Review

Blood Volume

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THERE is a growing interest in measurement of the circulating blood volume in health and disease. Judging from numerous publications, this procedure is now commonly applied in clinical practice. Several excellent reviews[29, 115, 121] and chapters in books[7, 31, 82] have been written on the subject of blood volume since World War I. Nevertheless, there is still some confusion and doubt about the significance of blood volume measurement, interpretation of results, and application to patient care. The basic difficulty arises from lack of understanding as to what is actually being measured and the inherent shortcomings of the methods employed. According to Gregersen and Rawson, and rightly so, "Methodology has been, and still is, of first importance to anyone interested in determining blood volume or in evaluating results reported by others."

From the point of view of the anesthesiologist, the significance of blood volume measurement in the surgical patient is best summarized by Sjöstrand,[123] ". . . variations in the blood volume between different individuals and under different conditions in one and the same individual imply that the pulmo-cardiac blood volume varies. A small total blood volume implies a decreased pulmo-cardiac blood volume, and as a consequence a decreased circulatory reserve and an increased risk that the cardiac output in connection with an alteration of the blood distribution or a bleeding shall be insufficient. The same effect will also be apparent in an increase of the intrathoracic pressure as by artificial respiration with positive pressure. . . . It is therefore important to realize . . . that the blood volume can be low, and if such is the case all efforts should be made to compensate this by pre-operative blood transfusions. It is likewise important to keep the blood volume under control during and after surgical operations and to pay attention to the incisions which may influence the distribution of blood. . . . Although the above principles are recognized, practical application has been delayed due to the lack of simple practical methods for determining the blood volume."

Today we have practical methods for measuring blood volume, and the purpose of this review is to summarize the pertinent aspects of blood volume measurement which are of interest to the anesthesiologist.

Blood Volume and Circulation

Blood circulates in the vascular system by virtue of the pump action of the heart and peripheral muscle action. Cardiac output is the product of stroke volume and heart rate. The stroke volume varies with the amount of blood that returns to the heart during diastole.[113, 114] From these considerations, there would seem to be a definite relation between venous return of blood to the heart, venous pressure, and the volume of blood that fills the vascular system. Alteration in venous return would directly affect cardiac output and the dynamics of circulation.

The high-pressure arterial system acts as a reservoir of relatively fixed volume and contains approximately 20 per cent of the total blood volume. In an adult, a 30 per cent reduction in arterial capacity would displace a relatively small volume of blood (250–300 ml.).[117] This blood displacement would not appreciably affect total volume, volume distribution, or venous return.

The capillary bed contains about 5 to 7.5 per cent of the total blood volume. Exchange of water and crystalloids between the intravascular and extravascular spaces takes place at this level of the vascular system and alterations in blood volume occur here as an acute adaptation process in order to maintain filling of the vascular bed.

The low-pressure venous system contains 75 per cent of the total circulating blood volume.[117] Venous vessels passively expand to

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accommodate large volumes of blood, contract actively to conform to a reduced volume, and maintain venous pressure and adequate venous return to the heart.[3] Reduction or increase in circulating blood volume of 5–10 per cent in a normo-volemic individual is compensated for either by active contraction or passive distention of the venous bed with no change in central venous pressure or venous return to the heart. Reflex adaptation in venous capacity with an intact autonomic nervous system functions normally, within certain limits, about ± 10 per cent change in circulating volume. Overload of the circulation by 15–25 per cent will increase venous return, enlarge cardiac volume and, in the presence of a weakened or damaged myocardium, lead to early cardiac failure and pulmonary edema. In the presence of a reduced blood volume (15–25 per cent), venous return to the heart is limited; filling of cardiac chambers is inadequate, resulting in a reduced cardiac output.

Venomotor Tone

Changes in venous tone alter distensibility characteristics of the venous vessels, venous pressure, and the return venous flow to the heart.[30] A change in venomotor tone in the presence of a reduced or elevated circulating blood volume may produce a marked alteration in venous return and cardiac filling during diastole. Studies on isolated venous strips *in vitro* and on hand volume[14–16,18] have shown that stimulation of the skin, pain, hyperventilation, positive-pressure breathing, low P_{O_2}, and chilling raise venomotor tone and reduce venous distensibility.[2,3,13] Catecholamines, and in particular norepinephrine,[2,3] have a marked constrictive effect on the venous system, causing a reduction in venous capacity and a rise in venous pressure. Moderate hypovolemia can, therefore, be masked by over-active venous constriction, limiting venous capacity and maintaining or even raising venous pressure.

A rise in P_{CO_2} and drugs that depress sympathetic tone reduce venomotor tone and venous vessels tend to distend readily under pressure resulting in a lowering of venous pressure.[13,14] Changes in venomotor mechanisms that alter distensibility and thereby the capacity of the venous system, may easily induce in a normovolemic patient, hemodynamic changes simulating either hypovolemia or hypervolemia.

Tachycardia

Tachycardia shortens the diastolic period and the duration of venous inflow, and filling of cardiac chambers is correspondingly reduced. The stroke volume is reduced, but the cardiac output may remain normal or even increase owing to the product of stroke volume times cardiac rate. With hypovolemia, the pressure gradient for venous return, the difference between the peripheral and central venous pressure, is reduced, cardiac volume is diminished, and the stroke volume is reduced to the extent that even with an increased cardiac rate the cardiac output is diminished.[1,3] Tachycardia may also have an adverse effect in hypervolemic conditions owing to an increase in pressure gradient and venous return with over-filling of cardiac chambers. Reduction in ejection time causes incomplete emptying of cardiac chambers, a gradual increase in end-systolic residual volume and blood accumulation. Pulmonary edema will ensue as a result of back pressure into the pulmonary circulation.

Red Cell Volume and Plasma Volume

Blood volume is the sum of red cell and plasma volumes. Red cells normally do not cross the capillary membrane and constitute a static volume, a filler of the vascular space. The rates of red cell production and destruction normally proceed at a regular and balanced pace. Changes in red cell volume are seen as a chronic adaptation process to hypoxia or as compensation for loss of red cells. The normal rate of erythropoiesis or red cell destruction does not appreciably alter red cell volume during the interval of a measurement. On the other hand, acute reduction in red cell volume owing to hemorrhage or hemolysis is not readily compensated for by mobilization from reservoirs or rapid red cell production. At this time measurement is apt to be faulty. To compensate for a reduction in cellular volume, plasma volume rapidly expands to fill the vascular system.

Plasma is essentially water-containing protein and crystalloids. The capillary membrane is freely permeable to water and crystalloids, and there is a constant rapid transfer of large

TABLE 1 Fluid Balance at the Capillary Level

Arterial Side			Venous Side		
H.P.	T.P.	Effective H.P.	H.P.	T.P.	Effective H.P.
30	8	22 mm. Hg	15	8	7 mm. Hg
C.O.P. Blood	C.O.P. Tissues	Effective C.O.P.	C.O.P. Blood	C.O.P. Tissues	Effective C.O.P.
25	10	15 mm. Hg	25	11	14 mm. Hg
Effective H.P.	Effective C.O.P.	Driving force	Effective C.O.P.	Effective H.P.	Sucking force
22	15	7 mm. Hg	14	7	mm. Hg

Filtration	Reabsorption	Plasma Volume
Increased filtration	Decreased reabsorption	
Arteriolar dilatation	Depletion plasma proteins	
Rise in hydrostatic pressure		Decreased
Rise in venous pressure		
Decrease in filtration	Increased reabsorption	
Arteriolar constriction	Increased plasma osmotic	
Decreased venous pressure	pressure	Increased

H.P. Hydrostatic pressure.
T.P. Tissue pressure.
C.O.P. Colloidal osmotic pressure.
Adapted from Rushmer,[27] Soderman,[7] and per oral communication from R. G. Wahlin, Professor of Physiology, Mayo Clinic.

quantities of water.[27] Proteins and high molecular weight crystalloids cross the capillary membrane in a selective manner which varies depending on the structure of the membrane in different areas. In the liver the capillary membrane is freely permeable to protein while the choroid plexus is quite impermeable. The net decrease or increase of plasma water content depends on the extent to which the processes of filtration and reabsorption of water are in balance. Under normal conditions, the mean effective capillary pressure and the effective oncotic pressure are in equilibrium and plasma volume is kept relatively stable. Filtration predominates when intracapillary pressure rises; the net result is a loss of water from the intravascular space and a contracted plasma volume. This is seen with a rise in hydrostatic pressure, with arteriolar dilatation, and in particular, with a rise in venous pressure.[7, 27, 28] A reduction in intracapillary pressure is seen with arteriolar constriction or loss of venomotor tone with reduction in venous pressure, causing retention or reabsorption of water from the extravascular space and expansion of the plasma volume.

The osmotic pressure of plasma, the force that tends to retain water in the intravascular bed, varies with the quantity and size of the protein molecules. Changes in osmotic pressure alter the balance between filtration and reabsorption, which is reflected as changes in plasma volume. Depletion of plasma proteins in chronic infections, debilitating disease, liver damage or inflammation and trauma that alter capillary membrane permeability to protein, alter plasma osmotic pressure, causing greater filtration, loss of water and reduction in plasma volume.[7, 29, 30] Finally, one should not overlook the fact that the capillary membrane is under regulatory mechanisms which affect both capillary tone and the permeability characteristics.[31] The sum total of these factors is shown in table 1.

Mechanisms That Regulate Blood Volume

Blood volume is maintained at a fairly constant level by an interplay of many mechanisms.[32, 33, 34, 35] Various receptors, have been credited as sensors in regulating fluid balance. Osmoreceptors in the diencephalon sensitive to changes in plasma osmolarity, linked with the posterior pituitary antidiuretic hormone, tend to retain water. These receptors are not volume sensitive but seem to play a part in water regulation when a volume change produces a shift in osmolarity.

Receptors, "volumeters" sensitive to changes

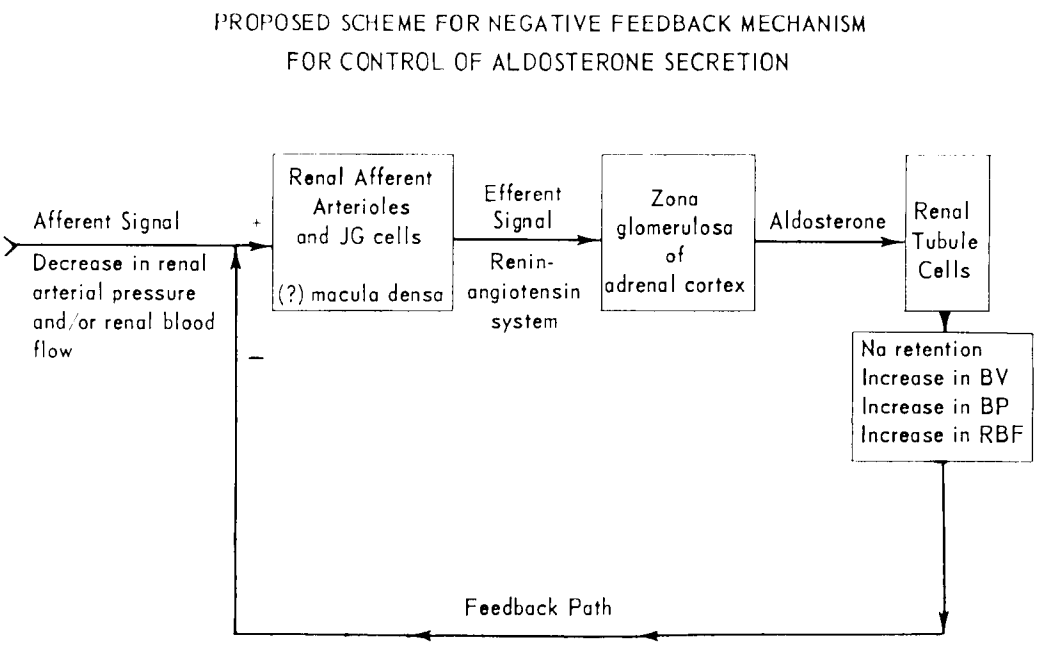


FIG. 1. JG = juxtaglomerular, B.V. = blood volume, B.P. = blood pressure, and R.B.F. = renal blood flow. (Reproduced by permission of Davis, J. O.: The Control of Aldosterone Secretion. Physiologist 5: 65, 1962.)

in volume, both vascular and extravascular, have long been sought. Distension of the thoracic vena cava and right auricle produces diuresis and loss of water.[1-3] This is reversed when the vena cava is less distended. It has been postulated that impulses originating in receptors located in the right auricle and vena cava and transmitted via the vagi[4-7] to the central nervous system regulate pituitary secretion of antidiuretic hormone and aldosterone secretion from the adrenal cortex. It was later discovered that the vagus played a limited role in transmitting afferent impulses from the right auricle.[8-11] Various sites for volume receptors have also been suspected in the left atrium, in the central nervous system, and throughout the vascular tree. There is ample evidence to support the view that there is an independent volume receptor mechanism in the kidney which is sensitive to variations in vascular distension,[12] in the afferent renal glomerular arterioles. A decrease in stretch in the afferent renal arteriole releases renin from the juxtaglomerular cells,[13] activation of the renin-angiotensin system,[14] and production of angiotensin II,[15] which acts on the zona glomerulosa of the adrenal cortex to stimulate secretion of aldosterone. Aldosterone acts on renal tubular cells to promote sodium retention and in turn reabsorption of water. This system is a negative feed-back system whereby an increase in volume, blood pressure, or renal flow causes distension of the afferent renal arteriole which in turn depresses release of renin (fig. 1).

The rate of secretion of aldosterone is also regulated by the plasma sodium level. A low sodium intake or hyponatremia, stimulates while sodium overload depresses aldosterone secretion. No definite relation has been established between potassium levels alone or in combination with sodium levels and aldosterone secretion. ACTH plays some part in the biosynthesis of aldosterone, although the exact mode of action has not been established.[16]

The liver plays an important role in regulating blood volume.[17-19] Antidiuretic hormone, aldosterone and the various hormones that tend to maintain homeostasis are inacti-

vated by the liver. Assuming that these regulatory hormones are produced and secreted at a constant rate, with an increase in blood flow rate through the liver, the rate of inactivation is increased and the blood level of hormones reduced; the result is loss of water by diuresis. With a reduced blood flow through the liver there is a rise in blood level of these regulatory substances causing retention of salt and water and expansion of the plasma volume. Besides regulating blood levels of neurohormones, the liver is responsible for protein synthesis which directly affects osmotic pressure and retentiton of water in the intravascular space.

The complexity of blood volume regulation becomes still more intricate when one tries to assess the effect of anesthesia on blood volume. Stress reactions due to anesthesia and operation, depressant action of drugs on the central and peripheral nervous system, or neurohormonal release, and the duration and site of action of drugs, all tend to affect the interrelated mechanisms.

Hematocrit

Hematocrit represents the volume occupied by red cells expressed as percentage in a given sample of blood. The percentage varies inversely with the plasma volume. Hematocrit determinations have been utilized to indicate red cell volume[27] and blood loss as a guide to replacement. This would be acceptable if expansion in plasma volume occurred simultaneously and volumetrically to compensate for the volume of blood removed from the intravascular bed. Replacement of blood loss by expansion of the plasma volume would alter the proportion of red cell to plasma volume, and hematocrit value would correspondingly be reduced. The extent of hemodilution, however, varies considerably and depends on the quantity of blood lost, preexisting volume, and available fluid in the extravascular space.[27] Hemodilution may be greatly delayed or conceivably absent,[5] and the corresponding drop in hematocrit, minimal and often considerably delayed, when blood loss is incurred on a previously existing hypovolemia, low total body water, anemia, in the elderly debilitated patient[5] or in the presence of a hyperactive venomotor tone.

Red cell distribution throughout the body varies with the caliber of the vessel.[27] Hematocrit determined on a venous blood sample, the large vessel hematocrit (LVH), is not representative of the ratio of red cells to plasma within the entire vascular bed. Whole body hematocrit (WBH) is obtained by measuring red cell volume and plasma volume separately, and is, on the average, lower than the venous hematocrit:

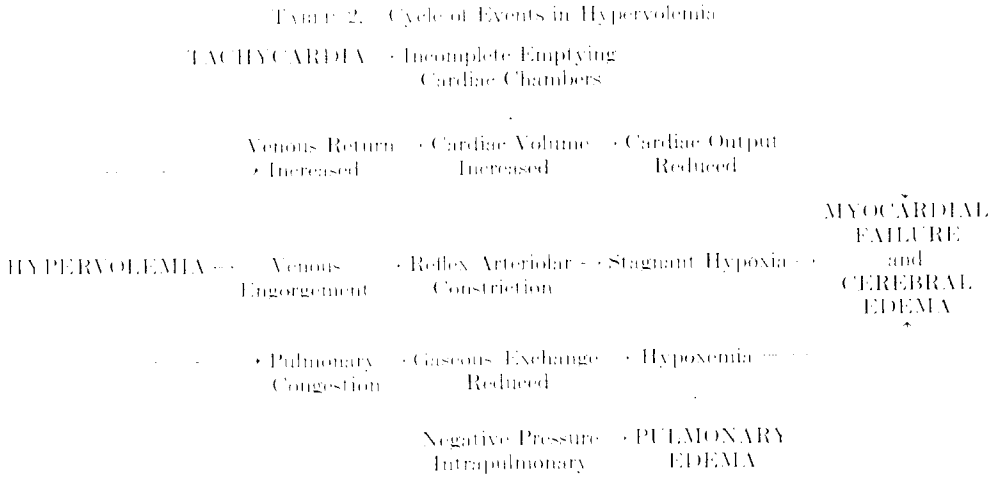
$$\text{WBH} = \frac{\text{Red Cell Volume}}{\text{Red Cell Volume} + \text{Plasma Volume}}$$

The ratio WBH/LVH is 0.91 (F_{cells}).[27, 28] The factor F depends greatly on the value obtained for the WBH which in turn varies with the accuracy with which plasma volume can be measured.[1, 28] Although this value is claimed to be constant, it may vary.[18, 153, 158] Low values[51, 133] have been reported in pheochromocytoma, marked vasoconstrictive states, and higher values in diseases of the hematopoietic system and during pregnancy.[19, 33, 97, 141]

Distribution of Blood

The blood reservoir, low pressure vascular space, plays an important role in regulating venous return to the heart. At the heart level the cardiopulmonary vascular space can accommodate 20–25 per cent of the total circulating blood volume. Below heart level, there are the splanchic area (including the liver and spleen), the lower extremities,[3] and the large venous conduits. The subpapillary venous plexuses that serve to regulate body temperature are on the body surfaces. The major portion of the circulating blood volume can be accommodated in the visceral space alone. Gravitational forces tend to pool blood in dependent portions of the body; a change in position, from supine to erect, in a normal conscious individual, causes 500–1000 ml. of blood to accumulate in the lower extremities.[112, 141, 143] To compensate for this diversion of blood and in order to maintain venous pressure and venous return, 80 per cent of the volume pooled in the lower extremities is diverted from the lesser circulation–blood reservoir located at heart level.[124] Thus the cardiopulmonary reservoir serves as a primary source of blood to adjust for a change in ca-

TABLE 2. Cycle of Events in Hypervolemia



pacity or volume deficit in the central circulation. With a reduced circulating blood volume, the cardiopulmonary blood content is markedly reduced.

From these considerations several important points emerge. With loss of venomotor tone, blood reservoir areas tend to distend more readily; and under the effect of anesthesia large quantities of blood can be pooled in dependent portions of the body. This is particularly important when dealing with hypovolemia. Slow induction of anesthesia in a 15-degree Trendelenburg position seems a logical approach to this problem. Sudden changes in position may divert blood to reservoir areas and cause circulatory collapse.

There must be care in lowering the legs from the lithotomy position, or leveling the table when the patient has been in Trendelenburg position during operation. On the other hand, a patient with hypervolemia will not tolerate the Trendelenburg position for any length of time; and pulmonary edema and circulatory failure can be precipitated when venous return to a weakened myocardium is suddenly increased.

Clinical Evaluation of Blood Volume

Standard methods currently utilized in clinical practice to estimate deficiencies in blood volume have proved of limited value.

Venous Pressure. Changes in venous pressure do not accurately reflect changes in volume. Active venomotor tone tends to equate venous pressure, a steady venous return of blood to the heart thus compensating for variations in blood volume.[36, 135]

Tilt Tests. Response to the head-up tilt test,[71, 135] or mobilization of blood from dependent reservoirs of the body, to improve venous return do not always reflect the state of intravascular volume.

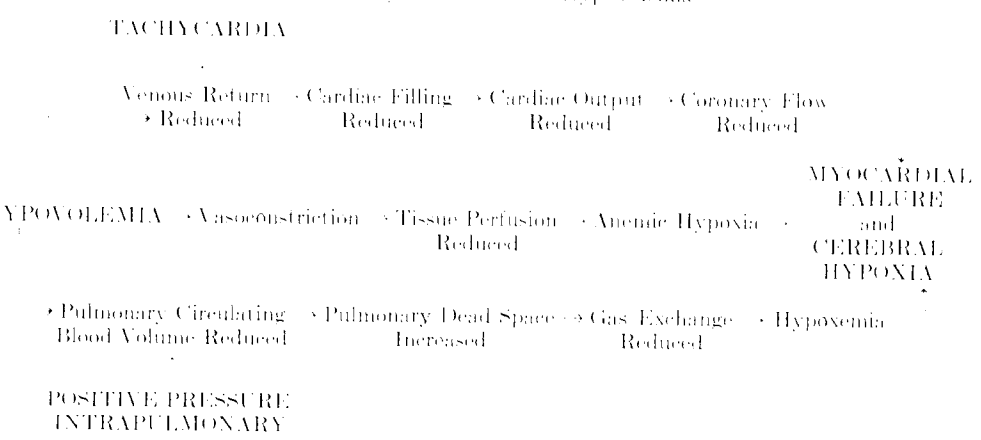
Blood Pressure and Pulse Rate. One may encounter a rise in blood pressure and low pulse rate with blood loss or a drop in pressure with slowing of the pulse rate.[20] Tachycardia is not invariable. One cannot rely on pulse rate, blood pressure, or pulse pressure alone to indicate changes in blood volume. In severe hemorrhage, of course, the clinical signs are diagnostic.

Hematocrit Changes. As noted earlier, expansion of the plasma volume to compensate for blood loss proceeds at a variable rate and extent, depending upon the rate and quantity of blood lost.[139] Emotional reactions, venomotor tone, and the state of hydration greatly alter the hemodilution processes. The hematocrit can remain temporarily within normal limits in the presence of active and extensive blood loss.

Blood Volume and Pulmonary Exchange

In hypovolemic states, the blood content of the cardiopulmonary bed is reduced, shunt systems come into being diverting blood from large areas of the lung capillary surface, physiologic dead space increases,[49] and effective gaseous exchange is reduced. Elevation of intrapulmonary pressure may further reduce

TABLE 3. Cycle of Events in Hypovolemia



blood flow through the pulmonary bed and venous return to the heart.[21, 164] One frequently encounters a steadily declining blood pressure in hypovolemic patients during anesthesia when respiration is assisted by inappropriate intermittent positive pressure on the rebreathing bag. This can be alleviated and venous return improved by introducing in the respiratory cycle a negative pressure on expiration.[59]

The complications that may arise from hypervolemia are just as serious as those encountered in hypovolemic conditions. Frequently, under the effect of anesthetic drugs, the two conditions cannot be clearly distinguished. With hypervolemia the volume of the lesser circulation is relatively increased, and effective gaseous exchange across the pulmonary membrane reduced. An obstructed airway, possibly an increase in negative intrapulmonary pressure, may precipitate pulmonary edema and cardiac failure in the presence of a depressed or diseased myocardium. Tables 2 and 3 present the cycles of events in hypovolemia and hypervolemia and the disturbances produced.

Vasopressors and Vasodilators

The effect of vasopressors on blood volume will vary according to the site of action of the pressor agent, whether the constrictive effect is predominately on the venous or arterial side of the circulatory bed.[59] Norepinephrine produces marked venous constriction,[41, 42, 119, 133] a rise in venous pressure, greater filtration at the capillary level, and the final outcome, a reduction in plasma volume. In contrast, angiotensin II [18, 43, 50, 92] with a predominant effect on the arterial side of the vascular system and precapillary sphincteric constriction, tends to be associated with an increase in plasma volume. This response may be related to the angiotensin-aldosterone mechanism noted previously.

With a reduction in sympathetic tone, vascular resistance and venous pressure, there is a greater reabsorption of fluids at the capillary level from the extravascular space with expansion of the plasma-blood volume.[8, 193] Reduction in venomotor tone in the presence of a reduced circulating blood volume will result in a marked pooling of blood, a drop in venous pressure and venous return, and impairment of cardiac output. The indiscriminate use of blocking agents in the presence of hypovolemia to overcome vasoconstriction and improve tissue perfusion may, therefore, produce catastrophic results on homeostatic mechanisms.[16]

Drugs Utilized in Anesthesia

Changes in plasma volume with drugs commonly utilized for preanesthetic medication and to induce anesthesia can be deduced from the effect these agents have on the cardiovascular system, related pre-existing conditions, blood volume deficit or overload, and the amount of expendable extravascular fluid.[82] In view of the forces that regulate filtration and reabsorption at the capillary membrane,

cyclopropane and ether, which raise venous pressure resulting in a loss of water from the intravascular bed, tend to reduce the plasma volume. Thiopental, morphine and to a limited extent, halothane, tend to reduce venous pressure and systemic pressure favoring reabsorption of water and increase in plasma volume.[2,3] From bleeding experiments in dogs, with moderate blood loss, halothane and thiopental may seem more advantageous than cyclopropane or ether.[2,3,4] These results are in all probability the outcome of fluid shifts at the capillary level, the amount of fluid reserve available from the extravascular space, and the effect of the agent on myocardial contractility (table 1).

TABLE 1 Changes in Plasma Volume with Anesthetics

Morphine	Increased
Cyclopropane	Reduced
Ether	
early	Reduced[1]
late	Increased
Thiopental	Increased
Halothane	?Increased
Spinal	
level T 10	No change
T 5	Increased

Adapted from our own observation,[2] and Price and associates.[3]

Infusions

Normal saline solution (0.9 per cent NaCl in water) does not increase a normal plasma volume for any appreciable length of time but is useful in restoring water and salt losses. Five per cent dextrose in water temporarily draws fluid into the intravascular space from the extravascular space.[4] This is followed by diuresis and rapid loss of fluid. Infusions prepared with high molecular weight crystalloids tend to maintain an elevated plasma volume for longer periods, 12 to 24 hours.[5] The significance of these observations is that in a dehydrated patient, normal saline would be the infusion of choice. For emergency rapid expansion of blood volume following blood loss, dextran or polyvinylpyrrolidone infusions are indicated, but one should remember that a subsequent transfusion to replace the oxygen-carrying elements of blood may produce circulatory overload.

Methodology

Direct techniques for measuring blood volume consist of exanguination and extraction of all available hemoglobin from the body. This procedure has been used in animals and in criminals after death.

Indirect techniques form the basis of present-day measurements of blood volume. Earlier attempts to measure blood volume by dilution of blood were impractical and the results unreliable. In order to obtain a measurable change in blood elements, large quantities of diluent had to be infused into the blood stream. Blood dilution measurement of blood volume is based on the following equation:

$$\text{Blood Volume} = \frac{C_2 \times \text{Volume of Diluent}}{C_1 - C_2}$$

where: C_1 = initial concentration of blood elements and C_2 = final concentration of blood elements after administration of a given volume of diluent.

Present-day methodology is based on the dilution principle whereby circulating blood volume is the diluting volume for measuring a change in concentration of a known tracer element introduced in small volume into the blood stream. In essence, this is the reverse of blood dilution measurement mentioned above. Blood volume is calculated according to the following equation:

$$\text{Blood Volume} = \frac{C_1 \times \text{Volume of Tracer}}{C_2}$$

where: C_1 = concentration of tracer, $C_1 \times$ Volume = total amount of tracer administered and C_2 = final concentration in blood.

Prerequisites of tracers utilized for indirect measurement *in vivo* by the dilution principle are:

(1) The tracer should be easily, accurately and quantitatively identified in blood.

(2) The tracer should be able to be administered in concentrated solution; volume of tracer solution should be small so as not to affect the overall blood volume.

(3) The tracer should have no harmful effects and should not be reactive or altered in the presence of blood.

(4) Above all, the tracer, when introduced into the blood stream, should remain in the

intravascular space for the duration of the measurement.

Radioactive tracers have definite advantages over dyes. Radioactive analysis of tracers is specific, and the tracers can be easily identified and quantitatively measured in minute concentrations. Discoloration or changes in the constituents of the blood sample do not interfere with quantitative measurement of the tracer.

Measuring Blood Volume by Dilution Methods

In order to measure total circulating blood volume, two types of tracer material should be used, each measuring primarily the component of blood in which it is distributed: a plasma protein-bound tracer that is distributed in plasma and, therefore, measures primarily plasma volume, and a red cell-bound tracer for measuring primarily red cell volume. Blood volume is the sum of these two measurements, plasma and red cell volume.

Plasma Protein-Bound Tracers for Measuring Plasma Volume

Of the many tracers that have been used to measure plasma volume the two most commonly used plasma protein-bound tracers are Evans blue (T-1824)[85] and radioactive iodinated human serum albumin (I-131, RIHSA).[109, 110] High-molecular-weight dextran[115, 118, 120] has been used, but chemical analysis for this tracer is laborious.

Certain difficulties are encountered with the behavior of plasma protein-bound tracers in blood. Plasma protein-bound tracers cross the capillary membrane into interstitial space and are detectable, in measurable quantities, in the lymphatic system within minutes from the time of injection.[95, 96] Therefore, a larger volume is actually measured, the actual plasma volume plus a portion of the extravascular space fluid.[5] The rate at which the tracer is lost from the intravascular space depends upon the changes that occur in capillary permeability[142, 143] which vary with changing physiologic conditions and existing pathologic states.

In order to correct for the rate at which the plasma protein-bound tracer is lost from the intravascular bed, several blood samples are withdrawn, analyzed, the concentrations plotted against time and extrapolated to give concentration at zero time.[85] There is doubt as to whether one actually measures true plasma volume and the validity of these measurements are questionable.[85] Plasma volume, when measured with either Evans blue or I-131 gives identical results.[85] Measurements of plasma volume performed in normal individuals with I-131 and high-molecular-weight dextran[28] (average molecular weight, 194,900) show a difference of 6 per cent, a lower volume measurement with dextran. Measurement of plasma volume in edematous patients resulted in volumes that were higher by 9.3 per cent with I-131 than with high-molecular-weight dextran.[28] The significance of this observation rests on the fact that there are alterations in capillary permeability and the rate of transfer of tracers across the capillary membrane will vary with the size of the molecule. These differences in plasma volume measurement definitely affect the F_{cell} factor noted in the section on hematocrit.

Red Cell-Bound Tracers for Measuring Red Cell Volume

Normally, red cells remain in the circulation and do not cross the capillary membrane. Owing to the great affinity for hemoglobin, carbon monoxide has been used as a tracer to measure red cell volume.[7, 8, 85, 89, 105] Carbon monoxide is introduced into the circulation by inhalation in harmless concentrations. The technique rests upon accurate measurements of carbon monoxide in blood and in the rebreathing bag. The difficulty encountered with carbon monoxide is that myoglobin and other pigments tend to absorb the gas[147] and volume measurements are, on the average, 10 to 12 per cent higher than with other techniques.[89] Although correction factors have been introduced, CO is rarely employed for blood volume measurement in this country.

Of the various radioactive isotopes presently available for labeling red cells, Fe-59[51, 91, 95, 107] is the only one which labels red cells *in vivo*. Red cells labeled with P-32[43, 45, 88, 104, 105] and K-42[43, 74, 84] are unstable and are not commonly used in clinical practice. Chromium-51,[51, 120, 150] first introduced by Sterling and Gray,[51, 95, 97] has gained wide use for labeling red cells. Hexavalent salt of Cr-51,

rapidly penetrates the red cells *in vitro* and firmly tags the hemoglobin radical; it is only liberated when the red cell is destroyed. The chromium is changed to a reduced form which can no longer penetrate the red cell membrane and is excreted rapidly.

Labeled red cells, once introduced into the circulation, mix freely with the circulating red cell volume and repeated sampling show no loss of concentration unless there is blood loss. Successive measurements of red cell volume are accurate and reproducible.

Simultaneous Measurements of Plasma and Red Cell Volume

For investigative work two tracers,[4,30] each distributed in their respective blood compartments are used; a dye for plasma volume and labeled cells for red cell volume. The technique is tedious and time consuming. For routine measurements in clinical practice and for the sake of convenience, one tracer is commonly used to measure blood volume. The dilution of the tracer is considered to represent the specific component of the blood volume, and by measuring the hematocrit of a blood sample, the other component, either plasma and red cell volume, is calculated. Use of a single tracer to measure blood volume introduces errors. The magnitude of the error varies with the technique used and the compartment of blood which is primarily measured and used as a basis to calculate both components. Blood volume is, therefore, measured either by a plasma-hematocrit or red cell-hematocrit calculation.

As already noted, protein-bound tracers primarily measure plasma volume and this entails the inherent error of loss of tracer from the intravascular bed during equilibration time.[4] In order to compensate for loss of protein-bound tracer from the intravascular bed during mixing time, three samples of blood are taken, analyzed, concentration plotted versus time and the curve extrapolated to zero time in order to obtain the corrected concentration before disappearance from the intravascular bed. Extrapolation of dilution curves is not always as simple as it seems. The hematocrit in turn may be erroneous due to technical difficulties in withdrawing the blood sample. Venous hematocrit does not reflect the distribution of red cells throughout the body and is corrected to represent whole body hematocrit.[25] Venous hematocrit is first corrected for trapped plasma[26, 125, 156] by an approximate average factor of 0.96 and for an approximate body hematocrit factor of 0.91.[25] Red cell volume calculated from a plasma volume measurement should be considered inaccurate.

Blood volume measured with a red cell tracer underestimates the total volume by 10 per cent. The same reservations apply to the hematocrit in this instance. The measured red cell volume itself is accurate and the results reproducible. A loss of blood can be detected by a deficit in red cell volume obtained with labeled cells.

In our experience over the past six years with blood volume measurements performed in a variety of pathologic conditions, we have found that if a single tracer is to be used, the red cell method gives reproducible and reliable measurements. Other investigators voice a similar opinion. For evaluation of surgical patients preoperatively,[5] during operation and postoperatively,[6] labeled red cells seem to serve the purpose best. Simple techniques[7] have been developed whereby either banked cells (O-Rh-negative cells) tagged with Cr-51 are utilized or the patient's cells tagged and prepared for reinjection within minutes.[4] To reduce errors in volumetric measurement of aliquots for radioactive analysis, all blood samples are analyzed in a plastic coil.[7]

Normal Values

Differences in the normal values obtained for blood volume stem from the variety of methods employed for measurment and the body parameters used in the calculations:[85] body weight, lean body weight,[71] height and weight,[93] height and weight squared[31] or cubed, or surface area. Normal values vary according to age,[51, 98, 124] sex, environment,[35, 44, 77, 126, 137, 146] and physical activity. Basically, blood volume is a function of body metabolic requirements.[21, 152] It is difficult in an ever changing dynamic system, such as the human body, to provide values according to a strict scale. Body requirements vary and change in the presence of pathologic states.

In our laboratory we have established minimal values based on measurement of blood volume with tagged red cells and on body weight. Although the values presented in table 5 seem lower than the average reported,

TABLE 5. Optimal Values for Normal Blood Volume in Milliliters per Pound of Body Weight

	Men	Women
Red cell volume	12.0	11.0
Plasma volume	18.0	16.5
Total volume	30.0	27.5

These values may be modified to correct for:
(1) Weight loss: Marked weight loss within 6 months normal values taken at original weight. Gradual weight loss over a long period normal values taken at present weight and raised 10 to 15 per cent.
(2) Obese and short normal values reduced by 10 per cent.
(3) Elderly patient normal values reduced by 10 per cent.

these figures are presented only as a guide for evaluating a minimal volume requirement. It is our opinion that the minimal requirement for red cell volume in a patient who is to undergo operation should be 10 ml. of red cell volume per pound of body weight; and as a general rule, in an adult patient, less than 1,000 ml. of red cell volume invites trouble during the anesthesia.

Blood Volume Changes in Pathologic Conditions

It is not always easy to predict what the blood volume change will be in pathologic conditions.[31] During anesthesia, a labile blood pressure or fluctuating pulse rate have been seen in either hypo- or hypervolemic states. With loss of fluid,[34] in diarrhea, burns or peritonitis, one expects to find a contracted plasma volume. With bed rest,[143] sedentary existence, chronic infection and active bleeding, the red cell volume may be low. Chronic hypoxia,[18] pulmonary insufficiency, cardiovascular anomalies[76, 119] with arterio-venous shunts,[78] are associated with hypervolemia and polycythemia. Hypervolemia is often seen in individuals with repeated small hemorrhage.

Table 6 presents blood volume measurements obtained on two patients. Both patients presented identical histories of vaginal bleeding. Patient *A* showed a marked compensatory response with an increase in plasma volume and no blood replacement was required. Patient *B* showed a decreased response; she required 1,000 ml. of blood preoperatively to compensate partially for pre-existing deficiency, and additional replacement during operation.

Blood measurements performed in the preoperative period serve to determine the extent of deficit or plethora in plasma or red cell volume.[132] The values obtained are valuable for the anesthesiologist in the management of the patient during the operation. It helps to determine when, how much, and what fraction of blood should be given, and whether cardiovascular and pulmonary complications may be expected owing to a deficit or increase in circulating blood volume. In the postoperative period, it is important in establishing the origin of refractory hypotension and shock.[32, 53, 127]

Many authors have stressed the importance of blood volume measurements before, during, and following surgical procedures.[16, 36, 143] This is particularly true in the very young and in the geriatric patient.[7, 9] Postoperative mortality and morbidity in the geriatric patient can be greatly reduced when these patients are prepared preoperatively and carefully followed with blood and fluid replacement, guided by blood volume measurement.

Blood Loss During Operation

The amount of blood lost during an operation can be evaluated by collecting and measuring the blood in suction bottles, by extraction of hemoglobin from sponges, or comparing body weights before and after operation. The values obtained are helpful, but do not reflect the amount of blood actually present within the intravascular space at a given time. Blood volume measurements assess the amount of circulating blood provided that active bleeding is not taking place. A patient with pre-existing hypovolemia may not tolerate blood loss under anesthesia while a patient with hypervolemia may tolerate a reduction in circulating blood volume with little effect. A patient in good physical condition can tolerate well a 25 per cent deficit in red cell volume.

In present-day air-conditioned and humidity-controlled operating rooms, water loss[74] by

TABLE 6. Blood Volume Measurements from Two Patients

Case A	Case B
38 year old, F., Wt. 152 pounds	32 year old, F., Wt. 156 pounds
Uterine fibroids	Uterine fibroids
Spotty bleeding	Spotty bleeding
Elective hysterectomy	Elective hysterectomy
B.P. 105/65	B.P. 120/70
Pulse 65	Pulse 75
Het. 30.2	Het. 42.0
Hgb. 9 g. 100 ml.	Hgb. 13.5 g. 100 ml.

	Normal Values	Measured Values	Per Cent Deviation	Normal Values	Measured Values	Per Cent Deviation
B.V.	4,180	6,386	+52	4,290	2,474	−42
R.C.V.	1,672	1,756	+ 5	1,716	944	−45
P.V.	2,508	4,630	+85	2,574	1,530	−41

B.V. Total blood volume calculated from a measured red cell volume with Cr-51 labeled red cells.
R.C.V. Red cell volume.
P.V. Plasma volume obtained by subtracting red cell volume from calculated total blood volume.
Case A: Reacted to continuous intermittent bleeding with hypervolemia. She required no blood during operation.
Case B: Compensation for repeated blood loss by limiting vascular bed to the reduced blood volume through vasoconstriction. Two pints of whole blood given prior to operation, one pint during the operation.

evaporation from exposed viscera and extensively denuded body surfaces may be considerable, and may present problems in the postoperative period. Excessive water loss alters the proportion of red cell to plasma volume and a rise in hematocrit found immediately postoperatively later drops rapidly with hydration. This gives the false impression that blood is being lost and compensated for by hemodilution. Cooling during operation also gives a false sense of security in the immediate recovery period. Reduced body temperature causes peripheral vasoconstriction and hemoconcentration which may be misinterpreted in relation to blood replacement for loss during operation.

Blood losses during various surgical procedures have been reported by many authors. There is a definite relationship between the amount of blood lost, dexterity of the surgeon, duration of operation, metabolic rate, infection, and condition of the tissues. Blood loss in trauma is invariably underestimated; accumulation of blood or plasma in the soft tissues and postoperative oozing cannot be predicted nor determined by hematocrit change, visual estimation, or weight measurements.

Comment on Routine Transfusion for Elective Surgery

Blood, red cells in particular, is a rare commodity for which there is no substitute. For replacement of the oxygen carrying element of blood, one must rely on human volunteers as the only source of supply. In recent years the use and misuse of blood has led to an appeal against promiscuous transfusion with special emphasis on the single transfusion.[34] The hazards associated with blood transfusion are many.[35] However, one point will be stressed here; the correct approach is, that before blood is withheld or administered, one should establish beforehand, by blood volume measurement, the quantity and fraction of blood necessary to correct a given deficit. A single pint of blood may mean survival in the event that a volume deficit exists, or death follows inadvertant overload. It is extremely difficult to establish beforehand, from a hematocrit reading, hemoglobin concentration or red cell count, what the blood volume is, or the volume of red cells or plasma actually circulating in the vascular bed.

Conclusions

From observations gathered over the past years and reported in this review, the following conclusions may be drawn:

(1) Currently accepted laboratory tests do not indicate the amount of blood circulating in the vascular bed; the only logical way to establish the fact of blood deficit or overload is by measurement of the circulating blood volume.

(2) Of the methods presently available to determine blood volume, it is our belief that the red cell tracer technique is the method of choice. Labeled cells primarily measure, with accuracy, the vital oxygen carrying element of blood.

(3) One cannot predict the deficit prior to or the amount of blood lost during operation.

(4) The benignity of the postoperative course and full recovery are directly related to properly managed supportive blood volume therapy.

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