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Prediction of Intradialytic Morbid Events in Hemodialysis Patients by Monitoring the Second Derivative of Relative Blood Volume

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Abstract—**Intradialytic morbid events (IME) are a major issue affecting hemodialysis (HD) patients. Change in relative blood volume (RBV) reflects change in plasma refilling rate (PRR) and variability of ultrafiltration rate (UFR). However, degree of fluid overload influences this relationship. We propose a method using a second derivative of RBV (SDRBV) model to detect decrease in PRR during HD which is a major factor associated with IME. Forty-five HD patients (age 55.7±14 years, height 167.7±10 cm, Pre HD weight 79.3±16.6 kg) were studied with a total of 245 treatments, with IME occurring in 124 treatments. Predictions of IME with the SDRBV model showed 92 % sensitivity for 124 IME and 43 % specificity of 121 non IME treatments respectively. The average time between prediction and IMEs was -30.8±36 minutes. A high positive predictive value was due to 1) using a low-pass filter to reduce possible interferences in the RBV curve and 2) use of 5 minutes sample frequency to apply the SDRBV model. These results indicate that the SDRBV model is a useful tool in clinical practice to predict and prevent IME.**

I. Introduction

One of the major problems in hemodialysis (HD) treatment is how to reduce the risk of hypotension during the treatment [1]. However, intradialytic morbid events (IME), which include hypotension, cramping and dizziness, are difficult to predict because no reliable and accurate technique is available to identify occurrence of hypotension [2]. The blood volume (BV) monitor provides a non-invasive and simple method to indicate changes in BV [3, 4]. Decrease in BV is a physiologic reason for hypotension and is mainly due to reduction in plasma refilling rate in the presence of continuing ultrafiltration. Monitoring of relative blood volume (RBV) by means of Crit-Line or by blood volume monitor (BVM) has been used to assess critical thresholds of RBV which may indicate risk of IME [5]. However, the relationship of RBV changes to subsequent IME depends on multiple factors including ultrafiltration rate (UFR), fluid overload, plasma refilling rate (PRR), and autonomic nervous control. For this reason, changes of RBV alone fail to reliably predict IME [1, 6, 7]. A recent study showed that the slope of RBV change is significantly lower in the first 30 min of treatment in patients with succeeding IME compared to patients without IME [8]. However, the change in slope of RBV i.e. the first derivative of RBV (FDRBV) depends on the difference between PRR and UFR, which is influenced by the degree of hydration. The aim of this study was to evaluate whether the degree of change in PRR as assessed by the second derivative of RBV (SDRBV) can be used to identify impending IME by continuous monitoring of RBV during HD.

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II. Methods

A. Principle of SDRBV model

The behavior of change in blood volume during HD can be described by a simple two compartment model (Fig.1). Excess fluid volume is removed from the blood volume (BV) by ultrafiltration (UF) and plasma refilling volume (PRV) from the interstitial volume (V_{IT}) transfers by a transport coefficient (K_{IB}) to compensate for the reduction of plasma volume in the BV compartment.

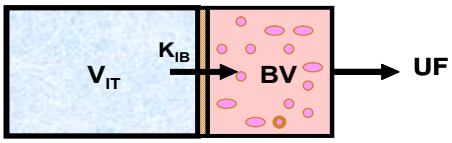

Figure 1. *Principle of two-compartment model*

The balance of the fluid volume in this system during HD can be described by the equation (1).

$$\frac{dBV}{dt} = K_{IB} V_{IT} - UFR \quad (1)$$

where $K_{IB}V_{IT}$ represents the plasma refilling rate (PRR) and UFR represents ultrafiltration rate. However, absolute blood volume is difficult to measure in the clinical practice of HD so instead the RBV (%), which is defined as the ratio of BV at any time to the initial BV_0 ($RBV=BV/BV_0$), is widely used in clinical research. The first derivative of RBV can then be expressed as follows.

$$\frac{dRBV}{dt} = \frac{1}{BV_0}[PRR - UFR] \quad (2)$$

Since UFR is set as a constant in this study, the second derivative of RBV can be derived as follows.

$$\frac{d^2RBV}{dt^2} = \frac{1}{BV_0} d[PRR - UFR]/dt = \frac{d[PRR]/dt}{BV_0} \quad (3)$$

This indicates that the ratio of the change of plasma refilling rate to the BV_0 during the treatment can be represented by the second derivative of RBV.

B. Clinical study

Forty-five patients (16 females, age 55.7±14 years, height 167.7±10 cm, pre HD Wt 79.3±16.6 kg) were studied. The number of study treatments for each patient was greater than one in order to reduce post HD weight if the target dry weight has not been reached [9]. RBV data were collected every minute during HD using the blood volume monitor (BVM, Fresenius AG). Pre and post HD body weight, systolic (SBP) and diastolic (DBP) blood pressures, heart rate (HR) every 10 minutes and ultrafiltration volume (UFV) and UFR continuously were recorded for each treatment. IMEs such as UF stopping, SBP<90 mmHg, HR>100/min, muscle cramps, dizziness or fainting were recorded.

C. Data analysis

The data were analyzed at 5 minute intervals (Δt). The FDRBV and SDRBV were defined as ΔRBV/Δt and $\Delta^2(RBV)/\Delta t^2$) respectively. The calculations were performed by $FDRBV=(RBV_i-RBV_{i-5})/(T_i-T_{i-5})$ and $SDRBV=(FDRBV_i - FDRBV_{i-5})/(T_i-T_{i-5})$, respectively, where subscript i represents the number of measurements and $5 \le i \le T_{End}$ is the elapsed treatment time in minutes and T_{End} is the time at the end of treatment. Two criteria of exclusion were applied for analysis of RBV raw data: 1) If the measurement of RBV were stopped more than five minutes and 2) Change in RBV of 1 % over the course of one minute. A low-pass filter was used to reject interference from non-physiologic signals. Data were divided into two groups: IME and non-IME according to clinical record. The threshold of SDRBV to identify impending IME was established by the mean +SD of the value of SDRBV in the IME group.

III. Results

A. Summary of the clinical results

Summary of data shows comparison of IME and non IME (Table 1).

TABLE I. SUMMARY OF RESULTS

		IME	Non IME	p
Number of measurement		124	121	
Age	year	55.7±13.7	52.5±113	ns
Height	cm	166.1±19.5	169±11	0.05
Pre Wt	kg	78.0±116.4	81.5±116	ns
Post Wt	kg	75.1±116.1	78.2±15	ns
Pre SBP	mmHg	134.6±23.7	136.7±23	ns
Pre DBP	mmHg	73.3±13.4	72.7±14	ns
Pre HR	1/min	79.5±11.9	79.5±12	ns
UFV	liter	3.21±0.96	3.41±0.98	ns
UFR	liter/hour	0.89±0.29	0.9±0.23	ns
SDRBV	$1/min^2$	-0.052±0.015	-0.045±0.025	<0.05
FDRBV	1/min	-0.77±3.1	-0.57±2.5	ns

No differences between IME and non IME groups in clinical parameters were observed. SDRBV was significantly lower in IME than in the non IME group. The threshold of SDRBV was defined as the criterion to identify impending IME and was established by setting $SDRBV_{threshold}$ = k*(mean–SD) = k*(-0.052+0.015) = -0.037*k, where the value of k can be 0.95 to 1.25 depending on the degree of hydration status. In order to reduce the error of missing the IMEs, in this study we chose k = 0.95, so that the $SDRBV_{threshold}$= -0.035 %/min^2.

B. Relationship of RBV, FDRBV and SDRBV

An example of results of the continuous measurement of RBV and the first and second derivatives of RBV is shown in Fig.2 and Fig.3 respectively. With the use of $SDRBV_{threshold}$, impending IME can be identified from continuous monitoring. However, the FDRBV has great variability during the time before the IME, so that the appropriate threshold is difficult to establish (Fig.2). In the case of treatments without IME (Fig.3), UFR was not stopped and the slope of RBV was almost constant over the entire treatment time so that only small changes in the curve of SDRBV were observed.

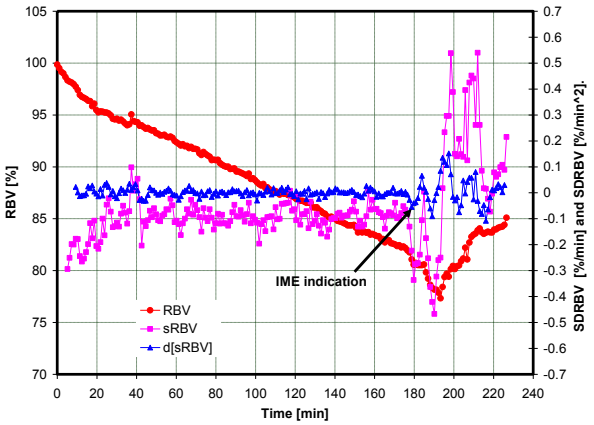

Figure 2. The curves of RBV (red circle), FDRBV (pink squar) and SDRBV (blue triangle) when the UF was stopped at 190 min. The signal predicting IME by SDRBV appeared at 180 min.

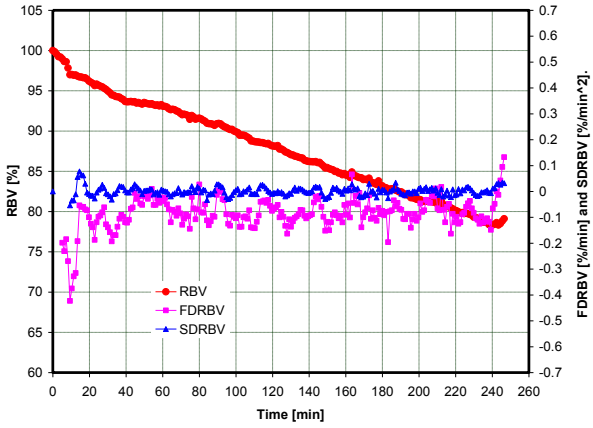

Figure 3. The curves of RBV(red circle), FDRBV (pink squar) and SDRBV (blue triangle) when the UF was continuous.

C. Identification of IME using $SDRBV_{threshold}$

Identification of IME true positive (TP) and non IME false negative (FP) were 114 (positive predictive value, 92 %) and 10 (8 %) cases respectively in a total of 124 actual

IME cases by using $SDRBV_{threshold}$ (Fig.4). In the 121 non IME cases, identification shows (false negative, FN) 69 (57 %) and (true negative, TN) 52 (43 %) cases in non IME using the $SDRBV_{threshold}$ (Fig.5). It is emphasized that data in the first 30 minutes of HD treatments were not analyzed because refilling volume did not begin to enter the blood compartment in the first 30 minutes.

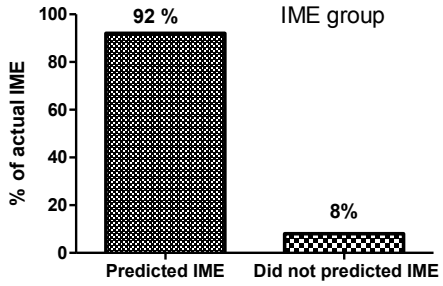

Figure 4. Identification of IME (TP=114) and non IME (FP=10) in the IME group

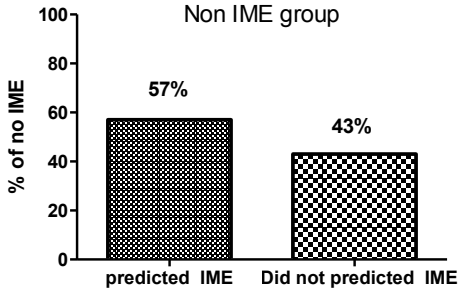

Figure 5. Identification of non IME (FN=69) and IME (TN=52) in non IME group

Sensitivity (ST) and specificity (SFT) of using the SDRBV model can be calculated as ST = PT/(PT+FN) = 114/183 = 62.3% and SFT = TN/(FP+TN) = 52/62 = 83.9, respectively. The average time of prediction for the IME was 120.5±58 minutes and the average time of the actual IME was at 155.6±62 minutes. The different time between predicted and actual IME was -30.8±36 minutes (Fig.6).

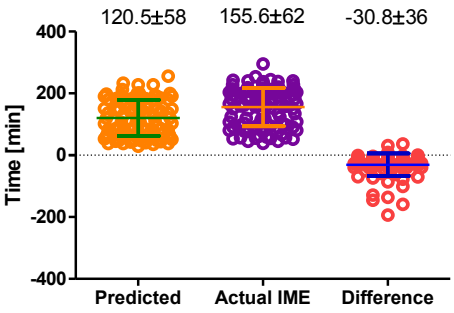

Figure 6. The average time of prediction of IME before the actual IME occurred is -30.8±36 minutes.

IV. Discussion

This study shows the sensitivity of identification of IME and non IME using a new criterion which is the second derivative of RBV model during HD by continuous monitoring. A high positive predictive value (92 %) for identification of IME was obtained due to 1) using an advanced model (SDRBV) to amplify the signal of decrease in PRR during HD; 2) pre-processing with a low-pass filter to reduce the interference in raw data and 3) selecting 5 minutes (Δt) for the change in RBV interval.

A. Improving sensitivity of identification using SDRBV

As shown in equation (3), change in SDRBV represents the ratio of decrease in PRR to the BV_0. Since the BV_0 and UFR were constant in individual treatments, reduction of PRR is the major factor decreasing the blood volume and causing intradialytic hypotension (IDH) when reduction of BV is in excess of the individual tolerance. In most cases, IDH or IME occurs when the UFR setting is in excess of PRR. However, PRR cannot be recognized from the RBV curve directly because changes in RBV were associated with BV_0 and UFR (Equation (2)), therefore, this is the main reason why RBV could not be shown to be useful in clinical studies by many authors [10-12]. FDRBV represents the change in RBV over time which is the method of RBV slope. Change in the first 30 minutes of RBV has been suggested to identify IDH or IME [8, 13]. However, this method does not to predict the IDH or IME during the treatment. In our study, a high variability of FDRBV was observed in most cases (Fig.1 and Fig.2). Further research using this FDRBV model is necessary to investigate the relationship of change in RBV to the degree of hydration.

B. Pre-processing of RBV data

RBV raw data could be influenced by several factors not associated with the change in the plasma refilling rate. One interference is a quick change in RBV curve which could result from sudden vasaconstricting shown as high frequency noise. To reduce this noise, a low-pass filter with moving average method was used to smooth the RBV curve before calculation of FDRBV and SDRBV. The other source of error from RBV raw data was occurred by sudden change in body position during the measurement. This error can produce about -0.08 to -0.1 %/min^2 variation in the curve of SDRBV. To reduce this error, when the value of SDRBV was lower than -0.08, it was considered as interference and was not utilized for data analysis. Accordingly, in this study the criterion for IME has been set as a range: $-0.08 < SDRBV_{Crit} < -0.035$, %/min^2.

C. Selection of the sample frequency of RBV

It is important to select the appropriate interval for data analysis because it determines the sensitivity of prediction. Fig 7 shows when a one minute interval was used, the curve of SDRBV (blue triangle) shows high variability although the signal for IME was much greater than using the 5 minute interval (Fig.2 and Fig.3). With one minute intervals, the noise in these curves was largely amplified. For this reason we used a five minute interval for analysis of FDRBV and SDRBV as a compromise with acceptable sensitivity and stabilization.

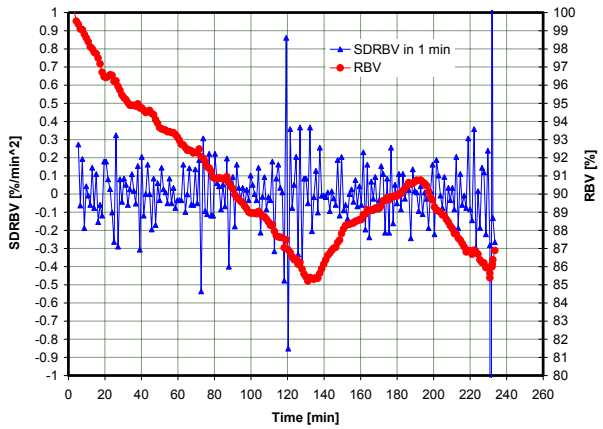

Figure 7. RBV (red line with round) recorded and SDRBV (blue line with triangle) calculated in every one minute

D. RBV and dry weight

Due to its ability to reflect relative changes in plasma refilling volume in the vascular (BV) compartment, decrease in the degree of RBV or RBV slope has been suggested for evaluating body hydration or dry weight for HD patients.[14, 15] However, from the equation (1) and (2) the change in BV or RBV during HD depends on the difference between PRR and UFR. A decrease in RBV or slope could be observed by using a high UFR regardless of the degree of PRR. Since the UFR is the major driving force in this dynamic system with two compartments (blood volume and interstitial volume), degree of fluid volume in interstitial compartment cannot be measured by change in the blood volume without UFR and value of PRR consideration. The plasma refilling volume (PRV) could be calculated if the absolute change in blood volume is known. Nevertheless, the degree of PRR or PRV depends on the difference in hydrostatic pressure between the interstitial and intravascular compartments and this gradient of pressure is determined by multiple factors such as hydration status, cardiovascular diseases, diabetes, and age. In summary, change in PRR or PRV cannot indicate hydration status in the interstitial space, and therefore, change in RBV cannot be used to estimate dry weight.

V. Conclusion

This study demonstrates that a two compartment model using the second derivative of RBV can be applied for predicting IME during hemodialysis treatments. However, the number of patients and measurements are still small so that a large clinical trial with this method is required. Since SDRBV represents PRR/BV_0 and BV_0 represents the individual initial hydration status, the accuracy of criterion of SDRBV for predicting IME should be improved by using an $SDRBV_{threshold}$ normalized by degree of hydration.

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