

Meta-analysis of hemodynamic optimization in high-risk patients*

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Objective: The aim of this evidence-based report was to review pertinent randomized controlled studies that describe hemodynamic goals in acute, critically ill patients and to evaluate outcome of resuscitation therapy in association with physiologic, clinical, and therapeutic influences.

Methods: MEDLINE was the source of randomized controlled studies written in English. The inclusion criteria were acutely ill, high-risk elective surgery, trauma, and septic patients. The goals of therapy were to resuscitate to either normal or supranormal values; the latter were described as a cardiac index of $>4.5 \text{ L}\cdot\text{min}^{-1}\cdot\text{m}^{-2}$, pulmonary artery occlusion pressure of $<18 \text{ mm Hg}$, oxygen delivery of $>600 \text{ mL}\cdot\text{min}^{-1}\cdot\text{m}^{-2}$, and oxygen consumption of $>170 \text{ mL}\cdot\text{min}^{-1}\cdot\text{m}^{-2}$. The outcome criterion was survival or death. We found 21 randomized clinical trials described in 20 articles. The studies were divided into groups based on the time that goals were implemented (i.e., "early," 8 to 12 hrs postoperatively or before organ failure, vs. "late," or after onset of organ failure) and the severity of illness, determined by the control group mortality as $>20\%$ (12 studies) or $<15\%$ (nine studies).

Results: In severely ill patients (control mortalities group

$>20\%$), six studies had a 23% mortality difference ($p < .05$) between the control and protocol groups with early optimization, but seven studies optimized after the development of organ failure did not have significantly improved mortality. Moreover, outcome was not significantly improved in less severely ill patients (control mortalities group $<15\%$) and normal values as goals or when therapy did not improve oxygen delivery.

Conclusion: Review of 21 randomized controlled trials with various approaches to treatment revealed statistically significant mortality reductions, with hemodynamic optimization, when patients with acute critical illness were treated early to achieve optimal goals before the development of organ failure, when there were control group mortalities of $>20\%$ and when therapy produced differences in oxygen delivery between the control and protocol groups. (Crit Care Med 2002; 30:1686–1692)

KEY WORDS: noninvasive hemodynamic monitoring; bioimpedance cardiac output; thermodilution cardiac output; pulse oximetry; transcutaneous oxygen and CO_2 monitoring; trauma; high-risk surgery; acute septic shock; therapeutic hemodynamic goals; organ failure

Goal-directed studies with the pulmonary artery catheter (PAC) are highly controversial. Many studies showed no advantage of the PAC in cardiac and other medical conditions or in postoperative patients admitted to the ICU after organ failures had developed (1–5). However, other investigators (6–21) reported that early, optimally increased cardiac index (CI) and oxygen delivery ($\dot{D}\text{O}_2$) <12 hrs after surgery or 24 hrs after trauma were associated with improved survival. However, a evidence-based meta-analysis by

Heyland et al. (22) showed that the attainment of supranormal hemodynamic goals did not significantly reduce mortality in critically ill patients. Recently, two consensus conferences also found insufficient evidence to fully determine whether PAC-guided therapy significantly alters outcome, but they did not consider time factors; by mixing early and late studies together, they concluded there were no significant differences in optimizing hemodynamic variables (23–25). In an insightful meta-analysis, Boyd (18) found no outcome improvement in seven prospective randomized studies of patients who entered the ICU after organ failure or sepsis had occurred (4, 5, 9, 11, 25, 26), but they noted significant outcome improvement in six other randomized studies when PAC-directed therapy was given early or prophylactically, that is, before organ failure or sepsis occurred (6, 7, 12, 14, 16, 17). Two recent studies also showed improved outcome with early goal-directed therapy (19, 20), suggesting that early optimization of $\dot{D}\text{O}_2$ and oxygen consumption values in high-

risk surgical patients improves outcome. If, in some clinical circumstances, the hemodynamic values of survivors may be compensatory responses that have survival values, it is important to identify clinical conditions that may be appropriate for this type of goal-directed therapy. Second, it may be even more important to define therapeutic goals relative to the primary diagnosis and age; the presence of diabetes, hypertension, chronic cardiac and respiratory illnesses, and other comorbid conditions; and the severity of illness, timing of therapy, dose ranges, and other limitations of this approach.

Evidence-based studies have become the standard for testing important therapeutic questions, but evaluation of a therapeutic intervention should be clearly related to the central scientific idea defined by the research plan. As a prerequisite for clinical trial evaluation, important aspects of experimental study designs should be considered, including: definition of diagnostic categories; timing and dose of the therapeutic modality being evaluated; the patients' age, sex, and se-

***See also p. 1909.**

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verity of illness; the presence of significant co-morbid conditions; and the clinical setting (Shoemaker WC, Bayard DS, Botnen A, et al., unpublished observations) (27, 28).

Clearly, lack of comparability of studies because of differences in the experimental design may preclude meaningful meta-analysis. Sweeping conclusions can hardly be justified by amassing many studies with large numbers of patients when the design features of the studies are not appropriately considered. Major questions include: In goal-directed therapy, are there outcome differences in the use of normal values compared with the supranormal values of survivors? What roles are played by time factors, various associated clinical conditions such as organ failures, mortalities of the control groups, and differences in therapy between control and protocol arms? Is there a single optimal hemodynamic goal for all critically ill patients, or does this depend on age, severity of illness, physiologic reserve capacities, organ failures, and other co-morbid conditions?

The present study reviewed 21 randomized clinical trials described in 20 articles to evaluate various influences that may contribute to outcome. Inclusion criteria of this meta-analysis were randomized clinical trials of high-risk elective surgery, trauma, and acute medical sepsis. We evaluated the definition of optimal therapy, time of optimization, age, types of illness, and severity of illness. The latter, for example, was defined by the mortality rate of the control group. The differences in mortality rates in the control and protocol groups were the main criteria for evaluation of therapeutic goals in various clinical circumstances, including acute illness, high-risk surgery, or trauma vs. chronic medical illnesses, the time that the therapeutic goals were implemented during the course of acute illness, and the presence or absence of organ failures. Hemodynamic values were used to evaluate the extent or aggressiveness of therapy to achieve the targeted protocol goals compared with the same therapy given to achieve the normal control goals. The differences between control and protocol groups were principally CI and $\dot{V}O_2$, because these have been reported to differentiate early survivor from nonsurvivor patterns (6–8, 27).

METHODS

A search strategy was developed with the assistance of a research librarian. The database for references was MEDLINE, and the search

was limited to include only references in English. The study design included randomized clinical trials of supranormal CI, pulmonary arterial occlusion pressure of <18 mm Hg, and $\dot{V}O_2$ and oxygen consumption indexed as therapeutic goals. The search terms that identified the most acceptable references were supranormal oxygen, resuscitation endpoints, cardiac output, oxygen delivery, oxygen consumption, survival and nonsurvival, and hemodynamics. The search identified 72 references; 52 of these were rejected after screening because of irrelevant interventions, patient populations, or outcome definitions.

Three inclusion criteria were used to define the patient populations, therapeutic goals, and interventions. These were: 1) critically ill patients after high-risk elective surgery, severe trauma, and septic shock; 2) therapeutic goals for resuscitation and subsequent management were either normal hemodynamic values or supranormal values observed in previous series of survivors and specified as a CI of $>4.5 \text{ L}\cdot\text{min}^{-1}\cdot\text{m}^{-2}$, pulmonary arterial occlusion pressure of <18 mm Hg, $\dot{V}O_2$ of $>600 \text{ mL}\cdot\text{min}^{-1}\cdot\text{m}^{-2}$, or oxygen consumption of $>170 \text{ mL}\cdot\text{min}^{-1}\cdot\text{m}^{-2}$ (6–8, 18, 27); and 3) initial intervention was fluid therapy, and if hemodynamic targets were not achieved, inotropes were then added. Twenty references, with 21 studies, were reviewed and accepted for meta-analysis (Table 1). Experimental designs of the studies revealed at least four different categories of patients or therapeutic regimens. These included normal vs. supranormal therapeutic goals, early vs. late administration of therapy to achieve the stated goals, and differences in severity of illness determined by the control group mortality. Late was arbitrarily defined as >12 hrs after surgery, 24 hrs after injury, or after occurrence of an organ failure.

We used the following characteristics to evaluate the quality of these randomized studies. An optimum randomization process may have included a third party, a table of random numbers, or a computer-generated list to assign impaneled subjects to either the treatment or control arm. The assignment to a treatment arm was "concealed" if a third party or sealed envelopes were employed to assign subjects to the treatment or control arm. The process was "blinded" when both the investigators and the subjects were not aware of the patients' assignment to the control or protocol arm. Finally, the withdrawal or dropout analysis was adequate if the investigators identified the number of subjects excluded, provided an explanation for exclusion, and provided the number remaining for evaluation. If the authors did not describe these processes, it was assumed that they did not employ the preferred method, and the study design was not considered optimal. The minimum criterion

for inclusion was proper randomization. If the processes for concealment, blinding, or withdrawal or dropout were not described or verified by direct communication, these design components were scored as "not clear."

All studies reviewed were randomized. There were 15 studies (4–7, 9–11, 13, 15, 17, 19, 20, 29–32) on high-risk elective surgical patients, five of these included medical patients, and two of these studies also included trauma patients. Four studied only trauma patients (14, 16, 25, 29), and two studied septic (medical) patients (12, 25). Two studies were blinded to the investigators in terms of the fluid management; the other studies were not blinded. Table 1 lists the characteristics for each study.

The general variance-based method was used to calculate the summary statistic for the meta-analysis (33). The effect size calculated was the rate difference between the protocol group and the control group. The summary statistic was the rate difference between the groups. This method is based on the fixed-effects model. A significant *p* value was $<.05$.

RESULTS

The results are expressed as the mortality rate difference and confidence limits, which are twice the sd. The mortality rate differences between control and protocol groups in the series as a whole varied from -0.35 to 0.2 . The average mortality rate difference for all 21 studies was $-0.05 + 0.02$, indicating statistically significant improvement with the protocol groups for the series as a whole ($p < .05$). Table 1 lists the studies compiled from the literature in which either normal values or the optimal therapy, defined as CI $> 4.5 \text{ L}\cdot\text{min}^{-1}\cdot\text{m}^{-2}$ and $\dot{V}O_2 > 600 \text{ mL}\cdot\text{min}^{-1}\cdot\text{m}^{-2}$, was given to the protocol groups, and their mortalities were compared with their corresponding control groups given standard therapy. In seven studies, the values of the protocol groups reached the proscribed therapeutic goals in the allotted time frame.

Figure 1 illustrates the values of the 14 randomized studies whose control group mortalities were $>20\%$. Seven early studies whose optimal therapy was completed before organ failure occurred had marked and significant overall reduction in the mortality rate of $-0.23 + 0.07$ ($p < .05$). Of the seven late studies of patients who had organ failure before initiation of the studies, the overall mortality rate difference was $0.01 + 0.06$, indicating no significant improvement with therapy. In these seven studies, only the study of Yu et al. (11) of patients aged

Table 1. Evidence for 21 studies and 20 articles

| Author (Reference) No.; Yr | Diagnostic Group (%) | Study Design ^a Average Age per Group, yrs | Purpose |
|--|--------------------------------------|--|---|
| I. Control groups with mortality rates >20% | | | |
| A. Goals to supranormal values after organ failure | | | |
| Alia et al. (24) n = 63; 1999 | Surgical Medical | Y, Y, N 66; 72 | To evaluate the effects of increased oxygen delivery on morbidity and mortality in patients with severe sepsis or septic shock |
| Yu et al. (10) n = 66; 1998 | Surgical | Y, N, N 63; 63 | To determine whether treatment to a \dot{D}_{O_2} of ≥ 600 mL·min ⁻² in patients unable to mount this \dot{D}_{O_2} response affects mortality |
| Yu et al. (10) n = 39; 1998 | Surgical | Y, N, N 81; 83 | To determine whether treatment to a \dot{D}_{O_2} of ≥ 600 mL·min ⁻² in patients unable to mount this \dot{D}_{O_2} response affects mortality |
| Gattinoni et al. (5) n = 762; 1995 | Trauma Surgical Medical | Y, Y, N 60; 62; 61 | To determine whether targeting hemodynamic treatment to achieve either supranormal values for the cardiac index or normal values for $S\bar{v}O_2$ would improve morbidity and mortality among critically ill patients |
| Hayes et al. (4) n = 109; 1994 | Surgical (40) Medical (60) | Y, N, N 62; 64 | To examine the effects of treatment intended to increase the cardiac index and oxygen delivery and consumption to the previously reported median values in survivors |
| Yu et al. (9) n = 72; 1993 | Surgical (85) Medical (15) | Y, N, N 58; 57 | To evaluate the effect of increased \dot{D}_{O_2} to >600 mL·min ⁻² on the morbidity and mortality of patients with sepsis, septic shock, hypovolemic shock, and ARDS |
| B. Goals to supranormal values before organ failure | | | |
| Lobo et al. (20) n = 42; 2000 | Surgical | Y, Y, N 63; 63 | To evaluate the effect of therapy aimed at achieving maximized oxygen transport values during the operation and in the first 24-hr postoperative period on outcome in a more homogeneous set of high-risk surgical patients |
| Wilson et al. (19) n = 138; 1999 | Surgical | Y, N, N 72; 70; 72 | To determine whether preoperative optimization of oxygen delivery improves outcome after major elective surgery |
| Bishop et al. (16) n = 115; 1995 | Trauma | Y, N, N 34; 29 | To test prospectively supranormal values of CI, $\dot{D}_{O_2}I$, \dot{V}_{O_2} as resuscitation goals to improve outcome |
| Boyd et al. (7) n = 107; 1993 | Surgical | Y, Y, N 69; 73 | To assess the effect of a deliberate perioperative increase in oxygen delivery on mortality and morbidity in patients who are at high risk of both after surgery |
| Tuchschmidt et al. (12) n = 70; 1992 | Medical | Y, N, N 49; 53 | To prospectively evaluate the therapeutic effect of augmenting cardiac output and therefore oxygen delivery on mortality in patients with septic shock |
| Shoemaker et al. (6) n = 70; 1988 | Trauma (13) Surgical (87) | Y, Y, N 56; 53; 55 | To test the hypothesis that the physiologic pattern empirically defined by the survivors may be the appropriate therapeutic goals for high-risk critically ill postoperative patients |
| Schultz et al. (14) n = 70; 1985 | Trauma | Y, N, N, Y 78; 67 | To determine whether treatment of preoperative and postoperative hemodynamic variables improves outcome after hip surgery |
| II. Control groups with mortality rates <15% | | | |
| A. Goals to supranormal values | | | |
| Velmahos et al. (29) n = 75; 2000 | Trauma | Y, Y, N 62; 64 | To evaluate the effect of early optimization in the survival of severely injured patients |
| Ueno et al. (15) n = 34; 1998 | Hepatectomy for cirrhosis | Y, NC, N 61; 58 | To evaluate the response to therapy aimed at achieving supranormal cardiac and oxygen transport variables in patients with cirrhosis |
| Durham et al. (25) n = 60; 1996 | Trauma (93) Medical (7) | Y, Y, N 35; 35 | To test the hypothesis that the use of supranormal values for $\dot{V}_{O_2}I/\dot{D}_{O_2}$ as end points for resuscitation results in improved outcomes |
| B. Goals to normal values | | | |
| Valentine et al. (31) n = 126; 1998 | Aortic surgery | Y, Y, N 64; 63 | To evaluate the routine use of PAC in patients who undergo aortic surgery |
| Bender et al. (32) n = 104; 1997 | Aortic and limb revascularization | Y, N, N ND; ND | To determine whether the preoperative placement of a pulmonary artery catheter with optimization of hemodynamics results in improved outcomes |
| Ziegler et al. (30) n = 72; 1997 | Aortic and limb salvage surgery | Y, N, N 67; 64 | To evaluate the effect of preoperative optimization of hemodynamic variables on outcome in patients undergoing aortic reconstruction of limb salvage procedures |
| Mythen and Webb (18) n = 60; 1995 | CABG or valve surgery | Y, Y, N 64; 63 | To test the hypothesis that perioperative plasma volume expansion would preserve gut mucosal perfusion during elective cardiac surgery |
| Berlauk et al. (13) n = 89; 1991 | Peripheral vascular surgery | Y, N, N 68; 62; 66 | To answer the question in patients with peripheral vascular surgery, does the use of a PA catheter to optimize LVF improve outcome? |

OF, organ failure; PAOP, pulmonary artery occlusion pressure; CI, cardiac index; \dot{D}_{O_2} , delivery of oxygen index; ICU, intensive care unit; $S\bar{v}O_2$, mixed venous oxygen saturation; ARDS, acute respiratory distress syndrome; PAC, pulmonary artery catheters; \dot{V}_{O_2} , oxygen consumption index; CABG, coronary artery bypass graft; CVP, central venous pressure; pH_i, gastric intramucosal pH; PA, pulmonary artery; LVF, left ventricular function.

^aStudy design: randomized, concealed, and blinded were described as Y = yes, N = no, NC = not clear, and ND = no data.

Table 1. (Continued)

| Optimize 1) Before, 2) During, 3) After Surgery or After OF | Targets (Protocol Group) | Outcomes PAOP 12–18 CI > 4.5 $\dot{D}O_2I > 600$ | Mortality Protocol/ Control (%) |
|---|--|---|---------------------------------------|
| Admission to ICU with Diagnosis of Sepsis and OF | PAOP 14–16 $\dot{D}O_2I > 600$ | Yes, No, No | 23/31 (74) 21/32 (66) |
| No, No, OF | PAOP 15–18 (both groups) $\dot{D}O_2I > 600$ | ND, ND, No | 9/43 (21) 12/23 (52) |
| No, No, OF | PAOP 15–18 (both groups) $\dot{D}O_2I > 600$ | ND, ND, No | 12/21 (57) 11/18 (61) |
| No, No, OF | PAOP < 18 (all groups) CI > 4.5, $\dot{D}O_2I > 600$ | Yes, Yes, Yes | 123/253 (49) 21/252 (48) |
| No, No, OF | PAOP NS (both groups) CI > 4.5, $\dot{D}O_2I > 600$ | ND, Yes, Yes | 25/50 (50) 15/50 (30) |
| No, No, OF | PAOP 15–18 (both groups) $\dot{D}O_2I > 600$ | ND, ND, Yes | 12/35 (34) 11/32 (34) |
| Yes, Yes, Yes | PAOP 12–16 CI > 4.5, $\dot{D}O_2I > 600$ | No, No, Yes | 3/19 (16) 6/18 (33) |
| Yes, Yes, Yes | PAOP > 12 (PAC group 1) $\dot{D}O_2I > 60$ | Yes, No, No | 2/46 (4) 17/46 (37) |
| No, No, Yes | PAOP < 18 (group 1) CI > 4.5, $\dot{D}O_2I > 670$ | ND, Yes, Yes | 9/50 (18) 24/65 (37) |
| Yes, Yes, Yes | PAOP \geq 12–14 (both groups) CI \uparrow to plateau, $\dot{D}O_2I > 600$ | Yes, No, Yes | 3/53 (6) 12/54 (22) |
| Admission to ICU within 4 hrs of Diagnosis of Sepsis | PAOP > 15 (both groups) CI > 6 | Yes, Yes, Yes | 13/26 (50) 18/25 (72) |
| No, No, Yes | PAOP < 18 CI > 4.5, $\dot{D}O_2I > 600$ | No, No, Yes | 1/28 (4) 18/60 (38) |
| Yes, NC, Yes | PAOP ND CI 3–3.5 | No, No, ND | 1/35 (3) 10/35 (29) |
| Yes, Yes, Yes | PAOP ND CI > 4.5, $\dot{D}O_2I > 600$ | ND, ND, Yes | 6/40 (15) 4/35 (11) |
| Yes, No, Yes | PAOP 9–18 CI > 4.5, $\dot{D}O_2I > 600$ | Yes, Yes, Yes | 0/16 (0) 2/18 (11) |
| No, No, OF | PAOP < 18 (both groups) $\dot{D}O_2I > 600$ | Yes, Yes, Yes | 3/27 (11) 3/31 (10) |
| Yes, Yes, Yes | PAOP 8–15 CI > 2.8 | ND | 3/60 (5) 1/60 (2) |
| Yes, Yes, Yes | PAOP 8–14 CI \geq 2.8 | ND | 1/51 (2) 1/53 (2) |
| Yes, No, Yes | PAOP \geq 12 | ND | 3/32 (9) 2/40 (5) |
| No, Yes, Yes | CVP; pHi | ND | 0/30 (0) 1/30 (3) |
| Yes, No, No | PAOP 8–15 CI > 2.8 | ND | 1/68 (1.5) 2/21 (10) |

50–75 yrs had improved outcome with optimized therapeutic goals.

Figure 1 also illustrates mortality rate differences in three groups of studies with control group mortalities of <15% or normal values for therapeutic goals. The first group consisted of two studies with control group mortalities of 10% and 11%. One study (26) consisted of patients with organ failures before therapy, and the second study (27), which excluded patients who died within 24 hrs of admission, had a control group mortality of 11% and a protocol mortality of 15%, but there was no difference in $\dot{D}O_2$ between the control and protocol groups. The latter suggested that the treatment of control patients were similar to that of the protocol patients. If there were no differences in therapy, no outcome differences should be expected, and none were found. Neither of these studies showed significant differences in the mortality rates between the control and protocol groups; the combined rate difference of these two studies was 0.03 ± 0.11 ($p > .05$). The fourth group in Figure 1 studied partial hepatectomy in cirrhotic patients who had an 11% control group mortality but a protocol group mortality of only 0% (16). The rate difference of -0.11 did not reach statistical significance, probably because the sample size was only 34 patients. The last group consisted of five studies that used normal values as goals and had control mortalities of <11%. Their subtotal rate difference was -0.01 ± 0.03 ($p > .05$). The three groups (ten studies) had control group mortalities that were <15%, with a mean of 7.1%, suggesting that these patients were not as severely ill as the first two study groups whose mean control mortality was 42.1% (Fig. 1 and Table 1). In high mortality series, fewer patients are needed to show improved outcome with different therapeutic goals.

DISCUSSION

Hemodynamic bedside monitoring by PACs has been considered by many as a standard for circulatory evaluation of critically ill patients, but its usefulness has recently been seriously questioned (1–5, 22–25), particularly in the late stages of illness after onset of multiple organ failures (23–25). The present review showed significantly improved outcome in randomized studies when PAC goal-directed therapy was administered early or prophylactically in patients who

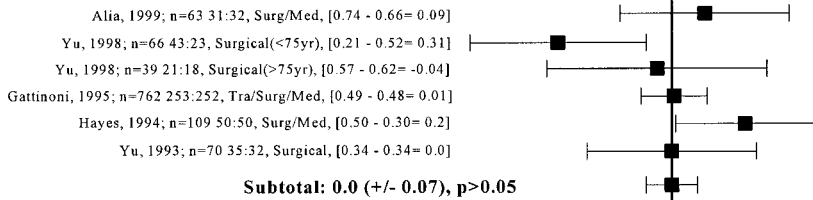
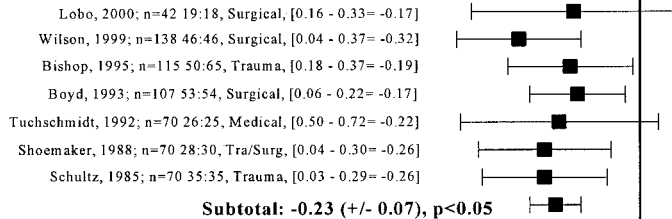
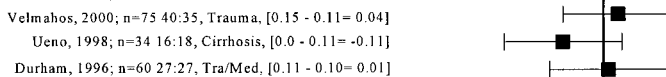
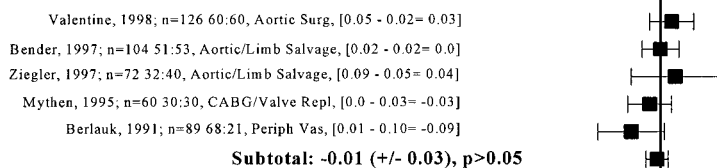
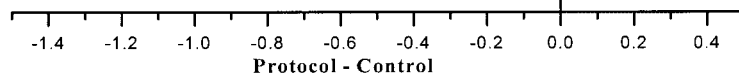
1. Control Groups with Mortality Rates Greater than 20%**A. Goals to Supranormal Values After Organ Failure****B. Goals to Supranormal Values Before Organ Failure****2. Control Groups with Mortality Rates Less than 15%****A. Goals to Supranormal Values****B. Goals to Normal Values****Overall: -0.04 (+/- 0.025), p<0.05**

Figure 1. Mortality differences between protocol and control groups with control group mortality of >20% (upper section) and <15% (lower section). Therapeutic goals are specified as supranormal or normal hemodynamic values. Note for each study the first author's name, date of publication, number or randomized subjects, number of subjects evaluated as protocol vs. control groups, populations, mortality of the protocol patients minus control mortality, and the difference between protocol and control mortalities. *Surg*, surgery; *Med*, medical; *Tra*, trauma.

were optimized preoperatively and maintained in the intraoperative and immediate postoperative period.

Early studies using invasive ICU monitoring in randomized trials reported that increased CI and $\dot{V}O_2$ to values characteristic of survivors of high-risk surgery in the immediate postoperative period improved outcome (6). At the initial stage in the development of this concept, it was realized that the survivors of acute critical illnesses had a wide range of higher-than-normal hemodynamic values (6, 8, 10, 18, 19, 31, 34). Because it is not

possible to test a range of values, the mean or median values were arbitrarily chosen as cutoff points, not to establish a set of optimal values but to test the hypothesis that critically ill patients have high metabolic rates and therefore require greater than normal hemodynamics and oxygen transport to sustain the increased body metabolism after trauma, surgery, or sepsis. Hemodynamic goals of surviving patients were proposed as a first approximation to optimal goals for the immediate postoperative period of high-risk surgical patients. These proposed op-

timal therapeutic goals were not intended to be generally applied to all patients at all times because metabolic requirements are affected by age, sepsis, blood loss, preexisting cardiac and pulmonary insufficiency, and other co-morbid conditions (10, 35). Ultimately, optimal goals may be calculated for each individual patient on the basis of his or her diagnosis, co-morbid conditions, past hemodynamic deficits, and temporal stage. This is presently approached by using discriminate analysis (27) and stochastic control programs (28).

In the initial randomized trial of supranormal hemodynamic values, the mortality was decreased, but more importantly, the prevalence of organ failures was reduced from 31 cases in the control group to 1 case in the protocol group (6). Moreover, in a series of postoperative patients invasively monitored before the diagnosis of ARDS, the non-survivors' CI values were in the normal range; the survivors who developed ARDS had CI values that were significantly elevated ($4 \text{ L}\cdot\text{min}^{-1}\cdot\text{m}^{-2}$) but less than the values of survivors who did not develop ARDS ($4.5 \text{ L}\cdot\text{min}^{-1}\cdot\text{m}^{-2}$) (34, 38, 39). Before the onset of ARDS, the mean pulmonary artery occlusion pressures were within acceptable limits for critically ill postoperative patients and none had a pulmonary arterial occlusion pressure of >18 mm Hg. Bishop et al. (16, 39) reported that supranormal goals within 24 hrs of the injury reduced the prevalence of ARDS and other organ failures after severe trauma; they reduced mortality from 39% to 18% ($p < .05$) and reduced prevalence of organ failure from 105 in 65 control patients (1.62 ± 0.28 organ failures per patient) to 37 in 50 protocol patients (0.74 ± 0.28 organ failures per patient) ($p < .05$). Less than optimal values in the early stage may lead to inadequate total blood flow and uneven microcirculatory blood flow from uneven vasoconstriction of the adrenomedullary stress response (8, 34, 38–42). Local hypoxia and acidosis of the capillary endothelium from uneven capillary blood flow is known to stimulate the systemic inflammatory response system and lead to organ failure (41, 42).

The definition of early as opposed to late studies is necessarily arbitrary. Cutoff points for the patient to reach the designated goals were: the first 12 hrs postoperatively in elective surgery, 24 hrs after injury in trauma patients, and before the onset of an organ failure. When

sepsis was the primary diagnosis, we accepted the definition of "early septic shock" proposed by Tuschmidt et al. (12), which was within 4 hrs of the time of diagnosis. However, when sepsis was a complication of elective high-risk surgery, as in the studies of Yu et al. (9–11), it was arbitrarily designated as an organ failure or dysfunction and therefore classified as late. Of these three published articles (9–11), the 1998 publication that was a continuation of their earlier studies seems to include 47 of the 50 subjects that were evaluated in the 1995 article. Therefore, to avoid redundancy, the 1995 study was not included in this meta-analysis. In the 1993 study, Yu et al. (9) demonstrated that when both the protocol and control groups were aggressively hydrated to a pulmonary artery occlusion pressure of 15–18 mm Hg, the difference in the mortality rates was insignificant. In the interim study (1995), Yu et al. (11) observed that when the subjects in both the protocol and control groups who generated a $\dot{D}O_2$ of $\geq 600 \text{ mL}\cdot\text{min}^{-1}\cdot\text{m}^{-2}$ after fluid resuscitation were excluded from the study, the mortality rate of the remaining protocol subjects was significantly less than the remaining control subjects. This difference was associated with the administration of inotropes and vasoactive drugs given to the protocol group to achieve a $\dot{D}O_2$ of $\geq 600 \text{ mL}\cdot\text{min}^{-1}\cdot\text{m}^{-2}$. In the 1998 study, Yu et al. (10) evaluated the larger series of patients randomized to protocol and control groups, and stratified the groups according to age: ≤ 75 yrs (50–75 yrs of age) and > 75 yrs. All subjects who achieved a $\dot{D}O_2$ of $\geq 600 \text{ mL}\cdot\text{min}^{-1}\cdot\text{m}^{-2}$ after fluid resuscitation were excluded. The mortality rate of the protocol group of the subjects aged ≤ 75 yrs was significantly less than the control group. However, the mortality rate in the protocol and control groups of subjects aged > 75 yrs was not different ($p > .05$). These findings suggest that the subjects aged > 75 yrs did not effectively respond, in terms of outcome, to aggressive vasoactive drugs or inotropes.

In the study of Wilson et al. (19), patients undergoing major elective surgery were randomized into three groups; two groups of 42 patients received invasively monitored fluid and either adrenaline or dopexamine to increase $\dot{D}O_2$, whereas the third group of 42 patients received routine postoperative care and served as the control. Only 3 of 92 patients (3%) in the optimized groups died, whereas 8 of 46

patients (17%) in the control group died ($p < .007$). The length of stay of the dopexamine group was significantly reduced compared with both the adrenaline group ($p = .02$) and the control group ($p = .009$). The authors concluded that because of the low doses of inotropes, fluid optimization was a major contributor to improved $\dot{D}O_2$ and improved outcome in their patients (19).

Three randomized trials not included in this meta-analysis deserve mention. In a study by Takala et al. (36) of postoperative patients with 13% control mortality that used relatively normal values as goals, patients were initially brought into the normal hemodynamic range, and then two dosage levels of dopexamine were tested in randomized trials, but the outcome was not significantly improved. Sinclair et al. (37) studied length of hospital stay in patients with proximal femoral fractures after optimizing stroke volume with repeated colloid fluid challenges measured by esophageal Doppler ultrasonography. They demonstrated significantly reduced hospital stay, but there was insignificant reduction in mortality because of only two deaths in the control group and one death in the protocol group. Polonen et al. (43) used mixed venous oxygen saturation and lactate levels as criteria for adequacy of resuscitation immediately postoperatively in 403 cardiac surgical patients. The median hospital stay was shorter in the protocol group (6 vs. 7 days, $p < .05$), and morbidity was significantly less at the time of hospital discharge (1.1% vs. 6.1%, $p < .01$), but mortality was very low and not significantly affected by the study.

Low control mortalities suggest that the patients were not very ill and therefore may not respond as clearly to increased hemodynamics and, at the same time, may require much larger numbers of patients to show statistical significance. In the studies of Mythen et al. (17) and Ueno et al. (15), the protocol patients given therapy to achieve optimal goals had 0% mortalities, but because of the small number of patients, statistical significance was not achieved. Moreover, in the study of Berlauk et al. (13), the mortality was reduced from 9.5% in the control group to 1.5% in the optimized group, which was not significant; however, the number of complications were significantly reduced.

Similarly, if the control and protocol patients were treated in a similar man-

ner, no differences in outcome should be expected. In the study of Velmahos et al. (29), the difference in DO_2 between control and protocol patients was not statistically significant because the treatment of control and protocol patients were not different, and therefore, the mortality was, not unexpectedly, not different.

We conclude that increased CI and $\dot{D}O_2$ with pulmonary arterial occlusion pressure of < 18 mm Hg should be considered as goals of therapy. When implemented early and aggressively, this reduces mortality and the prevalence of organ failures in acute postoperative and posttrauma conditions. Goal-directed therapy to achieve optimal goals is ineffective in the late stages after onset of organ failure because no amount of extra oxygen will restore irreversible oxygen debts, failed organs, or dead cells. In the late stage of acute illness after organ failure has occurred, aggressive therapy directed toward achieving the survivors' supranormal values is futile. When oxygen debt is no longer reversible, increased oxygen transport is not effective. Moreover, it is difficult to demonstrate significant changes after optimization when there are no significant differences between therapy given to the control and protocol groups. That is, there must be significant differences in the type of therapy or the amount of therapy given to expect significant outcome improvement. Furthermore, outcome differences may be extremely difficult to demonstrate when the patient population is not very ill, as indicated by control mortalities of $< 15\%$. Finally, no effect should be expected in chronic medical conditions in which physiologic compensations have already had their maximum effect.

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