The use and limitations of isotope studies in clinical shock

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Summary

Blood volume measurements can only be of value in the treatment of clinical shock if the results are obtained quickly. In a changing situation, such as continuing haemorrhage, erroneous conclusions are inevitable.

Assumptions which are commonly made concerning tracer loss rates and mixing rates may be invalid. Semi-automated machines can introduce new sources of error.

The measurement of blood volume should be regarded as an aid to assessing the relative contributions of intravascular volume and vascular tone to the resulting intravascular pressures.

Problems with single tracers

The principle use of isotopes in clinical shock has been in the determination of blood volume. Only a simultaneous measurement of both red cell mass and plasma volume can give a direct measurement of the blood volume; a single tracer technique always involves assumptions which may not be valid in the particular circumstances. This is because isotope techniques initially measure a tracer-dilution volume.

If the venous blood were representative of the whole circulation, this would be the same as the blood volume, and by measuring the haematocrit, red cell mass and plasma volume could be calculated equally well from either a red cell or plasma tracer-dilution volume.

However, if one measures both these dilution volumes simultaneously, the plasma tracer-dilution volume is found to be considerably greater than the red cell tracer-dilution volume. Using the haematocrit of the sample, the red cell and plasma volumes can be calculated and the sum of these gives the total blood volume. Under most circumstances a plasma tracer-dilution volume is larger than the blood volume and a red cell tracer-dilution volume is smaller. The size of the discrepancy increases with the haematocrit, and at a haematocrit of 60% the plasma tracer-dilution volume exceeds the actual blood volume by 15%. Although they are called blood volume computers, semi-automated machines,

since they use a single tracer, give an answer which is, in fact a dilution volume.

The discrepancy between a tracer-dilution volume and the blood volume exists because the haematocrit of blood drawn from large vessels differs from the haematocrit of the body as a whole, when this is calculated from red cell and plasma volumes measured independently. The ratio between the whole body haematocrit and the venous haematocrit has been called the F cell ratio (Reeve *et al.*, 1953). The ratio is about 0.9 in normal circulatory states. It is possible to convert a single tracer-dilution volume into the blood volume by assuming a normal value for this ratio, measuring the actual venous haematocrit, and applying a correction factor. These factors have been published (Heath & Vickers, 1968).

It is important to bear this discrepancy in mind when comparing measurements with predictions of blood volume. This, of course, is particularly relevant in clinical shock. A patient's normal blood volume is rarely known when he presents in a state of shock, and the value of a measurement will depend on how well it can be correlated with expectation. The best correlation between blood volume and simple body parameters has been made when using sex, weight and a cubed-height formula (Nadler, Hidalgo & Bloch, 1962). It is important to realize that the equations were either derived from simultaneous measurements of both volumes or from a dilution volume corrected by assuming a normal F cell ratio. The published nomograms are blood volume predictions, therefore, and not dilution volume predictions, and single tracer volumes should be corrected before being compared with such predictions of normal.

However, to make this correction one must assume a value for the F cell ratio, and it is clearly important to know how far this is justified in states of shock.

The F cell ratio is the resultant of the haematocrit of various parts of the circulation. The spleen has a pool of red cells, and this by itself would produce a higher whole-body haematocrit than the venous value, and patients with splenomegaly have a high F cell ratio (Brozovic *et al.*, 1966). This is counter-balanced by a relative excess of plasma in the liver,

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kidney and capillaries (Allen & Reeve, 1953; Pappenheimer & Kintner, 1956). Thus the ratio remains reasonably constant when the distribution of blood flow is normal (Chaplin, Mollison & Vetter, 1953).

However, it has generally been found to be more variable in states of shock, or associated with surgery or anaesthesia (Hope & Verel, 1955; Remington & Baker, 1961; Smith & Moore, 1962; Grable *et al.*, 1962; Karlson & Senn, 1963). It should be borne in mind, of course, that failure to find consistency may be poor methodology, and not all workers have published the reproducibility of their techniques. Assuming a value of 0.9 for the F cell fraction when in fact it was 1.0 would, of course, re-introduce errors comparable with those discussed earlier.

Choice of tracer

One must, nevertheless, accept the potential errors of single tracer studies in the management of clinical shock. Double tracer techniques demand either sophisticated apparatus or careful laboratory manipulation, and are not suited to producing an answer quickly. In the choice of tracer there are factors in favour of both cell and plasma labels. Red cells have a slightly faster mixing rate, which may be particularly valuable in shock, and there is no loss of tracer from the circulation. On the other hand, only exceptionally heavy routine use could justify maintaining a stock of ready-labelled O-negative donor cells, and the alternative of labelling the patient's own cells requires some laboratory facilities and imposes an additional minimum delay of 40 min between deciding on the need for the estimation and getting an answer. The balance in favour of an albumin tracer has been tilted even further by the ready availability of ^{125}I -labelled albumin, which has a useful shelf life, requires much less shielding, and gives a smaller radiation dose. Semi-automated machines using this isotope have brought blood volume measurements within the reach of all clinicians.

Special problems with semi-automated machines

Although the discrepancy between iodine-dilution volume and blood volume is one of the biggest sources of potential error with these machines, a few others are relevant to this symposium.

The measurement depends on counting radioactive disintegrations. These are random events, and the larger the number of counts recorded, the more accurately will any observed counting rate represent the mean counting rate. The confidence interval for any count is, therefore, dependent on the total number of counts. The semi-automated machines count 10,000 counts when the isotope is fresh and the 95% confidence interval for this number is $\pm 2.8\%$ for a computation depending on two counts.

The machine will not automatically reject a dose as too weak until it is registering only just over 4,000 counts. The 95% confidence interval for two counts of this size is $\pm 4.3\%$. The computation involves the difference between background and the dilution sample counts. For the first estimation this is large but after a second dose of isotope, dilution samples are only a little more than double the activity of the background samples. Successive doses of isotope progressively reduce the difference, and the 95% confidence interval for the difference increases to unacceptable levels unless the difference between the background and the dilution samples counts is at least half as high as the background counts alone. Incorrect placing of the dose cartridge, sedimentation of the sample, incorrect filling of the sample syringes and mains voltage surges can all add statistically highly significant errors (Heath & Vickers, 1968), although many of them can be avoided by careful technique.

Other technical problems

Irrespective of the method of measurement there are aspects of methodology that deserve special consideration in the context of clinical shock.

Mixing of tracer must be complete before the dilution samples are assayed. In shock, mixing has been found to be delayed by Weil, Shubin & Rosoff (1963), Noble & Gregersen (1946) and Suzuki, Baker & Sheemaker (1964), but others have failed to confirm this (Hoye, Ketcham & Berlin, 1966; Birkeland, 1966). However, the delay which has been found has not been very great and a sample at 15 or 20 min would be satisfactory. Apart from the special circumstances of burns and local trauma, loss rates are not abnormal in shock. There are reasons for thinking that a single sample at about 15 min is as accurate as attempting to correct for loss rates by linear logarithmic plotting of successive dilution volumes and extrapolating to zero time (Heath, Vickers & Dunlap, 1969).

In shock states it may be difficult to sample freely from veins, and to obtain separate veins for injecting isotopes and taking samples. Stasis caused by tourniquets is theoretically capable of producing errors with plasma labels by altering the haematocrit of the sample. Several investigators, however, have been unable to detect errors when stasis has been deliberately produced (Underwood, Boyan & Howland, 1966; Heath *et al.*, 1969). It is also possible to use the same vein for injecting isotopes and taking samples, if suitable precautions are taken (Fisk & Bodlander, 1967; Heath *et al.*, 1969).

The place of blood volume measurements in shock

Shock is a clinical diagnosis, and should be treated initially by transfusion. Treatment must not wait

upon blood volume measurement. As soon as possible central venous pressure should be monitored and used as a guide to transfusion. In the majority of cases this will lead to a completely satisfactory restoration of normal cardiovascular dynamics. In a few instances the clinical situation will remain unsatisfactory. Two syndromes have been described. In one a normal or high CVP is associated with inadequate tissue perfusion and a low cardiac output. Some authors (for example, MacLean, 1966) believe the primary pathophysiology of these cases to be a cardiac insufficiency, and the logical therapy to be an attempt to improve cardiac function. Others, such as Vick *et al.* (1965), believe that this syndrome is due to continuing adrenergic hyperactivity, and that α -adrenergic receptor blockade should be employed. Another clinical picture which may be seen is the development of pulmonary oedema at quite ordinary levels of CVP. There is a suggestion that this reaction is more likely when fluid replacement is given slowly (G. Walters, personal communication). Examples of both types of clinical situation have been reported by Brisman, Parks & Benson (1967), who point out that in both situations the CVP taken alone is misleading.

For example, one patient with a CVP of 15 cm H₂O had a low blood volume (46 ml/kg) and needed transfusing up to 18 cm H₂O before getting an adequate cardiac output, whereas another patient with a CVP of 11 cm and a tachycardia of 150 went into pulmonary oedema on further transfusion, was then found to have a blood volume of 104 ml/kg and improved on phlebotomy, although the CVP stayed the same.

In difficult diagnostic situations blood volume measurements can provide an additional guide to the relative contributions of intravascular volume and adrenergic activity to the resulting venous pressure. However, the magnitude of the difference between measured blood volume and predicted blood volume should not be accepted as a wholly reliable guide to transfusion. Blood volume is an additional measurement when the situation is unclear, and in only a small minority of cases does it provide the essential information for initiating the best therapy. To be of use, however, it must be both believed and interpreted. The former requires informed technique; the latter, clinical acumen.

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