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Editorial Comment

EDITORIAL COMMENT

Spinning the legs and blood: should intradialytic exercise be routinely offered during maintenance haemodialysis?

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ABSTRACT

Patients with end-stage kidney disease on haemodialysis (HD) have an elevated risk of cardiovascular disease (CVD). These patients also experience high levels of physical deconditioning and programmes of rehabilitation have been tested in a variety of forms with variable success. It has been suggested that programmes of exercise rehabilitation have a role to play in improving the physical condition of patients on HD and in addressing the traditional and non-traditional risk factors that drive CVD for this population. Intradialytic exercise has often been suggested as a convenient way of delivering rehabilitation for patients on HD, as it makes use of otherwise dead time, but there are legitimate concerns about this group of at-risk patients undertaking exercise at a time when their myocardium is already vulnerable to the insults of demand ischaemia from the processes of dialysis and ultrafiltration. A study in this issue of *Clinical Kidney Journal* provides reassuring data, showing that cycling during dialysis potentially reduces evidence of demand ischaemia (episodes of myocardial stunning). Together with the safety and quality of life data, we expect from the multicentre PrEscription of Intra-Dialytic Exercise to Improve quAlity of Life in Patients With Chronic Kidney Disease study (the protocol for which is published concurrently), rehabilitation programmes that include intradialytic exercise are perhaps closer than ever for patients on HD.

Keywords: exercise, haemodialysis, intra-dialytic, myocardial stunning

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CARDIOVASCULAR DISEASE AND EXERCISE IN PATIENTS ON HAEMODIALYSIS

Despite advances in recent years, for patients with end-stage kidney disease (ESKD) on haemodialysis (HD), cardiovascular disease (CVD) remains a major cause of morbidity and the leading cause of death [1]. It is well documented that there is a clustering of traditional and non-traditional risk factors for CVD [2, 3]. Indeed, the stresses of HD and ultrafiltration themselves are known to acutely affect cardiac function, haemodynamics and physiology, largely driven by the immediate effects on left-ventricular loading (pre-load). As net ultrafiltration volume increases over the course of a dialysis treatment, total circulating blood volume and reciprocal filling of the left ventricle are reduced. This reduction in cardiac loading leads to a reduction in stroke volume (Frank Starling's law) and to maintain cardiac output a physiological increase in heart rate is required that shortens diastole, the period of time during which coronary filling occurs. This response places additional demands on the heart and exposes vulnerable myocardium to demand ischaemia and consequent acute functional disturbance [4, 5]. The extreme phenotype of this process may manifest as intradialytic hypotension (IDH), particularly in individuals with overtly impaired systolic function or those with impaired autonomic function who fail to mount an appropriate response in either heart rate or systemic arterial tone to the haemodynamic challenge [6]. The poor outcomes for this patient group are well documented, but even in the absence of symptomatic episodes of IDH, the phenomenon of acute myocardial stunning, manifesting as regional wall motion abnormalities (RWMAs), during dialysis is well documented [7] and relate directly to adverse patient outcomes [4].

An observational study published in *Clinical Kidney Journal* (*CKJ*) using wrist-worn accelerometers has shown that people on dialysis are broadly half as active as age- and sex-matched general population controls [8]. That 'exercise' is good for both general and cardiovascular health is not disputed. The cardiovascular benefits of physical activity in a variety of chronic diseases are not in question [9], also ameliorating some of the non-traditional risk factors and processes that drive CVD in patients with chronic kidney disease (CKD) [10]. The question of 'when' and 'how' exercise should be delivered for patients with ESKD on HD is debatable. Programmes of intra- and interdialytic exercise have been trialled for patients on HD, and while programmes of interdialytic exercise tend to lead to superior cardiorespiratory adaptations [11], adherence to intradialytic programmes may be superior [12]. Pragmatically intradialytic exercise programmes make use of otherwise 'dead' time, but given the haemodynamic challenges and known detrimental cardiovascular effects of HD and ultrafiltration, can exercise during dialysis be considered wise for a group of patients at high risk of demand ischaemia and the resultant cardiovascular sequelae? These concerns are compounded by the fact that the normal physiological response to exercise is a period of vasodilation and resultant systemic hypotension, which is known to happen in subjects who exercise during dialysis—perhaps meaning the period of time following intradialytic exercise is an additional time of increased risk to the myocardium and other vulnerable vascular beds [13].

Intradialytic exercise is usually delivered as intradialytic cycling (IDC), and given that the cardiovascular benefits of IDC are not established [14], understanding the acute physiological effects of exercise during dialysis and the long-term effects on patient outcomes is essential. In recent publications in *CKJ*, two separate groups provide answers to some of these questions, with the promise of randomized data to arrive shortly [15, 16].

THE EFFECT OF INTRADIALYTIC EXERCISE ON MYOCARDIAL STUNNING

First, McGuire *et al.* [15] present data to suggest IDC may reduce myocardial stunning events caused by HD in a cohort of patients naïve to exercise during dialysis. This prospective cohort study assessed haemodynamic and echocardiographic changes in a group of 18 patients on HD under two conditions: patients undergoing standard dialysis treatment and the same patients completing dialysis with IDC. The cycling intervention in this study was undertaken on a semirecumbent cycle ergometer and was an intense effort. After a 5-min warm-up, 30 min of cycling was completed at an intensity equivalent to 90% of what subjects achieved during oxygen volume (VO_2) testing. Echocardiography was performed at intervals throughout the dialysis session, including before, during and after a period of time in which IDC was undertaken. The study elegantly showed that while the number of RWMAs was equivalent for the individuals under the two conditions up to 1.5 h (which included the period of time during which IDC was completed), in the hour following the end of IDC, RWMAs were significantly reduced when subjects had completed 30 min of IDC (total RWMAs during HD 110 ± 4 total segments, 7 ± 4 per subject, versus 77 ± 3 total segments, 5 ± 3 per subject when HD was accompanied by IDC; $P = 0.008$). This was despite the decrease in blood pressure known to occur following intradialytic exercise, which the group also demonstrated. While the study was relatively small, non-randomized and blinding was not feasible, the data are reassuring and physiologically interesting. The reduction in RWMAs occurred despite no measurable differences in cardiac output between the experimental conditions and despite an increase in heart rate when IDC was completed. One might reasonably expect the increase in heart rate to increase RWMAs, particularly in the absence of a measurable difference in cardiac output. Simple haemodynamic changes do not seem to account for the observed reduction in RWMAs in the period after IDC compared with the control experimental conditions and the authors suggest that ischaemic preconditioning may account for these differences. While there are no data in this article to confirm or refute this hypothesis, a similar study by a different group reported that RWMAs are reduced during IDC in patients on a programme of IDC when they complete IDC compared with when no exercise is completed [17]. This may support this theory, but confirmatory work is needed. An equally plausible explanation is increased myocardial perfusion following IDC from coronary dilation. Vasodilation occurs during and following exercise (this is the mechanism that leads to the post-exercise decrease in blood pressure) and, given the preservation of cardiac output described post-IDC, relative improvement in coronary blood flow would be highly likely to occur with coronary dilation. In any case, both of these mechanisms are worthy of future study in patients new to IDC and in those conditioned to such programmes.

THE SAFETY OF INTRADIALYTIC EXERCISE

This study has important implications for the safety of IDC and other programmes of intradialytic exercise. Not only did they demonstrate a reduction in RWMAs in the period following exercise, they also showed that there were no differences in

measures of acute myocardial injury (troponin). It must be noted that the sample size is small and of mostly Caucasian males. The sample is also not large enough to understand any impact of comorbid diseases. Only four participants had diabetes, two had 'heart failure' (not defined) and six had previous coronary artery disease (not defined). Additionally, there were significantly different ultrafiltration volumes (and rates) between the two experimental conditions that may limit the interpretation. Critically, when participants underwent HD only, the mean ultrafiltration rate was 589 ± 139 mL/h compared with 469 ± 209 mL/h when participants underwent dialysis with IDC. Faster ultrafiltration rates associate strongly with the development of RWMAs [18], and while the authors argue these differences in ultrafiltration rates would be unlikely to account for the differences in RWMAs at 2.5 h, given there were no differences at 1.5 h, this may not be true, as the cumulative frequency of myocardial stunning does increase with time on dialysis with a linear relationship to increasing ultrafiltration volumes over time [7]. Regardless, these data certainly suggest that IDC is safe in prevalent dialysis patients who are naïve to IDC and relatively free of comorbid illness when ultrafiltration rates are <500 mL/h.

To know whether the safety implications of this study can be generalized to dialysis patients beyond those included will require larger samples of patients with a broader variety of participant characteristics. Fortunately we will not have long to wait. In a second *CKJ* paper authored by Greenwood *et al.* [16], the design and baseline data for the PrEscription of Intra-Dialytic Exercise to Improve quAlity of Life in Patients With Chronic Kidney Disease (PEDAL) trial are presented [16]. This multicentre randomized controlled trial has completed recruitment and enrolled 335 prevalent HD patients who were randomized to 6 months of intradialytic exercise (a combination of IDC and lower limb strength exercises) or usual care dialysis. The intervention in the PEDAL study was designed to help participants build towards accumulating a total weekly physical activity goal of 150 min/week plus 2 days of resistance training for muscular endurance and strength. IDC was undertaken during the first 2 h of HD sessions and initially subjects completed an introductory period with the expectation of being able to complete at least 21 min of continuous cycling each dialysis session at a moderate intensity 8 weeks into the programme. Over the subsequent 12–14 weeks, exercise duration was increased up to 30 min per session and in the final 6 weeks of the programme the ambition was for participants to increase the duration of exercise up to 40 min at 55–70% of their VO_2 reserve (derived from VO_2 peak testing). Progress through the programme was guided by the patients rating of perceived exertion and objectively from VO_2 peak tests. Additionally patients in the intervention group completed lower extremity strength training with ankle weights after completion of the cycling component of the intervention. Physiotherapy assistants and technical instructors delivered the intervention. While this study is powered to detect a change in quality of life (measured with the Kidney Disease Quality of Life Short Form Physical Component Score), it will also report both safety data and changes in certain measures of haemodynamics and CVD in by far the largest study of its kind to date. Importantly, the baseline data suggest that this population of patients is more representative of a cohort of dialysis patients. There is a much higher proportion of females (37.6%), far greater ethnic diversity (50.4% white) and the population has representative rates of comorbid diseases (40% have diabetes, 10% overt heart failure and nearly 80% with hypertension). A favourable safety profile from the results of this study underpinned by the mechanistic work from the study by McGuire *et al.* [15] would be extremely reassuring, highlighting the importance of good mechanistic work in underpinning and explaining the findings of larger clinical studies.

A third study (soon to report) by our group in Leicester (the CYCLE-HD randomized trial) will assess the effects of IDC on left ventricular mass and measures of structural CVD [19]. Together, these studies and others [20] provide major updates to the field and potentially pave the way for similar studies with hard endpoints, including mortality, cardiovascular events and hospitalization.

THE FUTURE

If the PEDAL and CYCLE-HD studies confirm that intradialytic exercise is indeed safe and has measurable benefits, the study by McGuire *et al.* [15] gives us an understanding of why this might be the case. The health benefits of 'exercise' are generally accepted and if this becomes an accepted, proven, safe way of delivering exercise to a group at high risk of CVD, then it should be viewed as a step forward. It seems unlikely that intradialytic exercise will be a complete solution to all the physical activity needs of patients on dialysis, but it is likely to be a key component of pathways that seek to increase the physical activity levels and exercise habits of patients on dialysis, potentially improving both cardiovascular health and physical function. It may be that intradialytic exercise serves as a starting point for the most physically inactive patients to increase physical activity levels and perhaps the biggest questions remain around the implementation of these programmes. Staff and patient barriers are known, but are also manageable [21], and cost-effectiveness analyses will be published from both the PEDAL and CYCLE-HD studies. The UK Renal Association will imminently publish guidelines on the delivery of exercise for patients with CKD, including those on dialysis, so the remaining piece of the puzzle may simply be overcoming clinical inertia. This will not be easy and has been a long time coming, but as evidence of safety becomes secure and if evidence of clinical effectiveness continues to mount comprehensive programmes of rehabilitation for patients on dialysis that includes an intradialytic component may become an intervention we should routinely offer to patients on dialysis.

CONFLICT OF INTEREST STATEMENT

J.B. is chief investigator and M.G.-B. is an investigator on the CYCLE-HD study, which investigates the effects of intradialytic cycling on left ventricular mass. J.B. is a co-author of the PEDAL protocol paper. The authors declare no other conflicts of interest.

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