

Editorial Review

Measurement of relative blood volume changes during haemodialysis: merits and limitations

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Introduction

Dialysis hypotension is estimated to occur in ~20% of haemodialysis (HD) sessions [1] and can lead to serious vascular complications such as cerebral infarction and cardiac and mesenteric ischaemia [2,3]. It may contribute to chronic overhydration due to an inability to reach dry weight and may lead to under-dialysis [1,2,4]. Prevention of dialysis hypotension, therefore, is an important challenge to the dialysis staff. The initiating factor in the pathogenesis of dialysis hypotension is a decrease in blood volume which results from the imbalance between the ultrafiltration rate and the plasma refilling rate [5]. Devices that continuously and non-invasively monitor relative blood volume (RBV) changes during HD are being advocated as a tool to maintain an adequate volume of the intravascular compartment in order to avoid dialysis hypotension [6–8]. Nowadays, most manufacturers have incorporated an RBV monitor in their dialysis apparatus, but evidence-based knowledge on how to use the RBV data in order to optimize the dialysis prescription of the individual patient is lacking. Moreover, there are conflicting data in the literature on the predictive value of RBV changes for the occurrence of dialysis hypotension. In this review, we will outline the pathophysiological response to ultrafiltration-induced reductions in blood volume, evaluate the RBV measuring methods, discuss the relationship between RBV changes and blood pressure and discuss several factors that influence the validity of RBV measurements.

Cardiovascular compensatory mechanisms

Frank dialysis hypotension only occurs when the cardiovascular compensatory mechanisms can no

longer compensate for the reduction in blood volume [1]. The major cardiovascular compensatory mechanisms are a reduction of the venous capacity by venoconstriction of the capacitance vessels, active increases in arterial tone and increases in heart rate and contractility [1]. Venous constriction promotes venous return which helps to maintain systemic filling pressure, whereas arteriolar vasoconstriction helps to maintain blood pressure directly [9]. In addition, arteriolar vasoconstriction lowers capillary pressure, which facilitates vascular refill [9]. In particular, the combination of a critical decline in blood volume and impaired cardiovascular compensatory mechanisms may lead to cardiac underfilling, activation of the sympathoinhibitory cardiopressor reflex (Bezold–Jarish reflex) and sudden hypotension [10]. Structural cardiovascular changes such as left ventricular hypertrophy and diastolic dysfunction also play an important role since these conditions will oppose ventricular filling and, thus, predispose to an early fall in end-diastolic volume and stroke volume during HD, causing hypotension [11].

The compensatory mechanisms are affected by several patient and treatment factors that may vary between HD sessions in the same patient. For instance, differences in the ambient and dialysate temperature, food intake and the timing of the intake of anti-hypertensive medication as well as postural changes and exercise during HD may all influence the compensatory responses to hypovolaemia and may thus influence the level of RBV reduction at which dialysis hypotension will develop [12].

Non-invasive measurement of changes in blood volume

The classical way to measure plasma volume or red cell volume is by dilution techniques, using for instance ¹³¹I-labelled human albumin and/or ⁵¹Cr-labelled red blood cells. However, these methods are impractical in

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routine clinical practice. The attractive aspect of the non-invasive RBV monitoring devices is that they permit real-time and repetitive RBV assessments during the entire HD session. These non-invasive techniques are based on the principle of mass conservation: the concentrations of those blood constituents that are confined to the vascular space change proportionally as a result of changes of the plasma volume. The actual RBV change is calculated by means of the formula:

$$\text{RBV change (in \%)} = [(C_0/C_t) - 1] \times 100$$

in which C_0 and C_t represent the concentration of the blood constituent at the start of HD and at a certain moment during HD, respectively. Concentration changes of blood constituents can only accurately reflect changes in blood volume if both of the following assumptions are correct. First, the total amount of the constituent in the circulation must be constant. Secondly, there must be uniform mixing of the blood constituent throughout the vascular space or—if mixing is not uniform—the relative distribution of the blood constituent over the different vascular beds should not change during the dialysis procedure. As will be discussed later, these prerequisites are not always met during HD.

RBV monitors differ in the type of blood constituent that they use as a marker. Most devices that are currently used measure either haemoglobin (Hb) or haematocrit (Ht) [13–15] or the concentration of total plasma proteins (including Hb) [16,17]. The Hb- or Ht-based systems measure Hb by determining the optical absorbance of monochromatic light [14,15,18]. The total protein-based system uses the principle that the velocity of ultrasonic sound waves in blood depends on the total protein concentration [16,17]. Both systems seem to be accurate: compared with reference laboratory measurements, coefficients of correlation for the Hb- and the total protein-based method of 0.996 [18] and >0.88 [16], respectively, have been reported. Each of these techniques is subject to possible errors induced by, for instance, changes in oxygen saturation, osmotic pressure, blood flow or blood temperature. It is beyond the scope of this article to discuss these aspects in detail.

Relationship between RBV changes and blood pressure

Randomized studies on the value of RBV measurements in order to prevent dialysis hypotension are lacking. Many observational studies, however, have linked RBV changes during HD with the course of intra-dialytic blood pressure and the occurrence of dialysis hypotension. Only a minority of these studies demonstrated a relationship between the RBV and the development of dialysis hypotension [19–21], whereas most studies did not find a close relationship between the RBV course and the development of dialysis hypotension [22–27]. In particular, one of the largest observational studies demonstrated that the maximal RBV reduction during the HD session had no power in

predicting hypotensive episodes [25]. In this study, which is discussed in detail by Locatelli *et al.* in their recent review [28], no critical individual RBV reduction level for the appearance of symptomatic hypotension could be found. Interestingly, irregularity of the RBV course was the most powerful predictor of intra-HD hypotension in this study [25]. In another study, not the magnitude of the RBV reduction but the switch from an exponential to a linear decrease of the RBV predicted intra-dialytic hypotension [26]. To date, one study has explored the relationship between the RBV course and blood pressure in patients with acute renal failure in the intensive care unit [27]. In that study, there was no relationship between RBV course and intra-dialytic blood pressure.

In the individual patient, continuous measurement of the RBV course would be a perfect tool for the prevention of dialysis hypotension if hypotension would always occur at roughly the same level of RBV reduction. Observational studies, however, did not find a close relationship between the individual RBV level and the occurrence of hypotension [23–25]. Recently, Barth *et al.* tested the hypothesis that HD patients have an individual critical RBV below which dialysis hypotension will occur [29]. Based on the observation that the standard deviation (SD) of the critical RBV threshold was <5% in three-quarters of their total study population ($n = 60$), the authors concluded that an individual critical RBV threshold exists for nearly all patients. However, in 47.2% of their patients, the SD of the critical RBV threshold was >4%. If we assume a patient with a mean critical RBV threshold of 90% and an SD of 4%, this implies by definition (normal distribution) that one-third of the critical RBV threshold values of this patient will be outside the 86–94% range. With this variability, it would be difficult to use an RBV threshold for the prevention of dialysis hypotension in about half of their patients [12].

Modification of the dialysis prescription on the basis of RBV changes

There are some studies in which the dialysis prescription was modified by ‘nurse-driven’ adaptations of the ultrafiltration rate and/or infusion of intravenous fluids in response to the observed RBV changes as a means to reduce the frequency of dialysis hypotension episodes. Some relatively small (maximum number of patients: 11) studies have shown that adapting the ultrafiltration rate based on observed RBV changes has a positive effect in diminishing intra-dialytic hypotension [6,30,31]. Alternatively, automatic bio-feedback systems have been developed that alter certain treatment parameters in response to RBV changes. At present, two such biofeedback systems are commercially available.

The first system is based on the concept of blood volume tracking (BVT) [32]: based on target values for weight change and treatment duration, the BVT system guides the actual RBV along a pre-set individual RBV

trajectory by continuously adjusting the ultrafiltration rate and dialysate conductivity. Several authors have shown that treatment with BVT is associated with improved intra-dialytic haemodynamic stability in comparison with standard HD [4,32–39]. One would expect this increased stability to be related to less RBV reduction with this system in comparison with standard HD but, interestingly, the studies with BVT have reported divergent results in this respect. Some groups [32,34] have reported a slightly, but not significantly, better RBV preservation with BVT in comparison with standard HD. We and others, however, found that the better haemodynamic stability and the reduction of symptoms with BVT were not paralleled by better RBV preservation in comparison with standard HD [35,38,39]. Possibly, treatment with BVT exerts its favourable haemodynamic effect by avoiding rapid RBV fluctuations [32,33] or by avoiding prolonged linear RBV decreases which were important predictors of dialysis hypotension in the study of Andrulli [25] and Mitra [26], respectively.

A second system adapts the ultrafiltration rate in response to RBV changes in order to stay on the safe side of a pre-set individual RBV limit below which the patient is expected to be at risk for dialysis hypotension on the basis of earlier observations [40]. To date, only one study is available that demonstrated a better intra-dialytic haemodynamic stability with this system [40].

Problems related to the measurement of RBV changes

Influence of hydration status

Non-invasive RBV devices provide information on RBV changes but give no information on the actual (absolute) blood volume. Blood volume increases as the extracellular volume increases, both in healthy people [41] and in HD patients [42]. Therefore, the absolute blood volume at the start of the HD session is extremely variable depending on the hydration status of the patient [43]. It follows that the more overhydrated the patient is, the larger the absolute blood volume compartment and, as a consequence, the more the RBV may decrease to end up at the same post-HD absolute blood volume level. This consideration is in line with the ‘crash-crit concept’ which was based on the study by Steuer *et al.* in which they showed that in many (but not in all) patients, hypovolaemia-induced hypotension occurred at roughly the same value of Ht (i.e. at the same level of residual absolute blood volume) [21]. At the same time, the hydration status itself strongly influences the course of the RBV change during HD. The less overhydrated the patient is, the more pronounced will be the RBV decrease due to a lower refill rate when the patient is close to dry weight [44,45]. Thus, variations in the hydration status at the start of the dialysis sessions will contribute to the variability of the RBV course during HD [12,43]. Another problem of a more fundamental conceptual nature is

the lack of a straightforward relationship between RBV changes and residual absolute blood volumes. In the same patient, an identical RBV decrease may be associated with different residual absolute blood volumes due to the fact that the pre-HD absolute blood volume varies markedly, largely dependent on the pre-HD hydration status. More research is needed to clarify this issue. The availability of bedside absolute blood volume measurements may facilitate this kind of study [46].

Intravascular blood volume distribution

Calculation of RBV changes from changes of either Hb, Ht or total protein concentration relies on the assumption that there is uniform mixing of red cells and plasma throughout the whole circulation. However, this assumption is not valid: the whole-body Ht is lower than the Ht of arterial or venous blood [47]. The difference is due to a dynamic reduction in microvascular Ht in capillaries and venules (<200 μm), known as the Fahraeus effect [48]. The difference between the arterial or venous Ht and the whole-body Ht is expressed as the F-cell ratio, i.e. the ratio of the whole-body Ht to the arterial or venous Ht, and approximates 0.91 in non-dialysis individuals [49,50]. The lack of uniform mixing of erythrocytes throughout the circulation would not induce an error in the RBV calculation if the difference in Ht between the different vascular beds would remain constant during HD; in other words, if the F-cell ratio would not change. There are, however, strong indications that the F-cell ratio may change during HD (see below) [51,52].

In healthy individuals, exercise, heat stress and standing for a long time are all associated with an increase of the F-cell ratio, which reflects a redistribution of blood from the microcirculation to the central circulation [47,53]. This intravascular translocation of blood is considered to be a cardiovascular compensatory mechanism to maintain central blood volume in order to compensate for a decrease in plasma volume in these circumstances. It has been recognized that the change of the F-cell ratio in these circumstances negatively affects the validity of RBV reductions calculated from Hb or Ht changes [53,54]. A recent study suggests that translocation of blood from the microcirculation to the central circulation also occurs during HD [52]. The consequence of blood translocation from the microcirculation to the central circulation is that the observed RBV change in the mixed arterial/venous blood will underestimate the reduction of the ‘whole-body blood volume’ [52]. These interesting findings of Mitra *et al.* should be confirmed in future studies. In addition, the extent of the underestimation of blood volume changes will have to be investigated in stable as well as in hypotension-prone dialysis patients.

Postural changes

Postural changes have a profound effect on plasma volume in healthy subjects [54,55] as well as in HD

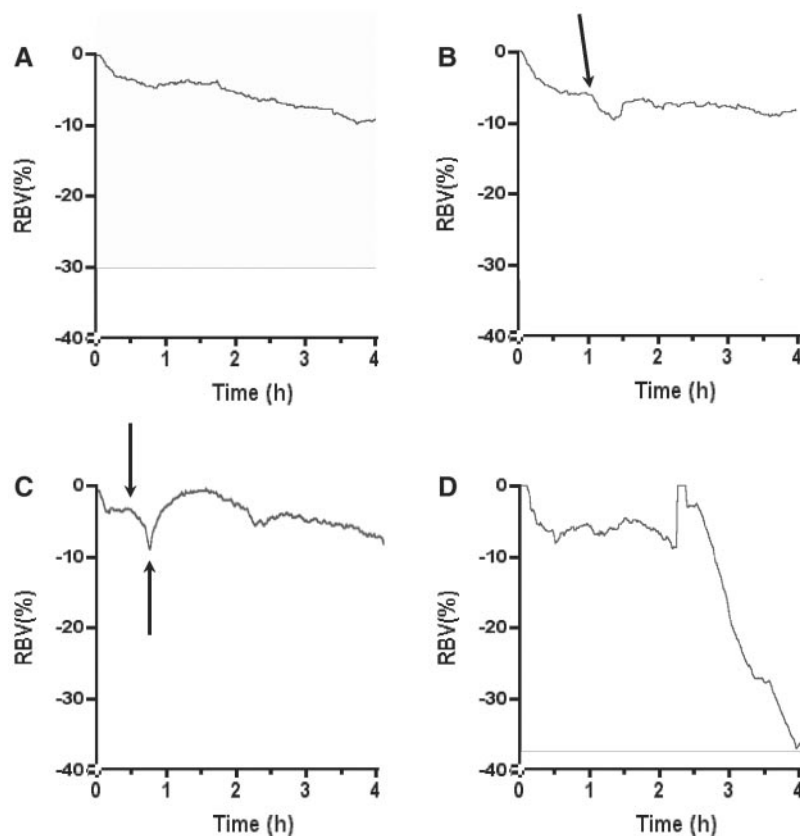


Fig. 1. Graphical representation of the relative blood volume (RBV) course during four haemodialysis sessions with constant ultrafiltration rate and conductivity. The *x*-axis represents the dialysis duration and the *y*-axis represents the RBV change. RBV curves (A), (B) and (C) are from the same patient. (A) Standard haemodialysis session in the supine position. The RBV declined gradually to -9% at the end of the treatment. (B) A change from the supine to the sitting position (indicated by an arrow) was associated with an abrupt decline of the RBV. (C) At 30 min into the dialysis session, the patient started bicycling (stationary) for a total of 5 min. The arrows indicate the points where the patient started and stopped bicycling. The RBV declined during bicycling and rose again after the exercise stopped. (D) After 2.5 h of dialysis, two units of packed erythrocytes were given to this patient. In the remaining 1.5 h of the dialysis session, the addition of erythrocytes to the circulation increased the haematocrit and haemoglobin concentration. The RBV device interpreted this Hb and Ht rise as a decline of the RBV.

patients [56,57]. Upon standing, the Ht increases because of a decrease in plasma volume due to a fluid shift from the circulation to the interstitial tissue of the dependent regions of the body (the legs) [54]. At the same time, the haemoconcentration during standing is often markedly underestimated in blood sampled from the standing subject because of slow exchange of haemoconcentrated blood in the dependent regions [54]. Resumption of the supine body position after standing facilitates mixing of blood between the circulatory compartments and leads to a rapid and marked increase in Ht [54,55]. Subsequently, the Ht will slowly decrease due to refill from the tissues, as has been shown in healthy subjects [54,55] and in HD patients [56,57]. Inagaki *et al.* have compared dialysis patients and healthy controls with regard to this haemodilution after the change from an erect to a supine position. Interestingly, these authors found that haemodilution and thus the fluid flux from the interstitial tissue to the vascular space took more time (>30 min) in comparison with healthy controls (<15 min) [56]. Many HD patients assume a supine or half-sitting position just before the start of the HD session (e.g. for the

connection of a central venous access) after a period of standing. The RBV device uses the first Hb, Ht or total protein measurement as the reference value to calculate subsequent RBV changes. However, at the time the reference value is being measured, there will often be no steady state of Hb, Ht or total protein concentrations as a result of the preceding postural change. It follows that RBV changes at the beginning of the HD session may well be due, in part, to the preceding postural change and are not caused exclusively by the imbalance between the ultrafiltration rate and refill rate. Postural changes during HD such as the resumption of the Trendelenburg position also have a profound effect on Hb and Ht [58]. These changes are being interpreted as RBV changes (Figure 1B) but, as discussed above, not all Hb and Ht changes reflect concurrent 'real' RBV changes that are of the same magnitude [54,55].

Miscellaneous factors that may influence RBV measurements

Contraction of splanchnic [59,60] and possibly splenic [59] vascular beds occurs during HD as a compensatory

mechanism. The RBV device will interpret the addition of relatively erythrocyte-rich blood from the spleen to the central circulation as a decrease in RBV, whereas, in fact, the central blood volume has increased. At present, it is not clear if splenic contraction during HD occurs in a substantial proportion of patients and to what extent it may lead to overestimation of the RBV reduction.

In one study, food intake during HD was associated with a reduction of the RBV [61]. In this study, the RBV decrease was more pronounced when the meal was taken in a sitting position than in a supine position [61]. The exact mechanism of the increase of Ht is unknown, but it could result from splenic vascular contraction and, thus, the addition of blood with a higher Ht to the central circulation.

Intra-dialytic exercise is associated with an RBV reduction (Figure 1C) probably as a consequence of fluid shifts from the microvasculature to the interstitium [62]. At the same time, exercise does not compromise haemodynamic stability in the majority of patients [62,63]. This may be due to the divergent effects that exercise has on the circulation. Capacitive areas of the circulation are contracted (which greatly increases mean systemic filling pressure) and cardiac output increases. On the other hand, peripheral vascular resistance decreases during exercise [62,64] and RBV decreases [62]. However, the overall effect of intra-dialytic exercise on blood pressure seems to be positive in many patients [62,63].

Intravenous administration of albumin or other protein-containing fluids will be interpreted as a decrease of the RBV by devices that are based on the measurement of total protein concentrations. Of course, infusion of erythrocytes (packed cells) will also be interpreted as an RBV decline (Figure 1D) by both the Hb- and Ht-based systems and—to a lesser extent—by the total protein-based systems. Accordingly, temporary changes in the lymphatic return of tissue proteins to the blood during HD might be interpreted as a change in RBV by the total protein-based systems.

It is commonly assumed that the total red cell volume is constant during HD. However, changes of the plasma osmolality theoretically can induce a change in red cell volume. Two groups reported that the erythrocyte volume during HD was stable based on the measurement of the mean corpuscular volume [65,66]. In contrast, Fleming *et al.*, who calculated erythrocyte volume from mean corpuscular haemoglobin concentrations (MCHC), found a significant decrease of 3.8% in erythrocyte volume after 2 h of HD with a high (154 mmol/l) dialysate sodium concentration [67]. More research is needed to clarify if, and to what extent, changes in plasma osmolality affect the validity of the RBV measurement.

Conclusions and recommendations

The current generation non-invasive RBV devices are able continuously and accurately to measure Hb, Ht

or total protein concentrations in the afferent blood during HD. The concentration changes are then used to calculate RBV changes based on the assumptions that the total mass of the blood constituent in the vascular space is constant and that there is uniform mixing throughout the vascular space. However, these assumptions are not always correct and, therefore, not all changes in Hb, Ht or total protein concentration automatically reflect concurrent RBV changes. One of the most obvious examples is the infusion of packed red blood cells. Furthermore, since Ht is not evenly distributed in the vasculature, translocation of blood from a region with a lower Ht to the central circulation will be interpreted as an increase of RBV, whereas, in fact, the total whole body blood volume stays more or less constant.

Given the many factors that influence Hb and Ht concentrations during HD, it is not surprising that the observed RBV course is so variable in many patients. In addition, haemodynamic stability is determined not only by the course of blood volume but also by the response of the compensatory mechanisms to hypovolaemia. The response of these compensatory mechanisms is affected by several patient and treatment factors that may vary between dialysis sessions in the same patient. All these factors together probably explain the poor predictive value of RBV reductions for the occurrence of dialysis hypotension in most studies [25,28].

Biofeedback techniques that use RBV measurements as input for the adaptation of the ultrafiltration rate and dialysate conductivity in order to guide the RBV course along a pre-defined trajectory are associated with a reduced frequency of dialysis hypotension episodes [32–35,38,39]. In these studies, RBV reductions did not differ significantly from those during standard HD sessions. However, this observation does not rule out a role for RBV changes in the development of dialysis hypotension. It is possible that these biofeedback techniques exert their favourable haemodynamic effect by avoiding rapid RBV fluctuations [25,26,32,33].

In the opinion of the authors, routine RBV monitoring in clinical practice should be used with caution until the major methodological and conceptual problems that are inherent in the indirect RBV estimation are clarified. The limitations (or pitfalls) of the use of these devices should be known to all the dialysis staff. In addition, practical guidelines should be developed on how to interpret and use the RBV results that are generated by these devices. Future studies should take into account the relationship between RBV changes and (residual) absolute blood volume and should attempt to standardize all factors that are known to influence the RBV course as much as possible, for example postural changes before and during HD, exercise, food intake, timing and dose of cardiovascular medication in relation to the start of the HD session, etc. At the same time, the wide availability of the RBV devices will undoubtedly facilitate further research on the relationship between RBV

changes and intra-dialytic haemodynamic stability and will hopefully lead to a better understanding of the pathophysiology of dialysis hypotension.

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