2009 Leffingwell Memorial Lecture

Physiology: The One True Guide to Patient Care

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First let me pay tribute to my family, some of whom are here to support me today. As this may be the first lecture of mine that they have attended, I think I am more nervous than ever before. As we all recognize, however, it is the support and love of our families that allows us to accomplish our career goals, and for that I will always be grateful.

I want to begin my discussion today by expressing my extreme gratitude to Dr. Michael Champeau and the CSA for the extraordinary honor of inviting me to present the CSA's 2009 Leffingwell Memorial Lecture and to add to the congratulatory comments and express the deepest respect I have for my good friend, Larry Sullivan, upon his receiving the CSA's Distinguished Service Award. His wonderful contributions, both here in California and nationally to our specialty, are well recognized and most appreciated. Congratulations, Larry.

My gratitude to this Society goes far beyond the honor bestowed on me today, for it was here as a member of the CSA that my career began. It was the CSA and its leadership over 30 years ago—Sol Statman, Gerry Nudell, Russ Jackson, Norm Catron and others—that provided me the opportunity to begin participating in first the local, and later the national, arena. The invitation to serve on our Educational Programs Division at the recommendation of its Chair, Ron Miller, and eventually to succeed Ron as Chair, provided me the opportunity to gain both local and eventual national recognition that led me on the road to a career that I hope gained me some degree of success as an educator. The support of the CSA continued in 1985 as they nominated me to the ASA for consideration as a Director of the American Board of Anesthesiology, a position for which I was selected and held for the requisite 12 years. I am confident that without the continued encouragement and support of the CSA, my career would certainly not have taken the direction it did, and for that I'm glad I'm here today with this opportunity to express my deepest appreciation.

It is appropriate to reflect on Dr. Forrest Leffingwell. I never had the fortune of meeting Dr. Leffingwell, as he passed away in 1969 when my training in anesthesia was just beginning. Although my career and accomplishments pale in comparison with those of Dr. Leffingwell, I do feel a sort of kinship to him. Both of us received our anesthesia training in California—he at the very beginnings of anesthesiology as a recognized independent medical specialty in 1940 with a fellowship in anesthesiology at the White Memorial Hospital in

Los Angeles, and I many years later at the Naval Hospital, San Diego. Both of us spent time in the military and upon his discharge following World War II—he returned to White Memorial, then the main teaching hospital of Loma Linda Medical School, becoming Chief of Anesthesia and establishing an anesthesia training program. I, on the other hand, left the Navy following the Viet Nam conflict and returned to California to establish a Critical Care Medicine training program. Although we both achieved similar rank, he as a Lt. Colonel in the Army and I as a Commander in the Navy, it is noteworthy that it took him five years and me ten.

Both Dr. Leffingwell and I were Directors of the ABA, with him serving from 1955 to 1969. In his final year on the ABA, Dr. Leffingwell served as its president. His career shows far more accomplishments than my own. He was the President of the ASA in 1962 and received their Distinguished Service Award posthumously in 1969. I gained some insight into the man we memorialize today with this lecture when I was writing a monograph detailing the history of the ABA with Frank Hughes, who recently retired as the ABA's Executive Vice-President. One cannot help but recognize Dr. Leffingwell's humanism, fairness, and profound respect for others. He always gave others his full attention, was extraordinarily tolerant of opposing views, and kept his counsel until he was able to digest all that was presented. Only then would he come up with some of the most profound recommendations and suggestions that served the ABA and our specialty extraordinarily well. Regarding these latter traits, I know my friends and colleagues in the audience will agree with me when I express my envy of him in this regard.

Let me now devote the remaining time for my presentation on the topic I have selected: "Physiology: The one true guide to patient care." Like Dr. Leffingwell, I never considered myself—nor would others consider me—a basic scientist because research was not a cornerstone of either of our careers. If I have had any success as an educator, it has been through my sincere belief that physiology must form the basis of our practice as perioperative clinicians. I have often referred to the views of Sir William Osler, the foremost example of the clinician physiologist, whose career at McGill, the University of Pennsylvania, Johns Hopkins, and eventually Oxford from1874 to his death from influenza pneumonia in 1919, that have been so well chronicled in numerous books and publications. His belief that a physiologic-based practice provides the best opportunity for success—without which, we are often blind as to the choices we make—and the expectations that ensue are best expressed by the following quotes attributed to him.

> *Patients don't die of their disease, they die of the physiologic abnormalities of their disease.*

and

> *The physician without physiology practices a sort of popgun pharmacy, hitting now the malady, then the patient, he himself not knowing which.*

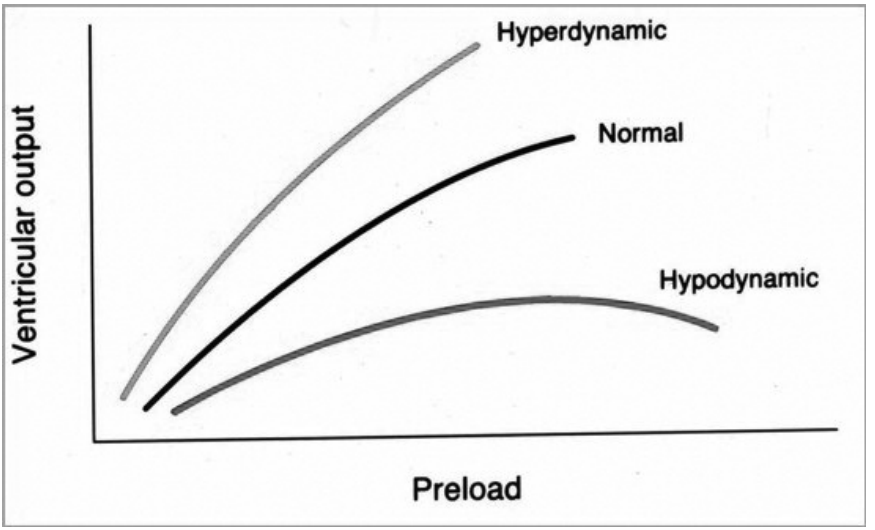
It is this approach to patient care—a monitored physiologic approach—that has led me to a concern that **the recent emphasis placed on evidence-based medicine, with its reliance on the most up-to-date published studies often followed unquestioningly, and at times divorced from well-established physiologic principles, may have a negative impact on the care we provide**. At the risk of disenfranchising myself from those academic institutions of which I am so proud to have been affiliated, I note that the origin of evidenced-based medicine as the basis for care coming from research institutions may be self-serving. However, let me be very clear that I certainly acknowledge the critical importance of properly derived scientific experimentation as a cornerstone of our very existence as a medical specialty. To deny the need for continued attainment of new knowledge to understand the basic etiologies of disease and the development of new therapies would be an egregious proposition, for it is certainly research that has provided—and will provide—the physiologic understanding of human health and disease that guides us today.

My approach to both educating medical students and house staff, as well as providing patient care in the ICU and operating room, involves a clear understanding of basic physiology, the delineation of individualized pathophysiology, and a monitored approach to therapy. Let me focus on hemodynamic management, as that has been the area in which I have had the most interest through my career. I hope to use this lecture as an opportunity for me to express my views as editorial comments on the current state of therapy for shock.

To begin this discussion and to set a tone for my comments, let me refer to one of the more erudite and oft-quoted individuals of our time—Lawrence Peter "Yogi" Berra—as he eloquently stated, "It's déjà vu all over again." I am not sure to what exactly he was referring, but his comment befits in many ways that with which we are being confronted in the treatment of shock. The resurgence of primary treatment in septic shock, often devoid of the monitoring necessary to determine precise pathophysiology, with vasopressor agents, most notably utilizing norepinephrine, deserves a far more cautious evaluation than that which is apparent in many of our institutions. The physiology that has guided us over the past several decades was introduced by the physiologists Ernest Starling (England) and Otto Frank (Germany) at the end of the 19th and the beginning of the 20th centuries. Ernest Starling, working on the isolated dog heart, demonstrated the dependence of the heart on preload for satisfactory

cardiac output. Years later, investigators further delineated the implications of altered myocardial contractility expressed as the family of ventricular function curves oft referred to as Starling curves shown in figure 1.

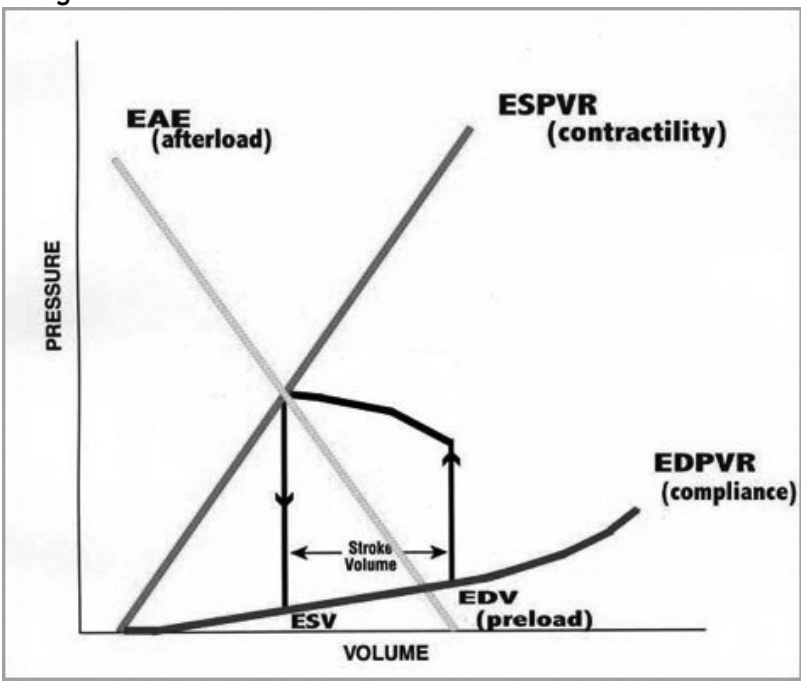
Figure 1



Starling ventricular function curves depicting the relationship of preload (ventricular end-diastolic volume), often indirectly monitored by pulmonary artery occlusive/wedge pressure or central venous pressure, and ventricular output (stroke volume).

Acknowledging the immense contributions of Starling and his colleagues, reliance on this descriptive physiology fails to allow the clinician to discern the implications of decreased ventricular compliance—diastolic or lusitropic dysfunction—and the effects on myocardial performance as a result of changes in vascular resistance. Otto Frank independently studied cardiac function by using an amphibian model, and in 1898 he described his findings leading to the physiologic description of hemodynamic function using the pressure-volume loop shown in figure 2. Although not as easy to derive at the bedside as the ventricular function curves of Starling, an awareness of the pressure-volume loop allows the clinician to better understand the implications of change in the full scope of altered hemodynamics and the expected response to therapy.

Figure 2



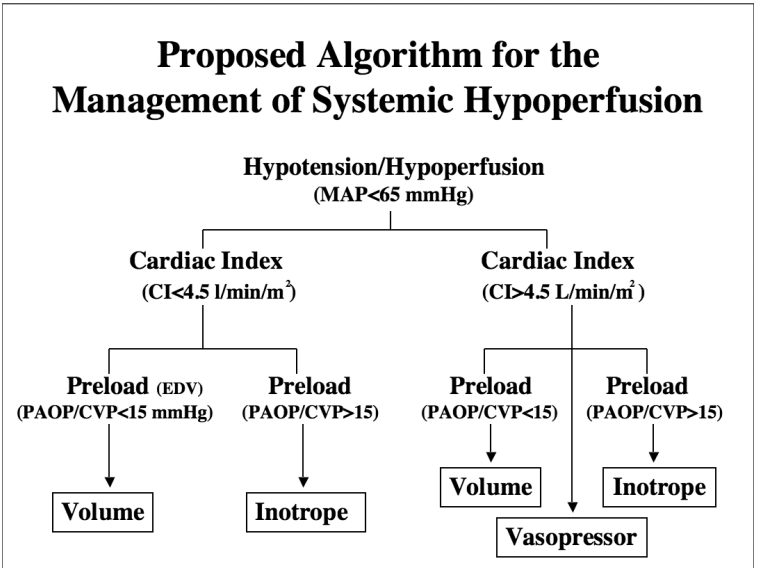
The pressure-volume loop showing the impact on cardiac performance by changes in preload, ventricular compliance, contractility and vascular resistance measuring intraventricular volume and pressure.
EDV = end-diastolic volume, ESV = end-systolic volume, EDPVR = end-diastolic pressure volume relationship, ESPVR = end-systolic pressure volume relationship, EAE = effective arterial elastance (vascular resistance).

With this as background, let us focus on supportive care for patients exhibiting signs and symptoms of hemodynamic insufficiency and shock. The goal of care should be for the heart to pump blood into the aorta in sufficient quantity and under sufficient pressure to maintain the pressure-flow relationship for adequate tissue perfusion and the maintenance of aerobic metabolism. Until recently, the approach to patients in shock was guided by a monitored physiologic approach to therapy, consisted of:

1. Assessment and optimization of preload
2. Assessment of cardiac function and inotropic support, if needed
3. Institution of vasopressor therapy if perfusion pressure remained inadequate in the presence of adequate intravascular volume and myocardial contractility

With the ability to assess indirect indices of preload (pulmonary artery occlusive pressure—PAOP, and/or central venous pressure—CVP) and cardiac output/index (CO/CI) and resultant calculation of systemic and pulmonary vascular resistance (SVR and PVR), many of us followed a physiologic algorithm in approaching the patient with systemic hypotension and hypoperfusion as shown in Figure 3.

Figure 3



An algorithm for an approach to hypotension and hypoperfusion in the critically ill patient. The values noted should be used only as a guideline, but not as absolute, and must consider the underlying co-morbidities of the patient, including chronic hypertension and coronary artery disease.

Figure 3 begins with a determination of a minimal satisfactory mean arterial pressure (MAP). If this is not present, then options for expansion of intravascular volume, inotropic therapy to increase myocardial contractility and/or vasopressor/vasoconstrictor therapy are determined by monitored parameters as shown. The reliance on an elevated cardiac index as noted in figure 3 is most appropriate in patients with hyperdynamic/septic shock, the area of most interest to investigators at present. Avoidance of well-recognized sequelae of vital organ ischemia, most notable in the splanchnic and renal circulations, from reliance on vasopressor therapy to normalize blood pressure requires that tissue flow originating from a sufficiently elevated cardiac index be present.

The 1950s and '60s was an era when vasopressor therapy with norepinephrine was the touchstone of treatment for shock, and the normalization of blood pressure was often accompanied by a prolonged course leading to eventual intestinal necrosis, renal failure, and death. The advent of CVP, CO and later PAOP monitoring in the 1970s awakened us to the detrimental effects of reliance on this vasopressor-based approach with recognition of the necessity for first insuring adequate preload and contractility.

It is at this point that I invoke Yogi's quote. The current decade has witnessed a change in care of these patients. The flow-directed pulmonary artery catheter, which was so effective in guiding our management and allowing insight and recognition of existing pathophysiology and the response to therapy has, as we are all very aware, nearly become extinct as numerous editorials and newspaper articles have emphasized the risks of its placement, the lack of relevance of the derived data, and a potential negative impact on outcome. Whether this is justified is still open to discussion. However, let it be recognized that studies have demonstrated that failure to accurately assess the indices provided—and to properly interpret and apply this information—was far more common than actual complications from insertion.

In 2001, Emanuel Rivers published a study in the *New England Journal of Medicine*, demonstrating that early aggressive therapy with defined goals for the first six hours in the emergency room for patients with septic shock improved survival compared to standard therapy. Therapy was guided by determination of CVP, hematocrit (Hct), and measurement of superior venal caval oxygen saturation, $ScvO_2$, from the CVP catheter as a surrogate for mixed venous oxygen saturation. Therapy was initiated with volume expansion to a CVP of 8 – 12 mmHg with normal saline. If the MAP remained below 65 mmHg, then norepinephrine was initiated and $ScvO_2$ and Hct were measured. If the $ScvO_2$ was below 70% and the Hct below 30%, the patient received transfusion, and if the Hct was above 30%, then dobutamine was added. This protocol has seen generalized acceptance throughout the critical care community and is often applied *incompletely* without $ScvO_2$ measurement, thus relying on a CVP of 12 mmHg and norepinephrine as full therapy. Only with definitive evidence of poor perfusion—oliguria, rising creatinine and BUN, lactic acidosis and signs of extremity hypoperfusion—is further therapy examined. Many of these signs are late and provide evidence of well established hypoperfusion and multi-organ failure. A number of concerns must be addressed, even with proper application of the protocols derived from River's study. Is the timing of the vasopressor therapy optimal? What monitoring is used to assure the adequacy of blood flow and tissue perfusion? Is dobutamine the optimal inotrope for patients in septic shock?

I have already commented regarding my concerns for the initiation of norepinephrine at such an early stage of evaluation without assurance for adequacy of cardiac output and flow. It is also of concern that the only monitor recommended to assess the adequacy of myocardial function and tissue oxygen delivery is a "poor man's" mixed venous oxygen saturation in a pathophysiologic state where the presence of peripheral circulatory shunting can induce false elevation of the mixed venous saturation. It has also been recognized that reliance on CVP as an indicator of left heart function is inadequate in a number of clinical conditions. I observed this about 30 years ago while caring for patients presenting with hypotension and viral pneumonitis/ARDS. From 1972 to 1974, five patients were admitted to the emergency room of a major medical center with respiratory failure, bilateral pulmonary infiltrates, and hypotension. Their admission findings after placement of arterial catheters, central venous cannulation and intubation were as follows:

Patient	MAP	CVP	F_IO_2	PaO_2	$PaCO_2$	pH
	(mmHG)	(mmHG)		(mmHG)	(mmHG)	
1	40	11	1.0	92	43	7.31
2	34	9	1.0	112	45	7.28
3	48	10	1.0	56	38	7.31
4	36	8	1.0	52	39	7.32
5	58	13	1.0	72	37	7.33

Those caring for the patients concluded that, with the high normal CVP and lung findings, therapy with furosemide, morphine and digoxin was indicated. Please remember this was 35 years ago. Not surprisingly, the patients became more hypotensive and attempts to institute PEEP were unsuccessful, leading to further hypotension. The patients were admitted to the ICU, where flow-directed pulmonary artery catheters (Swan-Ganz) were placed. The findings are shown below.

Patient	PAOP	Cardiac Output	PVR
	(mmHg)	(liters/min)	(dynes*sec*cm^{-5})
1	2	2.1	686
2	1	1.9	632
3	3	2.2	764
4	1	2.0	680
5	1	2.8	657

It is evident here that these patients were markedly hypovolemic and that the CVP values were erroneously elevated due to the high PVRs (normal < 150). This is only one small example of a number of studies that exist within the literature that have demonstrated the lack of reliability of the CVP in representing the true preload of the left ventricle in acute illness. A major deficiency in our ability to manage patients with shock and hypoperfusion is the absence of means to provide immediate, critical, continuous and accurate assessment of vital organ perfusion, most importantly in the splanchnic and renal circulations. With this current void in monitoring capability, the concentration on an optimal physiologic central hemodynamic supportive therapy affords the best opportunity to provide the necessary time for disease-directed therapy to be effective. The reluctance to utilize the pulmonary artery catheter, rather with inadequate surrogates for cardiac assessment, especially in non-intubated patients where transesophageal echocardiography is not practical, leaves us at a disadvantage in treating these patients. Blindly following such "evidence-based guidelines" as early goal-directed therapy may lead to treatment regimens that are counter-productive in both correcting the pathophysiology and providing the best opportunity for survival.

I also have raised a question regarding the choice of inotrope in patients with septic shock. The enthusiasm for dobutamine originated from publications showing better splanchnic perfusion with the combination of norepinephrine *and* dobutamine **when compared with** epinephrine. At first glance these articles were a surprise to those of us who have considered epinephrine to be a most predictable and reliable positive inotropic agent. The poor responsiveness of beta receptors in patients with bacterial sepsis and the elderly has often led to suboptimal effects of the weaker beta stimulants including dopamine and dobutamine. Also the strong beta-2 vasodilator effect of dobutamine often results in further hypotension requiring escalation of vasoconstrictor therapy. It was thus quite surprising to me when these articles became the basis for an evidence-based medicine approach to therapy. However, further examination of these publications revealed a protocol that insured the results that were observed. Our basic pharmacology textbooks, as well as a study in 1993 by Moran, informed us that the response of the circulatory system to epinephrine is dose-dependent. At doses below 200 nanograms/Kg/min, epinephrine lacks significant alpha vasoconstriction and acts predominantly as an inotropic agent to increase myocardial contractility and stroke volume. Careful review of the protocols in the studies examining dobutamine *and* norepinephrine **compared to** epinephrine show that the doses of epinephrine averaged in excess of 400 nanograms/Kg/min, hence insuring a profound alpha vasoconstrictor response, that impeded splanchnic perfusion. Guidelines for the management of patients with septic shock have repeatedly cited these articles

as the evidence for the evidence-based medicine approach to patients with septic shock. I do *not* agree with these conclusions.

In summary, the clinician has two approaches to the management of the critically ill unstable patient—"evidence-based medicine" and/or "physiologic." In an ideal situation, there should be no inconsistency. However, we are dealing with reality, where many publications appear with poorly designed protocols, results that cannot be properly explained, or may be misinterpreted by those performing the studies. Is evidence-based medicine leading us in the wrong direction, or are we interpreting and applying the evidence incorrectly? In 2008, in writing about this subject, Simon Finfer concluded, "Promulgation of evidence-based guidelines is an advance welcomed by many clinicians, although treatment recommendations are inevitably constrained by the quality of the available evidence." He went on to say, "Critical appraisal and an open mind may be more appropriate than unquestioning adherence to guidelines."

One of the advantages of being selected to present the Leffingwell is it often provides the opportunity for those of us at the twilight of our careers to be given a pulpit—or more aptly a soap box—to expound and editorialize on subjects dear to our hearts, with little concern for how it might affect our career development. We can also rely on some degree of tolerance from those in attendance who disagree with us, as we may be viewed as out of touch with reality or just in the grasp of senility.

I do not believe I am exaggerating when I state that the vast majority of medical students applying for anesthesia training positions write in their personal statements—and express in their interviews—that the application of physiology to patient care is one of the prime motivations for selecting our specialty. My plea here today is that this motivation not diminish, and that as we emphasize the importance of evidence-based medicine in determining therapeutic approaches, that we should critically examine that which has undergone peer review, while exercising caution when published results and recommendations appear contrary to our understanding of basic physiology. I thank you for this wonderful opportunity and the honor you have bestowed on me today and once again to the CSA for all of your support.

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