BJA

British Journal of Anaesthesia, 2015, 1–11

doi: 10.1093/bja/aev349
Review Article

REVIEW ARTICLE

A rational approach to fluid therapy in sepsis

P. Marik[1,*] and R. Bellomo[2]

[1]Division of Pulmonary and Critical Care Medicine, Eastern Virginia Medical School, 825 Fairfax Av, Suite 410, Norfolk, VA 23507, USA, and [2]Intensive Care Unit, Austin Health, Heidelberg, Victoria, Australia

*Corresponding author: E-mail: marikpe@evms.edu

Abstract

Aggressive fluid resuscitation to achieve a central venous pressure (CVP) greater than 8 mm Hg has been promoted as the standard of care, in the management of patients with severe sepsis and septic shock. However recent clinical trials have demonstrated that this approach does not improve the outcome of patients with severe sepsis and septic shock. Pathophysiologically, sepsis is characterized by vasoplegia with loss of arterial tone, venodilation with sequestration of blood in the unstressed blood compartment and changes in ventricular function with reduced compliance and reduced preload responsiveness. These data suggest that sepsis is primarily not a volume-depleted state and recent evidence demonstrates that most septic patients are poorly responsive to fluids. Furthermore, almost all of the administered fluid is sequestered in the tissues, resulting in severe oedema in vital organs and, thereby, increasing the risk of organ dysfunction. These data suggest that a physiologic, haemodynamically guided conservative approach to fluid therapy in patients with sepsis would be prudent and would likely reduce the morbidity and improve the outcome of this disease.

Key words: central venous pressure; fluid therapy; pulmonary edema; sepsis; septic shock

Editor's key points

- The authors review, in detail, the physiology of hypo-and hypervolaemia, and the effects of venodilation and arteriodilation.
- They contend that universal, aggressive fluid administration in septic shock carries considerable risk, and that a haemodynamically-guided, conservative approach is likely to produce better outcome.
- They also argue that early norepinephrine therapy is likely to improve outcome.

In the 19th century, patients with cholera dying from hypovolaemic shock were treated by venesection or blood-letting.[1 2] This treatment was considered the standard of care for this disorder. In the first part of the 21st century patients with septic shock were treated with massive amounts of crystalloids, approaching 17 litres in the first 72 h of hospitalization.[3 4] This approach was considered the standard of care and endorsed by International Guidelines.[5–7] Clearly, these treatment approaches failed to appreciate the pathophysiological changes of both disorders and that the prescribed treatments were harmful. Cholera is a disease associated with profound volume depletion through diarrhoea that requires replacement with i.v. fluids.[1 2] Severe sepsis and septic shock however, are not associated with volume loss. Sepsis is characterized by arterio- and venodilation together with microcirculatory and myocardial dysfunction, with septic patients being poorly responsive to fluid administration. Nevertheless, aggressive fluid resuscitation to achieve a central venous pressure (CVP) greater than 8 mm Hg ('Early Goal Directed Therapy' - EGDT), has been considered the standard of care in the management of patients with severe sepsis and septic shock.[5–7] However, recent multicentre clinical trials (ProCESS, ARISE and PROMISE) and a meta-analysis of EGDT have demonstrated that this approach does not improve the outcome of patients with severe sepsis and septic shock.[8–11] This article reviews the haemodynamic changes associated with sepsis and provides a rational approach to fluid management in this complex disorder.

Pertinent normal cardiovascular physiology

The amount of blood pumped out of the heart (cardiac output) is equivalent to venous return (volume entering the right atrium).[12] According to Guyton, venous return is determined by the pressure gradient between the peripheral veins and the right atrium (CVP).[13] The venous system can be divided into two theoretical compartments, the unstressed and stressed volume.[14] The intravascular volume that fills the venous system to the point where intravascular pressure starts to increase is called unstressed volume, whereas the volume that stretches the veins and causes intravascular pressure to increase is called the stressed volume. The mean circulatory filling pressure (MCFP) is conceptualized as the pressure distending the vasculature, when the heart is stopped (zero flow) and the pressures in all segments of the circulatory system have equalized.[14 15] The stressed venous system is the major contributor to the MCFP.[14 15] The MCFP in humans is normally in the range of 8–l0 mm Hg.[14 15] The MCFP is the major determinant of venous return.

The venous system has a large vascular capacitance and a constant compliance in which an increased blood volume is associated with a relatively small change in the MCFP.[14] However, because of the restraining effects of the pericardium and cardiac cytoskeleton, the diastolic compliance of the normal heart (both left and right ventricles) reduces as distending volume increases; consequently, with large volume fluid resuscitation, the cardiac filling pressures (particularly on the right side, i.e. CVP) increase faster than the MCFP, decreasing the gradient for venous return.[16–18] Organ blood flow is determined by the difference in the pressure between the arterial and venous sides of the circulation. The mean arterial pressure (MAP) minus the CVP is therefore the overall driving force for organ blood flow. A high CVP therefore decreases the gradient for venous return, while at the same time decreasing organ driving pressure and therefore blood flow. Venous pressure has a much greater effect on microcirculatory flow than the MAP; provided that the MAP is within an organ's autoregulatory range, the CVP becomes the major determinant of capillary blood flow.[19 20]

According to the Frank-Starling principle, as left-ventricular (LV) end-diastolic volume (i.e. preload) increases, LV stroke volume (SV) increases until the optimal preload is achieved, at which point the SV remains relatively constant.[21] This optimal preload is related to the maximal overlap of the actin-myosin myofibrils. Fluid administration will only increase SV if two conditions are met, namely: i) that the fluid bolus increases the MCFP more than it increases the CVP, thereby increasing the gradient for venous return, and ii) that both ventricles are functioning on the 'ascending limb' of the Frank-Starling curve.[22 23]

The vascular endothelium is coated on the luminal side by a web of membrane-bound glycoproteins and proteoglycans known as the endothelial glycocalyx.[24–26] The glycocalyx plays a major role as a vascular barrier, preventing large macromolecules moving across the endothelium, preventing leucocyte and platelet aggregation and limiting tissue oedema. An intact endothelial glycocalyx is a prerequisite of a functioning vascular barrier.[27] Increased cardiac filling pressures after aggressive fluid resuscitation increase the release of natriuretic peptides.[28 29] Natriuretic peptides cleave membrane-bound proteoglycans and glycoproteins (most notably syndecan-1 and hyaluronic acid) off the endothelial glycocalyx.[30–32] Damage to the glycocalyx profoundly increases endothelial permeability. In addition, increased natriuretic peptides inhibit the lymphatic propulsive motor activity reducing lymphatic drainage.[33–35]

Vascular dysfunction with sepsis

Septic shock is primarily a vasoplegic state with arterial and venous dilatation, as a result of failure of the vascular smooth muscle to constrict.[36] Vasoplegic shock is believed to be because of increased expression of inducible nitric oxide synthetase with increased production of nitric oxide (NO), activation of K_{ATP} channels resulting in hyperpolarisation of the muscle cell membrane, increased production of natriuretic peptides (which act synergistically with NO) and a relative vasopressin deficiency.[36] Arterial dilatation results in systemic hypotension. However, more importantly, profound venodilation occurs in the splanchnic and cutaneous vascular beds increasing the unstressed blood volume, decreasing venous return and cardiac output.[14 15] As approximately 70% of the blood volume is within the venous system, changes in venous blood volume play a major role in determining venous return.[15]

Sepsis is characterized by increased expression and activation of endothelial adhesion molecules with adhesion and activation of platelets, leucocytes and mononuclear cells and activation of the coagulation cascade.[37] This results in a diffuse endothelial injury, microvascular thrombosis, gaps between the endothelial cells (paracellular leak) and shedding of the endothelial-glycocalyx.[38 39] The combination of these mechanisms contributes to a reduction in functional capillary density, heterogeneous abnormalities in microcirculatory blood flow and increased capillary permeability.[40 41]

Cardiac changes with sepsis

Myocardial depression in patients with septic shock was first described in 1984 by Parker and colleagues[42] using radionuclide cineangiography. In a series of 20 patients, these investigators reported a 50% incidence of LV systolic dysfunction. Notably, in this study the initial ejection fraction and ventricular volumes were normal in non-survivors and these indices did not change during serial studies; it is likely that these patients had significant diastolic dysfunction. The initial studies evaluating cardiac function in sepsis focused on LV systolic function. However, LV diastolic dysfunction has emerged as a common finding in patients with severe sepsis and septic shock.[43] Adequate filling during diastole is a crucial component of effective ventricular pump function. Diastolic dysfunction refers to the presence of an abnormal LV diastolic distensibility, filling, or relaxation, regardless of LV ejection fraction. Predominant diastolic dysfunction appears to be at least twice as common as systolic dysfunction in patients with sepsis.[43] In the largest study to date (n=262), Landesberg and colleagues[44] reported diastolic dysfunction in 54% of patients with sepsis while 23% of patients had systolic dysfunction. Brown and colleagues[45] performed serial echocardiograms in 78 patients with severe sepsis or septic shock. In this study 62% of patients had diastolic dysfunction on at least one echocardiogram. Unlike systolic LV dysfunction, diastolic dysfunction is an important prognostic marker in patients with sepsis.[43–45] Diastolic dysfunction is becoming increasing recognized in the community, particularly in patients with hypertension, diabetes, obesity and with advancing age.[46–48] These conditions are associated with an increased risk of sepsis and may therefore further increase the prevalence and severity of diastolic dysfunction in patients with sepsis. Patients' with diastolic dysfunction respond very poorly to fluid loading.[44] This was demonstrated in a landmark study published by Ognibene and colleagues[49] in 1988, who reported an insignificant increase LV stroke work index and LV end-diastolic volume index in patients with septic