Fluid loading responsiveness

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Introduction

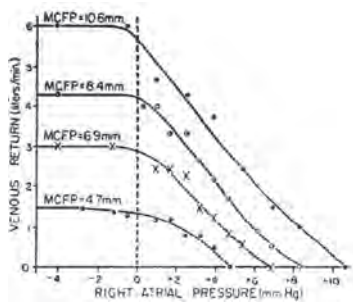
Patients in the intensive care unit (ICU) and in the peri-operative phase are dependent on physicians and nurses for their fluid intake. Moreover, alterations in volume status due to disease, co-morbidity, anaesthetic and surgical manipulations are to be compensated by inotropic support, additional fluid administration or diuretic therapy since sympathetic and hormonal auto-regulation are depressed and frequently myocardial dysfunction is present. Volume status optimization is required to maximize oxygen delivery to vital organs, like brain, kidneys and heart. Prolonged oxygen deficit can ultimately result in multi-system organ dysfunction [1]. On the other hand unnecessary fluid administration can lead to general and pulmonary oedema, cardiac failure, infections, prolonged hospitalization and death [2]. However, it is still not possible to directly determine volume status at the bedside. The quest for a method to directly or indirectly assess volume status continues.

Frank-Starling and Guyton physiology

Starling and Bayliss stated in 1894, that "the venous circulation was an important but disregarded chapter in physiology of circulation" [3]. Arthur Guyton, among others, tried to break with dominance of cardiac function in conceptual thinking about the circulation. In 1955, half a century later then Starling and Bayliss, Guyton postulated a conceptual model for flow in the (human) circulation [4]. In his model of flow, Guyton defines venous return, i.e. the flow towards the right atrium, to be largely dependent on the pressure gradient between central venous pressure (CVP) and mean systemic filing pressure (MSFP). MSFP was defined as the pressure that exists in the whole systemic circulation if flow is stopped and the blood volume is spread over the circulation at equal pressure. In their first experiments Guyton and co-workers arrested blood flow by heart defibrillation [5]. They avoided effects of circulatory control mechanisms by pumping blood from the arterial part to the venous part in a few seconds until blood pressures were equal. This pressure was called mean systemic filling pressure.

Using this technique as a reference technique they tested another technique in which right atrial pressure (or central venous pressure) was increased stepwise and the resulting decrease in venous return (VR) was measured (Figure 1).

Figure 1 The relationship of venous return and right atrial or central venous pressure at different mean systemic filling pressure (MSFP or here named MCFP) values in one normal dog from Guyton [4].



The relationship between CVP and VR was found to be linear. Extrapolation of the linear regression line to VR=zero, or the pressure were this line crosses the x-axis, gives mean systemic filling pressure (MSFP). The extrapolated value of CVP appeared to be equal to the value of MSFP determined with the method of cardiac arrest by defibrillation. The linear fit of the line through the data points is called the venous return curve and can be described according to:

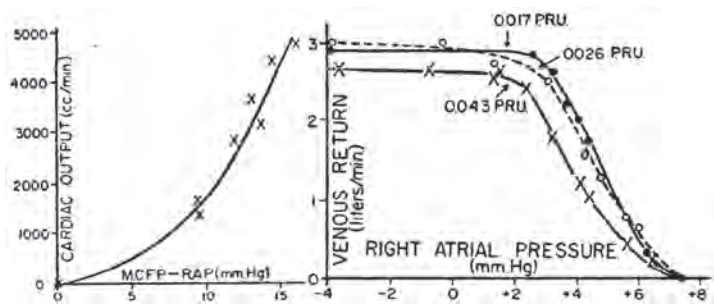
$$VR = (MSFP - CVP)/ Rsf$$

Were Rsf represent the flow resistance between MSFP and CVP. During steady state conditions VR becomes equal to cardiac output. In Figure 1 adapted from Guyton and co-workers, the effect of fluid loading on the venous return curve and MSFP is shown. Increasing circulatory volume shifted the venous return curve and increased MSFP. Different authors confirmed these findings in animal studies [6-8]. MSFP values between 7 and 20 mmHg were reported. Versprille and Jansen showed that these findings also hold for an intact circulation [6]. To arrange this they introduced inspiratory hold manoeuvres, i.e. inflations followed by and pause of 7 seconds. During such manoeuvres intra-thoracic pressure is increased, causing an increase in CVP and therefore a decrease in venous return and after a few heart beats in cardiac output. With seven different tidal volumes between 0 and 30 $ml \cdot kg^{-1}$ the resulting seven pairs of CVP and cardiac output (CO) values showed a linear relationship as mentioned above. Recently, we showed that MSFP can be determined in intensive care patients with an intact circulation with use of these inspiratory pause procedures, making estimations of circulatory compliance and serial measures of circulatory stressed volume feasible [9].

Analysis of cardiac output and right atrial pressure

Cardiac output is traditionally represented by the Frank-Starling heart function curves, which are dependent on heart rate, contractility and afterload. Another major contribution of Guyton and colleagues to the understanding of cardiac output regulation was that the venous return and heart function curve could be represented in the same graph (Figures 2-3).

Figure 2 Effect of the pressure gradient for venous return on cardiac output (MSFP is mean systemic filling pressure or named MCFP here; RAP is right atrial pressure equal to central venous pressure) and the effect of increasing peripheral resistance on venous return when the peripheral resistance is increased by occluding the small arteries with 250 micron glass beads in a normal dog [4]. The two graphs are the result of separate studies (points in the left and right graph do not correspond with the same measurement).



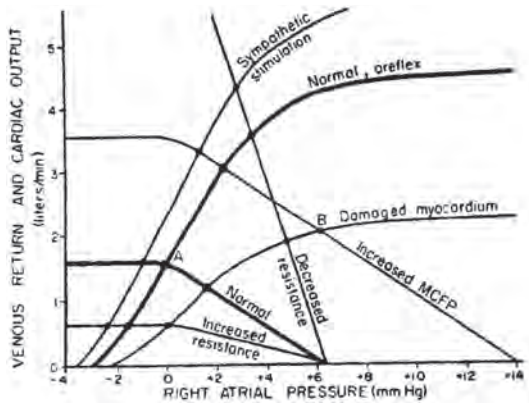
Indeed, in the complete circulation the heart and the systemic circulation must operate together. Thus, in steady state, VR and cardiac output are equal and the right atrial pressure is the same for both the heart and the systemic circulation. Therefore, actual cardiac output and right atrial pressure can be found at the intersection of the venous return curve and heart function curve as is shown in Figure 3. The two bold curves depict both the normal cardiac function curve and the normal function curve. The intersection is the working point of the circulation; venous return equals cardiac output at a certain right atrial pressure.

Effect of increased blood volume on cardiac output

A rapid volume loading of about 20% of total blood volume increases cardiac output to about 2.5 times normal [10]. The effect of increasing blood volume is depicted in Figure 3 by the venous return curve marked with increased MSFP. The intersection with the normal heart function curve shifted upwards increasing cardiac output and right atrial pressure. However

in the heart function curve damaged myocardium the intersection point B is on the flat part of the function curve. Additional fluid loading will not improve cardiac output. Furthermore, compared to the normal heart function curve, the change in right atrial pressure with volume loading is much greater.

Figure 3 Equilibration of various venous return curves with different cardiac response curves adapted from Guyton [4].



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In summary, the work of Arthur Guyton is an important step forward to the determination of volume status directly or at least the development of an accurate surrogate marker as will be discussed below and in the following chapters of this thesis.

Measurement of cardiac output

Besides signs like skin turgor, dieresis and skin colour, hemodynamic measurements like CVP and mean arterial pressure (MAP) are most often used for hemodynamic management. Organ perfusion is dependent on flow rather than pressure but flow is much more difficult to measure than pressure. CO is the amount of blood pumped through the circulation by the heart per minute. There are several reasons to use cardiac output in clinical practice. Cardiac output values, and trend, are often used as a substitute for volume status. The general conception is that an increase in cardiac output will improve perfusion of vital organs. Increased flow might also imply improved oxygen delivery to the tissues. This is the basis of the fluid loading responsiveness strategy that will be discussed later on in this introduction. Hence, an accurate determination of cardiac output is essential to allow not only for good patient assessment.

In the first chapter of this thesis we provide an overview of some of the most-often-used methods to measure cardiac output. We describe the Fick-method, ultrasound, indicator dilution techniques, arterial pulse contour analysis and bio-impedance. Characteristics like accuracy, precision, operator variability, invasiveness, interval of measurements, robustness and complications are reviewed. Thermodilution with a pulmonary artery catheter (PAC) is the de-facto gold standard for the measurement of cardiac output. The use of a PAC is however associated with several complications, like infection, pulmonary artery dissection, lung infarction, valvular lesion and pneumothorax [11]. In recent years, several less invasive methods have been developed. Pulse contour analysis is one of them and requires only a radial or femoral artery catheter [12]. In chapter two results are shown of an evaluation of the accuracy of the measurement of cardiac output using three methods (FloTrac–Vigileo, Modelflow and HemoSonic system) with thermodilution as the reference method [13]. Another parameter that can be estimated from the arterial pulse wave is stroke volume variation (SVV). Mechanical ventilation causes cyclic changes in venous return, pulmonary artery blood flow, and aortic blood flow. The changes in these parameters due to ventilation seem to be an indirect reflection of effective volume status [14]. SVV is the difference between the minimal and the maximum stroke volume divided by the mean stroke volume over a certain period of time. SVV is displayed as a percentage value. In some studies [15,16], stroke volume variation has been shown to have high sensitivity and specificity to predict of fluid loading responsiveness, i.e. the prediction of an increase in cardiac output with fluid loading. However, SVV requires full mechanical ventilation of the lungs and absence of arrhythmias when fluid loading responsiveness (FLR) is assessed [17]. Moreover, since stroke volume cannot be measured directly without a PAC, pulse contour methods are used. Different pulse contour methods are available but reports on their accuracy are rare. In chapter three, we present a comparison of the accuracy of SVV measured with the LiDCOplus and FloTrac-Vigileo system [18].

Parameters used in hemodynamic management in the ICU

Hemodynamic instability caused by relative or absolute intravascular volume deficiency are common in the ICU and OR. Physicians use several surrogate parameters to select patients who will benefit from fluid loading. We performed a survey to evaluate the use of these parameters by Dutch intensive care physicians. Results of this survey are shown in chapter four.

Fluid loading responsiveness

Traditional filling pressures like CVP often fail as a predictor [19-21]. Therefore, new methods are being developed or traditional parameters are used in a different setting to prevent fluid overloading by an accurate prediction of the response to fluid loading.

Relatively few strategies exist to assist the physician in hemodynamic management. One such strategy has recently received broad attention. This strategy is fluid loading responsiveness (FLR). FLR is used to predict whether cardiac output will significantly increase or not with fluid loading. A parameter that can accurately predict FLR has been sought for many years. New parameters like SVV have been developed and used in the FLR strategy. In chapter five we review the accuracy and limitations reported of the most frequently used methods in clinical practice to predict fluid responsiveness in patients undergoing mechanical ventilation. We provide a straightforward overview of determinants that can be used to predict a clinically significant effect of fluid administration on cardiac output.

Treating hypovolaemia

When hypovolaemia occurs and is diagnosed. Treatment is initiated. This will comprise the rapid administration of fluids. Fluid resuscitation is however not achieved immediately. The Trendelenburg position or head-down tilt, and passive leg raising (PLR) are routinely used in the initial treatment. In chapter six a meta-analysis is described into the hemodynamic effects of PLR and Trendelenburg. We asked ourselves which manoeuvre has the optimal effect on cardiac output (CO) while awaiting fluid resuscitation?

Mean systemic filling pressure

As we described above Arthur Guyton is responsible for some major steps in the development of a method to determine volume status directly. He defined mean systemic filling pressure as the mean pressure throughout the circulatory system under conditions of no flow. Together with the shape of cardiac output function curve, dimensions of the vascular system and blood viscosity, mean systemic filling pressure can be considered as a primary determinant of venous return and thus cardiac output. In chapters seven to nine, we present the results of three studies into mean systemic filling pressure. Ultimately, MSFP can be used to calculate stressed volume and, hence, quantify effective volume status in a specific patient [5].

However, in line with its definition determination of MSFP will require zero flow conditions throughout the circulatory system. Creating zero flow conditions at the bedside is unethical. We therefore developed a method to determine MSFP indirectly with two new methods; an arm model and a mechanical ventilator manoeuvre. In chapter seven, we studied the effect of dobutamine and hypovolemia on the circulation and tested the model of ventilatory holds with increasing airway pressure in pigs. In this model, CVP values can be used to extrapolate pressure at zero flow conditions. In chapter eight, we expanded on earlier work by Versprille and Jansen [6] to estimate MSFP with a ventilatory manoeuvre in humans. In chapter nine,

we use the second model (i.e. the arm model) to predict FLR in patients who underwent coronary artery bypass surgery.

Challenges to predict fluid loading responsiveness

In chapters ten to thirteen we study several challenges to predict FLR; +10 cmH_2O (chapter ten), the fluid challenge (chapter eleven), passive leg raising (chapter twelve) and the respiratory ventilator manoeuvre (chapter thirteen). New parameters like SVV and PPV are being developed to prevent fluid over-loading. But these parameters have their own limitations like inaccuracy in predicting FLR during low tidal volume ventilation [22] or in patients with arrhythmias [17]. In recent years traditional filling pressures like CVP often failed as a predictor for FLR [19-21]. We looked to re-use these traditional parameters, i.e. the changes induced by a challenge, to predict FLR.

A PLR-, fluid- or PEEP-challenge is aimed at determining the working point of the circulation on the Frank-Starling curve. It is assumed that when the patient is on the ascending portion of the Frank-Starling curve an (auto)transfusion will increase cardiac output. Once the heart is functioning near the ''flat'' part of the Frank-Starling curve fluid loading has little effect on cardiac output and central venous pressure will increase more. A PEEP-challenge on the other hand will give incrementally greater decreases in CO when the heart functions toward the flat part of the Frank Starling curve. We studied whether changes in parameters like CVP or CO as a result of a challenge can be used to estimate the working point on the Starling curve and consequently predict FLR.

In the discussion (chapter fourteen) of this thesis, we concentrate on the definition of fluid loading responsiveness and look for solutions and research directions for the future.

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