Chapter 5
Fluid Resuscitation

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Key Points
- The physiology of fluid compartments and fluid deficit in health and disease states are different.
- Crystalloids are the initial fluid of choice for resuscitation in most situations.
- Fluid resuscitation requires rational treatment end points during, i.e. fluid responsiveness, in order to prevent negative effects.
- The effect of over-resuscitation with fluid can be detrimental and lethal.

History of Intravenous Fluid Administration

The modern use of intravenous fluid began with William Harvey's demonstration of the human's circulation in 1616 [1]. Throughout the seventeenth century, various attempts were made to restore blood using animal to human blood transfusion and injection of various impure compounds into human veins, which resulted in poor outcomes. In 1832, Thomas Latta recognised that dehydration is the primary cause of morbidity in cholera and transfused 25 patients with 330 ml of normal saline solution over 12 h and noted 'a third of my patients have been restored to life' [2, 3].

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S.S. David (ed.), *Clinical Pathways in Emergency Medicine: Volume I*,
DOI 10.1007/978-81-322-2710-6_5

In 1880, Ringer's solution was discovered as the 'balanced and physiological' solution, which can retain better organ function than 'normal saline'. The solution was then refined in 1930 to make what is now known as lactated Ringer's solution.

In the early twentieth century, discovery of blood groups and the general acceptance of blood transfusion for the treatment of shock in World Wars I and II encouraged the modern development of intravenous fluid therapy.

Pathophysiology of Fluid Management

During illness or injury, fluid balance and distribution are impaired in different ways:

Intracellular and Extracellular Fluid Disturbance

- Cellular destruction, due to tissue hypoxia, can lead to release of intracellular contents including potassium and cytokines, which lead to imbalance in the equilibrium between intracellular and extracellular fluids [4]. This effect is more pronounced when renal function is compromised, e.g. acute kidney injury (AKI).
- In response to physiological stress such as illness or injury, the body increases metabolic rate and protein breakdown in order to deal with the physiological demands and promote healing. A degree of oliguria is a non-specific pathophysiological response to severe illness. This does not necessarily mean that the patient is fluid depleted. For these reasons, a critically unwell patient in the catabolic phase may become overloaded as a consequence of poorly controlled fluid therapy.
- During the recovery/rehabilitation phase after the inflammatory response has subsided, loss of the excess sodium and water accumulated during the catabolic phase results in negative fluid balance.
- During disease states, leaky capillary membranes allow intravenous fluid to leak into the interstitial space as extravascular volume until equilibrium is reached across the capillary membrane. Recent studies have shown that the resuscitative volumes of crystalloid and colloid are often similar in clinical practice [6–8]. Theoretically, this could be explained by the physiological leakage of colloid particles into the extravascular space, resulting in an increase of tissue oncotic pressure; this exacerbates fluid losses into the interstitial compartment and thereby worsens the associated problems (tissue and pulmonary oedema). This leads to a worsening of fluid distribution abnormality (Fig. 5.1).

Treatment Administration Strategy

- A tailored approach to fluid management is required for each patient, taking into account the phase of illness in which they present and the severity of their fluid/

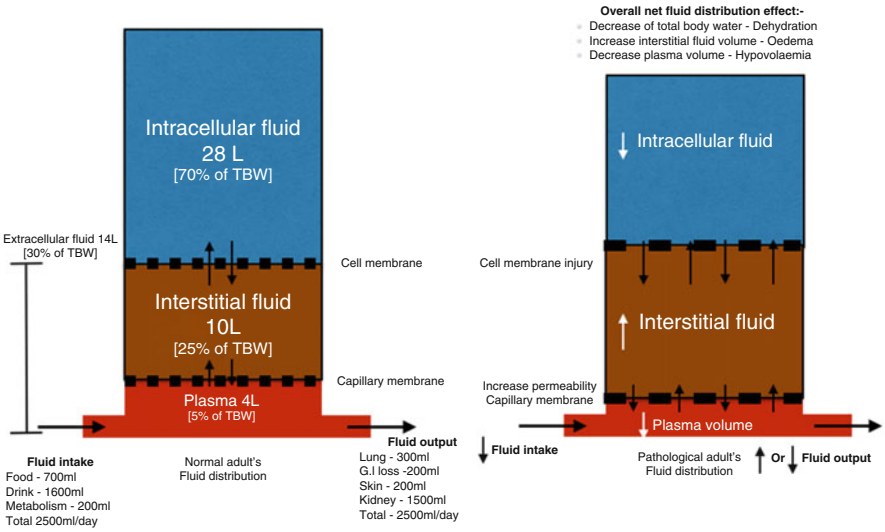

Fig. 5.1 Diagram of physiology and pathophysiology of fluid distribution

electrolyte disturbance. In order to make this assessment, a detailed medical history and examination are required. Important components of the 'fluid history' are:

- Any previous restriction of fluid intake
- Any ongoing fluid losses and its quantity and composition
- Co-morbidity, i.e. renal, liver and cardiac failure and gross oedema

Examination should include:

- Signs of shock: [quoted from NICE guideline [5] criteria for IV fluid resuscitation]
  - Systolic blood pressure <100 mmHg.
  - Heart rate >90 bpm.
  - Capillary refill time >2 s/cold peripheries.
  - Respiratory rate >20 breaths per minute.
  - National Early Warning Score (NEWS) ≥5.
  - Positive passive leg raise test, i.e. compared to a baseline measurement of stroke volume index (SVI). The patient is placed supine and the legs raised to approximately 30°. This produces a transient increase in preload of approximately 50 ml. An increase in SVI of ≥10 % indicates that a patient is not fluid responsive, while an increase of ≤10 %indicates fluid responsiveness and suggests further fluid therapy is required.
- *Signs of intravascular depletion*

  - Dry mucous membranes
  - Decrease skin turgor
  - Orthostatic hypotension and orthostatic increase in pulse rate
  - Cold peripheries
  - Low jugular venous pressure [JVP]
  - Fast and weak pulse

- *Signs of volume overload*
  - Pulmonary oedema
  - Increase in weight
  - Moist mucous membranes
  - Peripheral oedema
  - Elevated JVP

It is important to note that oral rehydration is often the preferred route of rehydration, if tolerated, in the maintenance and replacement phase of fluid administration.

Fluid administration should be divided into three stages:

1. *Resuscitation phase*
   - When intravascular volume is deplete resulting in inadequate tissue oxygenation, high flow oxygen should be administered. A bolus of 500 ml of IV fluid should be given within 30 min.
   - Effect should be reassessed immediately in order to assess the need for further fluid boluses.
   - Minimal clinical response to a total of 30 ml/kg of fluid administration [e.g. 2,100 ml in a 70 kg man]; a vasopressor would need to be commenced and alternative causes of shock would need to be considered.
2. *Replacement phase*
   - Characterised by a fluid deficit composed of fluid losses (i.e. haemorrhage, third space losses, diarrhoea, etc.) and an overall negative fluid balance (i.e. fluid losses exceed those given), but the patient is not in shock.
   - Detailed assessment is needed to determine the source of fluid loss as it determines the choice of replacement fluid.
   - Fluid therapy should include the routine maintenance requirement plus additional fluid and electrolyte supplements to replace the 'measured' abnormal 'ongoing' losses, i.e. a close titration of fluid and electrolyte losses to the choice of replacement fluid. Enteral supplement is often preferred if tolerated (see Table 5.1).
3. *Maintenance phase* – is characterised by a state with no identified ongoing fluid losses, no signs of shock and a balanced fluid input–output. Maintenance treatment should meet the normal daily fluid and electrolyte requirements, which are as follows:
   i. 25–30 ml/kg/day water – approximately 2 L in a 70 kg man

Table 5.1 Composition of fluid loss

Type of fluid loss	Na+[mmol/l]	K+[mmol/l]	Cl-[mmol/l]	H+ [mmol/l]	HCO3-[mmol/l]	Effect and ideal replacement
Gastric fluid [vomiting/NG tube loss]	20–60	14	140	60–80	Minimal	Excessive gastric fluid loss leads to hypochloraemic and hypokalaemic metabolic alkalosis
						Replace – K+ and Cl-
						Tx- 0.9 % NaCl +/– KCl
Biliary drainage	145	5	105	Minimal	30	High salt loss
						Tx- Hartman's/Plasmalyte
Diarrhoea/colostomy fluid	30–140	30–60	–	–	20–80	Dehydration with high salt loss especially potassium loss
						Tx- 0.9 % NaCl +/– KCl
High-volume ileal loss via new or high stoma/fistula fluid	100–140	4–5	75–125	–	0–30	Dehydration with hypochloraemic metabolic alkalosis if high volume
						Tx- Hartmann's solution
Lower volume ileal loss via established stoma/low fistula	50–100	4–5	25–75		0–30	Dehydration mainly
						Tx- Hartmann's solution/ Plasmalyte
Pancreatic fluid	125–138	8	56	–	85	Tx- Hartmann's solution/ Plasmalyte
Jejunal loss via stoma/fistula	140	5	135	–	8	Excessive fluid loss will lead to hypochloraemic acidosis
						Tx- 0.9 % NaCl +/– KCl
Urinary loss	Variable	Variable	Variable	Variable	Variable	Monitor electrolyte and treat accordingly
Insensible loss [i.e. fever/ hyperventilation, etc.]	Minimal	Minimal	Minimal	–	–	Tends to be 'pure water' loss with minimal electrolyte loss

ii. 1 mmol/kg/day sodium, potassium and chloride
iii. 50–100 g/day glucose [e.g. 5 % glucose = 5 g/100 ml]

The most common fluid of choice for maintenance fluid is 0.18 % NaCl with 4 % glucose and 30 mmol/KCl in each litre. Two litres of such solution would meet the daily requirement.

Choice of Fluid

Fluid choices can be categorised into three main groups; (1) crystalloid, (2) colloid and (3) blood-related products. This section will focus mainly on the differences between crystalloids and colloids. Blood products are beyond the scope of this chapter.

Crystalloid

A crystalloid is defined as an aqueous fluid containing substances with properties of a crystal, i.e. glucose or salts. Crystalloids can be classified into:

1. *Isotonic crystalloid,* i.e. 0.9 % sodium chloride, lactated Ringer's solution and other types of balanced crystalloid. Infusion of isotonic solution into plasma does not cause any loss or gain of water by osmosis. Isotonic crystalloids are most useful during the fluid resuscitation phase.
2. *Hypotonic crystalloid,* e.g. dextrose saline, which is available in various percentages (including 0.18 %, 0.45 %, 4 %). Infusion of hypotonic solution is equivalent to a bolus of water which is distributed to all fluid compartments including the intracellular fluid by osmosis until osmotic equilibrium is achieved. The main use of hypotonic solution is as a maintenance fluid.
3. *Hypertonic crystalloid,* i.e. 1.8–7.5 % sodium chloride. Infusion of hypertonic solution can draw water from intracellular and interstitial compartments into the intravascular compartment in order to increase intravascular volume. 7.5 % saline has been quoted to have a volume expansion of four to ten times of the infused volume. The main use of hypertonic solution is to provide a temporary treatment in osmotic intracranial pressure rescue and severe hyponatraemia (Table 5.2).

Colloid

Colloid is defined as a suspension of particles, with a diameter between 1 and 1,000 nm, which is homogenously mixed within the solvent and does not settle with gravity, i.e. milk is an example of emulsified colloid solution. The solvent often

Table 5.2 Composition of crystalloid therapy

Fluid	Plasma	0.9 % sodium chloride [normal saline]	Ringer's lactate [Hartmann's solution]	Sodium 0.18 % + 4 % dextrose	5 % dextrose	50 % dextrose	5 % sodium chloride
Na+ mEql/L	144	154	130	31	–	–	855
K+ mEql/L	5	–	4	–	–	–	–
Cl- mEql/L	107	154	110	31	–	–	855
Ca mEql/L	2.3	–	2	–	–	–	–
Mg mEql/L	1.8	–	–	–	–	–	–
Glucose mEql/L	5	–	–	222	278	2,778	–
Buffer mEql/L	Lactate-<1	–	Lactate – 28	–	–	–	–
Kcal/l	–	–	–	136	170	1,700	–
Calculated osmolality	290	308	275	262	278	2,778	1,711
Advantage		Cheap	Cheap	Glucose provision during fasting			Increase intravascular volume
		More sustainable volume effect than Hartmann's	Physiological composition with less chloride content can reduce the chance of hyperchloraemic acidosis	Treatment of hypoglycaemia			Small volumes can resuscitate effectively
		Common solvent for administration of drugs		Allows I.V. water to be supplied without haemolysis			Improved microcirculation with splanchnic vasodilatation

(continued)

Table 5.2 (continued)

Fluid	Plasma	0.9 % sodium chloride [normal saline]	Ringer's lactate [Hartmann's solution]	Sodium 0.18 % + 4 % dextrose	5 % dextrose	50 % dextrose	5 % sodium chloride
Disadvantages		Saline is an acidotic solution	Outcome benefit has not yet demonstrated	Hyponatraemia			Hypernatraemia and hyperchloraemic acidosis
		Hyperchloraemic acidosis	Dilutional procoagulant effect	Thrombophlebitis			Risk of central pontine myelinolysis
		Associated with renal failure		Poor intravascular volume expander			Rebound intracranial hypertension and coagulopathy
		Abdominal discomfort					No evidence of improved outcome in head injury patient
		Subtle cognitive deficit					
		Dilutional procoagulant effect					
Ideal choice		Fluid replacement	Fluid resuscitation during hypovolaemic shock of any cause	Fluid maintenance –25 ml/kg/day if added K+ to solution [30 mmol/L]	Intravenous glucose provision		Intracranial hypertension
		Dehydration secondary to G.I losses					Prehospital/low-volume resuscitation
Tonicity of solution		Isotonic crystalloid		Hypotonic crystalloids			Hypertonic crystalloids

contains water and electrolytes, either isotonic (i.e. Hartmann's solution) or hypertonic (i.e. 5–7.5 % hypertonic solution) properties.

The colloid component contains large molecules which theoretically should not cross the capillary membranes and instead remain in the intravascular compartment. These can exert an oncotic pressure and encourage fluid to be retained intravascularly. The breakdown of these colloid particles occurs over several hours; hence, it has a theoretical advantage compared with crystalloid as the effects are prolonged. In general, colloid solutions can be classified into two main categories:

1. Natural colloids, i.e. albumin
2. Synthetic colloids, i.e. starches, dextran and gelatins

Natural Colloids

Human Albumin Solution [HAS]

Albumin has been in use since the 1950s. It has a molecular weight of 66,000 Da and contributes up to 80 % of the plasma colloidal oncotic pressure. It has been quoted that it can expand to five times of its own volume over 30 min. Albumin preparations usually come in two different concentrations: 4–5 % or 20–25 %. It is usually diluted with either 5 % dextrose or 0.9 % normal saline. Albumin solution (4–5 %) is an isotonic solution, which has been used particularly for hypovolaemic resuscitation in some parts of the world, like Australia. Twenty to 25 % albumin is a hypotonic but hyperoncotic solution. It is often referred to as salt-poor albumin solution, as it can minimise the requirement for infusion of additional salts and fluid with high oncotic pressure.

The use of albumin remains controversial. Over the past two decades, there have been two meta-analyses produced by the Cochrane Review group comparing the use of albumin to crystalloid in managing critically ill patients. The current recommendation is not to use albumin as a resuscitation fluid [8, 9] as it is not deemed to be cost-effective.

Synthetic Colloids

Gelatins

Gelatins are derived from bovine collagen – gelatin. They have an average molecular weight of 35,000 Da with half-life of 2 h. They are rapidly excreted by the kidney, and only 20 % remains in the intravascular compartment by 90 min. Gelatins have fewer incidences of coagulopathy, pruritus or renal impairment on comparison with synthetic colloids. However, the major disadvantage is that they have relatively high rate of anaphylaxis [1 in 290] as the source of collagen is from cattle bone.

There is also a theoretical risk of new-variant Creutzfeldt–Jakob disease (CJD) transmission (see Table 5.3 for its properties). Gelatins are most suitable for short-term plasma expansion during anaesthesia; however, it is not the ideal solution for resuscitation, and there is a lack of evidence supporting its use.

Dextrans

Dextrans are polysaccharide molecules with a tendency to precipitate coagulopathy and acute renal failure. There is an intermediate risk of anaphylaxis. Due to these side effects, dextrans are rarely used in current clinical practice.

Starches

Starch solutions are derived from hydrolysed maize, and the newer generation molecule is commonly referred to as hydroethyl starch [HES]. This has a variable molecular weight from 130 to 200 kDa and a half-life of 24 h, which results in prolonged elimination of the drug relative to other fluids. The permissible daily maximum dose is 20 ml/kg/day. The advantage of HES is that it can have a sustained volume expansion effect and that there is a relatively low incidence of anaphylaxis. However, the disadvantages of HES are:

- Poor clearance of the drug.
- Reduction of factor VIII and von Willebrand activity and prolongation of the APTT, resulting in coagulopathy.
- Pruritus [approximately 10 %].
- Renal impairment – HES has been demonstrated to cause an increase in the incidence of acute renal failure and even nephrotoxicity. There is also the risk of raised serum amylase levels and anaphylactoid reaction [10, 11].
- Currently, the use of HES is not recommended (Table 5.3).

Ideal Choice of Fluid

Neither crystalloids nor colloids can improve oxygen-carrying capacity, and theoretically, both have the effect of diluting the oxygen-carrying capacity. The ideal resuscitative fluid should be a blood product, especially in acute haemorrhage. Blood products are precise, but expensive, and carry a risk of fatal transfusion reactions and may necessitate a delay for ‘crossmatching’. Consequently, these products should be restricted to bleeding patients or septic patients with critical anaemia. Recommended fluid strategies for various conditions are given in Fig. 5.2.

Table 5.3 Composition of colloid therapy

Fluid	Albumin 4.5 %	Albumin 20 %	Gelofusine	Haemaccel®	Dextran 40	Dextran 70	HES
Natural/synthetic	Natural colloidal solution		Synthetic – gelatins		Synthetic – glucose polymers		Synthetic –starches
Colloid	Albumin	Albumin	Succinylated gelatine	Urea-linked gelatin	Dextran 40	Dextran 70	Hydroxyethyl starch [tetrastarch]
MWw (kDa)		154	110	98	31	–	–
Plasma half-life[hr]	16	16	2	2	4	6	3
Acidity of solution	Neutral [7.4]				Acidotic		
Oncotic effect	++	++++	+	+	++++	+++	++
Calculated osmolarity	300	300	279	300	310	309	309
Overall initial intravascular volume effect [infusion volume: intravascular volume effect ratio]	1:1	1:2.5	1:1	1:1	1:2	1:1.4	1:1
Coagulopathy	+		++		+++++		+++
Skin itch	–		–		–		+++
Renal impairment	–		–		+++		+++
Anaphylactic reaction risk	++		+++		+++		+
Infection risk	+		+ [new-variant CJD risk]		–		–

(continued)

Table 5.3 (continued)

Fluid	Albumin 4.5 %	Albumin 20 %	Gelofusine	Haemaccel®	Dextran 40	Dextran 70	HES
Special note	Safe for septic patient		Collagen source from cattle bone		Poor side effect profile		Poor body clearance
	Safest colloid for use		High risk of anaphylaxis [1 in 290]		Out of favour due to its side effect		HES can accumulate in the skin, kidney and various organs
	No overall mortality benefit noted		Potential risk of new-variant CJD transmission				Coagulopathy, renal impairment and skin itch for up to 13 %
			Better side effect profile compare with starches and dextrans in coagulopathy and renal impairment				FDA has recently withdraw HES from its market due to its side effect profile
			No evidence to support its role in resuscitation				

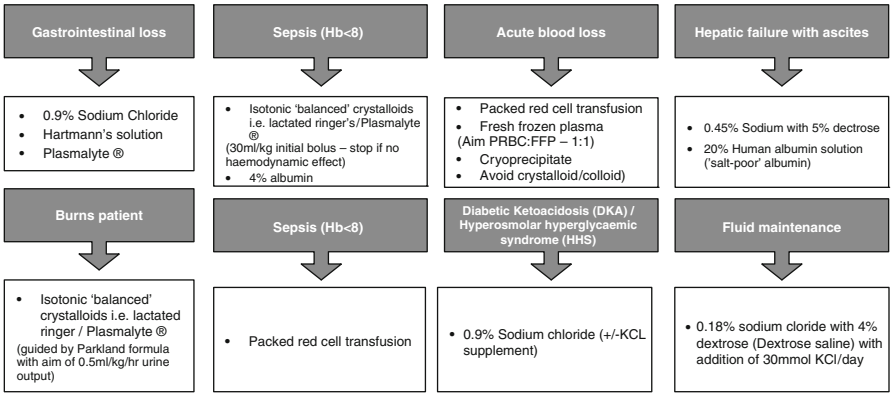

Fig. 5.2 Recommended choice of fluid in various situations

Treatment End Points

There is an increasing body of evidence suggesting the detrimental effect of fluid over-resuscitation. A cumulative positive fluid balance has been associated with longer period of 'ventilator-dependent days' and impaired renal function. If patients require renal replacement therapy to remove fluid as a result of a persistent positive fluid balance, it is associated with higher mortality [12]. Hence, fluid resuscitation should be rational and titrated to its treatment end points.

The risk–benefit ratio of fluid resuscitation can be demonstrated by the Frank–Starling curves. Intravenous fluid is beneficial when improving the preload results in improved cardiac output. However, when increasing the preload no longer results in improved cardiac output, it will lead to harm. It is termed 'fluid responsiveness'.

There are various different techniques to predict fluid responsiveness. Central venous pressure [CVP] has been commonly used to guide fluid management in critically ill patients; however, the correlation of CVP measurement and fluid responsiveness is very poor [13].

In spontaneously ventilating patients, the passive leg raise test and 'mini-challenge' test should be used to predict fluid responsiveness (Fig. 5.3a, b).

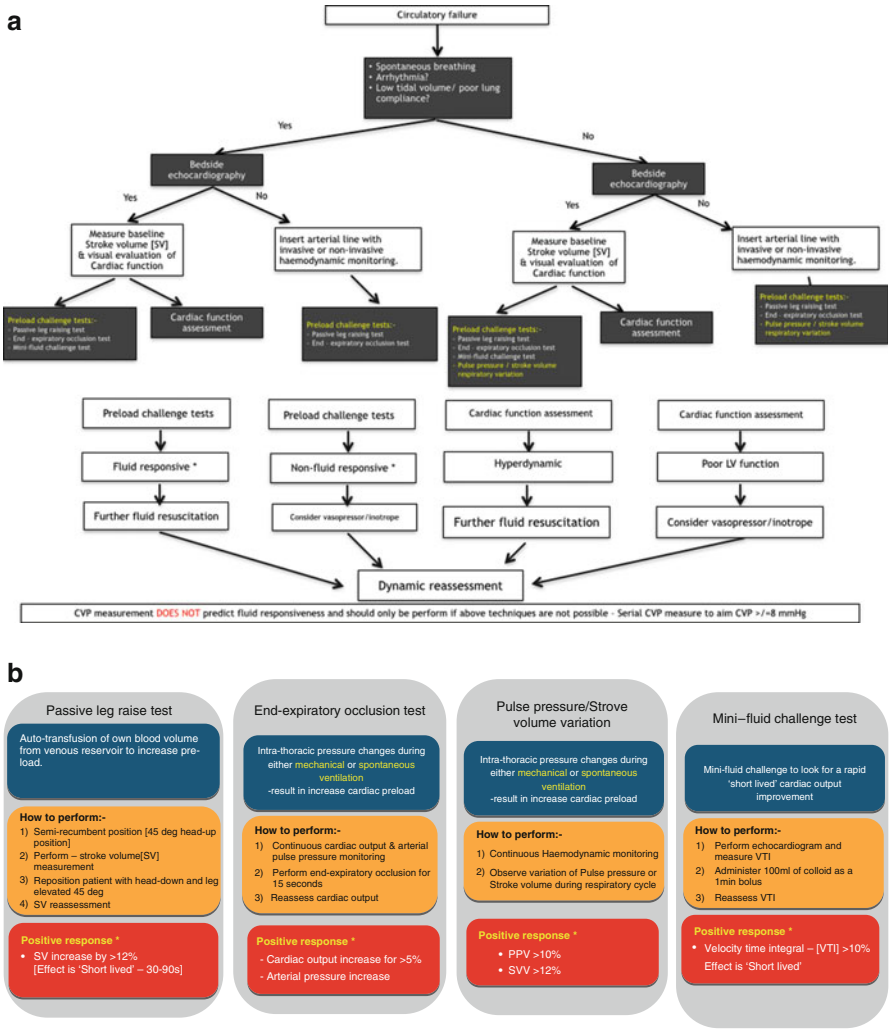

Fig. 5.3 (**a**) Fluid responsiveness decision making flowchart. (**b**) Fluid responsiveness test summary and its positive response

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