An analysis of frequency of continuous blood pressure variation and haemodynamic responses during haemodialysis

Short title: Blood pressure variation during haemodialysis

Latha Gullapudi[1], Kelly White[2], Jill Stewart[3], Paul Stewart[3], Mohammed T. Eldehni[2], Maarten W. Taal[1,2], Nicholas M. Selby[1,2]

1. Centre for Kidney Research and Innovation, Division of Medical Sciences and Graduate Entry Medicine, School of Medicine, University of Nottingham, Derby, United Kingdom

2. Renal Unit, Royal Derby Hospital, Derby, United Kingdom

3. School of Health and Social Care, University of Derby, United Kingdom

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Abstract

Background

During dialysis, higher beat-to-beat blood pressure (BP) variation, measured by extrema point (EP) frequency analysis of continuous BP monitoring, is associated with elevated cardiac damage markers and white matter ischaemic changes in the brain, thus suggesting its relevance to end-organ perfusion. We therefore utilised EP analysis to study intra-dialytic BP variation with an aim of improving individualised description of the haemodynamic response to haemodialysis (HD).

Methods

We recruited 50 participants receiving in-centre HD and performed continuous non-invasive haemodynamic monitoring during dialysis. EP mean arterial pressure (MAP) frequencies were extracted. Participants were divided into those with a greater proportion of low frequency (LF) (n=21) and high frequency (HF) EP values (n=22). Clinical and haemodynamic data were compared between groups.

Results

Median EP MAP frequencies of mid-week HD sessions were 0.54 Hz (IQR 0.18) and correlated with dialysis vintage (r=0.32, p=0.039), NT pro-BNP levels (r=0.32, p=0.038), and average real variability (ARV) of systolic BP (r=0.33, P=0.029), ARV diastolic BP (r=0.46, p=0.002) and ARV MAP (r=0.57, P<0.001).

In LF group, MAP positively correlated with Cardiac Power Index (CPI) in each hour of dialysis, but not with total peripheral resistance index (TPRI). In contrast, in HF group, MAP correlated with TPRI in each hour of dialysis but only with CPI in first hour.

Conclusions

EP frequency analysis of continuous BP monitoring during dialysis allows assessment of BP variation, and categorisation of individuals into low or high frequency groups,

which were characterised by different haemodynamic responses to dialysis. This may assist in improved individualisation of dialysis therapy.

Key points

What is already known about this subject:

Extrema point (EP) frequency analysis is a method that has been used to study beat to beat BP variation during haemodialysis. Higher EP variation in mean arterial pressure is associated with elevated cardiac biomarkers and ischaemic changes in the brains of HD patients, and so could be considered as surrogate measure of haemodynamic stress.

What this study adds:

We developed EP analysis method further by proposing a ratio of high EP frequency to low EP frequency changes (HFC/LFC) to categorise dialysis patients based on their predominant pattern of BP variation.

We have demonstrated that lower versus higher HFC/LFC ratios were associated with different baseline characteristics, differing haemodynamic responses and diverging trends of HFC/LFC ratios during the course of HD treatments. Hence may provide information on individuals physiological responses to HD induced haemodynamic stress.

What impact this may have on practice or policy:

Our findings might be helpful to provide personalised treatments based on the individual haemodynamic responses to stress induced by haemodialysis. Further prospective studies are required to determine if these groups respond differently to differening strategies for prevention or treatment of intradialytic hypotension. If proven to be beneficial then will have major impact in addressing significant clinical problem of haemodynamic instability in dialysis population and its consequences.

Introduction:

Intradialytic hypotension (IDH) is a commonly encountered problem during haemodialysis (HD) with a reported incidence of 10-40% (1-3). It is associated with ischaemic end-organ damage (4, 5) and mortality (6, 7). However, arbitrary blood pressure (BP) thresholds do not reliably predict end organ ischaemia (8), and asymptomatic IDH may result in reduced organ perfusion (9). Furthermore, subclinical myocardial ischaemia has also been demonstrated during continuous renal replacement therapies with apparently stable haemodynamics and low ultrafiltration rates (10). These observations imply that factors other than the absolute drop in BP play a key role in inducing ischaemic organ damage, one of which may be the degree and frequency at which BP varies.

Higher variation in systolic BP (SBP) has been linked to cardiovascular events, cerebrovascular events and increased mortality in the general population (11, 12) and in those with CKD (13, 14). In HD populations, higher variability in predialysis SBP is associated with a 15% increase in the risk of mortality (15, 16). Likewise, greater interdialytic SBP variability assessed using average real variability (derived from ambulatory BP monitoring during the 44-hour interdialytic period) is independently associated with cardiovascular mortality (17). In addition, the HD population face unique haemodynamic stresses related to dialysis treatment and are often subject to acute BP variations during dialysis. Many studies reporting intradialytic BP changes relied on intermittent, infrequent (every 15-60 minutes) BP readings from an arm cuff, which do not provide detailed resolution of more rapid BP variations that may occur during HD (18). Detailed study of intradialytic beat-to-beat BP variation using continuous monitoring is lacking. In patients with Transient Ischaemic Attacks or non-disabling stroke, higher beat to beat BP variability is a better predictor of recurrent strokes and cardiovascular events than day-to-day variations (11).

Extrema point (EP) frequency analysis, a method of measuring BP variation, utilises peaks and troughs of a continuously recorded BP waveform to calculate the frequency of variation (19). In a previous study, the EP frequencies of mean arterial pressure (MAP) during HD were reported to rise during HD and reached peak during the 3rd

quarter of HD session, at which time there was a drop in the absolute BP. Higher EP MAP frequencies during HD were associated with higher cardiac troponin levels and greater ischaemic changes in the brain white matter detected by magnetic resonance imaging. This suggests that higher EP frequencies, representing greater beat-to-beat BP variation, may adversely affect organ perfusion (4, 20). Importantly, in a randomised trial of standard versus cooled dialysate HD where the latter prevented subclinical brain white matter ischaemic injury, EP frequencies increased during standard HD but did not change significantly during cooled dialysis, indicating that EP frequency could be a potential modifiable target for interventions (4). Therefore, we aimed to prospectively study EP frequencies during dialysis to identify the factors associated with higher values, and to describe how EP frequencies relate to changes in central haemodynamics during dialysis. To do so, we propose a new method of categorising patients based on their individual intra-dialytic EP frequency data.

Methods:

Patients and Data Collection

We performed a prospective observational study at University Hospitals of Derby and Burton NHS Foundation Trust, United Kingdom between January 2018 to August 2019. The study was approved by the West Midlands Ethics Committee and written informed consent was obtained from all participants.

Participants were aged ≥18 years and had been receiving HD for more than 3 months. Baseline characteristics, details of the dialysis prescription, medication history and laboratory parameters were collected. HD was performed thrice weekly using Gambro Artis machines with participants' usual dialysis prescription. Net ultrafiltration was based on the individual's prescribed dry weight and anticoagulation was provided with unfractionated heparin.

Continous blood pressure monitoring

Continuous non-invasive monitoring of blood pressure and haemodynamics was performed using pulse wave analysis (Finapres NOVA, FMS, Netherlands) for the entirety of three consecutive dialysis treatments. This method of continuous monitoring has been validated in HD populations previously (21, 22).The Finopres uses a digital artery finger cuff and infrared plethysmography to detect digital artery diameter, which is then kept constant by an ultra-fast pressure servo controller that rapidly adjusts the cuff pressure. The pressure changes in the finger cuff are therefore representative of the intra-arterial pressure changes. The measured pulse waveform is used to calculate a full range of haemodynamic variables on a continuous basis for each heart beat (23); these include heart rate (HR), blood pressure (BP), stroke volume index (SV), cardiac index (CI) and total peripheral resistance index (TPRI). The device was fitted to the non-fistula arm (in participants with arteriovenous fistula as HD access) at the start of the investigatory HD session and left in place throughout.

Signal processing and identification of extrema points

The haemodynamic data generated by the Finapres were analysed by first identifying the frequency and amplitude of local extrema points (maxima and minima; EP) for

MAP as previously described (19), summarised in Figure 1. A modified Short-time Fourier Transform method was then applied as a moving asynchronous filter to extract the sinusoidal frequency and phase content of time-varying MAP signals (24). These spectra were then decomposed into constituent frequency events using the Freedman-Diaconis rule (25), and plotted as histograms for each individual patient (example shown in Figure 2).

Categorisation of participants based on EP MAP frequencies

As higher EP frequencies have been shown previously to associate with ischaemic brain injury, we hypothesised that patients could be characterised using the ratio of high to low EP frequency values during dialysis. To calculate ratios of high to low EP frequency values, we plotted histograms of EP frequencies for each individual (Figure 3) from processed data from a mid-week HD session (48-hour interdialytic gap) and defined:

- HFC (high frequency changes) as EP frequencies that were occurring within the same frequency range as the mean intradialytic heart rate ± two standard deviations, representing beat-to-beat variation in BP.
- LFC (low frequency changes) were defined as those occurring in the frequency range of three or more cardiac cycles, corresponding to those with a frequency range below one third of mean heart rate + two standard deviations.

Based on median HFC/LFC ratio the study population was divided into two groups: Low frequency (LF) group with HFC/LFC ratio ≤0.5 and High frequency (HF) group group with HFC/LFC ratio >0.5. Haemodynamic trends and clinical variables were then compared between these groups.

Haemodynamic data processing and definitions:

In addition to the haemodynamic data generated by the Finapres, we calculated

- Cardiac power index (CPI=*MAP x CI x 0.0022 w/m², normal range = 0.45 to 0.85 w/m²*) which has been shown to be independently associated with adverse outcomes in cardiogenic shock (26) and has been utilised to categorise patients with differing intradialytic haemodynamic responses to fluid removal (27).
- Average real variability ($ARV = \frac{1}{N-1}\sum_{K=1}^{N-1} x\ |BP_{K+1} - BP_K|$; *where K ranges from 1 to N-1; N is the number of intradialytic BP readings (28))*. Whilst EP analysis

evaluates frequency of BP change, ARV describes the magnitude of BP variation. Higher ARV (24-hour BP monitoring) has been shown to be associated with increased all cause mortality, cardiovascular mortality and non-fatal strokes (17, 29, 30), but has not been used to describe continuous BP recordings during dialysis.

- Baroreflex sensitivity (BRS) as a measure of cardiovascular autonomic integrity was derived as a regression of pulse interval against systolic blood pressure. Using Matlab (R2011a, MathWorks®, Natik, MA, USA) interbeat intervals and corresponding systolic blood pressures were computed from Finapres data. The geometric mean for the whole dialysis session was then used to assess BRS during HD for each individual.

Haemodynamic measures during the intradialytic period were averaged over 10 minute blocks to study the trends in BP and other haemodynamic measures during HD (apart from BRS).

Traditional definitons of IDH are difficult to apply to continuous BP data, hence we assessed IDH by recording:

1. Proportion of the SBP readings below 90mmHg from the total of intra-dialytic BP measurements,
2. Proportion of the SBP readings 20mmHg below the pre-dialysis brachial SBP from the total of intra-dialytic BP measurements.

Statistical analysis:

Continuous variables are expressed as mean ± SD for normally distributed variables, median and interquartile range for non-parametric data. Categorical variables are expressed as percentages. Spearman's correlation was used where the data were non-parametric. Friedman's nonparametric analysis of variance was used to test variations between time points and Kruskal Wallis test was used to test variance between groups. Matlab (R2018a) was used for extraction of EP frequencies. Statistical analysis was performed using IBM SPSS (Version 24). A $p< 0.05$ was considered significant.

Results:

A total of 50 participants was recruited, from which 43 participants completed at least one monitored mid-week HD session (48-hour interdialytic gap) (Figure 4). Characteristics of the study population are presented in Table 1a. Mean age was 61.5±16.6 yrs, 26 (60.5%) were male and 19 (44.2%) had diabetes. Median time since dialysis initiation was 24 months (IQR 75), and arteriovenous fistula was the predominant vascular access (83.7%). Median charlson comorbidity score (CCI) was 4 (IQR 2).

Haemodynamic parameters for the study population are described in Table 1b. Intradialytic trends of BP and other haemodynamics are illustrated in Figure 5: on average an initial brief rise was followed by gradual decline in SBP, MAP, DBP, CI and CPI. TPRI increased during dialysis.

The median proportion of recorded BP measures per participant that were <90mmHg was 0.79% (IQR 3.03%). The median proportion of SBP readings 20mmHg below the pre-dialysis brachial SBP was 9% (IQR 27.5%).

EP MAP frequencies and association with clinical variables:

The median of EP MAP frequencies was 0.54 (IQR 0.18) Hz across all participants. While BP declined during HD, EP MAP frequencies showed a tendency to increase with peak values in the third hour (Figure 6), although this did not reach statistical significance ($p=0.671$).

Dialysis vintage ($r=0.32$, $p=0.039$), NT-pro BNP levels ($r=0.32$, $p=0.038$), average real variability (ARV) of SBP ($r=0.33$, $p=0.029$), ARV of DBP ($r=0.46$, $p=0.002$) and ARV of MAP ($r=0.57$, $p\leq0.0001$) were correlated with higher intradialytic median EP MAP frequencies. Variables that were not associated with median EP frequency included age ($r=0.2$, $p=0.2$), CCI ($r=0.07$, $p=0.659$), diabetic status ($z=-1.48$, $p=0.139$), prescription of beta-blockers ($z=-1.84$, $p=0.278$), ultrafiltration volumes ($r=0.1$,

p=0.542), baroreflex sensitivity (r= -0.27, p=0.08) and the blood volume change during HD (r=-0.27, p=0.096).

HFC/LFC ratio and association with clinical variables:

Median intradialytic HFC/LFC ratio was 0.517 (IQR 0.42) for the study population. There was no significant difference in the median intradialytic HFC/LFC ratios of consecutively monitored HD sessions of each participant on repeated measures non-parametric anova (p=0.697), indicating intra-individual repeatability of this measure.

The demographics, clinical and biochemical variables across the groups defined by MAP frequency patterns are shown in Table 2. There were no differences in age, proportion with diabetes, CCI or dialysis vintage between the groups.

In the HF group, there was a higher proportion of participants on anti-hypertensive therapy including beta-blockers (HF group 45.5% vs LF group 14.3%, p=0.026). This group also had higher NT-pro BNP levels (HF group 6285.5 [IQR 20217] vs LF group 1949 [3941], p=0.045). ARV of BP during HD was higher in HF group (Table 2). However there was no difference in BRS between the groups (HF group 8.23 [IQR 3.54] vs LF group 9.55 [IQR 6.29]) (p=0.903).

In the entire study population, average hourly HFC/LFC ratios did not demonstrate any specific direction of change (Figure 7). However there was a decline in HFC/LFC ratio in the LF group during HD (reaching nadir in 3rd hour) and no change in HF group (Figure:8). The HFC/LFC ratios differed significantly between the groups during every hour of HD (Figure 8).

Intradialytic haemodynamic responses in LF and HF groups:

We examined the associations between intradialytic haemodynamic variables within the groups to assess if haemodynamic responses to dialysis differed depending on HFC/LFC ratio. To do so we calculated the mean intradialytic haemodynamics for the entire HD session (4 hours) and also means for each hour of HD.

In the LF group, mean intradialytic MAP correlated with mean intradialytic CPI (r=0.64, p=0.002) but not with mean intradialytic TPRI (Figure 9). The opposite was observed in HF group, with correlation of mean intradialytic MAP with mean intradialytic TPRI (r=0.66, p=0.001) but not with mean intradialytic CPI (Figure 9).

Comparisons between the hourly means of haemodynamics demonstrate two findings. Firstly, the hourly means of MAP, CPI and TPRI were not different between LF and HF groups (Table 3). Secondly, the association between various haemodynamic variables changed differentially in the two groups. In the LF group, MAP was positively correlated with CPI in each hour of dialysis, but not with TPRI (Table 4, Figure 10a and 10b). In contrast in the HF group, MAP correlated with CPI in the first hour of dialysis only; but MAP did correlate with TPRI in each hour of dialysis (Table 4, Figure 10c and 10d).

We performed a sensitivity analysis using intradialytic SBP instead of intradialytic MAP. Correlations between intradialytic SBP, CPI and TPRI were similar to that of intradialytic MAP. In the LF group there was a strong positive correlation of SBP with CPI (r=0.592, P=0.005) but not TPRI, and in the HF group SBP correlated with TPRI (r=0.713, P=<0.001) but not CPI (Figure 9).

Intradialytic Hypotension:

The average proportion of BP measurements with SBP <90mmHg in the LF group was 0.74% (IQR 3.6%) vs 0.91% (IQR 2.35%) in HF group (p=0.145). The proportion of measured BP values 20mmHG below initial predialysis SBP was 6.81% (IQR 15.17) and 14.56% (IQR 32.77%) in LF and HF groups respectively (p=0.884).

Discussion:

We have utilised Extrema Points frequency analysis to analyse continuous BP measurements during HD, and have further developed the method by proposing a ratio of high to low EP frequency changes to categorise dialysis patients based on the proportion of BP variation that occurs on a beat-to-beat basis, versus variation which happens more slowly over several cardiac cycles. We have demonstrated that lower versus higher HFC/LFC ratios were associated with differing haemodynamic responses and diverging trends of HFC/LFC ratios during the course of HD treatments.

BP variability has been described using several different methods and has been linked to adverse outcomes, including in HD populations. Shafi et al demonstrated that each standard deviation increase in BP variability was associated with increased risk of all cause mortality (HR 1.18; 95% CI 1.13-1.22), cardiovascular mortality (HR 1.18; 95% CI 1.12-1.24) and first cardiovascular event (HR 1.11; 95% CI 1.07-1.15) (15). Similarly, Wang et al reported that every 1% increase in the coefficient of variation of predialysis BP was associated with increased cardiovascular (HR 1.71; 95% CI 1.01-2.90) and all cause mortality (HR 1.80; 95% CI 1.11-2.92) (31). In a study involving 103 HD patients with interdialytic ABPM (ambulatory BP monitoring) and average real variability (ARV) assessment, Feng et al reported that higher ARV was independently associated with higher cardiovascular mortality after adjustment for demographics and clinical factors (HR: 1.143; 95% CI 1.022-1.279) (17). However, a comparable study by Sarafidis et al involving 227 HD patients, after adjusting for other clinical and demographic factors, reported no significant association of higher ARV of interdialytic SBP with composite endpoint of all cause mortality, non-fatal MI or non-fatal stroke (30). To our knowledge there are a limited number of studies examining intradialytic BP variability. Flythe et al (32) studied intradialytic BP using absolute SBP spline curves (i.e. curve fitting as opposed to assuming a linear change in SBP) and demonstrated that greater ultrafiltration volume (UFV), older age and shorter dialysis vintage were associated with increased SBP variability. They also reported high SBP variability (more than the observed median in their study population) was associated with greater risk of all cause mortality with HR 1.26, 95% CI 1.08-1.47, when compared to the patients with lower SBP variability (less than observed median) (18).

All of above described methods assess the magnitude of BP variability. However, our method of EP analysis approaches BP variability by assessing *frequency* of BP change. Previous studies involving EP MAP frequencies have shown that higher frequency of BP variation is associated with ischaemic changes in the brain and interventions (cooled dialysate) that reduce frequency of BP variation are protective against this (4). This suggests that frequency of BP variation is an important determinant of organ perfusion. The lack of correlation between UFV and EP MAP frequencies in our analysis indicates that EP frequency analysis may be less dependent on external factors that may affect magnitude of BP change and may be more reflective of the physiological reserve of the individual. This is supported by insignificant intra-individual variability of median EP frequencies between the three monitored HD sessions. In addition, we demonstrated a strong correlation between EP MAP frequencies (frequency of variability) and ARV (magnitude of variation) of BP, suggesting greater frequency of variation is associated with greater magnitude of variation. Thus interventions that reduce EP frequencies may help to address the magnitude of variability and we can speculate as to whether this will in turn lead to clinical benefit.

We have confirmed the intradialytic trends of EP MAP frequencies (reaching peak during the third hour of HD) and their associations with higher cardiac biomarkers (positive correlation with NT-pro BNP levels) as decribed in previous studies (20). Although there is ongoing debate about the appropriate cuff off values for BNP/NT-pro BNP in HD population, published literature supports their prognostic value at least at population level. A meta-analysis by Cheng et al (33) involving 27 studies with 8666 patients with ESRD reported that elevated BNP/NT-pro BNP were significantly associated with increased all cause mortality [OR: 3.85 (95% CI: 3.11 to 4.75)], cardiovascular mortality [OR: 4.05 (95% CI: 2.53 to 6.84)] and cardiovascular events [OR: 7.02 (95% CI, 2.21 to 22.33)]. Thus, we may conclude that patients with cardiac disease (known or subclinical) tend to have higher frequency of BP variability.

We also demonstrate for the first time that there are distinct patterns in the hemodynamic responses to HD in those with low vs high HFC/LFC ratio. In the LF group, MAP appeared to be more dependent on cardiac function (stronger associations with CPI), without significant dependency on TPRI. This suggests that

these patients have sufficient cardiac reserve to maintain BP during dialysis without the need for maximal vasoconstriction. In contrast, in the HF group, MAP was more dependent on TPRI. As the equation for CPI includes MAP values, it was therefore surprising to observe a loss of corelation of MAP and CPI in the HF group as dialysis progressed, and this may suggest a reduced cardiac reserve. As a result, participants in the HF group appeared to become dependent on TPRI for maintainence of BP. Comparable findings were demonstrated in a study of 54 HD patients by Levin et al. The authors described three different profiles of haemodynamic response during HD sessions with intradialytic hypotension episodes: (i) a reduction in CPI with little change in TPRI; (ii) a reduction in TPRI with little change in CPI; and (iii) reduction of both CPI + TPRI (34). Demonstration of these different patterns of haemodynamic response to dialysis in our study suggests that EP frequency analysis may allow better assessment of an individual's physiological behaviour. This may ultimately lead to more individualised approaches to prevent or manage IDH.

Although we have demonstrated novel interesting relationships and differences in the intradialytic haemodynamic behaviours of the individuals, there are some limitations of our study. Firstly, the categorisation of the participants in our study was based on 4 hours of intradialytic haemodynamic data that is not feasible in the standard clinical setting. Given that HFC/LFC ratios adopted diverging patterns as dialysis progressed (figure 9), there is a potential to categorise based on a shorter period of haemodynamic monitoring during HD and this should be evaluated in future. Secondly, we included patients with a low incidence of IDH and were therefore unable to adequately assess possible associations between BP frequency patterns and IDH. Further studies that include more hypotension-prone patients are required to explore associations with IDH and other clinical outcomes. Finally, our study also highlights an important technological gap in the haemodynamic monitoring adopted for HD patients. Intermittent BP measures, the current standard of practice, are not sufficient to allow EP analysis, whilst the currently available non-invasive continuous BP monitoring methods are not practical for HD patients outside of a research setting. Methods to achieve less burdensome continuous intradialytic BP monitoring are in development (35).

In conclusion, EP frequency analysis of continuous BP monitoring during dialysis allows assessment of BP variation, and individuals can be categorised into having patterns of low or high frequency variation. This may provide information on patients' physiological responses to haemodynamic stress during HD and in future may allow individualised treatment strategies to mitigate against dialysis-induced ischaemic injury.

References:

1. Kuipers J, Verboom LM, Ipema KJR, Paans W, Krijnen WP, Gaillard CAJM, et al. The Prevalence of Intradialytic Hypotension in Patients on Conventional Hemodialysis: A Systematic Review with Meta-Analysis. American Journal of Nephrology. 2019;49(6):497-506.
2. Sands Jeffrey J, Usvyat Len A, Sullivan T, Segal Jonathan H, Zabetakis P, Kotanko P, et al. Intradialytic hypotension: Frequency, sources of variation and correlation with clinical outcome. Hemodialysis International. 2014;18(2):415-22.
3. Yu J, Liu Z, Shen B, Teng J, Zou J, Ding X. Intradialytic Hypotension as an Independent Risk Factor for Long-Term Mortality in Maintaining Hemodialysis Patients: A 5-Year Follow-Up Cohort Study. Blood Purification. 2018;45(4):320-6.
4. Eldehni MT, Odudu A, McIntyre CW. Randomized Clinical Trial of Dialysate Cooling and Effects on Brain White Matter. Journal of the American Society of Nephrology. 2015;26(4):957-65.
5. 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.
6. Shoji T, Tsubakihara Y, Fujii M, Imai E. Hemodialysis-associated hypotension as an independent risk factor for two-year mortality in hemodialysis patients. Kidney International. 2004;66(3):1212-20.
7. Chou JA, Streja E, Nguyen DV, Rhee CM, Obi Y, Inrig JK, et al. Intradialytic hypotension, blood pressure changes and mortality risk in incident hemodialysis patients. Nephrology Dialysis Transplantation. 2018;33(1):149-59.
8. MacEwen C, Sutherland S, Daly J, Pugh C, Tarassenko L. Relationship between Hypotension and Cerebral Ischemia during Hemodialysis. Journal of the American Society of Nephrology. 2017;28(8):2511.
9. Polinder-Bos HA, Garcia DV, Kuipers J, Elting JWJ, Aries MJH, Krijnen WP, et al. Hemodialysis Induces an Acute Decline in Cerebral Blood Flow in Elderly Patients. Journal of the American Society of Nephrology : JASN. 2018;29(4):1317-25.
10. Slessarev M, Salerno F, Ball IM, McIntyre CW. Continuous renal replacement therapy is associated with acute cardiac stunning in critically ill patients. Hemodialysis International. 2019;23(3):325-32.
11. Webb AJS, Mazzucco S, Li L, Rothwell PM. Prognostic Significance of Blood Pressure Variability on Beat-to-Beat Monitoring After Transient Ischemic Attack and Stroke. Stroke. 2018;49(1):62-7.
12. Parati G, Pomidossi G, Albini F, Malaspina D, Mancia G. Relationship of 24-hour blood pressure mean and variability to severity of target-organ damage in hypertension. J Hypertens. 1987;5(1):93-8.
13. Ryu J, Cha R-H, Kim DK, Lee JH, Yoon SA, Ryu DR, et al. The clinical association of the blood pressure variability with the target organ damage in hypertensive patients with chronic kidney disease. J Korean Med Sci. 2014;29(7):957-64.
14. Sarafidis PA, Ruilope LM, Loutradis C, Gorostidi M, de la Sierra A, de la Cruz JJ, et al. Blood pressure variability increases with advancing chronic kidney disease stage: a cross-sectional analysis of 16 546 hypertensive patients. J Hypertens. 2018;36(5):1076-85.
15. Shafi T, Sozio SM, Bandeen-Roche KJ, Ephraim PL, Luly JR, St. Peter WL, et al. Predialysis Systolic BP Variability and Outcomes in Hemodialysis Patients. Journal of the American Society of Nephrology. 2014;25(4):799.
16. Brunelli SM, Thadhani RI, Lynch KE, Ankers ED, Joffe MM, Boston R, et al. Association Between Long-term Blood Pressure Variability and Mortality Among Incident Hemodialysis Patients. American Journal of Kidney Diseases. 2008;52(4):716-26.
17. Feng Y, Li Z, Liu J, Sun F, Ma L, Shen Y, et al. Association of short-term blood pressure variability with cardiovascular mortality among incident hemodialysis patients. Ren Fail. 2018;40(1):259-64.

18. Flythe JE, Inrig JK, Shafi T, Chang TI, Cape K, Dinesh K, et al. Association of intradialytic blood pressure variability with increased all-cause and cardiovascular mortality in patients treated with long-term hemodialysis. American journal of kidney diseases : the official journal of the National Kidney Foundation. 2013;61(6):966-74.
19. Eldehni M, Odudu A, McIntyre C. Exploring haemodynamics of haemodialysis using extrema points analysis model. Theoretical Biology and Medical Modelling. 2013;10(1):33.
20. Eldehni MT, Odudu A, McIntyre CW. Characterising haemodynamic stress during haemodialysis using the extrema points analysis model. Nephron Clinical practice. 2014;128(1-2):39-44.
21. Selby NM, Lambie SH, Camici PG, Baker CS, McIntyre CW. Occurrence of Regional Left Ventricular Dysfunction in Patients Undergoing Standard and Biofeedback Dialysis. American Journal of Kidney Diseases. 2006;47(5):830-41.
22. Selby NM, Burton JO, Chesterton LJ, McIntyre CW. Dialysis-Induced Regional Left Ventricular Dysfunction Is Ameliorated by Cooling the Dialysate. Clinical Journal of the American Society of Nephrology. 2006;1(6):1216-25.
23. van der Sande FM, Kooman JP, Burema JHG, Hameleers P, Kerkhofs AMM, Barendregt JM, et al. Effect of dialysate temperature on energy balance during hemodialysis: Quantification of extracorporeal energy transfer. American Journal of Kidney Diseases. 1999;33(6):1115-21.
24. Schechtman VL, Kluge, K.A. & Harper, R.M. . Time-domain system for assessing variation in heart rate. Med. Biol. Eng. Comput. 26, 367–373 (1988). .
25. Wendy L. Martinez ARM. Computational Statistics Handbook with MATLAB 3rd Edition.
26. Fincke R, Hochman JS, Lowe AM, Menon V, Slater JN, Webb JG, et al. Cardiac power is the strongest hemodynamic correlate of mortality in cardiogenic shock: a report from the SHOCK trial registry. Journal of the American College of Cardiology. 2004;44(2):340-8.
27. Feng Y, Zou Y, Zheng Y, Levin NW, Wang L. The value of non-invasive measurement of cardiac output and total peripheral resistance to categorize significant changes of intradialytic blood pressure: a prospective study. BMC nephrology. 2018;19(1):310-.
28. Mena L, Pintos S, Queipo NV, Aizpurua JA, Maestre G, Sulbaran T. A reliable index for the prognostic significance of blood pressure variability. J Hypertens. 2005;23(3):505-11.
29. Mena LJ, Felix VG, Melgarejo JD, Maestre GE. 24-Hour Blood Pressure Variability Assessed by Average Real Variability: A Systematic Review and Meta-Analysis. Journal of the American Heart Association. 2017;6(10):e006895.
30. Sarafidis PA, Loutradis C, Karpetas A, Tzanis G, Bikos A, Raptis V, et al. The association of interdialytic blood pressure variability with cardiovascular events and all-cause mortality in haemodialysis patients. Nephrology Dialysis Transplantation. 2018;34(3):515-23.
31. Wang Y, Qin Y, Fan X, Cai J, Ye W, Xia J, et al. Variability in Predialysis Systolic Blood Pressure and Long-Term Outcomes in Hemodialysis Patients. Kidney and Blood Pressure Research. 2018;43(1):115-24.
32. Flythe JE, Kunaparaju S, Dinesh K, Cape K, Feldman HI, Brunelli SM. Factors associated with intradialytic systolic blood pressure variability. American journal of kidney diseases : the official journal of the National Kidney Foundation. 2012;59(3):409-18.
33. Cheng Y-J, Yao F-J, Liu L-J, Tang K, Lin X-X, Li W-J, et al. B-Type Natriuretic Peptide and Prognosis of End-Stage Renal Disease: A Meta-Analysis. PloS one. 2013;8:e79302.
34. Levin NW, de Abreu M, Borges LE, Tavares Filho HA, Sarwar R, Gupta S, et al. Hemodynamic response to fluid removal during hemodialysis: categorization of causes of intradialytic hypotension. Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association. 2018;33(9):1643-9.
35. Stewart J, Walker T, Eldehini T, Horner DV, Lucas B, White K, et al. A feasibility study of non-invasive continuous estimation of brachial pressure derived from arterial and venous lines during dialysis. 2020.

Figures:

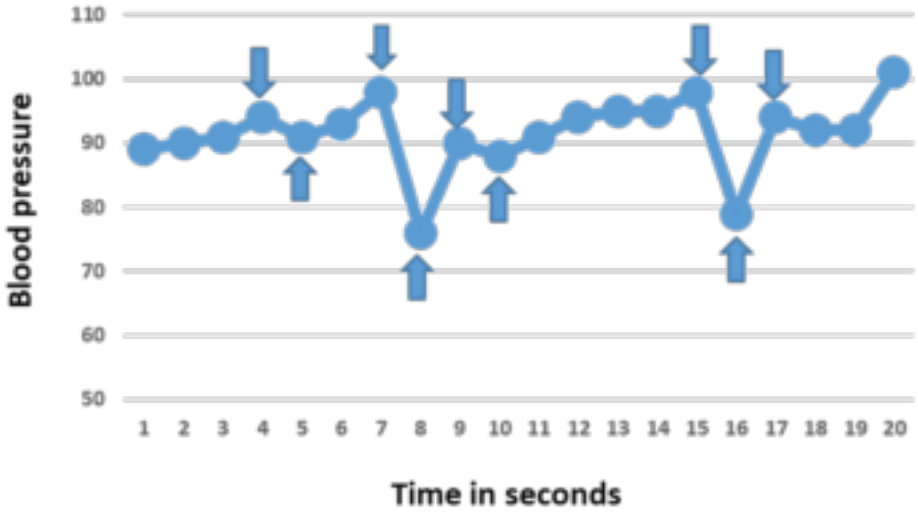

Figure 1: Illustration of identification of extrema points (minima and maxima identified by arrows) on a 20 second trace of MAP measurements. Once identified, frequency is calculated using the following formula:

$$f = {}^{1}/_{time\ difference\ between\ 2\ consecutive\ extrema\ points}$$

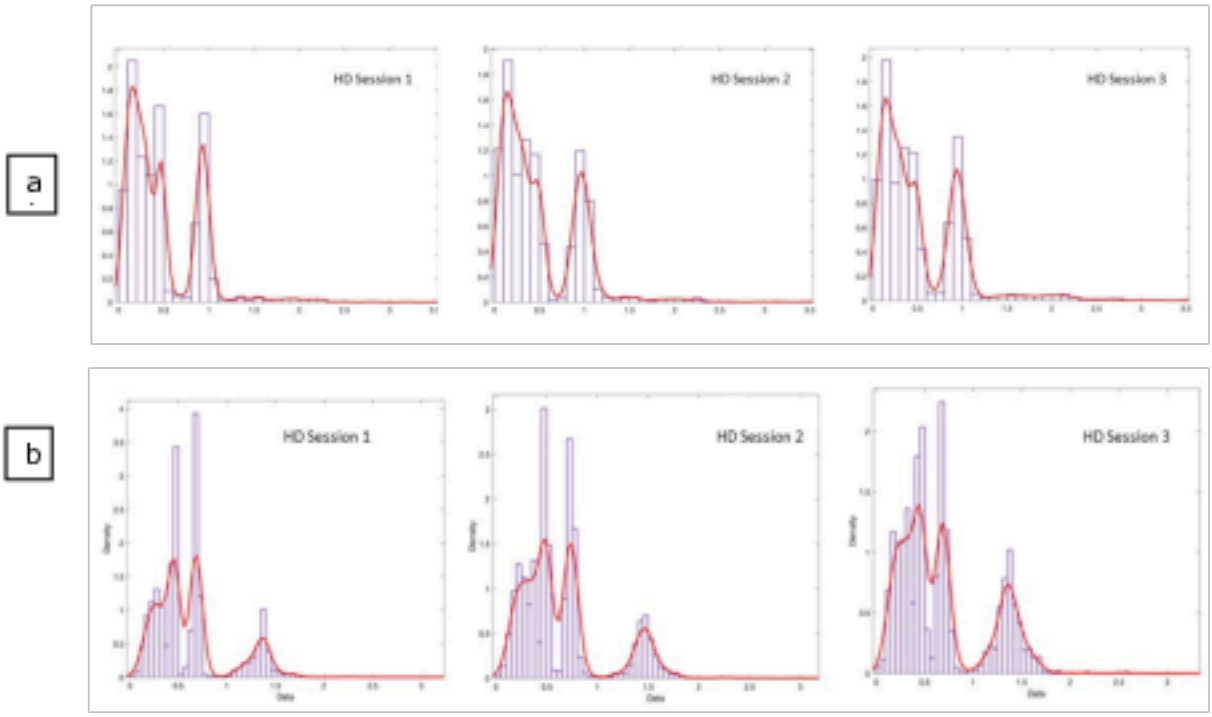

Figure 2: Histograms of EP MAP frequencies of 2 participants (a, b) across three consecutive monitored HD sessions (4 hours duration).. These demonstrate bimodal distribution of EP MAP frequencies and are similar across the 3 sessions in each participant. X-axis represents frequency values; Y-axis represents number of frequencies.

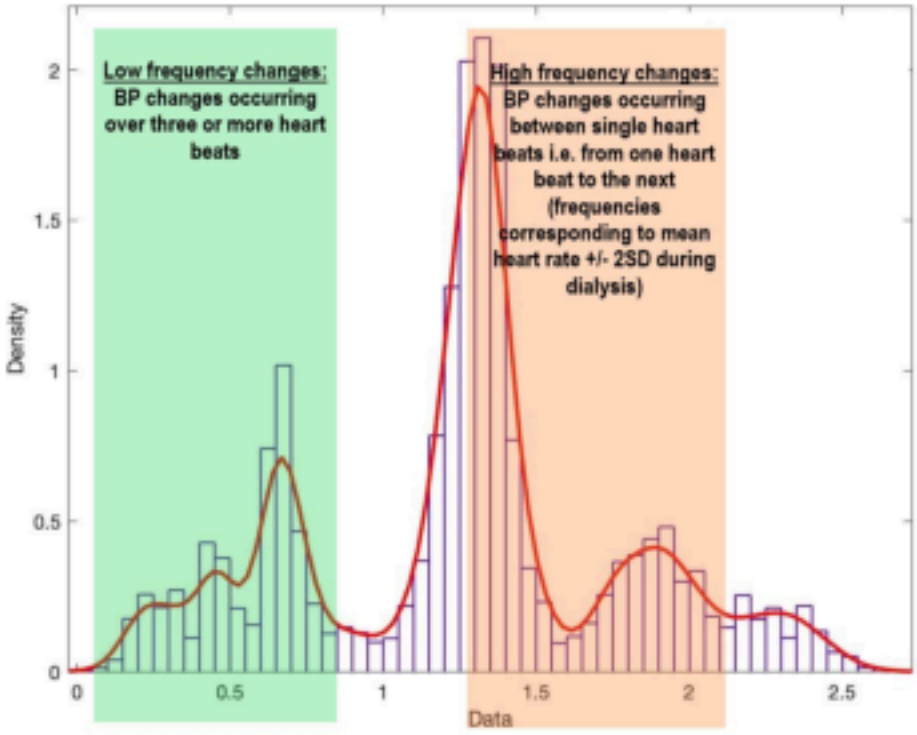

Figure 3: Schematic diagram demonstrating the categorisation of the EP MAP frequencies into low frequency changes (LFC) and high frequency changes (HFC) used to calculate the HFC/LFC ratio. X-axis represents frequency values; Y-axis density of frequencies.

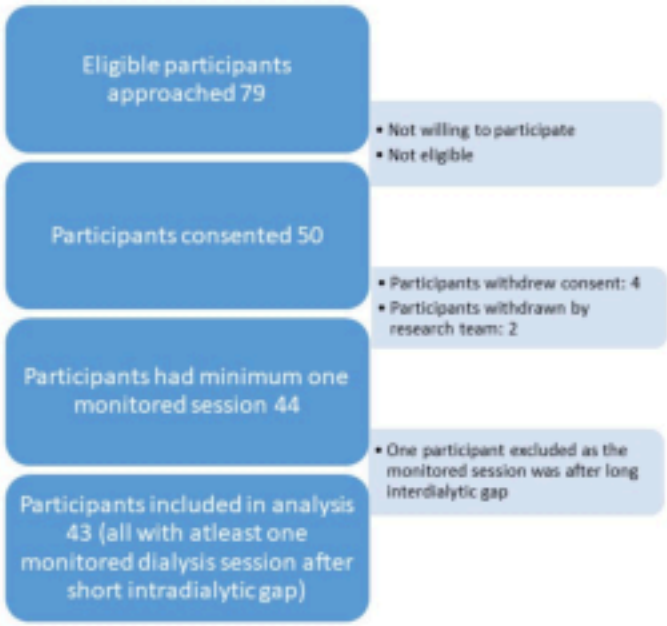

Figure 4: Consort diagram illustrating participant flow through the study

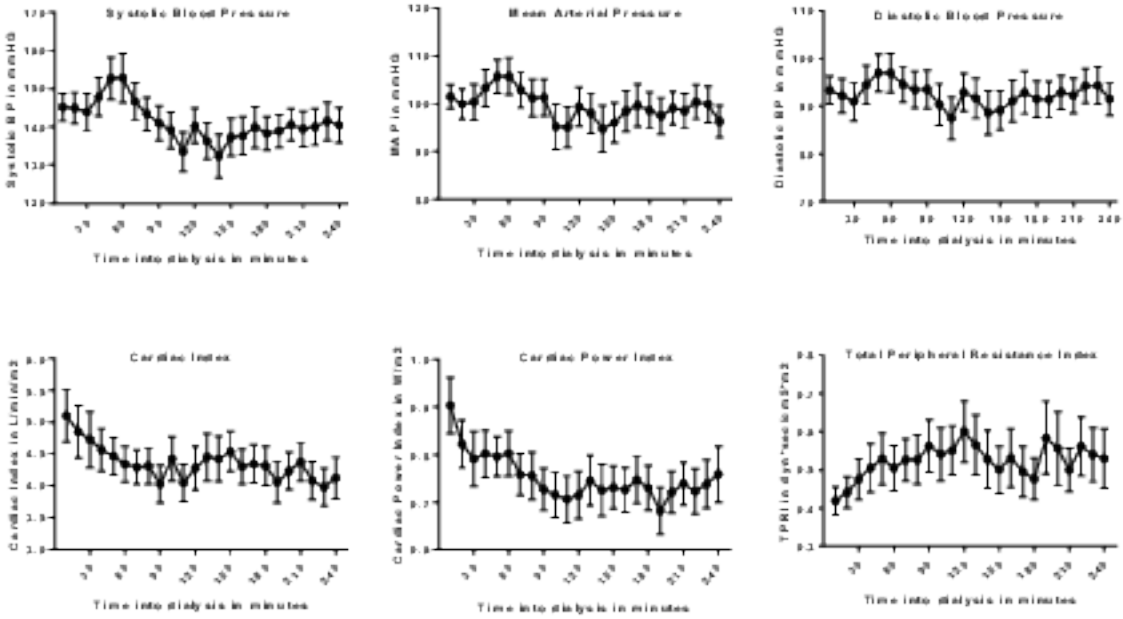

Figure 5: Intradialytic population trends in Systolic BP (SBP), Diastolic BP (DBP), Mean arterial pressure (MAP), Cardiac Index (CI), Cardiac Power Index (CPI) and total peripheral resistance index (TPRI). The total monitored dialysis duration (4 hours) was divided into 10minutes blocks and the average of each block is represented as a data point. An intial brief rise was followed by gradual decline in SBP, MAP, DBP, CI and CPI but TPRI increased as the dialysis progressed.

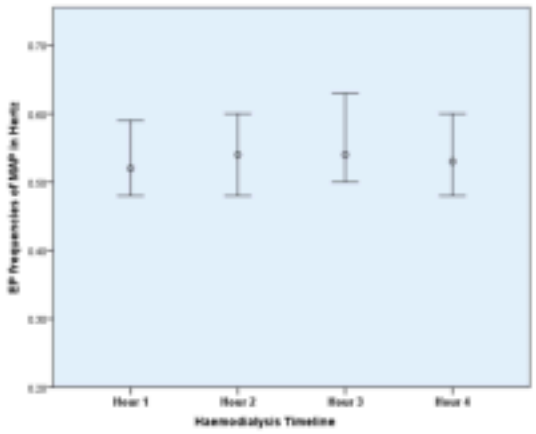

Figure 6: A graphical representation of population trend of EP MAP frequencies during 4 hours of Haemodialysis (HD). Each circle represents the median EP MAP frequencies of the cohort for every hour with 95% confidence intervals as error bars. There is trend towards slow rise upto the third hour and drop in the fourth hour (p=0.671).

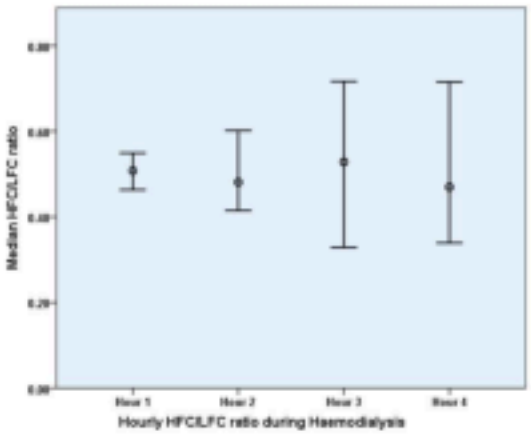

Figure 7: A graphical representation ofpopulation trend of HFC/LFC ratio during 4 hours of Haemodialysis (HD). Each circle represents the median HFC/LFC ratio of the cohort for every hour with 95% confidence intervals as error bars. There is no significant direction of change in HFC/LFC as dialysis progressed.

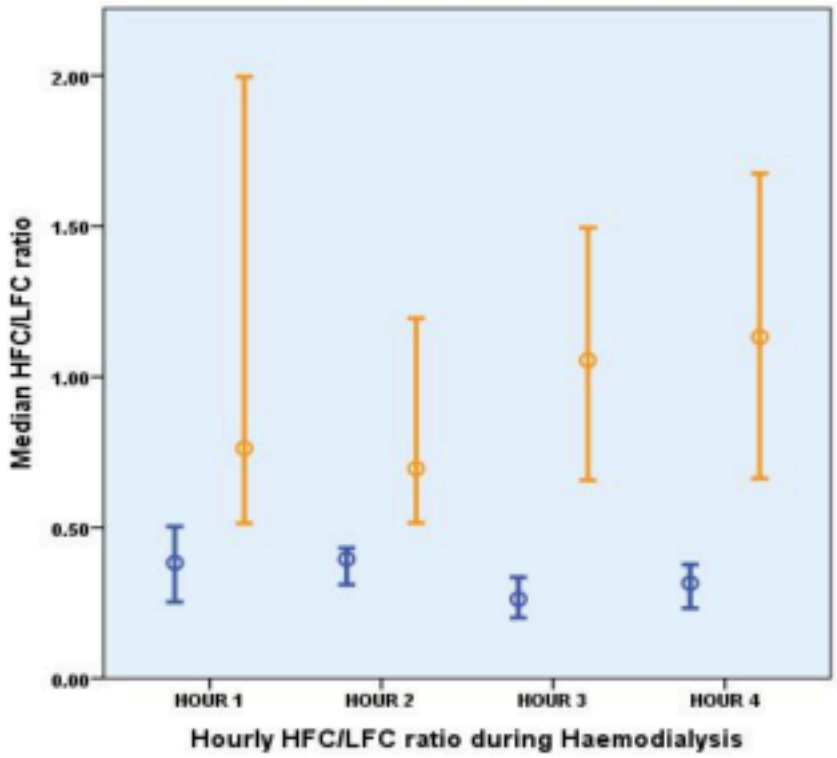

Figure 8: A graphical representation of HFC/LFC ratio patterns in the low frequency (LF) group (represented in blue) and high frequency (HF) group (represented in orange) during haemodialysis. Medians are represented with the circles for each hour of HD and the 95% confidence intervals as error bars. Friedman's test was used to compare between various time points and was significant in LF group (p value: 0.036) and not significant in HF group (p value: 0.532). Kruskal Wallis test was used to compare both groups at each time point and was significant across all 4 hours with p values of <0.001.

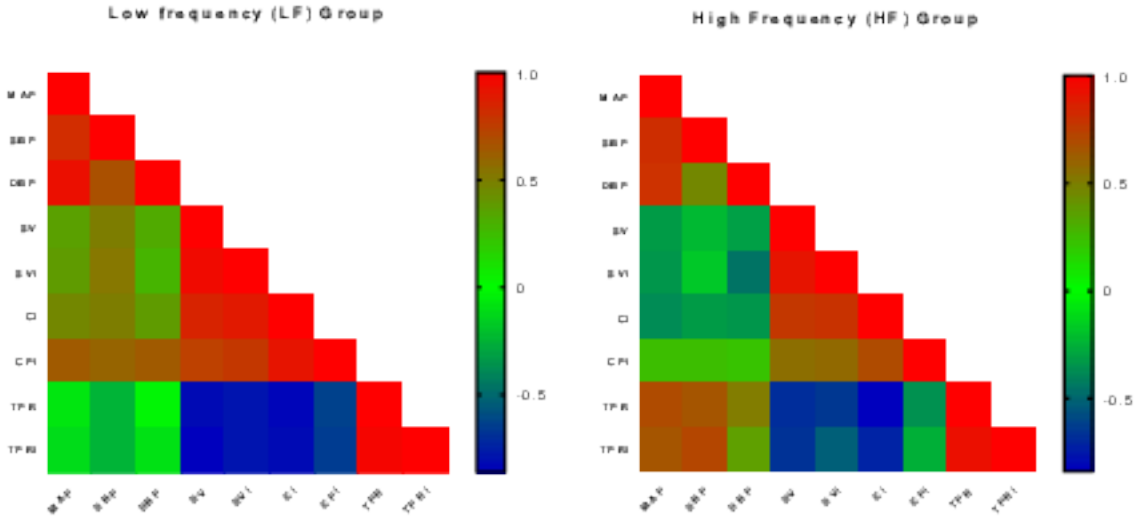

Figure 9: Correlation matrix for haemodynamic variables in the low frequency (LF) and high frequency (HF) groups. The colours are representative of the values of rho for each correlation. In LF group, MAP positively correlates with CPI (r=0.64, p=0.002) however in HF group, MAP positively correlates with TPR (r=0.69, p<0.0001) and TPRI (r=0.66, p=0.001). *MAP- Mean arterial pressure, SBP- Systolic blood pressure, DBP-

Diastolic blood pressure, SV-Stroke Volume, SVI- Stroke Volume Index, CI-cardiac index, CPI- Cardiac Power Index, TPR- Total peripheral resistance, TPRI- Total peripheral resistance index
*HF group- participants with higher proportion of high frequency extrema point (EP) MAP changes, LF group- participants with higher proportion of low frequency EP MAP changes.

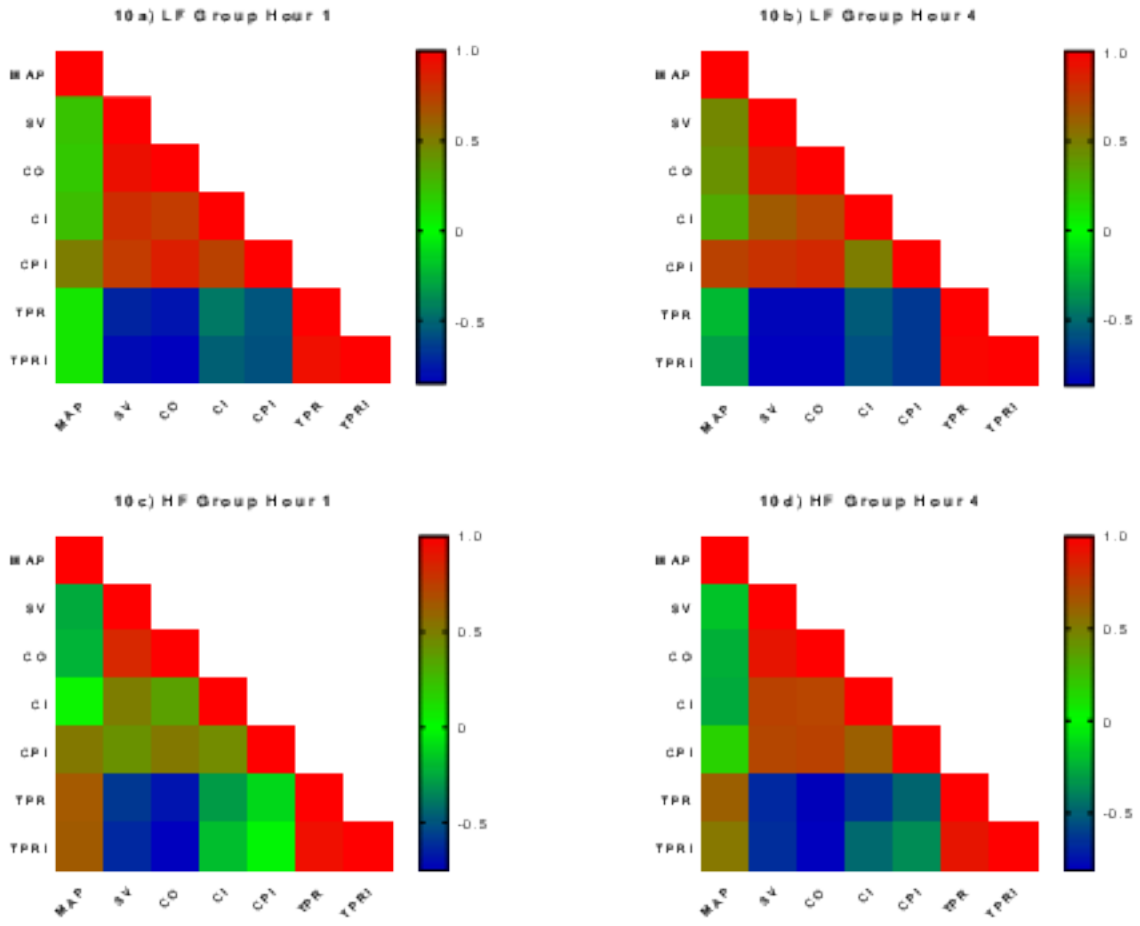

Figure 10: Correlations between average intradialytic variables in hour 1 and hour 4 of dialysis in the low frequency (LF) group (a, b) and high frequency group (c, d). The colours are representative of the values of rho for each correlation. In the LF group, MAP was positively correlated with CPI in each hour of dialysis, but not with TPRI (Table 4). In contrast in the HF group, MAP correlated with CPI in the first hour of dialysis only; MAP then correlated with TPRI in each subsequent hour of dialysis (Table 4). MAP- Mean arterial pressure, SBP- Systolic blood pressure, DBP- Diastolic blood pressure, SV- Stroke Volume, CI-cardiac index, CPI- Cardiac Power Index, TPR- Total peripheral resistance, TPRI- Total peripheral resistance index
*HF group- participants with higher proportion of high frequency extrema point (EP) MAP changes, LF group- participants with higher proportion of low frequency EP MAP changes.

Tables:

Table 1: Characteristics of the Participants and intradialytic haemodynamic findings	
(a) Demographics of study population (N=43 included)	
Age (years)	61.5 ± 15.63
Gender (% male)	26 (60.5%)
Ethnicity (%) White	37 (86%)
Diabetes	19 (44.2%)
Charlson Comorbidity Score	4 (2)
Weight	71 kg (31.9)
Body Mass Index	26.7 kg/m^2 (9.8)
Mean Interdialytic weight gain over 4 weeks prior to recruitment in Kilograms	1.51 ± 0.68
Number of participants with Intradialytic hypotension episodes in 4 weeks prior to recruitment	4 (9.3%)
Number of participants on Anti-hypertensives	25 (58.9%)
• Angiotensin Converting enzyme Inhibitors	9 (20.9%)
• Beta-Blockers	13 (30.2%)
• Calcium Channel blockers	12 (27.9%)
Number of participants receiving Dialysable anti-hypertensive therapy	3 (7%)
Dialysis vintage in months	24 (75)
Access type	
• Arteriovenous fistula	36 (83.7%)
• Arteriovenous graft	4 (9.3%)
• TNL	3 (7%)
Access flow (Qa) ml/min	754 (554)
(b) Intradialytic Haemodynamics of study population	
Systolic Blood Pressure	140 mmHg (25)
Diastolic Blood Pressure	75 mmHg (18)
Mean Arterial Blood Pressure	99 mmHg (18)
Cardiac Power Index	0.67 w/m^2 (0.32)
Cardiac Index	3.44 ± 1.03 L/min/m^2
Stroke Volume Index	46.36 ± 14.67 ml/m^2
Cardiac Power Index	0.67 w/m^2 (0.32)
Total Peripheral Resistance Index	0.39 dynes·sec/cm^5/m^2 (0.28)

Median and interquartile range (IQR) are reported for non-parametric data, Means ± standard deviation (SD) for normally distributed data; numbers (percentages) are reported for categorical data.

Table 2. Comparison of low frequency (LF) versus high frequency (HF) groups

	LF group (n=21)	HF group (n=22)	P-value
Age	58.2±17	64.9 ±13.8	0.164
Sex (females)	47.6%	31.8%	0.289
Charlson Comorbidity Score	3 (4)	4 (2)	0.292
Current Smokers/ex-smokers	10 (50%)	9 (42.9%)	0.68
Diabetes	38.1%	50%	0.432
Dialysis Vintage in months	24 (56)	26.5 (80)	0.846
Participants on Antihypertensive therapy	7 (33%)	18 (18.8%)	0.02
Participants on Dialysable Antihypertensives	0	3 (16.7%)	0.25
Participants on B-blockers	14.3%	45.5%	0.026
Participants on ACEi	9.5%	31.8%	0.072
Pre-dialysis-Troponin t (ng/L)	54 (52)	74 (64)	0.15
Pre-dialysis NT Pro BNP (ng/L)	1949 (3941)	6285.5 (20217)	0.045
Initial Brachial Systolic BP (mmHG)	130 (32)	154.5 (23.5)	0.018
Mean Systolic BP (SBP in mmHg)	132.45 (19.52)	140.19 (37.3)	0.264
Mean Diastolic BP (DBP in mmHG)	81.51 (19.44)	72.47 (19.24)	0.037
Mean Mean Arterial Pressure (MAP in mmHg)	99.01 (25.24)	98.46 (15.46)	0.409
Stroke Volume Index (ml/m^2)	42.35± 13.79	50.18±14.76	0.08
Cardiac Index(L/min/m^2)	3.356 ± 1.13	3.523±0.952	0.602
Cardiac Power Index (w/m^2)	0.65 (0.39)	0.68 (0.30)	0.771
Total Peripheral Resistance Index (dynes·sec/cm^5/m^2)	0.425 (0.29)	0.372 (0.34)	0.395
Baroteceptor Sensitivity (millisec/mmHG)	9.55 (6.29)	8.23 (3.54)	0.903
R/R-interval (milliseconds)	845.57±132.23	944.90±177.91	0.045
Heart rate (beats/min)	73.11 ± 13.73	66.46±17.9	0.181
ARV SBP (mmHG)	4.08 (3.26)	5.65 (4.56)	0.004
ARV MAP (mmHG)	2.496 (1.05)	3.394 (3.31)	0.004
ARV DBP (mmHG)	2.361 (1.61)	3.4042 (2.99)	0.008
Net UF (Ultrafiltration) in litres	1.58±0.959	1.56±1.07	0.955
Difference between prescribed and achieved UF	0.4 (0.35)	0.4 (0.53)	0.51
Kt/V	1.257 ± 0.245	1.263 ± 0.271	0.942
Participants on Dialysate temperature of <37°C	15 (71.4%)	13 (59.1%)	0.396
Median Frequency of MAP in Hertz (Hz)	0.4866 (0.19)	0.6129 (0.36)	0.002
Max percentage drop in SBP during HD compared to initial brachial SBP	-18.8 % (19.7)	-25.4% (27.43)	0.913
Proportion of 20mmHg drop in SBP (%)	6.81 (15.17)	14.55 (32.77)	0.145
Proportion of <90mmHg drop in SBP (%)	0.736 (3.6)	0.914 (2.35)	0.884

HF group - participants with higher proportion of high frequency extrema point (EP) MAP changes, LF group - participants with higher proportion of low frequency EP MAP changes.

ARV is average real variability which is calculated using the formula as described in methods section for Systolic, diastolic and mean arterial BP measurements and provides magnitude of variation

Median and interquartile range (IQR) are reported for non-parametric data, Means ± standard deviation (SD) for normally distributed data, numbers (percentages) are reported for categorical data.

Table 3. Comparisons of hourly haemodynamics between Low frequency (LF) and High frequency (HF) groups

	Groups	Hour 1	Hour 2	Hour 3	Hour 4	P value (across the timeline)
MAP	LF group	101.71 (18.22)	97.89 (19.46)	92.61 (22.06)	98.43 (19.96)	0.180
	HF group	98.34 (22.9)	94.35 (23.71)	95.43 (25.1)	93.59 (25.47)	0.760
	p value	0.285	0.451	0.99	0.811	
CPI	LF group	0.763 (0.49)	0.657 (0.35)	0.751 (0.4)	0.623 (0.29)	0.026
	HF group	0.784 (0.37)	0.705 (0.25)	0.633 (0.41)	0.644 (0.35)	0.09
	p value	0.528	0.662	0.95	0.772	
TPRI	LF group	0.4164 (0.33)	0.4402 (0.34)	0.3971 (0.34)	0.4472 (0.34)	0.491
	HF group	0.3503 (0.31)	0.3838 (0.35)	0.4210 (0.42)	0.3937 (0.32)	0.029
	p value	0.181	0.437	0.678	0.473	
HR	LF group	77.06 (20.57)	77.86 (20.44)	82.35 (16.41)	82.03 (20.18)	0.468
	HF group	66.21 (17.95)	66.32 (15.63)	68.53 (15.55)	67.43 (22.6)	0.564
	p value	0.029	0.049	0.016	0.013	

HF group - participants with higher proportion of high frequency extrema point (EP) MAP changes, LF group - participants with higher proportion of low frequency EP MAP changes.

MAP: Mean arterial pressure in mmHG; CPI: Cardiac Power Index in w/m^2; TPRI: Total peripheral resistance index in dynes·sec/cm^5/m^2; HR: Heart Rate in beats/min.

Median and interquartile range (IQR) are reported for non-parametric data.

Table 4. Correlations between MAP vs CPI and MAP vs TPRI-

	Groups	Hour 1	Hour 2	Hour 3	Hour 4
MAP vs CPI	LF group	0.50 (0.021)	0.43 (0.053)	0.59 (0.005)	0.74 (<0.0001)
	HF group	0.53 (0.012)	0.33 (0.135)	0.27 (0.246)	0.17 (0.471)
MAP vs TPRI	LF group	0.09 (0.687)	0.20 (0.382)	-0.04 (0.871)	-0.32 (0.153)
	HF group	0.63 (0.002)	0.60 (0.003)	0.59 (0.005)	0.53 (0.014)

MAP: Mean arterial pressure, CPI: Cardiac Power Index, TPRI: Total peripheral resistance index.

HF group - participants with higher proportion of high frequency extrema point (EP) MAP changes; LF group - participants with higher proportion of low frequency EP MAP changes

Correlation coefficient (r) values are provided with p-values (in brackets)