The art of treating cardiovascular insufficiency, "shock," is to prevent it. One of the basic parameters that plays a major role in maintaining homeostasis and tissue perfusion is the amount of blood that fills the vascular tree.

From every day experience we find that the accepted standards and indices for the quantitative adequacy of the circulating blood, such as hemoglobin-gms and hematocrit percents, are not adequate and do not reflect volume or mass. The laboratory tests that we have habitually adopted as guidelines denote percentage concentration per unit volume and not absolute amounts. There is all the difference in the world between an actual available volume and just a concentration. A patient may bleed to death, and yet, the hematocrit will show no changes; in fact, in some instances, it may rise, which would normally indicate improvement.

The extracellular fluid volume (EFC) comprises two fluid spaces—the intravascular and interstitial fluid volume. These two fluid spaces are in constant equilibrium and are measured simultaneously as one compartment. It is important to differentiate between the intravascular fluid volume and the interstitial fluid volume (IFV). The interstitial fluid volume is a buffer zone through which all metabolic elements have to cross either to reach or to leave the cell and at the same time acts as a reservoir of fluid to back up changes in the intravascular fluid volume in order to maintain an adequate venous return and cardiac output.

In recent years several papers have appeared in the literature advocating infusion of large quantities of crystalloid solutions, balanced salt solutions, to replace deficits in blood volume.1, 2 Some investigators prefer infusions of colloids or macromolecules to sustain intravascular volume. Specific regimen of replacement has been suggested—replace each ml of blood with 3-4 ml of crystalloid infusion. In most instances, these reports have been established by experiments conducted on animals and the information transposed to humans, regardless of the physiological age or systemic conditions of the patient.

Such physiological trespasses have led Moore and Shires3 to publish an editorial entitled Moderation, which
summarizes their concern, as investigators and clinicians, and calls to the attention of practicing physicians about judicious fluid and blood replacement in the surgical patient. The following is the closing paragraph of this editorial: “Instead of any such rule of thumb, the surgeon should carry on with his established habits of careful assessment of the patient's situation, the losses incurred, and the physiological needs in replacement. The objective of care is restoration to normal function of organs, with a normal blood volume, functional body water and electrolytes. This can never be accomplished by inundation."

With the patient's physiologic needs as guidelines in fluid therapy, actual measurements are necessary to determine the amount of blood or fluid the patient needs to reestablish a normal physiological state, red cells, plasma, crystalloids, colloids and fluids. This report summarizes our observations on blood volume and ECF measurements in surgical patients.

METHOD

A technique was developed whereby plasma, red cell and ECF volume were measured simultaneously utilizing three radioactive tracers.

Plasma volume is determined by the extent of dilution of 125I labeled albumin in plasma and red cell volume with 51Cr labeled red cells. These two nuclides have different gamma energies and are measured simultaneously on whole blood samples by a dual channel scaled analyzer in a specially designed well-type scintillation counter.* Blood samples drawn in plastic syringes serve as the counting container and are inserted into two geometrically related openings in the counter for radioanalysis.4

Extracellular fluid volume is measured in a separate system as a sulfate (35S) space. Sulfur-35, a weak beta-emitting nuclide, was prepared in a protein-free filtrate from plasma samples and measured in a liquid scintillation system.5,6

Four 10 ml blood samples were drawn in heparinized syringes. A pre-mix sample was drawn prior to the administration of the tracers and three postmix samples were drawn following the administration of the tracers at 15, 30 and 60 minute intervals.

Red cell, plasma volume and extracellular fluid volume are calculated according to the basic equation:

\[
\text{Dilution Volume} = \frac{\text{Quantity of Tracer Administered}}{\text{Net Final Concentration of Tracer in Sample}}
\]

NORMAL VALUES

Blood volume varies with metabolic needs and tissue requirements. Normal values based on body weight do not reflect accurately predicted red cell or plasma volume for a particular individual. Norms calculated as a ratio to body surface are more realistic and are adaptable to various clinical conditions. For this purpose the values established by Hidalgo, Nadler, and Block for blood volume have been utilized as predicted values.8,8

To compute red cell and plasma volume, a corrected average 40 percent hematocrit has been adopted to represent the normal distribution of

*Omniwell-Picker-Nuclear Corp.
the red cell volume in the body as a whole.

\[ B.V. = 0.0234H^{0.725}M^{0.423} - 1.229 \quad \text{(MALES)} \]

\[ B.V. = 0.0248H^{0.725}M^{0.425} - 1.954 \quad \text{(FEMALES)} \]

\[ H = \text{Height in centimeters.} \]

\[ M = \text{Body weight in kilograms.}^* \]

Since the extracellular fluid compartment comprises both plasma and interstitial fluid volume, we found that there is closer correlation between the ECF volume as a ratio to plasma volume, rather than an arbitrary value equivalent to 20 percent of body weight. The difference between ECF and plasma volume represents interstitial fluid volume.

**FLUID THERAPY**

Crystalloid and macromolecular solutions, when administered intravenously, alter fluid volume in the two compartments differently — interstitial and intravascular. One-thousand ml of a test solution was administered and the distribution of fluid between the interstitial and plasma compartments was compared before and one hour after the volume of fluid was administered by measuring plasma and ECF volume.

Balanced salt solution (Ringer's), when administered intravenously, followed a normal distribution pattern between the interstitial fluid space (IF) and intravascular space (IV) in a 3:1 ratio. From these observations one can infer that to raise intravascular volume by one unit volume, four units of balanced salt solution should be given.

Six percent Dextran '75,' a macromolecular solution, when administered intravenously, was retained in the intravascular space. In fact, there was a slight increase in intravascular volume beyond the amount of Dextran administered. The normal ratio of distribution of IF:IV did not remain in effect. The difference in response lies in the fact that the oncotic pressure exerted by the macromolecular polysaccharide solution tends to pull fluid from the interstitial to the intravascular space; moreover, the Dextran molecule seems to bind water.

**EFFECT OF RESTRICTING FLUID AND FOOD INTAKE**

Control measurements were effected the night before and kept N.P.O. for 12-18 hours. The following morning and just prior to surgery measurements were repeated. The patients in this study received no preoperative enemas the night before or premedication. In all instances there was a loss of 1000-1300 mls of fluid.

**HEMATOCRIT**

The hematocrit percent denotes the volume that red cells occupy in a unit volume of blood. In effect it is an index equivalent to concentration and does not reflect intravascular volume.

**CASE PRESENTATIONS**

Two patients with fractured hips developed hypotension upon induction of anesthesia. Case (A) went into mild pulmonary edema; Case (B) needed blood to re-establish an adequate circulation.

**Case (A):** F. V., an 84-year-old female, 5'8", 120 lbs., B.P. 190/100, P. 76, CVP 9 cms water.

The patient went into hypotension upon induction of anesthesia with signs and symptoms of cardiac decompensation.

**Case (B):** B. B., a 92-year-old female, 5'4", 121 lbs., B.P. 160/100, P. 80, CVP 11 cms water.

---

*Tables for male and female values have been established and are available from Picker Nuclear Corp., Publ. No. 60-30.
(CASE A)

<table>
<thead>
<tr>
<th>Expected Normals</th>
<th>Measured</th>
<th>Differences</th>
</tr>
</thead>
<tbody>
<tr>
<td>Red Cell Volume</td>
<td>1464</td>
<td>1750</td>
</tr>
<tr>
<td>Plasma Volume</td>
<td>2016</td>
<td>2600</td>
</tr>
<tr>
<td>Total Blood Volume</td>
<td>3480</td>
<td>4350</td>
</tr>
<tr>
<td>Hematocrit % (Corrected)</td>
<td>44.2</td>
<td></td>
</tr>
</tbody>
</table>

(CASE B)

<table>
<thead>
<tr>
<th>Expected Normals</th>
<th>Measured</th>
<th>Differences</th>
</tr>
</thead>
<tbody>
<tr>
<td>Red Cell Volume</td>
<td>1460</td>
<td>1000</td>
</tr>
<tr>
<td>Plasma Volume</td>
<td>2015</td>
<td>1900</td>
</tr>
<tr>
<td>Total Blood Volume</td>
<td>3475</td>
<td>2900</td>
</tr>
<tr>
<td>Hematocrit % (Corrected)</td>
<td>38.4</td>
<td></td>
</tr>
</tbody>
</table>

The patient went into hypotension upon induction of anesthesia with signs of inadequate cardiac output.

**WATER-LOGGING THE PATIENT POSTOPERATIVELY**

With the liberal use of balanced salt solutions there is a tendency to overload the patient with fluid with no apparent reflection of overload on the CVP.

**HEMOCONCENTRATION AND DEHYDRATION PREOPERATIVELY**

Patients with a deficit in ECF have no reserves to hemodilute or compensate in the event of vasodilation or blood loss.

**CASE (C): J. B., a 63-year-old male, 6', 185 lbs., developed hypotension upon induction of anesthesia. As a result, surgery was postponed until a later date. After proper hydration over a period of two days, he was again anesthetized and his blood pressure remained stable throughout the induction period of anesthesia and during the whole surgical procedure.**

This patient, although normovolemic, had a 2.3 liter deficit in ECF.

<table>
<thead>
<tr>
<th>Red Cell Volume</th>
<th>Measured</th>
<th>Differences</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma Volume</td>
<td>2220</td>
<td>2350</td>
</tr>
<tr>
<td>Total Blood Volume</td>
<td>3330</td>
<td>2620</td>
</tr>
<tr>
<td>Hematocrit % (Corrected)</td>
<td>5550</td>
<td>48.8</td>
</tr>
<tr>
<td>Plasma Protein (gms%)</td>
<td></td>
<td>7.3</td>
</tr>
<tr>
<td>Plasma Osmolality (mOs/Kg)</td>
<td>294</td>
<td></td>
</tr>
<tr>
<td>Extracellular Fluid Volume</td>
<td>16.0 L</td>
<td>13.7 L</td>
</tr>
<tr>
<td>Total ECF (Equilibrated-60-min-Urine)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
TABLE I (CASE D)
TWO DAYS POSTOPERATIVE LYSIS OF ADHESIONS
(FEMALE, 272 lbs.)
Pulse Rate 130, B.P. 180/110, C.V.P. 3 cms. H₂O, Urine Output 50 ml/hr

<table>
<thead>
<tr>
<th>Measured Values</th>
<th>Values For Ht. &amp; Wt.</th>
</tr>
</thead>
<tbody>
<tr>
<td>(A)</td>
<td>(B)</td>
</tr>
<tr>
<td>Red Cell Volume (ml)</td>
<td>2750</td>
</tr>
<tr>
<td>Plasma Volume (ml)</td>
<td>4125</td>
</tr>
<tr>
<td>Total Blood Volume (ml)</td>
<td>6875</td>
</tr>
<tr>
<td>Hematocrit %</td>
<td>44.0</td>
</tr>
<tr>
<td>Hematocrit % (Body)</td>
<td>40.0</td>
</tr>
<tr>
<td>F&lt;sub&gt;cell&lt;/sub&gt; Ratio</td>
<td>0.91</td>
</tr>
<tr>
<td>Plasma Osmolality (mOs/Kg)</td>
<td>290-300</td>
</tr>
<tr>
<td>Protein (gms %)</td>
<td>7.8</td>
</tr>
<tr>
<td>E.C.F. Volume (Liters)</td>
<td>22.7</td>
</tr>
<tr>
<td>Total Available E.C.F.</td>
<td></td>
</tr>
</tbody>
</table>

*Weight corrected for obesity.
**Values calculated according to body surface.

E.C.F. = 4.5 x expected Plasma Volume (Females).

sents measured values. One can note the marked measured overload in extracellular fluid volume (25 L — Column B) compared to expected values based on body surface (Column C — 16.2 L).

In this patient an infusion of 6 percent Dextran '75' was considered and following the administration of 500 ml her general condition improved. Her pulse rate dropped to 90 beats per minute, her dusky cyanotic color disappeared, venous pressure rose to 8 cms water and her urine output increased from 50 ml per hour to 150-200 ml per hour.

DISCUSSION

One is often confronted by a divergence of opinion when reviewing the literature and finding continuous changes in attitudes, concepts and even "revolutions" in fluid therapy. In some instances, such reports eminate from the same authors at different time intervals or from rival institutions. For example, we find that in one paper the authors have no use for blood volume measurements. A few years later, the same senior author changes his mind to state that the only rational way to follow replacement therapy is by blood volume measurements. Most of the changing patterns are basically due to two factors: (1) poor methodology and understanding of what and how measurements are performed and (2) applying physiological concepts and interpretation to measured values.

From continued experience with blood volume measurements over the past 14 years and ECF measurements for the past 4 years, we have come to report on numerous occasions two important observations: (1) results of experiments conducted in lower animals are not necessarily applicable to all species and specifically to man and (2) whenever volume measurements are performed, applying the dilution principle, blood sampling should be drawn at the time the tracer has been thoroughly mixed with the volume or medium being measured and corrections should be allowed for the quantity of tracer that is eliminated from the space being measured during the period denoted as mixing or equilibration period. This applies to all dilution-measuring techniques, and in this instance, when measuring red cell, plasma and extracellular fluid volume.
What is a normal value? This is a debatable question and, here again, sound judgement is important. Physiological needs are the basis for determining values; nevertheless, guidelines are needed. Different body parameters have been utilized as a basis to establish normal expected values for blood volume. Norms based on body weight alone presume that body composition of the patient is within normal limits—the distribution of the elements that constitute body mass—fat and lean body mass. This is far from being so: wide variations in fatty tissue will affect expected values. For this purpose, normal expected values for blood volume determined on the basis of body surface and ECF volume, as a function of plasma volume, seem to be realistic and fit the wide variations one meets in a hospital population.

Although the relationship of plasma volume to ECF volume seems to remain fairly constant under normal physiological conditions, in our studies, we were unable to predict the ECF volume from the measured plasma volume nor could we reconcile the figures by introducing correction factors to account for deviations in osmolality or protein content of plasma to equate the actual measured values. We have observed that in some patients with a normal blood volume that the ECF volume was contracted, while in others the reverse situation prevailed.

The normal transfer of fluid from the interstitial space to the intravascular space, following loss of vascular tone or hemorrhage, takes effect in a matter of seconds. These physiological responses tend to maintain intravascular blood volume and adequate venous return. When the interstitial fluid volume is contracted, this response is greatly delayed, or even fails to take effect. There must be a sufficient quantity of free interstitial fluid and patent capillaries in the circulatory circuit to permit fluid transfer.

It is important to realize that some patients may reach the operating table in a state of dehydration with a normal hematocrit and blood volume and respond adversely to anesthesia and blood loss. Proper preoperative hydration, especially in the chronically ill and geriatric patient, is important. An adequate ECF volume will act as a safeguard for maintaining intravascular volume in case of blood loss or vasodilation resulting from induced depression of the sympathetic autonomic nervous system and central nervous system.

We find in the literature that we are going through a period of massive fluid replacement for the purpose of circumventing the use of blood. We read that an empiric hematocrit range is the determining factor as to when blood should be given and gradually the term “octane” is added to the “gallons” of fluid given, indirectly inferring that the red cell mass should be respected. The real crux of the discussion appears in a final statement: “... or whatever appears a reasonable physiological level.”

Balanced salt solution tends to equilibrate between the interstitial and intravascular compartments in a 3 or 3.5:1 ratio. To raise the intravascular volume by one unit volume, one should administer approximately 4 unit volumes of fluid. This is where the magic figures of 3-4 ml replacement for each ml of blood loss came about. It is obvious that such a regimen of replacement will result in overhydration without any visible signs of overload or edema.
The deleterious effects of overhydration are quite apparent when one takes into consideration the basic principles that govern diffusion and exchange of nutrients, gases and metabolites to and from the bloodstream with the tissues. It takes longer for matter to diffuse between two points when the distance between the cells and the nutrient vessel is increased due to accumulation of fluid in the interstitial space, and as a result, tissues may be damaged. Takaori, et al. noted, at autopsy, that following infusion of large volumes of crystalloid solutions to dogs in hemorrhagic shock, there was effusion of fluid within body cavities. It is interesting to note that the proponents of fluid therapy now are starting to think in terms of diffusion and the effect overhydration may have on metabolic processes.

In view of these observations, expanding intravascular volume and improving venous return by administering large volumes of balanced salt solution would not seem to be totally justified. Humans who survived surgery with a 3-4 gms percent hemoglobin or a 10 percent hematocrit and animals that have survived experiments whereby all the blood was replaced by various fluids have been reported in the literature. One should realize that these physiological trespasses are only possible at the expense of an increase in cardiac output to compensate for a deficit in oxygen carrying capacity of blood with a steady accumulation of acidosis. The red cell is responsible for almost 85 percent of the carbon dioxide transport.

It is questionable whether the average hospital patient can tolerate the stress of surgery, the depressant effects of anesthetic agents on the central nervous system and myocardium and still be able to maintain an accelerated cardiac output for an appreciable extent of time. Hardaway, et al. in their studies on shock recommended that the red cell mass should be maintained within normal limits at all times while trying to re-establish venous return and circulatory dynamics.

Two recent cases were presented to prove that we could “almost live without red cells” by citing a case which survived. Needless to say, the cases cited were young individuals and in one case, an auxiliary measure (hyperbaric oxygen) was employed to achieve this miracle.

It is important to remember that the ideal hematocrit, with which nature has provided us, is between 35-45 percent. This ratio of red cells to plasma should be respected. The rationale for maintaining a near-normal hematocrit is based on numerous physical and physiological considerations. Oxygen delivery per unit of time and volume is maximal when the hematocrit is 40 percent. Animals with a normal hematocrit survive longer when subjected to traumatic shock. The hematocrit is responsible to a great extent for the viscosity of blood and the rheology of blood is altered with a low or high hematocrit.

Under anesthesia, the signs and symptoms of overload and underload are difficult to determine. Figures 1 and 2 illustrate the vicious cycle encountered in both situations.

Central venous pressure, a physiological monitor for venous return, measures intracardiac resting pressure and, according to Starling’s Law, there is a direct response curve: CVP...
versus cardiac output. This response curve does not always hold true and is shifted to the right with age, myocardial depression and sympathetic blockade. It is important to realize that central venous pressure, as a monitor, is a combination of three major factors and can be expressed in its most simple form by the following equation:

\[
\text{Central Venous Pressure} = \frac{\text{Effective Blood Volume}}{\text{Cardiac Function} + \text{Vascular Capacity}}
\]

TACHYCARDIA → Incomplete Emptying Cardiac Chambers

\[\downarrow \]

Venous Return → Cardiac Volume → Cardiac Output

\[\rightarrow \text{Increased} \quad \rightarrow \text{Increased} \quad \rightarrow \text{Reduced} \]

MYOCARDIAL FAILURE and CEREBRAL EDEMA

HYPOVOLEMIA → Venous Engorgement → Reflex Arteriolar Constriction

\[\rightarrow \text{Pulmonary Congestion} \quad \rightarrow \text{Gaseous Exchange} \quad \rightarrow \text{Hypoxemia} \quad \rightarrow \text{Negative Pressure} \quad \rightarrow \text{PULMONARY EDEMA} \]

Figure 1. Cycle of events in hypervolemia.

TACHYCARDIA

\[\downarrow \]

Venous Return → Cardiac Filling → Cardiac Output → Coronary Flow

\[\rightarrow \text{Reduced} \quad \rightarrow \text{Reduced} \quad \rightarrow \text{Reduced} \quad \rightarrow \text{Reduced} \]

MYOCARDIAL FAILURE and CEREBRAL HYPOXIA

HYPOVOLEMIA → Vasconstriction → Tissue Perfusion → Anemic Hypoxia → Reduced

\[\rightarrow \text{Blood Volume Reduced} \quad \rightarrow \text{Pulmonary Circulating} \quad \rightarrow \text{Pulmonary Dead Space} \quad \rightarrow \text{Gas Exchange} \quad \rightarrow \text{Hypoxemia} \quad \rightarrow \text{Increased} \quad \rightarrow \text{Reduced} \quad \rightarrow \text{Reduced} \quad \rightarrow \text{Reduced} \]

POSITIVE PRESSURE INTRAPULMONARY

Figure 2. Cycle of events in hypovolemia.

Thus, the value of the CVP is affected by three major parameters. Furthermore, other incidentals, which may be in effect during anesthesia or surgery, such as intra-abdominal splinting, positive intrapulmonary pressure, venous obstruction, etc., will also affect CVP readings. Central ve-
nous pressure has much more significance if one parameter, blood volume, is known and relative changes in the other two parameters could, therefore, be inferred.

Regarding the significance of the volume of blood and toxicity of drugs, it is appropriate to recall a comment we made some twelve years ago about the relationship of blood volume and the action of drugs on various receptor organs. One of the many factors that determines the action of the drug on the receptor area is the concentration of the drug. The concentration is inversely proportional to the volume of the solvent or vehicle, blood and fluids in the extracellular fluid space. Consequently, for a given dose based on body weight, one may produce different effects in two individuals having the same weight but who are of different body and fluid composition. Thus, the toxicity of drugs should preferably be based on concentration which is dose and volume related rather than on weight alone. It is gratifying to note that Stone and Brown of the National Institutes of General Medical Sciences have recently expressed similar views on the toxicity of drugs.

In conclusion, we refer to the opening statements and the comments made by Moore and Shires: "... restore physiologic needs." This entails an understanding of physiological processes and methods in measurement. In our present age of technology we have graduated from emperic values and relative values to actual quantitation. We no longer should be satisfied by saying that ventilation is adequate or circulation is sufficient unless they can be substantiated by quantitative measurement of specific parameters. This should also apply to circulating blood volume. And, "the art of treating shock is prevention" can only be achieved by proper preparation of the patient who is undergoing the ordeal of anesthesia or surgery.

It is true that we can live with marked deficits in red cell mass — provided we are physiologically in "balance." Anesthesia does put the organism in a state of "off balance" and it is wiser to know beforehand what we are dealing with than to use emperic trial methods and see if the patient survives. The only rational manner to determine the amount and nature of fluid, for replacement purposes in a particular case, is by volume measurement, crystalloid solutions to correct a deficit in interstitial fluid volume, colloidal or macromolecular solution to correct a deficit in intravascular volume and packed cells for a deficit in red cell volume.

SUMMARY

Proper hydration and blood replacement are important in the management of problem surgical patients. Volume disorders are best monitored by actual volume measurements rather than by the concentration of the various elements that constitute blood or other indirect indices such as blood pressure, heart rate, oxygen tension, pH, urine output, etc., which are often unpredictable.

Measuring blood volume and ECF volume is important in determining the quantity and nature of replacement necessary in the management of the surgical patient.

The techniques for measuring plasma, red cell and ECF volume simultaneously by the dilution method, utilizing three tracers, are practical and applicable in clinical practice. These measurements will reduce morbidity and mortality when performed
on the seriously ill, chronically ill, geriatric and complicated surgical patient.

Fasting deprives patients of a substantial volume of fluid. This loss of fluid preoperatively may play an important role in maintaining an adequate circulation when the patient is subjected to the insult of anesthesia, surgery and blood loss.

ACKNOWLEDGEMENT
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