

# Relative Hypovolaemia

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## Definition

Relative hypovolaemia may be said to exist when there is an imbalance between the intravascular fluid volume and the capacity of the vascular compartment or an imbalance between the vascular space and the remainder of the extracellular fluid (ECF) and intracellular fluid (ICF). There are four circumstances in which this kind of imbalance may exist:

- Hypovolaemia masked by vasoconstriction
- Normovolaemia with vasodilatation
- ECF and ICF volume depletion with maintained circulating blood volume
- Fluid overload with capillary leak

## Hypovolaemia masked by vasoconstriction

Unrecognised hypovolaemia is extremely common in hospital patients and a major cause of morbidity and mortality.<sup>1,2</sup> This is commonly encountered in early shock, accompanied by vasoconstriction and splenic contraction, both of which mask the relative volume depletion.

Similar imbalances of the relationship between plasma volume and vascular space can occur in the presence of excessive quantities of vasoconstrictor substances, either through iatrogenic administration or due to physiological catecholamine excess. Included in this latter group are conditions such as phaeochromocytoma and autonomic dysfunction states as seen in tetanus and chronic, high spinal cord injury. Patients with pre-eclampsia are also likely to be plasma volume depleted in the presence of elevated systemic vascular resistance. On a chronic basis, hypertensive patients, especially those on diuretic therapy are likely to have a relative volume deficiency.

## Normovolaemia and vasodilatation

Autonomic dysfunction and spinal shock can also result excessive vasodilatation in the presence of a normal plasma volume resulting in relative hypovolaemia. Septic shock and anaphylaxis have the added dimension of capillary leak to complicate the situation, leading to both inadequate plasma volume and vasodilatation.

Iatrogenic causes of excessive vasodilatation include regional anaesthesia, with high spinal or epidural blockade and the excessive use of vasodilator drugs.

## Normovolaemia with ECF and ICF depletion

Plasma volume is frequently well maintained by oncotic forces even in the presence of significant extracellular and intracellular fluid losses. Intracellular fluid depletion develops relatively slowly and can lead to significant total body fluid depletion. Although not primarily hypovolaemia, induction of anaesthesia can markedly inhibit the protective reflexes that maintain ECF at the expense of the ICF and lead to rapid development of hypovolaemia without any apparent volume loss. There are a number of situations in which such intracellular volume depletion can arise, including dehydration, fluid losses from vomiting and diarrhoea, excessive sweating (particularly with pyrexia) etc. Drug therapy, notably with diuretics or ACE inhibitors can also create this situation. Imbalance between the ECF and ICF can occur as a result of alterations in the osmotic state of the plasma.

## Hyperosmolar states

Diabetes, particularly hyperosmolar non-ketotic states, frequently leads to both extracellular and intracellular volume depletion. Heat stroke will result primarily in intracellular fluid depletion, as will hypernatraemia, with both conditions leading to a rise in the plasma sodium content, thus maintaining plasma volume. Hypercalcaemia results in inhibition of sodium, water, calcium and magnesium reabsorption and can result in severe extracellular and intracellular volume depletion.

## Use of hypertonic solutions

Hyperosmotic solutions, such as mannitol and hypertonic saline can result in significant ECF and ICF depletion.

## High output renal failure

The loss of renal tubular concentrating power in high output renal failure will result in significant ECF and ICF depletion.

## Capillary Leak

Aggressive resuscitation of patients with damaged capillary endothelial integrity will result in overload of the extracellular fluid compartment, often with associated intravascular volume depletion. Numerous conditions can lead to this situation including burns, major trauma and crush injuries; also pro-inflammatory insults leading to third space losses such as anaphylaxis, pancreatitis and septic shock. Excessive crystalloid administration in the presence of capillary leak can also result in overload of the extracellular space with relative intravascular volume depletion.

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## Consequences

Although the consequences of relative hypovolaemia will be at least in part dependent on the underlying pathology, the systemic results of inadequate organ perfusion constitute a medical emergency as any degree of hypovolaemia decreases tissue oxygen delivery and may contribute to tissue hypoxia. Renal dysfunction is a major risk and, in susceptible patients there is an increased risk of myocardial ischaemia.

## Clinical Picture

Hypovolaemia may be difficult to recognise, and is associated with a variety of clinical consequences, dependent on the underlying pathology.

## Vasoconstriction

Patients with excessive vasoconstriction may be normotensive or even hypertensive, and, particularly in the presence of excessive quantities of noradrenaline, may have bradycardia, although tachycardia is more common.

Decreased organ perfusion is usually present, frequently affecting renal function and may give the clinical picture of pre-renal kidney dysfunction. Excessive vasoconstriction will result in increased cardiac work and possibly myocardial ischaemia. CVP (central venous pressure) may be normal or even raised and there will be inadequate perfusion with global tissue ischaemia.

## Vasodilatation

Almost invariably, patients with relative hypovolaemia due to excessive vasodilatation will be hypotensive and may have warm peripheries. Tachycardia is common and the CVP is usually low to very low.

## ECF Depletion

Loss of extracellular fluid is particularly difficult to assess. Hypovolaemia usually appears only after vasodilatation, and is thus frequently seen following induction of anaesthesia, the establishment of a regional block or the administration of vasodilator drugs.

If the fluid loss is severe patients may show signs of dehydration such as skin laxity and dry mucous membranes. CVP is usually normal but urine output is low and the urine concentrated. Biochemical investigation may show signs of pre-renal dysfunction, with a disproportionately elevated urea relative to the creatinine concentration. Urinary sodium is low or very low unless renal function has been impaired.

## Capillary Leak

In patients with capillary leak syndromes, oedema may be marked, and the patients are usually hypotensive. CVP is variable and unreliable as a measure of volume status. Crystalloid therapy is generally ineffective in raising blood pressure and colloids may be necessary. Urine output is low and the urine concentrated as in ECF depletion. This form of hypovolaemia will frequently have an obvious cause.

## Assessment of Relative Hypovolaemia

The detection of relative hypovolaemia may be difficult, and is the subject of considerable controversy. Hypovolaemia is often occult and the traditional haemodynamic measures of filling pressures, cardiac output and urine output may be mis-

leading<sup>2-6</sup>, and are poor indicators of central blood volume. Clinicians frequently rely on surrogate variables such as cardiac filling pressures, although these are known to be of limited value<sup>4</sup> and as long ago as 1984 the statement was made that "the commonly monitored variables, in and of themselves, do not reflect adequately the blood volume status in critically ill patients".<sup>7</sup> Nevertheless, many clinicians continue to rely on simple numerical values of filling pressures as a guide to volume therapy. Biochemical indicators of volume status are also often misleading. Plasma osmolality may be useful, particularly if considered together with measures of urine volume and composition.

Numerous alternative approaches to the assessment of plasma volume status have been suggested. These approaches include direct measurements of blood and plasma volume using a variety of markers such as radio-labelled red cells, labelled albumin and exogenous indicators including indocyanine green and fluorescent-labelled hydroxyethyl starch.<sup>8-10</sup> While such markers may provide improved detection of reductions in blood and plasma volume, they are relatively limited in equating the adequacy of circulating volumes to the total vascular space, and are not readily available as clinical tools.

Other approaches to the problem of assessment of adequacy of circulatory filling volume have relied on cardiovascular performance indices, and thus attempted to derive the likely responsiveness of the circulation to volume therapy. Various aspects of systolic pressure variation as a marker of volume performance have been advocated by numerous authors<sup>11-16</sup>, and, while this measure seems to provide a reasonable guide to the fact that volume is deficient, it does not, currently, provide a quantitative assessment. Furthermore, the technique is not valuable in detecting volume overload. A variant of this technique, pulse pressure variation, has been reported to give better results, and either technique was shown to be superior to PAOP (pulmonary artery occlusion pressure) or CVP measurement<sup>17</sup> as a marker of patients likely to respond favourably to fluid therapy. These techniques are limited to patients on positive pressure ventilation.<sup>15</sup> Other approaches have included the use of preload (CVP or pulmonary capillary wedge pressure) responses to fluid challenges<sup>18;19</sup>, although these have only short-term reliability<sup>4</sup>. Various methods to determine intra-thoracic blood volume<sup>4;20;21</sup> have also been used with good correlation to cardiovascular responses to fluid loading, but are not generally clinically available. However, none of these is entirely reliable at present and it is likely that alternative forms of assessment of this crucial measure will be developed in the future.<sup>14</sup>

## Incidence

Hypovolaemia is very common in hospital patients and is frequently unrecognised.<sup>1</sup> It has been estimated over many years that relative hypovolaemia is present in 50% of ICU cases<sup>22;23</sup> and that haemodynamic variables are of little use in its detection. Although the other techniques reviewed above may assist in the diagnosis, no one finding in isolation is helpful and the overall clinical picture of the patient must be considered.

## Prediction of Hypovolaemia

A number of factors make the presence of hypovolaemia more likely including the existence of demonstrable fluid losses, negative fluid balance and evidence of poor peripheral perfusion such as the presence of skin mottling. Taken in conjunc-

tion with signs of absence of fluid overload including the absence of peripheral oedema, pulmonary oedema and CCF, a scoring system has been proposed indicating the likelihood of reduced central blood volume.<sup>23</sup>

### Management

The approach to management of volume deficits largely depends on the underlying pathology. The aim must be to reverse the pathological process if possible and to replace the deficit with appropriate fluids.

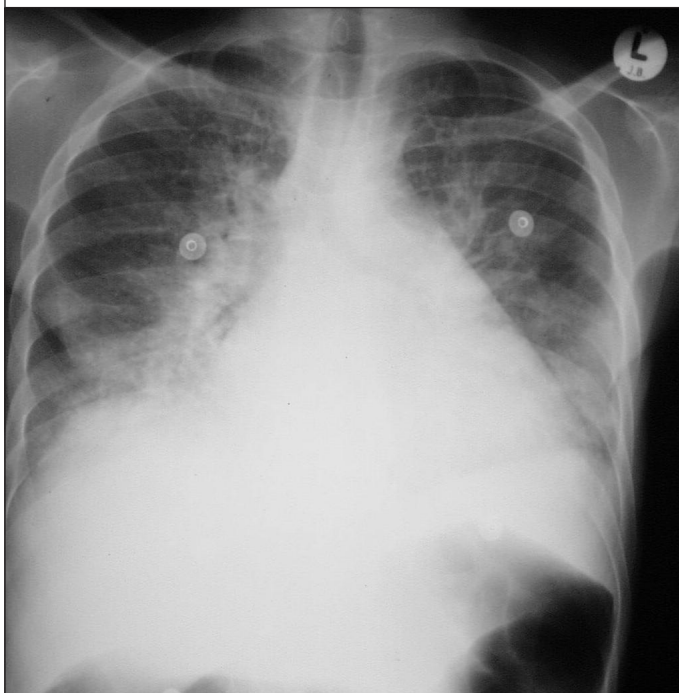
### Early shock

Here the objective must be to assess volume loss (likely to be in the range of  $\pm 1500$  ml) and to administer early, rapid fluid replacement. In this circumstance, crystalloid resuscitation should be adequate unless there is ongoing loss. Subsequent volume therapy should be based on an assessment of the estimated fluid losses, and a global assessment of the patient's haemodynamic status, using all of the surrogate markers available to indicate the requirements for volume therapy. Red cell infusions should be administered against measured values of haematocrit with a trigger level of 25% in otherwise healthy adults. Plasma products (particularly fresh frozen plasma and cryoprecipitate) should be reserved for the treatment of proven coagulation deficits. The use of a mixture of crystalloid and colloid resuscitation fluids appears rational, despite the lack of clear scientific evidence of benefit from colloid infusions. There appears to be no place for albumin in trauma resuscitation.

### Excess Vasoconstriction

The presence of excessive vasoconstriction with hypertension may be one of the most difficult diagnoses to make, and the recognition of occult hypovolaemia may be very difficult, as

**Figure 1.** Chest x-ray of a patient with a phaeochromocytoma crisis: left ventricular hypertrophy, left atrial hypertrophy and pulmonary oedema. Diuretic therapy was ineffective in resolving the pulmonary oedema, but vasodilator treatment and volume expansion improved cardiac function sufficiently to permit tumour excision, after which the patient made an uneventful and complete recovery.



**Table 1.** Biochemical data, on admission and after 4 days of vasodilator and fluid therapy, for the patient whose chest x-ray is shown in Figure 1. Admission biochemistry shows clear evidence of pre-renal dysfunction. The post-treatment data show marked haemodilution as evidenced by the drop in haemoglobin, with complete correction of renal function. At this stage the patient had a 4 litres positive fluid balance.

	On Admission	Post-treatment
Sodium	147 mmol/l	132 mmol/l
Potassium	3.0 mmol/l	3.9 mmol/l
Urea	20.6 mmol/l	5.9 mmol/l
Creatinine	193 mmol/l	77 mmol/l
Haemoglobin	12.7 gm/dl	8.9 gm/dl

the patients may present with hypertension and pulmonary oedema together with profound fluid deficits. The chest x-ray from a patient suffering from a phaeochromocytoma crisis (Figure 1) illustrates this point. As can be seen from the biochemical data (Table 1), the patient was profoundly hypovolaemic with pre-renal dysfunction. The use of diuretics in such a patient will simply worsen the already deranged organ perfusion and may, paradoxically, worsen the hypertension as the sympathetic nervous system attempts to correct the increasing volume deficit. The key step is to treat hypertension with appropriate vasodilator therapy. The traditional agents, such as the nitrates and ACE inhibitors are both arteriolar and venular dilators and may lead to profound hypotension. Initial therapy with magnesium sulphate may be preferable as it is a pure arteriolar dilator.<sup>24</sup> Once hypertension has been controlled, careful volume expansion can be undertaken, and, in these circumstances, response of haemodynamic measures to fluid challenges may be very useful. Patients with severely constricted central blood volume should be monitored with serial measurements of haematocrit. In the patient whose data are illustrated in the table, vasodilator therapy coupled with careful fluid loading resulted in a strongly positive fluid balance, with marked haemodilution, and simultaneous improvement in the cardiac failure (Table 1).

### Capillary Leak

Capillary leak is common in ICU and the management strategies depend on controlling the precipitating cause. Fluid therapy choices may be critical, particularly in sepsis, and inappropriate fluid strategies may adversely affect outcome.

The mechanism of endothelial damage is multifactorial, including the release of inflammatory mediators such as tumour necrosis factor and Interleukins<sub>1-6</sub>, histamine and serotonin. Leukocyte-endothelial cell interaction, with the activation of adhesion molecules and inhibition of nitric oxide results in capillary occlusion and worsening endothelial injury. This process is further compounded by oxygen-derived free radicals and the endothelial injury together with release of proteolytic enzymes activates complement cascade, leading to DIC.

This capillary leak may be indicated by the presence of micro-albuminuria, which correlates well with the time of onset of the insult and is proportional to the magnitude of the injury in many circumstances. Under normal conditions, the micro-albuminuria resolves within hours, but if it persists, it is associated with significantly worse outcome.<sup>25</sup> There is extensive animal evidence that volume therapy with hydroxyethyl starch products may decrease the endothelial injury.<sup>26-32</sup> However, there is currently very limited evidence that this translates into



demonstrable benefit in human subjects, although some advantages for the starches compared with the gelatins have been described.<sup>25,33-35</sup>

### Early, Goal-directed Therapy

In sepsis, early establishment of aggressive volume therapy together with cardiac support has been shown to improve outcome, and this emphasises the importance of the early and appropriate management of relative hypovolaemia.<sup>36</sup> The nature of the fluids best suited for resuscitation remains controversial, and the crystalloid-colloid debate is still not settled. As indicated above, there is good laboratory and some clinical evidence that the hydroxyethyl starches may ameliorate capillary leak, but currently there are no outcome studies that demonstrate the superiority of any one fluid over another. The recent SAFE study demonstrated only that small volume resuscitation with albumin resulted in similar outcomes to those achieved with saline resuscitation in a general ICU population, although there were suggestions that albumin may offer advantages in sepsis and be potentially harmful in trauma.<sup>37</sup> However, it should be noted that this study did not attempt to measure blood volume, and there is good evidence that the two groups were not equivalent in terms of resuscitation endpoints. Interpretations of the study should be limited to those put forward by the authors themselves: i.e. that this study showed that albumin, in the volumes administered, was not dangerous.

### Conclusions

Relative hypovolaemia is difficult to detect and a high index of suspicion is required, particularly in critically ill patients, if the adverse effects of hypovolaemia are to be avoided. The management demands accurate, appropriate volume therapy and aggressive management of the underlying pathology. The lack of sound, objective measures of intravascular volume requires that the entire clinical picture is considered when making decisions about volume therapy.

### References

1. Mythen M, Vercueil A: Fluid balance. *Vox Sang.* 2004; 87 Suppl1: 77-81
2. Jones JG, Wardrop CA: Measurement of blood volume in surgical and intensive care practice. *Br.J Anaesth* 2000; 84: 226-35
3. Boussat S, Jacques T, Levy B, Laurent E, Gache A, Capellier G, Neidhardt A: Intravascular volume monitoring and extravascular lung water in septic patients with pulmonary edema. *Intensive Care Med* 2002; 28: 712-8
4. Brock H, Gabriel C, Bibl D, Necek S: Monitoring intravascular volumes for postoperative volume therapy. *Eur.J Anaesthesiol.* 2002; 19: 288-94
5. Dabrowski GP, Steinberg SM, Ferrara JJ, Flint LM: A critical assessment of endpoints of shock resuscitation. *Surg.Clin.North Am* 2000; 80: 825-44
6. Junghans T, Bohm B, Haase O, Fritzmann J, Zuckermann-Becker H: Conventional monitoring and intravascular volume measurement can lead to different therapy after upper gastrointestinal tract surgery. *Intensive Care Med* 2002; 28: 1273-5
7. Shippy CR, Appel PL, Shoemaker WC: Reliability of clinical monitoring to assess blood volume in critically ill patients. *Crit Care Med* 1984; 12: 107-12
8. Mitra S, Chamney P, Greenwood R, Farrington K: Serial determinations of absolute plasma volume with indocyanine green during hemodialysis. *J Am Soc Nephrol* 2003; 14: 2345-51
9. Thomas E, Jones G, de Souza P, Wardrop C, Wusteman F: Measuring blood volume with fluorescent-labeled hydroxyethyl starch. *Crit Care Med* 2000; 28: 627-31
10. Tschaikowsky K, Neddermeyer U, Pscheidl E, von der EJ: Changes in circulating blood volume after cardiac surgery measured by a novel method using hydroxyethyl starch. *Crit Care Med* 2000; 28: 336-41
11. Beaussier M, Coriat P, Perel A, Lebret F, Kalfon P, Chemla D, Lienhart A, Viars P: Determinants of systolic pressure variation in patients ventilated after vascular surgery. *J Cardiothorac.Vasc.Anesth* 1995; 9: 547-51
12. Berkenstadt H, Margalit N, Hadani M, Friedman Z, Segal E, Villa Y, Perel A: Stroke volume variation as a predictor of fluid responsiveness in patients undergoing brain surgery. *Anesth Analg* 2001; 92: 984-9
13. Gunn SR, Pinsky MR: Implications of arterial pressure variation in patients in the intensive care unit. *Curr.Opin.Crit Care* 2001; 7: 212-7
14. Pinsky MR: Hemodynamic monitoring in the intensive care unit. *Clin.Chest Med* 2003; 24: 549-60
15. Preisman S, Pfeiffer U, Lieberman N, Perel A: New monitors of intravascular volume: a comparison of arterial pressure waveform analysis and the intrathoracic blood volume. *Intensive Care Med* 1997; 23: 651-7
16. Soncini M, Manfred G, Redaelli A, Attanasio A, Tosoni A, Venturino M, Susini G: A computerized method to measure systolic pressure variation (SPV) in mechanically ventilated patients. *J Clin.Monit.Comput.* 2002; 17: 141-6
17. Kramer A, Zygun D, Hawes H, Easton P, Ferland A: Pulse pressure variation predicts fluid responsiveness following coronary artery bypass surgery. *Chest* 2004; 126: 1563-8
18. Weil MH, Shubin H: The "VIP" approach to the bedside management of shock. *JAMA* 1969; 207: 337-40
19. Webb AR: Recognizing hypovolaemia. *Minerva Anesthesiol.* 2001; 67: 185-9
20. Bendjelid K, Suter PM, Romand JA: The respiratory change in pre-ejection period: a new method to predict fluid responsiveness. *J Appl.Physiol* 2004; 96: 337-42
21. Della RG, Costa MG: Hemodynamic-volumetric monitoring. *Minerva Anesthesiol.* 2004; 70: 229-32
22. Shoemaker WC, Monson DO: The effect of whole blood and plasma expanders on volume-flow relationships in critically ill patients. *Surg.Gynecol.Obstet.* 1973; 137: 453-7
23. Stéphan F, Flahault A, Dieudonné N, Hollande J, Paillard F, Bonnet F: Clinical evaluation of circulating blood volume in critically ill patients - contribution of a clinical scoring system. *Br.J.Anaesth.* 2001; 86: 754-64
24. James MF, Cronje L: Pheochromocytoma crisis: the use of magnesium sulfate. *Anesth.Analg.* 2004; 99: 680-6
25. Rittoo D, Gosling P, Burnley S, Bonnici C, Millns P, Simms MH, Smith SRG, Vohra RK: The protective effect of hydroxyethyl starch on pulmonary function in infra-renal aortic surgery is independent of neutrophil elastase. *Br.J.Anaesth.* 2000; 84: 683-a
26. Axon RN, Baird MS, Lang JD, Brix AE, Nielsen VG: PentaLyte decreases lung injury after aortic occlusion-reperfusion. *Am.J.Respir.Crit.Care Med.* 1998; 157: 1982-90
27. Chi OZ, Lu X, Wei HM, Williams JA, Weiss HR: Hydroxyethyl starch solution attenuates blood-brain barrier disruption caused by intracarotid injection of hyperosmolar mannitol in rats.

## REVIEW

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- Anesth.Analg. 1996; 83: 336-41
28. Collis RE, Collins PW, Gutteridge CN, Kaul A, Newland AC, Williams DM, Webb AR: The effect of hydroxyethyl starch and other plasma volume substitutes on endothelial cell activation; an in vitro study. *Intensive Care Med.* 1994; 20: 37-41
29. Harms BA, Rosenfeld DJ, Pahl AC, Conhaim RL, Starling JR: Pulmonary transvascular fluid filtration response to hypoproteinemia and Hespan infusion. *J.Surg.Res.* 1990; 48: 408-14
30. Hofbauer R, Moser D, Hornykewycz S, Frass M, Kapiotis S: Hydroxyethyl starch reduces the chemotaxis of white cells through endothelial cell monolayers. *Transfusion* 1999; 39: 289-94
31. Wisselink W, Patetsios P, Panetta TF, Ramirez JA, Rodino W, Kirwin JD, Zikria BA: Medium molecular weight pentastarch reduces reperfusion injury by decreasing capillary leak in an animal model of spinal cord ischemia. *J.Vasc.Surg.* 1998; 27: 109-16
32. Hoffmann JN, Vollmar B, Laschke MW, Inthorn D, Schildberg FW, Menger MD: Hydroxyethyl starch (130 kD), but not crystalloid volume support, improves microcirculation during normotensive endotoxemia. *Anesthesiology* 2002; 97: 460-70
33. Allison KP, Gosling P, Jones S, Pallister I, Porter KM: Randomized trial of hydroxyethyl starch versus gelatine for trauma resuscitation. *J Trauma* 1999; 47: 1114-21
34. Rittoo D, Gosling P, Burnley S, Bonnici C, Millns P, Simms MH, Smith SR, Vohra RK: Randomized study comparing the effects of hydroxyethyl starch solution with Gelofusine on pulmonary function in patients undergoing abdominal aortic aneurysm surgery. *Br.J.Anaesth.* 2004; 92: 61-6
35. Rittoo D, Gosling P, Bonnici C, Burnley S, Millns P, Simms MH, Smith SR, Vohra RK: Splanchnic oxygenation in patients undergoing abdominal aortic aneurysm repair and volume expansion with eloHAES. *Cardiovasc.Surg.* 2002; 10: 128-33
36. Rivers E, Nguyen B, Havstad S, Ressler J, Muzzin A, Knoblich B, Peterson E, Tomlanovich M: Early goal-directed therapy in the treatment of severe sepsis and septic shock. *N.Engl.J.Med.* 2001; 345: 1368-77
37. The SAFE Study Investigators: A Comparison of Albumin and Saline for Fluid Resuscitation in the Intensive Care Unit. *N Engl J Med* 2004; 350: 2247-56.

