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Towards a personalised 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

Andreas B Gevaert[1,2,3], Volker Adams[4], Martin Bahls[5,6], T Scott Bowen[7], Veronique Cornelissen[8], Marcus Dörr[5,6], Dominique Hansen[3,9], Hareld MC Kemps[10], Paul Leeson[11], Emeline M Van Craenenbroeck[1,2] and Nicolle Kränkel[12,13]

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. Personalised exercise prescription can help patients in achieving their individual greatest benefit from an exercise-based cardiovascular rehabilitation programme. Yet, we still struggle to provide truly personalised 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 recognisable, 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 cardiovascular rehabilitation.

Keywords

Cardiovascular rehabilitation, exercise, personalised medicine, responders/non-responders, immune system, machine learning, big data, animal models

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[1]GENCOR Department, University of Antwerp, Belgium
[2]Department of Cardiology, Antwerp University Hospital (UZA), Belgium
[3]Heart Centre Hasselt, Jessa Hospital, Belgium
[4]Department of Molecular and Experimental Cardiology, TU Dresden, Germany
[5]Department of Internal Medicine B, University of Greifswald, Germany
[6]German Centre for Cardiovascular Research (DZHK), partner site Greifswald, Germany
[7]School of Biomedical Sciences, University of Leeds, UK
[8]Department of Rehabilitation Sciences, KULeuven, Belgium
[9]Faculty of Rehabilitation Sciences, Hasselt University, Belgium
[10]Fitheid, Leefstijl, Ontwikkeling en Wetenschap (FLOW), Máxima Medical Centre, The Netherlands
[11]Oxford Cardiovascular Clinical Research Facility, University of Oxford, UK
[12]Department of Cardiology, Charité Universitätsmedizin, Germany
[13]German Centre for Cardiovascular Research (DZHK), partner site Berlin, Germany

Corresponding author:
Nicolle Kränkel, Charité-Universitätsmedizin Berlin, Campus Benjamin Franklin, Department of Cardiology, Hindenburgdamm 30, 12203 Berlin, Germany.
Email: nicolle.kraenkel@charite.de

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 has 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 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 this, 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.

Future targets and open questions in translational CR research

While exercise-based intervention programmes are recommended in cardiovascular prevention,[10,11] exercise parameters – type, intensity, duration, frequency – may differentially affect cardio-vascular and metabolic endpoints.[12] In addition, inter-individual differences in the response to different types or intensities exist and may explain why some studies describe comparable effects achieved with different exercise modalities.[13,14] Thus, in addition to improving implementation, the personalization of exercise interventions 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 needs of the patient, based on their underlying morbidities and risk profile.

Which factors contribute to the large variability in individual response to CR?

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.[15–17] Even small increments in VO_2peak result in a 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,[18,19] 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 programmes.[17,20,21] 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 with 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 $\pm 6\%$).[21–23] 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 summarised in Figure 1. We introduce some of the most important contributing factors below. Interested readers are referred to existing reviews for in-depth discussion of mechanisms of non-response.[24–26]

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.[27] 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.[28] Yet, the evidence regarding the additional beneficial effects of higher exercise intensities is still conflicting.[29] Total energy expenditure may be more relevant for

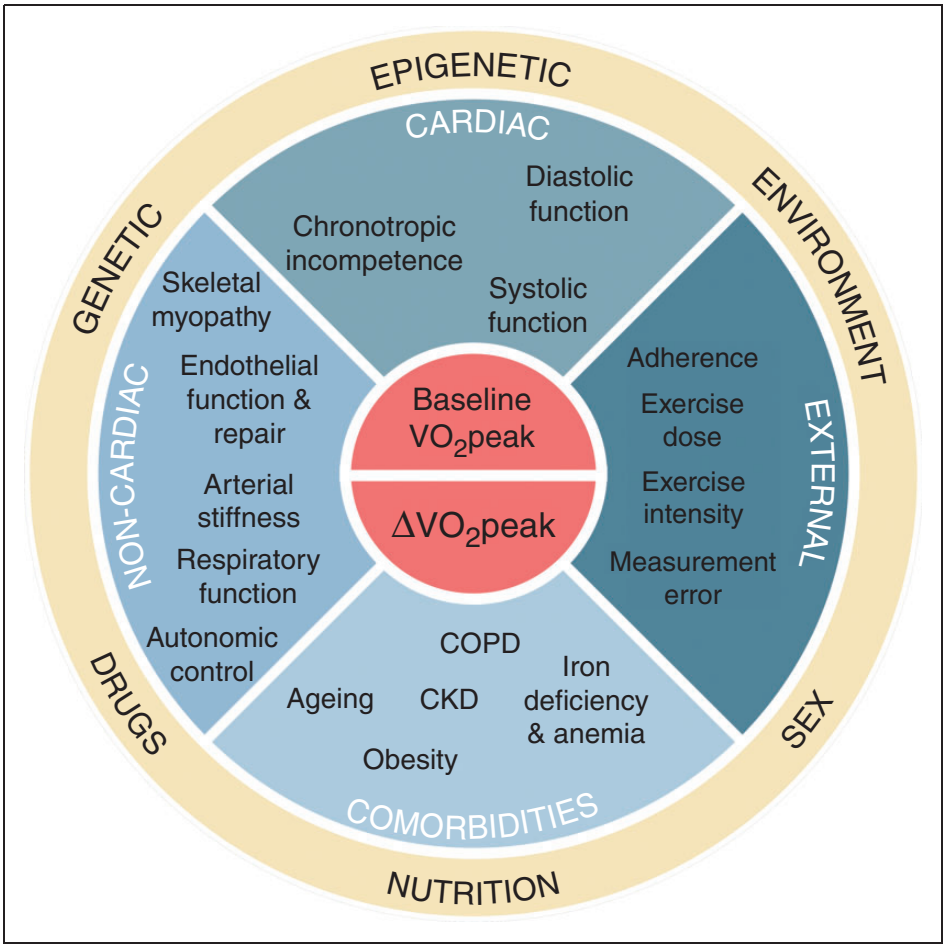

Figure 1. Known factors possibly influencing the response to exercise training. These factors are grouped as cardiac, non-cardiac, external and comorbidities. They possibly influence baseline peak oxygen uptake (VO_2peak) and/or relative change in VO_2peak following exercise training (ΔVO_2peak), and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

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 programmes (Figure 2).

It still remains to be elucidated which phenotypic and genotypic characteristics predict the response of a patient to these specific exercise interventions.[26] Previous studies have 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.[18,20,22,27] Moreover, an additional physiological factor that may influence ΔVO_2peak in patients with chronic heart failure (HF) is the circulatory response to acute exercise.[30,31] 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.[32,33] 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).[34] Heritability of training-induced changes in haemodynamic response and skeletal muscle characteristics are also relatively high.[35,36] Most importantly, the heritability of ΔVO_2peak was independent of baseline VO_2peak.[37] 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.[38] However, as data was mainly derived from underpowered sample sizes, this study did

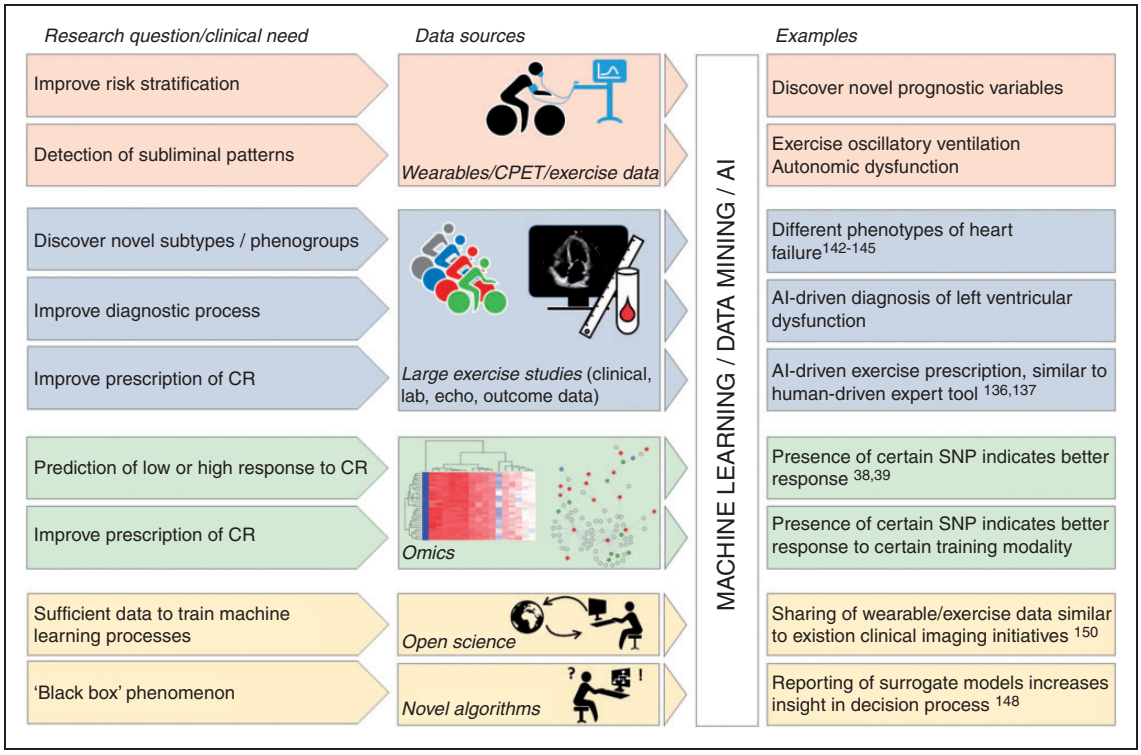

Figure 2. Suggested research areas for application of data mining and machine learning in exercise-based cardiovascular rehabilitation (CR). Left column: research questions or clinical needs in the area of exercise-based CR in which data mining and machine learning could play a role. Middle column: suggested data sources for machine learning input. Right column: examples and references. AI: artificial intelligence; SNP: single nucleotide polymorphism; CPET: cardiopulmonary exercise test.

not provide compelling evidence that DNA sequence variants in a given gene are associated with human variation in fitness and performance traits.[38] 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.[39]

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.[40] 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.[41] Unfortunately, there was no overlap between the genes identified by Timmons et al. and those reported by Bouchard et al.[42] 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.[43] 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.

Epigenetic 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.

Both, acute bouts of exercise and repeated training influence promoter DNA methylation.[44–46] Acute exercise-induced expression of key signalling pathways, including adenosine monophosphate (AMP)-dependent kinase (AMPK)/ Peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α), was paired with a hypomethylation of the respective promoter sequence.[45] 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.[45]

Deacetylation of histones and other proteins by sirtuins, is known to mediate adaptation to repeated exercise.[47] Lehmann et al. demonstrated that histone deacetylase 4 may be responsible for enabling or preventing heart failure depending on which metabolic pathway is switched on when the heart is put under stress.[48] In addition, histone deacetylase 3 plays a

major role in skeletal muscle by regulating fuel metabolism.[49] These findings are especially interesting with regards to insulin resistance in patients with metabolic syndrome. Whether or not pharmaceutical interventions targeting histone deacetylases add an additive effect to exercise-based CR alone, remains to be determined.

Finally, microRNAs are released into the circulation after acute exercise, and exercise training induces long-term changes in their expression.[50,51] In a rat model of HF, Souza et al. identified a set of 14 cardiac microRNAs of which expression was influenced by exercise training.[52] Other studies have identified additional exercise-responsive microRNAs in animal models of different cardiovascular diseases.[51] To date, only two small studies have assessed the effect of exercise training on microRNA expression in human patients with established cardiovascular disease.[53,54] 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 down-regulation of their gene targets.[53] Xu et al. identified three microRNA dysregulated by acute exercise in HF patients, but a clear correlation with VO_2peak was not found.[54]

None of these epigenetic mechanisms has yet been linked to ΔVO_2peak. Exercise epigenetics is a highly active research area, and more extensive studies, including larger numbers of patients, are still needed before reliable conclusions can be drawn.

For most studies, improvement of VO_2peak is the main target parameter of an exercise intervention. Yet, depending on the clinical need of the patient and based on their underlying morbidities and risk profile, other parameters such as improved submaximal exercise parameters, increased cardiac function, better glucose handling, reduced inflammation or improved vascular stiffness should be considered.[5,55–58] Of note, target parameters of the exercise intervention might even change over time in each patient.

- To summarise, 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.[15–17] 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 randomised 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.

The potential role of sex differences in response to CR

In general, VO_2peak is ~15% lower in women compared to men.[59] Intriguingly, however, women seem to experience better clinical outcomes following exercise training, despite similar improvements in exercise capacity.[60,61] While sex-specific effects thus likely play a key role in the clinical benefits associated with exercise interventions, the mechanisms responsible for these benefits are not completely understood.

Cardiovascular physiology as well as pathophysiology are markedly different between men and women, as has recently been reviewed in depth.[62–64]

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.[65] The vasodilating properties of oestrogen may play a role.[66] Also, RNA sequencing in cardiomyocytes revealed more than 600 genes with sexually dimorphic expression patterns.[67] 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).[63]

Thus, in addition to the obvious endocrine differences between men and women, a variety of anatomical, genetic and molecular differences exist within the heart. These may influence not just cardiovascular disease progression, but also affect secondary prevention strategies.[64]

While central haemodynamic differences likely explain some of the sex-specific effects in response to CR,[64] other factors are also involved. It is well established that 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.[68] 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.[69,70] 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.[71] 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.[60] 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, [72,73] 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.[74] Yet, little data is available to clearly demonstrate whether any sex-specific alterations are present following CR in patients.[64] Recent evidence from animal 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.[75,76] Whether these molecular benefits are paralleled in male and female patients with HF remains unclear. Furthermore, sex-specific substrate utilization 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.[77]

While CR programmes 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.[78] In large meta-analyses and randomised controlled trials, the amount of women recruited was 11–28%.[64] Given that women are also ~40 % less likely to enrol in CR and have a significantly lower adherence to the interventions compared to men,[79,80] the need to better understand sex-specific mechanisms in response to exercise training will initially 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.[60,81,82] 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).[83,84] 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 summarise, 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 men and women into a larger perspective, novel 'omics' techniques, which enable a systems biology approach, should be used to determine which differences contribute to the response to exercise-based CR.

Immune-metabolism interactions and inflammation

Both enhanced activation and impaired resolution of inflammation are major underlying principles of cardiovascular and metabolic pathologies.[85] Regular exercise training has been shown to lower systemic and vascular inflammatory load within a few weeks.[58] This has been partly attributed to active secretion of anti-inflammatory myokines from skeletal muscle.[86] 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. Those initial in vitro data have not yet been translated into therapeutic strategies. Unanswered questions include to what extent immuno-metabolic observations made in mouse macrophages can be translated to the human, and to what 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 two mechanisms: the decay of pro-inflammatory signals and the active production of pro-resolving factors.[87] The inability to resolve an

ongoing inflammatory process is a hallmark of inflammatory degenerative diseases, including atherosclerosis.[88] On the one hand, innate immune-activating signals – ligands of pattern-recognition receptors, such as modified lipids – do not disappear in atherosclerosis, as 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.[89,90] 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.[89,90] 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.[88]

A number of studies support the ability of exercise – ranging from a single session of high-intensity interval exercise to a three-month multicomponent exercise programme – to reduce cellular responsiveness to toll-like receptor-mediated signalling, induced by damage-associated molecular patterns.[91–93]

Dietary interventions targeting synthesis of specialised resolving mediators (SPMs) 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.[94] 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.[95–97] 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.[95,97,98] M2-like macrophages are better suited to perform efferocytosis than the M1-like phenotype and it is during efferocytosis that SPMs are released.[99] 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 3).

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.[100–102] In a similar manner, glycolysis is preferred by activated and proliferating myeloid and lymphoid cells[103] and stimulating glycolysis can activate macrophages.[104] 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.[105–107] In contrast, 'alternative' M2-like macrophages favour oxidative phosphorylation and fatty acid oxidation.[108,109] Indeed, oxidative phosphorylation is a prerequisite of M2-type phenotypic macrophage polarization.[109]

In addition to the 're-purposing' of the Krebs cycle to deliver inflammatory intermediates, mitochondrial integrity and biogenesis respond to both, inflammation and exercise. The leakage of reactive oxygen species – potentially indicative of mitochondrial damage – upregulates anti-inflammatory and mitochondrial repair programmes leading to increased mitochondrial mass in inflammation.[110] Similarly, reactive oxygen species have been shown to be crucial signalling mediators in exercise training, including exercise-induced activation of AMPK/PGC-1α signalling, inducing anabolic pathways as well as mitochondrial biogenesis.[111,112] Essential signalling pathways, including the mitogen-activated protein kinases (MAPKs), the nuclear factor-κB and the protein kinase B are employed in inflammation as well as in exercise. Similar to the severity of inflammation, exercise intensity appears to modulate activation of individual MAPK signalling pathways.[110,113,114]

Of note, the complex spectrum of M2-like macrophage phenotypes recognised with their diverse roles in atherosclerosis, have not been charted in detail for their inflammation-resolving and energy metabolism phenotype yet, nor for the effect of exercise in their polarization. Similarly, natural killer 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).[115]

Both the amount and type of energy substrates provided and physical exercise can affect the phenotype of monocytes and macrophages.[104,116–119] Energy sensors, such as AMP-dependent kinase, can be targeted by both diet and exercise. On the way to personalised 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

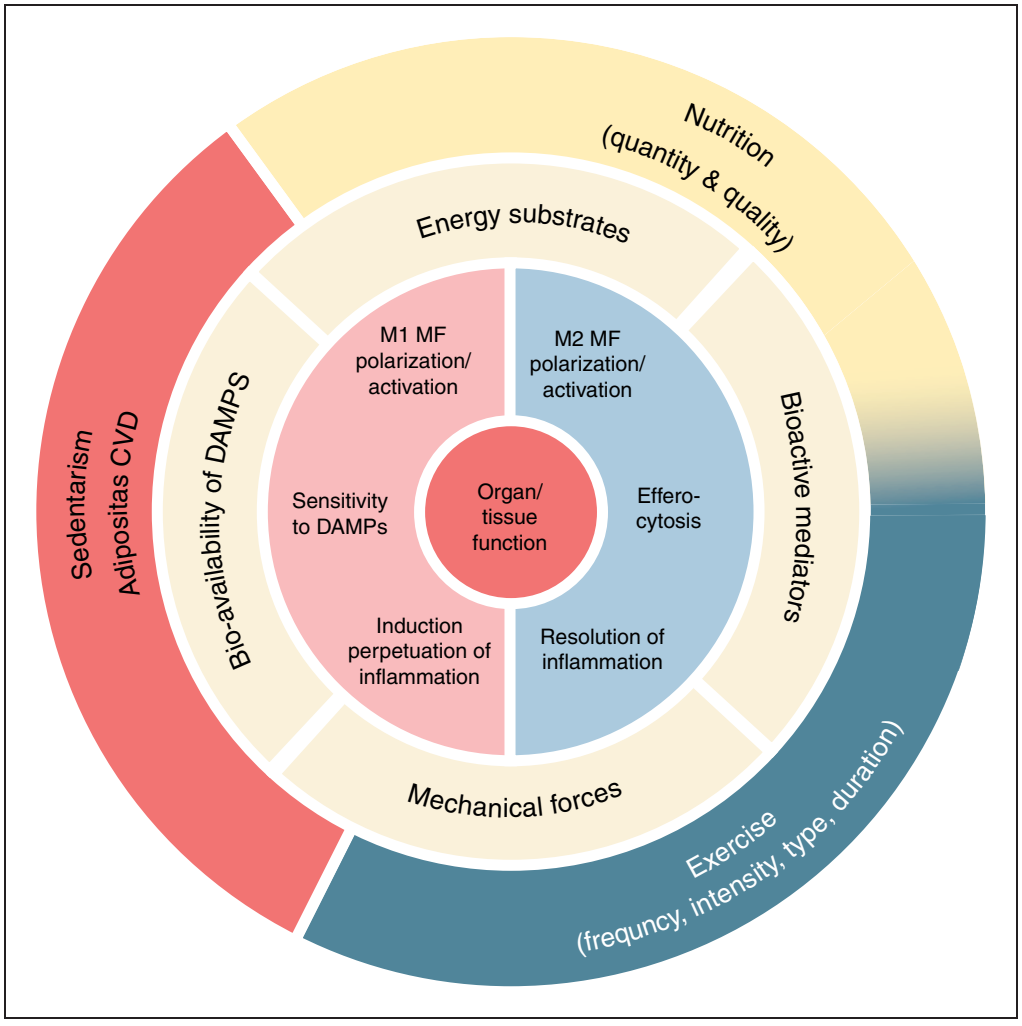

Figure 3. Known and unknown interactions between exercise, nutrition and pro-resolving macrophage polarization and function in cardiovascular disease. CVD: cardiovascular disease; DAMP: damage-associated molecular pattern; MF: macrophage.

and (thereby) the activation state of inflammatory cells in various tissues.[120–124] 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.[125–127]

- To summarise, 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 better resolution: continuously improved techniques of single-cell immuno-phenotyping[128] and assessment of cellular metabolism[129] allow for the fine-mapping of immune-inflammatory interactions and can be used to develop diagnostic tools, assessing individual response to exercise and personalising exercise parameters. In addition, better understanding of the cellular and molecular nodes of the immuno-metabolic network might help to optimise exercise parameters on an individual level to improve cardiovascular and metabolic benefit, potentially in combination with pharmacological and diet-based approaches.

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.[130,131] 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?

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.[131] These datasets cannot be readily viewed on any computer, which complicates human pattern recognition. Moreover, the analysis of 'big data' requires additional statistical precautions, taking into account the increased 'noise' of high-throughput techniques.[130] 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.[132,133]

Some of these novel techniques have already been applied to translational exercise research. In 2009, Goud et al. set up a cluster-randomised trial in 21 CR centres, comparing effects of a computerised decision support system to standard care.[134] 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.[135–139] Most of these studies describe a framework to automate exercise prescription based on patient demographics, comorbidities, test results and reason for referral. Randomised clinical trials evaluating fully computerised 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.[140]

But many more possibilities of 'big data' and machine learning exist in the field of CR, which we will demonstrate by means 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 the extraction of quantitative features.[132] 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. [141] Combined with the recent availability of large imaging datasets,[142] this has meant that 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.[132] As a result, automated quantification is now entering clinical use, but broader diagnostic application will require robust clinical validation before adoption.[143] Of particular interest in CR will be understanding whether imaging after 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).[144–147] Phenotyping through machine learning has predicted the prognosis of HF patients, and performed better compared to traditional predictors such as ejection fraction.[146]

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.[148] Thus, while some neural networks have been proven to outperform humans (for example in image recognition[149]), 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.[150]

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.[151] For example, several platforms have been set up to share anonymised cardiac imaging data with the goal of promoting its use in machine learning applications.[152]

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 improved health. To truly achieve a healthcare transformation,

behavioural changes are needed at both patient and physician level.[153] 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 the patient adheres to the prescribed training.

- To summarise, 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 computerised recommendations. We suggest some approaches in Figure 2.

Sense and nonsense of animal models

Appropriate animal models are important to unravel the molecular mechanisms of 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 of studying 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.[154–156]

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.[157] One future avenue to circumvent such translational problems may reside in humanised models, whereby mice expressing human transgenes or engrafted human cells/tissue are used in preclinical research.[158] 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,[159–161] 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.[75,162,163] More recently this line of research included a more clinically relevant animal model, in the way that HFpEF develops due to the onset of multiple comorbidities that mirror a metabolic syndrome.[76,164–166] Another problem with appropriate animal models may be that most models develop over a short time period, whereas in humans several years or decades sometimes 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).[167–172] 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,[164,173,174] diabetes[175,176] and neurodegenerative diseases.[177] Beside the classical animal models (mouse and rat) used to analyse the effect of exercise training on molecular and physiological parameters, other species have been used more recently such as drosophila and zebrafish.[178–181] 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 summarise, the 'sense' in the use of 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.

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 (a) 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 (b) 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 personalise 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.

Author contribution

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.

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