

“CLINICAL VALIDATION” OF MEAN SYSTEMIC FILLING PRESSURE (P_{ms}) AND HEART PERFORMANCE (E_h)

The derivation, validation and use of P_{ms} in cardiovascular physiology are reviewed together with the more recently defined parameter of heart performance, E_h . The benefits of using both these parameters in monitoring hemodynamic status to assist clinical management of the circulatory state in situations where there are multifactorial components influencing a patient’s individual responses to interventions is also considered.

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Abbreviations Used:

ICU Intensive Care Unit; P_{ms} Mean Systemic Filling Pressure; E_h Heart Performance; RAP Right Atrial Pressure; MAP Mean Arterial Pressure; CO Cardiac Output; SVR Systemic Vascular Resistance;

The use of hemodynamic monitoring forms a cornerstone that underpins the care of critically ill patients whilst they are in the ICU. Fundamental to this is an understanding of the determinants of cardiac output and blood flow distribution, of which the central factors defining both are venous return, cardiac performance and vasomotor tone. Conceptually, the regulation of cardiac output by the vasculature underlies most forms of circulatory shock, its diagnosis and treatment. Unfortunately, bedside physicians have traditionally had little to no ability to assess venous return or cardiac performance, relying primarily on measures of vasomotor tone and the cardiac output response to volume resuscitation or inotropic therapy. If bedside estimates of the determinants of venous return and cardiac performance were available, then cardiovascular management decisions and monitoring would be greatly simplified.

Within that framework, a number of mathematical and experimental models have been instrumental in enabling current understanding of the regulation of cardiac output and it is important to briefly review these to enable terminology and nomenclature to be placed in context.

Weber’s early work¹ was fundamental and laid the foundations with a model of the circulation constructed from a portion of small intestine, which was subsequently filled with fluid and pressurized. He established that the mean pressure in the model could only be increased by distending the tubes through the addition of more fluid. The significance of this was not recognized for more than four decades until Bayliss & Starling² reasoned that if blood were at a standstill, pressure everywhere in the system would be equal and when the heart started to pump pressure in the arteries would increase, accompanied by a decrease in the pressure in the veins. Famously, they noted “..... it follows that with the inauguration of the circulation, the point where the pressure is neither raised nor lowered must lie on the venous side of the capillaries”. They termed this pressure the mean systemic pressure (P_{ms}) and then measured it in a sympathectomised canine model, obtaining a value of ~ 7 mmHg. More recent experimental studies have corroborated this value in both animal models and human studies^{3,4}.

Starling's classic experiments^{5,6,7}, conducted in the early 1900s, demonstrated that cardiac output is largely determined by factors that depend on the venous side of the heart and relatively independent of cardiac function⁸.

Starr & Rawson⁹ recognized the importance of the work undertaken by Bayliss & Starling and developed a mechanical model to simulate congestive heart failure. Using the model, they demonstrated that P_{ms} increased, not as a result of congestive heart failure, but as a compensatory mechanism. This was validated by measurements made via a needle inserted into the heart or a great vein, within 30 minutes of death, in patients who had died from various causes¹⁰. The average P_{ms} recorded from those patients who had died of heart failure was almost twice that recorded from patients dying without heart failure. Since the increased P_{ms} was present *post mortem*, Starr & Rawson concluded that this represented a reflex circulatory response compensating for poor cardiac function and was not due to passive congestion behind the failing heart.

In 1954 Guyton¹¹ and his colleagues published the first of series of papers that were to have a profound impact on our understanding of cardiac and circulatory physiology. A subsequent paper¹², published in 1955 and which is recognized as one of the most significant publications in the history of clinical physiology, described the use of electric analogues and applied circuit analysis in the study of venous return. Guyton and his colleagues subsequently tested the analyses with elegant, well designed animal experiments, and thus simultaneously created the modern basis for research into the understanding and regulation of the cardiovascular system^{13,14}.

Guyton postulated that P_{ms} was the driving pressure for venous blood flow from the periphery to the heart. He validated this hypothesis in an animal model producing the now classic series of physiological curves¹⁵ that demonstrate how changes in P_{ms} affect venous return. (The reader is directed to an excellent review of Guyton's early work on the derivation and physiological validation of P_{ms} that has been published by Jacobsohn *et al.*¹⁶).

By the mid 1950s, two different views of cardiovascular control were being proposed. These approaches, cardiocentric - cardiac output is

controlled by the heart; and vasulocentric - blood pressure is controlled by vascular resistance; were conflicting. Guyton's theories and experimental data supported the latter approach and with his co-workers, he challenged the cardiocentric approach of others¹⁷.

The three component model detailed in Guyton's early paper was further developed into a computer model of the complete cardiovascular system and reported in another seminal publication in 1972¹⁸. The importance of this work cannot be understated.

In the years since the publication of his seminal papers, Guyton's original concepts, nomenclature, experimental data and his later work, see for example^{19,20,21,22}, have become fundamental teaching and reference materials for generations of medical students^{23,24,25,26}; have been the subject of reviews by dozens of authors and the driving force for further work by thousands of clinicians and physiologists. This has resulted in large numbers of papers and review articles in the clinical literature; see for example^{27,28,29,30,31,32,33,34,35,36,37,38,39,40,41,42,43,44,45,46,47,48,49}.

In addition to the classic descriptions of P_{ms} from the early literature, the derivation of P_{ms} from first principles has, more recently, been described by a number of authors; see for example^{50,51,52,53,54,55,56}.

In tandem, the determination and measurement of P_{ms} by clinicians has been the subject of many publications^{57,58,59,60,61,62,63,64,65}.

The clinical significance of P_{ms} and its validation as a measure of the intravascular volume state has also been reported by several authors^{66,67,68,69,70,71,72,73}. Knowledge of P_{ms} also enables the "stressed" and "unstressed" volumes^{74,75,76,77} to be distinguished in analyses of the vascular capacitance. It can also be used as an index of the effective filling of the circulatory system^{78,79,80,81,82,83}.

Central to cardiovascular homeostasis is cardiac performance. One way to quantify cardiac performance is to report its ability to sustain flow relative to a venous return driving pressure. Although it is axiomatic that the heart can only pump what it receives, one way to operationalize performance is to describe its required driving pressure relative to upstream pressure. E_h is a dimensionless measure of heart performance state, ($E_h = (P_{ms} - RAP) / P_{ms}$), and a prime

determinant of cardiac output and blood pressure. The derivation of this term from first principles together with its therapeutic importance and value has been comprehensively described by Parkin & Leaning⁸⁴. Consider a heart with poor performance. It will require not only a high RAP, but will also use most of the driving pressure (P_{ms} -RAP) to create this pressure, thus resulting in a low cardiac output. In comparison, a highly effective heart, for the same RAP, will have a much higher driving pressure (P_{ms} -RAP) and thus a much higher cardiac output. Both statements are empirically true and describe why an effective heart has a much higher cardiac output for the same RAP as a non-effective heart. Since blood flow is a function of venous return, which itself is a function of the P_{ms} -RAP driving pressure, this simple construct allows the bedside clinician to directly quantify cardiac performance at its most basic functional level.

The Navigator™ device quantitates the primary objects of circulation therapy, i.e. the patient's volume, resistance and heart states. Graphical information is presented for each primary object with the aim of gaining and holding nominated arterial pressure, blood and oxygen flow targets.

The "enabling technology" in the Navigator™ is the use of a model based measure of the effective circulating volume (i.e. mean systemic filling pressure ($P_{ms} = a.RAP + b.MAP + c.CO$)) to continuously define the volume state. This enables the patient's volume responsiveness, a measure of the dynamic response to a volume load, to be determined and displayed graphically. Knowledge of the volume responsiveness and E_h helps separate inotropic and lusitropic disorders, quantitates inotropic use and enables clinicians to assess the likely effectiveness of volume therapy.

The use of P_{ms} and E_h has been validated in two ways:

1. Clinical Observation

The Navigator™ screen display is designed to be orthogonal with the three prime therapeutic states. Two independent vertical axes are formed by the volume state (P_{ms}) and heart performance (E_h), with the transverse horizontal axis representing the resistance state ($SVR=(MAP-RAP)/CO$), which is the object of vasoactive medication. Increases in either P_{ms} or E_h increase the power output ($(MAP-RAP)*CO$) of the heart.

Administration of volume therapy results in the patient symbol on the display screen moving

vertically upwards, typically with little or no horizontal deviation. In contrast, the use of vasoactive agents changes the MAP/CO ratio but not the MAP*CO product and results in transverse movement at a constant P_{ms} altitude. Typically the resolution is sufficient to appreciate, for example, the small changes in venous compliance and their effect on volume state with vasodilator or vasoconstrictor use; or the effect on SVR movement of phase delay in CO signal measurement with respect to the MAP signal, a well described phenomenon with the Edwards Vigilance™ continuous CO catheter that was used in the Nav-1 clinical study⁸⁵.

2. Monitoring of hemodynamic parameters to assist management of circulatory status

For any given patient, the hemodynamic information provided by Navigator™ enables clinicians to monitor progress towards a required circulatory status.

Whilst the overall result of the Nav-1 clinical study was "non-inferiority" to conventional control over all hospitals, some individual open heart surgery units achieved statistically significant improvement in target acquisition over time compared to conventional therapy when using the monitoring information provided by Navigator™.

Furthermore and most importantly, in its first multi-hospital test the Navigator™ was able to provide continuous minute to minute monitoring of all appropriate hemodynamic indices at a level commensurate with that required by clinicians to inform and assist with the management of the complex circulatory problems of critically ill patients. This provides support to the underlying design principles.

More recently, Pinsky^{86,87} and Feihl & Broccard⁸⁸ (the latter in a further comprehensive review) have examined the same interactions and noted the benefit of having methods of monitoring the relevant physiological variables and devices capable of presenting these data in a clinically useful format.

When Navigator™ is used clinically, the displayed P_{ms} provides a measure of the volume state of the patient. The device provides monitoring and support information that assists clinicians with volumetric therapy involving fluids, diuretics or dialysis. E_h provides the clinician with a measure of global heart performance in the circulation, and as a consequence enables visualization of the action of agents affecting cardiac function such as inotropic agents and vasoactive drug therapy.

Michard & Teboul⁸⁹ strongly support the use of dynamic parameters in clinical decision making processes associated with volume expansion in critically ill patients in preference to static ventricular preload parameters.

The benefits of providing monitoring information relevant to volume, resistance and heart therapies in moving the patient towards a desired circulatory state have been demonstrated by the clinical literature. The Nav-1 clinical study⁹⁰ has also demonstrated this.

Volume responsiveness in a patient is a measure of the dynamic response (dMAP, dCO) to a volume change (dP_{ms}). It is ideally a predictive measure of whether or not volume therapy will produce a significant change in hemodynamics and therefore whether volume (dP_{ms}) or cardioactive therapies (dE_h) should be used to produce a commanded upward vertical motion on the Navigator™ graphic. The presence of volume responsiveness does not imply that the patient is volume requiring.

With the device's graphical display, E_h and the response of E_h to volume therapy may both be used to judge volume responsiveness in combination with the vertical motion of the patient symbol in response to a volume load.

Volume expansion is frequently used in critically ill patients to improve hemodynamics. However, a number of studies^{91,92,93,94} have shown that only 40-70% of critically ill patients significantly increase stroke volume or cardiac output in response to volume expansion. The need for predictive factors that enable the identification of patients who might benefit from volume

expansion was identified several years ago. In a review of twelve clinical studies investigating predictive factors of fluid responsiveness, Michard & Teboul⁹⁵ assessed the value of a number of different parameters. They concluded that the use of dynamic parameters in decision making about volume expansion in critically ill patients was supported by available clinical evidence.

In a 2008 editorial in *Minerva Anestesiologica*⁹⁶, Rocca & Costa reviewed more recent evidence from the clinical literature, noting the importance and greater clinical validity of functional hemodynamic variables over static preload variables. They stated "...a dynamic hemodynamic index must identify not only if the patient is or is not hypovolemic, but also if he is able to respond to a fluid challenge or needs drug support."

Summary

The publications cited throughout this review demonstrate the long standing knowledge, validation and use of P_{ms} in cardiovascular physiology; contain details of its derivations from first principles; and provide many examples of P_{ms} being used clinically. Additionally, the literature cited supports the derivation, from first principles, of the more recently defined parameter of heart performance, E_h, and demonstrates the clinical importance of this parameter. The benefits of using both these parameters in monitoring hemodynamic status to assist clinical management of the circulatory state in situations where there are multifactorial components influencing a patient's individual responses to interventions is also considered.

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