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Exercise training: the under developed elixir vitae of chronic disease?

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The salient feature of those living with chronic cardiovascular disease (CVD) is poor exercise tolerance, the criterion measure of which is aerobic capacity ($\dot{V}O_{2peak}$). $\dot{V}O_{2peak}$ reflects the integrated capacity of the pulmonary, cardiovascular and neuromuscular systems to transport and utilise O_2, and is strongly correlated with health-related quality of life, predictive of cardiac-related hospitalisations and is the most powerful predictor of prognosis. Indeed with every 1 $ml \cdot min^{-1} \cdot kg^{-1}$ reduction in $\dot{V}O_{2peak}$ there is an increase in all-cause mortality risk of ~16 % in both chronic heart failure (CHF)[1] and coronary heart disease (CHD).[2] In addition, poor exercise tolerance in CVD propagates a downward spiral of further inactivity and decreases in $\dot{V}O_{2peak}$ that reduce functional capacity, with this underpinning poor quality of life, increasing risk of death and the requirement for greater clinical support and intervention.

Exercise is one of nature's great panaceas, which in the context of rehabilitation programs can effectively improve function in a range of biological systems, conveying morbidity and mortality protection, reducing hospitalizations and increasing quality of life in those living with CVD. Thus, intervening with supervised exercise-based cardiac rehabilitation to slow, prevent or even reverse the downward spiral in functional capacity anticipated with the progression of CVD would be expected to convey a plethora of patient benefits that also reduce the clinical burden. Indeed, exercise-based cardiac rehabilitation can promote physiologic adaptations at all levels of the O_2 delivery and utilization cascade; for example reversing left ventricular remodeling to improve cardiac structure and function, and increasing both endothelial and skeletal muscle function.[3] While the specific mechanism and magnitude of effect that underpins any associated change in $\dot{V}O_{2peak}$ and functional capacity will be dependent on CVD etiology and severity, in HF-ACTION – a large randomized multicenter clinical trial in CHF patients – even a modest increase in $\dot{V}O_{2peak}$ (i.e. 0.6 $ml \cdot min^{-1} \cdot kg^{-1}$; 6 %) reduced the risk of all-cause and cardiovascular mortality and hospitalizations (Hazard ratios (HR) ranging from 0.92–0.95; 4–8 % reduction).[4] Similarly, a recent Cochrane review reported exercise-based cardiac rehabilitation to reduce cardiovascular mortality (HR

0.74; 95% CI 0.64-0.86) and risk of hospitalization (HR 0.82; 95% CI 0.70-0.96) in those with CHD.[5]

Debate still surrounds the optimal protocol of exercise-based cardiac rehabilitation. For example, several small, single-center studies have advocated the use of 'high-intensity' interval training (HIIT) in cardiac rehabilitation, which utilizes 3-4 bouts of 3-4 min exercise at 85-90 % $\dot{V}O_{2peak}$ interspersed with periods of recovery. Compared with standard moderate-intensity continuous exercise at 50-60 % $\dot{V}O_{2peak}$, HIIT promotes superior physiologic cardiac, vascular and skeletal muscle adaptations that presumably underpin greater increases in $\dot{V}O_{2peak}$ (e.g. 14 vs. 46 % increase in $\dot{V}O_{2peak}$ for standard vs. HIIT training).[6] However, the outcome of larger scale, multicenter trials assessing the effectiveness of HIIT on clinically relevant outcomes and safety remain outstanding.[7] Thus, many issues remain to be resolved in order to maximize the effectiveness of exercise-based cardiac rehabilitation, with the impact of variables such as protocol (e.g. continuous vs. interval exercise) and exercise intensity on safety, adherence and clinical outcomes key considerations. These issues notwithstanding, there is a large body of evidence that justifies the inclusion of supervised exercise-based cardiac rehabilitation in the UK National Institute for Health and Care Excellence (NICE) CVD management pathway.[8]

Conversely, supervised exercise-based 'cardiac' rehabilitation is noticeably absent from the type 2 diabetes mellitus (T2DM) NICE management pathway.[8] Although T2DM is a chronic metabolic disease, the risk of developing CVD in those with T2DM is more than twice that of the general population.[9] In addition, the primary cause of death in those with T2DM is CVD.[10] Furthermore, patients with T2DM and CVD experience greater morbidity [for example T2DM patients with concomitant CHF (CHF-T2DM) have worse CHF symptoms, and have a greater requirement for diuretics despite better cardiac function],[11] and cardiovascular mortality (~ 50% greater risk of death in both CHF-T2DM patients,[11] and T2DM patients who have had an acute myocardial infarction).[12] These adverse CVD

outcomes are of particular relevance given that it is predicted the global prevalence of T2DM will be 1 in 10 people (642 million) by 2040.[13]

A key mediator of the adverse CVD risk, increasing morbidity and mortality in T2DM, is the (metabolic) consequences of obesity and insulin resistance. These promote a pro-inflammatory, pro-atherosclerotic environment that detrimentally impacts endothelial function and underpins the vascular dysfunction that is common to both CVD and T2DM. Even in the absence of a CVD diagnosis there is evidence of cardiovascular dysfunction in T2DM. While pharmaceutical treatments are the mainstay intervention in T2DM, in the context of this commentary, as highlighted in Brozic et al.[14] it is significant that structured exercise-based 'cardiac' rehabilitation programs in T2DM reduce CVD risk by promoting physiologic increases in vascular function (e.g. flow-mediated dilatation, arterial stiffness), can reduce blood pressure and have positive effects on the blood lipid profile.[15] This reduction in CVD risk with structured exercise-based rehabilitation programs in T2DM is in addition to the improvement in glycaemic control that provides clinically meaningful reductions in HbA1c that can reduce the reliance on pharmaceutical intervention, and can be achieved in the absence of weight loss or dietary intervention.[16] Given the highlighted dual-benefits of supervised exercise-based rehabilitation programs on both the metabolic and cardiovascular risk aspects of T2DM it is unclear why these programs are not common place, and not part of the NICE T2DM management pathway. Instead, pharmaceutical interventions to manage hypertension, dyslipidemia and blood glucose are at the core of treatment, with no strategy to arrest, attenuate or attempt to reverse the anticipated decline in functional capacity that is an underlying driver for disease progression.

In the setting of a T2DM epidemic, given the adverse cardiovascular consequences with respect to CVD risk, morbidity and mortality, it would seem germane to (re)consider the inclusion of a structured, supervised exercise-based 'cardiac' rehabilitation program in the clinical management of T2DM to retard the progression of this disease. In the context of the

inflated risk of developing CVD in T2DM, evident even at the pre-diabetic stage, it is striking that CHF patients with concomitant T2DM (reflecting up to 50% of the heart failure population), despite better cardiac function, have worse functional capacity (NYHA score) than those without this co-morbidity.[11] Similarly, CHF-T2DM patients have a lower $\dot{V}O_{2peak}$ than CHF patients, and have an attenuated physiologic response to exercise-based cardiac rehabilitation: in HF-ACTION although the increase in $\dot{V}O_{2peak}$ was significant in all patients, this was smaller in CHF-T2DM than in CHF patients without concomitant T2DM (0.5 ± 2.4 vs. 0.9 ± 2.6 $ml \cdot min^{-1} \cdot kg^{-1}$), independent of reduced adherence.[17] Worse pre-rehabilitation status in CHF-T2DM raises the question of whether those with a primary diagnosis of T2DM would gain long-term benefit from early participation in exercise-based cardiac rehabilitation, prior to a CVD diagnosis and before functional capacity has declined to such an extreme extent. The multi-faceted physiologic improvements achieved with exercise-based cardiac rehabilitation means that, in addition to improving glycaemic control and reducing CVD risk, the anticipated increase in functional capacity ($\dot{V}O_{2peak}$) might be expected to reduce the adverse CVD morbidity and mortality risk in those with T2DM. Thus, intervening at an earlier stage in the disease induced decline in functional capacity may promote long-term clinical benefits in those with T2DM who develop overt CVD, and indeed in those who do not.

An additional consideration that has proved difficult to resolve, is the optimal protocol of the exercise rehabilitation. Combined resistance and aerobic exercise programs are more effective than aerobic or resistance training in T2DM, promoting greater reductions in HbA1c.[18]. It is possible that given the skeletal muscle and microvascular pathophysiologic derangements of T2DM, the mainstay aerobic exercise cardiac rehabilitation program in CVD is less effective than expected, and benefits limited by adverse skeletal muscle function when T2DM exists as a co-morbidity. Thus, trials to identify the optimal exercise rehabilitation program, and target this to the underpinning limitation to maximize physiologic benefits are warranted. HIIT is an interesting prospect in this regard as this exercise strategy

may allow different elements of the O_2 delivery and utilization cascade to be targeted by altering how the exercise is performed. For example, comprising an HIIT protocol of short duration bouts of exercise at a high mechanical power may allow for greater skeletal muscle and microvascular adaptations for a given cardiovascular strain than would be permitted through standard aerobic 'cardiac' rehabilitation alone. This potentially provides an approach that makes 'aerobic' HIIT rehabilitation analogous to combined resistance and aerobic exercise rehabilitation to optimize the physiologic adaptations attained. However, the issue of how to optimize the exercise rehabilitation program in T2DM, either in the presence or absence of CVD remains unresolved.

While theory and accompanying evidence-base supports the case for including supervised exercise-based rehabilitation as a fundamental component of clinical management strategies to alleviate the isolated or combined burden of CVD and T2DM, the elephant in the room with regards implementing this in practice is adherence. While not widely acknowledged, a self-selecting bias of physically active patients, or those ready for behavior change volunteering and adhering to exercise rehabilitation studies may exist. However, inactivity is a significant driver of the rising prevalence of both CVD and T2DM. Thus, those naïve to regular exercise (with this potentially a root cause of their clinical status) may be less willing or able to adhere to an exercise program. In the recent HF-ACTION study, adherence to exercise was lower in CHF-T2DM (2.5 vs. 3.3 metabolic equivalent $hr \cdot wk^{-1}$ in those without concurrent T2DM).[17] The obvious connotation is that regardless of how effective exercise interventions can be, exercise-based rehabilitation only works when the exercise program is adhered to.

Rehabilitation programs are therefore not just about identifying the optimal exercise strategy to optimize physiologic adaptations in CVD and T2DM to reduce morbidity and mortality risk. Exercise rehabilitation programs must also take account of how exercise can be prescribed to account for differences in exercise preferences, increase enjoyment and support behavior

change in a management scheme that promotes adherence to exercise-based rehabilitation. Thus, although Brozic and colleagues[14] highlight the clear potential of exercise-based cardiac rehabilitation to attenuate CVD risk in T2DM, and advocate access to such programs in clinical management, it is prudent to emphasize that exercise-based cardiac rehabilitation is likely to be most effective when this is embedded as part of a multidisciplinary strategy that balances approaches to optimize physiologic adaptations with tactics to improve adherence.

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