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Buchanan, Charlotte and Mohammed, Azharuddin and Cox, Eleanor and Köhler, Katrin and Canaud, Bernard and Taal, Maarten W. and Selby, Nicholas Michael and Francis, Susan T. and McIntyre, Christopher W. (2016) 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*, 27 (11). ISSN 1533-3450

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Intradialytic cardiac MRI to assess cardiovascular responses in a short term randomized controlled trial of haemodiafiltration and haemodialysis

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Key Words: Haemodialysis, haemodiafiltration, cardiac stunning, randomised controlled trial, cardiac MRI

Word count: 3188 (+ abstract 233)

Abstract

Haemodynamic stress during haemodialysis results in recurrent segmental ischemic injury (myocardial stunning) that drives cumulative cardiac damage. We have performed the first fully comprehensive study of the cardiovascular impact of dialysis sessions using intra-dialytic cardiac magnetic resonance imaging (MRI), applying this approach to examine the comparative acute effects of standard haemodialysis (HD) versus haemodiafiltration (HDF) in stable patients.

12 HD patients (32-72 years) were randomly allocated to either HD or HDF. Patients were stabilized on a modality for two weeks before undergoing serial cardiac MRI assessment during dialysis. Patients then crossed-over to the other modality, and were rescanned after a further two weeks. Cardiac MRI measurements included cardiac index (CI), stroke volume index (SVI), global and regional contractile function (myocardial strain), coronary artery flow and myocardial perfusion.

Ultrafiltration rate was 3.8 ± 2.9 ml/kg/hr during HD and 4.4 ± 2.5 ml/kg/hr during HDF ($p=0.29$) and both modalities provided a similar degree of cooling. All measures of systolic contractile function fell during HD and HDF, with partial recovery post-dialysis. All patients experienced some degree of segmental left ventricular dysfunction with severity proportional to ultrafiltration rate and blood pressure reduction. Myocardial perfusion was significantly reduced during dialysis for HD and HDF. Treatment modality did not influence any of the cardiovascular responses to dialysis.

In conclusion, in this randomized cross-over study, there was no significant difference in the cardiovascular response of haemodiafiltration or haemodialysis with cooled dialysate as assessed by intradialytic MRI.

Introduction

Cardiac magnetic resonance imaging (MRI) is regarded as the optimal technique for structural and functional assessment of the heart but due to the challenging environment of an MR scanner, has not previously been used during haemodialysis treatment. In addition to superior image quality, MRI is the only imaging modality that can provide a complete and simultaneous assessment of cardiac morphology, cardiac output, global/regional contractile function, fibrosis, coronary artery flow and contrast-free measurement of myocardial perfusion [1]. Haemodynamic instability during dialysis plays a central role in the pathophysiology of cardiac disease. A substantial body of evidence exists to demonstrate that subclinical myocardial ischaemia occurs during conventional HD, driven to a large extent by ultrafiltration volume (UFV) and change in blood pressure (BP) [2-5]. The repetitive nature of this ischaemic injury has a cumulative effect, leading to permanent reductions in left ventricular (LV) systolic function and conferring an increased risk of cardiac events and mortality [6]. To date, these findings have largely been generated using echocardiography to assess regional myocardial contractility [7, 8], alongside two small studies using positron emission tomography (PET) to measure myocardial perfusion during HD [9, 10]. On-line haemodiafiltration (HDF) is a modified haemodialysis (HD) modality incorporating increased convective clearance, which has long been reported to reduce intradialytic hypotension (IDH) [11-14]. However, despite three randomised controlled trials and several meta-analyses, opinion remains conflicted as to whether HDF improves patient outcomes and the mechanisms by which HDF may do so are not well elucidated [11-18].

This study had two principle objectives: to perform the first intradialytic assessment of the acute cardiac effects of dialysis using cardiac MRI; secondly to use this method to compare the acute cardiac effects of optimized conventional high-flux HD and HDF.

Results

Subjects

60 established HD patients were screened for eligibility, from whom 12 consented to participate (10 male, mean age 53 ± 12 years, dialysis vintage 56 ± 6 months). All had an arterio-venous fistula (AVF) with mean flow rate (Q_a) of 1051 ± 60 ml/min. Demographic data are shown in Table 1.

Dialysis treatment and hemodynamic response

Dialysis treatment and laboratory data are shown in Table 2. Of note, HD and HDF resulted in comparable patient cooling (-1°C). There were no significant differences between UFV or other dialysis treatment or laboratory parameters between study arms, except for a larger fall in troponin T (cTnT) following HDF.

BP was generally well maintained, with no significant differences between modalities at any time point (Figure 1A and Table 2). Five patients in each arm had a fall of $>20\%$ from baseline in at least one systolic BP (SBP) measurement, with an average maximum SBP fall of 18.1 ± 10 mmHg during HD and 19.5 ± 11 mmHg during HDF ($p=0.70$); there was only one episode of symptomatic hypotension.

Heart rate (HR) did not change significantly throughout either dialysis treatment (Figure 1C) and no arrhythmias were observed. Stroke volume index (SVI) and cardiac index (CI) were independently assessed using PC-MRI and cine MR data. The two methods gave tightly correlated results ($r=0.61$, $p<0.001$ for SVI; $r=0.49$, $p<0.001$ for CI), thus for primary analysis PC-MRI measures are presented. Cine MR data are provided as Supplementary Material including end diastolic (EDV) and end systolic volumes (ESV). SVI and CI both progressively decreased during treatment with lowest

values observed at 230min (Figure 1B). No significant differences were found between modalities. For HD, baseline CI was $3.6\pm 0.2\text{L}/\text{min}/\text{m}^2$ versus $2.6\pm 0.2\text{L}/\text{min}/\text{m}^2$ at 230min ($p=0.001$), compared with $3.3\pm 0.2\text{L}/\text{min}/\text{m}^2$ and $2.5\pm 0.2\text{L}/\text{min}/\text{m}^2$ ($p=0.001$) for HDF. A reduction was also seen in IVC flow, but no significant differences were found between modalities (Figure 1C). Cardiac output and systemic vascular resistance (SVR) data are provided in the Supplementary Material, together with individual patient data showing changes in key parameters for HD and HDF.

Global and segmental ventricular function

Significant reductions were seen in global circumferential and global longitudinal strain during HD and HDF (Figure 2A). During HD, global systolic contractile function deteriorated significantly, with longitudinal strain changing from $-7.7\pm 0.9\%$ at baseline to $-4.5\pm 0.8\%$ at 160min ($p=0.002$) compared with $-8.6\pm 0.8\%$ (baseline) and $-4.7\pm 1.0\%$ (160min) for HDF ($p=0.04$). There were no significant differences between HD and HDF. Changes were seen as early as 70min into dialysis treatment, with partial or complete recovery in the post-dialysis period.

Regional circumferential and longitudinal strain were each assessed in six LV segments, with eight patients demonstrating two or more dysfunctional segments during dialysis ($>20\%$ reduction in strain from baseline, Figure 2B). Mirroring changes in global strain, dysfunctional segments were detected at 70min, with the highest number of affected segments at 160min and 250min. There was no difference in number of dysfunctional segments between HD and HDF at any time point during dialysis. 30min after the end of dialysis, strain returned to baseline in some but not all affected segments. There were fewer persistently dysfunctional segments assessed in

the long axis view after HD compared to HDF (2.3 ± 0.4 vs. 3.4 ± 0.5 respectively, $p=0.0007$). There were no significant differences in fibrosis or myocardial water content (as assessed by myocardial T_1 signal) at baseline, or during dialysis (Supplementary material, Figure 2).

Myocardial perfusion and coronary artery flow

Whilst there was no clear change in mean myocardial perfusion during dialysis, group-averaged values masked significant individual variation. Myocardial perfusion fell from baseline in seven patients (three $\geq 50\%$) during HD compared with five patients (four $\geq 50\%$) during HDF (Chi-squared between modalities $p=0.36$). For HD, baseline perfusion was 3.3 ± 1.7 ml/g/min versus an intra-dialytic nadir of 1.9 ± 1.4 ml/g/min, $p=0.05$; for HDF, baseline perfusion was 3.4 ± 1.5 ml/g/min versus a nadir of 2.0 ± 1.3 ml/g/min, $p=0.019$. Nadir perfusion values did not differ between HD and HDF (Figure 3). Due to the limited spatial coverage of ASL imaging it was not possible to formally match myocardial perfusion values to strain on a segmental basis. However, 78% of patients who had more than two short axis dysfunctional LV segments during dialysis (same LV slice in which perfusion was measured) had a $>20\%$ fall in myocardial perfusion. During HD, four patients demonstrated an early (55min) fall in perfusion and three other patients evidenced a later fall (145 or 235min), compared with three early decreases and two later decreases during HDF. A significant correlation was found between percentage decrease in perfusion from baseline to 70min and number of stunned segments for HD, but not for HDF. At baseline, there was no significant difference in right coronary artery flow between modalities (mean flux index $1.4 \pm$

0.3L/min/m², p=0.25). Coronary artery flow did not significantly change during dialysis and there was no effect of treatment modality.

Factors associated with changes in cardiac function during dialysis

The number of dysfunctional long axis segments during dialysis was strongly associated with UFV (HD $r=0.70$, $p=0.017$; HDF $r=0.59$, $p=0.046$), Figure 4A(i). In the short axis, a similar association was found for HDF ($r=0.66$, $p=0.026$) but not for HD ($r=0.16$, $p=0.344$), although fewer stunned segments were identified in this view. Reductions in SVI and CI during dialysis were both associated with increased UFV (Figure 4A(ii) and (iii)). We also observed a trend towards greater UFV in those patients with a $\geq 20\%$ fall in myocardial perfusion ($0.91 \pm 0.7L$ versus $1.5 \pm 0.5L$, $p=0.06$). No significant correlations were found between UFV and ejection fraction, heart rate or IVC flow (as an indicator of venous return).

In addition, reductions in SVI and CI were associated with the number of dysfunctional segments during dialysis (Figure 4B(i) and (ii)). An association between BP and newly dysfunctional segments was also seen, with minimum SBP during dialysis correlating strongly with number of dysfunctional segments for HD ($r=-0.8$, $p = 0.004$) (Figure 4B(iii)), although not for HDF.

Discussion

We have, for the first time, used intra-dialytic MRI to provide a comprehensive assessment of the short-term cardiac response to dialysis treatment. Using this approach we observed significant intradialytic decreases in cardiac output, myocardial contractility and myocardial perfusion but did not observe any differences between the short-term cardiac effects of HDF and conventional high-flux HD in the presence of cooling.

The observed haemodynamic responses were in keeping with previous descriptions [19, 20]. However, using MRI we have been able to accurately and directly measure cardiac output during dialysis for the first time. We observed a substantial decline in CI and SVI that reached a nadir at 230min, with only partial recovery post-dialysis. Heart rate remained relatively fixed indicating a failure to respond appropriately to haemodynamic stress, a finding that is well described [21]. Corresponding reductions in IVC flow and EDV suggest that changes in SVI and CI were at least partly related to reductions in intravascular volume. However, the negative effects of dialysis on ventricular contractility also appeared important, with correlations between change in CI and number of newly dysfunctional segments.

Ventricular contractile performance was assessed using LV strain, with longitudinal strain being the most sensitive measure, as the sub-endocardial distribution of longitudinal fibres renders them particularly prone to hypoperfusion [22]. We observed reductions in both longitudinal and circumferential global strain during dialysis, although longitudinal changes were most notable. These global reductions were associated with regional/segmental dysfunction. Regional assessment of myocardial contractility in tandem with perfusion allowed us to study the

development of myocardial stunning more precisely, demonstrating co-existing reductions in contractile function and perfusion and only partial recovery post-dialysis. The pattern of injury, and peak of the effect, was in keeping with echocardiography-based studies performed by our group and others [6, 23]. We observed myocardial stunning as early as 70min from the start of treatment, consistent with early changes in myocardial perfusion described in PET studies [9]. This implies that whilst UFV remains a key driver of myocardial stunning, additional processes also contribute to regional cardiac injury. That dialysis-induced stunning occurs even within modest changes of BP and volume status suggests that there is no threshold of risk that can be determined from current clinical based approaches to assessment.

Myocardial perfusion was measured in only a single short-axis slice, due to current limitations of the arterial spin labelling scheme used. We observed wide inter- and intra-individual variation in myocardial perfusion, a feature not evident in previous studies of healthy controls. However, nadir values during dialysis did decline significantly during HD and HDF, consistent with previous cardiac PET based studies [9, 10]. Whilst coronary artery flow data should be regarded as preliminary, the lack of change during dialysis suggests that the observed decrease in myocardial perfusion was not due to reduced flow in the main coronary arteries. This strengthens the hypothesis that changes in microcirculatory blood flow are the dominant factor contributing to tissue ischaemia during dialysis [2].

Despite randomized controlled trials exploring long-term clinical effects and the results of our short-term study, it remains unclear why HDF may have cardio-protective effects. The Turkish HDF and CONTRAST studies found no difference in

mortality or cardiovascular events [15, 16] whereas the ESHOL study reported a large (30%) reduction in all-cause mortality [17]. This evidence base is further complicated by the divergent results of four meta-analyses, all of which showed reductions in IDH with HDF but only one suggested improved patient outcomes [11-14]. A more recent pooled individual participant data analysis suggested a survival benefit with HDF, particularly with higher convection volumes [18]. Although we observed no significant differences between HD and HDF in any of the short-term effects studied, it remains possible that HDF may be associated with improved intradialytic stability in more frail patient groups with higher UFV. It should be noted that we selected relatively healthy patients for this first intra-dialytic MRI study, with well-preserved ejection fraction (although baseline strain values were reduced as compared to normal values), relatively stable intra-dialytic BP and low UFV. The matched fall in body temperature that occurred during study sessions may also be relevant, as dialysate cooling improves intradialytic haemodynamic stability and provides short and long-term cardio-protection [24, 25]. Previous studies have demonstrated equivalent incidence of IDH between HD and convective techniques after controlling for thermal factors [26]. It remains possible that HDF may be associated with improved intradialytic stability in the long-term related to the cooling effect of large convective replacement volumes. HDF does provide superior solute removal over a wide molecular weight range as compared to conventional HD, explaining the observed greater clearance of cTnT during HDF. There may be additional, unknown short-term effects associated with the removal of other factors, such as cardiotoxic steroids, which have been experimentally associated with the development of uremic cardiomyopathy [27] but this remains speculative.

T_1 relaxation measures can provide an indication of the degree of myocardial fibrosis as collagen becomes associated with a supersaturated hydrogel and increases the water based signal [28], whilst a change in T_1 during dialysis would indicate altered myocardial water content. Our cohort had relatively normal baseline T_1 values suggesting a low level of cardiac fibrosis, and a lack of change in T_1 during dialysis indicates no change in myocardial water/oedema due to UFV or osmolality changes. However, further study of these measures may provide additional insights across a wider patient demographic.

The application of advanced cardiac MRI during dialysis is a major step forward towards understanding the pathophysiology of elevated cardiovascular mortality in dialysis patients. We have confirmed the development of myocardial stunning during optimal dialysis schedules and shown that cardiac MRI now provides an integrated tool for the discovery of new dialysis-based therapeutic targets, refinement of candidate interventions and ascertainment of robust biological plausibility, prior to large-scale studies to improve intradialytic haemodynamic stability directed at 'hard' clinical endpoints. In the setting of this study of stable cooled patients, HDF and high-flux HD were associated with similar short-term intradialytic cardiac effects.

Concise Methods

Subject Demographics and clinical data

Patients were recruited to the study from the renal unit at Royal Derby Hospital (ClinicalTrials.gov:NCT02494843). One of the investigators (AM) was responsible for enrolling participants. Ethical approval was granted by Derbyshire Research Ethics committee and all patients gave written informed consent. All patients had received thrice weekly HD for more than six months and had a mature arteriovenous fistula. Patients were excluded if they fulfilled the criteria for New York Heart Association Class 4 cardiac failure.

Study design

This was an open-label randomised crossover pilot trial (Figure 5A). Participants were randomised 1:1 to HD or HDF for two weeks using a computer generated randomisation sequence (Prism, GraphPad, San Diego CA), after which they underwent multi-parametric cardiac MRI scans before, during and after a single dialysis treatment (Figure 5B). Clinical parameters, dialysis treatment details and laboratory tests were obtained before and after dialysis. Thereafter, participants switched to the other modality for a further two weeks before attending for a second MRI study day. During the two-week run-in phases, dry weight was assessed as per standard clinical practice, and dialysis was performed with the same equipment as used on study days: Fresenius 5008 monitors, high flux polysulfone dialysers (FX800, Fresenius Medical Care, Germany), bicarbonate buffer, dialysate temperature 37°C. For HDF, a minimum of 20L replacement fluid per treatment was targeted. Anticoagulation was achieved using unfractionated heparin and dialysate composition

was sodium 137mmol/L, potassium 2.0mmol/L, calcium 1.5mmol/L, magnesium 0.5mmol/L, glucose 1.0g/L.

Cardiac imaging

Cardiac MRI data were collected on a 3T Philips Achieva MR scanner (Philips Medical Systems, Best, NL) using MultiTransmit and a 16-channel TorsoXL receive coil. There were a number of considerations to allow dialysis to be performed in the MR scanner, as described in the Appendix. Cardiac MRI data were collected at five time points (Figure 5B) and comprised multiple measures of cardiac structure and function, alongside VCG measures of patient heart rate, in a 50min scan session. MRI measures are summarised below, full technical details are provided in the Appendix.

Global cardiac contractile function: Left ventricular function was assessed using VCG-gated cine MRI to collect images of the LV across the cardiac cycle in the two-chamber (2CH) view. Data were analysed using ViewForum software (Philips Medical Systems, Best, NL). Cardiac output (CO), stroke volume (SV) and ejection fraction were determined. SV and CO measures were corrected for body surface area (BSA), to yield stroke volume index (SVI) (L/m^2) and cardiac index (CI) ($L/min/m^2$).

Aortic flow and central venous return: Phase contrast (PC) MRI of aortic flow was collected to provide a second independent estimate of SVI and CI, while PC-MRI of the inferior vena cava (IVC) was used to determine central venous return. PC-MRI data were analysed using ViewForum software to provide an estimate of aortic blood

velocity (mm/s), cross sectional area (CSA) of the aorta (mm²) and aortic strain (%), from which SVI and CVI could be obtained. For the IVC, velocity (mm/s), flux (L/min) and CSA (mm²) were calculated, with flux and CSA being BSA corrected.

Segmental cardiac function: Contractility and myocardial strain were assessed using SPAMM tagging. Data were collected in a 2CH short axis slice to compute peak systolic circumferential strain and in a long axis four-chamber (4CH) slice to measure longitudinal strain. Using CIM2D software (Auckland Uni Services), images were divided into six segments (short axis: anterior septum, anterior, anterior lateral, posterior lateral, inferior and inferior septum; long axis: basal inferior, mid inferior, apical inferior, apical anterior, mid anterior and basal anterior). Circumferential and longitudinal strain (%) was measured for each segment, and percentage change in each segment was assessed during dialysis. A reduction in strain >20% from baseline was taken to define segments that became dysfunctional during dialysis [29].

Myocardial fibrosis: Myocardial fibrosis was assessed in a 2CH short axis slice, using a modified Look-Locker inversion recovery (MOLLI) T₁ mapping scheme [30]. MOLLI data were analyzed using dedicated software to form short axis T₁ maps (in ms) of the myocardium (Matlab version 8.1, The MathWorks, Inc., Natick, MA, USA).

Coronary blood flow: PC-MRI was used to estimate flow in the right coronary artery. Using ViewForum software, the cross sectional area (mm²), flux of blood through the coronary artery (ml/min) and stroke volume (mL), were calculated and BSA corrected.

Myocardial perfusion: Myocardial perfusion was assessed in a 2CH short axis slice with a MOLLI arterial spin labeling (ASL) technique [31] using a flow alternating inversion recovery (FAIR) scheme. Myocardial perfusion data were quantified in units of ml/g/min (Matlab version 8.1, The MathWorks, Inc., Natick, MA, USA).

Statistical Analyses

Statistical analysis was performed using SPSS v22. Results are expressed as mean±standard error (SE) and median (interquartile range, IQR) for parametric and non-parametric data respectively. Paired T-test (or non-parametric equivalent) or repeated measures ANOVA were used to compare variables over two or more time-points and between modalities. Correlations were performed with Pearson tests. The null hypothesis was accepted for p-values ≥ 0.05 .

As cardiac ASL has never been assessed previously in the context of CKD5, and because of the technical considerations of performing intradialytic MRI, the sample size was selected pragmatically based on published norms of cardiac stunning during dialysis in human studies [25] and animal studies using cardiac MRI [32]. However, using data from previous echocardiography-based studies and assuming a mean±SD of 4.8 ± 1.3 new regional wall motion abnormalities (RWMAs) per patient with standard dialysis [33] [33], 11 patients per group would be required to have a 90% chance of detecting a decrease in new RWMAs from 4.8 in standard dialysis to 3.0 in the HDF group, significant at the 5% level. Such a reduction would be clinically significant and in keeping with other dialysis based interventions shown previously to reduce dialysis-induced myocardial stunning [23, 33].

Acknowledgments

This study was funded by a research grant from Fresenius Medical Care Deutschland GmbH.

Dedication

The authors would like to respectfully dedicate this study to the memory of our recently deceased friend and Chief Renal Technician, Paul Roome. We could not have overcome the technical challenges posed by this, or numerous other studies over the last 10 years, without his amazing expertise and unfailing 'can do' attitude.

Statement of competing financial interests

No further interests to declare.

References

1. Chiu DYY, Green D, Abidin N, et al. Cardiac imaging in patients with chronic kidney disease. *Nat Rev Nephrol.* 2015;11(4):207-20.
2. Selby NM, McIntyre CW. The acute cardiac effects of dialysis. *Semin Dial.* 2007;20(3):220-8.
3. McIntyre CW. Recurrent circulatory stress: the dark side of dialysis. *Semin Dial.* 2010;23(5):449-51.
4. McIntyre CW. Haemodialysis-induced myocardial stunning in chronic kidney disease - a new aspect of cardiovascular disease. *Blood Purif.* 2010;29(2):105-10.
5. McIntyre CW. Effects of hemodialysis on cardiac function. *Kidney Int.* 2009;76(4):371-5.
6. Burton JO, Jefferies HJ, Selby NM, et al. Hemodialysis-Induced Repetitive Myocardial Injury Results in Global and Segmental Reduction in Systolic Cardiac Function. *Clin J Am Soc Nephrol.* 2009;4(12):1925-31.
7. Burton JO, Jefferies HJ, Selby NM, et al. Hemodialysis-Induced Cardiac Injury: Determinants and Associated Outcomes. *Clin J Am Soc Nephrol.* 2009;4 (5):914-20.
8. Selby NM, Lambie SH, Camici PG, et al. Occurrence of regional left ventricular dysfunction in patients undergoing standard and biofeedback dialysis. *Am J Kidney Dis.* 2006;47(5):830-41.
9. Dasselaar JJ, Slart RHJA, Knip M, et al. Haemodialysis is associated with a pronounced fall in myocardial perfusion. *Nephrol Dial Transplant.* 2009;24(2):604-10.
10. McIntyre CW, Burton JO, Selby NM, et al. Hemodialysis-induced cardiac dysfunction is associated with an acute reduction in global and segmental myocardial blood flow. *Clin J Am Soc Nephrol.* 2008;3(1):19-26.
11. Mostovaya IM, Blankestijn PJ, Bots ML, et al. Clinical Evidence on Hemodiafiltration: A Systematic Review and a Meta-analysis. *Seminars In Dialysis.* 2014;27(2):119-27.
12. Nistor I, Palmer SC, Craig JC, et al. Convective versus diffusive dialysis therapies for chronic kidney failure: an updated systematic review of randomized controlled trials. *Am J Kidney Dis.* 2014;63(6):954-67.
13. Susantitaphong P, Siribamrungwong M, Jaber BL. Convective therapies versus low-flux hemodialysis for chronic kidney failure: a meta-analysis of randomized controlled trials. *Nephrol Dial Transplant.* 2013;28(11):2859-74.
14. Wang AY, Ninomiya T, Al-Kahwa A, et al. Effect of Hemodiafiltration or Hemofiltration Compared With Hemodialysis on Mortality and Cardiovascular Disease in Chronic Kidney Failure: A Systematic Review and Meta-analysis of Randomized Trials. *American Journal of Kidney Diseases.* 2014;63(6):968-78.
15. Ok E, Asci G, Toz H, et al. Mortality and cardiovascular events in online haemodiafiltration (OL-HDF) compared with high-flux dialysis: results from the Turkish OL-HDF Study. *Nephrol Dial Transplant.* 2013;28(1):192-202.
16. Grooteman MP, van den Dorpel MA, Bots ML, et al. Effect of online hemodiafiltration on all-cause mortality and cardiovascular outcomes. *J Am Soc Nephrol.* 2012;23(6):1087-96.
17. Maduell F, Moreso F, Pons M, et al. High-efficiency postdilution online hemodiafiltration reduces all-cause mortality in hemodialysis patients. *J Am Soc Nephrol.* 2013;24(3):487-97.

18. Peters SAE, Bots ML, Canaud B, et al. Haemodiafiltration and mortality in end-stage kidney disease patients: a pooled individual participant data analysis from four randomized controlled trials. *Nephrology Dialysis Transplantation*. 2015.
19. Nette RW, van den Dorpel MA, Krepel HP, et al. Hypotension during hemodialysis results from an impairment of arteriolar tone and left ventricular function. *Clin Nephrol*. 2005;63(4):276-83.
20. van Kuijk WH, Luik AJ, de Leeuw PW, et al. Vascular reactivity during haemodialysis and isolated ultrafiltration: thermal influences. *Nephrol Dial Transplant*. 1995;10(10):1852-8.
21. Chesterton LJ, Selby NM, Burton JO, et al., editors. Baroreflex sensitivity is important in the haemodynamic response to cool-temperature dialysis (abstract SA-PO750). American Society of Nephrology Congress; 2007; San Francisco.
22. Smiseth OA, Torp H, Opdahl A, et al. Myocardial strain imaging: how useful is it in clinical decision making? *Eur Heart J*. 2015.
23. Assa S, Hummel YM, Voors AA, et al. Hemodialysis-induced regional left ventricular systolic dysfunction: prevalence, patient and dialysis treatment-related factors, and prognostic significance. *Clin J Am Soc Nephrol*. 2012;7(10):1615-23.
24. Odudu A, Eldehni MT, McCann GP, et al. Randomized Controlled Trial of Individualized Dialysate Cooling for Cardiac Protection in Hemodialysis Patients. *Clinical Journal of the American Society of Nephrology*. 2015;10(8):1408-17.
25. Selby NM, Burton JO, Chesterton LJ, et al. Dialysis-Induced Regional Left Ventricular Dysfunction Is Ameliorated by Cooling the Dialysate. *Clin J Am Soc Nephrol*. 2006;1(6):1216-25.
26. Karamperis N, Sloth E, Jensen JD. Predilution hemodiafiltration displays no hemodynamic advantage over low-flux hemodialysis under matched conditions. *Kidney Int*. 2005;67(4):1601-8.
27. Bagrov AY, Shapiro JI, Fedorova OV. Endogenous cardiogenic steroids: physiology, pharmacology, and novel therapeutic targets. *Pharmacol Rev*. 2009;61(1):9-38.
28. Jellis CL, Kwon DH. Myocardial T1 mapping: modalities and clinical applications. *Cardiovasc Diagn Ther*. 2014;4(2):126-37.
29. Lang RM, Badano LP, Mor-Avi V, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *Eur Heart J Cardiovasc Imaging*. 2015;16(3):233-70.
30. Messroghli DR, Radjenovic A, Kozerke S, et al. Modified Look-Locker inversion recovery (MOLLI) for high-resolution T1 mapping of the heart. *Magn Reson Med*. 2004;52(1):141-6.
31. Buchanan CE, Cox EF, Francis ST. Measuring myocardial blood flow using modified look locker inversion (MOLLI) recovery arterial spin labelling (ASL). *Proc Intl Soc Mag Reson Med*. 2015;64:2015.
32. Saeed M, Hetts SW, Do L, et al. MRI study on volume effects of coronary emboli on myocardial function, perfusion and viability. *Int J Cardiol*. 2013;165(1):93-9.
33. Jefferies HJ, Virk B, Schiller B, et al. Frequent hemodialysis schedules are associated with reduced levels of dialysis-induced cardiac injury (myocardial stunning). *Clin J Am Soc Nephrol*. 2011;6(6):1326-32.

34. Belle V, Kahler E, Waller C, et al. In vivo quantitative mapping of cardiac perfusion in rats using a noninvasive MR spin-labeling method. *J Magn Reson Imaging*. 1998;8(6):1240-5.

Figure Legends

Figure 1: Blood pressure and cardiovascular responses pre-, during, and post- dialysis for HD and HDF treatments. A) Systolic blood pressure (SBP) and diastolic blood pressure (DBP) data, B) SVI and CI measured using PC-MRI of aortic flow, showing a significant decrease during dialysis reaching a nadir after 230min and partial recovery at 50min post-dialysis, C) IVC flux showing a decrease during dialysis and recovery following treatment. Heart rate which did not change significantly throughout either dialysis treatment, but at 240 min was significantly different (*) between HD and HDF ($p < 0.05$).

Figure 2: A) (i) Whole wall short axis circumferential strain and (ii) whole wall longitudinal strain. Strain is seen to decrease (i.e. become less negative indicating less strain) during dialysis and subsequently return to baseline 70min post dialysis. B) (i) Number of dysfunctional segments in the short axis and (ii) number of dysfunctional segments in the long axis at time points during HD or HDF. Dysfunctional segments (>20% reduction in strain from baseline) are evident from 70min and then decrease but do not return to baseline following treatment. There were no differences in number of dysfunctional segments between HD and HDF at any time point (Repeated measures ANOVA across the five time points and between treatments). However on performing a paired t-test, a significant difference was seen between the two treatments at 70 min post ($p = 0.01$).

Figure 3: Baseline perfusion and nadir perfusion during dialysis for both HD and HDF. A significant decrease in perfusion is seen for both treatment modalities.

Figure 4: A) (i) A positive correlation between number of dysfunctional LV segments in the long axis and UFV for HD ($r = 0.70$, $p = 0.017$) and HDF ($r = 0.59$, $p = 0.046$). (ii) A negative correlation between change in SVI during dialysis and UFV ($r = -0.813$, $p = 0.001$ for HD; $r = -0.838$, $p = 0.001$ for HDF). (iii) A negative correlation between change in CI during dialysis and UFV ($r = -0.831$, $p = 0.000$ for HD and $r = -0.845$, $p = 0.001$ for HDF). B) (i) A negative correlation between change in SVI during dialysis and number of dysfunctional LV segments ($r = -0.720$, $p = 0.014$ for HD and $r = -0.698$, $p = 0.018$ for HDF). (ii) A negative correlation between change in CI during dialysis and number of dysfunctional LV segments ($r = -0.502$, $p > 0.1$ for HD and $r = -0.716$, $p = 0.015$ for HDF). (iii) A negative correlation between minimum SBP and number of dysfunctional LV segments was found for HD ($r = -0.8$, $p = 0.004$) but not HDF.

Figure 5: A) Crossover randomised controlled trial design. Patients were randomised to HD or HDF for two weeks, after which they attended a cardiac MRI scan which was performed before, during, and after a dialysis session. Thereafter, participants switched to the other treatment for a further 2 weeks, after which cardiac MRI assessment was again performed. B) Details of cardiac MR scan sessions, with the timing of the acquisition of each of the multiple MRI measures of cardiac structure and function that were collected in each 50min MR scan session.

Tables

Table 1: Patient demographic data

Ethnicity: Caucasian (n)	9 (75%)
Male (n)	10 (83.3%)
Age (years)	53 ± 12
Dialysis vintage (months)	56 ± 6
Fistula flow rate, Q_a (ml/min)	1051 ± 60
BMI	24.7 (21.7 to 30)
Dry Weight (kg)	79 (56.5 to 92.8)
Primary Renal Diagnosis	
Unknown	3 (25%)
Polycystic kidneys	3 (25%)
Diabetic nephropathy	2 (16.7%)
Other	4 (33.3%)
Diabetes mellitus	4 (33.3%)
Current smoker	2 (16.7%)
Residual renal function (creatinine clearance, ml/min)	1 (0-4)
NYHA status	
No Heart Failure	11 (91.7%)
Heart Failure NYHA Class1	1 (8.3%)
Charlson Comorbidity Index (Age Adjusted)	4 (3 to 5)
Medications	
ACEi/ARB	5 (41%)
Beta-blockers	4 (33.3%)
2 or more anti-hypertensive agents	4 (33.3%)

Table 2: Dialysis treatment data and laboratory parameters for haemodialysis (HD) and haemodiafiltration (HDF) study sessions. IDWG = interdialytic weight gain, IDH = intradialytic hypotension, UF = ultrafiltration, SBP = systolic blood pressure, DBP = diastolic blood pressure, URR = urea reduction ratio. Data presented as mean \pm standard error or median (interquartile range).

	HD	HDF	p
DIALYSIS TREATMENT DATA			
IDWG (% body weight)	2.13% (0.90 to 3.6)	2.0% (1.4 to 3.47)	0.38
Blood flow rate (ml/min)	365 (350 to 387)	365 (352 to 389)	0.82
Substitution volume (L)	n/a	23.0 ± 2.5	
UF rate (ml/kg/hr)	3.8 ± 2.9	4.4 ± 2.5	0.29
UF volume (L)	1.1 ± 0.7	1.3 ± 0.6	0.41
SBP (mmHg)	Pre 150.2 ± 23.40	Pre 150.3 ± 22.78	0.43
	During 140.9 ± 6	During 142.2 ± 6	0.46
	Post 144.3 ± 18.20	Post 140.7 ± 21.26	0.25
DBP (mmHg)	Pre 80.58 ± 12.95	Pre 75.92 ± 13.05	0.93
	During 78.8 ± 12	During 77.0 ± 12	0.28
	Post 80.25 ± 14.69	Post 80.00 ± 12.21	0.21
Tympanic temperature pre- to post-dialysis (°C)	-1.0 ± 0.4	-1.0 ± 0.4	0.98
Number of IDH episodes	0	1	
BLOOD SAMPLE DATA			
Haemoglobin (g/L)	119.5 ± 7	120.8 ± 3	0.60
URR (%)	74.6 ± 9	75.6 ± 9	0.28
Bicarbonate (mmol/L)	24 (21 to 25)	23.5 (22 to 24.7)	0.83
Adjusted Calcium (mmol/L)	2.38 ± 0.13	2.48 ± 0.11	0.09
Phosphate (mmol/L)	1.43 ± 0.38	1.47 ± 0.31	0.69
PTH (ng/L)	191.0 (146.8 to 49.3)	200 (139 to 307.8)	0.52
Magnesium (mmol/L)	0.98 ± 0.14	1.03 ± 0.15	0.10
nT-proBNP (ng/L)	2145 (1102 to 3379)	1512 (1026 to 2261)	0.052
Pre dialysis cTnT (ng/L)	64.7 ± 70	62.4 ± 58	0.65
Post dialysis cTnT (ng/L)	53.8 ± 57	37.3 ± 32	0.043
Pre-dialysis sodium (mmol/L)	140.5 ± 0.7	140.6 ± 0.5	0.68
Post-dialysis sodium (mmol/L)	139.0 ± 0.5	138.8 ± 0.4	0.74

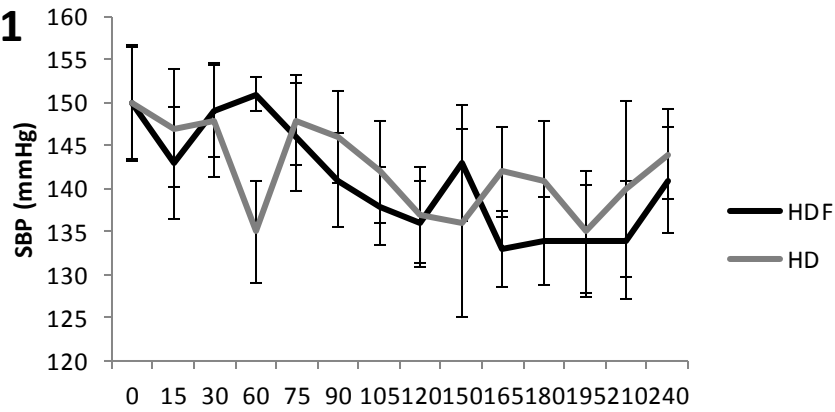
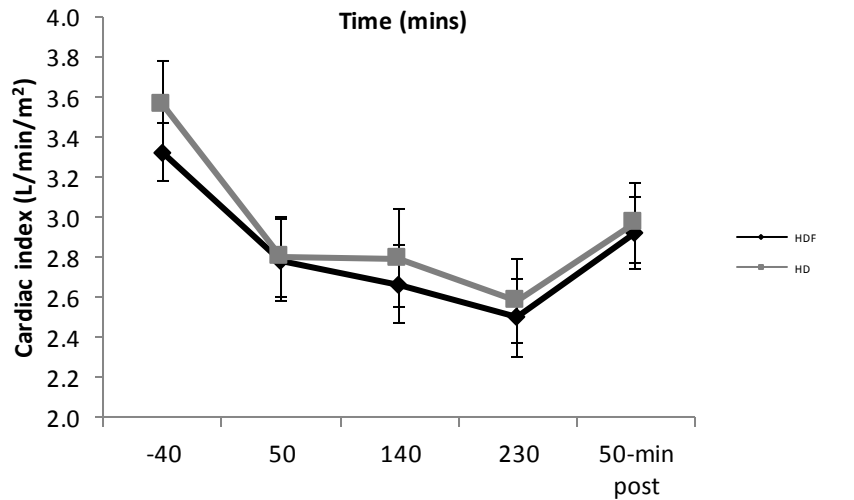
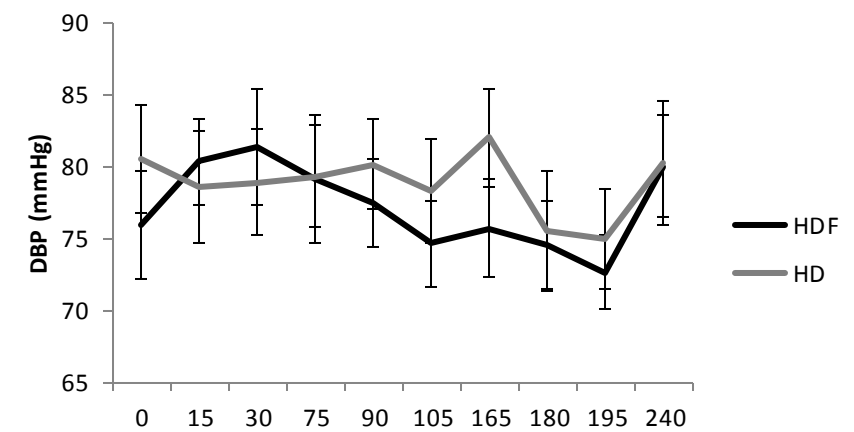
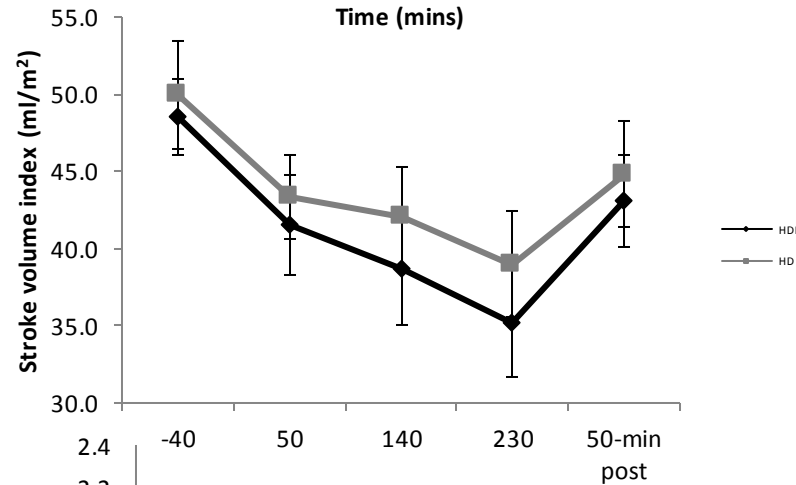
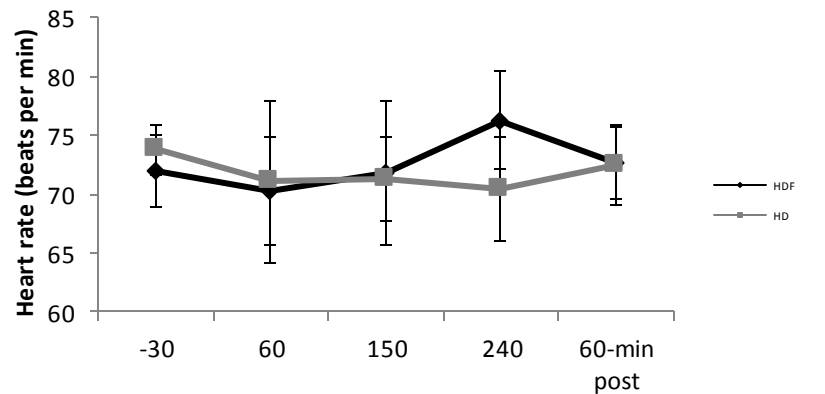
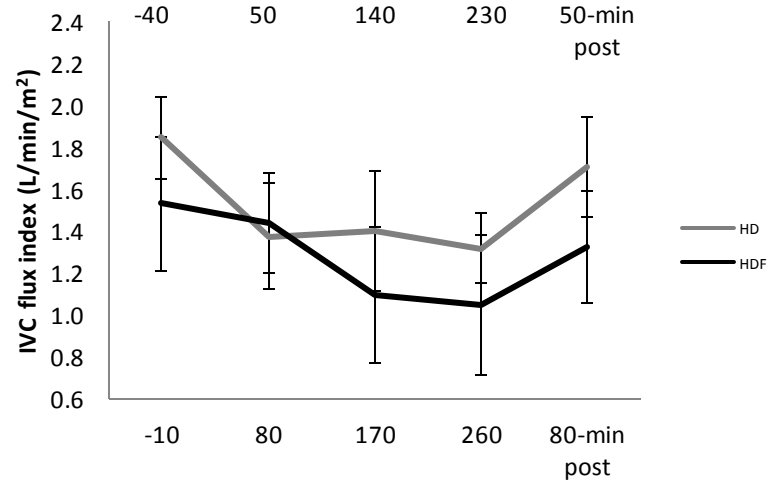
Figure 1**A****B****C**

Figure 2

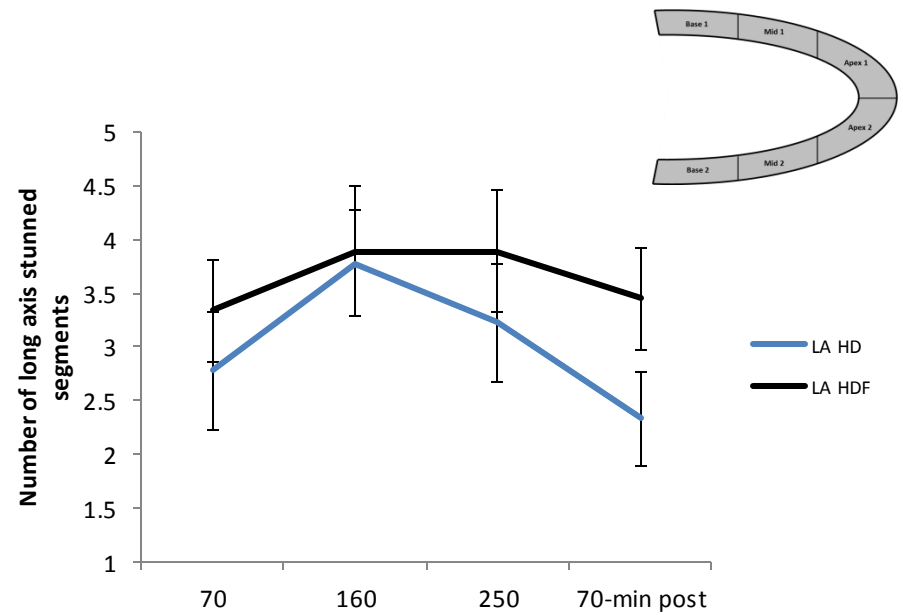
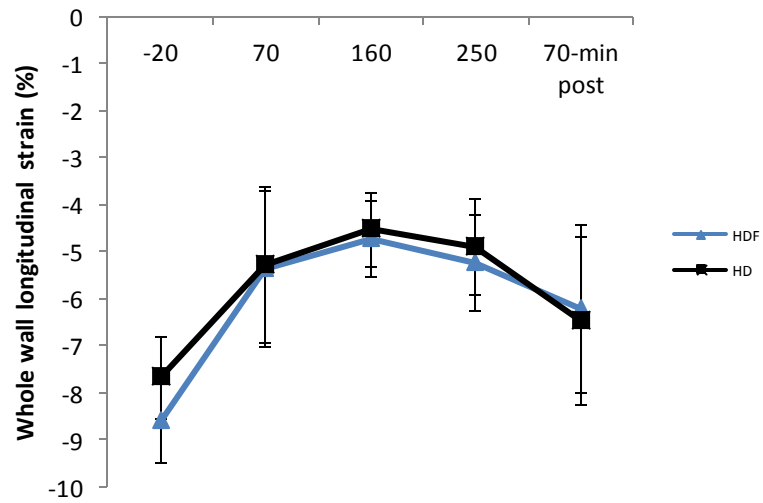
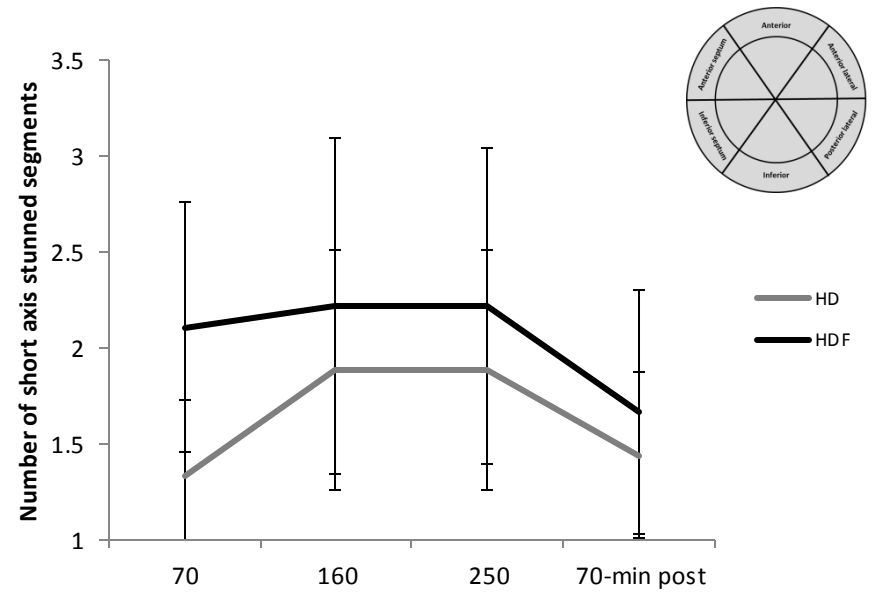
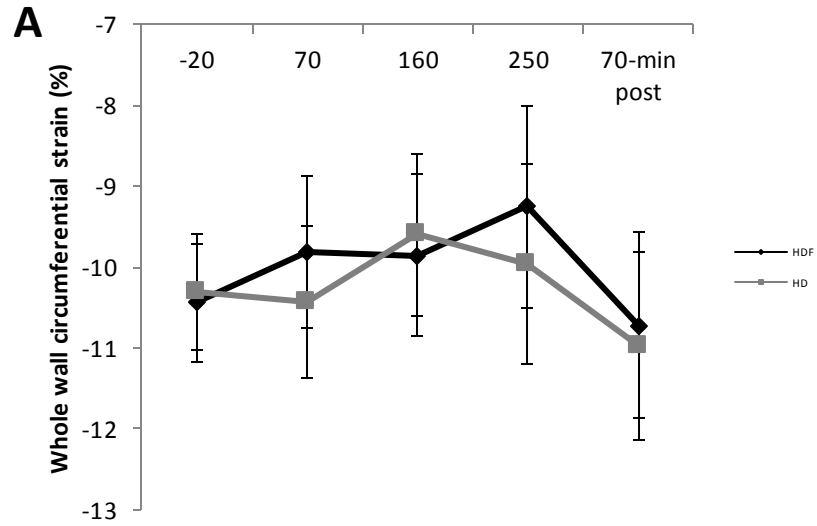


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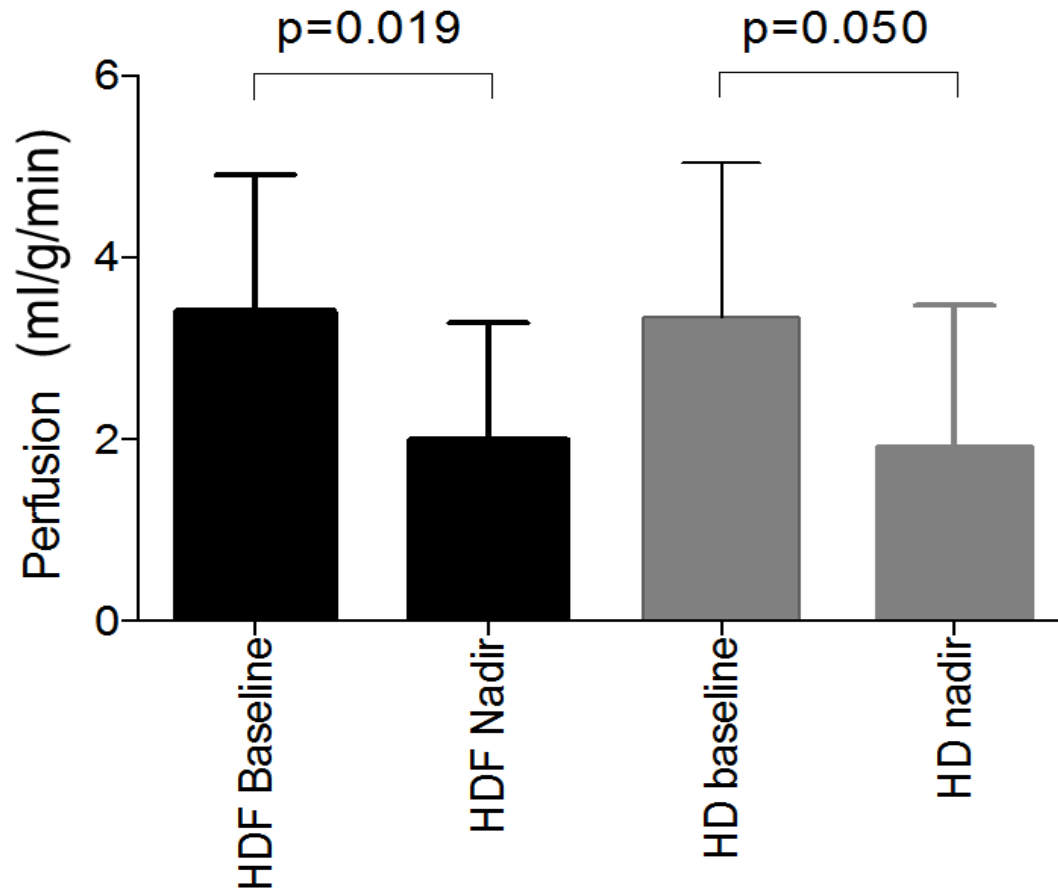


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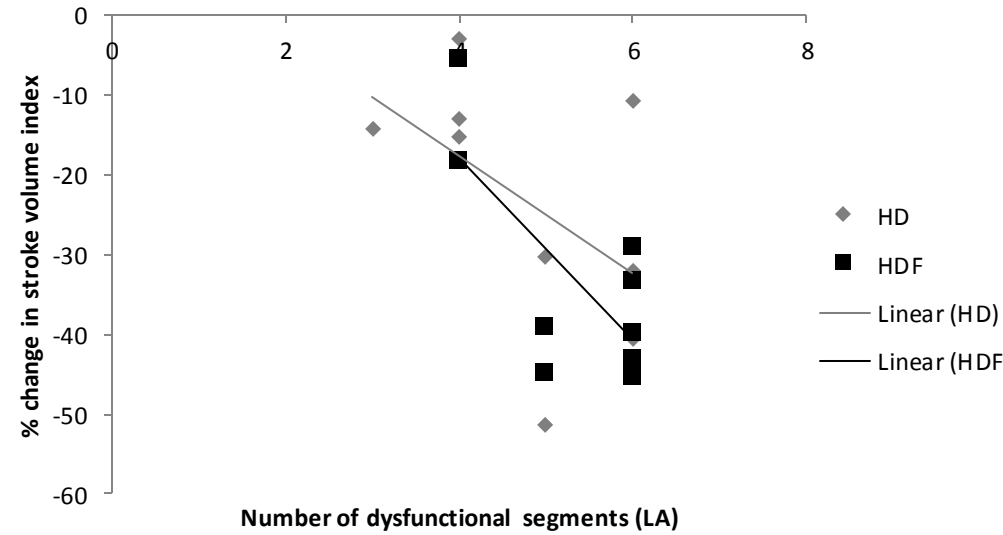
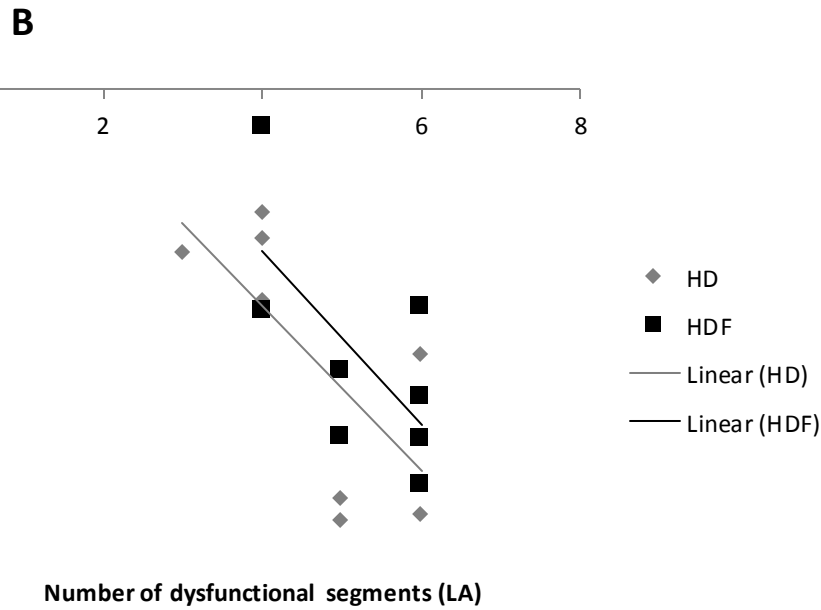
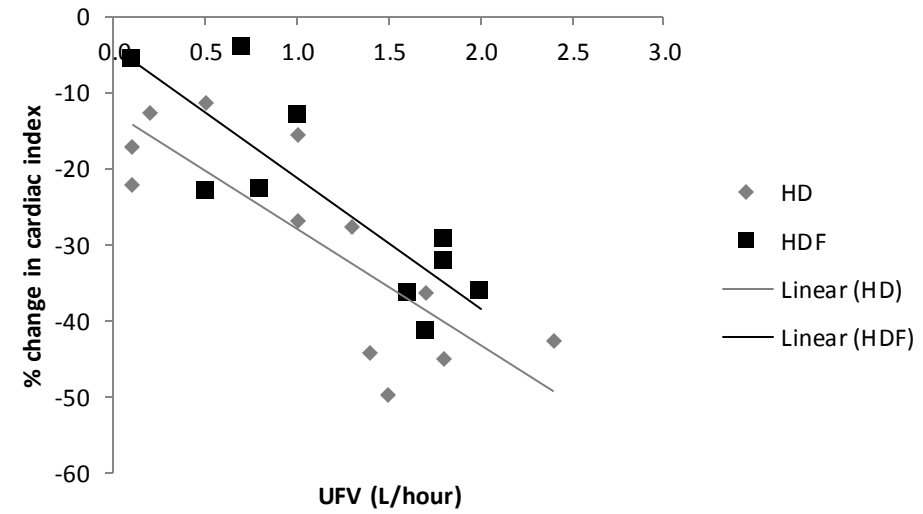
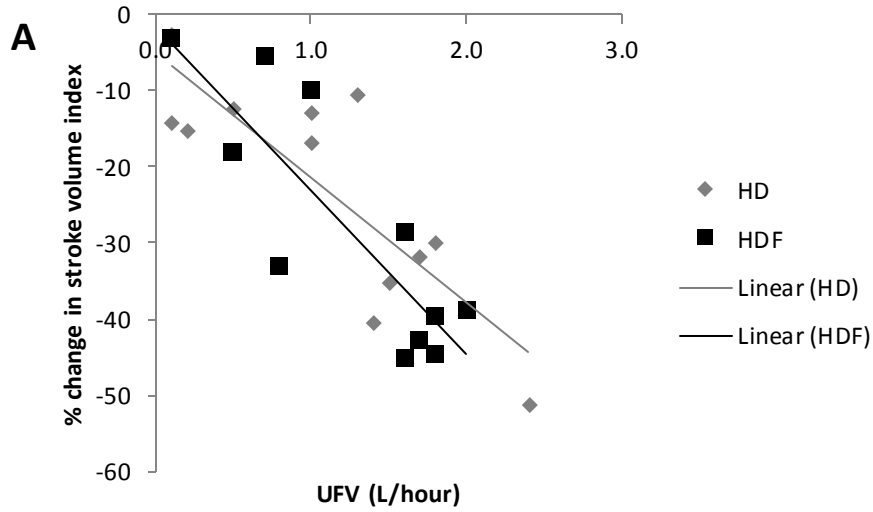
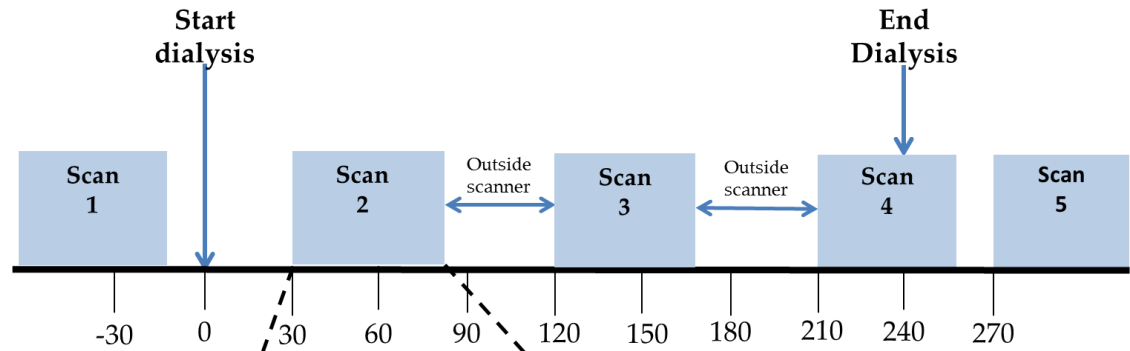
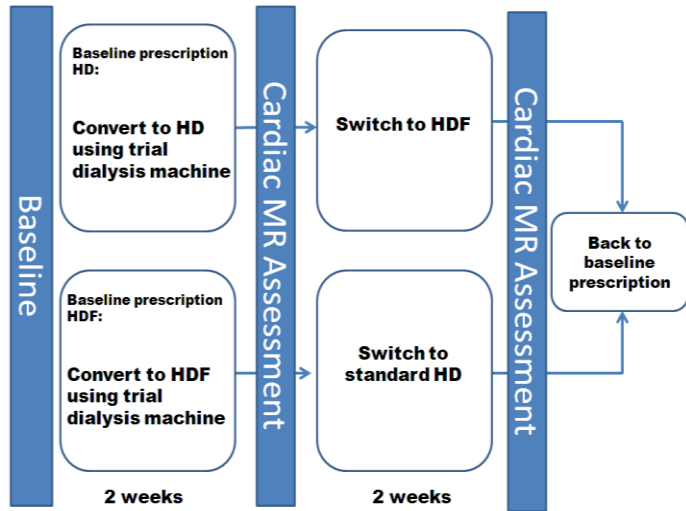


Figure 5

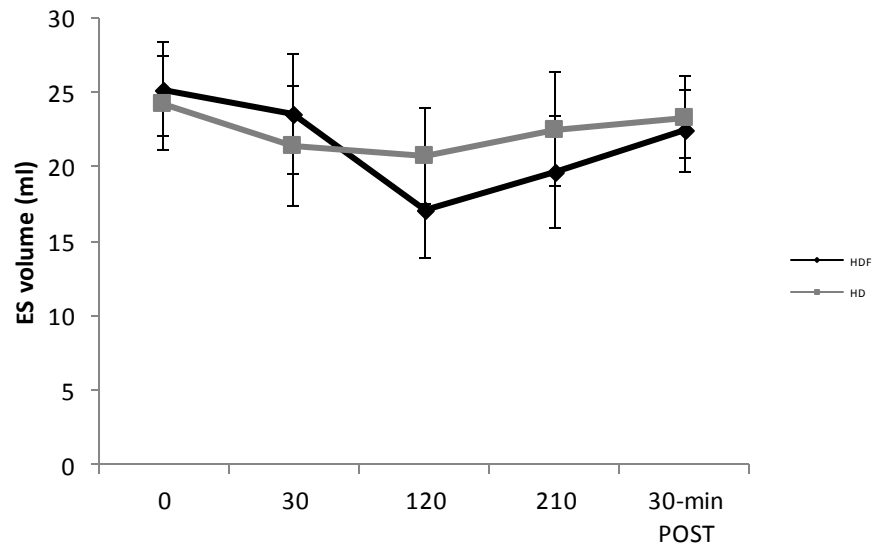
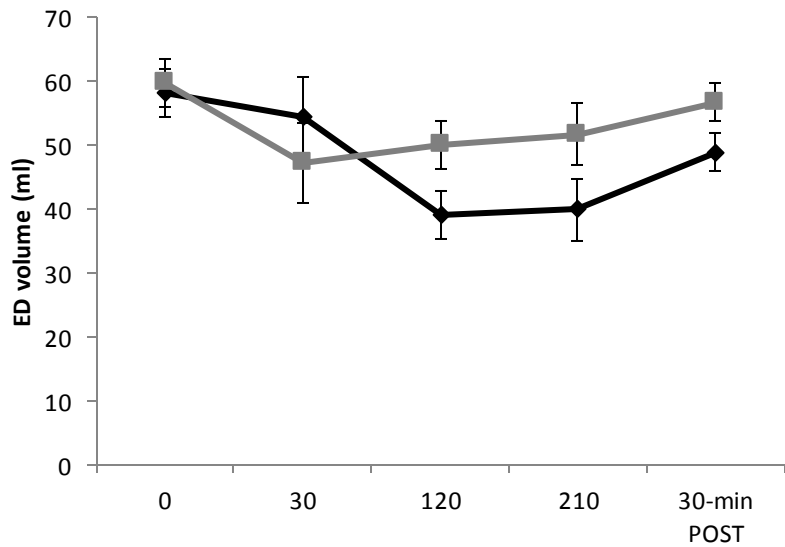
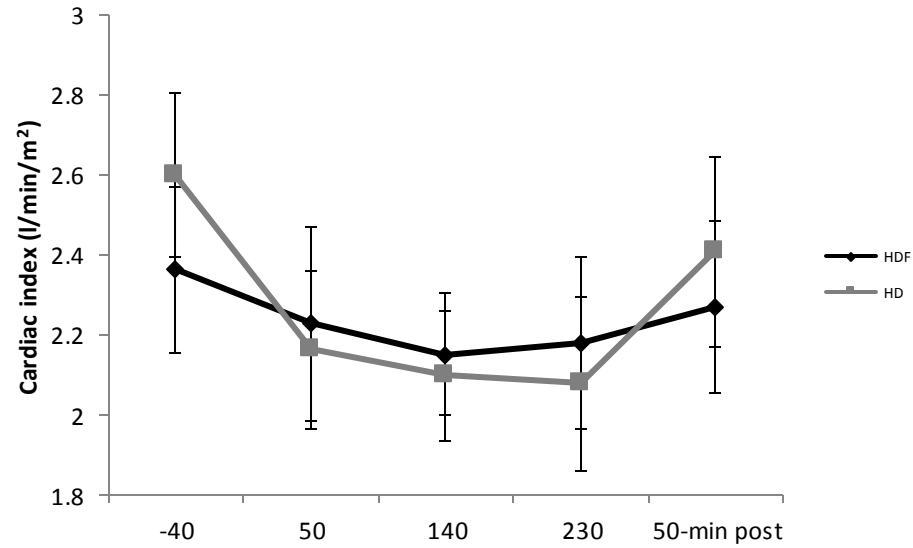
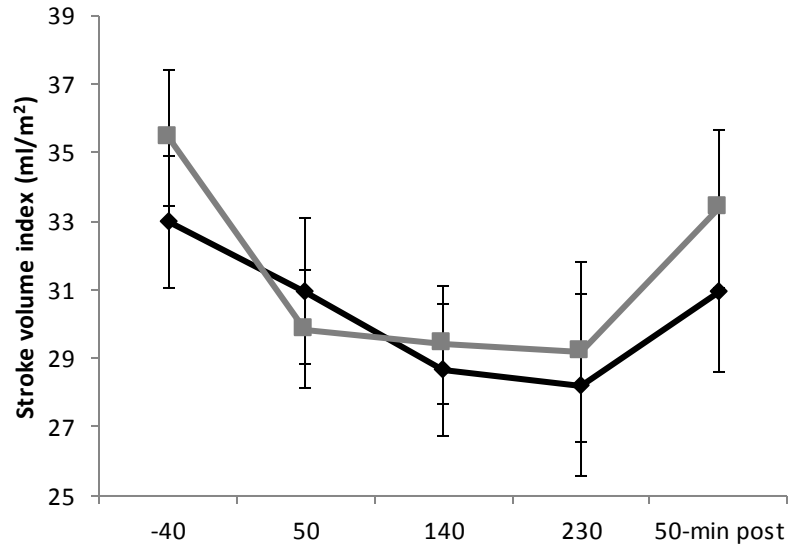
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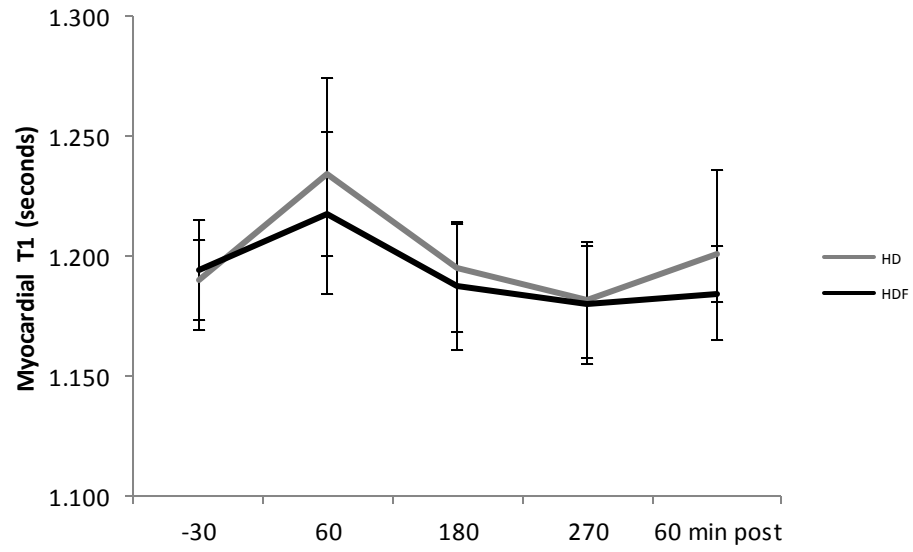
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Timing (minutes)	Scan
1 – 20	Survey and localisers
20	Short axis cine
25	MOLLI-ASL
30	MOLLI T ₁
36	Coronary artery PCA
38	Myocardial Tagging
50	Inferior vena cava PCA

Appendix Figure 1 - Cine MR data



Appendix Figure 2



Appendix Figure 3

Coronary flow and mean perfusion

