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Abstract

This paper describes a new combined impedance plethysmographic (IPG) and electrical bioimpedance spectroscopic (BIS) instrument and software that allows noninvasive real-time measurement of segmental blood flow and changes in intracellular, interstitial, and intravascular volumes during various fluid management procedures. The impedance device can be operated either as a fixed frequency IPG for the quantification of segmental blood flow and hemodynamics or as a multi-frequency BIS for the recording of intracellular and extracellular resistances at 40 discrete input frequencies. The extracellular volume is then deconvoluted to obtain its intra-vascular and interstitial component volumes as functions of elapsed time. The purpose of this paper is to describe this instrumentation and to demonstrate the information that can be obtained by using it to monitor segmental compartment volumes and circulatory responses of end stage renal disease patients during acute hemodialysis. Such information may prove valuable in the diagnosis and management of rapid changes in the body fluid balance and various clinical treatments.

Keywords: Bioimpedance, plethysmograph, spectroscopy, compartment volumes, blood flow

Introduction

Hemodynamic redistribution of fluids between body segments and between the intracellular and extracellular compartments within those segments are often of central importance to various fluid management procedures [1,2], disease states [3-6] and orthostatic dysfunction [7,8]. These redistributions affect cardiovascular function, water balance and perhaps skeletal muscle function through physiological mechanisms that may be better understood with simultaneous characterization of both the extent and rate of the inter-compartment redistributions that take place during fluid management therapy.

Objective methods to monitor such factors include tracer dilution techniques, which are invasive, time consuming, and expensive, and cannot be repeated in the short intervals that are required to follow events over the usual time course of interest. Bioelectric impedance instrumentation may be used to monitor these changes in the body and may be a valuable aid in clinical diagnosis and research.

Two different types of bioelectric impedance instruments are available. Fixed frequency bioelectrical impedance plethysmographic (IPG) techniques are valuable noninvasive tools that provide information about overall segmental volumes, blood flows, and hemodynamic status with a high degree of temporal resolution [9-12]. The second type, electrical bioimpedance spectroscopy (BIS) [13,14] is a multi-frequency technique that, when coupled with computer-aided equivalent circuit analysis, may be used to provide information about relative redistributions of fluids between the intra-and extracellular compartments of the monitored segments.

Tissues are ionic conductors of electric current, which by virtue of their structural heterogeneity, exhibit dielectric relaxation phenomena that give rise to frequency dependent variations of the impedance to such conduction [15]. In the 1 - 150 kHz range, the resultant dielectric dispersions arise principally from the capacitive reactances of cell membranes. At low frequencies in this range, high cell membrane reactances prohibit current flux through cells, so that tissular impedance is governed by properties of the extracellular fluid. At high frequencies, membrane reactance is negligible, allowing current to pass through both the extra- and intracellular spaces. Tissular impedance is then governed by the combined properties of the two compartments. Time series of tissue impedances measured as a function of frequency consequently embody tissue structural information that can illuminate changes in the relative distributions of fluids between the tissular intra- and extracellular compartments [16-19].

Various resistance/capacitance (R/C) models [15,16, 20,21] are used to quantify segmental volumes from recorded impedance measurements. The R/C model that is used by most currently available impedance systems (Figure 1) represents the tissue as two parallel conductance paths; one through an extracellular compartment having average resistance (Re), and the other through an intracellular compartment having average resistance (R_i) and capacitance (C_m). This model, which is limited to the determination of "intracellular" and "extracellular" resistances (Ri and R_e, respectively), can therefore only be used to estimate the corresponding intracellular, extracellular, and overall monitored segment volumes.
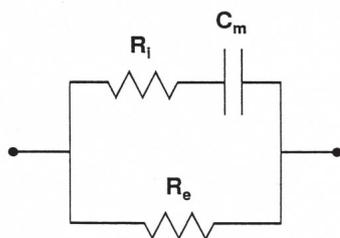

Figure 1: General equivalent circuit model of current conduction through tissue.

Unfortunately, an issue of principal concern in most clinical contexts is how the "extracellular volume" is distributed between its interstitial and intravascular compartments; an issue that the two component R/C models cannot address. We have developed a more complex model to remedy this deficiency.

This study will describe a new analytical procedure that uses BIS data to obtain quantitative values of intracellular, interstitial, and intravascular volume changes and relative transfer of fluids between these compartments of a given body segment. Potential applications of this capability in the clinical environment include monitoring of the hydration status of patients during surgery, during dialysis, or while in the intensive care unit, and of highly premature infants. It can also be used to investigate chronic fatigue syndrome and other disease states that involve autonomic impairment of the cardiovascular system.

Background

A major component of our analytical procedure is the development and application of a more complex equivalent circuit model [22-24], illustrated in Figure 2A, which can be used to calculate the interstitial and intravascular compartment volumes that comprise the previously calculated "extracellular" volume.

The extravascular soft tissue compartment of the monitored segment is then represented in our model as a cylindrical homogeneous suspension of identical oblate spheroidal cells with long axes, a, oriented parallel to the applied field, I, as shown in Figure 2B. Cells are allowed to change volume only through variation in minor axis, b. The cell volume fraction and the intracellular and extracellular conductivities of this compartment are related to the compartment's R_e, R_i, and C_m in Figure 1 with theory developed by Hugo Fricke [25-29].
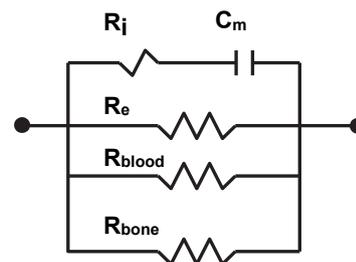

Figure 2A: Equivalent Circuit Diagram used in EIS Analysis for Intracellular, Interstitial, and Intravascular Volumes.
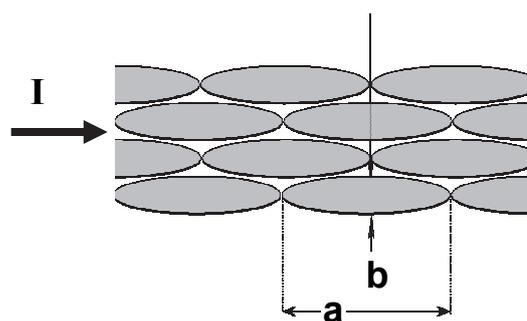

Figure 2B: Extra-vascular soft tissue compartment of EIS model.

Our model is based on an assumed physical structure of the monitored segment; particularly its extravascular compartment (Figure 2A); which governs the values and frequency dependence of the "resistive" and "reactive" components of the segmental impedance. The model is fit to each measured spectrum by an iterative numerical process in which values of the model parameters are found that bring model-prescribed spectra into closest possible agreement with the measured spectrum.

Because the model is a function of more parameters than are uniquely determined by information in an impedance spectrum, selected model parameters must be assigned "fixed" values in the fitting process.

Materials and methods
Device description
The Z-Spec-2, (UFI Inc., Morro Bay, CA) combines two bioimpedance instruments into a single device. It combines a fixed frequency impedance plethysmograph (IPG) and a multi-frequency electrical bioimpedance spectrograph into one unit. The IPG mode is used to quantify segmental blood flow and total segmental conductive volume. The BIS mode is used to monitor segmental intracellular and extracellular compartment volumes as is done by other BIS devices. However, our proprietary software also allows the Z-Spec-2 to divide the extracellular compartment volume into its intravascular and interstitial components.

The current Z-Spec-2 design, shown in Figure 3, is a unique bioimpedance measurement device that supplies subject tissue impedance while "sweeping" across 40 discrete excitation frequencies over a wide frequency range when functioning as a BIS for compartment volume measurements. The Z-Spec-2 can be paused at 50 kHz to function as a fixed frequency IPG for blood flow measurements.

The Z-Spec-2 provides a "scheduler" capability that can be used to operate the instrument continuously as either an IPG or an BIS or any desired time sequenced combination of the two modes.

The Z-Spec-2 includes a Lead I electrocardiographic (ECG) and a photoelectric plethysmographic (PPG) analog channel (via external transducers) which provide measures that are used to quantify segmental blood flow.

A built-in 16 bit microcontroller is responsible for management of all Z-Spec-2 functions.

Figure 4 shows the basic functional block diagram of our Z-Spec-2 EIS/IPG instrumentation.

Z-Spec-2 design features
The Z-Spec-2 final design has the following features:
1) Combines both BIS (Z-Spec-2) and IPG (Fixed Frequency) capability in a single device using the current BIS enclosure. Includes the current BIS Function and Circuitry. A "Pulsatile Size" switch is included on front panel for the IPG function.
2) Operates from an isolated power supply with either an in-line or wall-mount transformer for power from a 120V 60Hz AC power source (with no battery power).
3) Front panel includes an LCD display that shows real-time plots of ECG, photoelectric pulse signals (switch selectable) and Delta-Ro signals.

4) The software includes the current level and resistance/reactance values at each frequency. The software also includes an added Pulsatile Module that saves time segments of Pulsatile data as separate ASCII files. The software allows recording BIS, IPG, or a scheduled (software settable) combination of the two. The PC Software is designed and tested to operate under Windows 2000 and Windows XP operating systems, and support unit operation via either RS232 or USB interfaces under each of these operating systems.
5) The system includes internal signal conditioning and A-D conversion capability for ECG and photoelectric pulse (from UFI 1020) channels. ECG and photoelectric channels have variable size controls located on the front panel.
6) Instrument calibration factors are stored within the instrument to enable the use of generic support/ interface software on all similar BIS units.

Application
The application and capability of the BIS when operated in the IPG mode to quantify segmental blood flow and hemodynamics is described elsewhere (4,6). Details of the analytical algorithm used to derive individual fluid compartment volumes from the impedance spectroscopic recordings are given in previous articles [30-32].

We hypothesize that this new instrument will be able to quantify changes in the three fluid compartments as fluid volume is removed during hemodialysis. We therefore, aimed to evaluate the changes in the three volume compartments (intravascular, interstitial, and intracellular), and hemodynamic patterns associated with fluid volume removal during dialysis.

Equipment validation
Hemodialysis treatment sessions provide ideal opportunities to monitor exogenously induced inter-compartmental fluid shifts with minimal additional procedures. If the BIS net volume changes we compute do indeed provide a way to track three compartment fluid shifts, then such BIS-recorded fluid shifts should correlate with those of an independent physiologic measure of fluid volume changes.

The hemodialysis (HD) patient's hematocrit (HCT), expressed as %, rises (due to hemoconcentration) as excess fluids are removed by ultra-filtration (UF) – and falls or rises more slowly (due to hemodilution) as extravascular fluid moves into the vascular system as a result of compensatory osmotic and hydrodynamic pressure changes. Both changes in HCT and changes in the rate of vascular "refill" can be measured noninvasively during routine HD therapy sessions. Changes in HCT can be measured by a CritLine® optical monitor (HemaMetrics, Kaysville, UT). The rate of "refill" can be calculated from the BIS volume data.

Figure 3: Prototype Z-Spec-2 IPG/EIS system (shown with control/data recording laptop and Arc Simulator unit).
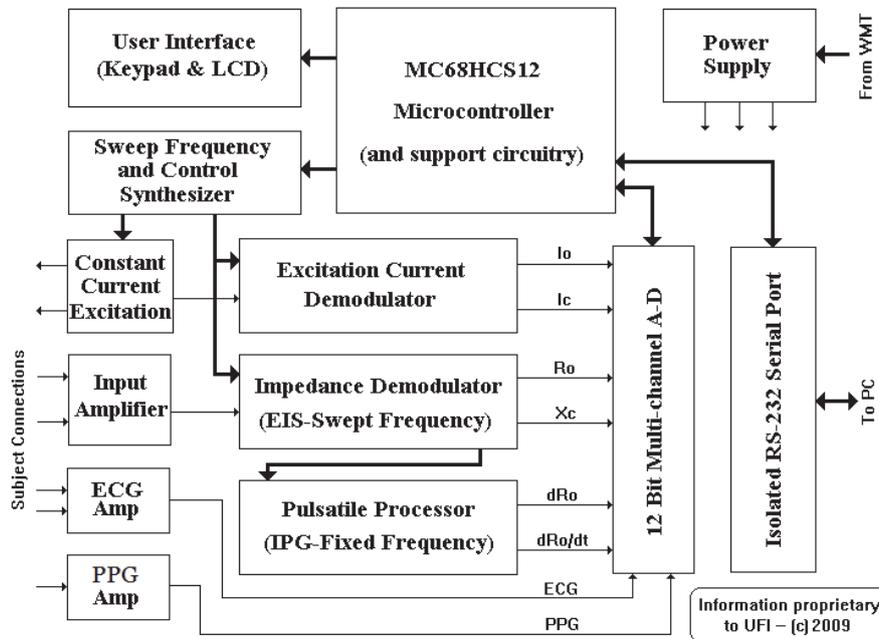

Figure 4: Z-Spec-2 functional block diagram.

A CritLine® optical monitor served as the "gold standard" for validation and was used simultaneously to detect on-line changes in hematocrit. The CritLine® measures the optical absorption and scattering properties of red blood cells as they pass through the HD circuit. Since red blood cell mass and hemoglobin do not usually change during treatment, the relative changes in hematocrit should parallel the changes in blood fluid content. The CritLine® instrument is well validated [33,34], FDA-approved [35,36], and routinely used for patient management.

Validation was previously performed in 60 End Stage Renal Disease patients during chronic treatment session by analyzing the time profiles of fluid redistribution, obtained from the BIS data during hemodialysis, to mathematically derive post hoc hematocrit profiles. These profiles were then compared to the simultaneously measured hematocrit values recorded independently using the CritLine® monitor. Regression and Bland Altman analyses were used to compare the BIS data and CritLine® hematocrits at sequential times during the 60 chronic HD sessions with the patients in a horizontal position. The statistical and graphical evidence obtained [31] confirmed that the BIS system reliably monitors the continuous and real time rates of change of the fluid volumes of the three compartments in the chronic treatment setting.

However, it has been shown that the fluid responses in the intracellular, interstitial and intravascular compartments may differ during the acute and chronic HD sessions [37].

It was therefore necessary to replicate the earlier validation procedures using the bioimpedance data from the 22 end stage kidney disease (ESKD) patients that took part in this study.

Statistics

Statistical analysis was performed using MedCalc Ver. 10.0.0.0. A Student's t test was used to compare paired observations. Pearson's correlation (38) and Bland-Altman (39) analyses were used to compare the BIS hematocrit (BISHCT) and the CritLine® hematocrit (CLHCT) results at each time point. Results are reported as mean ± SD.

Validation of BIS used during acute HD treatment

The institutional review board approved protocol allowed BIS measurement in consented adult ESKD patients receiving dialysis in an acute dialysis unit. Patients with the following conditions were excluded from the study: irregular heartbeat, unstable angina, active gastrointestinal bleeding, pregnancy, poor peripheral circulation, skin conditions such as psoriasis, damaged nerves in the arms or legs, liver failure, cancer, collagen vascular disease such as lupus, chronic swelling of the arms or legs due to obstruction of the lymph or blood vessels, implanted pacemaker, or other implanted electrical device, overactive thyroid disease, or chronic substance abuse. Studies were performed in patients who were resting in the supine position for at least 2 hours before obtaining measurements.

All patients were treated with Cobe Century hemodialysis machine and Polyflux 170H dialyzer. Dialysis fluid sodium concentration (140 mEq/L) and ultrafiltration rate (UFR) were kept constant throughout the treatment. Blood flow rate, dialysis fluid flow rate, treatment time, and total volume removed were ordered by the Attending physician according to the patient's requirement.

Blood Pressure (BP) and heart rate (HR) were measured and recorded by a technician immediately before dialysis, every 15 minutes throughout the treatment, and at the end of treatment. Signs and symptoms related to hypotension and dialysis complications were recorded. All patients were treated in the supine position.

Hematocrit (HCT), an indirect measure of blood volume (BV), was continuously monitored on-line using CritLine®-TQA (Hema-Metrics, Kaysville, UT). Percent change in BV (%BV) during HD was determined from the % variation of HCT.

A bioelectric impedance spectroscopic system (LDM, San Jose, CA and UFI, Inc., Morro Bay, CA) was used to obtain periodic, noninvasive relative measurements of intracellular (V_c), interstitial (V_i), and intravascular (V_b) volumes, segmental blood flow and hemodynamic properties during

dialysis. Compartment volume results were displayed in real time, while blood flow and hemodynamic properties were computed in post-session analyses. Changes in interstitial and intravascular volumes from the BIS recordings were used to calculate the HCT-time profile for each patient..
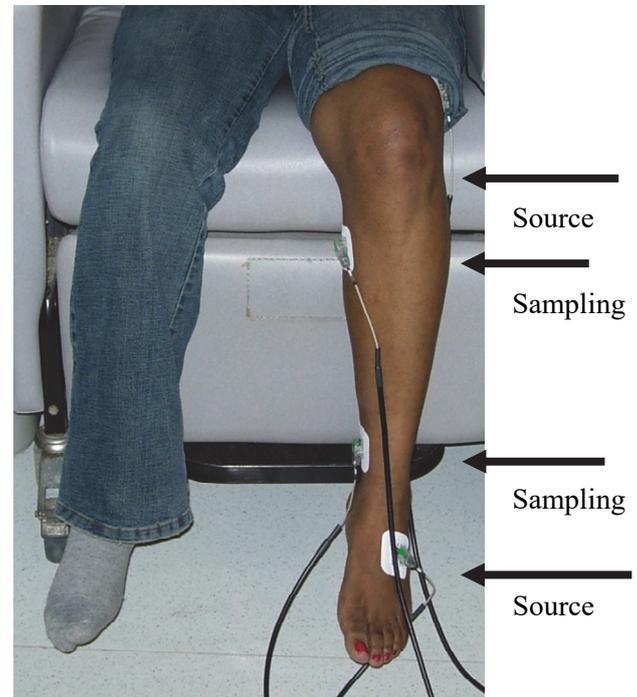

Figure 5: Electrode placement.

The BIS instrument was attached to the subject's dominant lower leg. The source electrodes were placed just above the knee, and just above the malleolus, laterally. The sampling electrodes were placed just below the knee and above the ankle, medially. Figure 5 shows electrode placement on the calf.

All dialysis sessions included in this analysis lasted at least 120 minutes. Shortly after 120 minutes some of the dialysis sessions were terminated for different reasons; patients experiencing syncope, cramps, completion of the required dialysis, etc. Mean calculated BIS and observed CritLine® hematocrit (± SD) values are presented in Table 1 for elapsed dialysis times of 30, 60, 90, 120, and END. The END values that are given in Table 1 were taken from the last minute before cessation of dialysis. The average (± SD) time for the END data is 171.2 ± 21.7 min. from the start of dialysis. The CritLine® hematocrit values measured by the optical sensor in Table 1 and the following tables and figures are designated CLHCT. The values calculated from the BIS measurements are designated by BISHCT. No significant differences were found between the BISHCT and the CLHCT values at any of the elapsed times listed in Table 1.

Results of the regression and Bland Altman analyses, at each of the elapsed times, are listed in Table 1. Graphical results of the regression and Bland Altman analyses at the specified elapsed times are given in Figures 6A and 6B, respectively.

Table 1. BIS and CritLine Hematocrit values ± SD at specified elapsed times during dialysis.

ELAPSED TIME (min)	N	BISHCT (%)	BISHCT SD	CLHCT (%)	CLHCT SD
30	22	31.91	4.68	31.91	4.68
60	22	32.14	4.73	32.12	4.71
90	22	32.36	4.73	32.32	4.67
120	22	32.52	4.71	32.59	4.68
End	22	33.06	4.96	33.09	4.96

The regression equation and R^2 value for BISHCT vs. CLHCT are given in Figure 6A. The solid trace in Figure 6A represents the corresponding regression equation. The BISHCT/CLHCT points included in the Bland Altman analysis for each time period are represented as: 30 min. are open circles, 60 min. are solid squares, 90 min. are solid circles, 120 min. are open triangles, and the END values are open squares.

Table 2 lists the corresponding Bland Altman results.

Table 2. Differences ± SD, limits of agreement, and independent t-test probabilities of significance between BISHCT and CLHCT values at specified elapsed times during dialysis.

ELAPSED TIME (min)	Difference with CLHCT	Limits of agreement (mean ± 1.96SD)	P (by non-pair t-test)
30	-0.00692 ± 0.0318	-0.0692 ± 0.0799	0.996
60	-0.01166 ± 0.1393	-0.2847 ± 0.3686	0.993
90	- 0.03235 ± 0.2469	-0.5163 ± 0.6415	0.982
120	0.06657 ± 0.2492	-0.4218 ± 0.7467	0.962
END	0.03746 ± 0.1590	-0.2742 ± 0.4715	0.980

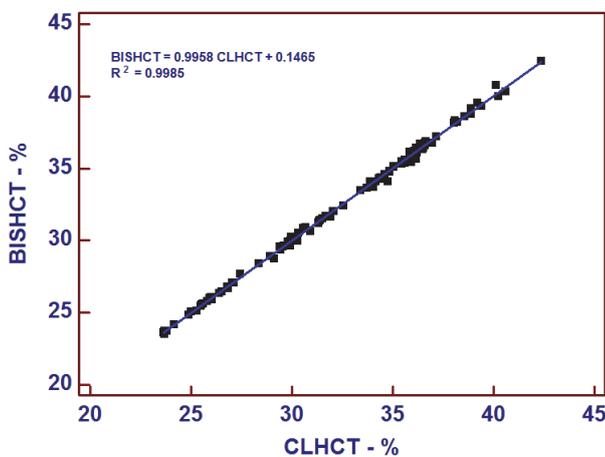BISHCT = 0.9958 CLHCT + 0.1465
R^2 = 0.9985

Figure 6A: Linear regression and Bland Altman analyses comparing the BISHCT and CLHCT results at specified times during dialysis.

These regression and Bland Altman analyses confirm that the BIS algorithm can be used to reliably derive the continuous and real time *rates of change* of the intra-cellular, interstitial, and intravascular compartmental fluid volumes in both acute and chronic ESKD patients.

Regression results yielded a R^2 > 0.99 between the two measures of hematocrit at different times during dialysis. The slopes of the regression equations at the different times were nearly identical, demonstrating an almost one to one correspondence between the calculated BIS and the measured CritLine® hematocrits.
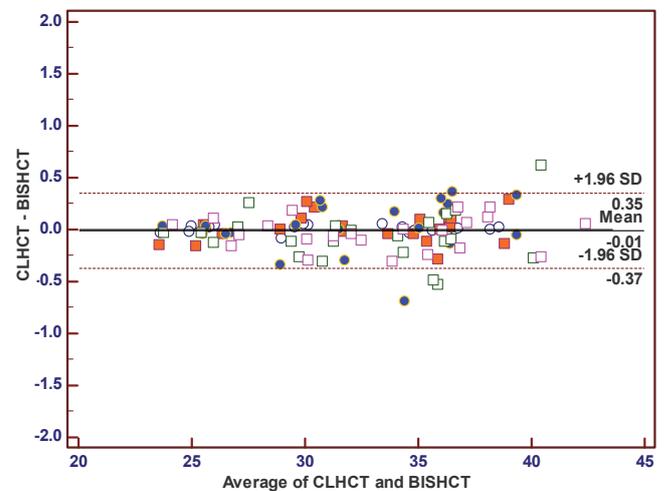

Figure 6B: Bland Altman analysis. The BISHCT/CLHCT points included above for each time period are represented as: 30 min. are open circles, 60 min. are solid squares, 90 min. are solid circles, 120 min. are open triangles, and the END values are open squares.

Bland Altman analyses show that the BIS algorithm can be used interchangeably with the CritLine® monitor for the measurement of hematocrit. In addition, it also shows that the calculated volume changes can then be used to derive other variables that can provide valuable insight into the various fluid responses that take place during fluid management therapy.

Dialysis Demonstration

The intracellular, interstitial and intravascular volume changes that were calculated from the series of HD sessions used in the above validation study are given in Figures 7A, B and C, respectively below. Figure 7 shows that the three component volumes of the acute patients undergoing HD varied widely among the individual patients. This finding may, in part, be attributed to the differences in the progression of ESKD and other accompanying diseases of the various patients. The patients monitored during these acute HD sessions were in the hospital for treatment of a number of disease states and/or complications of their kidneys. As such, they may have been given HD for the first time in our facility without knowledge as to their responses during previous HD treatments.
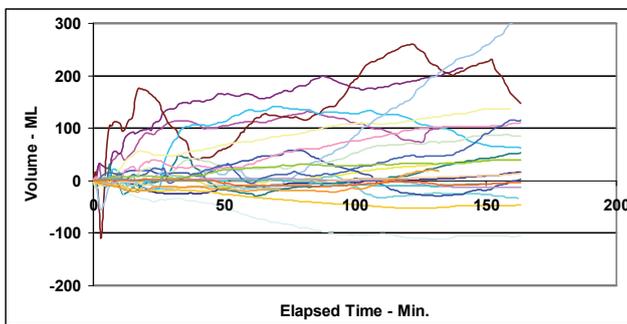
Figure 7A: Individual patient intracellular volume changes during dialysis vs elapsed time.
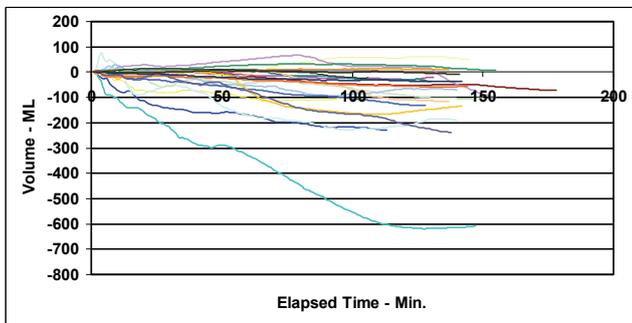

Figure 7B: Individual patient interstitial volume changes during dialysis vs elapsed time.
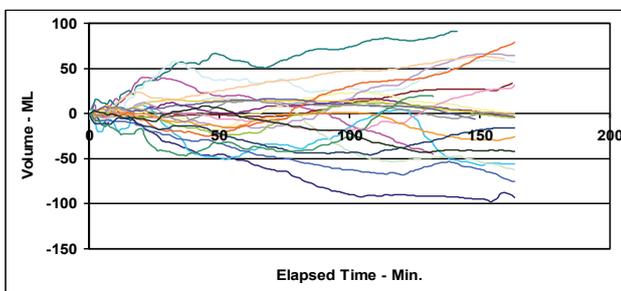

Figure 7C: Individual patient intravascular volume changes during dialysis vs elapsed time.

Due to the observed variance of the individual patients, each patient had to be considered as a specific case for HD treatment. Use of the BIS system, described herein, would greatly facilitate administration of HD in the acute patients or in those patients being treated during their initial fluid management therapy.

To demonstrate the capability of the ZSpec-2 to provide information regarding fluid compartment volume and circulatory changes for individual patients during HD we provide the results of two very different patients below. The results of BIS and CritLine® along with simultaneous BP and hemodynamic (blood flow) measurements were obtained in the two ESKD patients:

1) Patient Type A, a 57-yr old male with long-standing hypertension and past medical history of congestive heart failure and

2) Patient Type B, a 26 year old male with long-standing type-1 diabetes mellitus complicated by severe diabetic autonomic neuropathy, diabetic retinopathy, and diabetic nephropathy.

Prior to dialysis, both patients had no overt signs of congestive heart failure or fluid overload and showed comparable pre-dialysis BP. As shown in Figures 8A and 8B the ultrafiltration (UF) rates were similar, e.g. 1.0-1.3 L/hr and the total amount of fluid removed during dialysis was the same for both patients.
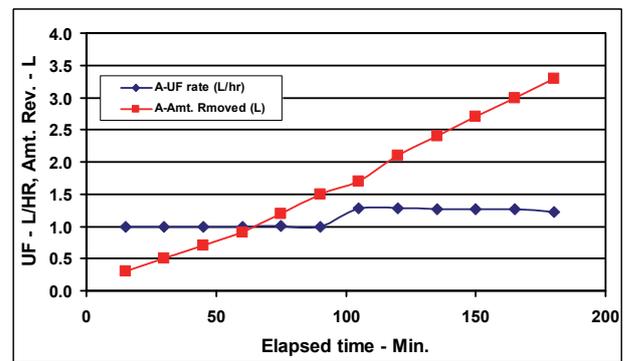

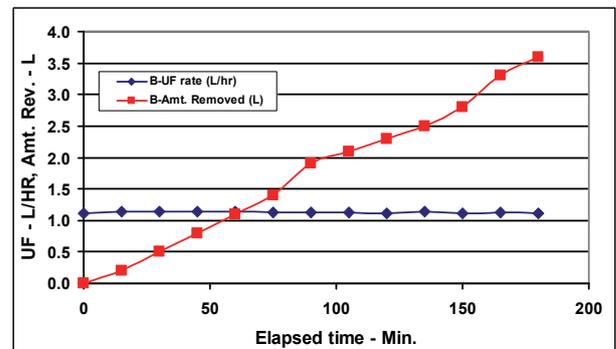Figure 8A: Patient Type A's - UF rate and amount removed vs. elapsed time.

Figure 8B: Patient Type B's - UF Rate an Amount Removed vs. elapsed time.

Figures 9A and 9B illustrate the change in the CritLine® HCT and the corresponding HCT calculated from the BIS data for the Type A and B patients, respectively. The HCT for the

Type A patient increased from 24% to approximately 27% during dialysis. That of Type B increased from ~37.5% to 39%. The extent of agreement between the CritLine® measured HCT and that of the calculated values for both patients show that the algorithms used to derive the three fluid compartment volumes may be used for both chronic and acute patients during dialysis.
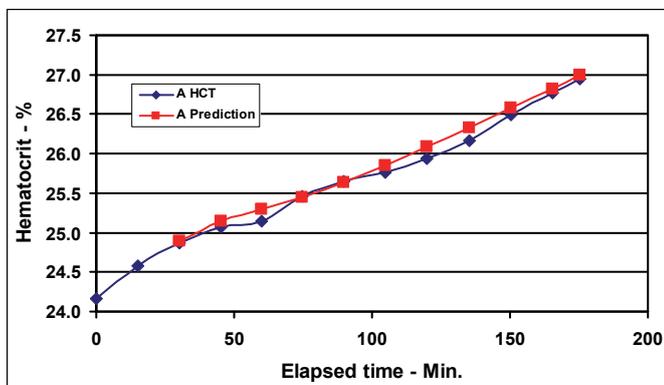

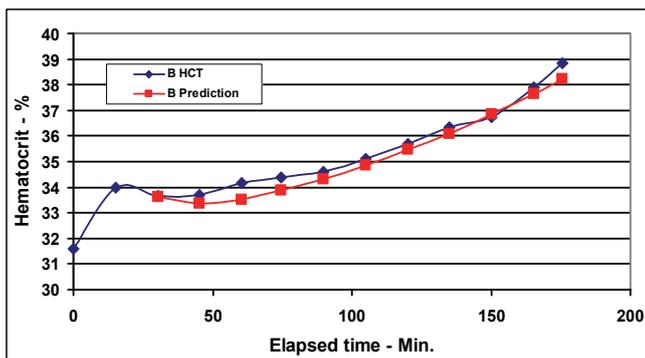Figure 9A: Measured and predicted HCT values for Patient Type A vs. elapsed time.

Figure 9B: Measured and predicted HCT values for Patient Type B vs. elapsed time.

Results

Compartment volume changes calculated from multi-frequency recordings

Figures 10A and 10B depict the volume changes of the intracellular, interstitial and intravascular fluid compartments of the Type A & B patients, respectively. HD in the Type A patient with minimal BV change was accompanied by removal of a large volume of fluid from the interstitial space and an increase in cellular volume. HD in the Type B patient with marked decrease in BV was accompanied by minimal net changes in both the interstitial and cellular volumes.

The fluid removed from the Type A patient appears to be primarily from the extravascular (Vb and Vi) space. Whereas, fluid removed from the Type B patient was mainly from the vascular space, leading to symptoms of low blood pressure and dizziness.
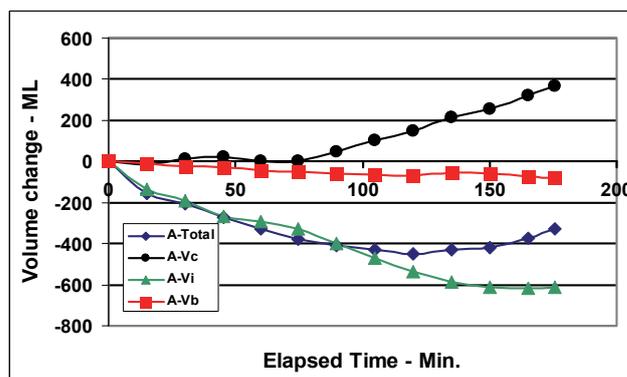

Figure 10A: Patient Type A's segmental and compartment volume changes vs. elapsed time.
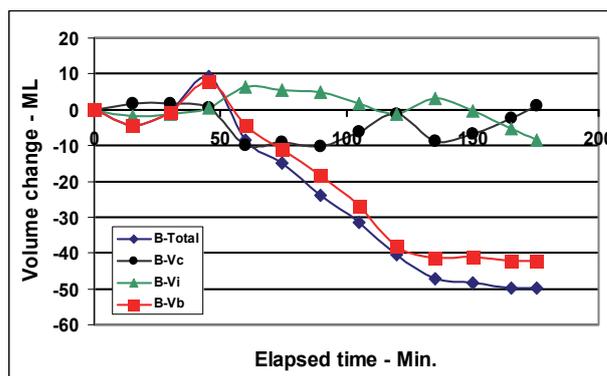

Figure 10B: Patient Type B's total segmental and compartment volume changes vs. elapsed time.

Subject A's BP remained stable throughout the entire HD session with practically the same UF rate of about 1 L/hr. Hence, there was no intradialytic hypotension (IDH) However, the decline in vascular volume during HD was temporally accompanied by a proportionate decrease in interstitial volume. This suggests that a proportionate amount of vascular refilling occurred, which may have prevented the development of IDH (Figure 10A).

Figure 10B shows that Patient B had a progressive decline in vascular volume, which reached its climax toward the end (130-180 min) of the HD session, while both interstitial and cellular volumes remained relatively stable. In Patient B an IDH episode was noted near the end of dialysis session when the same UF rate of about 1 L/hr was applied. This hypotensive response is consistent with his impaired autonomic function.

The individual compartment volumes are then used to provide a measure of outflow or "refill" from the extra-vascular (XV) space into the vascular system during dialysis. In patient Type A, XV fluid moved to refill the intravascular space, Figure 11A. Whereas in patient Type B, not much fluid was transferred from the XV space into the vascular system resulting in hypotension and symptoms of dizziness, Figure 11B.
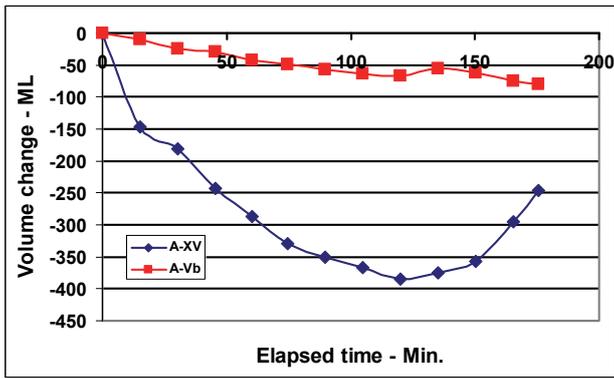
Figure 11A: Patient Type A's intravascular and extravascular volume changes vs. elapsed time.
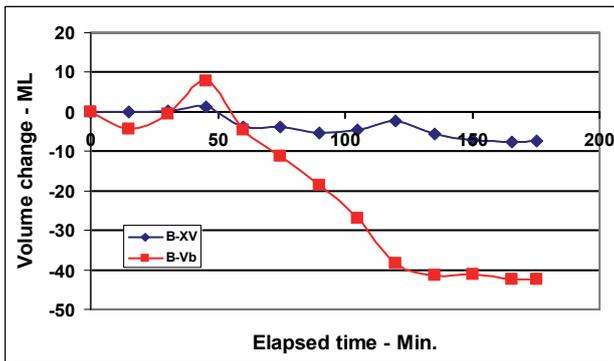

*Figure 11B: Patient Type **B**'s intravascular and extravascular volume changes vs. elapsed time.*

Segmental blood pressures, blood flow, and vascular state calculated from hand recorded blood pressures and fixed frequency impedance data

The following results were obtained from the hand recorded blood pressures and the output of the bioimpedance instrument when it was operated in its fixed frequency mode with a constant input current of 50 kHz and the pulsatile waveforms recorded for a period of 60 seconds. The parameter values provided below were calculated using the Rheosys computer program [16] and are mainly dependent upon the morphology and shape of the recorded pulsatile waveforms.

Blood pressure

Figure 12A shows that the systolic BP of the Type A patient remains relatively stable, dropping about 15 mmHg during dialysis.
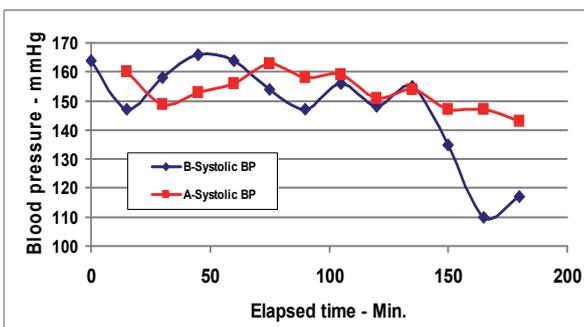

Figure 12A: Patient A and B's systolic blood pressure vs. elapsed time.

The systolic blood pressure of the Type B patient dropped about 55 mmHg during the total dialysis treatment, which included a 45 mmHg during the last hour of dialysis. Note that the large decrease in Type B's systolic blood pressure started at approximately 125 min elapsed time. This time was the period in dialysis at which the maximum amount of fluid was removed from the intravascular compartment (Figure 11B).

Figure 12B shows that the diastolic BP of the two patients experience decrease at the same points in elapsed time. Type B's diastolic blood pressure decreased approximately 30 mmHg and that of Type A decreased ~10 mmHg.
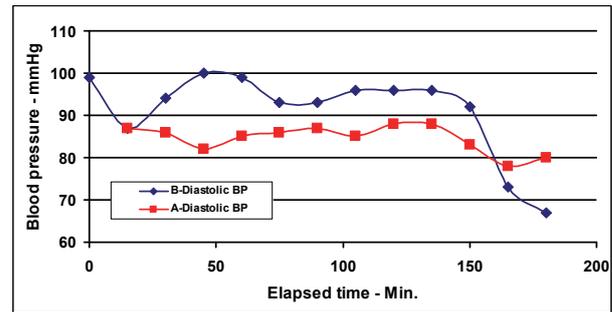

Figure 12B: Patient Type   A and B's diastolic blood pressure vs. elapsed time.

Figure 12C illustrates the mean arterial pressure = diastolic + 1/3(pulse pressure) that results from the blood pressure responses displayed above. MAP decreased from ~ 125 mmHg to ~85 mmHg for Type B and remained relatively constant for Type A, decreasing approximately 10 mmHg during the last period of dialysis.
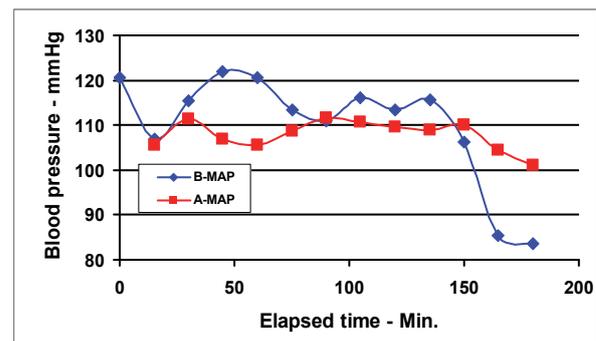

Figure 12C: Patient Type A and B's mean arterial blood pressure vs. elapsed time.

Segmental Blood Flow

The following results compare the changes in heart rate (Figure 13A), maximum pulse amplitude (Figure 13B) and resulting calf blood flow (Figure 13C) for Patients A and B during dialysis.

One potential contributing factor to Patient B's responses may be the observation that the various physiologic mechanisms that normally respond to minimize hypotension are inactive or become fatigued during dialysis

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of ESKD patients who exhibit serious complications or advanced kidney disease. Also, the various parameters that are displayed tend to become less effective after approximately 125 - 150 minutes elapsed time during which the compartment volumes experienced their maximum fluid removal.

These results were obtained even though both patients had the same relative UF rate and similar amounts of total fluid withdrawn. The Type B patient had several conditions that may have altered or influenced his autonomic/sympathetic responses to dialysis. The Type A patient did not have (at the time of study) any complications that might alter his natural responses to dialysis.

Heart rate (BPM - Figure 13A) was calculated from time between subsequent QRS peaks of the recorded ECG waveforms. The heart rate of both patients increased during dialysis. Patient A's heart rate increase from approximately 75 BPM to 90 BPM during dialysis while that of patient B only increased about 5 BPM.
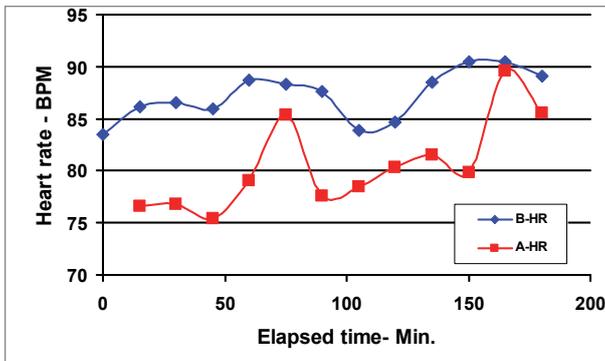

Figure 13A: Patient Type A and B's heart rate vs. elapsed time.

The maximum pulse amplitude (Amp) for each patient (Figure 13B) was taken from the maximum height of the systolic portion of the bioimpedance waveform when converted to ohms resistance. Amp increased for the Type A patient and decreased slightly for the Type B patient.

The heart rate and pulse amplitude responses above yield an increase in calf blood flow (ml/100ml/min) for Type A and a decrease of ~ 50% for Type B between 25 and 100 min of dialysis as shown in Figure 13C.

Pulse Transit Time and Peripheral Resistance

Pulse Transit Time (PTT - sec, Figure 14A) is the time interval between the ECG QRS complex and the start of the bioimpedance pulse waveform. PTT remains constant for Type A and increases markedly for Type B starting about 125 min elapsed time. This PTT increase indicates that the systemic circulation of the Type B patient dilated extensively starting at approximately 125 min elapsed time.

Peripheral resistance (PR, Figure 14B) is defined as MAP/%BF (where BF is in units of ML/100 ML/Min). PR remained constant during the Type A patient dialysis but

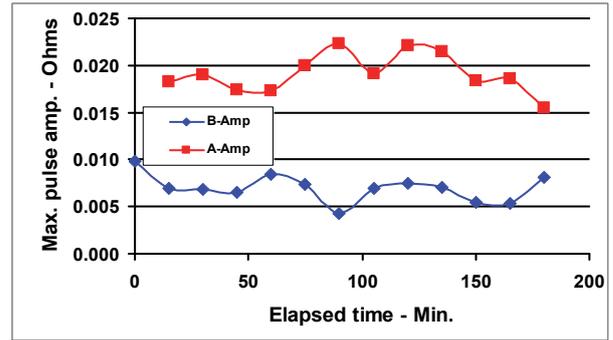increased dramatically twice during the Type B patient dialysis.

Figure 13B: Patient Type A and B's maximum blood pulse amplitude vs. elapsed time.
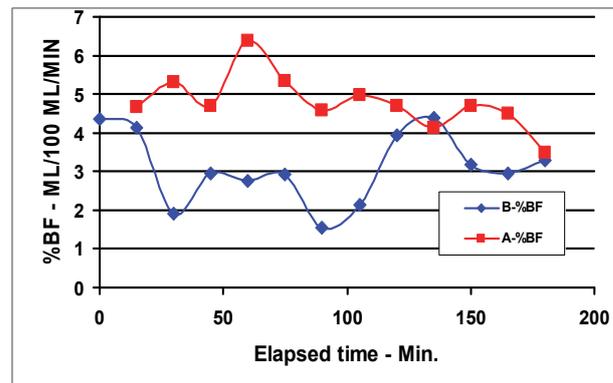

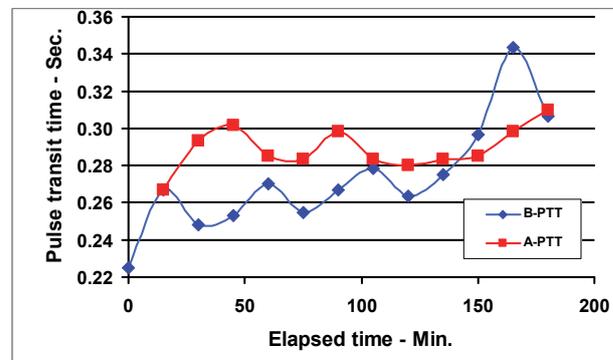*Figure 13C: Patient Type A and B's calf blood flow vs. elapsed time.*

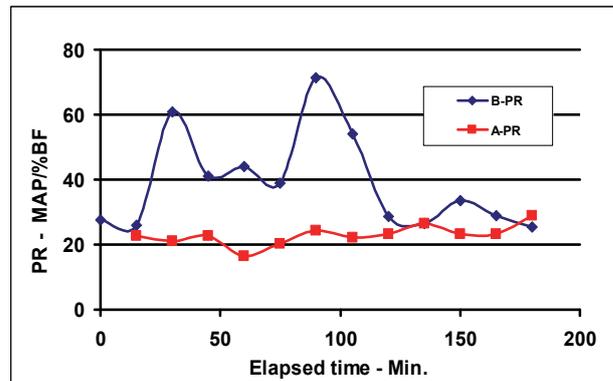*Figure 14A: Patient Type A and B's pulse transit time vs. elapsed time.*

Figure 14B: Patient Type A and B's peripheral resistance vs. elapsed time.

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In the Type A patient, PR remained relatively stable in association with no changes in BP. In the Type B patient, however, PR increased initially and became erratic subsequently but did not increase in association with the fall in BP near the end of dialysis session.

Contractility and Balance of Arterial and Venous Tone

The average blood pulse inflow angle (LA - between 10 and 90% of pulse amplitude) (Figure 15) is a measure of the contractility of the heart. An increase in LA indicates an increase in the contractility of the heart. LA of the Type A patient increases slightly during most of the dialysis period. LA is more varied for the Type B patient and decreases at 150 min showing a reduction in contractility at that point in time.
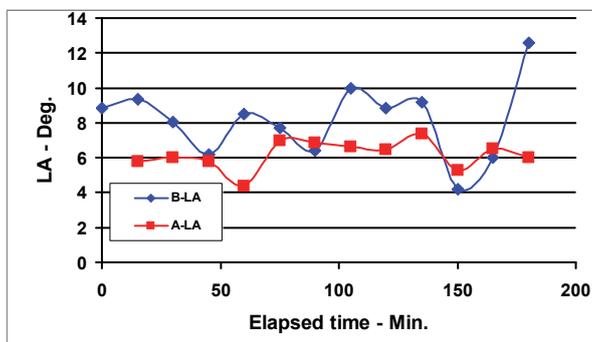

Figure 15: Patient Type A and B's average blood pulse inflow angle vs. elapsed time.

Arteriolar tone is expressed as the Dicrotic Index (DCI - Figure 16A) and is defined as the ratio of the maximum amplitude of the post-dicrotic segment of the impedance pulse waveform to the maximum amplitude of the pulse (17). Venular tone is given as the Diastolic Index (DSI - Figure 16B) and is defined as the pulse amplitude at the time of the dicrotic notch to the maximum amplitude of the pulse (18). DCI and DSI indicate the response of the local vascular bed in the calf segment during dialysis.

Figure 16A shows that there is a marked increase in arteriolar tone for Patient B while that of Patient A remains constant during dialysis.

The venular tone responses of the two patients (Figure 16B) are similar to the arteriolar tone responses; venular tone remained constant for patient A and increased for Patient B.

Discussion

The BIS system demonstrates the relative volume in each fluid volume compartment, namely, intracellular (V_c), interstitial (V_i), and intravascular (V_b). Moreover, we demonstrated fluid movement during hemodialysis in which there was net fluid removed from the human body. We observed two distinct patterns that patients experience.

Pattern type A represents a hemodialysis treatment in which the patient did not suffer any hypotensive symptoms.
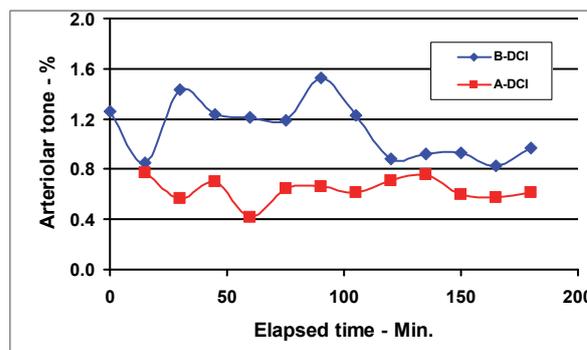

Figure 16A: Patient Type A and B's arteriolar tone vs. elapsed time.
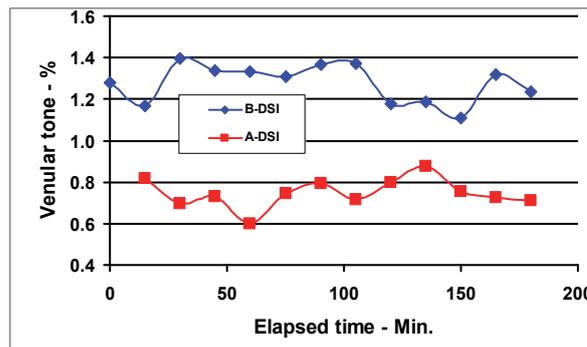

Figure 16B: Patient Type A and Bs venular tone vs. elapsed time.

The intravascular compartment was able to refill its fluid volume with that from the interstitial compartment. On the other hand, pattern type B represents a symptomatic hemodialysis treatment in which the patient experienced low blood pressure, tachycardia, cramps, and lightheaded- ness. In this situation, the intravascular compartment was unable to refill with fluid volume and the patient became hypotensive.

BIS also showed an increase in intracellular volume (V_c) while fluid was removed from the Type A patient. We speculated that the fluid originated from the extracellular compartments (V_i and V_b) (Figure 10A). The Type B patient was not able to tolerate fluid removal. The intracellular and interstitial fluid volume did not change significantly. Total body fluid removal originated from the intravascular compartment (V_b) (Figure 10B).

The BIS system reliably monitors the continuous and real time *rates of change* of the fluid volumes of the three compartments. The BIS intravascular volume changes correlate with the simultaneously measured changes in hematocrit (as the index of blood volume change).

During dialysis, progressive removal of fluid with UF in Patient A was associated with no change in systemic arterial pressure but a marked increase in arteriolar tone. By contrast, a similar rate of fluid removal resulted in a marked fall in arterial pressure with no change in arteriolar tone in Patient B. This lack of an increase in arteriolar tone during fluid removal may be related to impaired arteriolar constriction due to decreased sympathetic nervous activity, commonly found in diabetic patients with autonomic neuropathy.

There are several important physiological considerations regarding fluid volume changes during HD. The changes in intravascular volume during HD are primarily a function of the rate of fluid removal or ultrafiltration (UF) and the patient's vascular refilling of fluid from the extravascular space. During HD, the fluid removed by UF comes directly from the intravascular compartment. This fluid derives from both the intravascular and the interstitial compartments and, in some cases, from the intracellular fluid space. This implies a continuous refilling of fluid from the extravascular to the vascular compartment as a compensatory mechanism to minimize huge reductions in circulating blood volume, which if left unchecked leads to "overt hypovolemia". This, in turn, often results in low blood pressure during dialysis or "intradialytic hypotension", the most common complication of dialysis that is associated with increased morbidity and mortality. The plasma refilling rate can be simply calculated as the difference between the total fluid loss and plasma volume loss per unit time.

The most frequent complication of HD is hypotension as exemplified in Patient B in the present study. In this patient, intradialytic hypotension developed near the end of an HD session, as fluid is being removed at a steady rate by UF (vide supra). Of particular interest pertains to the simultaneously measured BIS showing a progressive decline in vascular volume, which reached its climax toward the end (130-180 min) of HD session, while both interstitial and intracellular volumes remained relatively stable. These findings can be explained as follows. During HD, continuous removal of fluid from the vascular compartment results in progressive decline in plasma volume perhaps because of insufficient or impaired vascular refilling. As a consequence, the interstitial volume changes little and the progressive decline in plasma volume in the absence of vascular refilling will ultimately result in intradialytic hypotension due to impaired vasoconstriction from autonomic dysfunction.

By contrast, Patient A did not develop intradialytic hypotension and blood pressures remained relatively stable throughout the entire HD session with the same UF rate of about 1L/ hour as in patient B. However, the measured BIS showed that the initial decline in vascular volume during HD was temporally accompanied by a proportionate decrease in interstitial volume with only a small decrease in blood pressure. In this case, it is possible a proportionate amount of vascular refilling occurred despite the same rate of UF removal, which may have preserved circulating blood volume and hence prevented the development of intradialytic hypotension.

These findings have several important therapeutic implications. During HD, circulating blood volume, a key determinant of blood pressure, may variably change as a result of ultrafiltration depending upon fluid volume shifts between intravascular and extravascular (interstitial and intracellular) compartments. The ability to accurately measure these changes during HD plays a central role to prescribing volume removal and control that will improve tolerance and avoid hypotension and other symptoms associated with hypotension. They also indicate that the system described above may find useful application in other clinical or research investigations.

Limitations of the study include:

1) We have used conventional R/C components in our revised equivalent circuit analysis model. This was done to ensure that our current representation would be completely compatible with our previous BIS analytical procedures. As explained in the Background section of this article, we use an ancillary cell model in our work that allows for cellular expansion and contraction. Inclusion of a 'constant phase element' in future equivalent circuit models may improve results from studies of this type.

2) A presumption that the intercompartmental fluid shifts in the limb during HD reflect total body fluid shifts.

3) Validation with the Critline.

This study demonstrates for the first time that the BIS method can reliably provide real-time continuous measurements of compartmental intravascular, interstitial, and intracellular fluid volume and cardiovascular changes that occur during HD treatment. Such information may prove valuable in the diagnosis and management of rapid changes in body fluid balance. Furthermore, BIS measurements can be used to predict who will have a symptomatic hemodialysis treatment with hypotension. As a result, the dialysis treatment could be adjusted accordingly so patient will not have hypotensive symptoms.

Conflict of interest statement

None of the authors have received or will receive any compensation or monetary benefit from the publication of this article. This article represents new research and has not been published elsewhere.

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