-type macrophages feature a 'broken' Krebs cycle, with increased output of intermediates that serve as substrates in the synthesis of pro-inflammatory mediators, or are pro-inflammatory mediators in themselves.[102] [102–104] In contrast, 'alternative' M2-like macrophages favour oxidative phosphorylation and fatty acid oxidation.[105,106] Indeed, oxidative phosphorylation was is a prerequisite of M2-type phenotypic macrophage polarization.[106]

<Interaction between mitochondrial biogenesis and inflammation here> In addition to the "re-purposing" of the Krebs cycle to deliver inflammatory intermediates, mitochondrial [illegible] species - potentially indicative of mitochondrial damage - but also increased in inflammation – upregulates anti-inflammatory and mitochondrial repair,/biogenesis programmes leading to increased mitochondrial mass/density in inflammation.[107] Similarly, reactive oxygen species have been shown to be a crucial signalling mediators in exercise training, including, **[Blinherpaper]** and exercise training exercise-induced also upregulates activation of AMPK/PGC-1α signalling, inducing general anabolic pathways as well as mitochondrial biogenesis **add references**.[108,109] Obviously, crucial Essential signaling pathways including the mitogen activated protein kinases (MAPK) extracellular signal-related kinase (ERK)1/2, p38, and c-Jun N-terminal kinases (JNK), the nuclear factor κB and the protein kinase B are employed in inflammation as well as in exercise, with partial overlaps and divergencies. Similar to the severity of inflammation, exercise intensity appears to modulate activation of individual MAPK signalling pathways.[107,110,111]

<Interaction between mitochondrial biogenesis and inflammation here mitochondrial damage versus repurposing of the Krebs cycle, reduced mitochondrial biogenesis> atherosclerosis, have not been charted in detail for their inflammation-resolving and energy metabolism phenotype yet, nor regarding the effect of exercise in their polarization. Similarly, NK cells and various T lymphocyte populations react to acute and chronic exercise and contribute to both, polarization of innate immune cells and functionality of various tissues and organs, including distinct fat depots (perivascular, subcutaneous, visceral).[112]

Both the amount and type of energy substrates provided and physical exercise can affect the phenotype of monocytes and macrophages.[101,113–116] Energy sensors, such as AMP-dependent kinase ,kinase, can be targeted by both diet and exercise. On the way to personalized lifestyle-based therapies, we need to learn more about the integration of exercise parameters (e.g. type, intensity, frequency, volume) with diet (e.g. macronutrient composition, amount and timing of eating/fasting) and pharmacological means to modulate energy metabolism and (thereby) activation state of inflammatory cells in various tissues.[117–121] Of note, activation of the relevant mechanisms might shift between individuals, being influenced by a number of factors such as hormonal status/sex, age, pharmacotherapy and co-morbidities as well as genetic background.[122–124]

- *To summarize, macrophage phenotype shift, leading to reduced release of pro-inflammatory mediators and an increased release of pro-resolving mediators, might well be a nexus of exercise-mediated anti-inflammatory and metabolic cardio-protective effects. The available seminal data, however, requires a better resolution: continuously improved techniques of single-cell immuno-phenotyping[125] and assessment of cellular metabolism[126] allow for the fine-mapping of immune-inflammatory interactions and can be used to develop diagnostic tools, assessing individual response to exercise and personalizing exercise parameters. In addition, better understanding of the cellular and molecular nodes of the immuno-metabolic network might help to optimize exercise parameters on an individual level to improve cardio-*

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vascular and metabolic benefit, potentially in combination with pharmacological and diet-based approaches.

3. Challenges and opportunities in translational CR research methodology

The advent of high-throughput molecular techniques, single-cell diagnostics and organs-on-a-chip have opened countless opportunities in exercise research, but some important challenges have surfaced simultaneously.[127,128] How can we successfully pinpoint important findings within these vast datasets? And if computers can handle increasingly complex tasks, what is the use of animal models in the future?

3.1 Impact of 'big data' and artificial intelligence on translational research in CR

As analytical techniques evolve, new challenges arise with regards to handling the enormous amount of data they generate. This is especially true in the area of genomics, epigenomics, proteomics and metabolomics, but also applies to datasets obtained from large clinical trials or registries, and epidemiological research.[128] These datasets cannot be readily viewed on any computer, which complicates human pattern recognition. Moreover, the analysis of 'big data' requires additional statistical precaution, taking into account the increased 'noise' of high-throughput techniques.[127] Novel 'data mining' techniques have been developed to derive relationships and statistical inference from these datasets, often relying on some form of artificial intelligence. These techniques, grouped under the term 'machine learning', can be either supervised (the user determines the relation between subjects) such as traditional regression analysis, or unsupervised (the computer determines the relation between subjects), such as clustering analysis.[129,130]

Some of these novel techniques have already been applied to translational exercise research. In 2009, Goud et al. set up a cluster-randomized trial in 21 CR centres, comparing effects of a computerized decision support system to standard care.[131] In centres implementing the decision support system, concordance with CR guideline recommendations were modestly increased, reducing both over- and under-treatment. Further efforts have been made with regard to artificial intelligence-based exercise prescription.[132–136] Most of these studies describe a framework to automate exercise prescription based on patient demographics, comorbidities, test results and reason for referral. Randomized clinical trials evaluating ~~these~~ fully computerized exercise prescription are still lacking.

Finally, the vast amount of data obtained from wearable devices opens up possibilities for data-driven personalization strategies. For example, one study succeeded in predicting active energy expenditure (a predictor of ΔVO_2peak) from photo-plethysmographic heart rate measurements, even in patients under beta blocker therapy.[137]

But many more possibilities of 'big data' and machine learning exist in the field of CR, which we will demonstrate at the hand of two examples from other areas within cardiovascular research: imaging and phenotyping.

Imaging is especially suited for the application of machine learning because images contain a rich amount of data both within the image itself and through extraction of quantitative features.[129] Furthermore, powerful computational approaches to handle image data have undergone extensive development within academic clinical research and non-medical fields such as facial recognition and image searching. [138] Combined with recent availability of large imaging datasets,[139] this has meant artificial intelligence approaches to identify images, automatically quantify image features and predict disease from the patterns in the image have developed rapidly within cardiology and radiology.[129] As a result, automated quantification is now entering clinical use, but broader diagnostic application will require robust clinical validation before adoption.[140] Of

particular interest in CR will be to understand whether imaging after ~~cardiac~~cardiovascular events (e.g. echocardiography) contains information of value for prediction of outcome, risk of HF and likelihood of response to exercise interventions.

Another approach of unsupervised machine learning is to find clusters of similar data items: subjects in the same cluster are similar to each other, and dissimilar to subjects in other clusters. This can aid in discovering subtypes of patients with a certain disease. For example, machine learning has been able to identify clusters of patients with HF based on their baseline characteristics and test results (including cardiopulmonary exercise tests).[141–144] Phenotyping through machine learning predicted the prognosis of HF patients, and performed better compared to traditional predictors such as ejection fraction.[143]

A major concern of artificial intelligence is the 'black box' phenomenon. More complex machine learning processes, such as neural networks, build layer upon layer of automated decisions up to a point where it is impossible to retrace the individual steps.[145] Thus, while some neural networks have been proven to outperform humans (for example in image recognition[146]), it is often hard to assess *how* the computer reached its decision or classification. One technique to overcome the 'black box' is to ask the computer to simultaneously create a simpler 'surrogate' model to gain insight in the reasoning process.[147]
Also, while the decision process can be fully automated and intelligent, large datasets still need to be imputed to train machine learning models. Availability of enough training data is currently still an issue, but the increased promotion of open science and data sharing will hopefully provide an answer to this problem soon.[148] For example, several platforms have been set up to share anonimized cardiac imaging data with the goal of promoting its use in machine learning applications.[149]
Finally, a major challenge will be to convert artificial intelligence-derived predictions and recommendations into effective action. Better phenotyping and improved risk stratification do not automatically lead to improve health. To truly achieve a health care transformation, behavioural changes are needed at both patient and physician level.[150] For example, artificial intelligence may improve exercise prescription, but a patient's health will only improve if his or her physician implements this improved prescription in practice, and he or she adheres to the prescribed training.

- *To summarize, early applications in CR research and advanced examples from imaging and phenotyping studies show that the advent of 'big data' and machine learning will likely change current practice. Major challenges include picking up useful signals between increased noise in big datasets, the 'black box' phenomenon, and implementing behavioural changes based on computerized recommendations. We suggest some ~~future research areas~~approaches in **Figure 3**. ~~**Table 2**~~*

3.2 Sense and nonsense of animal models

Appropriate animal models are important to unravel the molecular mechanisms for how exercise-based CR mediates its beneficial effects. Small rodents in particular are attractive models for cardiovascular research, possessing unique properties such as easy handling, short gestation time and low costs. Perhaps most important is the availability of transgenic mice and rats, which allow the possibility to study the involvement of specific molecules in transmitting the positive effect of exercise training, which otherwise would not be possible in humans. Nevertheless, a certain scepticism is warranted based on whether animal models appropriately translate to humans, which has resulted (and rightly so) in the value of such research being questioned.[151–153]

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Table 2
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An ideal disease model should mimic the human condition genetically, experimentally and physiologically. Therefore, using inbred mouse strains may not reflect the response generated in a genetically polymorphic human population, which may be one reason for the failure of many promising preclinical drugs when translated into human clinical trials. In support, a recently published comment stated that >80% of potential therapeutics fail when tested in humans, even after animal studies have provided evidence that the treatment is safe and effective.[154] One future avenue to circumvent such translational problems may reside in the use of humanized models, whereby mice expressing human transgenes or engrafted human cells/tissue are used in preclinical research.[155] Obviously, generating diseased animal models due to genetic defects is much easier than trying to mimic a more complex disease pattern, where several comorbidities contribute to the final clinical phenotype. One contemporary example of such a complex disease is heart failure with preserved ejection fraction (HFpEF). Since the development of HFpEF is driven by several comorbidities, which include hypertension, diabetes, obesity and ageing,[156–158] it remains difficult to define an animal model that appropriately mimics the HFpEF phenotype. As of yet, the animal models used to probe molecular changes occurring in HFpEF and in response to exercise training have been predominantly based on a single risk factor such as aging or hypertension.[72,159,160] More recently this line of research included a more clinically relevant animal model, in a way that HFpEF develops due to the onset of multiple comorbidities that mirror a metabolic syndrome.[73,161–163] Another problem with appropriate animal models may be that most models develop over a short time period, whereas in humans sometimes several years or decades pass before a clear phenotype is established.

Animals used for cardiovascular exercise studies most commonly range from small rodents (e.g. mice, rats) to large animals (e.g. rabbits, canine, goats, sheep, pigs, horses).[164–169] In these animal models exercise can either be voluntary (e.g., animal cage is equipped with a running wheel) or forced (e.g., animal is placed onto a treadmill for a specific period). Many exercise training studies have been employed using a variety of animal models of diseases that include HF,[161,170,171] diabetes,[172,173] and neurodegenerative diseases.[174] Beside the classical animal models (mouse and rat) used to analyse the effect of exercise training on molecular and physiological parameters, more recently other species have been used such as drosophila and zebrafish.[175–178] Exercise training in drosophila results in improvements of physiological and molecular measures, which include enhanced climbing speed, flight performance, aconitase levels, and cardiac contractility. Clearly, while the main advantage of using flies as an animal model is that you can train several thousand flies simultaneously, the question of whether and to what extent these findings translate to humans looms large. We also have to keep in mind that it is even more difficult in animal models to control for activity levels. In human studies most of the patients recruited into an exercise study exhibit a very low exercise level, which is difficult to control for in animals.

- *To summarize, the 'sense' to use animal models to investigate the benefits associated with exercise in disease is difficult to refute: animal studies have often provided the initial clues to help elucidate how exercise exerts its benefits for treating disease. However, animal research can also provide much 'nonsense' when translated to humans. Future studies should therefore continue focusing on developing more complex and robust animal models of disease that closely reflect the human condition.*

4. Conclusion and Outlook

Exercise-based CR has consistently shown positive effects on the course of cardiovascular disease. However, recent studies showed that there is a large variation in training effects at the individual level, with up to one third of patients failing to demonstrate a significant increase in exercise capacity despite adequate compliance. Therefore, in order to improve the effects of exercise-based CR it is crucial to (1) gain more in-

depth knowledge on the determinants and mechanisms governing the response to exercise in the organs - beyond the skeletal muscle, heart and vascular system - and (2) to acknowledge their interaction at a systemic level.

Heritable and non-heritable factors each determine approximately 50% of inter-individual heterogeneity in ΔVO_2peak. High-throughput technologies in combination with improved bio-informatics and bio-statistical approaches can help identify major regulatory nodes among large datasets that cannot be readily interpreted otherwise.

Sex-specific differences in the response to exercise in cardiovascular therapy are severely understudied. Although endocrine, anatomical and molecular differences between men and women are assumed to play a role, the exact mechanisms remain largely unknown. Future research therefore needs to include sufficient numbers of female patients to address these issues.

Based on these studies, a concise, easy-to-use panel of markers that could help personalize exercise parameters could be developed. This panel could include regulatory nodes identified in clusters of patients through their classical risk profile, but also inflammatory and metabolic status, and genetic traits identified through advanced bio-statistics. Finally, while animal models have inherent limitations complicating translation to humans, complex and robust animal models closely reflecting human cardiovascular diseases will be needed to test the hypotheses mentioned and to gain further insight in the complex physiology of exercise-based CR.

~~Abbreviations: EF = ejection fraction, LV = left ventricular~~
~~AI = artificial intelligence, CR = cardiac rehabilitation, SNP = single nucleotide polymorphism~~

Figure Legends

Figure 1: Known factors possibly influencing the response to exercise training. These factors are grouped as cardiac, non-cardiac, external and comorbidities. They possibly influence- baseline VO_2peak and/or ΔVO_2peak, and are themselves determined by genetic, epigenetic, and environmental factors and drugs, nutrition and sex. CKD = chronic kidney disease, COPD = chronic obstructive pulmonary disease, VO_2peak = peak oxygen uptake, ΔVO_2peak = relative change in VO_2peak following exercise training.

Figure 2: Known and unknown interactions between exercise, nutrition and pro-resolving macrophage polarization and function in cardiovascular disease. CVD = cardiovascular disease, DAMP = damage-associated molecular patterns.

Figure 3: Suggested research areas for application of data mining and machine learning in exercise-based CR. Left column: research questions or clinical needs in the area of exercise-based CR in which data mining and machine learning could play a role. Middle column: suggested data sources for machine learning input. Right column: examples and references. AI = artificial intelligence, CR = cardiovascular rehabilitation, SNP = single nucleotide polymorphism

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Conflicts of Interest

The Authors declare that there is no conflict of interest.

Author contributions

All authors contributed to the conception or design of the work, to the acquisition, analysis, or interpretation of data for the work. All authors drafted the manuscript. All authors critically revised the manuscript, gave final approval and agree to be accountable for all aspects of work ensuring integrity and accuracy.

References

1. Anderson L, Oldridge N, Thompson DR, et al. Exercise-Based Cardiac Rehabilitation for Coronary Heart Disease. *J Am Coll Cardiol* 2016; 67: 1–12.
2. Rauch B, Davos CH, Doherty P, et al. The prognostic effect of cardiac rehabilitation in the era of acute revascularisation and statin therapy: A systematic review and meta-analysis of randomized and non-randomized studies – The Cardiac Rehabilitation Outcome Study (CROS). *Eur J Prev Cardiol* 2016; 23: 1914–1939.
3. 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: 2024–35.
4. Harber MP, Kaminsky LA, Arena R, et al. Impact of Cardiorespiratory Fitness on All-Cause and Disease-Specific Mortality: Advances Since 2009. *Prog Cardiovasc Dis* 2017; 60: 11–20.
5. Kränkel N, Bahls M, Van Craenenbroeck EM, et al. Exercise training to reduce cardiovascular risk in patients with metabolic syndrome and type 2 diabetes mellitus: How does it work? *Eur J Prev Cardiol* 2019; 26: 701–708.
6. Kemps H, Kränkel N, Dörr M, et al. Exercise training for patients with type 2 diabetes and cardiovascular disease: What to pursue and how to do it. A Position Paper of the European Association of Preventive Cardiology (EAPC). *Eur J Prev Cardiol* 2019; 26: 709–727.
7. Schuler G, Adams V, Goto Y. Role of exercise in the prevention of cardiovascular disease: results, mechanisms, and new perspectives. *Eur Heart J* 2013; 34: 1790–1799.
8. Lavie CJ, Arena R, Swift DL, et al. Exercise and the cardiovascular system: clinical science and cardiovascular outcomes. *Circ Res* 2015; 117: 207–19.
9. Abreu A, Pesah E, Supervia M, et al. Cardiac rehabilitation availability and delivery in Europe: How does it differ by region and compare with other high-income countries? *Eur J Prev Cardiol* 2019; 26: 1131–1146.
10. Piepoli MF, Hoes AW, Agewall S, et al. 2016 European Guidelines on cardiovascular disease prevention in clinical practice. *Eur Heart J* 2016; 37: 2315–2381.
11. Piepoli MF, Corrà U, Dendale P, et al. Challenges in secondary prevention after acute myocardial infarction: A call for action. *Eur J Prev Cardiol* 2016; 23: 1994–2006.
12. Coeckelberghs E, Buys R, Goetschalckx K, et al. Prognostic value of the oxygen uptake efficiency slope and other exercise variables in patients with coronary artery disease. *Eur J Prev Cardiol* 2016; 23: 237–244.
13. Tabet J-Y, Meurin P, Beauvais F, et al. Absence of Exercise Capacity Improvement After Exercise Training Program. *Circ Heart Fail* 2008; 1: 220–226.
14. De Schutter A, Kachur S, Lavie CJ, et al. Cardiac rehabilitation fitness changes and subsequent survival. *Eur Hear J - Qual Care Clin Outcomes* 2018; 4: 173–179.
15. Vanhees L, Stevens A, Schepers D, et al. Determinants of the effects of physical training and of the complications requiring resuscitation during exercise in patients with cardiovascular disease. *Eur J Cardiovasc Prev Rehabil* 2004; 11: 304–312.
16. Ciani O, Piepoli M, Smart N, et al. Validation of Exercise Capacity as a Surrogate Endpoint in Exercise-Based Rehabilitation for Heart Failure. *JACC Heart Fail* 2018; 6: 596–604.
17. Bouchard C, Rankinen T. Individual differences in response to regular physical activity. *Med Sci Sports Exerc* 2001; 33: S446–S451.

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18. Schmid J-P, Zurek M, Saner H. Chronotropic incompetence predicts impaired response to exercise training in heart failure patients with sinus rhythm. *Eur J Prev Cardiol* 2013; 20: 585–592.

19. Witvrouwen I, Pattyn N, Gevaert AB, et al. Predictors of response to exercise training in patients with coronary artery disease – a subanalysis of the SAINTEX-CAD study. *Eur J Prev Cardiol* 2019; 26: 1158–1163.

20. Corrà U, Agostoni PG, Anker SD, et al. Role of cardiopulmonary exercise testing in clinical stratification in heart failure. A position paper from the Committee on Exercise Physiology and Training of the Heart Failure Association of the European Society of Cardiology. *Eur J Heart Fail* 2018; 20: 3–15.

21. Bouchard C, Rankinen T. Individual differences in response to regular physical activity. *Med Sci Sports Exerc* 2001; 33: S446–S451.

22. Sparks LM. Exercise training response heterogeneity: physiological and molecular insights. *Diabetologia* 2017; 60: 2329–2336.

23. Mann TN, Lamberts RP, Lambert MI. High responders and low responders: Factors associated with individual variation in response to standardized training. *Sport Med* 2014; 44: 1113–1124.

24. Williams CJ, Gurd BJ, Bonafiglia JT, et al. A Multi-Center Comparison of O2peak Trainability Between Interval Training and Moderate Intensity Continuous Training. *Front Physiol* 2019; 10: 1–13.

25. Montero D, Lundby C. Refuting the myth of non-response to exercise training: 'non-responders' do respond to higher dose of training. *J Physiol* 2017; 595: 3377–3387.

26. Kraal JJ, Vromen T, Spee R, et al. The influence of training characteristics on the effect of exercise training in patients with coronary artery disease: Systematic review and meta-regression analysis. *Int J Cardiol* 2017; 245: 52–58.

27. Wilson JR, Groves J, Rayos G. Circulatory Status and Response to Cardiac Rehabilitation in Patients With Heart Failure. *Circulation* 1996; 94: 1567–1572.

28. Gordon A, Tyni-Lenné R, Jansson E, et al. Beneficial effects of exercise training in heart failure patients with low cardiac output response to exercise - a comparison of two training models. *J Intern Med* 1999; 246: 175–82.

29. Schutte NM, Nederend I, Hudziak JJ, et al. Twin-sibling study and meta-analysis on the heritability of maximal oxygen consumption. *Physiol Genomics* 2016; 48: 210–219.

30. Bouchard C, Daw EW, Rice T, et al. Familial resemblance for VO2max in the sedentary state: the HERITAGE family study. *Med Sci Sports Exerc* 1998; 30: 252–8.

31. Bouchard C, An P, Rice T, et al. Familial aggregation of VO2max response to exercise training: results from the HERITAGE Family Study. *J Appl Physiol* 1999; 87: 1003–1008.

32. Bouchard C, Rankinen T, Timmons JA. Genomics and Genetics in the Biology of Adaptation to Exercise. *Compr Physiol* 2011; 1: 1603–48.

33. An P, Rice T, Gagnon J, et al. Familial Aggregation of Stroke Volume and Cardiac Output During Submaximal Exercise: The HERITAGE Family Study. *Int J Sports Med* 2000; 21: 566–572.

34. Skinner JS, Jaskólski A, Jaskólska A, et al. Age, sex, race, initial fitness, and response to training: the HERITAGE Family Study. *J Appl Physiol* 2001; 90: 1770–1776.

35. Bray MS, Hagberg JM, Pérusse L, et al. The human gene map for performance and health-related fitness phenotypes: the 2006-2007 update. *Med Sci Sports Exerc* 2009; 41: 35–73.

36. Kilpeläinen TO, Qi L, Brage S, et al. Physical Activity Attenuates the Influence of FTO Variants on

Obesity Risk: A Meta-Analysis of 218,166 Adults and 19,268 Children. *PLoS Med* 2011; 8: e1001116, 1–14.

37. Timmons JA, Knudsen S, Rankinen T, et al. Using molecular classification to predict gains in maximal aerobic capacity following endurance exercise training in humans. *J Appl Physiol* 2010; 108: 1487–1496.
38. Bouchard C, Sarzynski MA, Rice TK, et al. Genomic predictors of the maximal O2 uptake response to standardized exercise training programs. *J Appl Physiol* 2011; 110: 1160–1170.
39. Hoppeler H. Deciphering VO2max : limits of the genetic approach. *J Exp Biol* 2018; 221: 164327.
40. Rankinen T, Fuku N, Wolfarth B, et al. No Evidence of a Common DNA Variant Profile Specific to World Class Endurance Athletes. *PLoS One* 2016; 11: e0147330.
41. Rönn T, Volkov P, Davegårdh C, et al. A Six Months Exercise Intervention Influences the Genome-wide DNA Methylation Pattern in Human Adipose Tissue. *PLoS Genet* 2013; 9: e1003572.
42. Barrès R, Yan J, Egan B, et al. Acute Exercise Remodels Promoter Methylation in Human Skeletal Muscle. *Cell Metab* 2012; 15: 405–411.
43. Voisin S, Eynon N, Yan X, et al. Exercise training and DNA methylation in humans. *Acta Physiol* 2015; 213: 39–59.
44. Ferrara N, Rinaldi B, Corbi G, et al. Exercise training promotes SIRT1 activity in aged rats. *Rejuvenation Res* 2008; 11: 139–50.
45. Lehmann LH, Jebessa ZH, Kreusser MM, et al. A proteolytic fragment of histone deacetylase 4 protects the heart from failure by regulating the hexosamine biosynthetic pathway. *Nat Med* 2018; 24: 62–72.
46. Song S, Wen Y, Tong H, et al. The HDAC3 enzymatic activity regulates skeletal muscle fuel metabolism. *J Mol Cell Biol* 2019; 11: 133–143.
47. Sapp RM, Shill DD, Roth SM, et al. Circulating microRNAs in acute and chronic exercise: more than mere biomarkers. *J Appl Physiol* 2017; 122: 702–717.
48. Silva GJJ, Bye A, el Azzouzi H, et al. MicroRNAs as Important Regulators of Exercise Adaptation. *Prog Cardiovasc Dis* 2017; 60: 130–151.
49. Souza RWA, Fernandez GJ, Cunha JPQ, et al. Regulation of cardiac microRNAs induced by aerobic exercise training during heart failure. *Am J Physiol Circ Physiol* 2015; 309: H1629–H1641.
50. Taurino C, Miller WH, McBride MW, et al. Gene expression profiling in whole blood of patients with coronary artery disease. *Clin Sci* 2010; 119: 335–343.

Additional References to be supplied with the online supplement:

51. Xu T, Zhou Q, Che L, et al. Circulating miR-21, miR-378, and miR-940 increase in response to an acute exhaustive exercise in chronic heart failure patients. *Oncotarget* 2016; 7: 12414–12425.

52. Van Laethem C, Van De Veire N, De Backer G, et al. Response of the oxygen uptake efficiency slope to exercise training in patients with chronic heart failure. *Eur J Heart Fail* 2007; 9: 625–629.

53. Rakobowchuk M, Harris E, Taylor A, et al. Moderate and heavy metabolic stress interval training improve arterial stiffness and heart rate dynamics in humans. *Eur J Appl Physiol* 2013; 113: 839–849.

54. Alves AJ, Ribeiro F, Goldhammer E, et al. Exercise Training Improves Diastolic Function in Heart Failure Patients. *Med Sci Sports Exerc* 2012; 44: 776–785.

55. Conraads VM, Beckers P, Bosmans J, et al. Combined endurance/resistance training reduces plasma TNF-alpha receptor levels in patients with chronic heart failure and coronary artery disease. *Eur Heart J* 2002; 23: 1854–1860.

56. Sparling PB. A Meta-Analysis of Studies Comparing Maximal Oxygen Uptake in Men and Women. *Res Q Exerc Sport* 1980; 51: 542–552.

57. Piña IL, Bittner V, Clare RM, et al. Effects of Exercise Training on Outcomes in Women With Heart Failure. *JACC Heart Fail* 2014; 2: 180–186.

58. Colbert JD, Martin B-J, Haykowsky MJ, et al. Cardiac rehabilitation referral, attendance and mortality in women. *Eur J Prev Cardiol* 2015; 22: 979–986.

59. Beale AL, Meyer P, Marwick TH, et al. Sex Differences in Cardiovascular Pathophysiology. *Circulation* 2018; 138: 198–205.

60. Regitz-Zagrosek V, Kararigas G. Mechanistic Pathways of Sex Differences in Cardiovascular Disease. *Physiol Rev* 2017; 97: 1–37.

61. Witvrouwen I, Van Craenenbroeck EM, Abreu A, et al. Exercise training in women with cardiovascular disease: Differential response and barriers – review and perspective. *Eur J Prev Cardiol*. Epub ahead of print 19 March 2019. DOI: 10.1177/2047487319838221.

62. Pines A. Hormone therapy and the cardiovascular system. *Maturitas* 2002; 43 Suppl 1: S3-10.

63. Manhem K, Brandin L, Ghanoum B, et al. Acute effects of transdermal estrogen on hemodynamic and vascular reactivity in elderly postmenopausal healthy women. *J Hypertens* 2003; 21: 387–394.

64. Trexler CL, Odell AT, Jeong MY, et al. Transcriptome and Functional Profile of Cardiac Myocytes Is Influenced by Biological Sex. *Circ Cardiovasc Genet* 2017; 10: 001770.

65. Adams V, Reich B, Uhlemann M, et al. Molecular effects of exercise training in patients with cardiovascular disease: focus on skeletal muscle, endothelium, and myocardium. *Am J Physiol Circ Physiol* 2017; 313: H72–H88.

66. Duscha BD, Annex BH, Green HJ, et al. Deconditioning fails to explain peripheral skeletal muscle alterations in men with chronic heart failure. *J Am Coll Cardiol* 2002; 39: 1170–1174.

67. Duscha BD, Annex BH, Keteyian SJ, et al. Differences in skeletal muscle between men and women with chronic heart failure. *J Appl Physiol* 2001; 90: 280–286.

68. Keteyian SJ, Duscha BD, Brawner CA, et al. Differential effects of exercise training in men and women with chronic heart failure. *Am Heart J* 2003; 145: 912–918.

69. Nagai S, Ikeda K, Horie-Inoue K, et al. Estrogen modulates exercise endurance along with mitochondrial uncoupling protein 3 downregulation in skeletal muscle of female mice. *Biochem Biophys Res Commun* 2016; 480: 758–764.

70. Cardinale DA, Larsen FJ, Schiffer TA, et al. Superior Intrinsic Mitochondrial Respiration in Women Than in Men. *Front Physiol* 2018; 9: 1133, 1–12.

71. Kishimoto S, Kajikawa M, Maruhashi T, et al. Endothelial dysfunction and abnormal vascular structure are simultaneously present in patients with heart failure with preserved ejection fraction. *Int J Cardiol* 2017; 231: 181–187.

72. Adams V, Alves M, Fischer T, et al. High-intensity interval training attenuates endothelial dysfunction in a Dahl salt-sensitive rat model of heart failure with preserved ejection fraction. *J Appl Physiol* 2015; 119: 745–752.

73. Schmederer Z, Rolim N, Bowen TS, et al. Endothelial function is disturbed in a hypertensive diabetic animal model of HFpEF: Moderate continuous vs. high intensity interval training. *Int J Cardiol* 2018; 273: 147–154.

74. Tarnopolsky MA. Sex Differences in Exercise Metabolism and the Role of 17-Beta Estradiol. *Med Sci Sport Exerc* 2008; 40: 648–654.

75. Sumner J, Harrison A, Doherty P. The effectiveness of modern cardiac rehabilitation: A systematic review of recent observational studies in non-attenders versus attenders. *PLoS One* 2017; 12: e0177658, 1–14.

76. Minges KE, Strait KM, Owen N, et al. Gender differences in physical activity following acute myocardial infarction in adults: A prospective, observational study. *Eur J Prev Cardiol* 2017; 24: 192–203.

77. Oosenbrug E, Marinho RP, Zhang J, et al. Sex Differences in Cardiac Rehabilitation Adherence: A Meta-analysis. *Can J Cardiol* 2016; 32: 1316–1324.

78. Feola M, Garnero S, Daniele B, et al. Gender differences in the efficacy of cardiovascular rehabilitation in patients after cardiac surgery procedures. *J Geriatr Cardiol* 2015; 12: 575–9.

79. Anjo D, Santos M, Rodrigues P, et al. The benefits of cardiac rehabilitation in coronary heart disease: A gender issue? *Rev Port Cardiol (Engl Ed)* 2014; 33: 79–87.

80. Long L, Mordi IR, Bridges C, et al. Exercise-based cardiac rehabilitation for adults with heart failure. *Cochrane Database Syst Rev* 2019; 2019: CD003331.

81. Anderson L, Thompson DR, Oldridge N, et al. Exercise-based cardiac rehabilitation for coronary heart disease. *Cochrane Database Syst Rev* 2016; 2016: CD001800.

82. Ross R. Atherosclerosis — An Inflammatory Disease. *N Engl J Med* 1999; 340: 115–126.

83. Leal LG, Lopes MA, Batista ML. Physical Exercise-Induced Myokines and Muscle-Adipose Tissue Crosstalk: A Review of Current Knowledge and the Implications for Health and Metabolic Diseases. *Front Physiol* 2018; 9: 1307, 1–17.

84. Serhan CN. Pro-resolving lipid mediators are leads for resolution physiology. *Nature* 2014; 510: 92–101.

85. Fredman G, Tabas I. Boosting Inflammation Resolution in Atherosclerosis. *Am J Pathol* 2017; 187: 1211–1221.

86. Ridker PM. Anti-inflammatory therapy for atherosclerosis: interpreting divergent results from the CANTOS and CIRT clinical trials. *J Intern Med* 2019; 285: 503–509.

87. Ridker PM, Everett BM, Thuren T, et al. Antiinflammatory Therapy with Canakinumab for Atherosclerotic Disease. *N Engl J Med* 2017; 377: 1119–1131.

88. Durrer C, Francois M, Neudorf H, et al. Acute high-intensity interval exercise reduces human monocyte Toll-like receptor 2 expression in type 2 diabetes. *Am J Physiol Integr Comp Physiol* 2017; 312: R529–R538.

89. McKenzie AI, Briggs RA, Barrows KM, et al. A pilot study examining the impact of exercise training on skeletal muscle genes related to the TLR signaling pathway in older adults following hip fracture recovery. *J Appl Physiol* 2017; 122: 68–75.

90. Rada I, Deldicque L, Francaux M, et al. Toll like receptor expression induced by exercise in obesity and metabolic syndrome: A systematic review. *Exerc Immunol Rev* 2018; 24: 60–71.

91. Bhatt DL, Steg PG, Miller M, et al. Cardiovascular Risk Reduction with Icosapent Ethyl for Hypertriglyceridemia. *N Engl J Med* 2019; 380: 11–22.

92. Berrueta L, Muskaj I, Olenich S, et al. Stretching Impacts Inflammation Resolution in Connective Tissue. *J Cell Physiol* 2016; 231: 1621–1627.

93. Gangemi S, Luciotti G, D'Urbano E, et al. Physical exercise increases urinary excretion of lipoxin A 4 and related compounds. *J Appl Physiol* 2003; 94: 2237–2240.

94. Markworth JF, Vella L, Lingard BS, et al. Human inflammatory and resolving lipid mediator responses to resistance exercise and ibuprofen treatment. *Am J Physiol Integr Comp Physiol* 2013; 305: R1281–R1296.

95. Ruffino JS, Davies NA, Morris K, et al. Moderate-intensity exercise alters markers of alternative activation in circulating monocytes in females: a putative role for PPARγ. *Eur J Appl Physiol* 2016; 116: 1671–1682.

96. Dalli J, Serhan C. Macrophage Proresolving Mediators-the When and Where. *Microbiol Spectr* 2016; 4: 1–17.

97. Vander Heiden MG, Cantley LC, Thompson CB. Understanding the Warburg Effect: The Metabolic Requirements of Cell Proliferation. *Science* 2009; 324: 1029–1033.

98. Akins NS, Nielson TC, Le H V. Inhibition of Glycolysis and Glutaminolysis: An Emerging Drug Discovery Approach to Combat Cancer. *Curr Top Med Chem* 2018; 18: 494–504.

99. Board M, Humm S, Newsholme EA. Maximum activities of key enzymes of glycolysis, glutaminolysis, pentose phosphate pathway and tricarboxylic acid cycle in normal, neoplastic and suppressed cells. *Biochem J* 1990; 265: 503–9.

100. Allison KE, Coomber BL, Bridle BW. Metabolic reprogramming in the tumour microenvironment: a hallmark shared by cancer cells and T lymphocytes. *Immunology* 2017; 152: 175–184.

101. Bustos R, Sobrino F. Stimulation of glycolysis as an activation signal in rat peritoneal macrophages. Effect of glucocorticoids on this process. *Biochem J* 1992; 282 (Pt 1): 299–303.

102. Mills EL, O'Neill LA. Reprogramming mitochondrial metabolism in macrophages as an anti-inflammatory signal. *Eur J Immunol* 2016; 46: 13–21.

103. Jha AK, Huang SC-C, Sergushichev A, et al. Network Integration of Parallel Metabolic and Transcriptional Data Reveals Metabolic Modules that Regulate Macrophage Polarization. *Immunity* 2015; 42: 419–430.

104. El Kasmi KC, Stenmark KR. Contribution of metabolic reprogramming to macrophage plasticity and function. *Semin Immunol* 2015; 27: 267–275.

105. Rodriguez-Prados J-C, Traves PG, Cuenca J, et al. Substrate Fate in Activated Macrophages: A Comparison between Innate, Classic, and Alternative Activation. *J Immunol* 2010; 185: 605–614.

106. Vats D, Mukundan L, Odegaard JI, et al. Oxidative metabolism and PGC-1β attenuate macrophage-mediated inflammation. *Cell Metab* 2006; 4: 13–24.

107. Cherry AD, Piantadosi CA. Regulation of mitochondrial biogenesis and its intersection with inflammatory responses. *Antioxid Redox Signal* 2015; 22: 965–76.

108. Ristow M, Zarse K, Oberbach A, et al. Antioxidants prevent health-promoting effects of physical exercise in humans. *Proc Natl Acad Sci U S A* 2009; 106: 8665–70.

109. Thirupathi A, de Souza CT. Multi-regulatory network of ROS: the interconnection of ROS, PGC-1 alpha, and AMPK-SIRT1 during exercise. *J Physiol Biochem* 2017; 73: 487–494.

110. Galpin AJ, Fry AC, Chiu LZF, et al. High-power resistance exercise induces MAPK phosphorylation in weightlifting trained men. *Appl Physiol Nutr Metab* 2012; 37: 80–7.

111. Da Silva ASR, Pauli JR, Ropelle ER, et al. Exercise intensity, inflammatory signaling, and insulin resistance in obese rats. *Med Sci Sports Exerc* 2010; 42: 2180–8.

112. Antoniades C, Kotanidis CP, Berman DS. State-of-the-art review article. Atherosclerosis affecting fat: What can we learn by imaging perivascular adipose tissue? *J Cardiovasc Comput Tomogr*. Epub ahead of print March 2019. DOI: 10.1016/j.jcct.2019.03.006.

113. Kawanishi N, Yano H, Yokogawa Y, et al. Exercise training inhibits inflammation in adipose tissue via both suppression of macrophage infiltration and acceleration of phenotypic switching from M1 to M2 macrophages in high-fat-diet-induced obese mice. *Exerc Immunol Rev* 2010; 16: 105–18.

114. Oliveira AG, Araujo TG, Carvalho BM, et al. Acute exercise induces a phenotypic switch in adipose tissue macrophage polarization in diet-induced obese rats. *Obesity* 2013; 21: 2545–2556.

115. Walton RG, Kosmac K, Mula J, et al. Human skeletal muscle macrophages increase following cycle training and are associated with adaptations that may facilitate growth. *Sci Rep* 2019; 9: 969, 1–14.

116. Gao D, Bailey CJ, Griffiths HR. Metabolic memory effect of the saturated fatty acid, palmitate, in monocytes. *Biochem Biophys Res Commun* 2009; 388: 278–282.

117. Jing Y, Wu F, Li D, et al. Metformin improves obesity-associated inflammation by altering macrophages polarization. *Mol Cell Endocrinol* 2018; 461: 256–264.

118. Wang J, Ma A, Zhao M, et al. AMPK activation reduces the number of atheromata macrophages in ApoE deficient mice. *Atherosclerosis* 2017; 258: 97–107.

119. Börgeson E, Wallenius V, Syed GH, et al. AICAR ameliorates high-fat diet-associated pathophysiology in mouse and ex vivo models, independent of adiponectin. *Diabetologia* 2017; 60: 729–739.

120. Jose C, Hébert-Chatelain E, Bellance N, et al. AICAR inhibits cancer cell growth and triggers cell-type distinct effects on OXPHOS biogenesis, oxidative stress and Akt activation. *Biochim Biophys Acta - Bioenerg* 2011; 1807: 707–718.

121. Eleftheriadis T, Pissas G, Liakopoulos V, et al. IDO decreases glycolysis and glutaminolysis by activating GCN2K, while it increases fatty acid oxidation by activating AhR, thus preserving CD4+ T-cell survival and proliferation. *Int J Mol Med* 2018; 42: 557–568.

122. Bae S, Lee MJ, Mun SH, et al. MYC-dependent oxidative metabolism regulates osteoclastogenesis via nuclear receptor ERRα. *J Clin Invest* 2017; 127: 2555–2568.

123. Matlib MA. Action of bepridil, a new calcium channel blocker on oxidative phosphorylation, oligomycin-sensitive adenosine triphosphatase activity, swelling, Ca++ uptake and Na+-induced

Ca++ release processes of rabbit heart mitochondria in vitro. *J Pharmacol Exp Ther* 1985; 233: 376–81.

124. Han F, Li G, Dai S, et al. Genome-wide metabolic model to improve understanding of CD4 + T cell metabolism, immunometabolism and application in drug design. *Mol Biosyst* 2016; 12: 431–443.

125. Mei HE, Leipold MD, Schulz AR, et al. Barcoding of Live Human Peripheral Blood Mononuclear Cells for Multiplexed Mass Cytometry. *J Immunol* 2015; 194: 2022–2031.

126. Van den Bossche J, Baardman J, de Winther MPJ. Metabolic Characterization of Polarized M1 and M2 Bone Marrow-derived Macrophages Using Real-time Extracellular Flux Analysis. *J Vis Exp* 2015; 2015: e53424, 1–7.

127. Johnson KW, Torres Soto J, Glicksberg BS, et al. Artificial Intelligence in Cardiology. *J Am Coll Cardiol* 2018; 71: 2668–2679.

128. Topol EJ. High-performance medicine: the convergence of human and artificial intelligence. *Nat Med* 2019; 25: 44–56.

129. Dey D, Slomka PJ, Leeson P, et al. Artificial Intelligence in Cardiovascular Imaging. *J Am Coll Cardiol* 2019; 73: 1317–1335.

130. Krittanawong C, Zhang H, Wang Z, et al. Artificial Intelligence in Precision Cardiovascular Medicine. *J Am Coll Cardiol* 2017; 69: 2657–2664.

131. Goud R, de Keizer NF, ter Riet G, et al. Effect of guideline based computerised decision support on decision making of multidisciplinary teams: cluster randomised trial in cardiac rehabilitation. *BMJ* 2009; 338: b1440–b1440.

132. Kostopoulos K, Chouvarda I, Koutkias V, et al. An ontology-based framework aiming to support personalized exercise prescription: Application in cardiac rehabilitation. In: *2011 Annual International Conference of the IEEE Engineering in Medicine and Biology Society*. 30 Aug-3 Sep 2011, Boston, MA, USA: IEEE, pp. 1567–1570.

133. Lofaro D, Groccia MC, Guido R, et al. Machine learning approaches for supporting patient-specific cardiac rehabilitation programs. In: *2016 Computing in Cardiology Conference*. 11-14 Sep 2016, Vancouver, BC, Canada: IEEE, p. 7868701.

134. Lo C-L, Tseng H-T. Predicting rehabilitation treatment helpfulness to stroke patients: A supervised learning approach. *Artif Intell Res* 2017; 6: 1–9.

135. Hansen D, Dendale P, Coninx K, et al. The European Association of Preventive Cardiology Exercise Prescription in Everyday Practice and Rehabilitative Training (EXPERT) tool: A digital training and decision support system for optimized exercise prescription in cardiovascular disease. *Eur J Prev Cardiol* 2017; 24: 1017–1031.

136. Hansen D, Coninx K, Dendale P. The EAPC EXPERT tool. *Eur Heart J* 2017; 38: 2318–2320.

137. Bonomi AG, Goldenberg S, Papini G, et al. Predicting energy expenditure from photo-plethysmographic measurements of heart rate under beta blocker therapy: Data driven personalization strategies based on mixed models. In: *2015 37th Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBC)*. 25-29 Aug 2015, Milan, Italy: IEEE, pp. 7642–7646.

138. Lewandowski AJ, Augustine D, Lamata P, et al. Preterm Heart in Adult Life. *Circulation* 2013; 127: 197–206.

139. Coffey S, Lewandowski AJ, Garratt S, et al. Protocol and quality assurance for carotid imaging in 100,000 participants of UK Biobank: development and assessment. *Eur J Prev Cardiol* 2017; 24: 1799–1806.

140. Alsharqi M, Woodward WJ, Mumith JA, et al. Artificial intelligence and echocardiography. *Echo Res Pract* 2018; R115–R125.

141. Tromp J, Tay WT, Ouwerkerk W, et al. Multimorbidity in patients with heart failure from 11 Asian regions: A prospective cohort study using the ASIAN-HF registry. *PLoS Med* 2018; 15: e1002541, 1–22.

142. Shah SJ, Katz DH, Selvaraj S, et al. Phenomapping for Novel Classification of Heart Failure With Preserved Ejection Fraction. *Circulation* 2015; 131: 269–279.

143. Ahmad T, Lund LH, Rao P, et al. Machine learning methods improve prognostication, identify clinically distinct phenotypes, and detect heterogeneity in response to therapy in a large cohort of heart failure patients. *J Am Heart Assoc* 2018; 7: 1–15.

144. Kao DP, Lewsey JD, Anand IS, et al. Characterization of subgroups of heart failure patients with preserved ejection fraction with possible implications for prognosis and treatment response. *Eur J Heart Fail* 2015; 17: 925–935.

145. Castelvecchi D. Can we open the black box of AI? *Nature* 2016; 538: 20–23.

146. He K, Zhang X, Ren S, et al. Delving Deep into Rectifiers: Surpassing Human-Level Performance on ImageNet Classification. In: *2015 IEEE International Conference on Computer Vision (ICCV)*. 7-13 Dec 2015, Santiago, Chile: IEEE, pp. 1026–1034.

147. Haro Alonso D, Wernick MN, Yang Y, et al. Prediction of cardiac death after adenosine myocardial perfusion SPECT based on machine learning. *J Nucl Cardiol*. Epub ahead of print 14 March 2018. DOI: 10.1007/s12350-018-1250-7.

148. Krumholz HM. Open Science and Data Sharing in Clinical Research. *Circ Cardiovasc Qual Outcomes* 2012; 5: 141–142.

149. Suinesiaputra A, Medrano-Gracia P, Cowan BR, et al. Big Heart Data: Advancing Health Informatics Through Data Sharing in Cardiovascular Imaging. *IEEE J Biomed Heal Informatics* 2015; 19: 1283–1290.

150. Emanuel EJ, Wachter RM. Artificial Intelligence in Health Care. *JAMA* 2019; 321: 2281.

151. Buffenstein R, Nelson OL, Corbit KC. Questioning the preclinical paradigm: natural, extreme biology as an alternative discovery platform. *Aging (Albany NY)* 2014; 6: 913–920.

152. Pound P, Bracken MB. Is animal research sufficiently evidence based to be a cornerstone of biomedical research? *BMJ* 2014; 348: g3387–g3387.

153. Young NS. Mouse Medicine and Human Biology. *Semin Hematol* 2013; 50: 88–91.

154. Perrin S. Preclinical research: Make mouse studies work. *Nature* 2014; 507: 423–425.

155. Walsh NC, Kenney LL, Jangalwe S, et al. Humanized Mouse Models of Clinical Disease. *Annu Rev Pathol Mech Dis* 2017; 12: 187–215.

156. Juillière Y, Venner C, Filippetti L, et al. Heart failure with preserved ejection fraction: A systemic disease linked to multiple comorbidities, targeting new therapeutic options. *Arch Cardiovasc Dis* 2018; 111: 766–781.

157. Gevaert AB, Lemmens K, Vrints CJ, et al. Targeting Endothelial Function to Treat Heart Failure with Preserved Ejection Fraction: The Promise of Exercise Training. *Oxid Med Cell Longev* 2017; 4865756, 1–17.

158. Gevaert AB, Boen JRA, Segers VF, et al. Heart Failure With Preserved Ejection Fraction: A Review of Cardiac and Noncardiac Pathophysiology. *Front Physiol* 2019; 10: 638, 1–14.

159. Gevaert AB, Shakeri H, Leloup AJ, et al. Endothelial Senescence Contributes to Heart Failure

With Preserved Ejection Fraction in an Aging Mouse Model. *Circ Heart Fail* 2017; 10: e003806, 1–10.

160. Bowen TS, Rolim NPL, Fischer T, et al. Heart failure with preserved ejection fraction induces molecular, mitochondrial, histological, and functional alterations in rat respiratory and limb skeletal muscle. *Eur J Heart Fail* 2015; 17: 263–272.

161. Bowen TS, Herz C, Rolim NPL, et al. Effects of Endurance Training on Detrimental Structural, Cellular, and Functional Alterations in Skeletal Muscles of Heart Failure With Preserved Ejection Fraction. *J Card Fail* 2018; 24: 603–613.

162. Bowen TS, Brauer D, Rolim NPL, et al. Exercise Training Reveals Inflexibility of the Diaphragm in an Animal Model of Patients With Obesity-Driven Heart Failure With a Preserved Ejection Fraction. *J Am Heart Assoc* 2017; 6: e006416, 1–16.

163. Bode D, Guthof T, Pieske BM, et al. Isolation of Atrial Cardiomyocytes from a Rat Model of Metabolic Syndrome-related Heart Failure with Preserved Ejection Fraction. *J Vis Exp* 2018; 57953.

164. Billman GE. A comprehensive review and analysis of 25 years of data from an in vivo canine model of sudden cardiac death: Implications for future anti-arrhythmic drug development. *Pharmacol Ther* 2006; 111: 808–835.

165. Høydal MA, Wisløff U, Kemi OJ, et al. Running speed and maximal oxygen uptake in rats and mice: practical implications for exercise training. *Eur J Cardiovasc Prev Rehabil* 2007; 14: 753–760.

166. Delp MD, Armstrong RB, Godfrey DA, et al. Exercise increases blood flow to locomotor, vestibular, cardiorespiratory and visual regions of the brain in miniature swine. *J Physiol* 2001; 533: 849–859.

167. Janssen PM, Zeitz O, Keweloh B, et al. Influence of cyclosporine A on contractile function, calcium handling, and energetics in isolated human and rabbit myocardium. *Cardiovasc Res* 2000; 47: 99–107.

168. Barron BA, Laughlin MH, Gwirtz PA. Exercise effect on canine and miniswine cardiac catecholamines and enkephalins. *Med Sci Sport Exerc* 1997; 29: 1338–1343.

169. Verboven M, Cuypers A, Deluyker D, et al. High intensity training improves cardiac function in healthy rats. *Sci Rep* 2019; 9: 5612, 1–8.

170. Seiler M, Bowen TS, Rolim N, et al. Skeletal Muscle Alterations Are Exacerbated in Heart Failure With Reduced Compared With Preserved Ejection Fraction. *Circ Heart Fail* 2016; 9: e003027, 1–10.

171. Vujic A, Lerchenmüller C, Wu T-D, et al. Exercise induces new cardiomyocyte generation in the adult mammalian heart. *Nat Commun* 2018; 9: 1659, 1–9.

172. Liu H-W, Chang S-J. Moderate Exercise Suppresses NF-κB Signaling and Activates the SIRT1-AMPK-PGC1α Axis to Attenuate Muscle Loss in Diabetic db/db Mice. *Front Physiol* 2018; 9: 636, 1–9.

173. Chavanelle V, Boisseau N, Otero YF, et al. Effects of high-intensity interval training and moderate-intensity continuous training on glycaemic control and skeletal muscle mitochondrial function in db/db mice. *Sci Rep* 2017; 7: 204, 1–10.

174. Jahangiri Z, Gholamnezhad Z, Hosseini M. Neuroprotective effects of exercise in rodent models of memory deficit and Alzheimer's. *Metab Brain Dis* 2019; 34: 21–37.

175. Sujkowski A, Wessells R. Using Drosophila to Understand Biochemical and Behavioral Responses to Exercise. *Exerc Sport Sci Rev* 2018; 46: 1.

176. Gilbert MJH, Zerulla TC, Tierney KB. Zebrafish (Danio rerio) as a model for the study of aging and exercise: Physical ability and trainability decrease with age. *Exp Gerontol* 2014; 50: 106–113.

177. Boskovic S, Marín-Juez R, Jasnic J, et al. Characterization of zebrafish (Danio rerio) muscle ankyrin repeat proteins reveals their conserved response to endurance exercise. *PLoS One* 2018; 13: e0204312, 1–21.

178. van der Meulen T, Schipper H, van den Boogaart JGM, et al. Endurance exercise differentially stimulates heart and axial muscle development in zebrafish (Danio rerio). *Am J Physiol Integr Comp Physiol* 2006; 291: R1040–R1048.