

Advances of hemodynamic monitoring and the current state of fluid resuscitation in clinical practice

Antonius Hocky Pudjiadi

Abstract

Fluid resuscitation remains the most common and the most debated intervention for critically ill patients. Fluid resuscitation is recommended as a principal therapy in various critical care guidelines, despite the low quality of evidence backing its safety. Fluid overload may lead to a lot of adverse effects, necessitating a reliable method to predict the patient's hemodynamic response to fluid resuscitation. This review summarizes various hemodynamic monitoring

techniques developed over the years and their role in guiding fluid resuscitation, such as the Swan-Ganz catheter, transpulmonary thermodilution, Doppler ultrasound, and impedance cardiography. Each of these techniques comes with differing advantages and shortcomings, as well the appropriate clinical settings in which these techniques can be applied. Existing protocols, which recommend fluid resuscitation as well as evidences pointing against its clinical safety are also discussed.

Key words: Fluid resuscitation, hemodynamics, preload, stroke volume.

Introduction

Accurate assessment and manipulation of the hemodynamic system remains an integral part of managing critically ill patients. The main goal of manipulating the hemodynamic system is to achieve optimal oxygen distribution and blood flow. Among the many choices of therapy to achieve this desired effect is the use of fluid resuscitation, which has been the most common and most debated intervention for critically ill patients. (1) Fluid resuscitation is still strongly recommended as the primary therapy for patients with severe sepsis and septic shock despite the questionable evidence on its safety. (2)

The complexity of predicting the patient's fluid responsiveness stems from variations in the Frank-Starling curve influenced by the patient's ventricular systolic function. Fluid overload may lead to a lot of adverse effects including acute respiratory distress syndrome, intra-abdominal hypertension, and acute kidney injury. (3) Therefore, it's very important to find a reliable method of predicting the patient's hemodynamic response to fluid resuscitation in order to guide the management of critically ill patients.

Hemodynamics system

Hemodynamics of the heart

A profound understanding of hemodynamic principles is important for managing patients in the critical care. According to the concept of static hemodynamics, mean arterial pressure is influenced by cardiac output and peripheral vascular resistance. However, these parameters are also regulated by short-term and long-term mechanisms; blood volume helps determine venous return, which in turn determines the mean arterial pressure. On the other hand, short-term regulation of the hemodynamic system is regulated by the endocrine and nervous system. (4)

A patient's blood pressure is determined by their cardiac output and systemic vascular resistance.

From Department of Child Health, Cipto Mangunkusumo Hospital - Faculty of Medicine Universitas Indonesia, Jakarta, Indonesia (Antonius Hocky Pudjiadi).

Address for correspondence:

Antonius Hocky Pudjiadi MD, PhD
Department of Child Health, Cipto Mangunkusumo Hospital
Faculty of Medicine Universitas Indonesia
Jl. Salemba Raya No. 6, Jakarta 10430, Indonesia
Email: ahpudjiadi@gmail.com

Cardiac output is the amount of blood being pumped in a minute. Cardiac output is the product of stroke volume and heart rate, while stroke volume itself is influenced by the relationship of three components, namely preload, contractility, and afterload. Preload refers to the degree of myocardial distention right before contraction, and is very dependent on ventricular filling. Increased distention of the myocardium will result in elevated cardiac output. Contractility represents the power of the contraction itself. Impaired contractility will cause a decrease in cardiac output, while excessive contractility (in the case of excessive administration of inotropic agents) may lead to ventricular collapse and elevated mortality. Meanwhile, afterload is the pressure against which the ventricles must work in order to pump blood to the circulation. Afterload is greatly influenced by the arterial blood pressure and vascular tone. (5)

Arterial oxygen delivery (DO₂) is equally important with blood pressure in ensuring adequate oxygen supply and optimal hemodynamic status. Arterial oxygen delivery is regulated by both cardiac output and arterial oxygen content (CaO₂). Arterial oxygen content is comprised of hemoglobin-bound oxygen and dissolved oxygen. Hemoglobin-bound oxygen is determined by hemoglobin concentration (Hb), oxygen affinity of hemoglobin, and oxygen saturation (SaO₂). Dissolved oxygen is determined by partial pressure of oxygen (PaO₂). The relationship of these variables can be described with the following equation: (6)

$$\text{DO}_2 = \text{CO} \times \text{CaO}_2$$
$$\text{CaO}_2 = (\text{Hb} \times 1.34 \times \text{SaO}_2) + (0.003 \times \text{PaO}_2)$$

The relationship between these hemodynamic variables is illustrated in **Figure 1**.

Blood flow and vascular hemodynamics

The understanding of blood flow is based on the pressure and flow equation conceived by Daniel Bernoulli and JLM Poiseuille. (7) Bernoulli's equation explained how the sum of lateral pressure, gravitational potential, and kinetic pressure of the fluid remains constant in a non-viscous flow system. The main limitation of Bernoulli's equation was that it didn't factor in the viscosity of the fluid, which was studied by Poiseuille and Hagen. Poiseuille discovered that the pressure gradient between any two points of the flow varies, showing that precise control of blood vessel diameters plays an important role in modulating blood flow resistance in the vessels. (8)

The hemodynamic function varies in the various

vessels of the circulatory system due to the difference in blood flow diameters and other physical parameters. In the arteries, blood flow is very pulsatile due to the filling and ejection phases of the cardiac cycle. Pressure fluctuation during the cardiac cycle also contributes to the variation in the diameter of the arteries. In veins, blood pressure and blood flow velocity are relatively lower compared to arteries, hence the increased risk of thrombus formation. The venous valves are greatly involved in regulating the direction of blood flow to prevent this from happening. In microcirculations with vessel diameters below 300 μm, blood flow is very influenced by the blood's nature as a suspension, being comprised of 45% cellular components like erythrocytes, leucocytes, and platelets. This leads to a tendency for erythrocytes near the vessel walls to form a cell-free layer due to the reduction of intravascular hematocrit, apparent viscosity variation, and the unequal erythrocyte partition of the branches in microcirculation. (8)

Hemodynamics in relation to other systems

Besides internal factors such as blood flow, hemodynamic function is also governed by external factors like external stimuli such as trauma or physical activities. In certain conditions, which trigger the activation of the sympathetic nervous system, the reduction of blood flow will occur as a result of vasoconstriction and elevated vascular resistance. Renal function is also directly impacted by increase of sympathetic tone, in the form of elevated reabsorption of salt and water, elevated secretion of renin, as well as decreased glomerular filtration rate. Increased sympathetic activity of the kidneys is a part of both systemic and specific responses. (4)

Hemodynamics in children

There are physiological differences which distinguish the hemodynamic function in children from an adult, as presented in **Table 1**. In children, hemodynamic assessment of cardiac output and preload are poorly reflected from physical examination. (9) As a result of the difference in blood volume and a lower percentage of intracellular fluid, children are more prone to hypovolemic shock due to blood loss compared to adults. Difference in the level of physical activities can also lead to lower contractility in children.

Another hemodynamic difference between adults and children is the regulation of blood pressure. During low flow states of septic and cardiogenic shock, children are capable of maintaining their vascular tone and consequently, blood pressure. A

greater degree of vasoconstriction in children helps in keeping the children's systemic blood pressure within normal levels during shock, in contrast with adults. (10)

History of hemodynamics assessment and monitoring

Frank-Starling law of the heart

Until now, Otto Frank and Ernest Starling's concept of the relationship between the length of myocardium and its contraction force has extensively helped our understanding of how the regulation of ventricular contraction is mediated by the heart's ability to dynamically alter its contraction force depending on the ventricular filling. This concept, known as the Frank-Starling law or "law of the heart", is based on the *in vitro* study performed on heart muscle fibers, in which he proposed that initial diastolic tension or length of the fibers is related to the increase in the contraction force. (11,12) Ernest Starling further found through his study that the energy of contraction is heavily influenced by the sarcomere length during rest. (13) This relationship between sarcomere length and contraction force formed the basic mechanism of Frank-Starling.

The Frank-Starling law at its core explains the intrinsic nature of the myocardium. The increase in length of the myocardium during ventricular filling is positively correlated with the increase in ventricular pressure. In the molecular level, the increase in end-diastolic volume is correlated with the increase in cross-bridges between the thin filaments. This intrinsic characteristic of the myocardium can be applied clinically to increase a patient's stroke volume through increasing preload. (12)

Frank-Starling law of the heart was further expanded by Sarnoff and Berglund's study in a complete circulation system of the dog in 1954. In this study, they found that right ventricular performance and stroke volume will be proportionally elevated with the increase in preload, but only until a point in which the curve demonstrating the relationship between stroke volume and preload reaches a plateau. In this part of the curve, further increase in preload will no more be followed by the elevation of stroke volume. Furthermore, when the heart's coronary artery is restricted, the maximum left ventricular performance and stroke volume are lowered, and further increase in preload will instead cause a decline in left ventricular performance and stroke volume. (14) Therefore, the relationship between preload and stroke volume as was discovered by Sarnoff and Berglund was not linear

in nature, but curvilinear. (15) Once the patient reaches the plateau of the Frank-Starling curve, atrial pressures are elevated along with the increased secretion of natriuretic peptides, causing pulmonary and tissue edema due to the shift of fluids into the interstitial space. Tissue edema disrupts oxygen diffusion and capillary blood flow, as well as the interactions between cells. (16) This demonstrates that increasing preload through fluid resuscitation is only beneficial when still accompanied by a meaningful increase in stroke volume.

Swan-Ganz catheter

The pulmonary artery catheter (PAC) was first introduced by Harold James Swan and William Ganz as an application of physiologic principles of circulatory problems to identify an appropriate therapy for critically ill patients objectively and quantitatively. (17) Expanding on the catheter's early function to measure right heart and pulmonary artery pressures, they incorporated a thermistor to the device as well as applied the concept of thermodilution to measure cardiac output. Since then, the PAC has experienced technological advancements, especially in the case of its thermistor, which can now be used to continuously measure cardiac output (CO), right ventricular end diastolic volume (RVEDV), and right ventricular ejection fraction (RVEF). (18)

PAC is a catheter introduced to the body from the jugular, subclavian, or femoral vein, and through the right atrium and right ventricle, until it reaches the pulmonary artery. PAC makes it possible to simultaneously measure the central venous pressure (CVP), pulmonary artery pressure (PAP), and pulmonary artery occlusion pressure (PAOP) directly, which can be used to indicate the left atrium's filling pressures. The CO is measured through thermodilution by using the Stewart-Hamilton formula; a cold saline bolus is administered through the right atrium's opening and a thermistor is used to measure the change in temperature near the tip of the catheter. However, newer designs have replaced the use of cold saline bolus with a heating coil. PAC measures the average value of CO in every last 5 minutes, which limits its ability to detect any change in the CO during alterations of preload or afterload, making it unreliable for guiding fluid challenge. PAC also provides right ventricular contractility and preload monitoring through the continuous measurement of volumetric variables like RVEF and continuous monitoring of right ventricular end diastolic volume (CEDV). (19)

PAC was originally intended to be used for myo-

cardial ischemia, but its application has since been expanded to a variety of clinical conditions such as septic shock, acute respiratory distress syndrome (ARDS), heart failure, and high risk surgeries. (18) PAC is still primarily indicated for right ventricular heart failure or pulmonary hypertension, due to its ability to directly measure the right heart and pulmonary artery pressures. (19) However, the use of PAC as an invasive hemodynamic monitoring instrument has since declined over the years, as clinicians have switched to more reliable methods. (17,20) Several studies have also shown no clear benefit in using PAC in managing critically ill patients. (21,22)

Transpulmonary thermodilution

The transpulmonary thermodilution (TPTD) is a cardiopulmonary monitoring method capable of measuring multiple hemodynamic parameters by applying the principle of thermodilution. TPTD has the ability to measure CO, preload volumetric indexes like global end diastolic volume (GEDV) and intrathoracic blood volume (ITBV), as well as extravascular lung water. TPTD provides a more accurate CO measurement when compared to PAC. TPTD's pulse-contour technology also makes it possible to perform continuous CO measurement. Ever since its debut in the early 2000s, the method has been available in various hemodynamic monitors, one of the most prominently used being the PiCCO monitor. (23,24)

TPTD is performed by injecting a normal saline bolus through a central venous catheter inserted into the superior vena cava with a thermistor placed in the tip of femoral artery measuring the decrease in blood temperature. (23,25) The CO is measured by using the Stewart-Hamilton principle, as is the case with PAC. However, due to the difference in location of the bolus injection and the blood temperature change being measured in a systemic artery instead, the TPTD curve has a lower maximum change in temperature as well as a longer time to return to the baseline temperature. This makes the CO measured with TPTD less prone to the effect of confounding factors like respiratory variation or heart rate. TPTD's CO measurement has a comparable accuracy with PAC, making it reliable to be used as a continuous monitoring tool. (23) In order to achieve the desired reliability in the measurement, an injection of 15 ml of saline $<8^{\circ}\text{C}$ is recommended. (24)

TPTD has the ability to provide measurement of volumetric parameters of the preload based on thermodilution curve analysis. The intrathoracic thermal volume, which is the total distribution vol-

ume of the indicator between the injection and detection location, can be obtained by multiplying CO with the mean transit time. Meanwhile, the pulmonary blood volume is the multiplication of CO by the downslope time of the thermodilution curve. Subtracting the pulmonary blood volume from the intrathoracic thermal volume will yield the GEDV. ITBV and GEDV has been demonstrated to have a constant ratio, in which ITBV equals to 1.25 times GEDV, making the calculation of ITBV possible using the TPTD method. (23)

TPTD can also provide the measurement of extravascular lung water (EVLW), which reflects the volume of water contained in the perfused areas of the lung. This can be determined using TPTD by measuring the distribution volume of its cold indicator. This method of measuring EVLW has been found to be useful in real clinical setting, especially when using the single thermodilution technique. Since positive fluid balance in critically ill patients have been found to increase morbidity and mortality, the application of EVLW can potentially become an integral part in managing these patients. (23) The assessment of EVLW by using TPTD can be seen in **Figure 2**.

Despite its advantages, TPTD is still an invasive procedure, which comes with its own shortcomings and adverse effects. While the most common complications have been shown to be minor like hematomas, other complications like ischemia or femoral artery thrombosis may occur, albeit very uncommon and can be resolved with the appropriate measures. (26) TPTD is contraindicated in patients with femoral vascular prostheses. (24)

Doppler ultrasound

Doppler ultrasound is a reliable method to measure the volume of blood often applied in the clinical setting, as can be seen from the use of echocardiography. The concept of cardiac blood flow measurement using the Doppler ultrasound dates back to Franklin's experiment in 1961, which found it to be very sensitive. (27) Due to its non-invasive nature, efficiency, and reliability, Doppler ultrasound has the potential to be the future gold standard of stroke volume measurement. (28)

With the Doppler method, the velocity of the blood flow is measured directly by using a flow sensor placed at the point of ejection from both ventricles to the aorta and pulmonary aorta from the difference in frequency reflected by erythrocytes to the original frequency of the ultrasonic wave. By finding out the velocity of the blood flow and diameter of the vessels, stroke volume can be determined

through the integral of velocity and time (velocity time variable; vti), multiplied by the cross-sectional area of the blood vessel. (29)

The application of Doppler ultrasound is expanded by Smith and Madigan, who demonstrated the instrument's ability to determine the patient's inotropy through its measured values of stroke volume, flow time, and vti. Inotropy as defined by Smith and Madigan's study is expressed as the Smith-Madigan inotropy (SMI). The formula to determine SMI involves the calculation of the potential energy and kinetic energy produced by the heart using the aforementioned three parameters acquired from the Doppler ultrasound, as well as blood density from the concentration of hemoglobin. (30) This way of measuring inotropy further elevates Doppler ultrasound's versatility as a hemodynamic monitoring tool.

Impedance cardiography

Impedance cardiography (ICG) is a non-invasive hemodynamic assessment based on the Ohm's law. This method is performed by delivering a low amplitude and high frequency electrical current to the thorax to measure changes in the thoracic impedance, with an electrode receiving the voltage. (31) Due to blood being the most electrically conductive among biological tissues in a human body and the pulsatile changes of the arterial blood volume throughout the thorax, the impedance of the thorax to electrical current constantly changes as well. Parameters measured by the ICG method include heart rate, thoracic fluid content, velocity index, acceleration index, pre-ejection period, and left ventricular ejection time. Stroke volume and CO can be calculated by applying the measured impedance to an algorithm. (32)

Due to the method requiring several hypotheses in place for its calculation, the effectiveness of ICG is considerably limited. (31) A patient's height needs to be between 4-7 feet, with their weight between 67-341 pounds, in order to ensure the SV calculation is accurate. Patients with severe aortic regurgitation, advanced sepsis, presence of an intra-aortic balloon pump, or tachycardia >250 bpm can compromise the accuracy of ICG. Despite these limitations, the latest generation of ICG devices has demonstrated a comparable accuracy in determining CO and cardiac index (CI) compared to invasive techniques like thermodilution. ICG has seen diagnostic and prognostic applications in patients with heart failure. (32)

Fluid resuscitation in clinical practice

The need for fluid resuscitation in clinical practice

usually arises in patients with compromised circulatory system due to a problem in one or more of its components (volume, blood vessel, pump, etc.). In these patients, circulatory failure may emerge as a consequence of the resulting imbalance between the patient's oxygen supply and demand; this circulatory failure is known as shock. Shock can be differentiated based on its underlying etiology, which may be hypovolemic, cardiogenic, distributive, and obstructive. Hypovolemic shock happens due to inadequate circulating volume, such as in the case of massive hemorrhage. Cardiogenic shock, on the other hand, is the result of compromised cardiac pump function. Distributive shock is a result of peripheral vasodilatation and blood flow maldistribution due to various causes, such as sepsis. Obstructive shock, as its name implies, is a consequence of an extra-cardiac blood flow obstruction. (33)

Widely used clinical protocols

A lot of available clinical guidelines integrate fluid resuscitation as the first-line treatment in their protocols, such as the guidelines for sepsis, septic shock, and dengue. Initial crystalloid fluid resuscitation of at least 30 ml/kg within the first three hours is still strongly recommended as the principal management for patients with sepsis and septic shock, despite the low quality of evidence supporting the recommendation. (34) This strong recommendation remains in the 2016 update of Surviving Sepsis Campaign guidelines despite a presenting evidence of the risk in performing fluid resuscitation from a trial performed in African children by Maitland et al, which had shown significant increase in 48-hour mortality in critically ill children administered with fluid bolus. (35)

Fluid resuscitation has also been integrated to other guidelines in the clinical setting. One such example is its application in the WHO manual for emergency triage assessment and treatment training, especially in its circulation assessment. In patients with circulatory problems without severe malnutrition, rapid fluid resuscitation is recommended, either through intravenous route or other routes (external jugular line, intraosseous line) if intravenous access isn't possible. (36)

In the dengue guidelines for diagnosis, treatment, prevention, and control released by WHO, dengue patients with warning signs are recommended to receive isotonic fluid resuscitation in order to maintain perfusion and urine output approximately 0.5 ml/kg/hour. Fluid resuscitation is reduced gradually following the rate of plasma leakage. Intravenous fluid therapy is also recommended for

patients without warning signs who are unable to tolerate oral fluids. (37)

Criticizing the practice of fluid resuscitation

Several studies have shown that fluid overload in patients receiving fluid resuscitation may cause various adverse effects, which may lead to both increased mortality and morbidity in these patients, causing more harm than good. (38-43) Furthermore, other studies have also shown that fluid resuscitation in large volumes for patients with sepsis is significantly associated with an increase in mortality. (42,44,45)

In a study by Maitland et al, fluid resuscitation is found to increase the 48-hour mortality significantly in critically ill patients with perfusion problems. (35) Another study, performed by Ketharanathan et al, showcased how fluid overload in PICU patients is associated with the increase in 28-day mortality significantly. (38) Arikan et al, on the other hand, found that fluid overload may lead the disruption of oxygenation and organ dysfunction. (43)

An analysis of superimposed Frank-Starling and extra-vascular lung water (EVLW) curves has demonstrated that further volume expansion due to fluid resuscitation promotes a significant increase in EVLW as the patients become less responsive to fluid. Natriuretic peptides are released as cardiac filling pressures increases, causing damages to the endothelial glycocalyx. This causes intravascular fluid to rapidly shift into the interstitial space, which lead to tissue oedema. (46) Studies have shown that EVLW can be used as a predictor of mortality in critically ill patients. (47,48) These findings indicate that continuing fluid resuscitation until it reaches the peak of the Frank-Starling curve may be harmful to the patients.

These findings beg the question whether fluid resuscitation's place as the first line therapy in treating critically ill patients is truly warranted. Up until now, fluid resuscitation has been the corner-

stone of managing patients in the emergency and intensive care as has been demonstrated by a lot of guidelines embracing the practice. However, recent findings of the adverse effects related to the practice of fluid resuscitation may be the sign for practitioners to re-evaluate the exact role of fluid resuscitation in the grand scheme of emergency and critical care management.

Conclusion

In order to perform fluid resuscitation in critically ill patients, such as patients with shock, it's important to have an educated guess about the cause (e.g. cardiogenic, septic, hypovolemic) derived from clinical assessment of each individual patient. In some clinical settings, which do not have an adequate facility to perform these assessments, one of the possible routes to take is to perform fluid challenge in order to directly evaluate the response of the patient's circulation through physical examination. However, if the use of more advanced technologies such as USCOM is possible, more detailed analyses are possible. Hence, the approach in evaluating the patient's response to circulation greatly varies depending on the clinical setting; in the emergency care, simple and rapid methods of assessments are preferred, while the intensive care or surgical setting find more use in long-term and detailed hemodynamic assessments. Understanding when to use which method to evaluate the patient's circulation response and providing a tailor-made management to each patient is the key to an effective critical care management.

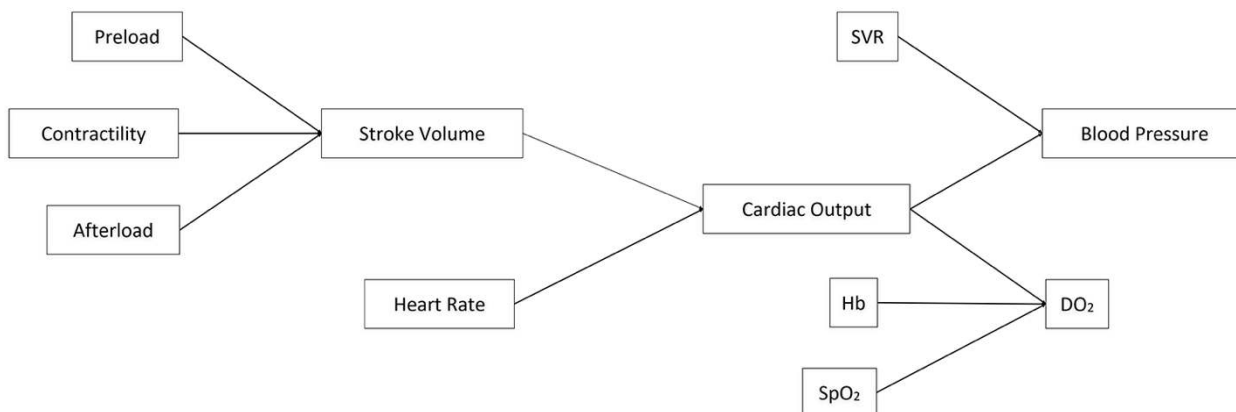
Acknowledgments

The author would like to acknowledge Marcel Aditya Nugraha, MD for his help in proofreading the article, and the whole staff of Department of Child Health of Faculty of Medicine, Universitas Indonesia, Cipto Mangunkusumo General Hospital for their support system.

Table 1. Hemodynamic differences between adults and children

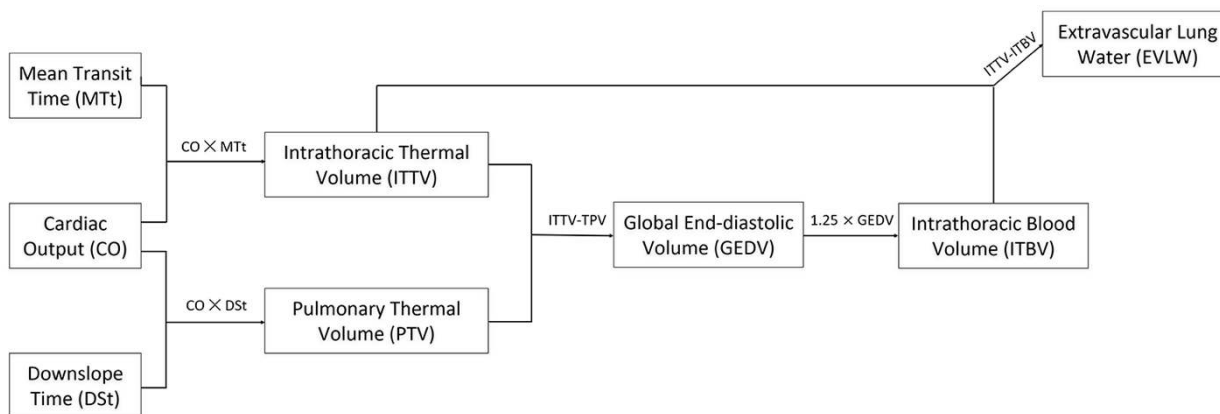
	Difference in children
Percentage of intracellular fluid	Lower than adults
Contractility	Likely lower due to less physical activity compared to adults
Regulation of blood pressure	Better maintenance of vascular tone and systemic blood pressure during shock

Figure 1. Hemodynamic variables influencing blood pressure and oxygen delivery



Legend: SVR=systemic vascular resistance; Hb=hemoglobin; DO2=oxygen delivery; SpO2=arterial oxygen saturation.

Figure 2. Extravascular lung water calculation using transpulmonary thermodilution



References

1. van Haren F. Personalised fluid resuscitation in the ICU: still a fluid concept? *Crit Care* 2017;21:313.
2. Byrne L, Van Haren F. Fluid resuscitation in human sepsis: Time to rewrite history? *Ann Intensive Care* 2017;7:4.
3. Monnet X, Marik PE, Teboul J-L. Prediction of fluid responsiveness: an update. *Ann Intensive Care* 2016;6:111.
4. Navar LG. Physiology: hemodynamics, endothelial function, renin-angiotensin-aldosterone system, sympathetic nervous system. *J Am Soc Hypertens* 2014;8:519-24.
5. Vincent J-L. Understanding cardiac output. *Crit Care* 2008;12:174.
6. Nebout S, Pirracchio R. Should We Monitor ScVO₂ in Critically Ill Patients? *Cardiol Res Pract* 2012;2012:370697.
7. Badeer HS. Hemodynamics for medical students. *Adv Physiol Educ* 2001;25:44-52.
8. Secomb TW. Hemodynamics. *Compr Physiol* 2016;6:975-1003.
9. Lemson J, Nusmeier A, van der Hoeven JG. Advanced Hemodynamic Monitoring in Critically Ill Children. *Pediatrics* 2011;128:560-71.
10. Arikian AA, Citak A. Pediatric Shock. *Signa Vitae* 2008;3:13-23.
11. Sequeira V, van der Velden J. Historical perspective on heart function: the Frank-Starling Law. *Biophys Rev* 2015;7:421-47.
12. Sequeira V, van der Velden J. The Frank-Starling Law: a jigsaw of titin proportions. *Biophys Rev* 2017;9:259-67.
13. Lakatta EG. Starling's law of the heart is explained by an intimate interaction of muscle length and myofilament calcium activation. *J Am Coll Cardiol* 1987;10:1157-64.
14. Sarnoff SJ, Berglund E. Ventricular Function. I. Starling's Law of the Heart Studied by Means of Simultaneous Right and Left Ventricular Function Curves in the Dog. *Circulation* 1954;9:706-18.
15. Napoli AM. Physiologic and Clinical Principles behind Noninvasive Resuscitation Techniques and Cardiac Output Monitoring. *Cardiol Res Pract* 2012;2012:531908.
16. Marik P, Bellomo R. A rational approach to fluid therapy in sepsis. *Br J Anaesth* 2016;116:339-49.
17. Bethlehem C, Groenwold FM, Buter H, Kingma WP, Kuiper MA, de Lange F, et al. The Impact of a Pulmonary-Artery-Catheter-Based Protocol on Fluid and Catecholamine Administration in Early Sepsis. *Crit Care Res Pract* 2012;2012:161879.
18. Robin E, Costecalde M, Lebuffe G, Vallet B. Clinical relevance of data from the pulmonary artery catheter. *Crit Care* 2006;10 Suppl 3:S3.
19. Huygh J, Peeters Y, Bernards J, Malbrain MLNG. Hemodynamic monitoring in the critically ill: an overview of current cardiac output monitoring methods. *F1000Res* 2016;5:F1000.
20. Teboul J-L, Cecconi M, Scheeren TWL. Is there still a place for the Swan-Ganz catheter? *No. Intensive Care Med* 2018;44:957-9.
21. Harvey S, Harrison DA, Singer M, Ashcroft J, Jones CM, Elbourne D, et al. Assessment of the clinical effectiveness of pulmonary artery catheters in management of patients in intensive care (PAC-Man): a randomised controlled trial. *Lancet* 2005;366:472-7.
22. Richard C, Warszawski J, Anguel N, Deye N, Combes A, Barnoud D, et al. Early Use of the Pulmonary Artery Catheter and Outcomes in Patients With Shock and Acute Respiratory Distress Syndrome: A Randomized Controlled Trial. *JAMA* 2003;290:2713-20.
23. Sakka SG, Reuter DA, Perel A. The transpulmonary thermodilution technique. *J Clin Monit Comput* 2012;26:347-53.
24. Monnet X, Teboul J-L. Transpulmonary thermodilution: advantages and limits. *Critical Care* 2017;21:147.
25. Assaad S, Shelley B, Perrino A. Transpulmonary Thermodilution: Its Role in Assessment of Lung Water and Pulmonary Edema. *J Cardiothorac Vasc Anesth* 2017;31:1471-80.
26. Belda FJ, Aguilar G, Teboul JL, Pestaña D, Redondo FJ, Malbrain M, et al. Complications related to less-invasive haemodynamic monitoring. *Br J Anaesth* 2011;106:482-6.
27. Franklin DL, Schlegel W, Rushmer RF. Blood Flow Measured by Doppler Frequency Shift of Back-Scattered Ultrasound. *Science* 1961;134:564-5.
28. Phillips RA, Smith BE, Madigan VM. Stroke Volume Monitoring: Novel Continuous Wave Doppler Parameters, Algorithms and Advanced Noninvasive Haemodynamic Concepts. *Curr Anesthesiol Rep* 2017;7:387-98.
29. Philip J, Chadee D, Yearwood RP. Health care students' reactions towards HIV patients: examining prejudice, emotions, attribution of blame and willingness to interact with HIV/

- AIDS patients. *AIDS Care* 2014;26:1236-41.
30. Smith BE, Madigan VM. Non-invasive method for rapid bedside estimation of inotropy: theory and preliminary clinical validation. *Br J Anaesth* 2013;111:580-8
 31. Nguyen LS, Squara P. Non-Invasive Monitoring of Cardiac Output in Critical Care Medicine. *Front Med (Lausanne)* 2017;4:200.
 32. Yancy C, Abraham WT. Noninvasive Hemodynamic Monitoring in Heart Failure: Utilization of Impedance Cardiography. *Congest Heart Fail* 2003;9:241-50.
 33. Taha M, Elbaih A. Pathophysiology and management of different types of shock. *NMJ* 2017;6:14-39.
 34. Dellinger RP, Levy MM, Carlet JM, Bion J, Parker MM, Jaeschke R, et al. Surviving Sepsis Campaign: International guidelines for management of severe sepsis and septic shock: 2008. *Intensive Care Med* 2008;34:17-60.
 35. Maitland K, Kiguli S, Opoka RO, Engoru C, Olupot-Olupot P, Akech SO, et al. Mortality after fluid bolus in African children with severe infection. *N Engl J Med* 2011;364:2483-95.
 36. World Health Organization. Emergency triage assessment and treatment (ETAT) [Internet]. 2005 [cited 2019 May 8]. Available from: <https://apps.who.int/iris/handle/10665/43386>
 37. World Health Organization. Dengue guidelines for diagnosis, treatment, prevention, and control: new edition. Geneva: World Health Organization; 2009. 147 p.
 38. Ketharanathan N, McCulloch M, Wilson C, Rossouw B, Salie S, Ahrens J, et al. Fluid Overload in a South African Pediatric Intensive Care Unit. *J Trop Pediatr* 2014;60:428-33.
 39. Bagshaw SM, Brophy PD, Cruz D, Ronco C. Fluid balance as a biomarker: impact of fluid overload on outcome in critically ill patients with acute kidney injury. *Crit Care* 2008;12:169.
 40. Favia I, Garisto C, Rossi E, Picardo S, Ricci Z. Fluid management in pediatric intensive care. *Contrib Nephrol* 2010;164:217-26.
 41. Cordemans C, De Laet I, Van Regenmortel N, Schoonheydt K, Dits H, Huber W, et al. Fluid management in critically ill patients: the role of extravascular lung water, abdominal hypertension, capillary leak, and fluid balance. *Ann Intensive Care* 2012;2:S1.
 42. Brandt S, Regueira T, Bracht H, Porta F, Djafarzadeh S, Takala J, et al. Effect of fluid resuscitation on mortality and organ function in experimental sepsis models. *Crit Care* 2009;13:R186.
 43. Arikan AA, Zappitelli M, Goldstein SL, Nainpaul A, Jefferson LS, Loftis LL. Fluid overload is associated with impaired oxygenation and morbidity in critically ill children. *Pediatr Crit Care Med* 2012;13:253-8.
 44. Miller TE, Bunke M, Nisbet P, Brudney CS. Fluid resuscitation practice patterns in intensive care units of the USA: a cross-sectional survey of critical care physicians. *Perioper Med (Lond)* 2016;5:15.
 45. Sadaka F, Juarez M, Naydenov S, O'Brien J. Fluid resuscitation in septic shock: the effect of increasing fluid balance on mortality. *J Intensive Care Med* 2014;29:213-7.
 46. Marik PE, Lemson J. Fluid responsiveness: an evolution of our understanding. *Br J Anaesth* 2014;112:617-20.
 47. Sakka SG, Klein M, Reinhart K, Meier-Hellmann A. Prognostic value of extravascular lung water in critically ill patients. *Chest* 2002;122:2080-6.
 48. Chung F-T, Lin S-M, Lin S-Y, Lin H-C. Impact of extravascular lung water index on outcomes of severe sepsis patients in a medical intensive care unit. *Respir Med* 2008;102:956-61.