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THERAPEUTIC CONTROL OF THE CIRCULATION

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ABSTRACT. By regarding the circulation from the perspective of the venous return, continuous therapeutic control of the mean arterial blood pressure, cardiac output and tissue oxygen flow can be seen to be the consequence of a series of equations based on conventionally measured variables. This approach permits a graphical solution to circulation guidance, open or closed loop control and goal directed therapy of broad general applicability.

KEY WORDS. circulation, therapeutic control, haemodynamics, oxygen delivery, clinical guidance system, clinical decision support, clinical decision support.

INTRODUCTION

The care of the critically ill patient requires many and diverse skills. One of those skills is the ability to provide rational external therapeutic control to physiological processes in subjects in whom the normal internal control has been lost by virtue of disease.

Sound mathematical analysis may help in understanding the processes and in designing and implementing superior controls.

This point is well illustrated in the case of ventilation control. If we remember that the arterial carbon dioxide partial pressure (P_{aCO_2}) is reciprocally related to the effective or alveolar ventilation ($\dot{V}_{alv}$) then

$$P_{aCO_2} = P_b\left(\frac{\dot{V}_{CO_2}}{\dot{V}_{alv}}\right) \quad (1)$$

where $\dot{V}_{CO_2}$ is the CO_2 production and P_b is the ambient pressure. This leads to the familiar P_{aCO_2} basis for the control of ventilation.

Despite its apparent simplicity, this equation contains much information of clinical value. If P_{aCO_2} is rising we have to increase $\dot{V}_{alv}$ to reduce it. If $\dot{V}_{CO_2}$ is rising, $\dot{V}_{alv}$ must be increased to maintain P_{aCO_2}. If $\dot{V}_{CO_2}$ is known, the amount by which $\dot{V}_{alv}$ should be changed to achieve a new target P_{aCO_2} is predictable. The equation provides mathematical shorthand to summarize and order the interaction of important gas exchange variables, and how to manage them clinically.

It is now easy to understand why the physiological control of alveolar ventilation is primarily based on chemoreceptor sensing of the arterial P_{aCO_2}, how the gain of this arrangement ($d\dot{V}_{alv}/dP_{aCO_2}$, the ventilatory response to CO_2) may be known and how this paradigm

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seamlessly translates to the situation where the ventilation is controlled artificially.

In clinical practice, where many different staff are caring for the patient, there is a common goal and understanding for the regulation of ventilation. Expressions like ''under-ventilated'' or ''over-ventilated'' may be given precise P_{aCO_2} -based numerical definition. The management of ventilation is made more predictable and a consistent framework provided for interpreting unusual observations. Use of the P_{aCO_2} in this way is now globally part of ventilatory management. Whilst there are many other issues in the regulation of ventilation, P_{aCO_2} is the key. A mathematical approach has helped.

CIRCULATORY DYNAMICS AND CONTROL

By contrast, in bedside control of circulatory dynamics, there is a general paucity of quantitative ideas for numerical guidance. There is no shortage of variables that can be measured, but no agreed unifying numerical theory to relate data to states, states to therapy and therapy to goals. Measurement rather than guidance appears on monitors. This is surprising in view of the high frequency with which the circulation must be resuscitated and controlled in the critically ill, sometimes by multiple staff over prolonged periods of instability.

The reason is in part historical. The notion that if the heart stops then so does the circulation is a powerful one. Restated, the heart is central to the functioning or operation of the cardiovascular system; however operation is not the same as control. Early ideas of circulation control were vested in the heart. Starling, and predecessors [1] with the Law of the Heart [2], provided scientific momentum to a cardio-centric approach, showing that the more the heart was filled in diastole, the greater the stroke volume and work in the following systole. This led to the widespread idea that isotonic volume therapy, a cornerstone of circulation control, was properly based on preload measures. The aim of these preload measures is to assess how well the heart is filled in diastole. This has been the dominant paradigm of circulatory control for the last century.

Measures of preload have changed but not the idea. In the 1960s right atrial pressure measurement became common. In the 1970s and 1980s pulmonary artery occlusion or wedge pressure (a left atrial pressure surrogate) measurement supervened. A European view in the late 1980s and 1990s suggested that atrial and ventricular volume measurement (ITBVI, GEDVI; [3]) were more appropriate as pressure measurement is corrupted by changes in intrathoracic and intrapericardial pressure. The emergence of echographic techniques to measure intracavity dimensions and volumes added another level of debate.

In the course of this evolution it was pointed out that it was difficult to draw valid quantitative relationships between changes in preload measures and changes in the circulatory dynamics. This was part of the case for the adoption of volumetric measures of preload, and hence for management of isotonic volume therapy. Generally the volumetric measures were little more predictively successful. The evidence did not suggest deep understanding.

Simple reasoning shows all intracardiac pressures and volumes (preloads) have cardiac, resistive and systemic volumetric determinants. For example, if the left ventricular end diastolic pressure or volume is rising it could equally be due to a failing heart, increased left ventricular afterload (arteriolar resistance), increased circulatory filling or a combination of all three. It would be incorrect to use ''preload'' measures and ''volume state'' as though they were interchangeable. If the adult ventricular end diastolic volume was for example 100 ml, it would be only 2 or 3% of the systemic blood volume of approximately four litres. Why use this volume alone in the assessment of the volume state? It suggests misunderstanding of the way in which volume exerts its effect.

The debate of course is not just about volume state and preload. If one is unable to separate out volume effects then one is on uncertain ground in seeking to understand the discrete contribution of the heart and resistances to dynamics, and to disentangle the control argument.

In 1996 the first of a number of papers [4] appeared showing that in large randomized studies the insertion of a pulmonary artery catheter did not appear to confer survival benefit to patients with serious illness. A consensus has emerged that this result was probably because of the inconsistent ways in which the catheter data are used rather than catheter complication or use in patients who were either too sick or too well to show a survival influence. There was no clear revelation in respect of how the data was improperly used. Did measuring the pulmonary artery wedge pressure or cardiac output not improve understanding?

By 2001, Norton was able to point to approximately thirty definitions of preload described in the recommended texts of American medical schools [5].

The first decade of this century has seen a more pragmatic approach. In the apparent absence of a robust numerical measure of the volume state, a focus has become dynamic measures of ''volume responsiveness'', predictors of an increase in cardiac output and/or blood pressure in response to volume administration [6]. Such

predictors include variation in systolic pressure, pulse pressure and pulse volume consequent upon positive pressure ventilation [7]. Importantly "volume responsive" does not imply "volume requiring", merely predicting the dynamic response if volume is given [8]. Many normal citizens would be volume responsive but not immediately volume requiring. Volume responsiveness is used as a binary "fill" or "don't fill" measure. Presently it is not a scalar quantity. A further limitation is that these measures require mechanical ventilation and a regular heart rhythm.

Part of the difficulty in cardiovascular control is the circular nature of the argument. When the controlled process is circular the dynamic behavior at any point depends on that at all of the others. If external control is required where does one measure or intervene?

The resolution of this longtime dilemma is twofold. First, for the most part, the circulation is not controlled (as opposed to operated) by the heart, but by the tissue flow requirements for gas exchange and metabolism. Second, unlike most pumps, the heart fills passively; it is not a suction pump [9]. The confluence of these two ideas provides a mechanism by which the input flow (the venous return) is both controlled and in turn controls the cardiac output (CO). The systemic venous return (VR) is determined by a simple ohmic (flow = pressure/resistance) equation,

$$VR = \frac{(P_{ms} - \mathrm{RAP})}{\mathrm{RVR}} \tag{2}$$

P_{ms} is the mean systemic filling pressure (see below), RAP is the right atrial pressure and RVR is the resistance to venous return.

Starling's Law is best seen as the mechanism that ensures the output of each ventricle is servocontrolled to its venous return. If the venous return to a ventricle is incrementally different from the output, time integration of the $CO-VR$ difference ensures that the diastolic volumes in the heart will change until, at the present ventricular performance, there is an equal change in CO. Such an arrangement allows for example for massively different outputs from the two ventricles in the case of septal defects. Separately, the cardiac output is reduced appropriate to a decreasing venous return preventing stalling of the heart.

The focus in this is the venous return and its determinants, not the diastolic volume or preload. As Guyton notes, the mean circulatory filling pressure "turned out to be the first measurable quantity that allows one to relate the blood volume mathematically to the control of cardiac output and arterial pressure." [10]

The venous return equation (Equation 2) is arguably one of the more important equations in all of physiology.

THE DETERMINANTS OF THE SYSTEMIC VENOUS RETURN

The mean systemic filling pressure, P_{ms}

In elastic sided structures, such as a tyre inner tube or vascular element, a certain volume is required to fill the structure to a circular unstressed state. This is called the unstressed volume, V_0 (ml.) and causes no pressure rise. Further volume addition (V_e the stressing volume) stretches the wall and causes a pressure rise equal to

$$P = {}^{V_e}/_{C} \tag{3}$$

where C is the wall compliance.

Essentially all parts of the circulation, with the exception sometimes of the central veins and the right atrium, have a positive pressure with respect to atmosphere. It follows that all include a stressing volume. When the heart is stopped and the blood volume redistributes from arteries to veins it follows that a positive pressure will exist in the entire circulation. This positive pressure is thus a measure of the fullness of the circulation.

For the circulation of a 70 kg adult, the blood volume ($V_o + V_e$), is of the order of 5000 ml, V_e is in the range 500–1000 ml and C in the range 1–2 ml/kg/mmHg [11]. Thus the static pressure when the heart is stopped is normally about 7 mmHg.

For the whole circulation, this static pressure is called the mean circulatory filling pressure, (P_{mc}). For the systemic circulation, in which it may have a different value, it is called the mean systemic filling pressure (P_{ms}). Difference in P_{mc} and P_{ms} is accounted for by variation in P_{mp}, the mean pulmonary filling pressure. P_{ms} and P_{mc} are controlled in the long term by the kidney to a normal value of approximately 7 mmHg in several mammals including humans [12]. In subjects with heart or renal failure, P_{ms} not infrequently exceeds 20 mmHg. It is worth noting that virtually all gains to and losses from the circulation take place via the systemic circulation. Thus control of the volume state in the first instance relates to control of P_{ms}.

In exactly the same way as the static internal pressure measures the volume state or state of fullness of a tyre, P_{ms} – and not any measure of preload - is the proper measure of the volume state of the systemic circulation. Unlike preload measures, P_{ms} is not directly affected by the operation of the heart or the circulatory resistances, depending only upon the stressing volume and compliances. Equation (2) shows the quantitative link between that static volume state and the dynamics of venous return and cardiac output. P_{ms} is critical to the quantitative understanding of the circulatory dynamics [13].

Experimentally, P_{mc} may be measured by fibrillating the heart, measuring the equilibrium pressure in the circulation, defibrillation and a return to normal circulation. Occasionally P_{mc} is observed clinically, for example at termination of ventilation in the brain dead or with pacemaker failure (personal observation). Though stopping the global circulation is impractical as a method of measuring P_{ms}, one can temporarily retard venous return with positive pressure ventilation and observe effects related to the influence of rise in RAP upon the $P_{ms} - RAP$ difference [14].

The right atrial pressure, RAP

The total pressure RAP in the right atrium is the sum of the internal pressure plus the pressure (or restraint) p_t external to the atrium. p_t is determined by both the intrapericardial and intrathoracic pressures. To a degree all these pressures are interdependent. The total pressure is given by

$$RAP = \frac{V_{rae}}{C_{ra}} + p_t \tag{4}$$

where V_{rae} is the excess volume in the right atrium and C_{ra} the atrial compliance

$$V_{rae} = V_{ra} - V_{rao} \tag{5}$$

where V_{ra} is the total right atrial volume and V_{rao} is the unstressed volume.

In turn, V_{ra} is equal to the time integral of the difference of F_{rai}, the inflow to and F_{rao}, the outflow from the atrium.

$$V_{ra} = \int (F_{rai} - F_{rao})dt \tag{6}$$

F_{rai} is equal to the venous return, which is a function of P_{ms} (the volume state), the right atrial pressure RAP itself and RVR, the resistance to venous return (Equation 2). F_{rao}, the flow from the atrium is a function of the right and left heart performances and characteristics of the pulmonary circulation.

Thus the right atrial pressure, often used as a preload measure, is in fact a complex signal dependent upon the volume state, systemic and pulmonary resistances, the intrathoracic and intrapericardial pressures and their determinants, atrial compliance and unstressed volume, biventricular performance and itself. The right atrial pressure only measures the volume state when the heart is stopped.

Since the right atrial pressure is the lowest pressure in the circulation, it may be seen as analogous to a "floating ground" in an electrical circuit. In normal subjects RAP approaches zero as with a fixed ground.

The tricuspid valve inlet within the right atrium is the horizontal datum to which intravascular pressure measurement is referred, the phlebostatic axis.

The resistance to venous return, RVR

The resistance to venous return is defined as the resistance encountered by the average circulating element in returning to the heart. Since the average element includes those in both the arteries and the veins, RVR is influenced not only by the arterial and venous resistances but by the proportionate volumetric disposition of the elements in relation to the resistances. This relative volumetric disposition is influenced in turn by arterial and venous compliance. The further downstream a resistance is placed in relation to the various compliances, the greater is its effect upon circulatory dynamics [9].

Changes in the venous component of the resistance to venous return, which are not easily measured, are dynamically indistinguishable from changes in P_{ms} of opposite sign. Inferior vena cava compression (increased RVR) for example is used experimentally to simulate hypovolaemia (i.e. decreased P_{ms}). Putting aside clinical situations such as the supine hypotension syndrome in pregnant subjects, conditions of increased venous resistance are generally managed by increasing the volume state. A common cause of an increase in venous resistance is the compensatory venoconstriction of hypovolaemia.

It is thus the arteriolar resistance, approximated by the systemic vascular resistance (SVR), that is the frequent or usual object of therapeutic vasoactive control. It is appreciated that measuring a dc resistance in an ac system is at best an approximation.

ALGORITHM FOR ESTIMATING MEAN SYSTEMIC FILLING PRESSURE, P_{MS}

As volume state increases, so does P_{ms}. This causes venous return (Equation 2) and hence cardiac output (Starling) to rise, which in turn causes arterial pressure to rise. At some point, the heart's Starling curve will flatten out and limit further increase in stroke volume and cardiac output; the right atrial pressure will rise correspondingly to limit venous return. Thus in seeking a mathematical algorithm for estimating P_{ms} from the observable dynamic data we can expect it to depend on cardiac output, mean arterial pressure and right atrial pressure (and possibly other factors).

Mathematical modeling techniques are increasingly used to better characterize biological processes in fields as diverse as pharmacodynamics, respiratory mechanics, and blood glucose control. Such techniques might be expected

to play an increasing role in bedside instrumentation particularly in situations where a value is to be inferred from indirect measurement. An example is derivation of the cardiac output from the arterial pulse signal, e.g. the FloTrac (Edwards Lifesciences, Irvine, CA, USA), LiDCO (LiDCO Ltd, London, UK) and PiCCO (Pulsion Medical Systems AG, Munich, Germany) devices.

We have used a mathematical modeling technique to develop an algorithm for estimating an analogous value of P_{ms} from normally measured circulatory variables without stopping the heart [15]. In this approach, the model consists of a heart and a systemic circulation comprising compliant arterial and venous compartments and resistances to blood flow. Rather than stopping the patient's heart, the model parameters are adjusted so that the model variables match those of the patient's current measured variables. The model heart is then stopped. This results in the following formula for estimating the analogous value P_{msa}

$$P_{msa} = a\text{RAP} + b\text{MAP} + c\text{CO} \tag{7}$$

where a and b are dimensionless constants ($a + b = 1$, typically $a = 0.96$, $b = 0.04$). c has the dimensions of resistance and is determined by patient anthropometrics. c scales the equation for patients of different height, weight and age. The normal cardiac index for age was taken from Guyton [12].

For ABC simplicity this is remembered as:

P_{msa} = $a \times$ Atrial pressure + $b \times$ Blood pressure + $c \times$ Cardiac output

In a patient in whom RAP = 0, MAP = 100, $CO = 6$ and $c = 0.5$

$$P_{msa} = 0.96 \times 0 + 0.04 \times 100 + 0.5 \times 6 = 7 \tag{8}$$

If the heart stops, all pressures in the circulation become equal (MAP = RAP) and $CO = 0$. P_{msa}, the volume state, is unaffected. Notice how RAP, one of many preload measures, rises from 0 to 7 without any volume change.

$$P_{msa} = 7 = 0.96\text{RAP} + 0.04\text{RAP} = \text{RAP} \tag{9}$$

Equation (7) informs that knowledge of MAP and CO are important in the assessment of the volume state, a point lost in preload approaches. Hypertension in the intensive care patient often has its origins in overfilling; the same is true for abnormal elevation of the cardiac output. In such patients preload measures may be low if the heart is functioning vigorously.

The clinical validity of the P_{msa} equation was tested in a study of 10 critically ill patients with multi system organ failure including acute renal failure [16]. Volume replacement of the filtrative loss in continuous venovenous haemodiafiltration was closed loop servo-controlled to a P_{msa} target. Circulatory stability considerably exceeded that obtained with conventional volume based replacement in a total of over 600 l of exchange. The closed-loop contoller had no knowledge of the magnitude of filtrative loss or controller addition. This approach provided support for the idea of measuring P_{msa} as the measure of the volume state and the object of volume servo-control.

MEASURING THE PERFORMANCE OF THE HEART

If P_{ms} as a volume measure and the subtleties of RVR are understood there remains the question of measuring the performance of the heart as it is functioning in the current circulation. The behaviour of reservoirs provides useful illustration for the venous return and understanding of the role of the heart (Figure 1).

A large reservoir of pressure head P_D has an exit pipe of resistance R through the base of the wall. The pipe fills a small chamber of head P_C. Within the chamber a person buckets water back into the reservoir. The person is careful to keep P_C low and constant; their bucketing output thus equals the flow F into the chamber where

$$F = \frac{(P_D - P_C)}{R} \tag{10}$$

In this arrangement, P_D is analogous to P_{ms}, P_C to the right atrial pressure RAP, R to the resistance to venous return RVR, F to the venous return and the bucketer to the operation of the heart.

The following characteristics of this arrangement are noted.

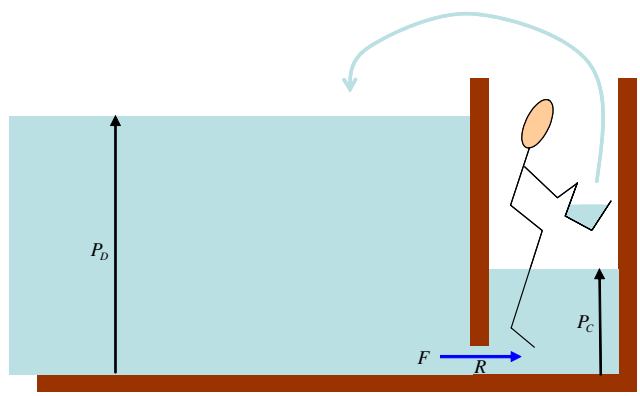

Fig. 1. Two reservoir analogy.

i. Water enters the chamber passively, even when the bucketer is still. Equally, the venous return is passive.
ii. Since reservoir volume >> chamber volume, variation in bucketing rate has no measurable effect upon P_D the ''head'' of the reservoir. Equally P_{ms} is unaffected by the operation of the heart.
iii. If P_D increases, the bucketer must increase output to maintain constant P_C. If the right atrial pressure is held constant and P_{ms} is increased the venous return and cardiac output will increase.
iv. For constant P_D and P_C, decrease in R will increase F. At constant P_{ms} and RAP, decrease in RVR will increase venous return and cardiac output. RVR is affected by both arterial and venous resistance.
v. The same $P_D - P_C$ difference and therefore the same flow Fmay be achieved at different values of P_D. Clinically the same venous return and cardiac output may be achieved by raising P_{ms} if the heart fails and RAP rises. This is achieved by renal sodium and water retention.
vi. The dimensionless expression,

$$E_H = \frac{P_D - P_C}{P_D} = 1 - \frac{P_c}{P_D} \tag{11}$$

may be used to describe the person's bucketing efficiency. If the person stops bucketing P_C approaches P_D and E tends to zero. Vigorous bucketing causes P_C to approach zero and E tends to unity.

Using this analogy, we can define the overall pumping efficiency of the heart as E_H using the analogue value P_{msa} where

$$E_H = \frac{(P_{msa} - \mathrm{RAP})}{P_{msa}} = 1 - \frac{\mathrm{RAP}}{P_{msa}} \tag{12}$$

This dimensionless ration ($0 \le E_H \le 1$) is a very useful clinical guide to assessing heart performance. If the heart stops pumping, RAP approaches P_{msa} and E_H approaches zero. E_H may be used for example in inotropic control. A measure of the volume state (P_{msa}) has thus enabled derivation of a measure of heart performance.

RAP (see above) and hence E_H may be affected by mechanical factors external to the heart (e.g. tension pneumothorax, over-inflated lung, raised intrathoracic pressure, pericardial tamponade) in the same way that the bucketer would be impeded by a rising water level in the chamber. Clinically, if $E_H < 0.3$, such factors should always be sought.

E_H is also determined by factors intrinsic to the heart: rate, rhythm, inotropy, lusitropy, etc. analogous to the rate and strength of the bucketer. E_H defines the value of RAP for a given volume state and heart performance, from Equation (12),

$$\mathrm{RAP} = P_{msa}(1 - E_H) \tag{13}$$

Control of the circulatory dynamics is much simpler when seen in the context of the smooth ''waterfall'' of the venous return. Importantly, this is how the dynamics are normally regulated. The motion of the heart is more variable, dimensionally complex and potentially irregular. Intercavity septa may be incomplete or show paradoxical motion. Heart valves may be stenosed or incompetent. The ''heart'' might only exist as a centrifugal pump. Ultimately, in all situations, a venous return will be required and will determine the cardiac output.

DERIVATIVE FORMULAS FOR CARDIAC OUTPUT AND MEAN ARTERIAL PRESSURE

Much has been written of measuring the adequacy of perfusion in regional circulations. While many strategies exist for optimization of regional or organ blood flow and pressure, most ultimately depend upon adequate global perfusion and pressure and intact regional physiology. Controlling the circulation within user determined pressure (MAP), flow (CO) and oxygen flow (ODI or S_{vO2}) boundaries is a common practical clinical requirement.

We can form equations for CO and MAP as follows. From Equation (2), equating venous return and cardiac output,

$$CO = VR = \frac{(P_{ms} - \mathrm{RAP})}{\mathrm{RVR}} \tag{14}$$

Substituting for RAP from Equation (13)

$$CO = \frac{(P_{ms} - P_{ms}(1 - E_H))}{\mathrm{RVR}} \tag{15}$$

$$CO = \frac{P_{ms}E_H}{\mathrm{RVR}} \tag{16}$$

Equally

$$\text{Since SVR} = \frac{\mathrm{MAP} - \mathrm{RAP}}{CO} \tag{17}$$

$$\mathrm{MAP} - \mathrm{RAP} = CO \cdot \mathrm{SVR} \tag{18}$$

Substituting for CO using Equation (16) gives

$$\mathrm{MAP} - \mathrm{RAP} = P_{ms}E_H{}^{\mathrm{SVR}}/_{\mathrm{RVR}} \tag{19}$$

where resistances in these equations are in mmHg/l/min.

From (16) and (19) we note that both the flow and pressure drop across the circulation, as with most

cardiovascular dynamic signals are volume, resistance and heart dependent. In the normal circulation as RAP approaches zero and E_H approaches unity (Equation 12), Equation (19) reduces to

$$MAP \approx P_{ms} \frac{SVR}{RVR} \quad (20)$$

Implications for the role of the kidney in long-term circulatory control

Equations (19) and (20) highlight the role of P_{ms} in the long term control of the blood pressure in which the effector organ is the kidney operating according to the principle of infinite gain [17]. It provides understanding as to why some authors believe that the mean arterial blood pressure IS the volume state [18]. The case for diuretic use in hypertension management is equally apparent.

Equation (20) together with Equation (16) illustrates how the kidney, in controlling P_{ms}, can maintain the blood pressure at widely varying values of *CO,* SVR, RVR and oxygen flow. The role of P_{ms} and the SVR/RVR ratio allow for a remarkable redundancy and agility in the independent control of pressure and flow.

The prime renal sensor for the regulation of sodium-water balance, P_{ms} and resistance, the juxtaglomerular apparatus together with the renin-angiotensin -aldosterone system is primarily sensitive to the arterial blood pressure and flow, a logical feedback consequence of Equations (16) and (19).

It can also be seen from Equations (16) and (19) how, if the heart fails and E_H decreases, the arterial pressure and flow will be significantly maintained by renal sodium and water retention and elevation of P_{ms}.

DEVELOPING A THERAPEUTIC GUIDANCE ALGORITHM

We have outlined methods and equations for estimating the volumetric (P_{msa}), resistive (SVR) and cardioactive states (E_H) from normally measured cardiovascular variables (MAP, RAP, *CO*) and patient anthropometrics (age, height, weight). If these states are evaluated for the present and desired circulations, the nature and direction of therapeutic change required to gain and hold the desired circulation may be continuously known. The approach is illustrated in examples.

Example 1

A 67 y patient currently has RAP = 6 mmHg, MAP = 68 mmHg and *CO* = 4.7 l/min. The patient's "c" value in Equation (7) is 0.75 mmHg/l/min. The present value of P_{msa} is thus 12.0 mmHg and of SVR is 1055. The physician has set a desired *CO* of 6.0 l/min and a desired MAP of 85 mmHg. The desired values of P_{msa} and SVR are calculated as 13.7 mmHg and 1053 respectively. Thus to achieve the desired target a +1.7 mmHg (or +13.8%) change is required in P_{msa} and very little change of −2 (or −0.2%) change is required in SVR. The patient requires volume to increase P_{msa} and no change to vasoactive therapy. The patient's heart performance $E_H = 0.5$ suggesting no need for additional inotropic support.

Example 2

A 44 y patient currently with RAP = 5 mmHg, MAP = 104 mmHg and *CO* = 5.5 l/min, with c = 0.57 mmHg/l/min. Present values of P_{msa} and SVR are 12.1 mmHg and 1440. Desired *CO* and MAP are 6.5 l/min and 90 mmHg. Desired values of P_{msa} and SVR are calculated as 12.1 mmHg and 1046 respectively. Thus to achieve the target no change is required in P_{msa} and a −394 (or −27.4%) change is required in SVR. The patient requires vasodilatation.

Example 3

The patient in example 2 deteriorates to RAP = 14 mmHg, MAP = 70 mmHg and *CO* = 4.5 l/min. Current P_{msa} is 18.8 and desired is 20.7 mmHg. Hence volume therapy is required (however, see notes on volume responsiveness below). There is a low present E_H of 0.26. Once mechanical impediments to venous return have been ruled out (see above), inotropic support is also indicated.

Sequencing of therapy

Frequently, changes will be needed to volume, resistive and inotropic therapies to acquire the desired circulatory state. It is important that these changes are applied in the appropriate order. Sequencing of therapies may be achieved by choosing a trajectory which moves both mean arterial pressure and cardiac output monotonically towards targets, thus avoiding hazardous regions in the circulation space.

Setting cardiac output target

The desired cardiac output may also be set from a desired cardiac index, knowing body surface area, or from a desired oxygen delivery index, given hemoglobin and arterial oxygen saturation.

PRACTICAL REALIZATION

The ideas outlined above have been developed with the aim of providing practical support and improved hemodynamic management by the bedside of the critically-ill patient, and improving patient outcomes.

The authors have developed a real-time clinical guidance or decision support system based on the above principles for circulatory and oxygen delivery optimization and management (Navigator™, Applied Physiology Pty Ltd, Sydney, Australia). The system provides the bedside clinical team with continuous therapeutic information – the targets sought, where the patient currently is, what therapy should be used and in what order. The aim is to systematize cardiovascular management, simplify the cognitive tasks for the clinicians, consistent achievement of targets, minimize variation and improve outcomes.

The system automatically acquires the circulatory variables from the bedside multi-parameter and hemodynamic monitors (including RAP, MAP, *CO*, S_{aO_2}). A touchscreen enables the clinician to enter target or desired ranges for blood pressure, cardiac output (or index) and oxygen delivery, as well as age, height and weight.

The system's display is shown in Figure 2. On the right hand side are the current values acquired from the monitors, targets and other patient data. The left hand side contains an innovative 2D graphical display depicting the patient's position on volumetric (P_{msa}) and resistance (SVR) axes. We are able to do this because P_{msa} and SVR are orthogonal; changing the patient's volume state does not affect resistance and vice versa. Lines of constant MAP and *CO* are shown corresponding to their upper and lower target ranges. The equivalent oxygen delivery indices are shown on the *CO* lines. The patient's current position is shown as a red dot in the yellow arrow. The latter provides guidance on which next therapy (i.e. volumetric, vasoactive/resistive or cardioactive) will take the patient toward the desired blood pressure, cardiac output and oxygen delivery targets. The value of heart performance E_H is assessed from a vertical axis that runs parallel to the P_{msa} axis. MAP and *CO* can both be increased by increasing P_{msa} or E_H using volume or inotropes. Hence the two axes can be displayed together. The axes move independently as the patient's state changes.

The patient in Figure 2 requires both volume and vasodilatation. The guidance arrow shows that volume should be given first. The direction of this arrow is based on the sequencing strategy discussed earlier. Following volume therapy, the patient moves to the position shown in Figure 3, where the arrow now recommends vasodilatation. In clinical terms, this has avoided the risk of hypotension with vasodilatation prior to adequate filling.

The patient shown in Figure 4 has both a low volume state and a low heart performance (E_H = 0.20). First, this patient should be investigated for mechanical problems that may be restricting blood flow return to the heart (e.g. tension pneumothorax, over-inflated lung, etc.). If these are excluded then the low E_H indicates inotropic therapy.

The system provides continuous assessment and guidance to the clinical staff, augmenting the clinical information available and assisting their clinical decision

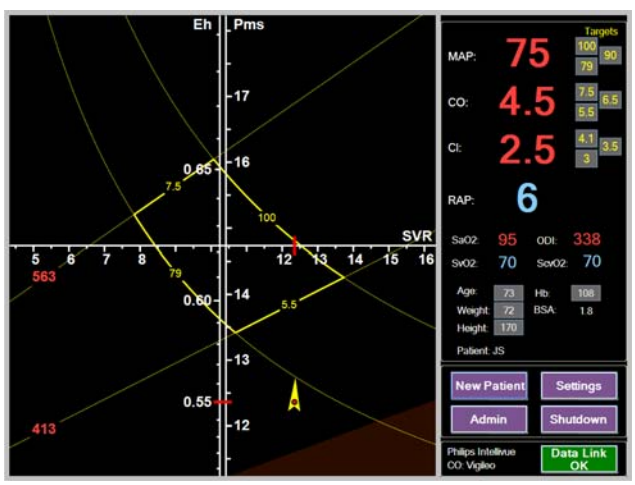

Fig. 2. Navigator™ display.

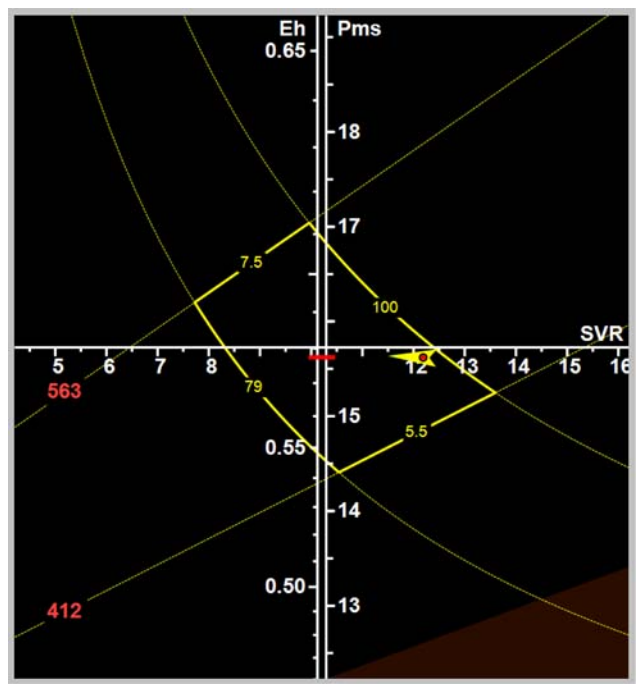

Fig. 3. Patient requiring vasodilatation.

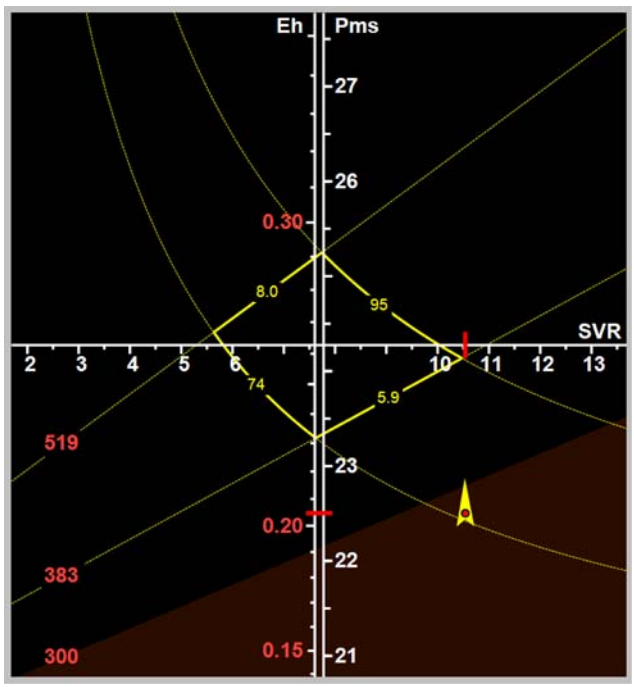

Fig. 4. Patient requiring volume and inotropes.

making. Targets may be changed at any time as judged necessary by the physician, and the consequent changed to therapy will be automatically recomputed.

VOLUME RESPONSIVENESS

A pragmatic approach to volume therapy of the last decade is the evaluation of volume responsiveness. This assesses the likely dynamic (MAP, *CO*) response to a volume load. Pulse pressure variation, systolic pressure variation and stroke volume variation on positive pressure ventilation have been shown to predict volume responsiveness [6].

The methods presented here, and their computer realization, provide a new approach to volume responsiveness. The administration of volume expanders causes P_{msa} to increase. If the patient's position on the (SVR, P_{ms}) display gets closer to the desired circulation with increasing P_{msa}, then the patient is volume responsive. Further, the degree to which this is achieved may be quantitated with a scalar measure. Equally, if P_{msa} is increasing, but E_H is falling, then the patient has low or no volume responsiveness. This will work in all patients in whom cardiac output is measured, regardless of whether they are mechanically ventilated or spontaneously breathing, and with a regular or irregular heart rhythm. The local slope of the $E_H - P_{msa}$ relationship is predictive of volume responsiveness.

This new approach will overcome the limitations of other methods based on stroke volume variation or pulse pressure variation that require positive pressure ventilation or passive leg raising, and a regular heart rhythm [6].

Role of pulmonary capillary wedge pressure (PCWP)

Since the pulmonary and systemic circulations are separated by energy sources, the mean pulmonary (P_{mp}) and mean systemic (P_{ms}) filling pressures may be different. Isolated left ventricular failure in the presence of a competent right ventricle may lead to elevation of P_{mp} to the detriment of P_{ms} with a reduction in the systemic venous return. In such a situation the left atrial pressure (LAP) and the pulmonary capillary wedge pressure (PCWP) may be elevated and the patient at risk of pulmonary oedema if further volume is administered.

In the absence of PCWP measurement, some protection from high pressure pulmonary oedema is available in the assessment of volume responsiveness. A patient with severe isolated left ventricular failure of a magnitude that will lead to pulmonary oedema is likely to be poorly volume responsive, a positive contraindication to further volume administration.

There are a number of theoretical reasons why PCWP might be a poor predictor of the development of pulmonary oedema. PCWP may not equate to LAP and is not indicative of pulmonary capillary permeability. It is likely that PCWP and LAP are not just indifferent guides to the volume state, the need for volume and volume responsiveness but relatively poor predictors of pulmonary oedema.

Avoidance of low pressure pulmonary oedema may be achieved in part by identifying subjects likely to be at risk, minimizing or optimizing target circulatory power and reducing fluid requirements with cardioactive use.

CONCLUSIONS

Consideration of the determinants of the venous return allows numerical descriptors of the volume, resistance and heart states that determine cardiovascular dynamic variables. Evaluation of the three therapeutic states for the present and desired circulations enables continuous quantitative description of the therapeutic change required to achieve any desired circulation. This approach has been realized in a practical system for clinical therapeutic guidance and optimization.

The approach described in this paper enables the clinician to better achieve cardiac output targets. It also

allows the targeting of oxygen flow and oxygen delivery index measures.

This is achieved with graphical guidance. Constraint of the upper bound of oxygen delivery is part of the strategy of limiting fluid therapy and inotropic use.

> The difficulty lies not in the new ideas but in escaping from the old ones.
>
> *John Maynard Keynes (1883–1946), British economist. The General Theory of Employment, Interest and Money, preface (1936).* [19]

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