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Using Respiratory Variations Of Plethysmographic Waveforms To Track Changes In Intravascular Volume During Hemodialysis

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Abstract

Using Respiratory Variations of Plethysmographic Waveforms to Track Changes in Intravascular Volume during Hemodialysis

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Whereas dynamic indices have been shown to accurately predict volume status in mechanically ventilated patients, we still lack a reliable noninvasive means of intravascular volume status assessment in spontaneously breathing patients. The present study was undertaken to determine the impact of incentive spirometry (IS) on plethysmographic (PPG) waveforms in spontaneously breathing end stage renal disease (ESRD) patients. Furthermore, the impact of ultrafiltration on plethysmographic waveform variability in spontaneously breathing patients with and without incentive spirometry was analyzed.

With IRB approval, data were collected and analyzed for 44 hemodialysis cases. PPG waveforms were recorded at 100 Hz with a data acquisition system (S5 Collect) with patients first spontaneously breathing (SB) and then performing IS breathing. The waveforms were analyzed (spectrum, 4K, Hamming, Amplitude density) using Chart software (ADInstruments). Data were presented as mean ± SD. The results were compared using the 2-tailed t-test, and $P < 0.05$ was considered statistically significant.

There was significant increase in the PPG DC with the use of IS, p value = 0.0000002. The average PPG DC at baseline was 1.06 ± 0.82 with SB while average PPG DC with IS was 3.54 ± 1.58, with percent change of 234% increase from baseline. Similarly, at the end of dialysis, a comparison between SB and IS showed a 203% change in the PPG DC value (1.92±1.03 with SB versus 5.819±2.84 with IS, p=0.000023). Whereas IS was consistently associated with a significant increase in PPG DC at the end of dialysis, SB was not associated with a significant increase in PPG DC at the end of dialysis when the ultrafiltrate rate exceeded 1000cc/hr.

Dynamic noninvasive hemodynamic evaluation has been shown to be more accurate than conventional hemodynamic static pressures; among the noninvasive methods is the PPG. This study showed a significant increase in PPG DC amplitude density during IS, and a significant increase in PPG DC during IS at the end of dialysis as

compared to the beginning. This suggests that IS can be used as a tool to track changes in PPG DC variability in spontaneously breathing ESRD patients undergoing dialysis.

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Introduction

Normal Physiologic Responses to Hypovolemia

The normal physiologic response to hypovolemia is comprised of three main mechanisms aimed at: (1) decreasing venous capacity (2) increasing total peripheral resistance, and (3) increasing cardiac chronotropy and inotropy [1].

(1) Decreased venous capacity

At baseline, a significant portion of the total blood volume remains sequestered in the high capacitance venous system. During the normal response to hypovolemia, this sequestered volume is mobilized centrally, which helps to mitigate the decrease in venous return and thus maintain cardiac filling and, subsequently, cardiac output. There are two proposed mechanisms by which this decrease in venous capacity occurs:

I. The DeJager-Krogh phenomenon. In this mechanism, hypovolemia stimulates constriction of the resistance vasculature (arterioles), which in turn has the downstream effect of decreasing blood flow to a capillary bed. The decreased regional blood flow results in a decrease in distending pressure that the blood is able to exert on the walls of the veins. As such, there is a passive recoil of the veins, which reduces venous capacity and mobilizes the sequestered blood towards the heart[2]. This phenomenon is visually depicted on page 234 of the journal article entitled 'Dialysis Hypotension: A hemodynamic analysis'[1]. The two vascular beds that have been shown to contribute most significantly to augmenting venous return via this mechanism of decreasing venous capacitance are the splanchnic and the cutaneous circulations.

II. Direct contraction of the veins and venules. This may be neurogenically or hormonally controlled[2,3].

(2) Increase in Total Peripheral Resistance

The increase in total peripheral resistance that normally occurs with hypovolemia has multiple functions.

I. Vasoconstriction in the arterioles that supply the kidneys and the muscles, allows for preferential diversion of the depleted blood volume to crucial organs such as the heart and the brain.

II. The increase in peripheral resistance in the splanchnic and cutaneous circulation (via arteriolar constriction) serves to passively mobilize blood initially sequestered in the venous circulation, thereby helping to maintain venous return to the heart [1].

(3) Increased Cardiac Chronotropy and Inotropy

In hypovolemia, there is an early increase in heart rate, which later returns to baseline or sub-baseline levels. Cardiac contractility also increases during hypovolemia. Notwithstanding this, cardiac output appears to be limited by the amount of blood returning to the heart, while optimization of the heart's pumping performance plays a very minimal role in the maintenance of cardiac output[1].

Intra-Dialysis Hypotension

Symptomatic intra-dialysis hypotension (IDH) is a major cause of morbidity in hemodialysis patients[2]. IDH is most commonly defined as a drop in SBP of ≥30 mmHg, or a drop in MAP of ≥10 mmHg, and occurs in 10-30% of dialysis treatments[4]. Furthermore, there is a subset of dialysis patients who are plagued by IDH in at least 50% of their treatments[4]. Risk factors predisposing patients to more frequent IDH events are summarized in the table 1.

Table 1[4].

Patient Comorbidities that Increase Risk for Intradialytic Hypotension
Physiology of elderly patients
DM
Cardiac Disease
Autonomic Dysfunction
Primary or Secondary Autonomic Neuropathies
Structural Heart Disease
Left Ventricular Hypertrophy
Diastolic Dysfunctions
Dilated Cardiomyopathy
Systolic/Diastolic Dysfunction
Right Heart Failure/Pulmonary Hypertension
Cardiac Arrhythmias
Atrial fibrillation
Ventricular ectopy
Pericardial Disease
Pericardial effusion
Constrictive pericarditis
Cirrhosis

The symptoms of IDH stem from decreased perfusion pressure which causes end-organ ischemia. Hypoperfusion of the musculature manifests as cramps, hypoperfusion of the GI tract presents as nausea and vomiting, and hypoperfusion of the brain results in symptoms of blurred vision, dizziness, fatigue, and weakness[2,4]. Needless to say, these symptoms make for a very unpleasant dialysis treatment, and can result in their early termination. The more serious potential sequelae of IDH events include cerebrovascular insufficiency (syncope, TIA, stroke, seizure), and cardiac instability (acute myocardial infarction, arrhythmias). In the long term, recurrent episodes of IDH increase the risk of asymptomatic cardiac ischemia, and heart damage. Repeated IDH is also associated with an elevated risk of vascular access thrombosis and a decline in the patient's remaining renal function [5]. Overall, recurrent IDH may be linked to an increased mortality rate[5,6].

Pathophysiology of IDH in ESRD Patients

The pathophysiology of dialysis-induced hypotension can be conceptualized as a multifactorial process[3,4].

1) The rapid or excess removal of ultrafiltrate, with inadequate replacement of the intravascular compartment with fluid from the extra vascular space. This ultimately results in intravascular volume depletion. However, intravascular volume depletion alone is not sufficient to cause hypotension, as there are patients who are able to maintain their blood pressures despite a reduction in their circulating blood volume [3].
2) A concomitant failure of the cardiovascular system to mount an adequate compensatory response to the volume loss[3,4]. Many dialysis-dependent patients exhibit aberrant responses to volume removal/ultrafiltration. As such, these ESRD patients are less well able to maintain their blood pressures in states of decreased blood volume. These

anomalous responses can be grouped into the following categories:

I. Failure to reduce venous capacity

A. Autonomic neuropathy: results in failure to recruit sufficient venous-sequestered blood into the central circulation to offset the decrease in blood volume. [4].

B. Vasodilation: warming of the body's core that occurs with hemodialysis triggers a thermoregulatory vasodilation of cutaneous blood vessels, which can further exacerbate the failure to mobilize blood centrally[4].

II. Failure to Increase Total Peripheral Resistance

A. Autonomic neuropathy: studies have shown that many ESRD patients, and particularly those with comorbid diabetes, have significant impairments of their autonomic nervous systems[7]. For instance, baseline baroreflex impairments has been shown to distinguish hypotension-prone patients from their hemodynamically stable counterparts[8]. Uremia may also contribute significantly to autonomic dysfunction[7]. The consequence of this autonomic impairment is that these patients are unable to appropriately constrict their resistance vessels to increase SVR, thus making them susceptible to a drop in blood pressure with volume depletion.

B. Imbalance of other mediators: disequilibrium of endothelin-1 (vasoconstrictive factor) and nitric oxide (vasodilatory factor), elevated adenosine levels, impaired norepinephrine release, inadequate vasopressin release in response to volume removal, and elevated levels of endotoxin[4].

III. Heart Disease

ESRD patients do not have "normal hearts" and may not be able to respond appropriately to intravascular volume removal. Blood pressure maintenance may

become dependent upon increases in the heart rate and contractility especially in the face of an inappropriate reduction in SVR. For instance, long standing hypertension and/or hypervolemia, AV shunts, and anemia, result in left ventricular hypertrophy (LVH) in more than 70% of dialysis-dependent patients [4,9]. Systolic or diastolic dysfunction, the sequelae of LVH, has been shown to put ESRD patients at risk for hypotension[4]. It has also been shown that uremic patients exhibit impairments in heart rate responses to Valsalva, and other maneuvers that induce blood pressure changes[1].

Current Treatment Strategies in the management of IDH

Current strategies targeting a reduction of IDH events include a combination of patient-focused and dialysis-focused interventions.

1) Lowering the temperature of the dialysate helps to prevent the increase in core body temperature that occurs with dialysis, and thus reduces the cutaneous vasodilation that shunts blood away from the central circulation [2,4]. Furthermore, dropping the temperature of the dialysate has been shown to augment baroreceptor sensitivity variability, and the peripheral vasoconstriction response to volume reduction[4]. However, caution must be exercised as patients may experience undesirable symptoms related to being excessively cooled[4].
2) Avoiding food ingestion before or while on dialysis also reduces the risk of IDH. This is because food ingestion normally causes vasodilation of the splanchnic circulation, and thus splanchnic venous pooling.
3) Medical treatment directed at stimulating vasoconstriction has also been successfully utilized in reducing IDH. Such medications include midodrine (an alpha-1 agonist), sertraline, and L-carnitine. In one study, the intravenous administration of AVP improved blood pressure

during hemodialysis [4]. Other medications that have been studied and shown to have a positive effect on the frequency of IDH events include adenosine antagonists, hypertonic saline, and glucose[4].

4) Dialysate electrolyte concentrations can also be adjusted to reduce the risk of IDH. For instance, use of higher Ca2+ concentrations in the dialysate help to optimize cardiac function [2,4], an important consideration for patients with LVH and concomitant heart failure. Historically, increasing the dialysate sodium concentration has also led to improved intradialysis hemodynamics[2,4]. Higher levels of sodium in the dialysate prevent the drop in plasma osmolality that accompanies rapid solute removal. This maintenance of extracellular sodium in turn facilitates the diffusion of intracellular water to the extracellular space[4].
5) Using lower ultrafiltration rates (and thus lengthening treatment time), or increasing the frequency of dialysis to daily treatments, would decrease the problem of IDH. This has in fact been proven true in multiple studies[10,11] The risk of IDH increases when patients accumulate large interdialytic weight gain, thus necessitating exuberant ultrafiltration rates to return the patient back to his dry weight. It follows therefore that more frequent and longer dialysis treatments could be beneficial in reducing IDH events, but this is unlikely practical given the inconvenience and cost of increasing treatment times or frequency.

While the aforementioned treatment strategies have certainly helped to reduce the incidence of IDH, it still remains the most commonly encountered problem in hemodialysis[4]. None of the interventions described above effectively target the primary inciting event in IDH: the excessive or rapid removal of ultrafiltrate. Currently, the amount of ultrafiltrate to be removed in any one session is calculated by subtracting the patient's 'dry weight' from the patient's current weight. This method of prescribing the ultrafiltrate is completely reliant on the assumption that the dry

weight assigned to the patient truly reflects a euvolemic state. In practice, however, the dry weight is determined by trial and error, and is the weight at which the patient has neither signs nor symptoms of volume depletion or volume excess[4]. The eradication of IDH is dependent upon the development of a more objective predictor of volume status that can sensitively track changes in volume status during ultrafiltration.

Assessment of Volume Status:

A- ***Using Traditional Clinical Signs***

The traditionally taught clinical signs of hypovolemia (whether due to dehydration or volume depletion) which include hypotension, tachycardia, postural vital sign instability (an increase in pulse of >30 beats/min, or a BP drop >20 mmHg), and increased capillary refill time, are notoriously insensitive markers, especially when the degree of volume loss is small or moderate in quantity[12]. For example, only 1 in 5 patients exhibits postural pulse increase (from supine to standing) of >30 beats/minute, or severe dizziness preventing standing, after a moderate blood loss of 450-630 mL[12] . The sensitivity of these signs increases to 97% for patients with a large volume loss of 630-1150 ml[12]. Postural hypotension (defined as a decrease in SBP of >20 mm Hg) has even poorer sensitivity. In patients <65 years, it has a sensitivity of 9% for 450-630 mL of blood loss, and for patients >65 years of age, it has a sensitivity of 27% for 450-630 mL of blood loss[12]. These values correspond closely to the false positive rates in the same age groups (10% for patients <65 years of age, and 28% for patients >65 years of age), making the use of postural hypotension a very poor tool in the detection of moderate amounts of blood loss [12]. There appears to be limited data on the sensitivity of postural hypotension with larger blood volume losses of 630-1150 mL. Similarly, static measurements of supine blood pressure and heart rate are very insensitive to (but fairly specific for) blood loss.

B- ***Invasive Static Pressures***

Invasive measures of CVP and pulmonary artery occlusion pressure, many studies have shown that these static measurements are not helpful in determining fluid status, and as such, it is no longer recommended that they be used to guide fluid management[13].

The Plethysmographic Waveform

The peripheral plethysmographic waveform (PPG) is a waveform obtained from the pulse oximeter, the ubiquitous clinical monitoring device that is comprised of a light source and a detector. The detector may be positioned either directly across from the light source (as in the finger plethysmography) or next to the light source (as in forehead plethysmography). The PPG waveform is determined by the equation known as Beer's law, which states the following:

$$A_{total} = E_1C_1L_1 + E_2C_2L_2 + \ldots + E_nC_nL_n$$

where

A= Absorbance at a particular wavelength

E=extinction coefficient (absorbency)

C=concentration

L= path length between the light source and the detector

The PPG waveform represents the changes in blood volume over time in a tissue of interest (usually the finger or the earlobe) to which the pulse oximeter is applied[14]. The source of this waveform is most likely the "point of maximal pulsation"[15] of peripheral arterioles, just proximal to the point at which pulsatile blood flow is converted to smooth capillary flow.

The PPG waveform was initially conceptualized as comprising of an invariant "DC" component (which was thought to represent a constant volume of venous blood and tissue), and a pulsatile "AC" component (which reflected changes in arterial blood volume as affected by cardiac

activity). The DC component can be isolated from the original waveforms by applying a low pass filter, and the AC component can be similarly isolated by applying a high pass filter as shown in (figure 1).

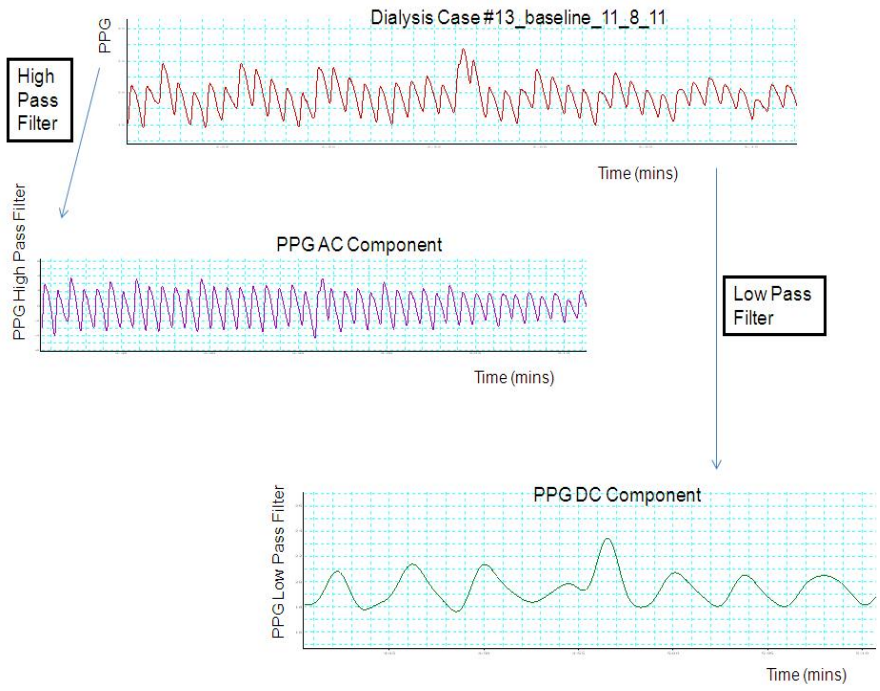

Figure 1. PPG DC and PPG AC components illustrated. The PPG AC component is isolated from the original waveform by applying a high pass filter, whereas the PPG DC component is obtained by applying a low pass filter. The data used to generate this plot are the original results of this thesis work.

The term "DC component" turns out to be somewhat of a misnomer. This component is hardly invariant, but instead fluctuates under the effects of respiration, vasomotor activity, thermoregulation, and other influences[14]. Similarly, the AC component not only reflects cardiac activity, but also shows a slower variation that is also under the influence of respiration[16].The respiratory-induced cyclic changes in both the DC and AC components of the plethysmograph are illustrated in figure 2, and will be further discussed in the section on 'respiratory variation of the PPG waveform as a predictor of fluid status'.

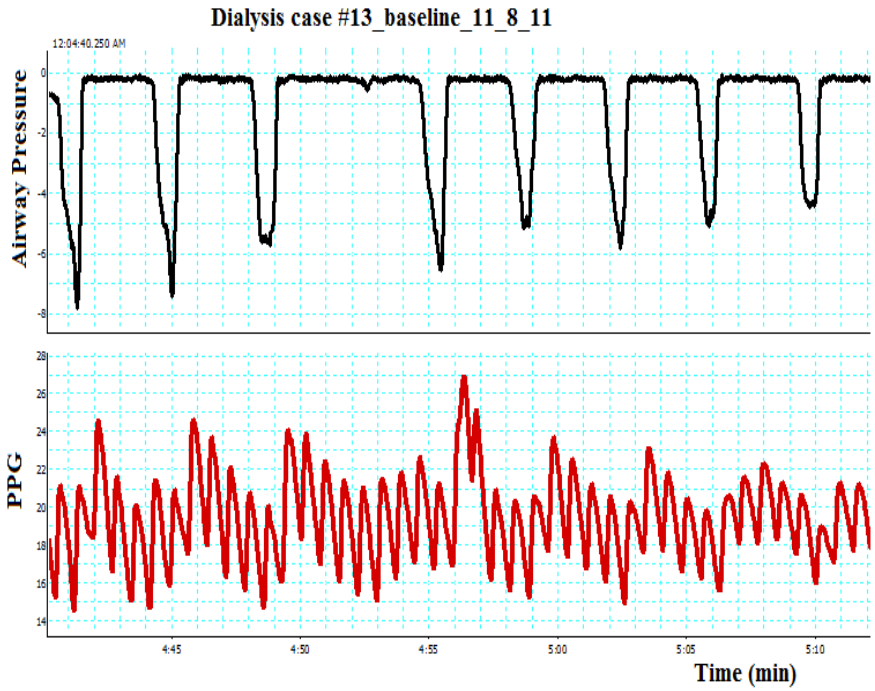

Figure 2. Impact of respiration on the plethysmographic waveform. Top shows the airway pressure versus time, where each deflection from zero represents an inhalation using incentive spirometry. The bottom plot shows the changes in the DC component and the AC component of the plethysmograph. An overlay of these two plots illustrates the influence of respiration on PPG parameters. The data used to generate this plot are the original results of this thesis work.

It is worth mentioning that the PPG signal visualized on most commercial pulse oximeters is the end result of significant signal processing. Typically, it is only the AC component of the plethysmograph that is displayed, whereas the DC component is routinely eliminated via an autocentering function[15]. Additionally, an autogain function is used to maximize the amplitude of the AC component, thereby maximizing the size of the waveform for optimum visibility on the display screen[17]. The data processing pathway that is involved in generating the displayed PPG waveform is pictorially represented in the journal article 'Photoplethysmography and its application in clinical physiological measurement'[14]. Utilization of the plethysmograph for

research purposes necessitates the removal of autogain and autocentering functions such that critical data are not lost.

There are many factors both intrinsic and extrinsic to the subject that can cause variability in the plethysmograph waveform. For one, the pulse oximeter waveform is responsive to the autonomic nervous system. The degree of impact of the sympathetic nervous system on the PPG waveform is commensurate with the amount of sympathetic nervous innervation in the tissue of interest; the sympathetic innervation of the cutaneous blood vessels of the finger is greater than that of the earlobe, and correspondingly the finger-derived PPG waveform is more sensitive to alterations in the sympathetic nervous system than the earlobe-derived PPG waveform [15.] At the same value of cardiac output, the amplitude of the PPG waveform depends on the degree of vascular distensibility. Thus in conditions of high sympathetic tone, peripheral cutaneous vascular compliance is low, the amplitude of the PPG waveform decreases with respect to baseline[15]. Conversely, when the vessels are more compliant, the amplitude of the PPG waveform increases with respect to baseline. Table 2 gives a short list of the other determinants of the PPG amplitude; this list is by no means exhaustive.

Table 2[15].

Factors Affecting Pulse Oximeter Waveform Amplitude

Increased Amplitude due to Vasodilation

1. Pharmacological-nitroprusside

2. Physiologic-warming, sedation

3. Anesthetic-regional sympathetic blocks (spinal and epidural)

Decreased Amplitude due to Vasoconstriction

1. Pharmacological-phenylephrine, ephedrine

2. Physiologic-cold, surgical stress

Respiratory Variation of the PPG Waveform as a Predictor of Fluid Responsiveness

Fluid responsiveness is commonly defined as a >15% increase in stroke volume in response to administration of a 500cc bolus of fluid. Another way of thinking about this is that fluid responsive patients are operating on the steep portion of the Frank-Starling curve (figure 3), and therefore an increase in venous return translates into an increase in cardiac output. Conversely, fluid non-responders are those patients who are operating on the flat portion of the Frank Starling curve, and for whom fluid administration will simply cause tissue edema.

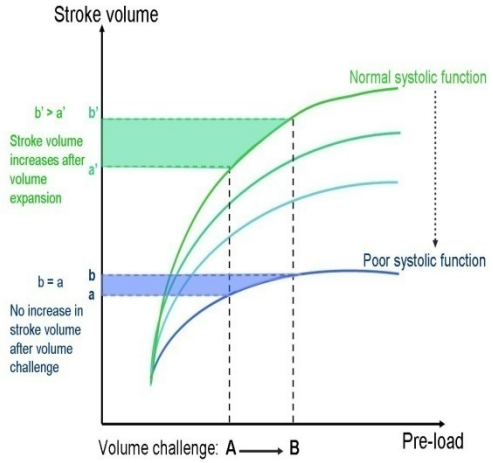

Figure 3. The Frank Starling Curve. Fluid responsive patient operate on the steep portion of the Frank Starling curve, and there is a greater than 15% increase in stroke volume from the point a' to the point b'. Fluid non-responders however, operate on the flat portion of the Frank Starling curve, where point b = point a[18]

Functional Hemodynamics

To understand the physiologic basis of dynamic fluid indices based on heart lung interactions, one must first understand two concepts that relate to the heart.

The first concept is that of the parallel diastolic ventricular interdependence[19]; the right and left ventricles of the heart are mechanically coupled due to their sharing of a common pericardial sac,

common circumferential fibers, and a common septum. The consequence of this mechanical coupling is a phenomenon known as the direct ventricular diastolic interdependence in which the diastolic filling of one ventricle compromises the filling of the contralateral ventricle by directly affecting its compliance and shape[19].

The second concept is that of the series ventricular interdependence[19], which states that after a lag of a few heart beats (corresponding to the pulmonary transit time), changes in the output of the right ventricle must necessarily be propagated forward to the left ventricle, thus affecting the left ventricular preload[19]. In positively ventilated patients, each "inspiration" introduces positive pressure into the thorax, which compresses the pulmonary vasculature temporarily augmenting arterial flow out of the thorax and into the left atrium, while also reducing the left ventricular afterload[19]. This results in an **immediate and transient** increase in left ventricular stroke volume during inspiration. Simultaneously, the positive pressure breath also temporarily impedes venous return to the heart. Given the series interdependence of the two ventricles, this reduction in venous return is "seen" by the left ventricle **after a few heartbeats** (corresponding to the transit time through the pulmonary vasculature), and results in a temporary reduction in stroke volume[20].In low intravascular volume states (when the patient is preload dependent and therefore operating on the steep portion of the Frank Starling curve), this respiratory effect on the cardiovascular system is particularly pronounced, as the heart's stroke volume is sensitive to the ventilation-induced changes in venous return. Conversely, in euvolemia or hypervolemia, when the patient is operating on the flat portion of the Frank-Starling curve, the respiratory effect on the cardiovascular system is minimal resulting in smaller impacts on the stroke volume. Thus there is a greater respiration-induced variation in stroke volume with hypovolemia as compared to euvolemia and hypervolemia. It has already been well established that for mechanically

ventilated adult patients with no cardiac arrhythmias receiving more than 8ml/kg of tidal volume, the volume dependent respiratory variation in left ventricular stroke volume corresponds to ventilation-induced changes in systolic arterial pressures [16,21] . Numerous studies shown that the respiratory-induced variation in the arterial pressure waveform in ventilated patients (fig 4) is a reliable predictor of fluid responsiveness in the absence of abnormal heart rhythms[16,21,22]

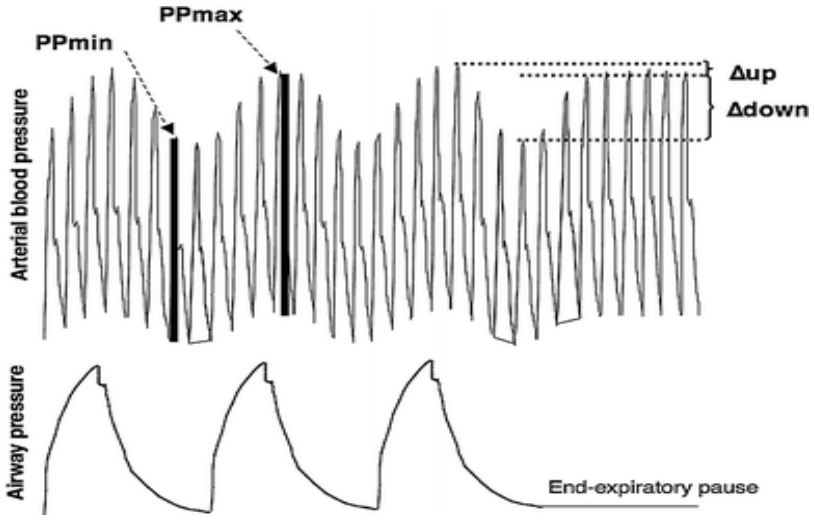

Figure 4. Influence of positive pressure ventilation on arterial blood pressures in volume-controlled ventilation. ΔUp is the increase in systolic arterial blood pressure during expiration with respect to the systolic arterial blood pressure during a period of apnea. ΔDown is the decrease in systolic arterial blood pressure during positive pressure inspiration with respect to its value during a period of apnea. Both ΔUp and ΔDown require a period of apnea to obtain a reference value for their measurement. PPmin and PPmax are the minimum and maximum values of pulse pressure over the respiratory cycle. Higher values of ΔDown and PP (PPmax-PPmin) are predictive of hypovolemia.

Subsequent to the establishment of this relationship between fluid responsiveness and respiratory variability in arterial pressure parameters, researchers began to focus on the striking resemblance between the arterial pressure waveform and the plethysmograph [16,21,23], in the hope that the latter could be used in noninvasive fluid status monitoring. For instance, Shamir et al compared changes in the arterial pressure waveform and the plethysmographic waveform after subjects

underwent 10% loss of total blood volume, and again with volume replacement[16]. These authors found significant correlations in changes that occurred in the plethysmographic and arterial pressure waveforms with volume depletion[16]. In a second study, the plethysmographic variability index (PVI) (an automated value that indicates the degree of variability in the plethysmographic waveform over the respiratory cycle) was found to be highly accurate in predicting fluid responsiveness immediately after intubation during mechanical ventilation and before the beginning of surgery, and fairly accurate in predicting fluid responsiveness during surgery[24]. This work corroborated similar findings that had been published on the use of the PVI to predict fluid responsiveness in patients during heart[25] and major abdominal surgeries[26].

There are several points to be noted on the current body of research that relates fluid responsiveness with respiratory variability in the plethysmograph. These points are delineated below.

1. Most studies on the use of dynamic indices to predict fluid status have been done on mechanically ventilated patients. As previously mentioned, the pleth variability index has only been proven to have predictive value in patients ventilated with a tidal volume of 8ml/kg, and in the absence of cardiac arrythmias. There is a relative dearth of information on how these concepts may be applied to predict fluid responsiveness in spontaneously breathing patients. The few studies that have been published on the use of dynamic indices to predict fluid responsiveness in spontaneously breathing patients have reported mixed results. For instance, in one study the pulse pressure variation (ΔPP) was not found to be predictive of preload responsiveness in spontaneously breathing patients[27,28]. In another study, the authors compared using ΔPP (respiratory change in arterial pulse pressure) and ΔSP (respiratory change in arterial systolic pressure) during spontaneous

breathing and during Valsalva maneuvers to predict fluid responsiveness in non-ventilated patients[29]. The authors found that the dynamic indicators, ΔPP and ΔSP were significantly higher in fluid responders than non-responders, and predicted fluid responsiveness with high specificity. However, the sensitivity of ΔPP and ΔSP was very low. For instance, a cutoff value of 12% for ΔPP was associated with a 92% specificity but a 63% sensitivity[29]. In comparison with mechanically ventilated patients, the sensitivity of ΔPP in this study of spontaneously breathing patients was much lower[29].There are several posited explanations for why this relationship breaks down in non-ventilated patients. For one, the intrathoracic pressure changes associated with spontaneous respiration may be insufficient stress on the system to have a measurable impact on venous return and thus left ventricular stroke volume[29]. Additionally, spontaneous breathing is associated with significant breath-to-breath variability in tidal volume, and ΔPP is influenced by tidal volume[27]. Thus the variability in tidal volume associated with spontaneous breathing may mask the degree of pulse pressure variation. As for Valsalva maneuvers, the mechanism of exhaling against a closed airway may change the afterload seen by the left and right ventricles, which in turn complicates the relationship between respiration and stroke volume [27].

2. The published literature has focused almost exclusively on the pulsatile 'AC' component of the plethysmograph to predict fluid responsiveness. However, emerging research from our lab suggest that the largely ignored 'DC' component (which reflects the venous circulation) may be more sensitive to changes in fluid status, and begins to exhibit changes earlier in volume loss than the AC component. In a study of eleven children scheduled for spinal fusion surgery , the effect of blood loss and fluid boluses on the PPG

and arterial waveforms was investigated[30]. The pilot study found that parameters related to the PPG DC modulation (ie the slow, ventilation-induced modulation of the PPG DC component) were the only parameters that changed significantly with blood loss, and again with fluid resuscitation. Conversely, parameters related to the AC modulation (respiratory modulation of the PPG amplitude) showed significant changes with blood loss only, but not with fluid resuscitation. These preliminary results suggest that the respiratory effects the DC component (ie the venous side) are more sensitive to fluid changes than the respiratory AC modulation (ie the arterial side). Consistent with the poor predictive ability of vital signs, the blood pressure and heart rate showed no significant changes with either blood loss or volume replacement[30].

3. Furthermore, despite the obvious advantages, these principles of respiratory variability in the plethysmograph have never been used to track excess or too-rapid removal of intravascular volume in hemodialysis patients.

Statement of Purpose and Hypothesis

The purpose of this study is to examine changes in the plethysmograph waveform during hemodialysis as a potential means of tracking progressive volume removal in non-intubated patients. As compared to spontaneous breathing, incentive spirometry breathing poses a greater challenge to the cardiovascular system by displacing more venous and arterial blood. As such, we hypothesized that use of incentive spirometry would amplify the respiratory modulation of the PPG DC component and thus improve our ability to track volume removal in non-intubated patients.

Methods

Forty-four hemodialysis patients were recruited for this study. The study was approved by the IRB, and verbal informed consent was obtained from all patients. Patients were monitored using 5-lead EKG, and a finger pulse oximeter placed on one of the upper extremity digits contralateral to the patient's fistula in order to avoid arterialization of the plethysmographic waveform. The autogain function of the pulse oximeter was turned off to keep the scale constant throughout the study. At the beginning of the hemodialysis session, baseline values of the EKG, and plethysmograph (PPG) were recorded for 5 minutes, first with the patient spontaneously breathing, and then with the patient performing incentive spirometry breathing. The waveforms were recorded with a sample frequency of 100Hz using the data acquisition software S5 Collect. Baseline values of the blood pressure and heart rate were also recorded for each patient. Records were kept of any vasoactive medications (e.g. midodrine) administered to the patient during HD, as well as any symptoms (nausea, vomiting, fatigue) that prevented the patients from fully complying with the research protocol. A chart review was performed retrospectively to obtain the subjects' demographic information such as weight, age, height, and medical comorbidities. Additionally, chart review of subjects' vital signs, which were collected by nursing staff every 15-30 minutes during dialysis, was used in order to identify any IDH episodes.

Waveform Analysis

All waveforms were analyzed using the LabChart data analysis software. There are two possible ways in which to analyze waveform data: the time domain (which describes changes in the waveform amplitude, width, area, upstroke, downslope,etc), and the frequency domain (in which the amplitude density in on the y axis is plotted versus frequency on the x axis). The time and

frequency domains are two different methods for analysis of the waveforms. The time domain has the disadvantage of being highly susceptible to movement artifact. Conversely, the frequency domain is a less familiar form of visualizing waveform data, but is less susceptible to movement artifact.

This work uses frequency analysis of PPG waveforms. In order to generate the frequency domain, LabChart's fast fourier transform function (Hamming window, 4K, 2FFT, 93.75% overlap) was applied to data segments of approximately 60 seconds. The fourier transform is a mathematical operation used to decompose the time domain waveform into the sum of component sinusoidal waves of varied amplitudes, frequencies, and phases. The amplitude densities of the component waves are then plotted against their respective frequencies to create the frequency domain. Thus the frequency domain allows one to visualize the contributions of waves of various frequencies to the original waveform. Figure 5 below illustrates the frequency domain of PPG waveforms. The frequency domain was used to derive the following parameters:

-respiratory frequency

-amplitude density of the respiratory frequency

-PPG DC *(amplitude density of the PPG wave at the respiratory frequency, which corresponds to the amount of respiratory modulation of the DC component)*

-pulse/cardiac frequency

-pulse AD *(amplitude density of the PPG wave at the cardiac frequency)*

-pulse AC (*amplitude density at the respiratory frequency of the PPG height wave, which corresponds to the amount of respiratory modulation of the PPG height).*

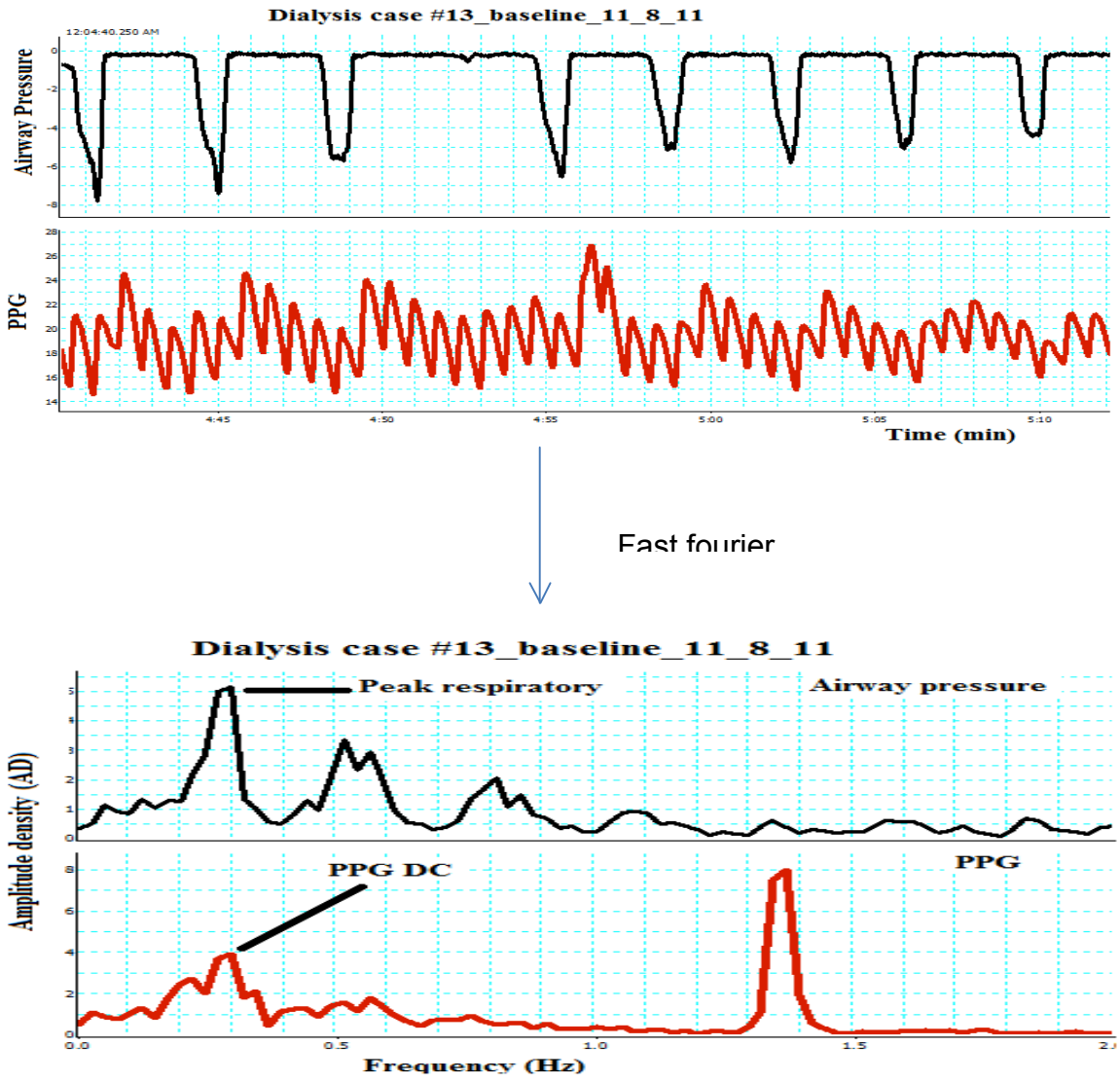

Figure 5. PPG waveform and frequency domain.. Amplitude density of respiration and PPG DC are indicated on the plot.

Statistical Analysis

Baseline values (at the beginning of dialysis) were compared with values obtained at the end of hemodialysis. Also, spontaneously breathing values were compared with incentive spirometry values. Results were compared using the 2-tailed t-test and values of $p<0.05$ was considered statistically significant. Unless otherwise stated, data were presented as mean +/- SD.

Results

Forty-four subjects were studied using our protocol described in the methods section. 23 subjects were of poor data quality (e.g. significant movement artifact in the plethysmographic waveform), and were not included in the final analysis. Therefore, we analyzed 21 data sets for this study. The subjects' demographic data and dialysis parameters are summarized in tables 3 and 4 respectively below. Eight subjects met IDH criteria (decrease in SBP of ≥30 mmHg, or a decrease in MAP of ≥10 mmHg); two of these subjects (subject 16 and subject 21) received treatment for IDH. Subject 3 had a history of IDH and was given prophylactic midodrine both prior to and during the dialysis treatment in order to maintain his intradialysis blood pressures. Additionally, subject 1 received a transfusion of 1U of PRBC while on dialysis.

Patient Demographic Data

Parameter	Values	
Age (yr)	59.9±17.16	
Male/Female (n)	14/6 (20)	
Comorbidities	Diabetes Mellitus	12
	Hypertension	12
	Heart Disease	5
	Liver Disease	3

Table 3. Demographic data and Medical History of the 21 patients enrolled in the study

Dialysis Parameters

Average Filtration Rate (cc/hour)	Case No.	IDH episodes (Y/N)	Treatments Received
<500	5	N	None
	6	Y	None
	9	Y	None
	12	N	None
	13	N	None
	17	Y	None
	18	Y	None
500-1000	2	N	None
	3	N	Midodrine
	4	N	None
	7	N	None
	8	N	None
	11	N	None
	14	Y	None
	19	Y	None
>1000	1	N	1U PRBC, 1U Albumin
	10	N	None
	15	N	None
	16	Y	Midodrine
	20	N	None
	21	Y	200cc NS

Table 4. Dialysis parameters for each of the twenty one cases. IDH was defined as a decrease in SBP >30mmHg or a decrease in MAP > 10mmHg with concomitant symptoms.

Hemodynamic Data

Hemodynamic Data Grouped By Volume of Ultrafiltrate Removed and Ultrafiltration Rate

The hemodynamic data of the 21 cases are presented in three groups based on **the rate of ultrafiltration**. By grouping the data into ultrafiltration rates, dialysis time (plotted on the x-axis) can be used as surrogate for the volume of ultrafiltrate removed. In this way, any predictive vital sign trends that occur with volume removal may be elucidated. There were **nonuniform changes in blood pressure and heart rate responses to volume removal** as shown in figure 6-8. These data are consistent with the poor predictability of vital sign data in tracking successive volume removal, as the presence or absence of compensatory cardiovascular mechanisms result in a confusing and misleading picture of vital signs with ultrafiltration.

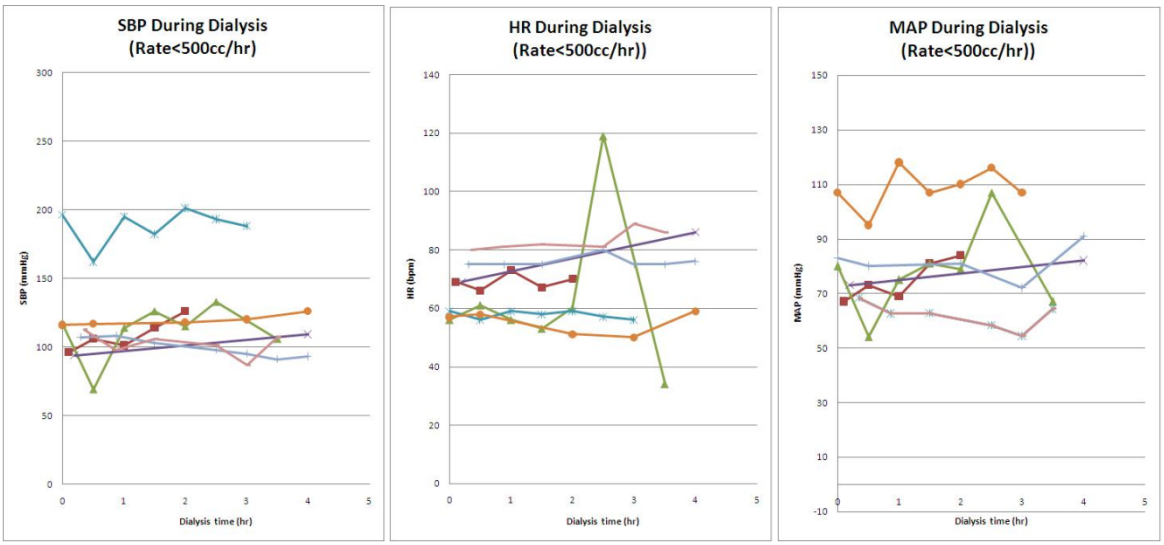

Figure. 6 a-c Variations in SBP, HR, and MAP during dialysis for subjects whose rate of ultrafiltration was <500 ml/hr.

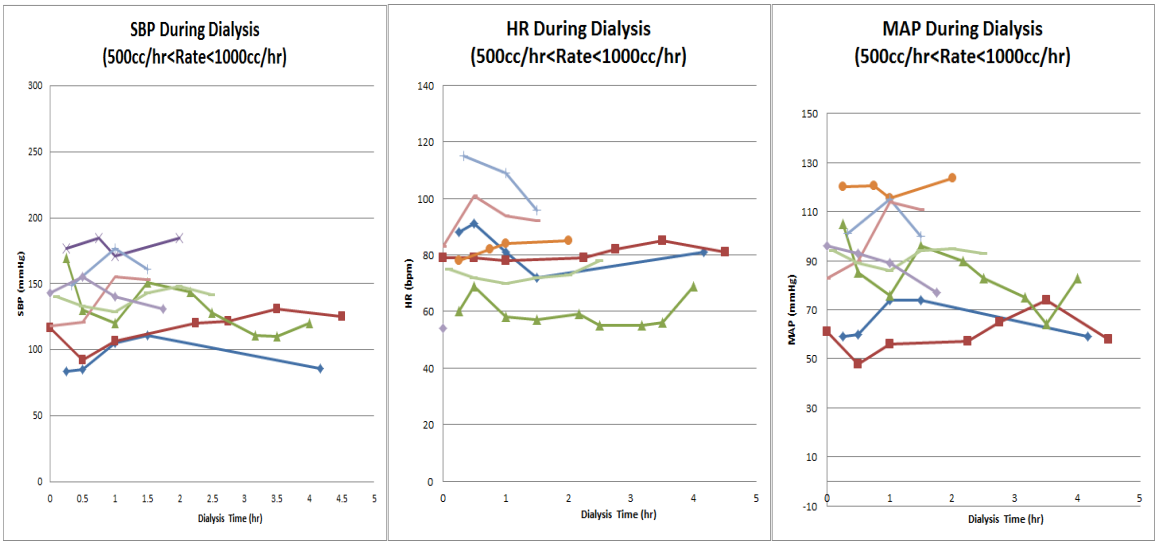

Figure.7 a-c Variations in SBP, HR, and MAP during dialysis for subjects whose rate of ultrafiltration was 500 ml/hr >Rate<1000 ml/hr.

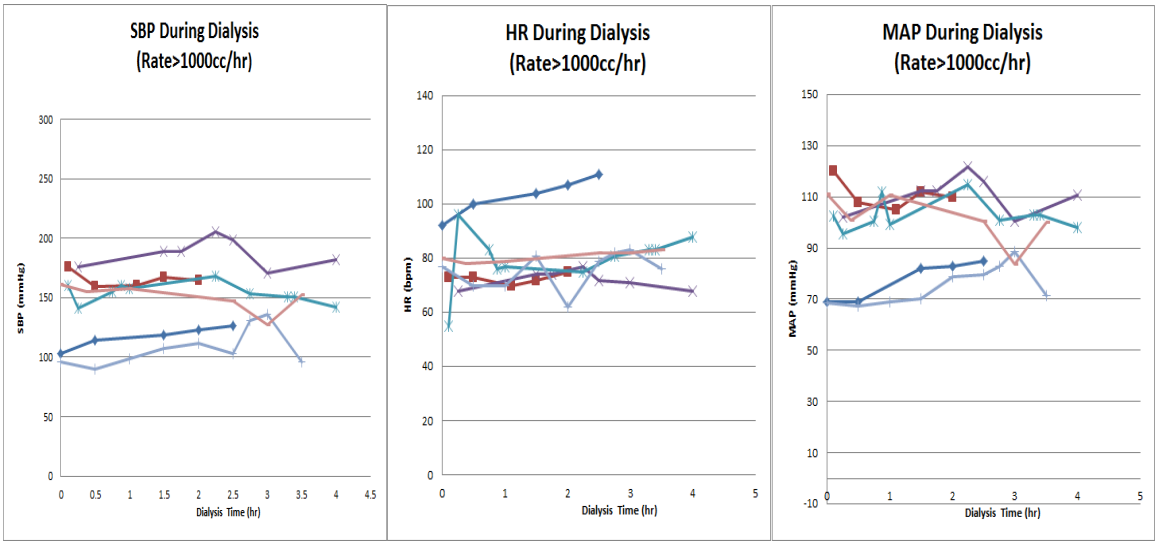

Figure.8 a-c Variations in SBP, HR, and MAP during dialysis for subjects whose rate of ultrafiltration was >1000 ml/hr.

In order to better visualize any existing trends in the hemodynamic data, the data were further subdivided into groups based on the **amount of ultrafiltrate (UF) removed** during dialysis, as **well as the rate of ultrafiltrate removal (Rate)**. Again, as illustrated in figures 9-13, for each subcategory, there were **nonsignificant changes in blood pressure and heart rate responses to volume removal**.

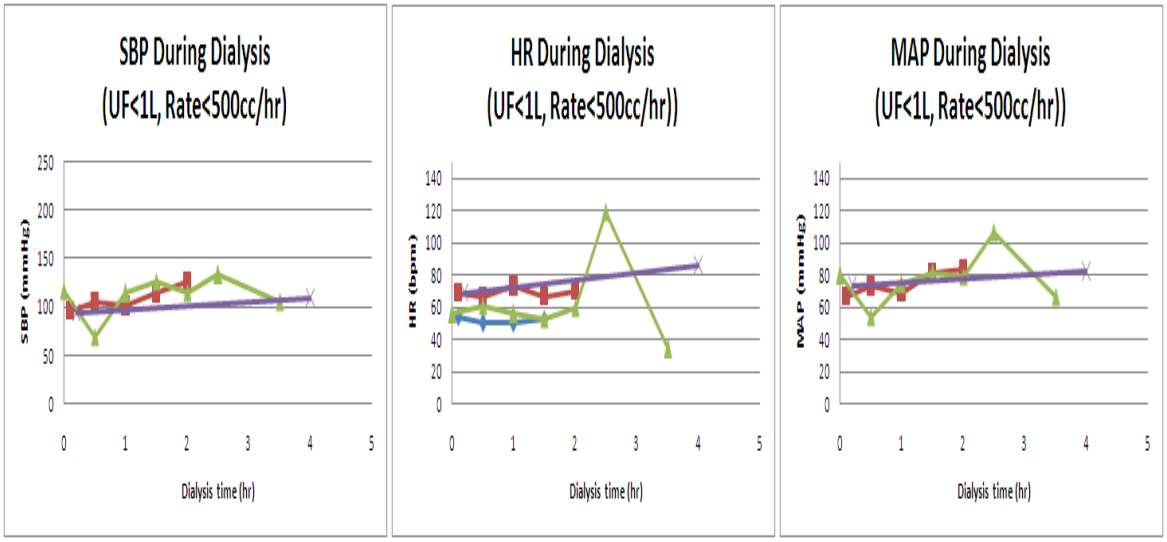

Figure. 9 a-c. Variations in SBP, HR, and MAP during Dialysis for subjects who had <1L of ultrafiltrate removed at a rate of <500ml/hr.

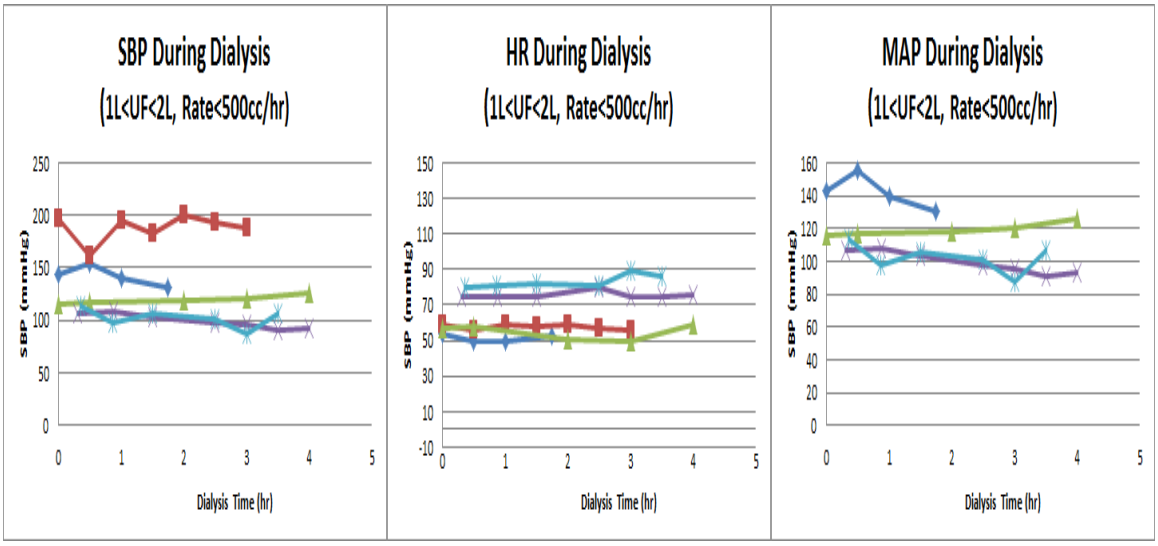

Figure. 10.a-c Variations in SBP SBP, HR, and MAP during dialysis for subjects who had 1L-2L of ultrafiltrate removed and at a rate of <500ml/hr.

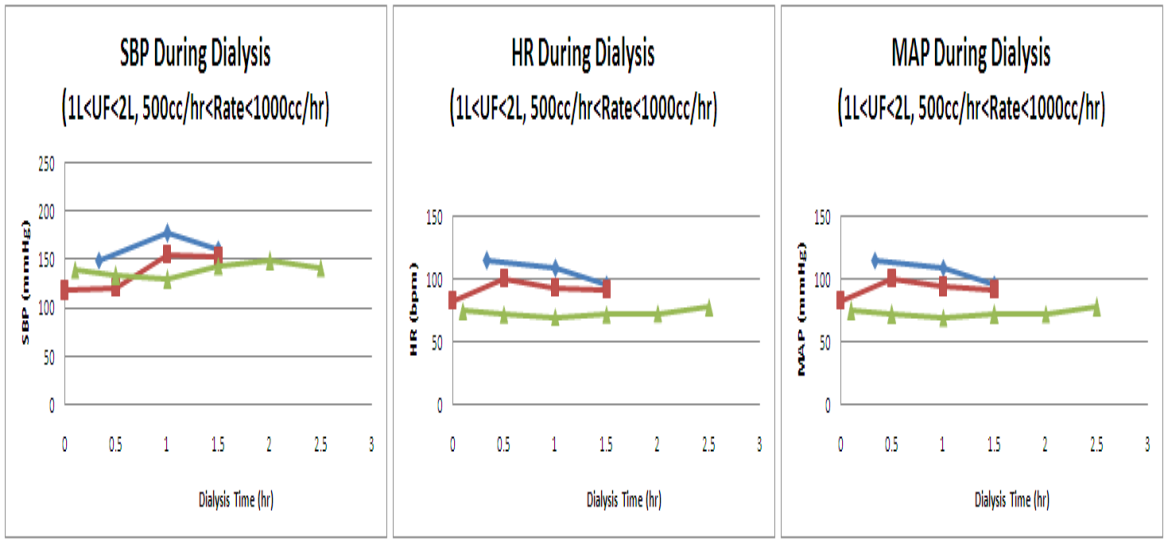

Figure. 11. a-c Variations in SBP, HR, and MAP during dialysis for subjects who had 1L-2L of ultrafiltrate removed and at a rate of 500-1000 ml/hr.

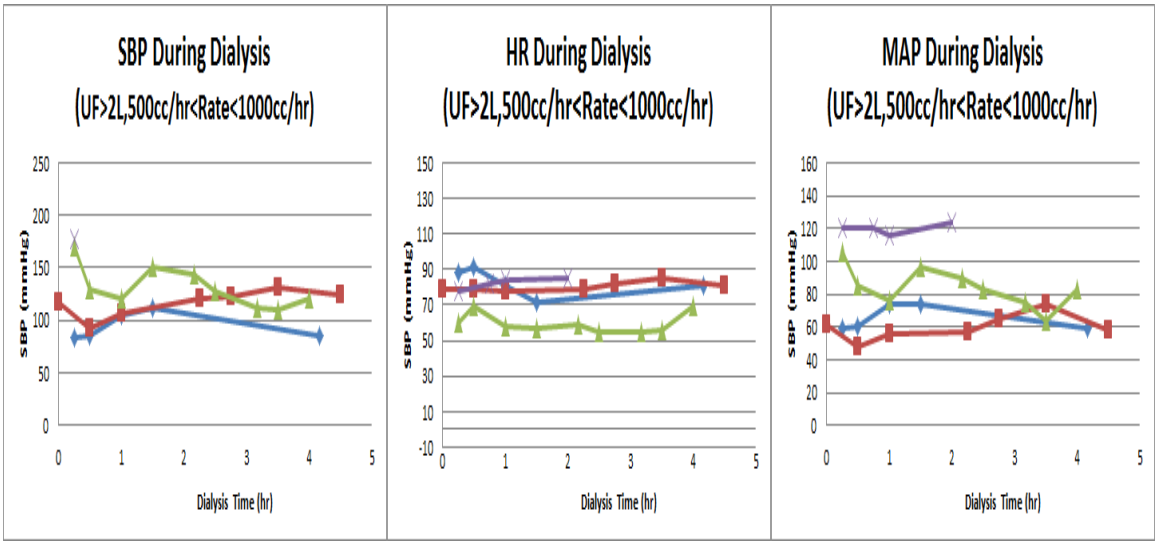

Figure.12 a-c Variations in SBP, HR, and MAP during dialysis for subjects who had >2L of ultrafiltrate removed and at a rate of 500-1000 ml/hr.

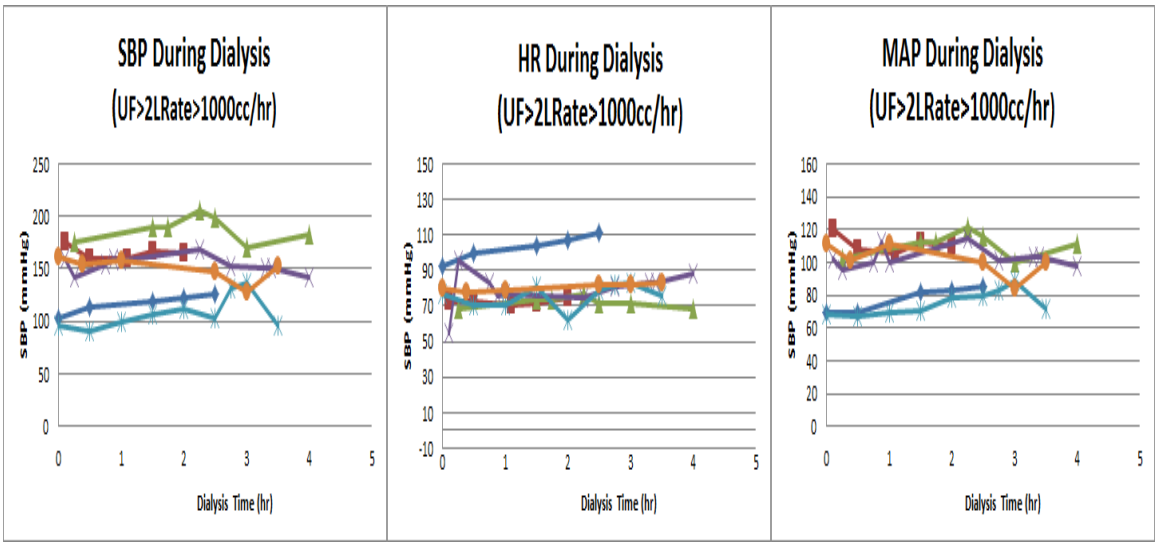

Figure.13 a-c Variations in SBP, HR, and MAP during dialysis for subjects who had >2L of ultrafiltrate removed and at a rate of >1000 ml/hr.

Incentive Spirometry Breathing Amplifies the PPG DC Value

Compared with simple spontaneous breathing, the use of incentive spirometry (IS) breathing greatly enhances the respiratory-induced variability of the DC component of the plethysmograph (PPG DC). At the beginning of dialysis, we found that with incentive spirometry breathing there was an increase in the mean PPG DC value by 234% ($p=0.0000002$) from 1.06 ± 0.82 to 3.54 ± 1.58 (see figure14).

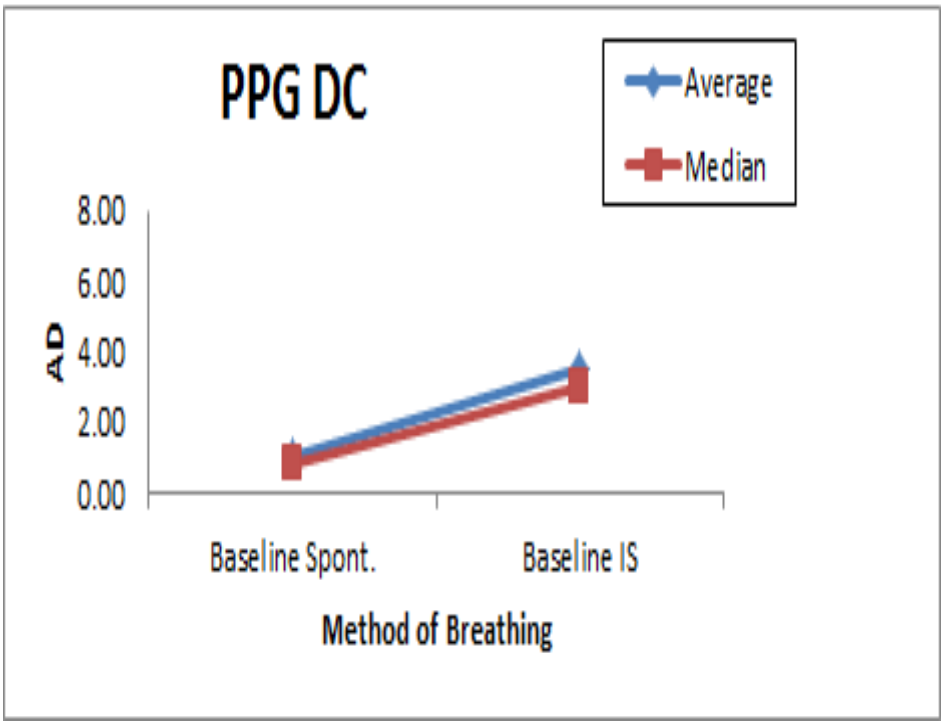

Figure 14. The effect of incentive spirometry on baseline PPG DC values. The figure illustrates that incentive spirometry breathing greatly enhances the respiratory induced variability of the PPG DC component (PPG DC).

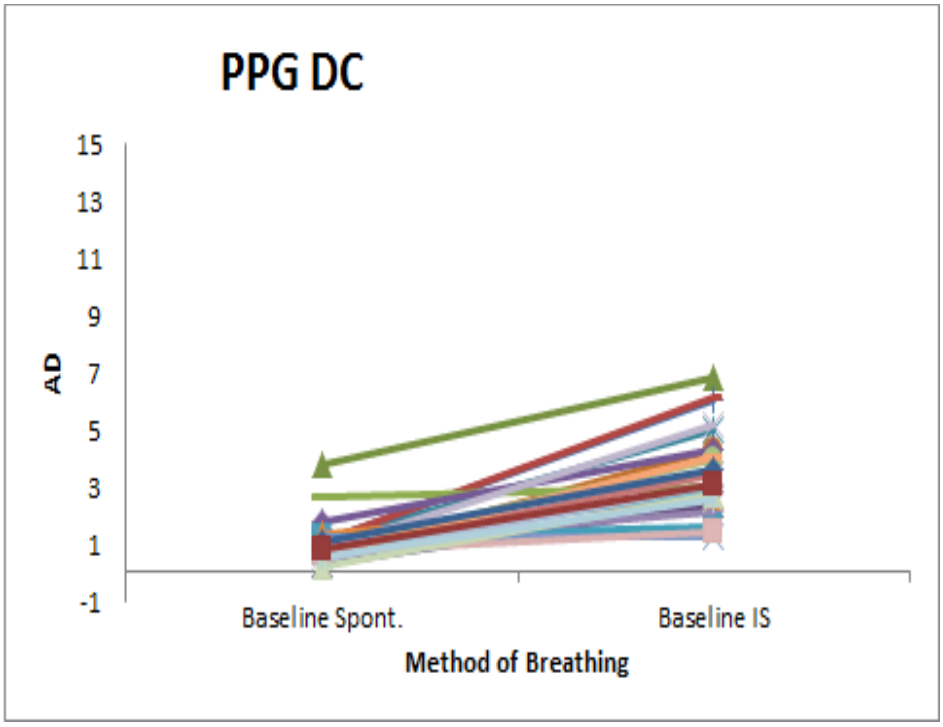

Figure 15. The effect of incentive spirometry breathing on individual baseline PPG DC values. It is noted that the degree of PPG DC amplification varies by case.

At the end of dialysis treatments, we again compared the PPG DC values for spontaneous and incentive spirometry breathing, and again found that incentive spirometry breathing resulted in an increase in the PPG DC value (fig 16). Relative to spontaneous breathing, incentive spirometry resulted in a 203% increase in the average PPG DC value at the end of dialysis (1.92 ± 1.03 vs 5.819±2.840, p=0.000023).

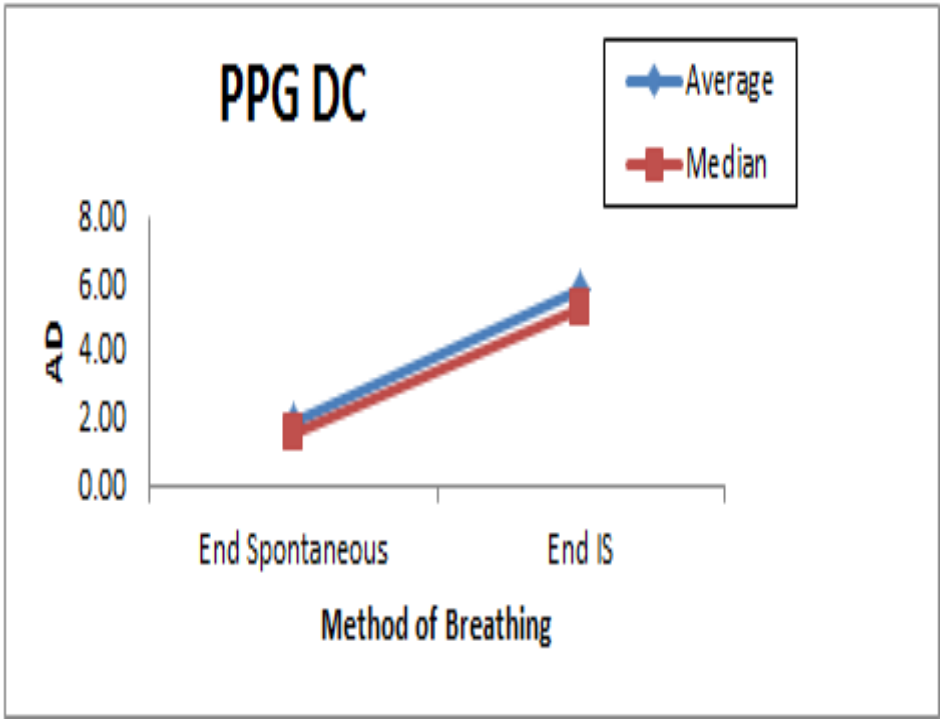

Figure.16. The effect of incentive spirometry breathing on PPG DC values at the end of dialysis. The figure again illustrates that incentive spirometry breathing greatly enhances the respiratory induced variability of the PPG DC component .

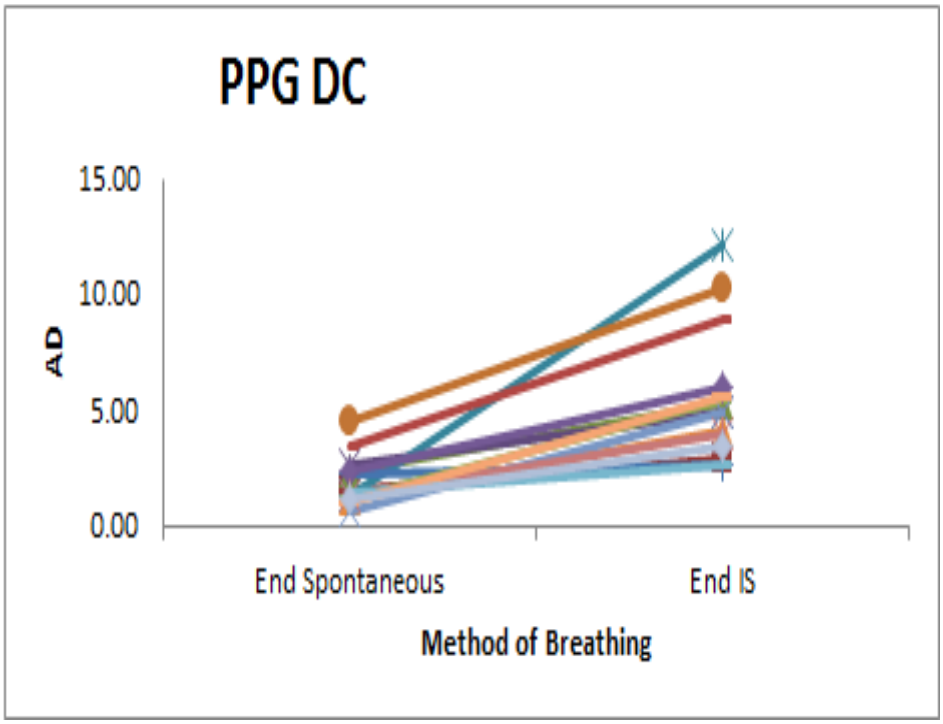

Figure. 17. The effect of incentive spirometry breathing on PPG DC values at the end of dialysis. It is again noted that the degree of PPG DC amplification is nonuniform.

Table 5. PPG DC values associated with Spontaneous Breathing and IS breathing at the beginning of dialysis.

	PPG DC		
Case	Baseline Spont.	Baseline IS	%Change
1	3.749	6.788	81.062
2	0.276	2.345	749.638
3	1.049	4.938	370.734
4	0.531	4.245	699.435
5	1.079	5.995	455.607
6	1.09	6.11	460.550
7	2.645	3.007	13.686
8	1.723	4.304	149.797
9	1.229	1.562	27.095
10	1.34	2.64	97.015
11	1.209	1.226	1.406
12	0.673	3.4	405.201
13	0.794	3.936	395.718
14	0.939	2.125	126.305
15	0.665	2.911	337.744
16	0.62	3.996	544.516
17	0.408	3.047	646.814
18	0.669	1.41	110.762
19	0.179	2.68	1397.207
20	0.804	5.16	541.791
21	0.513	2.49	385.380
Average	1.06	3.54	234
Median	0.80	3.05	
SD	0.82	1.58	
P Value	0.0000002		

Table 6. PPG DC values associated with Spontaneous Breathing and IS breathing at the end of dialysis

	PPG DC		
Case	End Spontaneous	End IS	% change
2	1.62	3.015	86
3	2.43	5.425	124
4	2.67	4.979	86
6	1.35	12.120	798
8	4.62	10.230	121
9	2.24	2.670	19
11	1.46	9.261	534
12	3.55	8.900	151
13	1.19	5.444	356
14	2.41	6.060	151
15	1.19	4.184	251
16	0.75	4.975	562
17	1.34	4.010	199
18	1.51	2.680	77
19	1.10	5.590	408
21	1.24	3.561	187
Average	1.92	5.819	203
Median	1.49	5.202	
SD	1.03	2.840	
P value	0.00002503		

The amplification of average PPG DC with IS breathing at both the beginning and at the end of dialysis suggests that incentive spirometry breathing could be utilized as a strong stimulus to amplify the respiratory-induced variation in the plethysmograph in the spontaneously breathing patient. This magnification of the PPG DC with IS breathing can facilitate the tracking of subsequent changes in the PPG DC value that occurs with volume removal in dialysis of the spontaneously breathing patient. This can be a useful test especially in the preoperative period to assess the volume status in ESRD patient scheduled for surgery.

The Degree of Amplification of PPG DC with IS is Related to the Respiratory Effort

The plastic balls located within the incentive spirometry device offer a means of measuring respiratory effort. Air flow rate of 600 ml/sec corresponds to movement of one ball; 900 ml/sec corresponds to two balls; and 1200 ml/sec corresponds to three balls. In order to better understand the different degrees of IS PPG DC amplification, the data were subgrouped by the subjects' respiratory efforts as represented by the average number of balls they were able to lift while performing incentive spirometry breathing: **group 1:** patient was able to lift ≤1.5 balls, **group 2:** patient was able to lift between 1.5 and 2.5 balls, and **group 3:** patient was able to lift between 2.5 and 3 balls. For each of these subgroups, we calculated the average PPG DC value for spontaneous breathing and IS segments respectively, as well as the percentage increase in PPG DC with IS breathing as shown in figure 18 and 19.

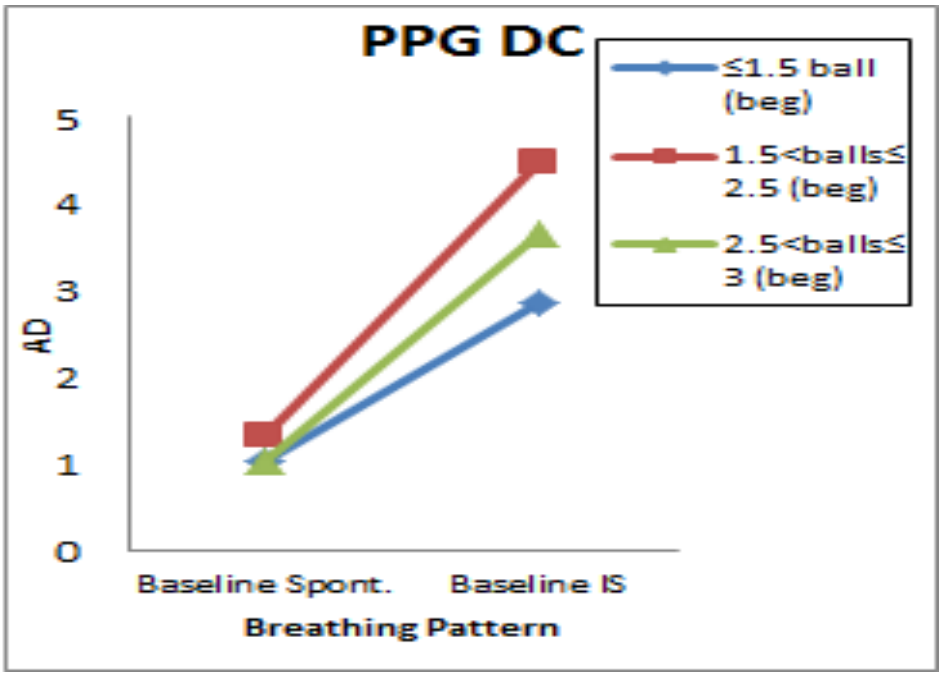

Figure 18. The degree of amplification of PPG DC with varying respiratory effort in IS breathing at the beginning of dialysis. The greater the respiratory effort, the greater the degree of PPG amplification.

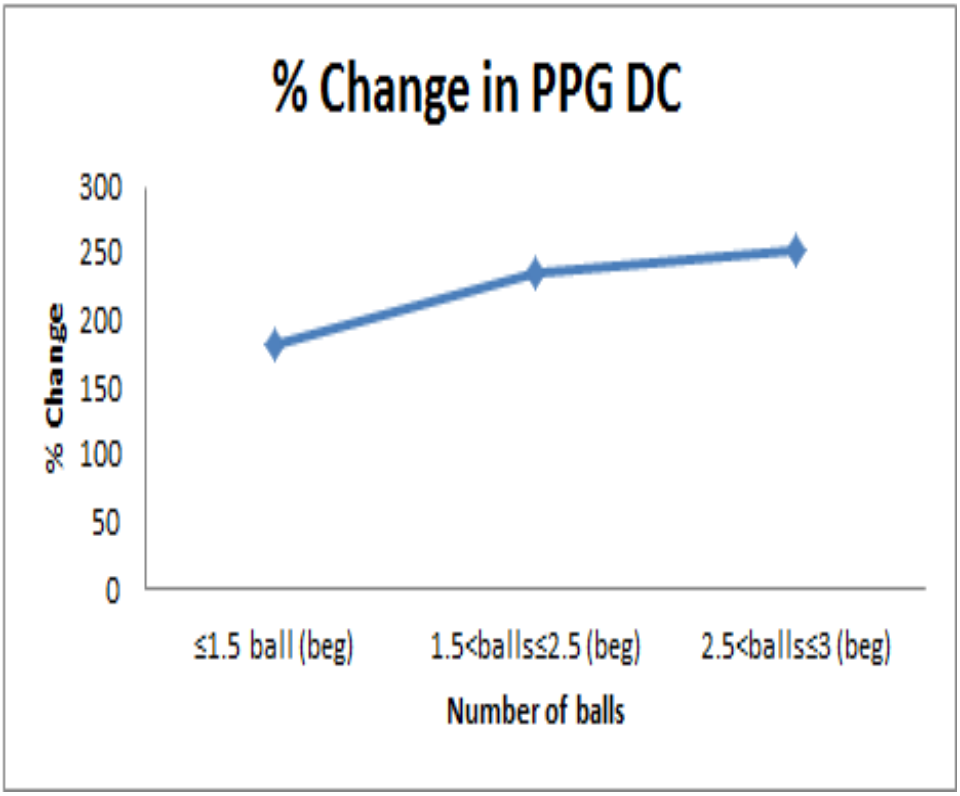

Figure 19. The percentage change in PPG DC for ≤1.5 balls, 1.5< balls≤ 2.5, and 2.5< balls≤ 3 at the beginning. The average percent change in PPG DC increases with increasing respiratory effort.

Just as a tidal volume of > 8 ml/kg in controlled ventilation is esssential to detect volume-induced changes in the PPG, our findings suggests that a spontaneously breathing subject has to move at least 1.5 balls during IS breathing to optimize the respiration-induced PPG DC changes via our method.

Changes in PPG DC during Dialysis for SB vs. IS

With both spontaneous breathing and incentive spirometry breathing, the average PPG DC value increased at the end of dialysis compared to the initial baseline value. That is, ultrafiltration in dialysis was associated with an increase in the respiratory-induced variability of the DC component of the plethysmograph, a finding consistent with our expectations based on the physiology of the heart-lung interaction.

Figures 20-22 are plots of the average PPG DC value for SB at the beginning and at the end of dialysis. For each of the three ultrafiltration rate categories (Rate<500, 500 ≤Rate≤ 1000, and Rate>1000), the PPG DC value was higher at the end of dialysis than at the beginning. This increase in PPG DC value was statistically significant for the Rate<500 ($p=0.04$), and 500 ≤Rate≤ 1000 ($p=0.00352$) groups, but was **not** statistically significant for the Rate>1000 group ($p=0.118$). The mean, median, standard deviation, and p values for this data can be seen in table 7 below.

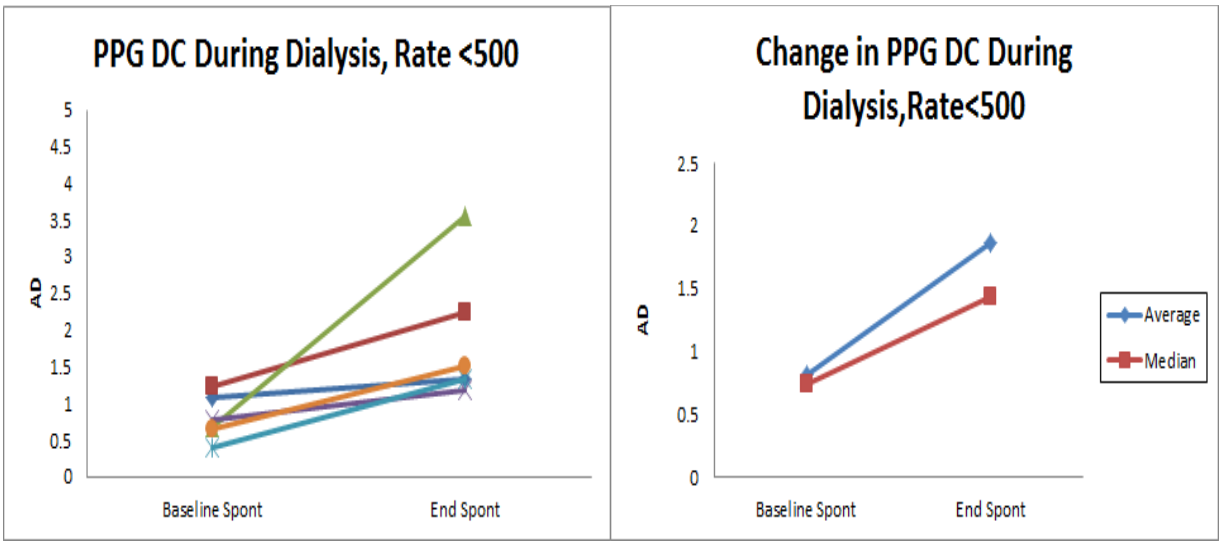

Figure 20a-b. PPG DC value at the beginning and end of dialysis with spontaneous breathing, Rate<500. The figure on the left shows the individual cases (n=6). The figure on the right shows the average and median PPG DC value. The PPG DC value at the end of dialysis is greater than that at the beginning of dialysis.

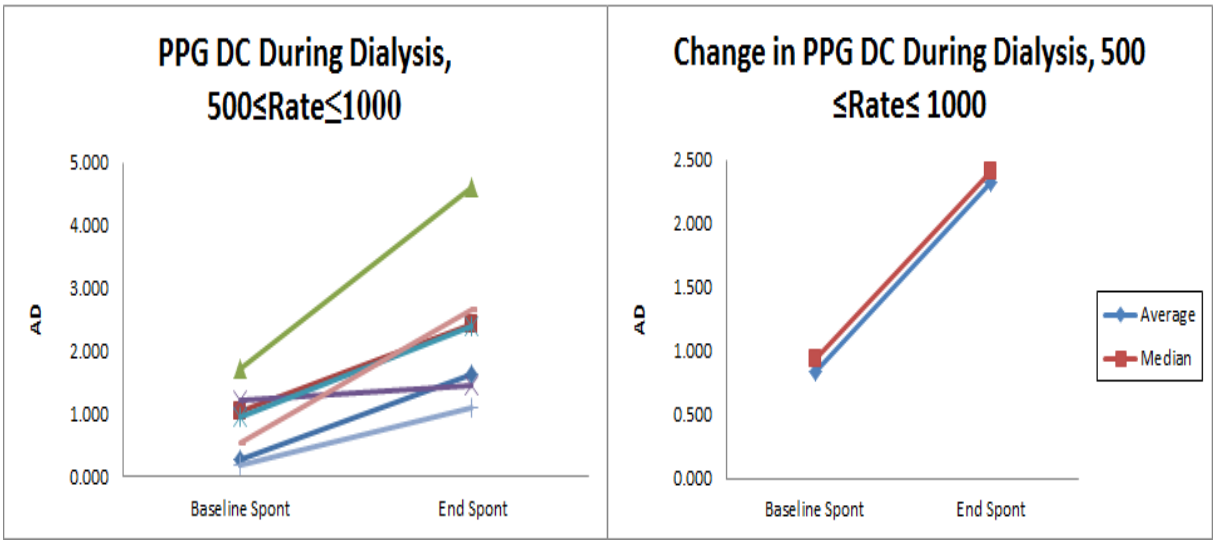

Figure 21a-b. PPG DC value at the beginning and end of dialysis with spontaneous breathing, 500≤Rate≤1000. The figure on the left shows the individual cases (n=7). The figure on the right shows the average and median PPG DC value. The PPG DC value at the end of dialysis is greater than that at the beginning of dialysis.

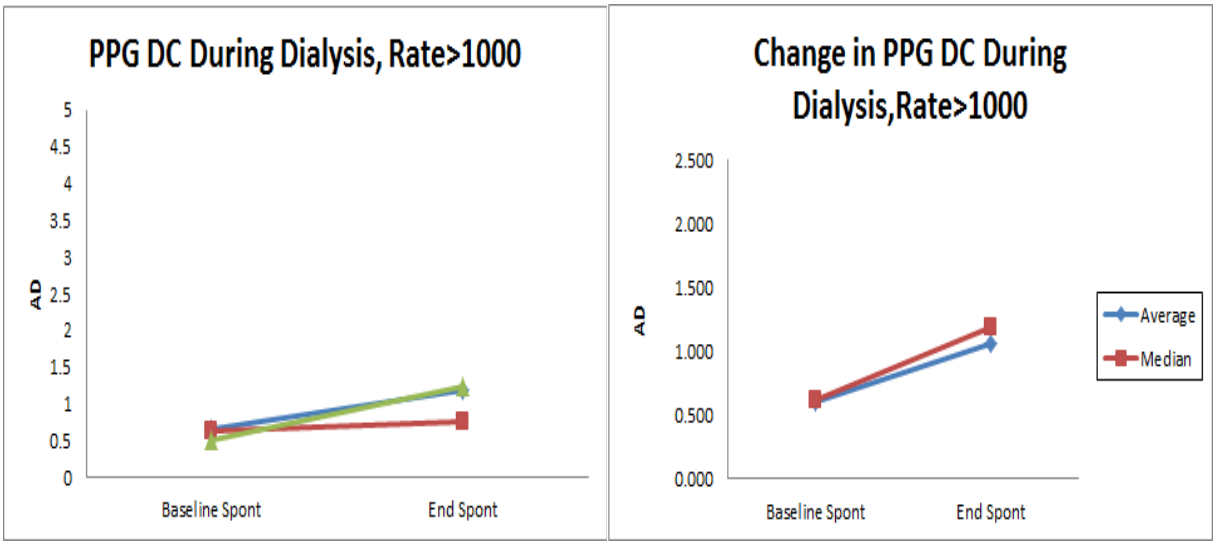

Figure 22a-b. PPG DC value at the beginning and end of dialysis with spontaneous breathing, Rate>1000 The figure on the left shows the individual cases (n=3). The figure on the right shows the average and median PPG DC value. The PPG DC value at the end of dialysis is greater than that at the beginning of dialysis, however this increase was not statistically significant.

Table 7. PPG DC for Spontaneous Breathing at the Beginning and End of Dialysis.

Average Filtration Rate (cc/hour)	Spontaneous Breathing PPG DC value	
<500	Average baseline PPG DC	0.8105
	Average end PPG DC	1.86
	Average % change	129.96
	Median baseline PPG DC	0.7335
	Median end PPG DC	1.43
	SD baseline	0.3015
	SD end	0.9043
	P value	0.0408
500-1000	Average baseline PPG DC	0.844
	Average end PPG DC	2.33
	Average % change	176.12
	Median baseline PPG DC	0.939
	Median end PPG DC	2.41
	SD baseline	0.551
	SD end	1.166
	P value	0.00352
>1000	Average baseline PPG DC	0.599
	Average end PPG DC	1.061
	Average % change	76.97
	Median baseline PPG DC	0.62
	Median end PPG DC	1.19
	SD baseline	0.07807
	SD end	0.26858
	P value	0.11844

The average PPG DC value for IS at the beginning and at the end of dialysis as shown in figure 23-25. Again, for each of the three ultrafiltration rate categories, the PPG DC value was higher at the end of dialysis than at the beginning. This increase in PPG DC value was statistically significant for **all three ultrafiltration rate groups**. The mean, median, standard deviation, and p values for this data can be seen in table 8 below.

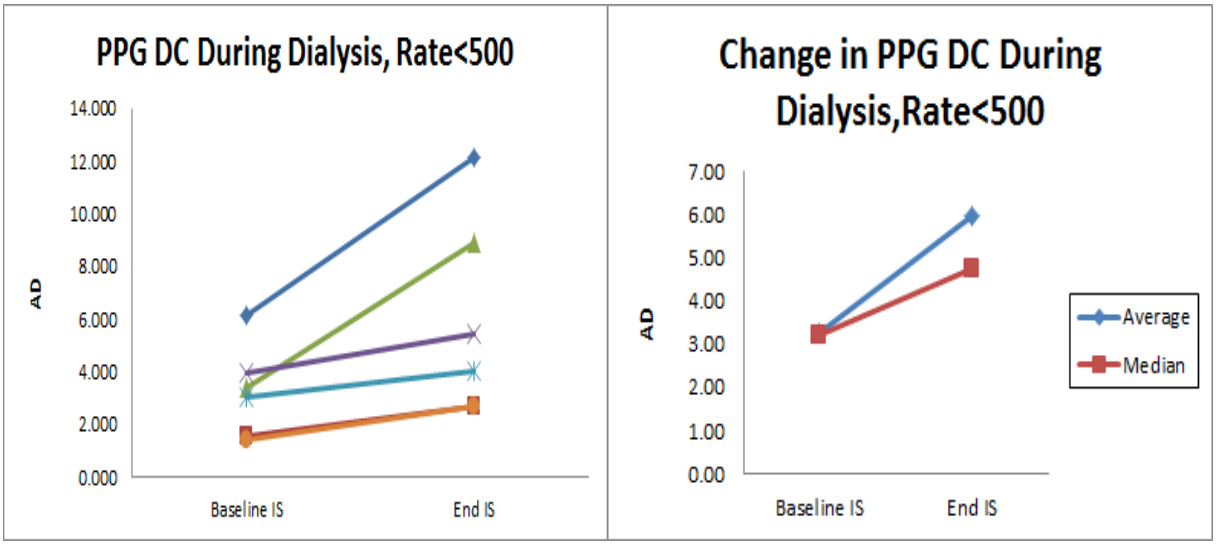

Figure 23a-b. PPG DC value at the beginning and end of dialysis with IS breathing. The figure on the left shows the individual cases (n=6). The figure on the right shows the average and median PPG DC value. The PPG DC value at the end of dialysis is greater than that at the beginning of dialysis.

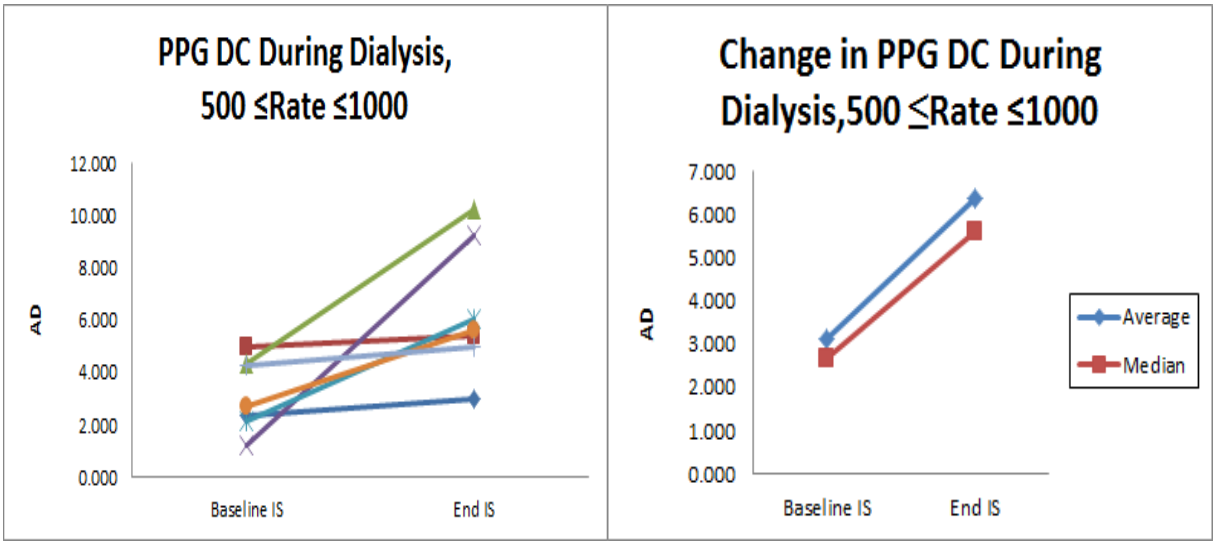

Figure 24a-b. PPG DC value at the beginning and end of dialysis with IS breathing. The figure on the left shows the individual cases (n=7). The figure on the right shows the average and median PPG DC value. The PPG DC value at the end of dialysis is greater than that at the beginning of dialysis.

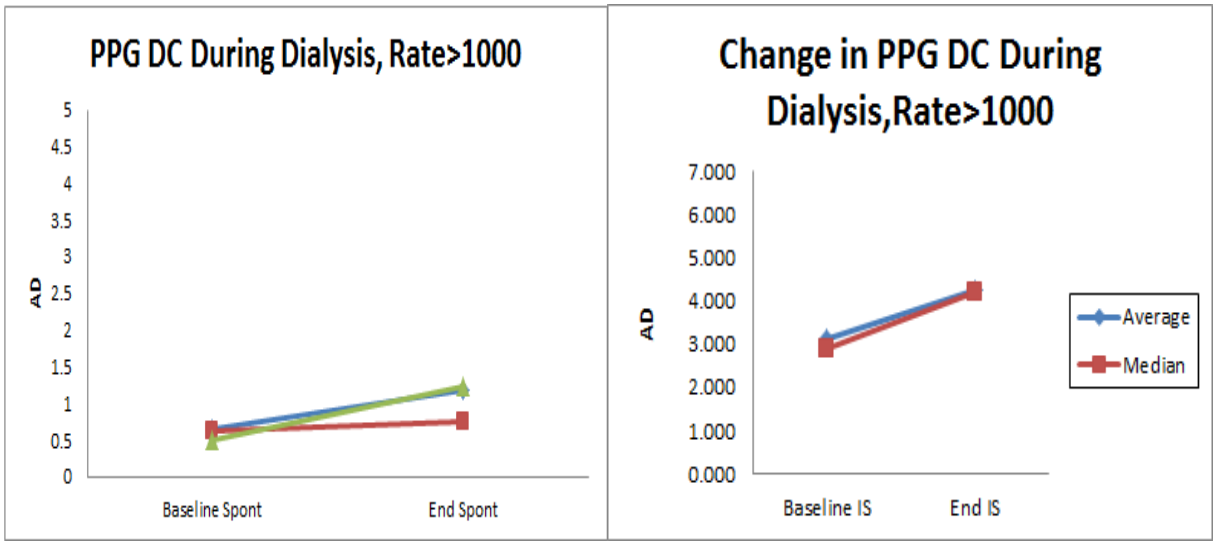

Figure 25a-b. PPG DC value at the beginning and end of dialysis with IS breathing. The figure on the left shows the individual cases (n=3). The figure on the right shows the average and median PPG DC value The PPG DC value at the end of dialysis is greater than that at the beginning of dialysis.

Table 8. PPG DC for Incentive Spirometry Breathing at the Beginning and End of Dialysis.

Average Filtration Rate (cc/hour)	IS Breathing PPG DC value	
<500	Average baseline PPG DC	3.24
	Average end PPG DC	5.97
	Average % change	84.05
	Median baseline PPG DC	3.22
	Median end PPG DC	4.73
	SD baseline	1.72
	SD end	3.801
	P value	0.037
500-1000	Average baseline PPG DC	3.12
	Average end PPG DC	6.366
	Average % change	103.8
	Median baseline PPG DC	2.68
	Median end PPG DC	5.59
	SD baseline	1.38
	SD end	2.52
	P value	0.026
>1000	Average baseline PPG DC	3.132
	Average end PPG DC	4.2
	Average % change	35.36
	Median baseline PPG DC	2.911
	Median end PPG DC	4.184
	SD baseline	0.777
	SD end	0.709
	P value	0.006

Therefore, our study suggests that incentive spirometry breathing can be used to reliably track changes in the PPG DC value that occurs with volume removal during dialysis. In each of the three ultrafiltrate rate categories, there was a statistically significant increase in the PPG DC value associated with IS breathing from the beginning to the end of dialysis. Conversely, spontaneous breathing resulted in statistically significant increases in PPG DC in the two slower ultrafiltration rate categories, but did not result in a statistically significant increase in the

Rate>1000 category. We had anticipated that the percentage increase (from beginning to end) in PPG DC with IS breathing would be greater with SB for all three ultrafiltrate rate categories. However, our results showed the converse pattern: for Rate <500cc/hr, there was a 129% increase (from beginning to end) in PPG DC with SB compared to an 84% increase with IS; for 500≤ Rate≤1000 there was a 176% increase in PPG DC with SB compared to a 103% increase with IS; and for Rate > 1000cc/hr there was a 76% increase in PPG DC with SB compared to an 35% increase with IS.

Discussion

The results of our study clearly illustrate the poor sensitivity and indeed the very confusing picture of vital signs during ultrafiltration over the time course of dialysis treatments. Thus vital sign data does not allow us to accurately track volume removal in dialysis patients. And yet ironically enough, vital sign monitoring and symptomatology remain the primary means of assessing patients during dialysis. This discrepancy serves as justification for our investigation into the potential use of the IS induced changes in PPG DC value for tracking the course of dialysis ultrafiltration.

We found that on average, and in individual cases, IS breathing amplified the PPG DC value compared to spontaneous breathing. Furthermore, the degree of PPG DC amplification with IS breathing depended on the respiratory effort exerted by the subject: our data suggests the subject should move at least 1.5 balls during IS breathing to optimize respiration-induced PPG DC changes via our method.

While previous studies have demonstrated the superiority of dynamic indices for tracking volume status changes, none of these prior studies were successful in spontaneously breathing patients, nor did they utilize frequency domain analysis. The crucial difference in our experiment was the novel use of the incentive spirometry as a stimulus to sufficiently stress the cardiorespiratory system such as to facilitate measurement of the changes in PPG DC value that occurred with volume removal. To further drive home this point, our results showed that IS breathing resulted in statistically significant increases in PPG DC at the end of dialysis for all three ultrafiltrate rate categories. Conversely, SB was not associated with a significant change in PPG DC value at the end of dialysis when the ultrafiltrate rate was greater than 1000cc/hr.

LIMITATIONS:

1) In order to more convincingly demonstrate the potential of our method for tracking changes in volume status during dialysis, values need to be collected at more frequent intervals to assess the consistency of this trend of increasing PPG DC value with ultrafiltration. Initially, attempts were made to repeat all measurements at half an hour intervals until the patient completed hemodialysis. Unfortunately most subjects were unable to comply with this frequency of data collection and, as such, measurements were repeated at various time points and at the end of dialysis, according to the subject's willingness to complete the required incentive spirometry breathing. This is one major limitation of the method: it relies heavily on subject motivation to perform the incentive spirometry breathing exercise.

2) Also, the quality of results is dependent on the respiratory effort that the patient is able to exert: the greater the respiratory effort exerted, the greater the intrathoracic pressure changes, and the greater the change in PPG DC value with IS breathing. Encouragingly, we found that there was a steep learning curve associated with incentive spirometry breathing, as subjects were usually able to perform the task better with successive attempts. Thus, patients can quickly acquire the skill of adequately performing the incentive spirometry task.

3) Finally, given the susceptibility of the plethysmograph to movement artifact, our results include only twenty-one cases, as much of the data initially collected was unusable. Thus this method requires constant online monitoring of the quality of the data being collected,

and constant reminders to the subjects of the need to remain still while data are being collected.

Future study:

Rather than time in dialysis, percent of body mass removed during dialysis may have been a better unit for presenting this data, however, upon chart review body weight for each case was not available for all subjects in this study. Further analysis (time domain and frequency analysis) of PPG waveforms changes induced by IS should be correlated with changes in stroke volume during dialysis.

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