Clinical control in shock

G. WALTERS

From the Chemical Pathology Laboratory, New Cross Hospital, Wolverhampton

When major studies of the pathogenesis of shock began during the 1914-18 war, 'shock' was defined in clinical terms. It is now becoming increasingly accepted that shock should be regarded as a pathological state of acute circulatory failure, resulting usually from a low cardiac output. The low cardiac output may be caused by several factors, the most frequent after injury being a reduction of the blood volume usually due to haemorrhage, but also to plasma loss in burns, peritonitis, and crush injuries, or to loss of extracellular fluid. Whatever the cause of hypovolaemia the resulting haemodynamic changes are much the same and the principle of treatment is to restore an adequate blood volume with an appropriate fluid. Sometimes, hypovolaemia is complicated by other factors such as hypoxia or infection, which may also affect the circulatory system adversely and may call for specific therapy and modify transfusion requirements. The following remarks are concerned only with transfusion therapy.

Reduction of the blood volume has been shown in both experimental and clinical studies to produce a fall in central venous pressure, ie, the pressure in the great veins returning blood to the right atrium. The fall in venous return leads to decreased cardiac output, and this in turn tends to produce a fall in arterial pressure. This sequence is opposed by compensatory reflexes mediated through the baroreceptor nerves and the sympathetic nervous system, and the clinical signs are dependent partly on these mechanisms and partly on the effects of other complicating factors such as sepsis.

The result of all these factors can vary considerably between individuals so that the clinical signs do not correlate well with the magnitude of the underlying pathological change,

even in cases of uncomplicated injury; the relationship of physical signs to blood volume changes after injury is discussed in detail by Grant and Reeve (1951). Most patients with a deficiency in blood volume of 30% will have a low blood pressure, but the converse is not true and hypotension may be associated with only a slight reduction of the blood volume. Some such cases can be explained by vagal overactivity, but sepsis is a far more serious cause and the effect on transfusion requirements are discussed below.

The poor correlation of clinical signs with the blood volume changes has, in the past, led to considerable underestimations of blood loss and therefore to undertransfusion. Indeed, Grant and Reeve (1951) concluded that failure to recognize the extent of the haemorrhage was the cause of death in a number of the patients they studied. However, not until the Korean war was the true magnitude of transfusion requirements fully appreciated. At that time, it was found necessary to administer very large volumes of blood in order to maintain circulatory homeostasis, particularly in limb injuries. In some cases the volume of blood transfused amounted to more than double the patient's normal blood volume, yet this rarely resulted in expansion of the blood volume to above normal (Prentice, Olney, Artz and Howard, 1954).

The variable clinical response of patients to a given blood-volume deficit indicates the need for a more refined technique than clinical observation for determining the transfusion requirements of any given patient. Superficially it would appear that blood-volume measurements, which have been so useful in defining the pathological changes, would provide this refinement, but in practice there are limitations to the use of blood volume measurements for this purpose.

Blood-volume Measurements

All methods of measuring the blood volume in patients depend upon the dilution principle. A known quantity of an appropriate substance is injected intravenously, and after mixing has occurred the concentration of the substance in the blood or plasma is determined and hence the volume by which it has been diluted can be calculated. The markers most often used are red cells labelled with ^{51}Cr , which measure the red cell volume, and ^{125}I -labelled albumin or Evans blue, both of which measure the plasma volume.

However, the blood volume calculated from the red cell volume or the plasma volume and the venous haematocrit value, differs from the total blood volume obtained by adding the measured plasma volume to the measured red cell volume. The blood volume calculated from the plasma volume and the venous haematocrit value will be on average some 10% higher than the true value, the exact amount varying with the haematocrit value; blood volumes calculated from the red cell volumes and the venous haematocrit values will be approximately 10% too low. This is believed to be due to variations in the ratio of red cells to plasma in blood vessels of different calibre, so that the peripheral venous haematocrit value is not representative of the whole body. When calculating total blood volume from either the measured plasma volume or the measured red cell volume, it is the haematocrit value¹ for the whole body and not the venous haematocrit value that should be used. However, in normal subjects the ratio (F_{cells}) of the whole body haematocrit value to the venous haematocrit value is constant at about 0.91, so that the whole body haematocrit value can readily be calculated (see review by Gregersen and Rawson, 1959). In practice it is sometimes permissible to use the venous haematocrit value to calculate the blood volume, but the whole body haematocrit value must be taken into account when comparing blood-volume results obtained by different methods, and it must also be taken into account when selecting a method of predicting the normal blood volume. In some pathological states the ratio (F_{cells}) is known to vary (Gregersen and Rawson, 1959), thus necessitating separate measurements of red cell and plasma volumes if an accurate estimate of the total blood volume is to be obtained. What happens to the ratio in shock is a matter of dispute, some authors maintaining that it changes and hence that in shock syndromes accurate measurements cannot be obtained with a single tracer technique (Smith and Moore, 1962).

The value of blood-volume measurements has

¹Body haematocrit =

$$\frac{\text{percentage of red cells in the total blood volume} = \frac{\text{measured red cell volume}}{\text{measured red cell volume} + \text{measured plasma volume}} \times 100.$$

also been criticized on other grounds. Variations in mixing time, which may be prolonged in shock syndromes, and loss of the marker from the circulation during the period of measurement affect the accuracy of measurements based on a single sample. Such criticisms apply equally to manual techniques and to results obtained with semi-automatic instruments, which, though they have simplified the technique of measurement in some ways, have their own sources of analytical error (Heath and Vickers, 1968). These criticisms probably do not amount to very much when compared with the magnitude of the blood-volume changes found in pure hypovolaemic shock. A far greater problem is that of interpreting the results.

In order to calculate the volume of blood to be given it is necessary to calculate the deficit by subtracting the measured blood volume from the patient's normal value. The normal blood volume is almost invariably not known when the patient is admitted in a state of shock and therefore must be predicted from some other physical parameter(s).

When related to weight, height, or surface area, the standard deviation is about $\pm 10\%$ and several attempts have been made to devise improved methods of predicting the normal value. Probably the most widely recommended today are the equations derived by Nadler, Hidalgo, and Bloch (1962) from computer analysis of data obtained from 166 normal persons. These results relate the blood volume to the body weight and height cubed as follows.

For males blood volume

$$= 0.3669H^3 + 0.03219W + 0.6041 \text{ litres}$$

and for females blood volume

$$= 0.3561H^3 + 0.03308W + 0.1833 \text{ litres}$$

where H = height in metres, and W = weight in kilograms.

Nadler *et al* (1962) demonstrate a considerable improvement in the accuracy of the prediction when compared with values predicted on the basis of weight, height, or surface area alone, but the scatter is still quite large. In a series of 41 normal subjects, comparison of blood volumes predicted according to these formulae with values obtained by measurement revealed errors in the predicted values greater than 500 ml (10%) in 40% of the subjects and greater than 700 ml (15%) in 20% of subjects. In two subjects, the error of prediction was as high as 1,500 ml (Walters, Riordan, and McGowan, 1970). This difficulty of predicting an individual's normal blood volume greatly limits the usefulness of such measurements. If, despite this, blood-volume measurements are to be interpreted relative to a predicted normal value, then the method of prediction must at least be appropriate for the method of measurement. One firm supplying semi-automatic instruments for blood-volume measurement recommends predicting the normal

blood volume according to the above formulae. But Nadler *et al* (1962) used the *whole body* haematocrit to calculate total blood volume; these instruments use the *venous* haematocrit, thereby introducing immediately a discrepancy between the two methods which may exceed 15% with high haematocrit values.

Central Venous-pressure Measurements

A further limitation of the usefulness of blood-volume measurements stems from the fact that sometimes the normal blood volume is not relevant to the problem of resuscitation. In the later stages of pregnancy for example, the blood volume is well known to be higher than 'normal', but by an amount which varies from case to case in an entirely unpredictable manner. In patients with sepsis, shock occurs with little or no reduction of the blood volume (Walters and McGowan, 1965), and yet transfusion may be life saving.

The exact mechanism by which bacterial infection leads to circulatory failure in man is not fully understood, but the circulation is affected in a variety of ways. The most important effect in the early stages is usually, as in haemorrhage, a fall in central venous pressure. As this pressure is dependent both on venous tone and the blood volume, decreased venous tone can lower the central venous pressure in the presence of a normal blood volume. Such a fall in pressure can be reversed by transfusion which expands the blood volume above normal to an extent that will distend the veins sufficiently to produce an adequate central venous pressure. Thus, in states with a low cardiac output resulting from a low central venous pressure, transfusion will raise the pressure whether it be low due to hypovolaemia, to decreased venous tone, or to a combination of both. The central venous pressure thus indicates the adequacy of the blood volume, but obviously it is not an indication of the absolute blood volume; a low central venous pressure does not necessarily mean a low blood volume and a high central venous pressure does not necessarily mean a high blood volume. Indeed, a high central venous pressure may occur with a low blood volume if there is heart failure.

Once the factors of altered venous tone or myocardial failure become involved in the shock process it is impossible to predict what blood volume a patient needs to maintain an adequate central venous pressure, and hence how much transfusion will be necessary to achieve it if the pressure is low. A carefully observed therapeutic infusion is the only way I know of determining this. Fluid is given rapidly and the central venous pressure measured very frequently, continuing until the patient is either resuscitated or the pressure starts to rise rapidly to abnormal levels.

Central venous pressure may be measured in one of two ways. The simpler is to observe the pressure directly in the external jugular vein relative to the sternal angle. Alternatively a plastic catheter can be passed from a peripheral vein into the superior vena cava, connected to a saline manometer, and the pressure determined relative to a particular point. Both methods have advantages and disadvantages, but both are satisfactory when used properly in appropriate circumstances (Riordan, McLay, and Walters, 1969). It is important to realize that different reference points may be used, and allowance must be made for this when comparing values quoted by different authors.

Most patients are resuscitated when the central venous pressure is restored to the upper limit of normal, though sometimes an improved cardiac output may be reflected in an improved pulse volume without a rise in blood pressure. Sometimes it is necessary to raise the central venous pressure to levels which are considered to be abnormally high, before improvement begins. Then, as cardiac function improves, the pressure falls possibly to levels as low as the original (Riordan *et al*, 1969), thus emphasizing the importance of not interpreting central venous pressure measurements in isolation but always with due regard to the other prevailing haemodynamic conditions. Recurrent episodes of circulatory failure due to haemorrhage or uncontrolled sepsis sometimes occur, and continuous monitoring of the central venous pressure greatly facilitates the management of such patients.

SAFETY OF RAPID TRANSFUSION CONTROLLED BY MEASUREMENTS OF CENTRAL VENOUS PRESSURE

I believe, in common with many others, that transfusion given to resuscitate a shocked patient, should be given rapidly, at a rate, say, of about a litre in thirty minutes. Where the central venous pressure is low this applies both to hypovolaemic and normovolaemic patients. The suggestion that the blood volume should be expanded at this rate, sometimes to as much as 30% above normal is on occasion regarded as being a very hazardous procedure and likely to precipitate fatal pulmonary oedema. But several authors have shown that even the normal circulation can tolerate well the rapid transfusion of up to 2 litres of serum or blood (Sharpey-Schafer and Wallace, 1942; Wilson and Harrison, 1950), and the safety margin should be much greater when the central venous pressure is low at the beginning. Ideally, it is the pulmonary venous pressure or pulmonary capillary pressure that should be measured to protect against the development of pulmonary oedema, but it is the experience of most authors that measurement of the central

Case No.	Sex	Age (yr)	Diagnosis	Lung Weight (g)		Heart Weight (g)	Coronary Arteries
				Right	Left		
1	M	58	Streptococcal septicaemia	1000	680	398	Normal
2	M	65	Local peritonitis, appendicitis	845	780	375	No occlusion
3	F	83	Peritonitis, diverticulitis	880	480	397	No occlusion
4	M	73	Pyonephrosis	850	600	348	Normal
5	F	42	Staphylococcal ^a septicaemia	'Gross oedema' (radiologically)		314	Normal

Table *Pulmonary oedema in bacterial shock (from Riordan and Walters, 1968)¹*

¹No intravenous fluid was given to any patient.

^aIn this case the lungs were not weighed, but on admission gross pulmonary oedema was shown clinically and radiologically.

venous pressure does afford considerable protection against pulmonary oedema due to overtransfusion in syndromes of clinical shock. Indeed recent observations suggest that the more difficult measurements of pulmonary arterial or left heart pressures may prove to be no more helpful in this respect than central venous pressure measurements (Anderson, James, Bredenburg, and Hardaway, 1967; Cohn, Tristani, and Khatri, 1969).

The fear of producing pulmonary oedema stems at least in part from what I believe to be misinterpretation of pulmonary oedema found at necropsy. There has been a very marked tendency to equate this with overtransfusion, and the fear of overtransfusion probably operates to the detriment of the patient far more often than to his benefit.

Pulmonary oedema is, in fact, often an agonal event. Sometimes, however, it may be considerable and a contributory cause of death. But such oedema should not be attributed to overtransfusion too readily, as it is clear that it may be due entirely to other factors. The Table shows data from five patients with gross pulmonary oedema associated with non-pulmonary infection, without serious organic heart disease or intracranial lesion. Intravenous fluid could not be implicated in these cases even as a contributory factor, because no intravenous fluid was given. Little is known of the mechanism of this phenomenon in man (MacLean, Milligan, McLean, and Duff, 1967) but it is clear that the occurrence of pulmonary oedema in such a patient who is receiving intravenous fluid is not necessarily indicative of overtransfusion.

This point is of therapeutic importance because systemic circulatory failure may occur in a patient who has pulmonary oedema due to infection, a head injury, a chest injury, or fat embolism. Pulmonary oedema would generally be regarded as a contraindication to transfusion and death could result from the untreated low cardiac output. It may be possible in some such

cases to control the oedema by intermittent positive pressure ventilation, in which case, if the central venous pressure is low, transfusion may be life saving; a case of gas gangrene which illustrates this point has been described elsewhere (Riordan and Walters, 1968). This, of course, is not to say that pulmonary oedema is never due to overinfusion, and I have seen it occur where a mistaken belief that the central venous pressure should be maintained at an arbitrary level has led to the administration of an unnecessarily large volume of crystalloid solutions. Fortunately, this type of case is likely to respond to the quick-acting diuretics now available, unlike many cases where pulmonary oedema is due to other mechanisms.

Although transfusion to raise the central venous pressure to the upper limit of normal, or even slightly above normal, very rarely results in pulmonary oedema, it does not always bring about recovery, and the circulation may not improve even though the central venous pressure persists at high levels. This is very unusual in uncomplicated hypovolaemia, but is seen in many patients in whom infection is a dominant factor, and also in elderly patients in whom hypotension has persisted for some hours because of too slow a rate of transfusion, due possibly to the fear of producing pulmonary oedema. It is at this stage that drug therapy becomes important.

The vogue for using vasoconstrictor drugs has largely given way to the use of vasodilator drugs, on the grounds that vasoconstriction is harmful. The drugs most often recommended are alpha-adrenergic blocking drugs such as phenoxylbenzamine (Wilson, Jablonski, and Thal, 1964) and hydrocortisone in doses of up to 10 g (Dietzman and Lillehei, 1968). The vasodilatory effect may be combined with cardiac stimulation as with isoprenaline (MacLean *et al.*, 1967) or by the simultaneous use of the former drugs with digitalis or other cardiac stimulants. Whatever combination is used, success depends on a rise in cardiac output, which remains partially dependent on the central venous pressure. Vasodilator drugs usually produce a fall in central venous pressure and additional transfusion may be required to counteract this. Continuous monitoring of the central venous pressure is therefore as essential during drug therapy as during transfusion.

References

- Anderson, R. W., James, P. M., Bredenburg, C. E., and Hardaway, R. M. (1967). Phenoxylbenzamine in septic shock. *Ann. Surg.*, 165, 341-350.
- Cohn, J. N., Tristani, F. E., and Khatri, I. M. (1969). Studies in clinical shock and hypotension, relationship between left and right ventricular function. *J. clin. Invest.*, 48, 2008-2018.
- Dietzman, R. H., and Lillehei, R. C. (1968). The nature and treatment of shock. *Brit. J. Hosp. Med.*, 1, 300-304.
- Grant, R. T., and Reeve, E. B. (1951). Observations on the general effects of injury in man. *Spec. Rep. Ser. med. Res. Coun. (Lond.)*, 277.

- Gregersen, M. I., and Rawson, R. A. (1959). Blood volume. *Physiol. Rev.*, **39**, 307-342.
- Heath, M. L., and Vickers, M. D. (1968). An examination of single-tracer semi-automated blood volume methodology. *Anaesthesia*, **23**, 659-669.
- MacLean, L. D., Mulligan, W. G., McLean, A. P. H., and Duff, J. H. (1967). Patterns of septic shock in man. *Ann. Surg.*, **166**, 543-562.
- Nadler, S. B., Hidalgo, J. U., and Bloch, T. (1962). Prediction of blood volume in normal human adults. *Surgery*, **51**, 224-232.
- Prentice, T. C., Olney, J. M., Artz, C. P., and Howard, J. M. (1954). Studies of blood volume and transfusion therapy in the Korean battle casualty. *Surg. Gynec. Obstet.*, **99**, 542-554.
- Riordan, J. F., McLay, W. D. S., and Walters, G. (1969). The significance of central venous pressure and cardiac output measurements in shock. *Postgrad. med. J.*, **45**, 506-511.
- Riordan, J. F., and Walters, G. (1968). Pulmonary oedema in bacterial shock. *Lancet*, **1**, 719-721.
- Sharpey-Schafer, E. P., and Wallace, J. (1942). Circulatory overload following rapid intravenous injection. *Brit. med. J.*, **2**, 304-308.
- Smith, L. L., and Moore, F. D. (1962). Refractory hypotension in man—is this irreversible shock? *New Engl. J. Med.*, **267**, 733-742.
- Walters, G., and McGowan, G. K. (1965). Significance of oligoemia in hypotensive surgical patients. *Lancet*, **1**, 1236-1238.
- Walters, G., Riordan, J. F., and McGowan, G. K. (1970). The error in predicting the normal blood-volume. *Injury*, **1**, 235-239.
- Wilson, J. R., and Harrison, C. R. (1950). Cardiovascular, renal, and general effects of large rapid plasma infusions in convalescent men. *J. clin. Invest.*, **29**, 251-257.
- Wilson, R. L., Jablonski, D. V., and Thal, A. P. (1964). The use of Dibenzylamine in clinical shock. *Surgery*, **56**, 172-183.