sin-receptor blocker at discharge for patients with systolic dysfunction, timely initiation of reperfusion with thrombolysis or percutaneous intervention, and smoking cessation. All measures in the this bundle should be completed if not contraindicated. Completion of all the measures in all the bundles by the almost 3,000 hospitals that have signed on to the campaign has the potential to reach the goal of lives saved. It is time to add a sepsis bundle to our efforts to comply with the other components of the Campaign to Save 100,000 Lives.

Previously, timely delivery of appropriate therapy in the first hour has been shown to be critical in other shock-associated states such as trauma with hypovolemic shock (5), cardiogenic shock due to acute myocardial infarction (6), and obstructive shock due to massive pulmonary embolus (7). Now septic shock must be added to the list. A performance measure should be constructed that measures compliance with antimicrobial administration within 1 hr (the “golden hour”) of onset of hypotension in septic shock. If we are to save more lives, time is of the essence.

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The pulmonary artery catheter and critical care: The cart is before the horse*

In this issue of Critical Care Medicine, Dr. Friese and colleagues (1) examine the association between pulmonary artery catheter (PAC) use and mortality in a large cohort of critically injured trauma patients. These investigators reviewed data from 53,312 adult patients found in the National Trauma Data Bank, of which 1,933 patients had been managed with a PAC. This retrospective, observational, cohort study demonstrated that as age and injury severity increased, the association of death with PAC use decreased. This apparent association with improved mortality was strongest for the patient groups that were the oldest (61–90 yrs), in shock (base deficit, ≤11), and with the highest injury severity (injury severity score, 25–75). Conversely, patients without these severe injury characteristics had an increased mortality in association with the PAC. This result is similar to that found in a previous observational study (2). These study results may be a manifestation of the truth, because this type of study design possesses the advantage of having external validity via its reflection of real-world standard practice. The benefit, if true, could be explained by the earlier insertion of the PAC in patients who are severely ill with the correction of a tissue perfusion deficit that is best directed by the PAC. The treatment may have a U-shaped effect resulting in a higher mortality if the perfusion defect is under- or over-corrected and optimal outcomes resulting when it is “just right.”

The disadvantage that all studies of this design suffer from include confounding by indication. The reason why clinicians decide to place the PAC is linked to the patient’s outcome. These additional risk factors cannot all be known and measured and, hence, control of them is incomplete outside of properly designed randomized, controlled trials (RCTs). Why should the readership be interested in the results of the study by Dr. Friese and colleagues (1) when several previous multi-center, randomized, controlled trials involving the PAC have demonstrated “no benefit”?

We should be interested because I believe the RCTs fail to inform us adequately because of the following problems: 1) poor external validity; 2) inadequate sample size; and 3) efficacy vs. effectiveness.

The RCT is the most reliable method of determining the effectiveness of an intervention such as the PAC. The design and conduct of such trials must be such that bias is minimal to be internally valid. However, to be clinically useful, the results must also be relevant to a specified group of patients in a particular setting. The effect of an intervention such as the PAC is very dependent on factors such as the patients’ characteristics, methods of application, and setting (3). Selecting RCTs that have at least an 80% power to detect a 10% difference in mortality yields four recent trials (4–7). One trial was in heart failure patients (4), two in adult intensive care unit (ICU) patients (6, 7), and one in a high-risk elective surgical population (5). None of these trials contains critically ill, traumatized patient to any significant degree. Hence, only two studies inform us of the effect of PAC in a general ICU population that may remotely reflect a population of interest for the critically injured trauma patient (6, 7).

The sample size of these two trials are such that neither study was powered to demonstrate a mortality difference of
<10%, even though the difference suggested by observational trials was felt to be 5% or fewer (8).

In addition, neither trial dictated or, for that matter, measured any differences in therapy that was provided to the patients in the two groups. It is this part of randomized, controlled trial design to date that is the crux of the problem. We consistently put the cart before the horse! It is impossible for the presence of a monitoring device alone to alter outcome. It must be linked to a therapy that is known to improve outcome, otherwise the negative results of these trials become somewhat predictable. In addition, clinicians are probabilistic thinkers, and when faced with uncertainty in complex decisions, they will inevitably seek out more information to decrease this uncertainty (9). So, we are never comparing the information derived from the PAC with no information at all but instead with other sources of information that will be highly variable, depending on the clinician's certainty. So, the comparison is likely to be to information from things such as a more detailed physical examination, information from central venous pressure measurements, measurements of venous oxygen saturation, esophageal flow probes, and echocardiographic data. Unfortunately, we have not measured the decision making that surrounds these other sources of hemodynamic data that the clinicians in the control arm of these trials are using. Not knowing what type of interventions were provided to patients in these RCTs only raises more questions than answers. This is evidenced by mortality rates that are considerably higher than one would predict with APACHE II scores of 22 and a predicted mortality rate of <40% but an actual mortality rate of almost 70%. This result is in contrast with other reports of mortality in association with PAC use (2), which raises concerns about the types of interventions that were provided to both groups. Trials that cannot have the intervention blinded need to strongly consider strict protocolization of care. Then, and only then, can we draw reasonable conclusions about the ability of a monitoring device to direct care that ultimately improves patient outcome.

We know very little about the efficacy of our therapy with some exceptions. Take the example provided by Rivers et al. (10), in which outcomes were improved in patients receiving early goal-directed therapy that resulted in patients receiving greater amounts of resuscitative saline, transfused red blood cells, and dobutamine. If Rivers et al. had decided to use a PAC as the monitoring device, we might have an alternate opinion about its usefulness in acute resuscitation. This study suggests that the timing of our interventions may be the more important factor and that by the time the patients are in the ICU, any manipulation in fluids and vasoactive agents beyond just good supportive care is unlikely to be of benefit. I would also argue that if benefit exists in the ICU setting, the effect size of such a benefit is smaller than any we have tried to measure to date. It is in this timing phenomenon that we may find explanation for the results of Friese and colleagues (1). Traumatized patients who are older and more severely ill will have greater uncertainty surrounding their hemodynamic profile and most appropriate subsequent treatment. It may, therefore, be reasonable to assume that the PAC is placed earlier in the treatment of these patients. The phenomenon of improved outcomes may be the result of earlier intervention. Unfortunately, these data are not available in the study by Friese and colleagues.

I think we often lose sight of the fact that the PAC is a diagnostic device. As with the chest radiograph, you make a diagnosis (pneumonia/shock) and institute a therapy (antibiotics/fluids and vasoressors). We understand that the chest radiograph is not a very specific tool by which to diagnose pneumonia, but no one has ever asked for it to be subjected to a RCT of its effectiveness or suggested a moratorium on its use. So why have we done this with the PAC? I would argue that it is the question of safety, not effectiveness. What our RCTs inform, together with a recent meta-analysis, is that they support the safety of the PAC, an explicit primary goal of at least two of the trials (6, 7, 11).

So where do we go from here?

The observational study by Friese and colleagues (1) has another role that is often overlooked. Observational studies play a crucial role in the optimal design and interpretation of RCTs (12). They are invaluable in stimulating the pursuit of new knowledge and improved patient outcomes. The article by Dr. Friese and colleagues does just that. I would like to congratulate Dr. Friese and colleagues on reminding us that we are by no means finished when it comes to questions about the efficacy of the PAC. I would also like to challenge them and the trauma surgery community to design a trial that takes the above into consideration. The real question is, "Does the PAC allow for more accurate titration of a known effective therapy over some alternative monitoring approach?" Such a trial could be a comparison of the PAC vs. the right atrial central venous catheter with continuous oximetry using the Rivers protocol to direct therapy (10). It should include careful documentation of care decisions made as a result of the data. It needs to be early in the resuscitation phase, because this may be a time when we can influence outcome. It should also be powered to detect a 5% difference in mortality and should measure other morbid and safety events thoroughly.

One pending RCT deserves mention. This trial has adopted a design with explicit protocols directing the interventions based on the data available. The Fluids and Catheters Treatment Trial (FACTT) is a study run by the ARDSnet group of investigators. The study plans to enroll 1000 patients with acute respiratory distress syndrome in a 2 × 2 factorial design comparing the PAC with central venous catheter and a fluid-liberal with a fluid-conservative strategy. The study has stopped recruiting and is in active follow-up (13).

We eagerly await the results of this and future studies of the PAC.

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Blood transfusion in burns: Benefit or risk?

Blood transfusions can improve the outcome in critically ill patients but are also associated with negative effects such as immune suppression, infection, and fluid overload (1–6). The threshold hemoglobin level when to transfuse blood is still under discussion and varies from 7 mg/dL hemoglobin to 10 mg/dL. Major burns with a total body surface area burn of >20% require blood transfusions during their acute clinical course because of the nature of the injury and the necessary treatment. The study by Dr. Palmieri and colleagues (1) in the current issue of *Critical Care Medicine* investigates the effect of blood transfusion on outcome, such as mortality after a major thermal injury in adult patients. The study was designed as a multicenter retrospective cohort analysis. The authors found that mortality of severely burned adult patients was related to patient age, total body surface area burn, presence of inhalation injury, number of units transfused outside the operation room, and total number of transfusions. They further showed that the number of infections per patient increased with each unit of blood transfused. The authors concluded that the number of transfusions is associated with mortality and infectious episodes (1).

The finding of Dr. Palmieri and colleagues (1) that high amounts of blood products worsen the outcome in burn patients is paralleled in other patient populations. Transfusion of blood products have been shown to worsen the outcome of critically ill, oncologic, and surgical patients (2–6). In a recent study that is under review in *Critical Care Medicine*, our group investigated the effect of blood transfusions on the outcome of severely burned children (7). We showed that after a similar notion as observed in burned adults, transfusion of high amounts of blood products in severely burned children is associated with an increased risk of sepsis and subsequent death.

Blood loss in burned patients is multifactorial, and significant predictive variables are age (older age > younger age), male sex, weight, height, body surface area, percentage of third-degree burn, surgery time, and total area excised (8). The single most predictive independent variable, however, is surface area excised (8). Area excised accounts for approximately 50% of the variability in operative hemorrhage. Type of excision (tangential vs. fascial), percentage of total surface area burned, donor site area, the use of saline or epinephrine, and delay from burn to excision were not significant predictors (8). The underlying causes by which blood transfusions worsen the outcome are not entirely understood. There is evidence that blood transfusion impairs the immune system, increases the risk of infections, and induces the inflammatory response (3–6, 9). The systemic inflammatory response after burn leads to hypermetabolism and thus to protein degradation and catabolism (10, 11). Consequently, the structure and function of essential organs such as the muscle, skin, heart, immune system, and liver are compromised, contributing to multiple organ failure and mortality (10–12). Uncontrolled release of proinflammatory mediators such as interleukin-6, interleukin-8, and acute-phase proteins trigger and enhance protein wasting and organ dysfunction (13, 14). Organ function breakdown can then lead to increased prevalence of infection and sepsis, ultimately leading to multiple organ failure and death (14).

The main question that results from the studies in burned patients is: what can be done to reduce the amount of blood transfused? One possible approach would be to lower the threshold for hematocrit from 30–32% to 25–28% and for hemoglobin from 10 mg/dL to 7–8 mg/dL. However, during the surgical intervention, hemoglobin and hematocrit levels have to be maintained. New surgical strategies to diminish blood loss are necessary to decrease the amount of transfused blood. We suggest that the use of tourniquets, epinephrine, or the use of fibrin sealant could be possible solutions that can be clinically applied. Newer studies further indicate that it is not the blood received during the operation but rather the blood received between operating room visits that affect survival, suggesting that emphasis should be placed on transfusion indications during the acute

*See also p. 1602.
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