Spinning the legs and blood: should intra-dialytic exercise be routinely offered during maintenance haemodialysis?
Matthew P.M. Graham-Brown\textsuperscript{1,2,3}, William G. Herrington\textsuperscript{4,5,6}, James O. Burton\textsuperscript{1,2,3,6}

\textsuperscript{1}Department of Cardiovascular Sciences, University of Leicester and NIHR Leicester Cardiovascular Biomedical Research Centre, Glenfield Hospital, Leicester, UK
\textsuperscript{2}John Walls Renal Unit, University Hospitals Leicester NHS Trust, Leicester, UK
\textsuperscript{3}NIHR Leicester Biomedical Research Centre, University Hospitals of Leicester NHS Trust, Leicester, UK
\textsuperscript{4}Clinical Trial Service Unit and Epidemiological Studies Unit, Nuffield Department of Population Health, University of Oxford, Oxford, UK
\textsuperscript{5}Medical Research Council Population Health Research Unit at the University of Oxford, Nuffield Department of Population Health, Oxford, UK
\textsuperscript{6}Oxford Kidney Unit, Churchill Hospital, Oxford, UK
\textsuperscript{7}National Centre for Sport and Exercise Medicine, School of Sport, Exercise and Health Sciences, Loughborough University, Loughborough, UK

Correspondence to: James O. Burton; E-mail: jb343@le.ac.uk

© The Author(s) 2021. Published by Oxford University Press on behalf of ERA-EDTA. This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (http://creativecommons.org/licenses/by-nc/4.0/), which permits non-commercial re-use, distribution, and reproduction in any medium, provided the original work is properly cited. For commercial re-use, please contact journals.permissions@oup.com
Patients with end-stage kidney disease (ESKD) on haemodialysis have elevated risk of cardiovascular disease. 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 haemodialysis and in addressing the traditional and non-traditional risk factors that drive cardiovascular disease for this population. Intra-dialytic exercise has often been suggested as a convenient way of delivering rehabilitation for patients on haemodialysis 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 CKJ 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 multi-center PEDAL study (the protocol for which is published concurrently), rehabilitation programmes that include intra-dialytic exercise are perhaps closer than ever for patients on haemodialysis.

**Keywords:** exercise, haemodialysis, intra-dialytic, myocardial stunning
**Cardiovascular disease and exercise in patients on haemodialysis**

Despite advances in recent years, for patients with end stage kidney disease (ESKD) on haemodialysis, 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 haemodialysis and ultrafiltration themselves are known to acutely affect cardiac function, haemodynamics and physiology, largely driven by the immediate effects on left-ventricular loading (preload). 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 which 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 intra-dialytic 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 CKJ using wrist-worn accelerometers has shown 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 CKD (10). The question of when and how exercise should be delivered for patients with ESKD on haemodialysis is debatable. Programmes of intra- and
inter-dialytic exercise have been trialed for patients on haemodialysis and whilst programmes of inter-dialytic exercise tend to lead to superior cardio-respiratory adaptations (11) adherence to intra-dialytic programmes may be superior (12). Pragmatically intra-dialytic exercise programmes make use of otherwise ‘dead’ time, but given the haemodynamic challenges and known detrimental cardiovascular effects of haemodialysis 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 intra-dialytic exercise is an additional time of increased risk to the myocardium and other vulnerable vascular beds (13).

Intra-dialytic exercise is usually delivered as intra-dialytic 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 are 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 intra-dialytic exercise on myocardial stunning**

First, McGuire et al. present data to suggest IDC may reduce myocardial stunning events caused by haemodialysis in a cohort of patients naïve to exercise during dialysis (15). This prospective cohort study assessed haemodynamic and echocardiographic changes in a group of 18 patients on haemodialysis under 2 conditions. Firstly, patients undergoing standard dialysis treatment and secondly the same patients completing dialysis with IDC. The cycling intervention in this study was undertaken on a semi-recumbent cycle ergometer and was an intense effort. After a 5-minute warm-up 30 minutes of cycling was completed at an intensity equivalent to 90% of what subjects achieved during VO$_2$ testing. Echocardiography was performed at intervals throughout the dialysis session, including before, during and after the period of time at which IDC was undertaken. The study elegantly showed that whilst the number of RWMAs was equivalent for
the individuals under the two conditions up to 1.5 hours (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 minutes of IDC (total RWMAs during haemodialysis 110±4 total segments, 7±4 per subject, versus 77±3 total segments, 5±3 per subject, when haemodialysis was accompanied by IDC; P = 0.008). This was despite the drop in blood pressure known to occur following intra-dialytic exercise, which the group also demonstrated. Whilst the study is 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 to the control experimental conditions and the authors suggest ischaemic preconditioning may account for these differences. Whilst there are no data in this paper to confirm or refute this hypothesis, a similar study by a different group has reported that RWMAs are reduced during IDC in patients on a program of IDC when they complete IDC compared to 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 post exercise drop 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 intra-dialytic exercise**

This study has important implications for the safety of IDC and other programmes of intra-dialytic exercise. Not only did they demonstrate a reduction in RWMAs in the period following exercise, but they showed 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 co-morbid diseases. Only 4 participants had diabetes, 2 had ‘heart failure’ (not defined) and 6 had previous coronary artery disease (not defined). Additionally, there were significantly different ultrafiltration volumes (and rates) between the 2 experimental conditions that may limit the interpretation. Critically when participants underwent HD only, the mean ultrafiltration rate was 589 ± 139 mL/h compared to 469 ± 209 mL/h when participants underwent dialysis with IDC. Faster ultrafiltration rates associate strongly with development of RWMAs (18) and whilst the authors argue these differences in ultrafiltration rates would be unlikely to account for the differences in RWMAs at 2.5 hours given there were no differences at 1.5 hours this may not be true as 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 co-morbid illness when ultrafiltration rates are less than 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. the design and baseline data for the PEDAL trial are presented (16). This multi-centre randomized controlled trial has completed recruitment and enrolled 335 prevalent haemodialysis patients who were randomized to 6-months 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 150min/week plus 2 days of resistance training for muscular endurance and strength. IDC was undertaken during the first 2 hours of haemodialysis sessions and initially subjects completed an introductory period with the expectation of being able to complete at least 21 minutes continuous cycling each dialysis session at a moderate intensity 8 weeks into the program. Over the subsequent 12-14 weeks exercise duration was increased up to 30 minutes per session and in the final 6 weeks of the program the ambition was for participants to increase the
duration of exercise up to 40 minutes at 55-70% of their VO\textsubscript{2} reserve (derived from VO\textsubscript{2} peak testing). Progress through the program was guided by the patients rating of perceived exertion and objectively from VO\textsubscript{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. Whilst 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 cardiovascular disease in by far the largest study of it’s kind to date. Importantly, the baseline data suggest this population of patients are more representative of a cohort of dialysis patients. There are a much higher proportion of females (37.6%), far greater ethnic diversity (50.4% white) and the population have representative rates of co-morbid diseases (40% have diabetes, 10% overt heart failure, nearly 80% with hypertension). A favourable safety profile from the results of this study underpinned by the mechanistic work from the study by McGuire and colleagues 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 affects of IDC on left ventricular mass and measures of structural cardiovascular disease (19). Together these studies, and others (20), provide major updates to the field and potentially pave the way for similar studies with hard end-points, including mortality, cardiovascular events and hospitalisation.

**The future**

If the PEDAL and CYCLE-HD studies confirm that intra-dialytic exercise is indeed safe and has measurable benefits, the study by McGuire and colleagues 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 cardiovascular disease then it should be viewed as a step forward. It seems unlikely that intra-dialytic 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 intra-dialytic exercise serves as a starting ramp for the most physically inactive patients to increasing 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 PEDAL and CYCLE-HD. 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 intra-dialytic component may become an intervention we should routinely offered to patients on dialysis.

CONFLICT OF INTEREST STATEMENT

None declared.
REFERENCES

1. UK Renal Registry. Adults on in-centre haemodialysis (ICHD) in the UK at the end of 2018. 2020.

2. Yusuf S, Hawken S, Ôunpuu S, Dans T, Avezum A, Lanas F, et al. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. The lancet. 2004;364(9438):937-52.

3. Chiu DYY, Sinha S, Kalra PA, Green D. Sudden cardiac death in haemodialysis patients: preventative options. Nephrology. 2014;19(12):740-9.

4. Burton JO, Jefferies HJ, Selby NM, McIntyre CW. Hemodialysis-induced cardiac injury: determinants and associated outcomes. Clinical Journal of the American Society of Nephrology. 2009;4(5):914-20.

5. Buchanan C, Mohammed A, Cox E, Köhler K, Canaud B, Taal MW, et al. Intradialytic cardiac magnetic resonance imaging to assess cardiovascular responses in a short-term trial of hemodiafiltration and hemodialysis. Journal of the American Society of Nephrology. 2017;28(4):1269-77.

6. Kanbay M, Eruglu LA, Afsar B, Ozdogan E, Siriopol D, Covic A, et al. An update review of intradialytic hypotension: concept, risk factors, clinical implications and management. Clinical Kidney Journal. 2020.

7. Burton JO, Jefferies HJ, Selby NM, McIntyre CW. Hemodialysis-induced repetitive myocardial injury results in global and segmental reduction in systolic cardiac function. Clinical Journal of the American Society of Nephrology. 2009;4(12):1925-31.

8. Nawab KA, Storey BC, Staplin N, Walmsley R, Haynes R, Sutherland S, et al. Accelerometer-measured physical activity and functional behaviours among people on dialysis. Clinical Kidney Journal. 2020.

9. Lee I, Shiroma EJ, Lobelo F, Puska P, Blair SN, Katzmarzyk PT, et al. Effect of physical inactivity on major non-communicable diseases worldwide: an analysis of burden of disease and life expectancy. The lancet. 2012;380(9838):219-29.

10. Heiwe S, Jacobson SH. Exercise training in adults with CKD: a systematic review and meta-analysis. American Journal of Kidney Diseases. 2014;64(3):383-93.

11. Kouidi E, Grekas D, Deligiannis A, Tourkantonis A. Outcomes of long-term exercise training in dialysis patients: comparison of two training programs. Clin Nephrol. 2004;61 Suppl 1:S31-8.

12. Konstantinidou E, Koukouvou G, Kouidi E, Deligiannis A, Tourkantonis A. Exercise training in patients with end-stage renal disease on hemodialysis: comparison of three rehabilitation programs. J Rehabil Med. 2002;34(1):40-5.

13. Dungey M, Bishop NC, Young HM, Burton JO, Smith AC. The impact of exercising during haemodialysis on blood pressure, markers of cardiac injury and systemic inflammation—preliminary results of a pilot study. Kidney and Blood Pressure Research. 2015;40(6):593-604.

14. Young HM, March DS, Graham-Brown MP, Jones AW, Curtis F, Grantham CS, et al. Effects of intradialytic cycling exercise on exercise capacity, quality of life, physical function and cardiovascular measures in adult haemodialysis patients: a systematic review and meta-analysis. Nephrology Dialysis Transplantation. 2018;33(8):1436-45.
15. McGuire S, Horton EJ, Renshaw D, Chan K, Jimenez A, Maddock H, et al. Cardiac stunning during haemodialysis: the therapeutic effect of intra-dialytic exercise. Clinical Kidney Journal. 2019.

16. Greenwood SA, Koufaki P, Macdonald J, Bhandari S, Burton J, Dasgupta I, et al. The PrEscription of intraDialytic exercise to improve quAlity of Life in patients with chronic kidney disease trial: study design and baseline data for a multicentre randomized controlled trial. Clinical Kidney Journal. 2020.

17. Penny JD, Salerno FR, Brar R, Garcia E, Rossum K, McIntyre CW, et al. Intradialytic exercise preconditioning: an exploratory study on the effect on myocardial stunning. Nephrology Dialysis Transplantation. 2019;34(11):1917-23.

18. Jefferies HJ, Virk B, Schiller B, Moran J, McIntyre CW. Frequent hemodialysis schedules are associated with reduced levels of dialysis-induced cardiac injury (myocardial stunning). Clinical journal of the American Society of Nephrology. 2011;6(6):1326-32.

19. Graham-Brown M, March DS, Churchward DR, Young H, Dungey M, Lloyd S, et al. Design and methods of CYCLE-HD: improving cardiovascular health in patients with end stage renal disease using a structured programme of exercise: a randomised control trial. BMC nephrology. 2016;17(1):1-13.

20. Jeong JH, Biruete A, Tomayko EJ, Wu PT, Fitschen P, Chung HR, et al. Results from the randomized controlled IHOPE trial suggest no effects of oral protein supplementation and exercise training on physical function in hemodialysis patients. Kidney Int. 2019;96(3):777-86.

21. Young HM, Hudson N, Clarke AL, Dungey M, Feehally J, Burton JO, et al. Patient and staff perceptions of intradialytic exercise before and after implementation: a qualitative study. PLoS One. 2015;10(6):e0128995.

http://mc.manuscriptcentral.com/ckj