Blood Volume: Not one Single Volume but the Sum of Two Volumes with Various Mixing in Different Parts of the Circulation

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The earliest attempts to determine blood volume date from the 18th century. The tracer dilution method was introduced in 1915 by Keith et al. [1]. Since then, circulating volume has been repeatedly claimed to be an important clinical parameter, with potential relevance in the monitoring of critically ill patients. Up to now, however, there has been no method available which is both easy to use and accurate. Furthermore, there is still considerable debate as to whether plasma or red cell markers should be used as determinants of blood volume. Various studies have attempted to establish standardized values for blood, plasma or red cell volumes. The volumes are mostly standardized to body weight or body surface area but nevertheless there remain considerable interindividual variations. As with many new or not widely used diagnostic parameters it is not clear whether this standardized ‘normal’ volume represents the optimal volume in the individual clinical situation in the critically ill patient. In intensive care medicine and during anesthesia the intravascular volume is mostly estimated using blood pressure and heart rate, the central venous pressure or the pulmonary occlusion pressure. These pressures may reflect cardiac function rather than the actual volume state of the patient [2].

Tracers for volume determinations are either markers of the plasma or of red cells. In recent years, radioactive isotopes were most commonly used with radioactively labeled human serum albumin for plasma volume and radiochromate tagged red cells for red cell volume determinations [3]. These tracers are difficult to handle in clinical routine and are contraindicated for repeated measurements because of radioactive contamination. Dyes used as tracers in plasma volume estimation are Evans blue [4-7] and indocyanine green [8-12]. These dyes seem to combine accuracy with lack of toxicity. But for repeated measurements, the half-life of Evans blue is too long (corresponding to the half-life of serum albumin) and, as an azo dye, Evans blue may possess a mutagenic potential as indicated in a few in vitro studies [13, 14]. A suitable non-radioactive tracer for red cells is still lacking.

In this issue of INFUSIONSTHERAPIE und TRANSFUSIONSmedizin Lauermann et al. [pp 138] report a new method of labeling red cells with sodium fluorescein, a substance widely used in ophthalmology. After the first report of red cell volume measurements with fluorescein (using fluoresceiniso-thiocyanate which is more stable than sodium fluorescein) in animals by Hansen [15] and a preliminary study by Lauermann [16] the method is compared with radiochromate labeled red cell volume determination as a criterion standard in Lauermann’s study. The results demonstrate good correlation between the two methods. The applicability of the method in the
clinical settings may be jeopardized by its complexity. However, sodium fluorescein is to our
knowledge the only nonradioactive and readily available red cell marker for use in humans.
However, to suggest as these authors do that total blood volume can be estimated by tagging of
red cells is misleading. There is considerable evidence from microvascular studies [17], tracer
dilution studies in animals [18], and from human studies [19,20] that the hematocrit in large
vessels is not representative of the entire circulation. In other words, the hematocrit in peripheral
venous or arterial blood may only in some circumstances be the same as the average hematocrit
of the total circulating blood. Studies in humans revealed that the ratio of whole body to large
vessel hematocrit (the so-called f-cell ratio) may vary between 0.6 and 1.1 [19], thus indicating
that there may be a substantial difference between the hematocrit measured in large vessels and
the average hematocrit of the entire circulation. Hence, calculating blood volume from the
concentration of either a red cell or a plasma marker in a peripheral blood sample may lead to
erroneous results. For these reasons, the method of obtaining the whole body hematocrit by
applying a fixed f-cell ratio correction factor to the measured peripheral hematocrit – as is done
in many studies [2, 20, 21] – is not satisfactory. The only way to measure blood volume using
indicator dilution techniques is to use separate markers for each compartment of blood, i.e. red
cells and plasma, and to summate these values [22].

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In situations where red cell volume is unlikely to change, as in some physiologic studies or in
nonsurgical patients, plasma volume may be the focus of interest. On the other hand, in surgical
patients the volume of oxygen carrying cells may be of more relevance than plasma volume.
From a theoretical point of view, in certain clinical situations, e.g. acute bleeding, volume
replacement therapy or after ‘isovolemic’ hemodilution, the peripheral hematocrit may not
reflect the actual number of circulating red cells.
The volume actually measured in the study of Lauermann et al. was the red cell volume,
calculated from the concentration of the two tracers (sodium fluorescein and radiochromate) in
the red cells of the drawn blood samples. Red cell volume is thus calculated as the quotient of the
injected tracer amount and the tracer concentration in the drawn blood specimen multiplied by
the hematocrit of the same blood sample. Lauermann et al. have successfully developed a readily
available method for red cell tagging without the use of radioactivity. The authors conclude that their
method measures total blood volume and indeed they showed a good agreement between this
new method and the standard one using radiochromate. However, we would suggest that while
both methods are measuring the same volume and are in good agreement neither is actually
measuring total blood volume. With the reintroduction of blood sparing techniques such as
perioperative isovolemic hemodilution, methods for the determination of red cell and plasma
volume will become more and more important. In the practice of anesthesiology and intensive
care medicine, the alterations in the constitution of blood induced by therapeutic interventions
such as intentional hemodilution are not yet well understood. Red cell and plasma volume
measurements may be important tools for future investigations. So this editorial ends as many of
its kind: further studies are needed.
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