

Controlled Observations in Critical Care Medicine: The Therapeutic Trial

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Abstract

The practice of critical care medicine revolves around the monitoring of patients to identify acute physiologic deterioration and the titration of therapies aimed at supporting internal homeostasis. Central to this practice is the evaluation of therapies or stresses designed to assess homeostatic reserve and to uncover pathologic processes. Both the cardiovascular and respiratory systems have received particular attention because of the ease with which specific haemodynamic and respiratory parameters can be measured, the ability to modulate their status with therapies, and the intimacy of both cardiovascular and respiratory status to overall homeostasis. These forms of assessment are referred to as clinical trials, and if performed in a rigorous fashion are referred to as controlled clinical trials. Clinical trials form much of the basis for titration of therapy, wherein a specific therapy is adjusted so as to optimise its effectiveness in an individual. Titration is typically done once a diagnosis has already been made or a treatment identified, such as with the titration of antihypertensive therapy in either hospital or outpatient setting. This review will focus on the exploratory aspect of clinical trials wherein a specific manoeuvre is performed to determine either the aetiology or severity of a pathophysiologic problem.

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Rationale for Controlled Clinical Trials

Central to the combined diagnostic and therapeutic approach to the critically ill subject is the evaluation of both the basal physiologic status and its subsequent change over time consequent to a therapeutic intervention.* The essential questions asked at the patient's bedside are:

- 1) "What is the primary (and secondary) stress that is affecting the patient?"
- 2) "How are the patient's homeostatic mechanisms coping with the stress?"
- 3) "What are the primary determinants of the inability to cope with the stress?"

Diagnostic approaches or therapies based on data derived from bedside monitoring in the critically ill patient assume that specific sets of derangements or abnormalities of these data sets reflect specific disease processes which will respond appropriately to an intervention.² For example, hypovolaemia may present with either tachycardia, low urine output, cool extremities or postural hypotension or some combination of these signs and symptoms, which should resolve with effective treatment. The clinical presentation of a critically ill patient is often confounded by co-existing disease proc-

esses. This increases the difficulty of interpreting diagnostic data and response to therapies. Similarly, it is difficult to formulate universally accepted therapy or diagnostic approaches to a particular critical care problem.

Specific combinations of haemodynamic variables often reflect certain disease states. However, there may be considerable overlap among markedly different pathological states that may require different therapies. This is the result of individual patient differences, complex cardiovascular interactions, inaccuracies in the measures themselves and incorrect assumptions as to what is the primary pathophysiology and the expected response. This confusion can be reduced by performing an experiment at the bedside. Examples of such clinical trials include fluid therapy, diuresis or increased inotropic therapy. The specific haemodynamic response of the individual to a particular therapy is examined.³ Accordingly, in a controlled clinical trial, all known or "controllable" variables are either held constant by design or not allowed to change markedly because of the rapidity of the challenge and its measurement. Examples of rapid challenges that limit associated compensatory changes from confounding the initial physiologic response include rapid intravascular fluid challenge or a T-tube

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weaning trial.

Because no organ system functions without numerous feedback processes, clinicians can use these feedback processes to assess the level of disease or homeostatic reserve. These interactions form the basis of controlled clinical trials. Certain combinations and changes in cardiovascular variables are reflective of specific disease processes, such as heart failure, hypovolaemia and sepsis. Awareness of specific aspects of each component of the system and their response to stress and disease is central to understanding how the other components of the cardiovascular system will respond.

Numerous examples of similar patterns of haemodynamic dysfunction but differing response to intervention exist. For instance, both septic shock and acute cardiogenic shock may present in the unresuscitated patient with a low cardiac output, hypotension and a low normal Ppao.⁴ However, in response to an intravascular volume challenge, septic patients will tend to selectively increase cardiac output with less of an increase in arterial pressure and possibly no change in Ppao demonstrating a relatively selective loss of peripheral vasomotor tone. Whereas patients with acute heart failure will tend to increase both Ppao and blood pressure with less of an increase in cardiac output because vasomotor tone is already high and only cardiac contractility is impaired. Thus, not only initial haemodynamic profile data, but their change in response to therapy aid in making clinical diagnoses and guiding therapy."

Tools to Monitor a Controlled Clinical Trial

Inherent in any controlled clinical trial is not only the artificial handling of the physiologic state by varying limited variables while holding others constant, but also the measure of some output function which defines that the trial shows one thing or another. For example, measures of haemodynamic status are essential in assessing a haemodynamic modulation. These may be less specific and often less sensitive than we would like. Thus, a basic understanding of the tools available for monitoring, as well as their limitations, is essential for any clinician partaking in this form of diagnostic approach.

Invasive haemodynamic monitoring, including arterial, central venous, and pulmonary arterial catheterisation, allow assessment of numerous physiologic variables which may be important in a specific clinical situation. In pulmonary arterial catheterisation, a large number of different measures may be made from a single catheter, including continuous measures of central venous pressure (CVP), pulmonary arterial pressure, mixed venous O₂ saturation (SvO₂)^{6,7} and, in specialised catheters, cardiac output.⁸ Furthermore, intermittent measures of pulmonary artery occlusion pressure (Ppao), SvO₂, car-

diac output⁹ and right ventricular ejection fraction (RVef)^{10,11} can be made. Continuous measures of arterial and central venous pressures can be made from an indwelling arterial or central venous catheter, respectively, allowing for analogue analysis of wave from variation, and rapid assessment of dynamic changes over time. Finally, arterial O₂ saturation can be measured by non-invasive pulse oximetry and interfaced to the above measured variables to give a more complete picture of the overall physiologic state.

Still, these measures only reflect part of the cardiovascular system; they do not answer the three essential questions posed above. To do that, one must follow the subject over time or as they respond to some external intervention. How these responses define the diagnosis or direct therapy is based on an understanding of cardiorespiratory physiology in general and the patient's own physiology in particular. These points are briefly reviewed below.

Applied Physiology at the Bedside

The primary goal of the cardiorespiratory system is to maintain tissue perfusion with blood enriched with enough O₂ to allow for normal metabolism and responses to stress. To that end complex adaptive mechanisms coordinated both at a local tissue level and through the autonomic nervous system function to maintain cardiopulmonary status within a narrow range despite significant stresses to the system. Thus, the measures taken at the bedside of blood pressure, cardiac output, and arterial blood gases are exactly the ones that the body tries to keep constant despite stress. One method of assessing such a system is to induce a change, allowing any coping process to become accentuated. However, to do that and to correctly understand the significance of the response, a good working knowledge of basic physiology and pathophysiology of common disease states is essential.

Left Ventricular Function

The heart can only pump into the arterial circuit that which it receives. Furthermore, the force of contraction of the left ventricle is related to left ventricular (LV) end-diastolic volume (EDV),¹² such that increasing LV EDV usually increases LV stroke volume, and for a constant heart rate, cardiac output as well. The relation between LV EDV and LV output is referred to as the Frank-Starling relationship (Fig. 1). These simple points form the basis of most of the resuscitative efforts done in unstable patients. LV EDV is synonymous with LV preload, and the primary determinant of LV preload is venous return from the body to the heart. Finally, fluid resuscitation or vasoactive drug infusions all increase venous return, albeit by different mechanisms, thereby increasing LV preload and cardiac output. Thus, in any

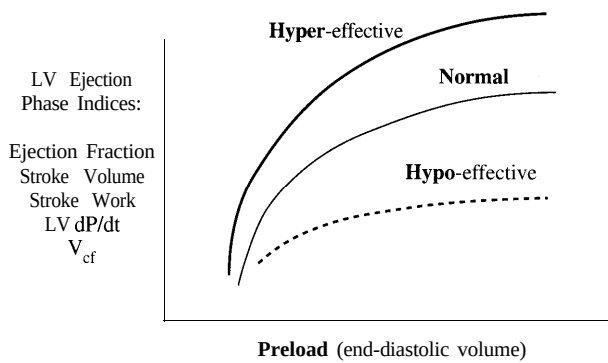


Fig. 1. Relation between left ventricular (LV) end-diastolic volume and various LV ejection phase indices. As compared to normal function, a hyper-effective heart has a high LV ejection phase response and a hypo-effective heart has a low ejection phase response. However, almost all hearts will increase their output somewhat in response to increases in end-diastolic volume.

patient in whom the cardiovascular status is unknown but in whom evidence of hypoperfusion is suspected (*infra vidae*), an intravascular fluid challenge is usually performed in an attempt to correct the observed defect.

If LV pump function is impaired, as may occur in heart failure or cardiac tamponade-like states, then for the same increase in LV EDV, LV stroke volume will not increase as much. Thus, if the fluid challenge described above does not reverse the presumed defect, many physicians assume that heart failure is present and is the primary cause of the dysfunction. Accordingly, inotropic agents, such as dobutamine, norepinephrine or dopamine are infused with the hope of improving LV inotropy. The concept that cardiac output is responsive to changes in LV EDV that can be directly altered by intravascular loading, is central to most diagnostic and therapeutic protocols used to assess cardiac function. For example, if these agents increase inotropy and impaired inotropy was the cause of the haemodynamic instability, then LV stroke volume and stroke work should increase for the same LV EDV. In a vast majority of single pathologic process conditions, such as haemorrhage, myocardial infarction, and non-thoracic trauma, this simple approach works well enough to prevent further tissue hypoperfusion and organ failure. Documenting that LV EDV is above some minimal value, despite cardiac output and stroke work both being depressed is essential for the diagnosis of heart failure. Similarly, demonstrating that LV EDV is reduced in the setting of haemodynamic instability presumes the diagnosis of inadequate circulating blood volume as the most likely cause of the haemodynamic instability, even though other aetiologies, such as tamponade, cor pulmonale and restrictive cardiomyopathies can co-exist and require different treatments. This simple approach is often less effective in the setting of combined cardiorespiratory dysfunction, cor pulmonale, valvulopathy, established sepsis and other complex scenarios. With these, a more rational approach based on known deter-

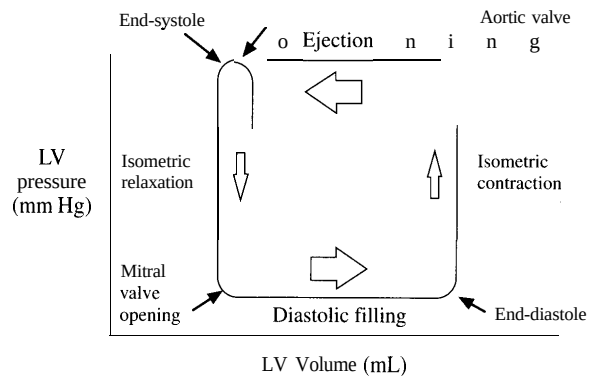


Fig. 2. Schematic diagram of the left ventricular (LV) pressure-volume relation during a complete cardiac cycle.

minants of cardiovascular dysfunction need to be employed.

LV performance is determined by more factors than LV preload alone. The primary determinants of LV performance can be grouped into those factors that alter preload, afterload, heart rate and contractility. LV preload is LV wall stretch at end-diastole and is often equated with LV EDV. LV afterload is the LV wall stress during contraction and is related through LaPlace's Law to LV volume and ejection pressure, such that increases in either LV EDV or pressure will increase afterload and vice versa. Heart rate can directly alter contractility through chronotropic changes in calcium availability for actin-myosin contraction. Intrinsic contractility reflects the ability of the heart to contract for a constant preload, afterload and heart rate. It is related to the wellness of the myocardium and is influenced by coronary blood flow, fibrosis, hypoglycaemia and hypoxaemia. The interaction between preload, afterload and contractility is better described using the LV pressure-volume relation than with the Frank-Starling relation. By examining the LV pressure volume relation, most of the determinants of LV function can be characterised and quantified (Fig. 2). Although not feasible at the bedside today, this approach is useful even if one wished to use the Frank-Starling relation because it underscores the weakness of the latter allowing the clinician at the bedside to assess the multiple potential determinants of the cardiovascular derangement seen. Using the LV pressure-volume relation one can characterise both diastolic compliance as the pressure-volume relation during LV filling (Fig. 3), and systolic performance as the LV end-systolic pressure-volume relationship (ESPVR) (Fig. 4) which is proportional to contractility (Fig. 5). Accordingly, decreases in LV diastolic compliance will shift the LV pressure-volume relation during filling upward with pressure on the y-axis, while impaired LV contractility will decrease the slope of the LV ESPVR.¹³ Acute myocardial ischaemia causes both a decrease in diastolic relaxation and a reduced ability to increase wall tension

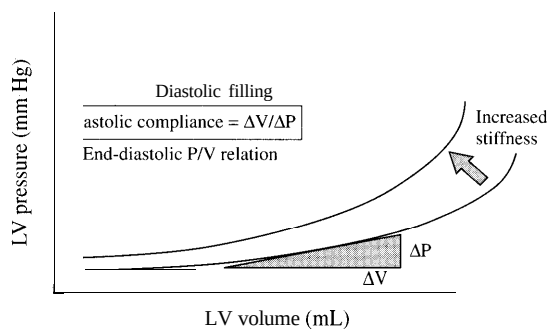


Fig. 3. Schematic representation of the left ventricular (LV) pressure-volume relation during diastolic filling showing effect of increased stiffness (decreased diastolic compliance) on this relation.

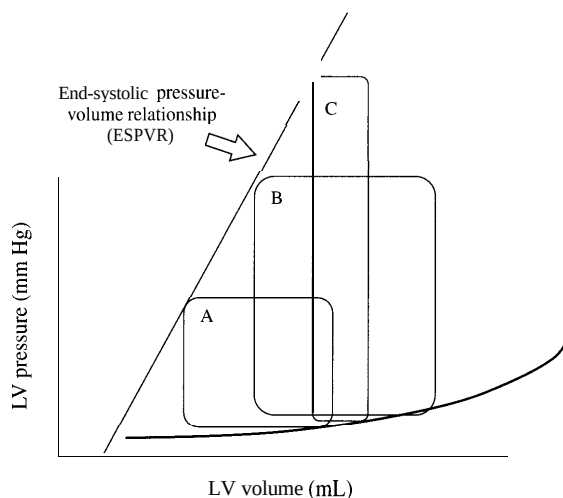


Fig. 4. Interaction between changing end-diastolic volumes and end-systolic pressures on the subsequent end-systolic pressure-volumes. In this example three different cardiac cycles with differing end-diastolic volumes and ejection pressures are depicted. Note that despite these different end-diastolic volumes and end-ejection pressures, all three pressure-volume loops line on a common end-systolic pressure-volume relation determined by cardiac contractility.

during contraction. Thus, both diastolic compliance and ESPVR are altered during acute myocardial ischaemia.

Having said that LV ESPVR is a good marker of contractility, how then can it be assessed at the bedside? One can examine LV ESPVR indirectly by measuring the relation between LV stroke work and EDV, which is called preload-recrutable stroke work. LV stroke work is the product of the stroke volume and the LV ejection pressure gradient. If intravascular volume loading occurs, then both LV stroke work and EDV should increase. However, the relation between the change in LV stroke work to the change in EDV is determined primarily by the slope of the LV ESPVR, thus making this modification of the Frank-Starling relation reflective of myocardial reserve. Thus, in heart failure states when either LV diastolic compliance or LV contractility is reduced, the relation between change in LV stroke work to change in EDV will also be decreased (Fig. 6). Accord-

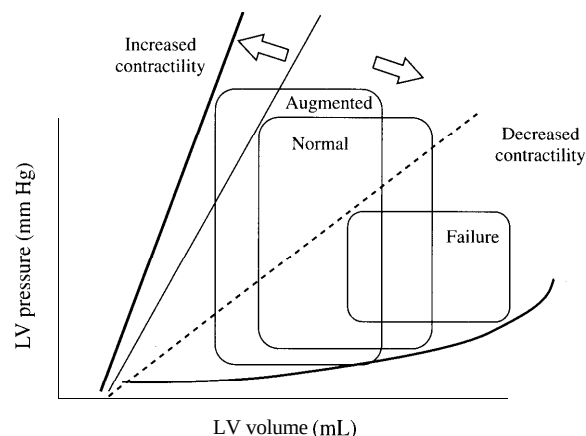


Fig. 5. Based on the format of Figure 4, three different left ventricular (LV) pressure-volume relations are shown with either augmented, normal or failure levels of contractility but a common stroke volume. Note that in failure, end-diastolic volume must increase to maintain a constant stroke volume, whereas with increased contractility end-diastolic volume decreases.

ingly, measures of LV stroke work relative to EDV can be used to see if a subject's myocardial contractility has increased in response to an inotropic agent. This is important because many inotropic agents have other effects as well, including increased chronotropy, and either vasodilation or vasoconstriction. For example, norepinephrine may increase cardiac output in a patient assumed to be in heart failure, primarily by increasing coronary perfusion pressure thereby reducing myocardial ischaemia rather than increasing myocardial contractility per se. This is relevant to patient care because other vasopressors may be as effective in such a case without increased risk of arrhythmias seen with the use of combined α and β adrenergic stimulants.

The major clinical obstacle to the simple application of these principles at the bedside is that accurate measures of LV EDV on a continual or repetitive basis are, at present, impractical. One can measure LV volume to a reasonable level of accuracy using commonly available echocardiographic imaging techniques. However, these techniques are neither quantitative, continuous nor easily repeated over time in the assessment of response to therapy. If one substitute LV end-diastolic pressure for LV EDV as an approximation of preload there is still the requirement for LV catheterisation. Measures of Ppao as a surrogate of LV filling pressure, using bedside pulmonary artery catheterisation has markedly improve our ability to assess LV performance in the haemodynamically unstable patient. Ppao is often used synonymous with "preload". This presumption is not only incorrect, but can lead to important mismanagement of haemodynamically unstable patients. Ppao does not reflect LV EDV as an absolute value.¹⁴ Furthermore, a change in Ppao may not mirror a change in LV EDV. Ppao is linked to LV EDV through LV diastolic compliance," pericardial volume constraints and intrathoracic pressure. Some

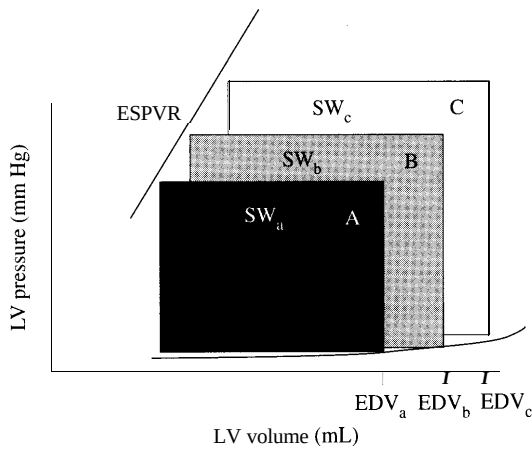


Fig. 6a. Effect of changing left ventricular (LV) end-diastolic volume on LV stroke work, defined as the area within a pressure-volume loop.

useful clinical applications of Ppao in controlled clinical trials, however, are possible. If changes in intravascular volume are induced rapidly with little else changing, then the directional changes in Ppao should be similar to changes in LV EDV. Thus, changes in Ppao should directly tract changes in EDV if no other intervention occurs simultaneously. The one caveat to this assumption is that in acute cor pulmonale, wherein right ventricular (RV) ejection is severely limited, volume loading may selectively dilate the right ventricle further, decreasing LV diastolic compliance by the mechanism of ventricular interdependence, such that Ppao may increase as LV EDV remains constant or decreases.

Complicating these issues further, preload even if accurately measured is intimately connected to both ejection wall stress or afterload and cardiac contractility. This makes it difficult to ascertain which of the three factors—preload, afterload and contractility—determines the haemodynamic state. For example, increases in LV EDV will increase afterload because as the LV contracts, its maximal volume-pressure product will increase. LV output is delivered, against an aortic pressure, which is also coronary perfusion pressure. If aortic pressure increases (increased afterload), coronary perfusion pressure may also increase and result in increased contractility. Reciprocally, systemic hypotension, though reducing LV afterload, will also impair cardiac contractility by reducing coronary blood flow.¹⁶ Furthermore, LV afterload can be considered as maximal LV wall stress, which by the Law of LaPlace is proportional to the product of the developed pressure and the radius of curvature of the ventricle. The maximal LV pressure-radius of curvature product for normal subjects occurs at the start of ejection when LV volume is maximal (EDV) and pressure is elevated (diastolic arterial pressure). For the same ejection pressure, therefore, decreasing LV EDV will decrease LV wall stress

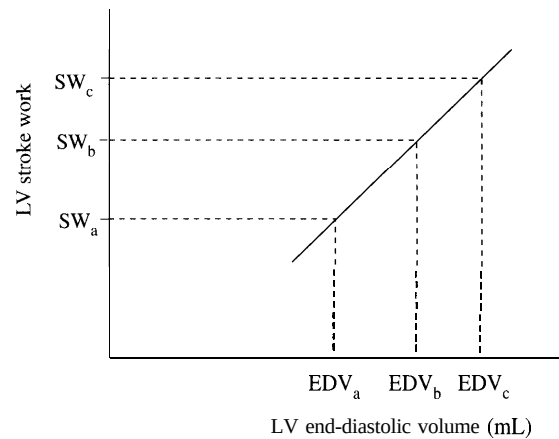


Fig. 6b. The relation between LV stroke work to end-diastolic volume is called preload-recruitable stroke work.

augmenting LV ejection for the same ejection pressure and level of contractility.^{16,17} Thus, LV EDV is a primary determinant of preload, contractility and afterload.

Arterial Pressure and Vasomotor Tone

Arterial pressure is a function of both vasomotor tone and cardiac output. For a constant vasomotor tone, vascular resistance can be described by the relation between changes in arterial pressure and cardiac output. Working via the aortic and carotid body baroreceptors, the body defends organ perfusion pressure above all else in its autonomic hierarchy through alterations in α -adrenergic tone. Thus, if cardiac output decreases, baroreceptor mechanisms sense the associated decrease in arterial pressure and increase sympathetic tone. This induces an increase in arterial pressure through a combined α -adrenergic (increased vasomotor tone) and β -adrenergic (increased heart rate and cardiac contractility) effect. Thus, arterial pressure is essentially an independent function of cardiac output. Increased α -adrenergic tone not only increases arterial tone but increases venomotor tone as well, increasing effective circulating blood volume such that for a constant circulating blood volume, venous return increases allowing the body to maintain a higher cardiac output than it would otherwise be able to sustain on the same blood volume. This is one of the fundamental mechanisms by which exercise states and the exogenous infusion of vasopressors can be associated with an increased cardiac output. The baroreceptor system has a marker that is very useful for controlled clinical trials. Associated with the increase in vasomotor tone is an increase in heart rate, such that tachycardia becomes an early though non-specific marker of hypovolaemia. In fact, an increase in heart rate upon sitting up from the supine position is an indication of functional hypovolaemia.

For practical purposes, organ perfusion of all capillary

beds is determined only by the perfusion pressure and local vascular resistance. If no haemodynamic instability exists to increase sympathetic tone, then flow will also be proportional to local metabolic demand. Cardiac output enters into this equation by maintaining arterial pressure constant despite differing degrees of organ blood flow. Since cardiac output is proportional to metabolic demand, there is no level of cardiac output that reflects normal values in the unstable and metabolically active patient. One can never know if any elevated level of cardiac output and oxygen transport is adequate for tissue oxygenation. Clearly, however, lower blood pressures (<60 mmHg) and cardiac indices (<2.0 l/min/m²) are less well tolerated than higher values. This is an area of cardiovascular physiology where no firm data supporting any set of values or therapeutic approaches based on these values has proven to be more beneficial than other approaches. Accordingly, empiricism is the rule regarding target values of both mean arterial pressure and cardiac output.

In severe stress states, homeostatic mechanisms functioning through baroreceptors vary arterial vascular tone to maintain a constant MAP despite varying cardiac output and peripheral α -adrenergic tone. This process tends to maintain cerebral and coronary blood flow at the expense of the rest of the body, since these two vascular beds have little α -adrenergic receptors. Thus, in subjects with normal renal function, oliguria is an immediate and sensitive marker of this adaptive response. Thus, MAP may be a remarkably stable physiologic parameter and is relatively insensitive as a marker of cardiovascular instability.

Blood Flow and Oxygen Delivery

Blood flow equates with systemic venous return. Except at the very ends of compensation for severe heart failure, increases in systemic venous flow results in a similar increase in cardiac output independent of cardiac pump function. Intravascular volume resuscitation primarily increases cardiac output by increasing the pressure gradient for venous blood flow through increases in upstream venous pressure. The total blood volume in the body is distributed throughout the vascular compartment, but a slight majority of it resides in the veins at any given moment. The relation between venous blood volume and venous pressure is complex, highly variable and forms a major part of the adaptive and therapeutic part of resuscitation. Filling of veins that are empty will result in an initial increase in their blood volume without a change in the distending pressure. This is because at low luminal volume, the veins change shape as they fill, without stretching their vessel walls. Eventually, venous filling will result in the development of a measurable pressure as the veins start to distend. The volume of blood in the veins up to that amount that

results in an increase in luminal pressure is referred to as the unstressed volume of the circulation. Adding or subtracting volume below this point will not result in any measurable change in venous pressure. However, once this volume threshold is reached, further increases in venous volume will increase luminal pressure greatly. One of the primary mechanisms by which the body maintains cardiac output constant despite loss of intravascular blood volume is by reducing the absolute number of vascular beds perfused. This effectively decreases the unstressed volume. Accordingly, acute volume resuscitation in amounts well below the actual volume lost may result in a markedly improved cardiac output even though much more fluid resuscitation is needed. There are good and bad aspects to this. It is good in that one can quickly identify volume-responsive hypotension by a rapid volume infusion; bad because hypovolaemia may be quite marked before signs of low output or systemic hypotension occur.

The primary goal of the cardio-respiratory system is to continuously maintain adequate amounts of oxygen to meet the metabolic demands of the tissues. Neither LV preload nor mean arterial pressure is sensitive or specific measures of this function. Clearly, the best measure of adequacy of blood flow is the continued maintenance of normal end-organ function. Normal urine output, gut activity, mentation, and spontaneous voluntary muscular activities reflect the most easily validated measures of body health.¹⁸ Regrettably, many patients present with co-existent organ-system dysfunction, either pre-existent or due to a pathophysiological insult. Furthermore, changes in organ function often cannot be monitored quickly enough to allow for titration of acute care, especially in the setting of a controlled clinical trial. Thus, one cannot rely on these absolute markers to direct therapy.¹⁹ Perhaps a more functional marker of adequacy of oxygen delivery to the tissues is the SvO₂.²⁰ Although values of SvO₂ >70% do not insure that all vascular beds are adequately perfused, SvO₂ values <60% is associated with oxidative impairment of tissues with a high metabolic rate and values <50% are uniformly associated with evidence of anaerobic metabolism in some vascular beds.²¹ Thus, as a predictive marker, an SvO₂ below 50% carries a poor prognosis. If resuscitative efforts increase SvO₂ to greater than 60%, one may assume that there is an improvement in organ perfusion though there is no clue as to how the increased cardiac output is distributed from the SvO₂ value.

If metabolic demand changes, cardiac output should co-vary with it.²² Since this puts an added variable on the analysis of haemodynamic stability, a common approach in controlled clinical trials is to minimise the extraneous metabolic demands of the patients during intervals in which therapeutic interventions and diagnostic processes are being performed. This is to maintain a stable

baseline for comparison. For example, mechanical ventilation is kept constant during a volume challenge and fever is reduced prior to a measurement of VO_2 . This is often more difficult than imagined.²³ Even a sedated and mechanically-ventilated subject can be expending much effort assisting or resisting the ventilator-derived breaths. Muscular activities, such as moving in bed or being turned, "fighting the ventilator," and breathing spontaneously can easily double resting oxygen consumption.²⁴ Operationally, oxygen supply and demand must co-vary as a normal and expected aspect of homeostasis under almost all conditions. In cardiovascular insufficiency states, such as cardiogenic shock or hypovolemic shock, total cardiac output is often limited and can not increase in response to increasing metabolic demand. Under these conditions oxygen consumption tends to remain constant by varying the extraction of O_2 in the tissues rather than by varying total blood flow.

The Clinical Trial: An Experiment of One

Although the above physiological concepts are very useful as starting points in the assessment of the critically ill patient, they do not define what the patient's optimal status is or what endpoints therapy should be achieved. There is neither an ideal physiological state nor clear pathway to achieve stability in all patients even when sub-selected by disease process. This is because no two people are alike in their functional status, biological makeup or metabolic demands. For example, what would be an adequate Ppao for one subject may induce pulmonary oedema in another and hypovolaemic shock in a third. Clearly, it does not matter what the physiology books say if the patient behaves contrary to them. Importantly, if a patient's response to a specific intervention is different than either predicted or expected, then the primary diagnosis the patient is carrying may be questioned. Thus, if a patient is haemodynamically unstable with evidence of organ hypoperfusion, hypotension and a Ppao of 23 mm Hg, all else being equal, most physicians would start an infusion of an inotropic agent, such as dobutamine. However, if one also knew that this patient's history was one of acute pulmonary embolism then additional fluid resuscitation and thrombolytic therapy may be started instead. In fact, a controlled clinical trial is a bridge that links known physiology and pathophysiology with the patient's own status. Accordingly, one should both observe carefully the results of a controlled clinical trial and also give it much weight in defining the subsequent therapy given to an unstable patient.

Based on the above discussion, there is no level of Ppao, arterial pressure or more importantly cardiac output that is "normal". However, we need to be aware of some threshold values. A Ppao above 25 mm Hg will likely be associated with increased lung water and may

be associated with frank pulmonary oedema. A mean arterial pressure less than 60 mm Hg may be below the autoregulatory range for renal, cerebral and coronary blood flow inducing ischaemic organ dysfunction. Thus, only a low arterial pressure (mean pressure <60 mm Hg) reflects a potential hazard to global organ perfusion. An oxygen delivery below which normal metabolism can no longer occur will be associated with a decrease in visceral organ blood flow. Although an SvO_2 of <60% is consistent with some vascular beds being at the brink of dysoxia, an SvO_2 above this level does not mean that tissue hypoxia does not exist.²⁰

The controlled clinical trial juxtaposes several haemodynamic measures from one or more invasive catheters and related data in such a fashion that the above individual cardiovascular functions can be assessed at once so that patterns of haemodynamic response among systems can be readily seen. The presumption is that specific patterns of haemodynamic variables connote specific pathologic processes with specific prognoses and specific therapies. It is seldom that a single variable can be used to adequately monitor a pathologic cardiovascular process or its response to therapy. In the assessment of the response to therapy, it is the juxtaposition of several variables during the trial that determines a good or a bad response.

The mechanics of performing a controlled clinical trial should be formal. First, the caregiver should assess the clinical scenario to the extent necessary to determine one or more potential problems and aetiologies that need to be identified. Second, each presumed diagnosis can be sequentially excluded or identified as the primary cause of the dysfunction based on additional laboratory data or by a clinical trial. A certain hierarchy in diagnoses should be followed in which the most lethal and the most treatable diagnoses should be explored first, with greater degrees of sophistication and complexity of therapy followed. For example, the presentation of haemodynamic instability associated with hypotension, tachycardia, evidence of tissue hypoperfusion would lead one quickly to hypothesise that the primary problem was a decrease in cardiac output. Other diagnoses ranging from the common, such as early sepsis, to the uncommon, such as a traumatic arterio-venous fistula, may have similar presentations. However, they would not be the first diagnoses to be considered in a previously healthy patient. Based on simple diagnostic aids, including electrocardiogram, serum electrolytes, haemoglobin, pulse oximetry and urine output, several causes for a low cardiac output could be excluded. Third, depending on the degree of haemodynamic instability and ease with which a therapeutic trial would be tolerated, an acute intervention would be carried out. In the case of haemodynamic instability, it is almost always some measure to rapidly increase venous return. Important in

doing a therapeutic trial is the *a priori* declaration that the presumed diagnosis is decreased venous return or hypovolaemia and that increasing venous return (preload) will reverse some specific component or components of the haemodynamic profile that was originally found to be consistent with hypovolaemia. Then, if the therapeutic trial does not improve these components though demonstrating increased LV filling, then it may be assumed that the increase in preload accomplished by this trial was either inadequate to reverse the process or that reduced preload was not the cause of the process.

Use of the Controlled Clinical Trial to Diagnose Disease Hypovolaemia

Haemodynamic instability is most often attributed to hypovolaemia in the acutely ill patient. Hypovolaemia is the cardiovascular state in which the total or effective circulating blood volume is inadequate to sustain a level of cardiac output necessary for normal function, without supplemental sympathetic tone or postural changes to insure adequate amounts of blood volume. It is important to remember that hypovolaemia is a relative process and can occur through absolute blood loss, fluid and electrolyte loss, interstitial volume loss, evaporation from large burn surfaces, or relative volume loss from loss of vasomotor tone. The normal reflex response to hypovolaemia is increased sympathetic tone, vasoconstriction and tachycardia.²⁵ Cardiac output is often sustained by these mechanisms such that heart rate is increased and stroke volume decreased, whereas blood flow distribution is delivered away from the skin, resting muscles and gut.²⁶ With tissue hypoperfusion, lactic acidosis develops as a marker of tissue anaerobic metabolism.²⁷

The classic clinical signs of hypovolaemia are tachycardia, tachypnoea, decreased arterial pulse pressure, decreased CVP and Ppao, decreased urine output, peripheral cyanosis,²⁰ diaphoresis with cold extremities, agitation and lactic acidosis. If a fluid challenge is said to be effective then some of these measures must return toward their baseline values. For example, heart rate may slow, urine output increase, pulse pressure increase and extremities warm up and become pink. However, for a fluid challenge trial to be negative then despite a lack of change in any of these outcome measures, one must also see evidence that the volume challenge was adequate enough to increase venous return. Examples of an adequate volume challenge include an increase in either CVP or Ppao, otherwise, there is no documentation that the volume challenge altered filling. Importantly, vasopressor agents may increase venous return by decreasing unstressed vascular volume, thus giving signs of increased CVP or Ppao, as well as increased cardiac output. Thus, the clinician will incorrectly assume that the patient's condition was due to impaired

vasomotor tone and/or impaired cardiac contractility. This is not a minor problem because the "beneficial" effects of vasopressor agents in hypotension occur at the expense of visceral organ perfusion. Renal and splanchnic hypoperfusion can rapidly lead to ischaemic dysfunction of either organ with associated increased morbidity and mortality.

Left Ventricular Failure

LV failure, as described above and in Figure 5, is usually manifest by an increased LV EDV and by extension Ppao to sustain a constant stroke volume. The most common cause of LV failure is acute myocardial infarction.^{28,29} Usually LV stroke work is reduced and heart rate increased due to the combined decrease in contractility and increased sympathetic tone. In chronic heart failure both cardiac output and systemic vasomotor tone may be normal, whereas in acute LV failure states, both may be reduced.³⁰ However, neither cardiac output nor systemic vascular resistance are sensitive markers of LV failure until cardiogenic shock develops.³¹ Since Ppao is the back pressure to pulmonary blood flow, increases in Ppao associated with LV failure may lead to pulmonary oedema inducing reflex hyperventilation. The normal adaptive response of the host to impaired LV contractile function is to increase sympathetic tone, induce tachycardia, activate the renin-angiotension system, retain sodium by the kidneys and thus increase the circulating blood volume.²⁸ Fluid retention takes time, whereas acute impairment of LV contractility can occur over seconds in response to myocardial ischaemia. Thus, the presentation of acute and chronic LV failure can be different. Acute LV failure is manifested by increased sympathetic tone (tachycardia, hypertension), impaired LV function (increased filling and reduced stroke volume) with minimal RV effects (normal CVP),^{16,17} increased O_2 extraction manifested by a low SvO_2 ,^{20,21} and ECG changes consistent with ongoing myocardial ischaemia and infarction. Cardiac output need not be reduced and may in fact be elevated, owing to the release of catecholamines inducing a reduction in unstressed circulating blood volume, as part of the acute stress response. However, vascular resistance is increased. These findings made the diagnosis of acute myocardial ischaemia relatively easy. In severe acute LV failure, RV pressures also passively increase leading to systemic venous hypertension, hepatic congestion and even acute elevations in liver enzymes.

A major issue in the haemodynamic management of a patient in acute LV failure is to ascertain if he remains preload responsive, will benefit from afterload reduction or need increased inotropy. These three therapies can have opposite effects on cardiac output and myocardial oxygen demand, and all three can be answered by controlled clinical trials.

A patient with acute myocardial infarction will have an ischaemia-induced reduced LV diastolic compliance as well as a reduced ESPVR. Thus, even a "normal" Ppao of 10 to 12 mm Hg may reflect hypovolaemia. If the subject with acute LV failure due to ischaemia is also hypotensive, then a therapeutic trial of afterload reduction is not an option. If the subject has evidence of pulmonary oedema then a presumed diagnosis of cardiogenic shock can be made. However, without this finding the primary aetiologies of acute LV failure include coronary hypoperfusion due to occlusive atherosclerosis and /or systemic hypotension and hypovolaemia. If a trial of fluid resuscitation is undertaken then the presumed hypothesis is that the subject has an inadequate LV EDV. The same caveats as with hypovolaemic shock apply here. Accordingly, following a rapid infusion of 250 ml of saline one would expect either heart rate to decrease, mean arterial pressure or arterial pulse pressure to increase and /or Ppao or CVP to increase. If any of these occurred, then the patient would be said to be volume responsive.

If the patient with LV failure was also hypotensive, with a mean arterial pressure <60 mm Hg, then hypoperfusion of the coronaries could also be contributing to the observed LV dysfunction. If this is the working hypothesis, then a trial of a vasopressor, either phenylephrine or norepinephrine can be started with the end point of increasing mean arterial pressure to some physiologic target value, such as 70 mm Hg. If such a trial were successful, one would predict that evidence of ongoing myocardial ischaemia, such as ECG evidence of ischaemia would abate. Similarly, if contractility were improved by increased coronary perfusion pressure then Ppao may decrease and cardiac output may actually increase.

If the presumption is that preload is adequate and the cardiogenic shock is not associated with hypotension, then one can either give a trial of afterload reduction or increased inotropy. Afterload reduction is the preferred treatment of choice if bradycardia is not present, because it should increase LV ejection while reducing myocardial O₂ demand by reducing LV wall stress. Accordingly, with the infusion of an afterload-reducing agent, such as nitroprusside or nitroglycerin, there should be a marked decrease in Ppao associated with an increase in SvO₂ and evidence of increased organ blood flow (urine output). Interestingly, in severe LV failure states, mean arterial pressure may not decrease despite the infusion of a vasodilator because the reduction in LV EDV will account for all of the reduced LV wall stress.

Finally, if LV contractility is impaired, as in stunned myocardium, or reductions in arterial pressure are not desired, as in a patient with essential hypertension for fear of stroke, then a trial of increased inotropy, using dobutamine, dopamine or norepinephrine, may be in-

dicated to increase cardiac output while reducing Ppao. Accordingly, a trial of increased inotropy should reduce Ppao while increasing cardiac output. Unfortunately, if heart rate also increases with dopamine infusion, it becomes unclear if the beneficial effect of the drug was through increased contractility or heart rate.

Conclusion

Treating patients without fully understanding their underlying disease state represents a real life situation that can rarely be avoided in the management of the critically ill patient. In such situations, where the effect of delaying treatment is measured in morbidity and mortality figures. Therapeutic trials need not be nihilistic or without benefit even if they are proven incorrect. They must be done within the context of learning about the specific aspects of the patient that are determining the final physiologic phenotype. If the hypothesis being tested and the expected results and their implications are defined before initiating a specific therapy, then a controlled clinical trial with an "n" of one can be concluded with more power than a prospective randomised clinical trial. The information attained describes that particular patient better than any large clinical trial can ever do. It is the accurate observation and application of these research principles at the bedside that defines the controlled clinical trial. Such an approach can help to identify the patient who will benefit most from empiric therapy.

REFERENCES

1. Charette A L. Bridging the gap between haemodynamics and monitoring. *Crit Care Nurs Clin North Am* 1989; 1:539-46.
2. Wiedemann HP, Matthay M A, Matthay R A. Cardiovascular-pulmonary monitoring in the intensive care unit (Part 1). *Chest* 1984; 85:537-49.
3. Abou Khalil B, Scalea T M, Trooskin S Z, Henry S M, Hitchcock R. Haemodynamic responses to shock in young trauma patients: need for invasive monitoring. *Crit Care Med* 1994; 22:633-9.
4. Schremmer B, Dhainaut J F. Heart failure in septic shock: effects of inotropic support. *Crit Care Med* 1990; 18:S49-55.
5. Haimowitz I J. Intelligent diagnostic monitoring using trend templates. *Proc Annu Symp Comput Appl Med Care* 1994:702-8.
6. Kandel G, Aberman A. Mixed venous oxygen saturation: Its role in the assessment of the critically ill patient. *Arch Intern Med* 1983; 143:1400-2.
7. Nelson L D. Continuous mixed venous oximetry in surgical patients. *Ann Surg* 1986; 203:329-33.
8. Yelderman M. Continuous measurement of cardiac output with the use of stochastic system identification techniques. *J Clin Monitor* 1990; 6:322-32.
9. Forrester J S, Ganz W, Diamond G, McHugh T S, Chonette D W, Swan H J C. Thermodilution cardiac output determination with a single flow-directed catheter. *Am Heart J* 1972; 83:306-11.
10. Jardin F, Gueret P, Dubourg O, Farcot J C, Margairaz A, Bourdarias J P. Right ventricular volumes by thermodilution in the adult respiratory distress syndrome. A comparison study using two-dimensional echocardiography as a reference method. *Chest* 1985; 88:34-9.
11. Dhainaut J F, Brunnet F, Monsallier J F, Villemant D, Devaux J Y, Konno M, et al. Bedside evaluation of right ventricular performance using a rapid computerized thermodilution method. *Crit Care Med* 1987; 15:148-52.

12. Ross Jr J, Peterson K L. On the assessment of cardiac inotropic state. *Circulation* 1973; **47**:435-8.
13. Suga H, Sugawa K. Instantaneous pressure-volume relationships and their ratio in the excised supported canine left ventricle. *Circ Res* 1983; **53**:306-18.
14. Raper R, Sibbald W J. Misled by the wedge? The Swan-Ganz catheter and left ventricular preload. *Chest* 1986; **89**:427-34.
15. McKenney P A, Apstein C S, Mendes L A, Connelly G I, Aldea G S, Shemin R J, et al. Increased left ventricular diastolic chamber stiffness immediately after coronary artery bypass surgery. *J Am Coll Cardiol* 1994; **24**:1189-94.
16. Mason D T. Afterload reduction and cardiac performance. *Am J Med* 1978; **65**:106-25.
17. Ross J. Afterload mismatch and preload reserve. *Prog Cardiovasc Dis* 1976; **18**:255-70.
18. Marik P E. Gastric intramucosal pH. A better predictor of multiorgan dysfunction syndrome and death than oxygen-derived variables in patients with sepsis. *Chest* 1993; **104**:225-9.
19. Pinsky M R. Beyond global oxygen supply-demand relations. In search of measures of dysoxia [editorial]. *Intensive Care Med* 1994; **20**:1-3.
20. Kandel G, Aberman A. Mixed venous oxygen saturation. Its role in the assessment of the critically ill patient. *Arch Intern Med* 1983; **143**:1400-2.
21. Miller M J, Cook W, Mithoefer J. Limitations of the use of mixed venous pO₂ as an indicator of tissue hypoxia. *Clin Res* 1979; **27**:401A.
22. Pinsky M R. The meaning of cardiac output [editorial]. *Intensive Care Med* 1990; **16**:415-7.
23. Weissman C, Kemper B A, Damask M C, Askanazi J, Hyman A I, Kinney J M. Effect of routine intensive care interventions on metabolic rate. *Chest* 1984; **86**:815-8.
24. Mohsenifar Z, Goldbach I, Tashkin D P, Campisi D J. Relationship between O₂ delivery and O₂ consumption in the adult respiratory distress syndrome. *Chest* 1983; **84**:267-71.
25. Blalock A. Shock: further studies with particular reference to the effects of haemorrhage. *Arch Surg* 1937; **29**:837-48.
26. Shenkin H A, Cheney R H, Govons S R. On the diagnosis of haemorrhage in man: a study in volunteers bled large amounts. *Am J Med Sci* 1944; **208**:241-52.
27. Vitek V, Cowley R. Blood lactate in the prognosis of various forms of shock. *Ann Surg* 1997; **173**:308-15.
28. Alonso D R, Scheidt S, Post M. Pathophysiology of cardiogenic shock: quantification of myocardial necrosis; clinical, pathologic, and electrocardiographic correlations. *Circulation* 1973; **48**:588-602.
29. Weber K T, Ratshin R A, Janicki J S. Left ventricular dysfunction following acute myocardial infarction: a clinicopathologic and hemodynamic profile of shock and failure. *Am J Med* 1973; **54**:697-712.
30. Scheidt S, Ascheim R, Killip T. Shock after acute myocardial infarction: a clinical and hemodynamic profile. *Am J Cardiol* 1970; **26**:556-61.
31. Shub C. Heart failure and abnormal ventricular function. Physiology and clinical correlation. *Chest* 1989; **96**:636-40.