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Invited review article

Complexity of blood volume control system and its implications in perioperative fluid management

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Abstract
The use of fluid therapy attempts to optimize blood circulation by manipulating the circulating blood volume (BV). BV may be a key intermediate parameter between fluid therapy and the blood circulation, and it has been assumed that BV can be controlled by fluid therapy. In order to construct a fluid therapy protocol, firstly, we have to confirm whether BV can actually be controlled by fluid therapy. Volume kinetics studies and dilution techniques for BV measurements have enabled the actual effects of fluid management on BV to be analyzed in the presence of various pathological conditions. Various studies have shown that the effect of fluid, especially crystalloid, on BV varies considerably among individuals, and even BV values measured at a single time point vary from 40 ml·kg^{-1} to 110 ml·kg^{-1}. It has become apparent that such wide variations in interindividual BV preclude the establishment of universal optimal fluid management protocols. Thus, secondly, it should be clarified how BV is controlled, and whether or not we can control it. Perioperative BV reportedly changes in a manner that is independent of the in-out fluid balance, but is related to hormonal factors. Because inflammation and some hormones control vascular permeability and the renal adjustment of solutes and fluids, such factors may readjust the BV even after interventional fluid therapy. Perioperative BV may be predominantly controlled by an internal regulatory system, regardless of whether "restrictive" or "liberal" fluid management strategies are employed. Recognizing this physiological control of BV may help us to develop individualized fluid management strategies.

Key words Blood volume · Plasma exchange · Interstitium · Crystalloid · Fluid balance

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Introduction

The final goal of fluid management is to optimize the circulatory system to ensure the sufficient delivery of oxygen to organs. A universal regimen for optimizing fluid management is difficult to establish because responses to fluid therapy vary widely between individuals [1,2]. Beneficial effects of both "liberal" and "restricted" fluid management strategies have been reported [3,4], and even the goal of fluid management is controversial [2]. Blood volume (BV) is an intermediate parameter that clinicians try to control to optimize circulation through fluid therapy. Most of us believe that we can control BV through fluid therapy. Simultaneously, we are vaguely aware that we can control BV through fluid therapy in only a limited condition. There could be a mechanism controlling BV, which we are not aware of, that is responsible for the inconsistent effectiveness of fluid therapy.

In order to optimize cardiac load, the estimation of stroke volume, using transesophageal echography, and the use of conventional preload parameters such as pulmonary arterial wedge pressure, are useful. These parameters are indirect values that only reflect BV. These parameters are quite useful for guiding short-term management to stabilize the circulation. However, fluid management guided by these parameters occasionally results in fluid overload or transfusion-associated cardiac overload (TACO), because these parameters focus only on cardiac performance, and not on whole-body hydration or the filling conditions in the intravascular space.

The quantitative BV value may not be useful for immediate circulatory management; however, the value may provide important information to evaluate the appropriateness of the perioperative management of fluid and volume therapy for longer periods. Isbister [5] points out in his review article on BV regulation that: "In the short term, the maintenance of adequate venous

return and cardiac output is obvious. However, in the overall picture, the total blood volume is probably predominantly determined by requirements for a reserve to respond to stresses.". Because the primary endpoint of our routine work is short-term circulatory stabilization, and we do not have convenient measurements of BV, we do not imagine the whole picture. We should be aware that the human body could adjust the BV by way of a complicated and elaborate regulatory system even after "invasive" fluid therapy.

In this article, I review experimental data of quantitative BV measurements and try to find the mechanism underlying the way that BV is regulated. Approaching the mechanism of BV regulation could help our understanding of why it is difficult to establish a uniform fluid therapy protocol. This review could provide material for the discussion of "restrictive" and "liberal" fluid management strategies.

Fluid movement according to Starling's law

Approximately 70% of our body is water. The water compartment is divided into intracellular fluid and extracellular fluid. The extracellular fluid volume accounts for 30% of the whole body, and is divided into interstitial fluid (23%) and plasma (7%). The BV consists of the plasma, as part of the extracellular fluid, and erythrocytes. Focusing on the plasma, plasma volume and interstitial fluid volume is highly exchangeable. Fluid exchange through a capillary is regulated by Starling's law:

$$dV/dt = Kf((Pc - Pisf) - R(\pi c - \pi isf))$$

where Kf is the filtration coefficient; Pc and Pisf are the hydrostatic pressures in capillary and interstitium, respectively; πc and πisf are the osmotic pressures in capillary and interstitium, respectively; and R is the reflection coefficient of protein.

Note that "dV/dt" does not represent the quantity, but just the speed of water movement. Distribution terminates when the balance of the hydrostatic pressure and the osmotic pressure cancel each other out. Because the interstitium consists not only of free space but also of absorbent gel, captured water in the gel does not contribute to lowering the osmotic pressure in the interstitium (Fig. 1). Therefore, the osmotic pressure does not easily change until the gel is saturated by water movement. This is a mechanism of edema formation. Thus, Starling's law does not determine the distribution ratio between plasma and interstitium, it just explains the movement of water through the capillary wall. As explained above, water moves to the interstitial space. The back-force of water movement into a vessel, which should be exerted quickly according to Starling's law, is not produced easily (Fig. 1). The property of the gel in the interstitium, and the pore size of the capillary complicate the principle of water movement. Consequently, fluid distribution cannot be readily estimated by Starling's law.

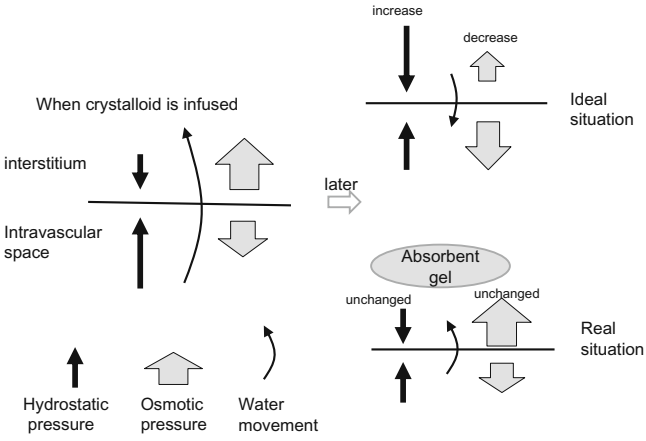

Fig. 1. Water movement according to Starling's law. Starling's law represents the speed of water movement. Distribution terminates when the balance of hydrostatic pressure and osmotic pressure cancel each other out. Because the interstitium consists not only of free space but also of absorbent gel, hydrostatic pressure and oncotic pressures are not easily changed even after water moves into the interstitium until the gel becomes saturated with the water flow. Thus, Starling's law does not determine the distribution ratio between plasma and interstitium; it just explains the water movement through the capillary wall

Estimation of BV

Because Starling's law expresses only the speed of fluid movement, the actual intravascular BV cannot be estimated by physiochemical principles only. Actual BV measurement may clarify how BV is controlled. Blood volume (BV) is defined as the volume of blood in the body, and as such includes stored blood in the spleen, liver, and bone marrow that is partly recruited to the bloodstream, where it is referred to as the circulating BV. Most methods of measuring BV utilize the dilution rate of labeled plasma or red blood cells a few minutes after tracer injection; thus, the term "BV" used in this review refers to the intravascular BV, which is almost synonymous with the circulating BV.

BV is sometimes optimized using preload parameters, i.e., central venous pressure and left atrial pressure, as guides. However, these parameters are actually poorly correlated with quantitative BV values [6–8]. If the vessels are not completely filled to the limit of their unstressed volume, the preload parameter should not change when fluid is administered into the circulatory

system. Furthermore, cardiac function itself, not only BV, strongly influences the preload parameters.

Hematocrit is a simple measure that we sometimes rely on to estimate BV. However, a poor correlation between hematocrit values and BV has been confirmed [9,10]. Low hematocrit levels seen in bleeding patients result from the dilution of bodily fluid with infused fluid. Therefore, the hematocrit level is no more than an alarm for bleeding and cannot be used as a quantitative parameter to measure BV, although the acute relative change of hematocrit can be a reference to estimate BV change.

Several methods have been used to measure BV, all of which utilize an indicator-dilution method. The BV consists of the plasma volume and the red cell volume; therefore, the tracing isotopes used target red cells or plasma. ^{51}Cr is used for red-cell labeling, and ^{131}I is used for plasma labeling. After obtaining the red-cell volume or plasma volume, the hematocrit value is used for conversion to the total BV. Therefore, the total BV values obtained by two different tracers should agree with each other in the steady state. If the F-cell ratio (the ratio between central hematocrit and peripheral hematocrit) changes, the two values may show a discrepancy. Human serum albumin (^{131}I-HSA) is now a more widely used indicator for the measurement of BV [11]. The stable decay of this indicator and the ability to precisely estimate its radioactivity are two reasons why this method is used as the gold standard. Volume kinetic study is also a reliable methodology that shows relative changes in BV without relying on an exogenous indicator. Indocyanine green (ICG) is an alternative indicator that binds to lipoprotein, rather than albumin [12], and is used to measure BV without subjecting the patient to the biohazards of radioisotopes. Pulse dye-densitometry is a recently introduced method for performing BV measurements [13–16]. This method employs an optical probe similar to pulse oximetry to measure the intraarterial ICG concentration. Another optical method utilizing an intraarterial catheter is also used clinically for the bedside measurement of BV [6]. These measurements employ an indicator-dilution technique, and validation studies have confirmed the accuracy of the techniques using ^{51}Cr (0.06 +/– 5.9%)[16], and ^{131}I (3.99 +/– 10.54%)[13]. The mixing time of the indicator varies between compartments. ICG decays rapidly; thus, the BV must be calculated during the initial few minutes of mixing time. On the other hand, isotope-labeled albumin or red cells decay slowly, and the BV must be calculated 1 h after the mixing time. Thus, ICG theoretically visualizes the fast compartment (Vβ; distribution volume of β-phase), while ^{131}I-HSA shows the slow compartment (Vss; distribution volume of steady state). Nonetheless, validation studies comparing results obtained using ICG and isotope indicators have agreed closely [13,16]. And even the values obtained with different tracers (^{51}Cr for red cells and ^{131}-I for plasma) agreed well with the values obtained by ICG.

Physiological distribution of BV

Individual BV values range widely. Jones and Wardrop [17] reported that BV—as determined using radioisotopes—ranged from 40 ml·kg^{-1} to 110 ml·kg^{-1} (Fig. 2). The distribution of reported BV values during anesthesia also ranged widely, between 40 ml·kg^{-1} and 110 ml·kg^{-1}, as measured using ICG [18]. Such large variations have also been confirmed in sports medicine (50 ml·kg^{-1} to 100 ml·kg^{-1}) [19]. These correlated findings suggest that BV may vary not only interindividually but also intraindividually. Guyton [20] has stated that: "... these values vary greatly in different individuals; also, sex, weight, and many other factors affect the BV". Therefore, BV values are unlike arterial pressure or heart rate values, which are closely regulated within limited ranges.

Sixty percent of albumin is distributed outside the vascular space. Albumin shuttles between the intravascular and extravascular spaces. Considering the nature of plasma exchange, it is conceivable that BV varies even on an individual basis. Catecholamine levels, which have a strong effect on blood vessel volume, are one

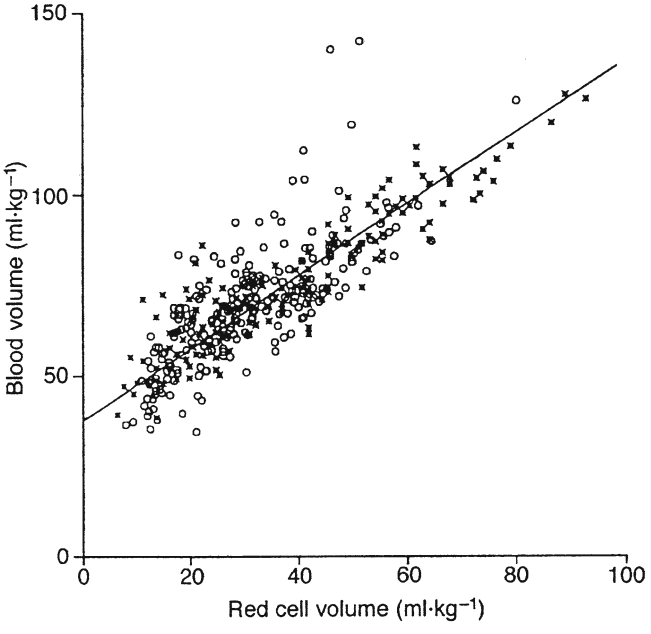

Fig. 2. Relationship between circulating blood volume (BV) and red-cell volume in hospitalized adults (*crosses*) and neonates (*open circles*). A large distribution range of BV was confirmed. (Adapted from Jones and Wardrop [17], with permission)

example of a factor affecting BV status. In a pediatric patient with an active pheochromocytoma, the BV increased by more than 1.2 l from a baseline value of 2.8 l after the resection of the tumor, then decreased to almost the preoperative value within 1 week [21]. The intraoperative in-out balance contributed to this change to some extent. However, drastic changes in the concentrations of serum catecholamines, mainly norepinephrine, likely had an even more profound effect on the BV status. Such catecholamine-dependent changes in BV have also been confirmed in pheochromocytoma patients after alpha-blocker therapy [22,23]. Intraoperative infusions or transfusions are often regarded as effective methods for managing BV. However, BV may actually be controlled by factors other than the in-out fluid balance.

Clinical findings regarding crystalloid infusions and BV

Crystalloid infusion and BV in minimally hemorrhagic patients

Crystalloid volume loading may be routinely employed for anesthesia-induced hypotension. Such regimens have been repeatedly demonstrated to be ineffective for preventing hypotension during spinal anesthesia for cesarean sections [24,25]. This is an example of the insufficient effect of crystalloid infusion on volume expansion. Volume kinetic studies can precisely predict the trend in volume expansion after the infusion of Ringer's solution [26]. The volume-expanding effect of crystalloid infusions is transient [24,25], although an initial expanding effect has been confirmed. Once the infusion of crystalloid is stopped, the intravascular volume rapidly shrinks, even if as much as 100 ml·kg^{-1} of crystalloid has been rapidly infused [26] (Fig. 3). This phenomenon suggests that BV expansion depends on the speed of infusion, not on the amount of infusion. Svensen et al. [27] have also demonstrated that the response to fluid loading varies between individuals. The concept of BV and body fluid status is often confused. As mentioned above, it is difficult to predict how much crystalloid fluid is retained in the intravascular space. Fluid balance cannot predict BV, and it should represent the hydration of the whole body, not the BV. Quantitative measurements of BV in intensive care unit (ICU) patients have confirmed that fluid balance is not correlated with the BV status [28,29]. Because crystal-

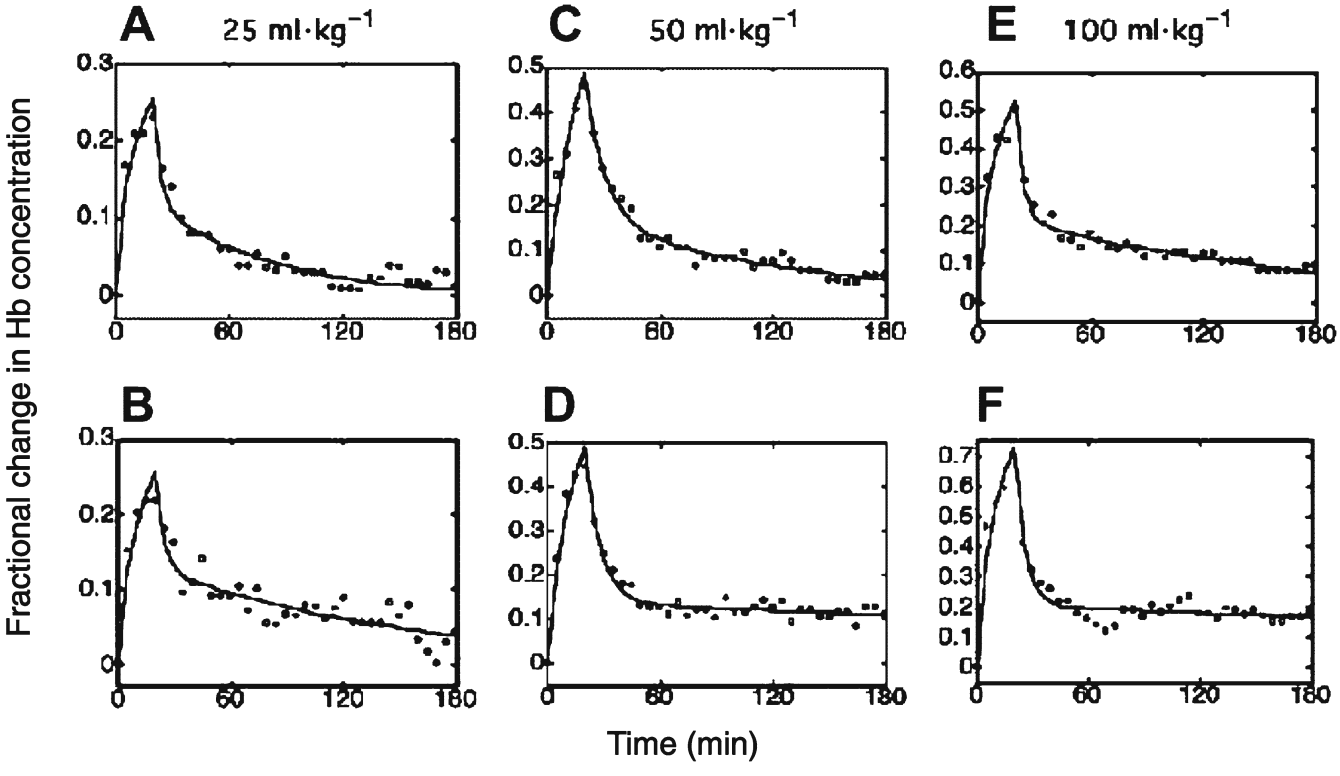

Fig. 3A–F. Measured data points (*dots*) and the optimal curve fit generated by volume kinetic analysis (*lines*) in two representative sheep undergoing three experiments in which three volumes of 0.9% saline were infused intravenously over 20 min on separate days. *Note the different scales on the y-axes*. Once the infusion of crystalloid was stopped, the intravascular volume was rapidly reduced, even if as much as 100 ml·kg^{-1} of crystalloid had been rapidly infused. *Hb*, Hemoglobin (Adapted from Svensen et al. [26], with permission)

loid is a composite of water and electrolytes, the vessel wall is not a robust barrier to distribution outside the vessel.

Guyton et al. [30,31] previously presented the concept of "interstitial pressure". The extracellular space acts as a large fluid buffer that can accept a large volume of fluid. Interstitial pressure does not increase unless it exceeds a critical point after a considerable amount of fluid has shifted to the interstitium. Thus, from the perspective of the pressure gradient for fluid movement, the feedback loop that stops fluid shift to the interstitium, forming edema, is not sufficiently exerted before this critical point is reached. This concept supports the limitation of Starling's law, as explained in Fig. 1 Liberal intraoperative infusions may only contribute to an increase in interstitial pressure, and not to the appropriate maintenance of BV. Considering this concept, it seems feasible that BV, which represents intravascular volume, may not be easily changed by fluid balance.

In contrast to crystalloid infusion, colloid has quite different properties from crystalloid. It has been reported [32] that hydroxyethyl starch (HES) consistently increases the BV (1 l HES increased BV from 5.30 l to 6.33 l, corresponding to the volume of infusion); thus, we may be able to control BV with colloid. Because colloid remains in the intravascular space much longer than crystalloid, we can expect various favorable effects through colloid fluid therapy, i.e., patency of vessels in the microcirculation [33], maintenance of urinary output owing to the maintenance of intravascular volume in the kidney, and prevention of the release of inflammatory factors [34,35]. The discussion comparing colloid and crystalloid needs more space. I leave this important issue to another review, focusing on crystalloid in this review.

Crystalloid infusion during hemorrhage

The role of crystalloids in BV expansion during hemorrhage differs from that in nonhemorrhagic patients. The rapid infusion of crystalloids into the body before the arrival of packed red cells is an effective method for preventing hypotension. A reduction in the hydrostatic pressure in the small arterioles is the first event during hemorrhagic hypotension, followed by the movement of interstitial fluid and solute into the intravascular spaces. Crystalloid infusion effectively maintains the intravascular space. Secondly, proteins move into the intravascular space via the lymphatic circulation [36,37]. Crystalloids also help to maintain the intravascular volume of recruited proteins through lymph. Therefore, crystalloid infusion during hemorrhage is reasonable and enhances the restitution of the BV. In the event of massive hemorrhage, a decrease in hematocrit and hemoglobin is observed. Crystalloid infusion may dilute the blood and contribute to anemia, but the largest factor contributing to anemia during hemorrhage is the fluid shift from the interstitium to the intravascular space. The interstitium is squeezed to give protein and fluid to the vessels through the lymphatic circulation [36–38] or by the pressure gradient between the interstitium and capillaries, thereby maintaining BV and reducing the extracellular fluid volume during acute hemorrhage. Such a fluid shift is triggered by hypotension and considerable volume deficits started to be replenished as early as 15 min after bleeding; the volume was maintained for 12 h until blood pressure became normalized [36]. Another study, in sheep, showed that lymph flow increased 6 h after bleeding [39]. Thus, crystalloid infusions for hemorrhagic patients are efficient, in terms of this recruiting mechanism, for irrigating both the intravascular spaces and the interstitium. This could explain why a large volume of crystalloid is necessary to maintain arterial pressure during hemorrhage. In other words, crystalloid infusion can be regarded as a means of irrigating the whole body. Although a large volume of crystalloid is necessary to resuscitate patients in hemorrhagic shock, the effect is transient and is limited by the effective amount; this has been confirmed by mathematical simulation [40,41]. The results of this mathematical model almost agree with our clinical experience, as we feel that there is a ceiling effect of crystalloid therapy for hemorrhagic hypotension (Fig. 4). This simulation employs the values of such parameters as vascular permeability and the ratio of lymph drainage from experimental data. Therefore, this simulation seemed to provide a feasible result (for details, refer to published articles [40,42]).

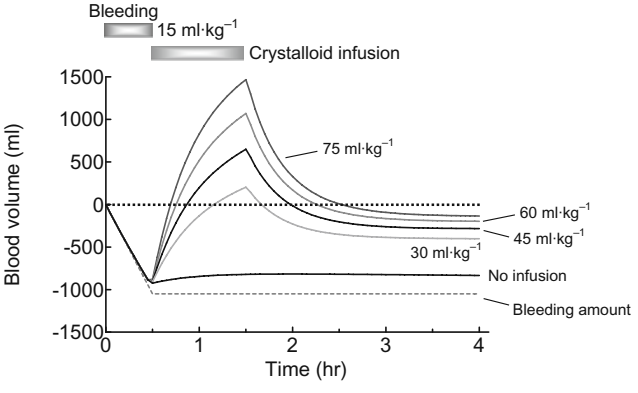

Fig. 4. Volume expansion effect of crystalloid (simulation of water and solute distribution). After15 ml·kg^{-1} of bleeding, crystalloid was administered, at each speed noted on the Fig., for 1 h. Note that even a higher dose of crystalloid does not provide volume expansion to the control level. (Adapted from Tatara from [42], with permission)

BV in the postoperative period

A pathological increase in vascular permeability induces the extravasation of intravascular fluid, lowering the BV. Clinical experience in patients with sepsis with intractable hemodynamic instability has allowed us to recognize that maintaining the intravascular BV is hard to achieve, despite loading with large volumes. Early goal-directed fluid therapy for such patients is a concept in which the early commencement of fluid management is thought to possibly be effective for circulatory control [43]. This concept suggests that circulatory control during the preseptic stage could prevent the vicious circle that leads to shock and uncontrollable vascular leakage. The increase in vascular permeability may commence in the preseptic stage. The postoperative conditions in surgical patients may be similar to this preseptic stage in regard to the presence of systemic inflammation. This concept may explain why BV after major surgery seems to decrease in spite of a large positive fluid balance.

Cardiac patients who have undergone cardiopulmonary bypass and hemodilution exhibit a lower BV after surgery [28], and their BV remains low on the first postoperative day, despite a large positive fluid balance caused by the liberal administration of fluids during surgery (Fig. 5). Such studies suggest that during the postoperative period, a patient's BV may not be determined by the fluid balance and may, instead, be regulated by individual conditions, including hormonal factors, as Barta et al. [44] have demonstrated a contribution of the renin-angiotensin-aldosterone system to BV after cardiac surgery. Thus, BV is not easily manipulated by fluid balance after cardiac surgery, and independently performed studies have confirmed a reduction in BV after cardiac surgery despite a positive fluid balance [45–47].

BV measurements in patients with extensive burns provide another context for discussing the BV status in patients with increased vascular permeability. In a study by Inoue et al. [48] in burn patients, although massive fluid was given according to the Parkland formula, the BV was found to be significantly low, with a value of less than 60 $ml \cdot kg^{-1}$ (Fig. 6), corresponding to 63.2%–77.7% of the values obtained in control surgical patients. The values for the burn patients corresponded to less than the mean –1.5 SD. These findings support the concept that BV can be influenced by pathological conditions and may not be altered just by crystalloid volume loading.

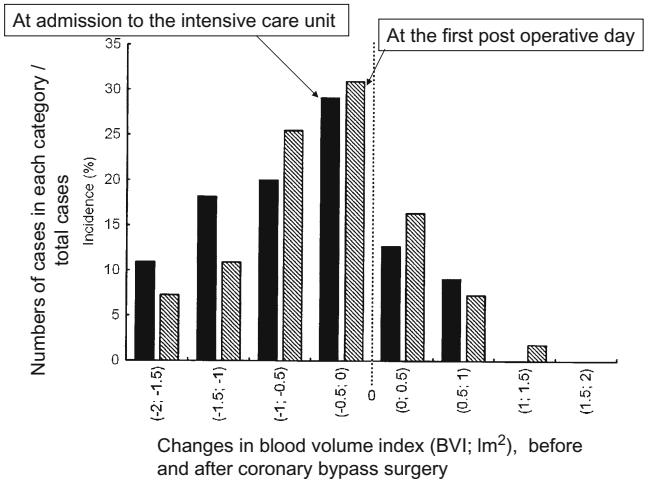

Fig. 5. Reduction of blood volume (BV) after cardiac surgery. Because BV varies between individual patients, BV is standardized by body surface area as the BV index (*BVI*). The frequency distribution of differences in BVI is shown before and after coronary bypass surgery (postoperative-preoperative) within distinct volume ranges following admission to the intensive care unit (*solid bars*) and on the first postoperative day (*hatched bars*). Despite a marked positive fluid balance during surgery, the mean BVI decreased significantly after surgery. Postoperative BVI deficits vs the preoperative values were observed in 78% of the patients; these BVI deficits were profound in 29% of the patients. (Modified from Bremer et al. [28], with permission)

Hormonal control of BV

Hormones from the kidney may be the main determinants of both the plasma volume and the red-cell volume. The red-cell volume is controlled by erythropoietin, and the plasma volume is controlled by the renin-angiotensin system through the reabsorption of sodium and water into the microtubules. The production of erythropoietin is regulated by angiotensin II, so the renin-angiotensin system entrains the production of erythropoietin as part of the effector signals of a feedback loop controlling BV [49]. The efferent limb of BV sensing involves cardiovascular and renal hepatic receptors. It is quite reasonable that these neurohormonal systems control BV. These neurohumoral controls would have a purpose and a target. The assumed target may be optimal oxygen-carrying capacity [19, 49]. It is likely that BV may be controlled to match oxygen consumption and oxygen delivery. Further studies are necessary to confirm this assumed mechanism.

As mentioned above, Barta et al. [44] suggested that the reduction in BV after cardiac surgery correlated with renin-aldosterone. Hirasawa et al. [50] also suggested that renin and aldosterone, as well as epinephrine/norepinephrine were associated with the reduction in BV observed after craniotomy. Catecholamines such as norepinephrine and epinephrine also increase in parallel with renin and angiotensin. It remains to be eluci-

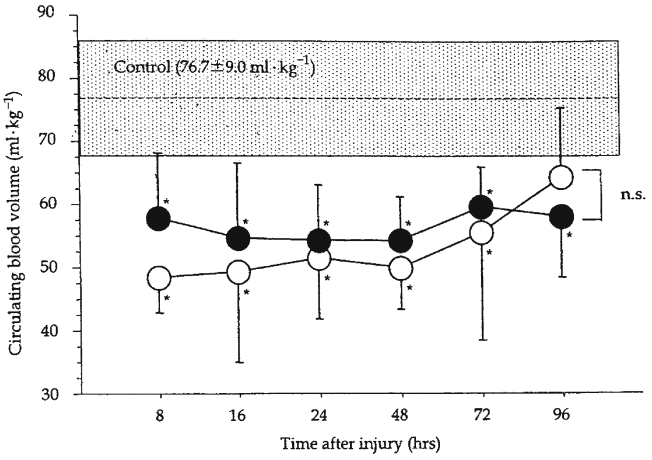

Fig. 6. Comparison of circulating blood volumes between two groups of patients: group I (smoke-inhalation injury group; $n = 10$) and group B (severe cutaneous burns; $n = 6$). The *dotted area* represents the mean and SD of the control value. The *solid* and *open circles* represent the values of group I and group B, respectively. The *asterisks* indicate significant differences between the control level and the values for each group. The control value represents the value obtained in other surgical patients before surgery. The circulating blood volume in both injury groups was significantly lower than the control level, except for that of group B at 96 h after the injury. All the participants were given an ordinary fluid regimen based on the Parkland formula, with an hourly urine output of 1.0 to 2.0 ml·kg^{-1} as the resuscitation endpoint. No significant differences between group I and group B were observed throughout the study period. *n.s.*, Not significant (Adapted from Inoue et al. [48], with permission)

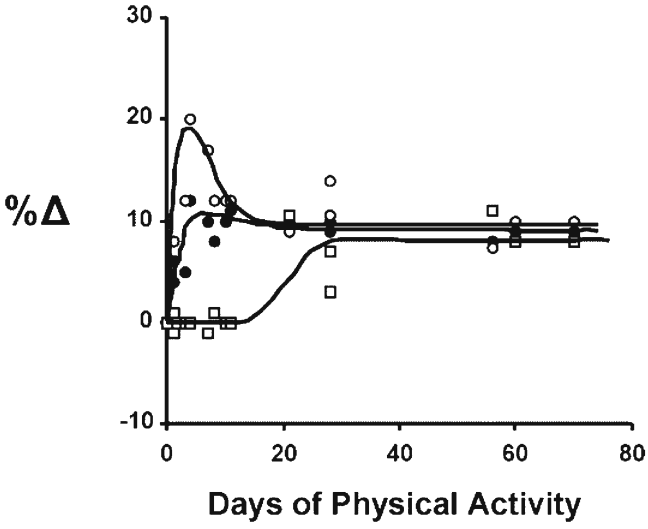

Fig. 7. Estimated time course of relative change (%Δ) in blood volume (*closed circles*) plasma volume (*open circles*), and red-blood cell volume (*open squares*) during adaptation to regular physical activity (e.g., exercise training). *Each point* represents the average change reported in a group of subjects from one investigation. Data were extracted from 18 independent investigations in which all three vascular volumes were reported. (Modified from Sawka et al. [52], with permission)

dated whether these factors contribute synergistically to the determination of BV.

Studies of the physiological control of renin-aldosterone may be a good reference for understanding this mechanism. Exercise requires that the BV be maintained while counteracting fluid loss as a result of dehydration. The plasma volume seems to be supported by the activation of renin-aldosterone during exercise-induced dehydration. Interestingly, in subjects with dehydration induced by exercise a greater plasma volume is maintained than that in subjects with dehydration induced by heat exposure [51]. The oxygen-sensing system seems to regulate BV. A positive correlation between oxygen consumption and BV has also been confirmed [19]. Again, erythropoietin and renin-angiotensin play a major role in determining BV in response to oxygen demand. As shown in Fig. 7, an increase of oxygen consumption caused by exercise training led to an increase in BV in athletes.

These physiological mechanisms for BV control indicate that BV can be adjusted by hormonal factors. However, only a few studies have explored how hormonal factors influence fluid therapy in perioperative patients. The hormonal response may be a long-term response, and may not be involved in the acute phase. However, considering the clinical data noted above, the hormonal response may be exerted earlier than we expect. Further studies are needed to elucidate this interesting system of controlling BV.

Such physiological adjustment of BV is favorable for optimization of the circulation; however, this adjustment may not ensure organ circulation. Mild hypovolemia switches on a compensatory mechanism, but this does not influence blood pressure, although it decreases gut blood flow [53]. The early hormonal response may be an emergent regulatory system. Subsequent long-term adjustment of the circulation may be necessary to optimize the systemic circulation, including organ circulation.

Conclusion

BV changes dynamically in various conditions. This concept is not a new one; rather, it is a very traditional one. Sjoestrand [54] reviewed BV in the 1950s and stated that: "The variation of blood volume between individuals and in an individual should be analyzed from these two view points [size and metabolism of the tissue, circulatory requirements influenced by external circumstances; note by this author] in order to deter-

mine whether such variations are bound by any law". Sjoestrand describes the variation of BV in various physiological circumstances. Probably because the circulation has been managed according to preload parameters since the clinical use of these parameters has become widely accepted, the BV quantity now holds no more interest for clinicians. At present, BV has been only assumed and it has been believed that administered fluid would have a certain effect on BV.

Administered fluids and solutes can generally move throughout the entire body, including the large extra- and intracellular spaces. However, a fraction of the administered fluid, especially crystalloid, may not consistently remain in the intravascular space, as would be expected. We have to understand how BV is physiologically and pathologically controlled. Hormonal factors, rather than fluid therapy interventions, dominate the control of fluid distribution throughout the body. Large variations in BV between individuals can be explained by the hormonal control of BV. BV may be basically an invariant parameter which is not easily controlled by artificial fluid therapy, although BV occasionally becomes variant, a feature that is triggered by internal homeostatic changes. This concept of BV offers basic knowledge for the establishment of fluid therapy protocols.

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