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

Short title: Frequency of Blood pressure variation during haemodialysis

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Abstract

Background

Higher beat-to-beat blood pressure (BP) variation during haemodialysis (HD) has been shown to be associated with elevated cardiac damage markers and white matter ischaemic changes in the brain suggesting relevance to end-organ perfusion. We aimed to characterise individual patterns of BP variation and associated haemodynamic responses to HD.

Methods

50 participants underwent continuous non-invasive haemodynamic monitoring during HD and BP variation was assessed using extrema point (EP) frequency analysis. Participants were divided into those with a greater proportion of low frequency (LF,n=21) and high frequency (HF,n=22) of BP variation. Clinical and haemodynamic data were compared between groups.

Results

Median EP frequencies for mean arterial pressure (MAP) 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.

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 studies of intradialytic beat-to-beat BP variation using continuous monitoring are sparse. 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 one 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 (IRAS number: 217655) 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; biofeedback settings were not used. 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. The Finapres uses a digital artery finger cuff pressure changes 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 [21]; these include heart rate (HR), blood pressure (BP), stroke volume index (SV), cardiac index (CI) and total peripheral resistance index (TPRI). This non-invasive method of monitoring BP has been shown to be a valid alternative to less practical invasive monitoring of BP and reliable for tracking BP changes [22, 23]. It has also been validated in HD population previously [24, 25]. 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 [26]. These spectra were then decomposed into constituent frequency events using the Freedman-Diaconis rule [27], 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 MAP frequency changes that occurred between single heart beats i.e, from one heart beat to the next (frequencies corresponding to mean intradialytic heart rate ± two standard deviations).
* LFC (low frequency changes) 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 [28] and has been utilised to categorise patients with differing intradialytic haemodynamic responses to fluid removal [29].
* Average real variability ($ARV=\frac{1}{N-1}\sum\_{K=1}^{N-1}x \left|BP\_{K+1}-BP\_{K}\right|$; *where K ranges from 1 to N-1; N is the number of intradialytic BP readings [30])*. 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, 31, 32], 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 preceding 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 index (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≤0.0001) 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), barorelex 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. Intradialytic trends of BP and other haemodynamics were not different between the groups (figures not included).

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=0.59, P=0.005) but not TPRI, and in the HF group SBP correlated with TPRI (r=0.71, 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) [33]. 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 [32]. To our knowledge there are a limited number of studies examining intradialytic BP variability. Flythe et al [34] 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. Eldehni et al studied the prevalence of brain microstructure using diffusion tensor magnetic resonance imaging and its association with beat-to-beat BP variation (obtained by non-invasive haemodynamic monitoring using Finopres) using EP analysis and concluded that higher EP MAP frequencies were associated with ischaemic white matter changes in the brain along with demonstration that reduction of this variation with interventions (cool dialysate) are protective against these [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 [35] 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, however further studies are required using appropriate cardiovascular functional assessments to evaluate these possible associations in the future.

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 [36]. 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. We speculate that future interventions to reduce IDH could be targeted based on individual EP frequency profile, underpinned by ongoing work to develop more clinically relevant approaches for continuous BP measurement [37, 38]. For example, interventions which improve the vascular tone like cool dialysis might be more effective in HF group to improve haemodynamic stability on HD. Furthermore, additional work to examine the potential link between EP frequency profile and tendency to haemodialysis-induced end-organ ischaemia would also be important.

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 [38].

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.

Statements

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###### Statement of Ethics:

The study was approved by the West Midlands Ethics Committee (IRAS number: 217655) and written informed consent was obtained from all participants.

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Conflict of Interest Statement:

US Patent Office and Overseas Licence 62/855069 “MEASURING PRESSURE WAVES IN DIALYSIS LINES TO DERIVE CONTINUOUS ARTERIAL BLOOD PRESSURE” P Stewart, J Stewart, VRL Gullapudi, T Eldehni, MW Taal, NM Selby.

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Author Contributions:

###### VRL Gullapudi designed the work, played key role in acquiring the data, analysis, interpretation of the results and writing the manuscript; K White helped in acquiring the data; J Stewart and MT Eldehni assisted in the design of the work, analysis and interpretation; P Stewart assisted in the design of the work and interpretation; MW Taal and NM Selby played role in designing the work, interpretation and revising the manuscript.

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Figures:

**Legend Figure 1: I**Ilustration 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:
$$f=^{1}/\_{time difference between 2 consecutive extrema points }$$

**Legend 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 (in Hertz); Y-axis represents number of EP MAP frequencies in each group.

**Legend 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 (in Hertz); Y-axis number of frequencies of EP MAP frequencies in each group. HFC (represented in red block) were defined as EP MAP frequencies changes that were occurring between single heart beats i.e from one heart beat to the next (frequencies corresponding to mean intradialytic heart rate ± two standard deviations). LFC (represented in green block) 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. We used these definitions to allow adequate separation between the HFC and LFC changes i.e., to avoid overlap between the two groups of changes.

**Legend Figure 4:** Consort diagram illustrating participant flow through the study

**Legend 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.

**Legend 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).

**Legend Figure 7:** A graphical representation of population 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.

**Legend 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.

**Legend Figure 9:** Correlation matrix for haemodynamic variables (mean intradilaytic values of the haemodynamic parameters were used for this analysis) 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.

**Legend 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:

Total 4 tables are included in separate document.