

American Society of Critical Care Anesthesiologists State of the Art Session

- 1:00 p.m. *Tight Glycemic Control*
Aristides P. Koutrouvelis, M.D.
University of Texas Medical Branch
Galveston, Texas
- 1:15 p.m. Question and Answer
- 1:20 p.m. *The PA Catheter: Evidence Based?*
Avery Tung, M.D.
University of Chicago
Chicago, Illinois
- 1:35 p.m. Question and Answer
- 1:40 p.m. *Replacement Doses of Steroids in Sepsis Who? When?*
Joel B. Zivot, M.D.
University Hospital of Cleveland
Cleveland, Ohio
- 1:55 p.m. Question and Answer
- 2:00 p.m. *Intentional Hypothermia Following In-Hospital CPR - What Should We Be Doing?*
Brenda G. Fahy, M.D.
University of Kentucky
Lexington, Kentucky
- 2:15 p.m. Question and Answer
- 2:20 p.m. *Protein C - Who Should Get It? Who Shouldn't?*
Michael S. Avidan, M.B.,B.Ch.
Washington University St. Louis
St. Louis, Missouri
- 2:35 p.m. Question and Answer
- 2:40 p.m. *Beta blockers - How Do They Really Work?*
Andrew J. Patterson, M.D.
Stanford University
Stanford, California
- 2:55 p.m. Question and Answer
- 3:00 p.m. Coffee Break and Poster Viewing

Tight Glycemic Control

Aristides P. Koutrouvelis, M.D.

Introduction

Tight glycemic control is currently being adopted by many ICUs all over the world. Glucose, protein and fat metabolism interrelate both in every-day activity, and in critically ill states; where glucose has been suggested to play a central role in metabolic homeostasis during both the acute and chronic stress response, typified in many critically ill scenarios. Increases in metabolic rate, altered fuel utilization, protein catabolism, and neuroendocrine factors, all contribute to the overall glucose concentration in critically ill patients. Although, no two illnesses are identical there is substantial evidence that suggests strict glucose control may benefit a variety of populations ranging from burns to pediatrics in both diabetic and non diabetic patients.

Certainly, not all patients with hyperglycemic issues are diabetics, yet, an alarming projection of the dramatically increased prevalence of diabetics in the near future promises to populate the ICUs, unless there is a movement primarily, toward education on diet and exercise. Consequently, there will be a larger than expected group of undiagnosed diabetics that present postoperatively with insulin resistant states and hyperglycemia in ICUs. These pathologic states may be related to the altered hepatic glucose production, the decrease in the peripheral utilization of glucose with respect to protein and fatty acid metabolism or any combination. It has been shown that, in diabetes, tightly controlling blood sugars has been demonstrated to delay the onset of microvascular induced neuropathy, retinopathy and nephropathy.

Aside from diabetes, several independent risk factors contribute to the “hyperglycemic state” in the critically ill population. They include: stress, catecholamine infusions, elderly, obesity, severe illness, excess nutrition, pancreatitis, SIRS, uremia, cirrhosis, hypothermia, hypotension and hypoxemia.^[1] It is not surprising that a majority of the ICU admitted patients present with hyperglycemia, even though a large group of those patients are not diagnosed with diabetes; whatever the mechanisms, they all have laboratory evidence of hyperglycemia. Yet to be described neuroendocrine processes may contribute to the insulin derangement; and in the case of a traumatized, diabetic patient with sepsis there may be overlapping and competing mechanisms.

Such a seemingly simple facet of medical care, that is, strictly titrating the blood sugar concentration within a narrow range from 80-110 mg/dL, as described by Van den Berghe and colleagues, improved overall in-hospital mortality, bloodstream infections, and acute renal failure requiring dialysis or hemofiltration.^[2] Further studies in trauma, pediatrics, burns, and heterogeneous medical populations have echoed beneficial relationships with glycemic control.

Delineating whether the benefit is either from euglycemia or from the effects of insulin is difficult, although, overlapping contributions of both are likely.^[3] Insulin effects of normalizing abnormalities in serum lipid profiles contribute in part to the improvement in outcome of critically ill patients.^[4] Furthermore, other unseen benefits which are nestled in the methods of some of these studies, such as: timing, composition, route and amount of nutrition have specific impact on inter-organ metabolism. Future studies need to evaluate these parameters, for example, the 19 kcal/kg/day (of mostly carbohydrates), given in the Van den Berghe study, may turn out to be excessive in certain critically ill populations, yet not enough in others.^[5]

Several questions posed by Drs. Coursin and Murray regarding hyperglycemia in critical care. These questions are slowly being resolved.^[6] First, that the reported benefits in the Van den Berghe study are related to both glycemic control, as well as, insulin administration.^[2,3] Second, early feeding may be necessary to curb the catabolic state imposed by the early insulin resistance in the setting of increased metabolic demands. Third, application of these

findings has been demonstrated to some degree in the burn, septic and trauma, as well as mixed population group. A recent randomized controlled trial by Krinsky, studying intensive insulin therapy showed decreased mortality, organ dysfunction, and length of stay in the ICU in a heterogeneous population of critically ill adult patients.^[19] Fourth, the pediatric population has demonstrated beneficial effects with glycemic control. Finally, novel mechanisms to identify, insulin resistance and attenuate its effects are being examined at the neuroendocrine level; looking into relationships with resistin, adiponectin, ghrelin, and lectin; as well as, at the molecular level; examining ways to enhance the utilization of glucose aiming at specific transcriptional, signal transduction mechanisms and altering cell membrane and mitochondrial components.

Whether the stress is from trauma, cold, infarction, sepsis, burns, or surgery, the *blood glucose concentration* is dependent on *two specific rates*: the rate of presentation of glucose into the blood stream and the rate of its removal. This summary will review both endogenous and exogenous *sources* of blood glucose, as well as their *fates*: the uptake, utilization, storage and elimination routes in the ICU setting.

Hyperglycemia- What's too high?

Numerous predisposing hyperglycemic factors are present in the ICU population. The cause of the critical illness-induced hyperglycemia (>200 mg/dL or 11 mmol/L) in the absence of diabetes is complex and varies from insulin deficiency to resistant states, as well as, endogenous over production and excess exogenous supply. Aberrations in utilization and storage, as well as, drug administration whose mechanisms are yet to be identified, may be other causative factors of hyperglycemia.^[7] While, in some instances, the transient increased levels may be appropriate physiologic responses. Still there is no denial that there is an association between hyperglycemia and increased hospital mortality in heterogeneous critically ill populations, causality aside.^[8]

It is important, then, to differentiate these circumstantial factors of hyperglycemia, and appreciate that although the raw numbers may not classically fall in the realm of critical-illness "hyperglycemia", as it is defined. As such, deleterious effects of "elevated" blood glucose levels just above 110 mg/dL have been reported in clinical trials.^[9] "Normoglycemia" (80-110mg/dL) has been associated with a better outcome than an (apparently not so normal) intermediate blood glucose level (110-150 mg/dL), which now, for many, is considered too high of a glucose concentration. Van den Berghe claims that it is the lowered blood glucose level rather than the insulin dose that is primarily responsible for the reduced mortality, critical illness polyneuropathy, bacteremia, and inflammation but not for prevention of acute renal failure, for which the insulin dose was the determining factor.^[6]

Are high glucose levels in acute illness OK? As mentioned, adaptive responses of acute hyperglycemia enable the body to overcome certain compromised states. The hyperglycemic response to stress, for example, maintains adequate supply of substrate to inadequately perfused tissues. However, profound early elevations in blood glucose concentrations have been demonstrated to correlate with significantly higher infection rates and mortality in trauma patients independent of reported injury characteristics.^[10]

Even so, the concept of area under the curve is important, as well as peak levels, as most likely, prolonged states of hyperglycemia are maladaptive. Improving immunologic function of macrophages and T helper cells has been described as a benefit of insulin therapy as well.^[3] Immunity may be compromised in a poorly controlled setting, as sternal wound infections are a reported complication associated with post bypass hyperglycemia.

Early sepsis has been associated with hyperglycemia and decreased levels of TNF-alpha, as well as, increased proinflammatory markers like IL-6. Experimentally, increased leukocyte adhesion is stimulated by high glucose concentrations via NF-kB-dependent transcription, so, theoretically, insulin may decrease the inflammatory nidus for thrombus formation, not to

mention the anti-inflammatory and vasodilatory properties touted by insulin itself. In addition, early studies show a detrimental effect on blood pressure with hyperglycemia. This response is through glycosylation of transcription factors which increase angiotensin production.^[11]

In septic patients who exhibit a large degree of shunting the likelihood that microvascular perfusion is compromised decreases the availability of not only oxygen but also nutrients such as glucose and as a consequence will not be utilized, even increased levels of insulin do not always promise uptake.

In addition, the inflammatory cytokines as well as the peroxynitrites have been implicated in rendering the electron transport chain ineffective which would further exacerbate the balance of glucose production and glucose utilization. As a consequence, any increases in glucose levels in the cell may promote more DAG production if higher levels of glucose accumulate. DAG induced PKC activation has many ischemic effects on end organs, by vascular occlusion through increased levels of PAI-1, and vasoconstriction by ET-1.

Hyperglycemia promotes atherosclerosis through glycosylation of proteins and lipids that leads to increase in oxidative stress and vascular endothelial changes via PKC signals.^[12] There is much evidence that sorbitol pathway, also, can be activated and is one of many purported burdens of oxidative stress. This stress which is in the form of increased free radical formation, soon depletes, the already compromised reductive pathways in the surgical and critically ill patient. These free radicals can come from the autooxidation of free glucose itself. This can contribute to organ damage and can accelerate the dysfunction of a variety of lipids and proteins specifically, those serpins of the hemostatic pathways.

In addition, indirect receptor mediated and non receptor mediated atherosclerotic changes can result from long term glycation products in diabetic patients. The nutritional state and underlying redox potential of the critical care patient has particular importance in the subsequent ability to deal with the inflammatory response. And an increase in the oxidative stress load in the mitochondria in response to hyperglycemia causes the insulin producing beta cells, which are particularly sensitive, to be somewhat dysfunctional.^[18]

Once the blood sugar gets above the 180mg/dl threshold, the kidneys are unable to reabsorb the glucose load imposed on it. The resultant osmotic diuresis can induce dehydration which in itself has a host of other ill effects on the compensating body.

There are many reports of poor outcomes in both head injured patients and stroke patients that do poorly with higher levels of presenting blood sugars. Although the brain is an insulin independent glucose utilizing organ and is responsible for roughly 80% of the basal glucose consumption, increased levels during hyperglycemia may suggest that some molecular or osmotic mechanism may be responsible for poorer outcomes, or possibly that the damage itself causes increased levels of glucose.

Notable effects, such as an increased risk of death, from stress induced hyperglycemia in acute MI patients as well as, reports of poor outcomes in head injured patients, both with and without diabetes have been reported.^[13,14] Much of this injury can be attenuated by glucose, insulin and potassium (GIK) infusions which induce membrane stabilization at the cellular level with subsequent improvements at the functional level of the whole organ.

Hypoglycemia –What's too low?

The main concern for over treating blood sugar elevation is hypoglycemia, particularly for the brain. Since glucose is considered the predominant source for brain metabolism, as well as, for adrenal medulla, bone marrow, and erythrocytes. As such, the brain may not tolerate prolonged states of hypoglycemia, unless alternate sources such as ketones can serve as alternative substrates. Hence, an infusion of glucose may be necessary in the critically ill patient who is compromised from a nutritional standpoint. The compromise may not only be

from inability to eat or have proper gut motility, but also in a starved or fasted state in a nutritionally depleted patient whose endogenous stores may be compromised. The combination of sepsis and hypoglycemia portend a poor prognosis, the mechanisms are yet to be elucidated but may include inflammatory inhibitory factors that decrease the hepatic production of glucose, and alternatively it may be malnutrition and liver disease.

Another concern is the individual variability of tolerating hypoglycemia. Some individuals will experience mental status changes in the normal titration range of blood sugars whereas others are comfortable in what may be considered panic low values. How are these groups going to be appreciated? Are the acceptable ranges of hypoglycemia the same under the influences of anesthesia as in the post operative period or are they even lower? It may be that the plasma levels do not correlate well with the tissue levels or that they correlate extremely well in those individuals and they have a higher need for cellular substrate.

Sources of Glucose

Both endogenous and exogenous sources of glucose provide for an important component of the body's overall fuel composition. Both proteins and fat participate in the endogenous production of glucose. Also there is interplay between the endogenous and exogenous sources of glucose. When the body senses an exogenous supply the endogenous resources are typically shut off. Is this signal preserved in critically ill individuals?

The hormone glucagon is a key regulator of mobilizing endogenous fatty acid, amino acid and glucose sources. These endogenous glucose sources typically come from either degradation of glycogen storage (glycogenolysis), or the denovo production from either amino acids or glycerol (gluconeogenesis). Glucagon's effect of increasing glycogenolysis, decreasing glycolysis, and increase in gluconeogenesis contribute to the endogenous hepatic glucose production. In addition to glycogen there are other hormonal, as well as, non-hormonal antagonists to insulin responsible for increases in blood sugar concentration because of decreased glucose uptake in muscle and fat.

Glycogen depletion. The amount of potential fuel storage in the 70 kg adult is around 159,000 kcals. Only a small portion of this, about 800 kcals exists in the form of glycogen, and in nutritionally or pathologically compromised individuals, there is much less. In the fasting state glycogen is responsible for degradation of this fuel which would typically last a day, however in the hypercatabolic state, and physiologically compromised be it nutritional or other, this fuel storage is even more rapidly depleted. Though muscle can store glycogen, only the liver and kidney possess the phosphatases necessary to allow glucose to enter the blood stream for remote organ consumption. Again, compromised organs attenuate this provisional fuel source; unless, of course, exogenous sources of glucose are provided.

Gluconeogenesis. Consequently, the catabolic state is hastened by the need for fuel, in the hypermetabolic phase of critical illness, usually degrading proteins and later fats by gluconeogenesis. Provision of glucose by the method of gluconeogenesis to other organs is limited by the liver and to some extent the kidney. Substrates for gluconeogenesis include glycerol, amino acids, and lactate.

The production of glucose by the liver is typically suppressed by insulin. This suppression is lost during critical illness and is another source of hyperglycemia in the insulin resistant state. Besides the fact that uptake of glucose by muscle is limited, there is inadequate suppression of glucose production both manifesting in hyperglycemia. Overcoming the resistant states by decreasing hepatic glucose production may be integrated with the inadvertent benefits of compensatory fatty acid oxidation, as well. Insulin resistance in burns displays a differential sensitivity to substrate targets: being relatively insensitive with respect to carbohydrate metabolism while preserving anabolic function of protein.

Sinks of glucose

The mechanisms by which glucose is removed from the circulation is utilized by the cells, stored or eliminated. Acutely, the levels of glucose are increased from several stress response mechanisms. As such the response of how the body deals with this load is complex, and dependent on a variety of conditions not all necessarily under control of the patients physiology, which during attempts at resuscitation are dramatically altered. Typically glucose sinks are impaired during critical illness.

Insulin secreted from the pancreas or administered by the caretakers removes glucose from the circulation and into the tissues where it may be utilized by a variety of metabolic processes, one of which is glycolysis, or it may be stored in the form of glycogen. Furthermore, it may enter the cell and not be completely oxidized, as in septic patients. However, studies may suggest using oral hypoglycemic drugs or similar agents will enhance mitochondrial processing of the pyruvate derived from glucose by upregulating carnitine palmitoyl transferase, which is important in the balance of glucose and fat metabolism.

In the stressed individual a number of mechanisms blunt the effects of insulin. The insulin: glucagon ratio may be altered. Simultaneously, counter regulatory factors may in part account for this relative insulin resistance. They include cortisol, growth hormone, catecholamines and angiotensin II. In the acute setting, ACTH stimulates CRH, cytokines and the sympathetic response. Hypercortisolism acutely shifts carbohydrate, fat and protein metabolism and so the anabolic events are delayed until more substrate is shunted and utilized by the vital organs. As a consequence, the balance of immunosuppressed and immunostimulatory endocrine signals may be perturbed.

Furthermore an appreciation of pain relief is paramount in the stress response. In the postoperative setting its neglect will amplify both the stress and sympathetic response together. This can further complicate the picture by increasing the metabolic demand, potentially in a state with a compromised supply, while being insulin resistant.

Aside from the fact that insulin resistance dampens the utilization of glucose, there are pleiotropic and putative beneficial effects from exogenous insulin administration. Insulin has been shown to be anti-inflammatory and vasodilatory. It has also been shown to have beneficial effects with respect to normalization of free fatty acid levels. Insulin also will spare the need for gluconeogenic precursors, as such, confer favorable effects toward anabolic protein metabolism. Insulin suppresses Insulin-like growth factor binding protein-1 which in itself is an independent predictor of mortality.

Glucose storage mechanisms. One of the predominant glucose storage hormones is insulin. Insulin has effects on endothelial dysfunction and as a result on, coagulation and fibrinolysis, as well as correcting dyslipidemias. Insulin resistance, on the other hand, has been reported to decrease the synthesis of vasodilators prostacyclin and nitric oxide while increasing endothelin-1 levels favoring a vasoconstrictive and procoagulant state. Although there are many nuances of insulin resistance and differences in diabetics and non diabetics, there are probably many similarities and interesting clues can be gleaned from these comparisons.

Improving glucose utilization. Insulin promotes glucose utilization, while decreasing the use of amino acids and fats. In critical illness counterregulatory factors predominate and reverse the effects of insulin on lipids, proteins and carbohydrates, promoting lipolysis and gluconeogenesis decreased glucose transport across cell membranes and utilization, increasing not only the blood concentration of glucose but also amino acids from protein catabolism and fatty acids from lipolysis.

In diabetics decreased adenopectin levels have been implicated in insulin resistant states, which is a marker for poor outcome in diabetics. Mechanistically, PPAR-gamma has been demonstrated to be a link to improve the metabolic machinery and the balance of fatty acid

oxidation and glucose utilization. A new class of oral hypoglycemic drugs, the TZD's have been shown to redistribute visceral fat, decrease hepatic glucose production, improve muscle function and control vascular inflammatory processes, while improving overall insulin sensitivity. These drugs, although not presently used in the critical care arena, at present, have shown dramatic improvements in the microvascular and in the macrovascular aspects of diabetic pathophysiology.^[9]

Implementing Protocols

Many protocols, including those for glycemic control, ensure a certain standard and can be superior to carrying out a wide range of discretionary orders.^[15] Before these imposed standards, however, all the relevant studies are evaluated and the information assimilated. Then, the first difficulty regarding implementing a protocol is its multidisciplinary acceptance. Agreements must be made regarding the concentration and mode of administration of insulin, the monitoring of glucose levels, determining the proper range of glucose concentration; and the population(s) for which the protocol will be implemented. At the same time, allowing for individual variation and the unseen potential pitfalls regarding caloric intake and other medications may enable more tactical protocol applications.

Included in the analysis is also the inherent cost, logistics and continual updating of the protocol, as well as, the putative benefits provided it's applied effectively. It is hard to argue that the risks of implementing a protocol outweigh the benefits, since euglycemia has been shown to improve neurologic, respiratory, cardiac, renal, and infectious outcome. Nonetheless, continued audits of various insulin protocols ensure the evaluation of their safety and efficacy and provide the basis for which future protocols are improved.^[16]

Some obvious considerations in the ICUs are paralysis and the decreased muscle metabolism of glucose as a consequence and potential for the catabolism of muscle in this stressed state. Also, are adequate anxiolytics used to curb both the stress response and the sympathetic tone consistent from patient to patient? Do feedings routinely begun preoperatively, intraoperatively or postoperatively (with supplements and vitamins) or is this physician dependent? What mode of ventilation is employed in the vent protocols; is the patient scheduled for nebulized beta agonists? What novel fluids are being used and at what rate? Have stress dose steroids been administered? What are the underlying states of the organs? The answers to these questions should be entertained before implementing a blood glucose protocol, as the actions of the above will without doubt have implications in the blood sugar levels.

The avoidance of extremes in glucose levels and the anti-inflammatory, immune, endothelial, inotropic, anticoagulant, and metabolic benefits of insulin contribute to the wonderful effects of intensive insulin therapy.^[17] Ultimately less infection, less need for dialysis, fewer multiple-organ failures, less critical care polyneuropathy, fewer days on the ventilator, shorter hospital stay and less mortality is sweet. Acquiring more knowledge of the intricacies of the various sources and sinks of glucose, which manifest as alterations in blood sugar levels whose concentrations correlate with the well being of the patient, will guide our palate in the future.

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The PA catheter: Evidence based?

Avery Tung, M.D.

Outline

The PA catheter represents one of the most fascinating dilemmas for practicing critical care physicians today. Despite 20+ years of research, little evidence has emerged to indicate that use of the PA catheter confers benefit. Yet, many physicians find it extremely difficult, and consider it harmful, to practice without one. While the majority of studies today find no benefit, and possibly harm from PA catheter use, flaws in study design have raised reasonable doubt about these findings, and it is unlikely that any future study will significantly change the minds of either side. This talk will focus primarily on the dissonance between the literature and cognitive models of hemodynamic management, which seem inextricably linked to PA catheter use.

History

In continuous use since its introduction in 1970, the pulmonary artery catheter is a mainstay of critical care therapy for hemodynamically unstable patients. Used by cardiologists, intensivists, anesthesiologists, and general medicine practitioners, the PA catheter allows indirect measure of left atrial pressures, and direct measurement of cardiac output using the thermodilution technique. At least two generations of physicians in the United States have encountered the PA catheter during medical school training, and can clearly articulate a specific role for the device in their therapeutic armamentarium. Anesthesiologists are particularly involved in the use of these catheters as 55% of all PA catheter placements occur perioperatively (1).

Nevertheless, arguments against the use of the PA catheter are almost as old as the catheter itself, and contribute to a chaotic, divided literature regarding the utility of the device. Arguments against the catheter range from a consideration of the technical risks of PA catheterization, to the possibility that difficulty in the interpretation of PA catheter data combined with a lack of knowledge regarding its use detract from its beneficial effect (2). Despite ongoing, heated debate with lurid titles such as "Death by PA catheter (3)", use of the device has increased dramatically over the past 20 years. In 1996 an estimated 2 million catheters were sold annually, with total US costs exceeding \$2 billion (1).

Although the PA catheter is one of the most intensely studied monitoring devices in clinical medicine today, it represents a logical conundrum for physicians seeking to base clinical decisions on evidence from the medical literature. The first of many attempts to clinically assess a beneficial effect with PA catheter use vs. CVP appeared in the literature in 1987 (4). In a retrospective study, Gore et al. studied 3,263 patients after acute myocardial infarction, and compared the 15% who received a PA catheter to those that did not. He found, strikingly, no evidence of benefit, but instead greater mortality and increased length of stay in patients who received the device. Although controversy in the literature followed, this study generated nearly no confusion among practicing physicians. It was clearly perceived at the time that methodological flaws, particularly the greater severity of illness in the PA catheter group, had compromised the Gore result.

In the ensuing 10 years, studies with small numbers argued for and against the use of the PA catheter while its use increased dramatically. Several of these included use of the PA catheter to target supranormal oxygen delivery in critically ill patients (5). But in 1996, a second large trial appeared in JAMA (6). Attempting to rectify some of the flaws of the Gore trial, this new study examined 2,184 critically ill patients who had received the PA catheter and compared them to 3,551 matched controls. Their results were similar to the Gore study; worsened hospital, 30 and 60 day survival, and increased length of stay with catheter use. Moreover, they found that any unaccounted-for factor would have to increase the risk of death 6-fold to change their result. This study received widespread media attention. In both the New York Times and Newsweek, physicians were chastised for using technologies that had not been tested under experimental conditions, and physician failure to immediately jettison the use of the catheter was attributed to stubbornness, ignorance or both. Confusion about the utility of the PA catheter persists even

today, as evidenced by a recent 2003 New England Journal study finding no benefit to its use in nearly 2,000 ASA III and IV patients undergoing major noncardiac surgery when compared to CVP alone (7).

Despite the media coverage and calls for a moratorium on PA catheter use in prominent journals (3), the majority of physicians continue not to be swayed. How could a device capable of continuously providing otherwise unknowable data have no effect, or worsen outcomes? The studies had to be misleading or wrong. In addition to arguing that the patients were insufficiently randomized, arguments began to surface that physicians, even in published trials, failed to use the catheter effectively, that general hemodynamic knowledge among physicians prevented them from taking advantage of such a tool, and that even when used appropriately, information gleaned from the catheter does not correlate with other monitors of hemodynamic function.

The Dilemma

In a way, PA catheter usage today represents the exact opposite of evidence based medicine. Despite a preponderance of “evidence” finding no benefit to PA catheter use, physicians in all branches of medicine continue to use it aggressively to diagnose and treat hemodynamic abnormalities. This apparently insurmountable gap between the literature and clinical practice represents a dramatic schism between physician practice and scientific findings, echoed by the most recent ASA practice guidelines on PA catheter use:

“...these benefits have not been demonstrated in currently available research because of deficiencies in study design and performance. It is suggested that a properly designed, randomized controlled trial with adequate sample size, well trained physicians and nurses, well defined interventions, and meaningful outcome measures would reveal the benefits observed in practice (1)”

Since these guidelines were published in October, 2003, four subsequent studies ranging in size from 150 to 2,000 patients have emerged, all essentially demonstrating the same result: that benefits from PA catheterization are small or nonexistent, isolated to high risk patients only, and that in some cases PA catheters may actually worsen outcome (8-11). However, it is unlikely that these trials have swayed physician opinion about the PA catheter, and even less likely that further trials, regardless of their methodology or power, will change usage patterns. The controversy seems forever mired in clinical equipoise, neither side able to gain a decisive advantage.

But how can such discord between clinical practice and the literature exist at all? If physicians are not basing their practice on “best evidence” with regard to the PA catheter, then what ARE they basing it on? Are they, as the media suggest, obstinate and stupid enough to refuse the evidence before us? Or, as defenders of the PA catheter imply, can a poor understanding of PA catheter data, combined with the risk of invasive monitoring, be responsible for completely obscuring any benefit of PA catheter use in randomized trials? Regardless, most physicians trained in hemodynamic management with the PA catheter find it extraordinarily difficult to NOT use it in the care of critically ill patients.

Although reasonable explanations exist for why the PA catheter does not improve outcomes, none satisfactorily explain why physicians continue to believe it useful. The precordial stethoscope and slide projector effectively argue against a theory that physicians are too conservative to “let go” of outmoded technology. And, the argument that physicians do not understand how to use the monitor that they feel they need is relatively weak. Why would physicians feel they need a monitor that they a) don’t understand and b) are unable to use effectively to improve outcome?

This dissonance between cognitive models of critical care practice and literature evidence is not new, and several reasons have been hypothesized. The pulse oximeter is a similar device, perceived as useful despite randomized trials finding no benefit (12). As with this device, it may be that a randomized, controlled trial is simply unable to address a complex issue such as PA catheter use. In addition, learning bias may have minimized the benefit of PA catheterization by boosting

outcomes in the control group. Because the PA catheter had been in use for 15 years before the first clinical trials were undertaken to test its effectiveness, it is possible and even likely that use of the catheter facilitated diagnosis and therapy in ways that allowed physicians to become better even without the catheter. Finally, it may be that placing an invasive monitor, particularly in a critically ill patient, permits physicians to feel as if they are “doing everything possible” to treat the patient. Under such circumstances, an evidence-based argument to not place the PA catheter can seem callous and uncaring. Moreover, placing a PA catheter may, in academic centers, allow supervising physicians at night to better direct resident care of the patient.

A look at another Discipline

The 2002 Nobel Prize in Economics suggests another possible answer to this dilemma. Awarded to Dr. Daniel Kahneman, a psychologist at Princeton University, this prize celebrated the development of a conceptual framework for observing, testing, and understanding human decision making under conditions of irreducible uncertainty. In particular, Kahneman found systematic, pervasive, and replicable differences between “rational” and “intuitive” decision making with incomplete information. He proposed that instead of calculating probabilistically, humans are much more likely to take mental “shortcuts” (called heuristics) that simplify the process of assessing risk and uncertainty. Because these shortcuts led to “severe, systematic biases” (13), his findings argued that many economic models based on the “rational” human might not adequately represent reality.

Many of Kahneman’s findings are well known to physicians. Humans are risk averse with respect to gains, but risk seeking with respect to losses (13). Thus, therapeutic choices framed in terms of survival elicit different responses from patients than choices framed in terms of dying (14). Humans diagnose intuitively based on ease of recall more than statistical likelihood. Thus, medical students are more likely to think of obscure diseases with narrow symptom profiles as the source of a complaint than of more common diseases with more protean manifestations. In these respects, physicians are well calibrated to biases generated by their intuition.

But some of his other observations may be relevant to the PA catheter controversy (and may not be as well calibrated). Humans not only judge based on ease of recalled examples (the “availability” heuristic) but also on degree of plausibility. This shortcut leads to what Kahneman termed the conjunction fallacy, wherein a more specific (and plausible) but less likely scenario is favored over a more general one (15). Consider the following two statements, for example:

1. Mr. F has had one or more heart attacks
2. Mr. F is over 55 years old, and has had one or more heart attacks

Even though the second statement is probabilistically less likely, it seems intuitively more likely because of its greater plausibility. Kahneman demonstrated this effect in physicians also, posing to 66 Boston internists in 1983 the following question:

A 55 year old woman had a pulmonary embolism documented angiographically 10 days after a cholecystectomy. Please rank the following conditions in terms of the probability that they will be experienced by the patient (1= most likely, 6= least):

1. *Dyspnea and hemiparesis*
2. *Calf pain*
3. *Chest pain*
4. *Syncope and tachycardia*
5. *Hemiparesis*
6. *Hemoptysis*

When this experiment was performed, the average rating for condition 1 was 2.7 and for condition 5 was 4.6, even though condition 5 is statistically more likely (15).

It is easy to see how PA catheter data can reinforce such wayward intuition. Which might be more likely in the above 55 year old woman?

1. *Hemiparesis*
2. *A sudden rise in PA pressures to 60/30 mmHg, a patent foramen ovale, and hemiparesis*

In this circumstance, one can posit that placement of the PA catheter simultaneously attributes a causality to the hemiparesis, reinforces the diagnosis, and distorts the assessment of likely causes. Thus, physicians need the catheter to increase the likelihood of selected diagnoses, even though it may distort correct probabilistic analysis and not lead to meaningful therapy.

Another heuristic, termed “representativeness”, may also act to distort perception with the PA catheter. Kahneman found that when given some evidence, humans generally fail to adequately take prior probabilities into account. Thus, when confronted with the description:

Steve is very shy and withdrawn, invariably helpful but with little interest in people or in the world of reality. A meek and tidy soul, he has a need for order and structure, and a passion for detail.

most would consider Steve a more likely librarian than salesman, even though there are many more salesmen than librarians in the world. In this case, similarity to the mental model of a librarian intuitively causes people to disregard prior probability. But what Kahneman also found was that irrelevant descriptive information also caused people to ignore baseline incidences (13). When posed the following question:

A group is composed of 70 engineers and 30 lawyers. One member of the group is 30 years old, married, with no children. He is skilled and motivated, and is likely to be quite successful in his field. He is well liked by his colleagues. What is the likelihood that he is an engineer?

even statistically sophisticated graduate students provided a figure other than 70% (16). Again, it is reasonable to imagine that PA catheter data may play a similar role of an irrelevant descriptor, possibly distorting rational analysis of possible causes.

Other heuristics may also play a role. Studies suggest that humans tend to be overconfident in their predictions, that overconfidence increases as people become more confident, and that overconfidence seems to associate with more constrained social networks where one person exists in a central, coordinating position such as in an ICU (17). In the case of the PA catheter, overconfidence as a result of PA-derived values may lead to overly bold therapeutic decisions, and explain why patients with CVP catheters alone may be managed more cautiously, and thus be more likely to eventually arrive at the right diagnosis or therapy. Hindsight bias, in which people who know the outcome of an event falsely overestimate the likelihood that they would have predicted it, may also lead physicians to perceive the PA catheter as more useful than it really was (18). Such effects are enhanced when persuasive causal explanations are available to connect the causes to the outcomes. Thus, when given an outcome AND a plausible causal mechanism, people are less likely to be surprised than if given an outcome alone. In the embolism case above, an elevated PA pressure may serve as a mechanistic link between embolism and hemiparesis, reinforcing the role of the swan by inducing hindsight bias and reducing surprise at a relatively rare consequence of PE (hemiparesis).

Finally, people clearly tend to prefer risk to ambiguity. This element of intuitive decision-making was first described by Daniel Ellsberg in 1961 (19), who proposed the following paradox:

Consider an urn containing 9 balls. Three are red; the other 6 are either black or yellow.

A ball is selected at random from the urn. If you guess the color of the ball correctly, you win \$1000. What do you guess?

When confronted with this choice, most guess red, reasoning that red guarantees a win probability of 1/3, but that the win probability of black or yellow is ambiguous, and therefore a less desirable bet. But this choice is a paradox, as illustrated by the rest of Ellsberg's construct:

Now, repeat the above game. This time, if you guess a color that the ball is NOT, you win \$1000. What do you guess?

Again, most guess red, based on probability estimates that the likelihood of not red (2/3) is higher than the likelihood of red (1/3). But it makes no sense to guess red in the first example AND red in the second...the first question requires one to select the higher probability color, the second requires one to select the lower probability color. Unless one factors in a human preference for certainty, and a willingness to accept risk as a result. An intuitive preference for risk over ambiguity may also play a role in altering risk/benefit calculations with use of a PA catheter, potentially increasing risk without a corresponding increased benefit.

Summary

Reconciling cognitive models of PA catheter use with the current trend towards evidence based medicine sets up an intellectual dilemma for physicians dedicated to practicing based on the "best evidence". What is particularly compelling about the PA catheter is the perceived need for it, even in the face of accumulating evidence suggesting that the benefit is slight. One partial explanation lies in the pervasive and systematic differences between probabilistic analysis of uncertainty and risk, and intuitive "shortcuts" used by humans in decision making under uncertain conditions. Several of these characteristics: risk vs ambiguity, the conjunction fallacy, representativeness and overconfidence may all affect the decision to place a PA catheter, and more importantly, distort its perceived necessity to the practitioner.

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Intentional Hypothermia Following, In Hospital CPR-What Should We Be Doing? Brenda G. Fahy, M.D., F.C.C.M., F.C.C.P.

Therapeutic hypothermia after cardiac arrest has received renewed interest. It has now been recommended(24) by the Advanced Life Support Task Force of the International Liaison Committee on Resuscitation (Nolan JP, Morley PT, Vanden Hoek TL, Hickey RW: Therapeutic Hypothermia After Cardiac Arrest: An advisory Statement by the Advanced Life Support Task Force of the International Liaison Committee on Resuscitation. Circ 2003; p 118). Current recommendations are that unconscious adult patients with spontaneous circulation after out-of-hospital arrest should be cooled to 32°C to 34°C for 12 to 24 hours when the initial rhythm was ventricular fibrillation (VF). The recommendations state that for other rhythm or in-hospital cardiac arrest such cooling may also be beneficial.

Introduction

Many technologies have been instituted over the past 40 years to improve outcome after cardiopulmonary arrest. Despite these advances, prognosis for neurological outcome after return of spontaneous circulation following out-of-hospital resuscitation remains poor (1,26). For in-hospital resuscitation, only 25% of ICU patients admitted with return of spontaneous circulation had a good recovery or moderate disability (22). However, two independent prospective randomized trials (3,17) in adults following ventricular fibrillation(VF)/pulseless ventricular tachycardia (VT) cardiac arrest showed mild hypothermia improved outcome. The following will provide a brief review of the literature concerning hypothermia as a therapeutic option following successful resuscitation after cardiac arrest.

History of Therapeutic Hypothermia

Intentional hypothermia as a therapy is not new. One of the earliest clinical uses of hypothermia occurred in 1937 when a metastatic cancer patient was cooled to 32°C for 24 hours (12). Since the 1950s, hypothermia has been utilized during certain cardiac procedures (4) to protect the brain from global ischemia. Hypothermia subsequently became standard of care (8) during cardiopulmonary bypass. Therapeutic hypothermia has also been used for neuroprotection during certain neurological surgeries (10,25).

Therapeutic hypothermia in a human following cardiac arrest was described in 1958 (32). Despite this report, hypothermia as a therapy after cardiopulmonary arrest does not appear to have been widely utilized. Recognition of potential complications including arrhythmias and coagulopathy (11) as well as logistical problems with its implementation may have prevented its widespread use. Other cardiopulmonary resuscitation advances including external defibrillation (36) may have also been contributory.

Therapeutic Hypothermia-Animal Models

During the 1980's, Safar's group rekindled interest in therapeutic hypothermia using a reproducible canine model. Postresuscitation moderate hypothermia improved neurological outcome. (15,21). Realizing that brain hypothermia might protect against global ischemia during cardiac arrest, subsequent studies (16,28) discovered that "accidental" mild cerebral hypothermia (brain temperature 34-36°C) was beneficial at the start of global brain ischemia. In addition, this mild degree of hypothermia avoided a great deal of the earlier complications associated with colder temperatures.

With renewed interest in the potential cerebral protective effects of mild hypothermia, further research examined the timing and duration of hypothermia. In a rat model of incomplete forebrain ischemia, the beneficial effect of mild hypothermia was proven histologically and extensive biochemical investigations were preformed (5,6). The lower the prearrest temperature the better the outcome in this rat model; hypothermic induction after cardiac arrest did not improve outcome. Prearrest hypothermia in the clinical setting of unanticipated cardiac arrest is not feasible. In

addition, the canine model provides a better clinically relevant model for human global ischemia following cardiac arrest than the rat.

The degree of cooling that provided cerebral protection with minimal hypothermic complications was investigated in the canine model. Mild resuscitative total body hypothermia (20,31) had improved outcome with fewer complications compared to moderate (21) or deep hypothermia. Postulated mechanisms for this outcome difference included adverse circulatory side effects of lower temperature after cardiac arrest.

The appropriate timing of hypothermic induction was subsequently explored. A 15 minute delay resulted in less protection than immediate cooling (19). Different methods of cooling were investigated (19,20,27,30,31, 33). The optimal cooling was obtained with head surface and peritoneal cooling (27). In an attempt to improve cerebral blood flow, additional therapeutic measures included hemodilution and induced hypertension. At this point Dr. Safar recommended that clinical trials with induction of mild hypothermia during standard external CPR or as rapidly as possible be employed.

Therapeutic Hypothermia after Cardiac Arrest-Human Studies

This recommendation spawned human trials of induced mild hypothermia as a therapy to improve neurological recovery in patients with successful return of spontaneous circulation following CPR. In a nonrandomized pilot trial of out of hospital cardiac arrest (2), 22 patients who remained unconscious after return of spontaneous circulation had moderate total body hypothermia (33 °C) induced and maintained in the ICU for 12 hours by surface cooling. These patients were rewarmed slowly for 6 hours and then retrospectively compared to case-matched controls. Compared to matched controls, they showed significant improvement in Glasgow Outcome Scores prior to hospital discharge and a reduced mortality. In this series, one patient developed ARDS with nonoliguric renal failure but fully recovered. No other significant hypothermic complications (e.g. sepsis, coagulopathy, neutropenia, thrombocytopenia) occurred.

In a small study of 28 patients, the Hypothermia After Cardiac Arrest Group (HACA) was unable to confirm these findings (34). There was no 6 month outcome difference compared to historic case-matched controls. However, a higher incidence of pneumonia was noted. However, further study was warranted. Subsequent studies by the HACA group (35) evaluated the feasibility of hypothermia after cardiac arrest. Mild hypothermia was able to be induced in comatose survivors of out of hospital cardiac arrest utilizing only head and body surface cooling. This cooling was started within 5 minutes of arrival in the emergency department and maintained for 48 hours. Compared to case-matched historic controls, the hypothermia induced patients had a twofold improvement in outcome without significant hypothermic complications. Some of the patients had delay in initiation of hypothermia and a prolonged time to reach target temperature.

The HACA Group performed a human prospective randomized studies comparing standard normothermia with mild hypothermia. (17). This European multicenter trial enrolled 275 adult patients who had return of spontaneous circulation following an initial witnessed VF or pulseless VT. Inclusion criteria included return of spontaneous circulation within 60 minutes with a collapse to initiation of resuscitation within 15 minutes. Exclusion criteria included response to verbal commands, hypotension (mean BP less than 60 mmHg) for 30 minutes after resuscitation, and admission tympanic membrane temperature less than 30 °C Patients randomized to hypothermia received sedation, paralytics and mechanical ventilation. The hypothermia group was cooled to a bladder temperature of 32 to 34 °C initially with use of a specialized bed that delivers cool air over the entire body. If cooling was not achieved with this method within four hours of return of spontaneous circulation, ice packs were added. Temperature was maintained for 24 hours from the start of cooling (not achievement of target temperature) with passive rewarming over 8 hours. The normothermia group was placed on a regular hospital bed and received the same standard ICU care as the hypothermic group. Six month outcome revealed a favorable neurological outcome in the hypothermic group. In the hypothermic group, discharge to home or a rehabilitation facility occurred with 55% of the 136 compared to 39% of the 137 normothermic controls. The

hypothermic group had a lower mortality (41%) compared to normothermia (55%). Complication rates for the initial 7 days did not differ significantly between the two groups although there was an increased trend of sepsis and bleeding in the hypothermic group.

An Australian human prospective study evaluating the efficacy of mild hypothermia after cardiac arrest was published in the same issue of the New England Journal of Medicine (3) as the European multicenter trial. This Australian multicenter trial enrolled 77 patients who remained comatose with return of spontaneous circulation after cardiac arrest with an initial rhythm of VF or pulseless VT. The hypothermia group was cooled to 33°C for 12 hours with external cooling (ice packs). Target temperatures were achieved in 2 hours. At the time of hospital discharge, 49% of the patients in the hypothermic group were discharged home or to a rehabilitation facility compared to 25% of the normothermic group. Hypothermia group also had a lower mortality at hospital discharge (51% versus 68%). Compared to normothermic controls, the hypothermic patients were noted to have a lower cardiac output and an increased systemic vascular resistance. There were no other reported complications (i.e. sepsis).

Both of these multicenter studies are open to criticism as clinicians could not be blinded due to the cooling techniques which may have resulted in better care for the hypothermic patients than the controls. In the European trial, 19 patients never reached the 34 °C target temperature. Earlier initiation of hypothermia may improve outcome. Eight hours were required with the European cooling method to achieve target temperatures. In the Australian study, it took 120 minutes to achieve target temperatures. Four patients randomized to receive hypothermia had to be excluded because of the emergency room not initiating cooling and one patient being rewarmed after ICU admission. Both of these studies excluded patients that were unlikely to benefit from hypothermia.

Therapeutic Hypothermia-Physiologic Effects

Hypothermia affects numerous cellular functions. However, for the purpose of this paper, the cerebral effects will be the main focus. Cerebral ischemia injury following return of spontaneous circulation after cardiac arrest resuscitation involves several mechanisms which can only be covered briefly in this review. Cerebral ischemia injury occurs when energy supply does not meet demand. This leads to changes in the intracellular milieu, membrane damage, as well as secondary process which further aggravate the injury. Neuroprotective strategies including hypothermia may help protect the brain from these insults. Cerebral metabolic rate decreases by 6-7% (13) for each degree Celsius temperature decrease. Hypothermia reduces the energy consumption related to electrophysiological energy consumption as well as the energy utilization related to maintenance of cellular integrity. Mild hypothermia may have more effect on the decrease of energy utilization related to maintenance of cellular integrity (18). Hypothermia may have a beneficial effect on several steps in the biochemical cascade of ischemic injury. These have been reviewed extensively elsewhere and will not be discussed in detail (7,23) Possible postulated mechanisms include inhibition of apoptosis, inhibition of proinflammatory cytokines, reduction of free radicals, preservation of postischemic enzyme function, and decreased excitatory neurotransmitter release.

Therapeutic Hypothermia In-Hospital Cardiac Arrest

The International Liaison Committee on Resuscitation states that in-hospital cardiac arrest victims may potentially benefit from cooling. Obviously, further randomized prospective studies need to be performed to provide data for this therapy. The strict exclusion criteria for the out-of-hospital patients must be taken in to consideration when considering therapeutic hypothermia as a treatment option for in-hospital resuscitation. To date, the two multicenter randomized prospective human studies (3, 17) only included patients who had an initial rhythm of VF/pulseless VT. This initial rhythm may be an indicator of survival (9). Further studies are needed to elucidate benefit for other initial cardiac rhythms which may be noncardiac in origin.

Mild hypothermia does have potential complications although fewer than with colder temperatures. This therapy can be labor intensive and the patient must still receive critical care services. This therapy can require sedation and paralytics to prevent shivering. Hypothermia if utilized as a

therapeutic option should be instituted as early as possible and target temperatures reached as quickly as possible. But precise timing and indications need to be examined. Target temperatures may be reached faster following the in-hospital cardiopulmonary arrest population compared to out-of-hospital arrest. This remains to be studied.

With the above mentioned prospective out-of-hospital cardiac arrest trials (3, 17), external cooling was utilized. Cooling methods may not have similar efficacies. Feasibility and safety of various cooling methods to achieve mild hypothermia are beginning to appear in the literature (14,29). The optimal cooling method would achieve target temperatures rapidly with minimal risks. These cooling methods need further investigation as well as concomitant sedation/paralytics for this therapy. The duration of cooling that improves neurological benefit and minimizes hypothermic side effects must also be further elucidated. The method and duration of rewarming may also impact neurological outcome and needs further controlled study.

The 2005 CPR and Emergency Cardiac Care (ECC) Evidence Evaluation Task Force Topics identified a need to have these topics further evaluated. The AHA website lists as some of the topics to be included in the January 2005 International Consensus of Science and Treatment Recommendations for CPR and ECC Conference are:

1. Does the use of therapeutic hypothermia in the management of the patient after cardiac arrest improve outcome?
2. What modifications are applicable to the resuscitation technique for hypothermia?

Therapeutic hypothermia is a promising therapy to improve functional recovery after return of spontaneous circulation following cardiac arrest.

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Who Should Receive Recombinant Human Activated Protein C

Michael Avidan, M.D.

Severe sepsis remains both an important clinical challenge and an economic burden in intensive care. An estimated 750 000 cases occur each year in the US alone (300 cases per 100 000 population).¹ The publication of the PROWESS study in 2001 heralded new hope in the treatment of sepsis.² In a randomized, double-blind, placebo-controlled, multicenter trial, patients with systemic inflammation and organ failure due to acute infection were enrolled and assigned to receive an intravenous infusion of either placebo or recombinant human activated protein C (rhAPC) for a total duration of 96 hours. A total of 1690 randomized patients were treated (840 in the placebo group and 850 in the rhAPC group). The mortality rate was 30.8 percent in the placebo group and 24.7 percent in the rhAPC group. This represents an absolute reduction in the risk of death of 6.1 percent ($P=0.005$). The incidence of serious bleeding was higher in the rhAPC group than in the placebo group (3.5 percent vs. 2.0 percent, $P=0.06$). The trial concluded that treatment with rhAPC significantly reduces mortality in patients with severe sepsis and may be associated with an increased risk of bleeding.² Interestingly, patients in the PROWESS study who were older than 74 years appeared to derive even greater benefit in subgroup analysis.³

Subsequent to this trial, data on the safety of treatment with rhAPC in 2786 adult patients with severe sepsis enrolled in all phase 2 and 3 clinical trials, and in an estimated 3991 patients receiving the drug in commercial use, were evaluated in 2003.⁴ The 28-day mortality rate for all adult patients who received active treatment in all clinical trials was 25.3% (704/2786).⁴ Serious bleeding events during the infusion period occurred in 2.8% (79/2786) of patients.⁴ The efficacy and safety profiles of rhAPC were concluded to have remained consistent over the conduct of multiple clinical trials.⁴ The most important serious adverse event associated with rhAPC appears to be bleeding. Additional clinical experience indicates that invasive procedures are associated with a substantial percentage of serious bleeding events, particularly those occurring at the start of infusion of the drug.⁴

In the ENHANCE study⁵, published in 2004, 273 adult patients with a diagnosis of severe sepsis, which was defined as a systemic inflammatory response due to acute infection and one or more sepsis-induced organ dysfunctions present for less than 48 hours, as in the PROWESS trial.² RhAPC at 24 mcg/kg/hr was administered as a continuous IV infusion for a duration of 96 +/- 1 hours. The 28-day all-cause mortality rate was 26.4%. Serious bleeding events during the infusion period occurred in 11 patients (4.0%).⁵

Recent reports on cost effectiveness suggest that when rhAPC treatment is targeted to those patients most likely to achieve the greatest benefit, the drug is cost effective by the standards of other well accepted life-saving interventions.^{1,6} If this was all there was to it, there would be no controversy and rhAPC would be given according to an extensive evidence base to those who would benefit. Activated protein C has been suggested to be relatively cost effective when targeted to patients with severe sepsis, greater severity of illness (an APACHE II score of 25 or more), and a reasonable life expectancy if they survive the episode of sepsis.⁷ The problem is the water becomes a little murky when we try to define exactly who is likely to derive the most benefit. Careful examination of the evidence base also reveals certain concerns, which were not highlighted in the original publications.⁸

Although several studies have suggested strongly that rhAPC confers a survival benefit in severe sepsis, the mechanisms by which this is achieved are unclear.

The protein C pathway serves as a regulatory pathway with anti-inflammatory and anticoagulant properties. Studies with other inhibitors of coagulation, such as tissue factor pathway inhibitor and recombinant human antithrombin have not shown decreased mortality in the setting of severe sepsis.^{9,10} In an intriguing volunteer study, an infusion of low dose endotoxin was used to study mechanisms of action of rhAPC on markers of coagulation.¹¹ Twenty-four volunteers were randomized to receive either 24 mcg/kg/hr rhAPC or placebo intravenously for 8 hours.

Lipopolysaccharide (LPS, 2 ng/kg) was administered 2 hours after starting the infusions. RhAPC decreased basal tissue factor (TF)-mRNA expression, and thrombin formation and action. In contrast, rhAPC did not significantly blunt LPS-induced thrombin generation. Consistently, rhAPC did not reduce LPS-induced levels of TF-mRNA or D-dimer and had no effect on fibrinolytic activity or inflammation. Endogenous APC formation was enhanced during endotoxemia and appeared to be associated with inflammation rather than thrombin formation. Even low-grade endotoxemia induces significant protein C activation. Infusion of rhAPC decreases "spontaneous" activation of coagulation but does not blunt LPS-induced, TF-mediated coagulation in healthy volunteers.¹¹ Unfortunately this study did not look at the effect of rhAPC on inflammatory mediators in this setting. However, anti-inflammatory actions have been demonstrated in other studies. For example, rhAPC acts as a modulator of nuclear factor-kappaB to aid in the host immune response in endothelium and monocytes.¹² Inhibition of apoptosis is an example of the possible protective effect of rhAPC on endothelial and mononuclear cell dysfunction.¹²

The findings that two other potent anticoagulants, antithrombin III and recombinant tissue factor pathway inhibitor, failed to decrease mortality in sepsis, suggest that the anti-inflammatory and anti-apoptotic effects of rhAPC may be involved in its beneficial actions.¹³ Recombinant human APC therapy conveys an increased risk of serious bleeding complications due to APC anticoagulant activity.^{2,4,5} Coagulation proteases enhance inflammation during endotoxemia by activating protease-activated receptors within the vasculature.¹⁴ Recombinant human APC may dampen the effect of some of these proteases in inducing inflammation.¹⁴ In an attempt to generate rhAPC variants with reduced risk of bleeding due to reduced anticoagulant activity, an attempt was made to dissect rhAPC's anticoagulant activity from its cytoprotective activity by site-directed mutagenesis. Intriguingly, it has been found that it may be possible to reduce anticoagulant activity while preserving anti-apoptotic activity of rhAPC variants.¹³ Therapeutic use of such APC variants could in theory reduce serious bleeding risks while still providing the beneficial effects of rhAPC in sepsis.¹³

It is not easy to make clear recommendations for the rational use of rhAPC for several reasons. As noted earlier, other anticoagulants have not improved outcome in sepsis. Attributing the benefit associated with rhAPC to decreased inflammation and apoptosis are theories, which are firmly in the realm of hypotheses. Currently there is no compelling biologically plausible explanation as to why rhAPC should decrease mortality in sepsis when so many other agents, whether anti-coagulant or anti-inflammatory, have failed. When the data on rhAPC were presented to the FDA, only half the committee felt that the evidence clearly supported the use of this drug and several very serious reservations were raised.⁸ (www.fda.gov/ohrms/dockets/ac/01/briefing/3797b1_02_FDA briefing.doc & www.fda.gov/ohrms/dockets/ac/cder01.htm#Anti-Infective)

After the results of the PROWESS trial² were published, it was revealed that the rhAPC formulation was changed midway during the trial. Survival benefit was only evident in the latter part of the trial.⁸ The reasons behind this improvement are unclear. If indeed the specific formulation of the recombinant drug is important, this poses a problem, as it is not clear that the drug currently on the market has the same characteristics as the batch where benefit was evident. There is no laboratory test that can predict the efficacy of future lots.⁸ It goes without say that changing the drug's formulation halfway constituted a dubious practice in clinical research.

RhAPC seems to have been effective in numerous subgroups. Its efficacy was most apparent in patients older than 50 years of age, in patients with more than one dysfunctional organ system, in patients with an APACHE II score of more than 24 before the infusion of the drug, and in patients who had shock at the time of the infusion.⁸ Subgroups in which benefit was not apparent included patients who had undergone surgery and patients with failure of a single organ.⁸

The FDA licensed activated protein C for the treatment of adult patients with severe sepsis who have a high risk of death, as indicated by an APACHE II score of 25 or more. The problem with this is that APACHE II is a dynamic score and is subject to inter-rater variability. This criterion for administering a drug has never previously been validated.⁸ A large multi center study with rhAPC in "healthier" patients with sepsis was recently abandoned owing to "futility". Perhaps most worrying is

that administering rhAPC to an inappropriate candidate may not merely be a costly and futile intervention. RhAPC is also associated with a risk of fatal bleeding and increased mortality when given to healthier patients.

In summary, activated protein C is a new therapy that has revolutionized treatment in sepsis and should be given to all critically ill septic patients. As long as they are not too well (Apache II score < 25)⁸, and they have more than one organ system failure, and they have not been septic for too long (>48hours), and the right batch of rhAPC is given, and they have not had recent surgery, and they require no urgent invasive procedure, and they are not at risk of bleeding, and their insurance can pay for the drug.

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β Blockers: How Do They Really Work?

Andrew J. Patterson, M.D., Ph.D.

Objectives

- Present Evidence that β Adrenergic Receptor Blocking Agents (βBlockers) Do Work
- Introduce Mechanisms by which β Blockers May Benefit Specific Groups of Patients
- Consider the Heterogeneity of β Blocking Agents
- Identify Patients for whom β Blocker Therapy is Recommended
- Review the β1 and β2 Adrenergic Receptor (AR) Signaling Pathways and How they Might Explain Some of the Beneficial Effects of β Blockade
- Discuss the Unique Properties of Carvedilol

Key Words: β blocker, adrenergic receptor, cardiac protection, ventricular remodeling, neurohormonal

What is the Evidence that β Blockers Work?

Several studies provide evidence that β blockers work and that specific patient populations derive benefit from β blocker administration. For example, the MERIT-HF study demonstrated a 34% decrease in all cause mortality after administration of Metoprolol CR/XL in patients with stable New York Heart Association (NYHA) class II-IV congestive heart failure (CHF) receiving standard medical therapy.¹ The CIBIS I trial demonstrated marked improvement in functional class and a decrease in hospital admissions among patients with moderate CHF who received Bisoprolol. CIBIS II revealed that Bisoprolol had a significant mortality benefit and reduced all cause hospital admissions as well as sudden death in patients with moderate CHF.² The Australia, New Zealand, and United States Carvedilol Clinical Trial Program demonstrated a significant overall reduction in mortality, hospitalizations due to cardiovascular causes, and the combined end point of hospitalization or death.^{3, 4} The COPERNICUS trial revealed a significant survival benefit of Carvedilol in NYHA class III-IV CHF patients who were receiving optimal medical therapy but had left ventricular ejection fractions (LVEF) less than 25%.⁵

The CAPRICORN trial revealed that Carvedilol reduced the incidence of cardiovascular mortality, recurrent non-fatal myocardial infarction (MI), and the combined endpoint of death or re-infarction in patients with left ventricle dysfunction following MI.⁶ The CAFE trial demonstrated that the combination of Carvedilol and Digoxin was superior to Digoxin alone in slowing ventricular rate as well as improving LVEF and symptom score.⁷ And, two separate studies demonstrated that administration of Atenolol or Bisoprolol to patients at risk for ischemic cardiac disease undergoing non-cardiac surgery reduced mortality.^{8, 9}

By What Mechanisms Might β Blockers Benefit Specific Groups of Patients?

How β blockers convey protection remains unclear. In fact, different β blockers probably benefit different patients in different ways. For instance, in patients with ischemic coronary artery disease, β blockers like Atenolol and Bisoprolol may improve oxygen balance by decreasing cardiac rate and contractility. They may also reduce oxygen utilization, prevent dislodging of coronary atherosclerotic plaques, and increase the threshold for ventricular fibrillation in the presence of ischemia.⁹

In several groups of patients, β blockers may convey benefit by reducing detrimental myocardial remodeling. For instance, patients who suffer from CHF, patients who experience myocardial ischemia or infarction, patients who undergo cardiac surgery, and patients who endure emotional stress all demonstrate evidence of sympathetic nervous system hyperactivity. Continuous release of norepinephrine from sympathetic nerve terminals innervating the heart can lead to cellular and

subcellular changes. These changes are commonly referred to as myocardial remodeling and include myocyte hypertrophy, myocyte apoptosis, re-activation of fetal gene programs, and alterations in the quantity and composition of the extra-cellular matrix. β blockers may reduce detrimental remodeling of the myocardium in patients who experience sympathetic nervous system hyperactivity.

Agents like Carvedilol (and to some degree Metoprolol) may convey benefit by reversing abnormal intracellular calcium handling by promoting expression of sarcoplasmic reticulum calcium ATPase (SERCA) mRNA. They may also decrease expression of detrimental β myosin heavy chain mRNA while increasing beneficial β myosin heavy chain mRNA expression.¹⁰ Carvedilol in particular may enhance secretion of atrial natriuretic peptide (ANP),¹¹ which may benefit CHF patients by inhibiting the rennin-angiotensin-aldosterone and sympathetic nervous systems. Celiprolol may increase myocardial endothelial nitric oxide synthase (eNOS) levels and activity. Nitric oxide production has been found to be diminished during cardiac remodeling.¹²

<u>β1, β2 Blockade</u>	<u>β1 Blockade</u>	<u>β1, β2, α1 Blockade</u>
Carteolol	Acebutolol	Bucindolol
Nadolol	Atenolol	Carvedilol
Penbutolol	Betaxolol	Labetalol
Pindolol	Bisoprolol	
Propranolol	Celiprolol	
Sotalol	Esmolol	
Timolol	Metoprolol	
	Xamoterol	

Figure 1. **β Blocker Classifications.** β blockers can be classified according to which adrenergic receptor subtypes they antagonize.

β Blockers are a Heterogeneous Group of Agents

It is important to emphasize that β blockers vary considerably in terms of their mechanisms of action. In fact, the effectiveness of each agent in conveying benefit to specific patient groups may be greatly influenced by its unique properties. β blockers can be classified according to which adrenergic receptor subtypes they antagonize as well as by other criteria (see Figure 1). For example, Atenolol, Bisoprolol, Esmolol, Metoprolol, and Xamoterol are β 1AR selective antagonists, while Bucindolol, Carvedilol, Labetalol, and Propranolol are non-selective β 1 β 2AR blockers. Bucindolol, Carvedilol, and Labetalol also block β 1 ARs. Carvedilol is also an anti-oxidant.

Several β blockers actually stabilize the activated state of β ARs, leading to coupling of the receptor to stimulatory G protein (G_s). These agents are considered partial agonists (see Figure 2). They block the effects of potent agonists such as epinephrine and norepinephrine while generating low-level β AR stimulation. Bucindolol and Xamoterol are examples of a partial agonist.¹³

Other β blockers are inverse agonists, which stabilize the inactivate state of β ARs. They lead to receptor up-regulation rather than causing the desensitization and down-regulation observed with Xamoterol. Metoprolol, Betaxolol (used in the treatment of open-angle glaucoma) and Sotalol (approved for treatment of atrial fibrillation and flutter) are examples of inverse agonist β AR blocking agents.¹³

Many of the β blockers commonly used by Intensivists and Anesthesiologists are neutral antagonists, which bind to β receptors without affecting their activation states. They simply block the binding of agonists. Carvedilol and Propranolol are examples of neutral antagonists.¹³ There are theoretical benefits to β 1AR subtype-selective antagonist activity, to β 1AR blocking activity,

and to neutral antagonist or partial inverse agonist activity. These theoretical benefits will be discussed later in the lecture.

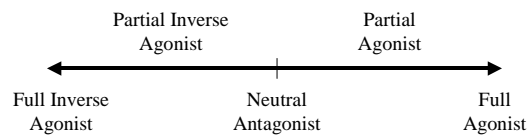


Figure 2. **Spectrum of β Adrenergic Receptor Ligand Efficacy.** β adrenergic receptor agonists and antagonists are not simply polar opposites in terms of their abilities to activate or inactivate β receptors. β adrenergic receptor agonists and antagonists lie on a continuum. Full agonists stabilize the activated state of the receptor. Full inverse agonists stabilize the inactive state of the receptor. Neutral antagonists have no effect upon receptor activation. Neutral antagonists simply block the binding of agonists. Most β blockers are partial inverse agonists or neutral antagonists. A few β blockers are partial agonists.

β Blocker Therapy is Advised for Four Groups of Patients

β Blocker therapy is recommended for patients with CHF, patients at risk for myocardial infarction in the perioperative period, patients who are experiencing or have experienced myocardial infarction, and patients with stable angina and hypertension.

Congestive Heart Failure (CHF)

β blocker therapy is now an accepted part of the medical management of CHF patients. β blocker therapy is associated with a 30% reduction in mortality and a 40% reduction in hospitalizations in patients with NYHA class II-IV CHF.¹⁴⁻¹⁸ β blocker therapy has been shown to improve left ventricular ejection fractions in patients with CHF,¹⁹ attenuate left ventricular remodeling,^{20, 21} and reduce the incidence of tachyarrhythmias.²²

Perioperative Period in Patients at Risk for Myocardial Infarction

Two studies have demonstrated the benefit of β blockade during the perioperative period in patients at risk for myocardial infarction. The first study was a randomized, double blind, placebo controlled trial of Atenolol in two hundred patients with known coronary artery disease or risk factors for atherosclerosis who underwent non-cardiac surgery. The investigation demonstrated a significant benefit in terms of death at six months post operation if patients received β blockade.⁸

In the second study, 112 patients with one or more clinical risk factors for ischemic cardiac disease or ischemia by dobutamine stress echocardiography scheduled to undergo abdominal aortic aneurysm repair or infra-renal arterial reconstruction were randomly assigned to receive Bisoprolol or placebo. The study was terminated early when Bisoprolol was found to markedly reduce perioperative mortality (17% versus 3.4%). The incidence of perioperative myocardial infarction was also shown to be significantly reduced in patients receiving Bisoprolol (17% versus 0%).⁹

It should be pointed out, however, that continuing chronic β blocker therapy during the perioperative period may not provide the same protective effects as acute β blocker administration during the perioperative period in patients not previously treated with these agents.²³

During or After Myocardial Infarction

In patients with acute coronary syndromes (unstable angina or myocardial infarction), hypertension should be treated initially with β blockers and angiotensin converting enzyme (ACE) inhibitors.²⁴ In patients post myocardial infarction, β blockers, ACE inhibitors, and aldosterone antagonists have proven to be most beneficial.²⁵ β blockade has also been shown to reduce the risk of recurrent ischemia and infarction for patients receiving t-PA.

Coronary Artery Disease and Hypertension

The Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure recommends β blocker therapy for patients with hypertension and stable angina pectoris.²⁶

Contraindications to β Blocker Administration

Severe heart failure, hypotension, bradycardia or heart block, and bronchospasm are contraindications to β blocker administration.

Myocardial β AR Signaling

To understand the important mechanisms by which commonly used β blockers may benefit patients in the clinical realm, it is necessary to consider the mechanisms by which β ARs stimulate the myocardium.

β ARs are heptahelical G-protein coupled receptors that mediate the primary physiological responses to catecholamines. There are three β ARs subtypes in the mammalian heart (β 1AR, β 2AR and β 3AR). β 1ARs and β 2ARs modulate cardiac contractility and rate. The role of the β 3AR in the mammalian heart is not clear. β 1ARs account for approximately 80% of ARs in the heart and play the predominant role in mediating cardiac inotropic and chronotropic response to catecholamines.²⁷

Catecholamine agonists initiate β AR signaling by binding to the receptor and causing it to undergo a conformational change to an activated state. In the activated state, both β 1ARs and β 2ARs couple to the heterotrimeric stimulatory G protein (G_s) located in the cytosol. Receptor activation of G_s causes the dissociation of two subunits, the GTP-binding G_α subunit that stimulates adenylate cyclase and $G_{\beta\gamma}$. The β 2AR is known to couple initially to G_s and later to inhibitory G protein (G_i) if activation continues.

β AR-mediated stimulation of adenylate cyclase via G_s leads to production of cAMP and subsequent activation of protein kinase A (PKA). PKA phosphorylates numerous substrates important for regulating sarcoplasmic calcium ion concentrations (such as the ryanodine receptor and phospholamban). Activation of G_s also directly increases L-type calcium currents, which leads to increased cytosolic calcium concentrations. The net effect of this activity over the short term is augmented myocyte inotropy, chronotropy, and lusitropy. However, if continuous G_s activation occurs, the elevated cytosolic calcium can promote myocyte toxicity and apoptosis by activating calcium/calmodulin kinase II.²⁷

Continuous β 1AR Stimulation leads to Cardiomyocyte Toxicity

Studies of mice that overexpress β 1ARs suggest that continuous β 1AR stimulation leads to G_s -mediated cardiomyocyte toxicity.²⁸ Studies in which the β 1 β 2 agonist isoproterenol was administered to β 2AR knockout (KO) mice also support this finding. Based upon these results, one might hypothesize that the continuous β 1AR activation caused by Bucindolol and Xamoterol (partial agonists) may explain the disappointing performance of these β blockers in CHF treatment trials.^{29, 30}

β 1AR and β 2AR Desensitization

Continuous and prolonged activation of cardiac β ARs also leads to receptor desensitization. Desensitization can produce a 50% reduction in the number of cell surface β 1ARs during persistent β 1AR activation.³¹ Two pathways lead to a reduction of the receptor number: degradation of receptors and a reduction in receptor mRNA. β 1ARs are desensitized when agonist-occupied receptors are phosphorylated by PKA and by G-protein-coupled receptor kinase 2 (GRK2).³² The cellular expression of GRK2 increases during continuous β 1AR stimulation. Following receptor phosphorylation, a small protein known as β -arrestin binds to each receptor and sterically blocks G-protein activation. β -arrestin binding also directs the internalization of desensitized receptors.

In contrast to β 1ARs, β 2ARs uncouple from the G_s signal transduction cascade during periods of continuous activation. PKA-mediated phosphorylation of the β 2AR switches coupling from G_s to G_i . This appears to be a form of negative feedback where PKA generated by the G_s pathway phosphorylates the receptor and switches coupling to G_i , limiting further cAMP production and PKA activation. More importantly, this switch in coupling may lead to activation of β 2AR-mediated cell-protective processes, such as G_i -mediated reduction in myocyte apoptosis.³³

Excessive β 1AR Desensitization can Impair Myocardial Function

β 1AR desensitization may represent a protective response at the level of the myocyte. It may reflect each cell's attempt to protect itself from the toxic effects of prolonged β 1AR activation. However, desensitization may also lead to a reduction in the heart's response to inotropic stimulation.³⁴ For instance, desensitization of cardiac β 1ARs may lead to depressed myocardial function and difficulty in separation from coronary artery bypass.³⁵

Inhibition of GRK2-mediated desensitization of β 1ARs has been shown to ameliorate CHF in several mouse models, suggesting that GRK2 mediated desensitization of β 1ARs may be maladaptive on the organ level. Both Bisoprolol and Carvedilol have been shown to reduce GRK2 expression in animals.²⁷

Protecting the Myocardium: A Role for the β 2AR in the Heart

Although β 2ARs were once believed to be functional and structural duplicates of the β 1AR, it is now known that the two receptor subtypes differ significantly. In fact, the β 2AR gene is located on a different chromosome (5) than the β 1AR gene (chromosome 10). The receptor subtypes differ in size. The β 2AR is 477 amino acids in length whereas the β 1AR is 413 amino acids. And, (as previously stated) it has been demonstrated that their signaling pathways differ in important ways.

During periods of continuous activation, β 2AR receptors change their coupling from G_s to G_i , which has been shown to mediate activation of anti-apoptotic pathways in cultured myocytes.³⁶ β 2AR activation has also been shown to reduce myocyte apoptosis and mortality in mice during continuous β 1AR activation,³⁷ and it has been reported to attenuate β 1AR mediated arrhythmias in dogs.³⁸ The protective effects of β 2AR activation suggest that selective β 1AR blockers may offer advantages over non-specific β 1 β 2AR blocking agents. It is unclear whether selective β 1AR

blocking agents like Atenolol and Bisoprolol offer added benefit over non-specific $\beta_1\beta_2$ AR blockers during the perioperative period due to continued activation of β_2 ARs.

The Unique Properties of Carvedilol

Carvedilol is a non-selective $\beta_1\beta_2$ AR and β_1 AR blocking agent with a unique carbazol moiety. It has demonstrated greater clinical benefit than other β blockers in the management of CHF patients and in the post-MI setting. Carvedilol is an anti-oxidant with anti-arrhythmic, anti-apoptotic, and anti-proliferative properties that affects carbohydrate and lipid metabolism. It has proven beneficial in the management of comorbid conditions such as coronary artery disease, diabetes mellitus, renal insufficiency, and atrial fibrillation.³⁹

The unique ancillary properties of Carvedilol may account for positive results in a number of clinical trials. However, additional studies are warranted.⁴⁹ For instance, while the β_1 AR blocking properties of Carvedilol do mediate advantageous effects such as afterload reduction, β_1 AR blockers alone have not been shown to be effective in the management of CHF.⁴⁰ Further, while the anti-oxidant properties of Carvedilol may offer additional protection from myocardial remodeling, anti-oxidant therapy for heart failure has not proven beneficial in clinical trials.⁴¹ A better understanding of Carvedilol's actions may provide further insight with regard to how β blockers really work.

Summary:

Several studies provide evidence that specific patient populations derive benefit from β blocker administration. β blocker therapy is recommended for patients with CHF, patients at risk for myocardial infarction in the perioperative period, patients who are experiencing or have experienced myocardial infarction, and patients with stable angina and hypertension. However, the exact mechanisms by which β blockers convey their benefits remain unclear.

β blockers probably benefit different patients in different ways, and they vary considerably in terms of their mechanisms of action. Carvedilol is a non-selective $\beta_1\beta_2$ AR and β_1 AR blocking agent that has demonstrated greater clinical benefit than other β blockers in the management of CHF and in the post-MI setting.

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