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A TRIAL OF GOAL-ORIENTED HEMODYNAMIC THERAPY IN CRITICALLY ILL PATIENTS

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Abstract Background. Hemodynamic therapy to raise the cardiac index and oxygen delivery to supranormal levels may improve outcomes in critically ill patients. We studied whether increasing the cardiac index to a supranormal level (cardiac-index group) or increasing mixed venous oxygen saturation to a normal level (oxygen-saturation group) would decrease morbidity and mortality among critically ill patients, as compared with a control group in which the target was a normal cardiac index.

Methods. A total of 10,726 patients in 56 intensive care units were screened, among whom 762 patients belonging to predefined diagnostic categories with acute physiology scores of 11 or higher were randomly assigned to the three groups (252 to the control group, 253 to the cardiac-index group, and 257 to the oxygen-saturation group).

Results. The hemodynamic targets were reached by 94.3 percent of the control group, 44.9 percent of the car-

diac-index group, and 66.7 percent of the oxygen-saturation group ($P < 0.001$). Mortality was 48.4, 48.6, and 52.1 percent, respectively ($P = 0.638$), up to the time of discharge from the intensive care unit and 62.3, 61.7, and 63.8 percent ($P = 0.875$) at six months. Among patients who survived, the number of dysfunctional organs and the length of the stay in the intensive care unit were similar in the three groups. No differences in mortality among the three groups were found for any diagnostic category. A subgroup analysis of the patients in whom hemodynamic targets were reached revealed similar mortality rates: 44.8, 40.4, and 39.0 percent, respectively ($P = 0.478$).

Conclusions. Hemodynamic therapy aimed at achieving supranormal values for the cardiac index or normal values for mixed venous oxygen saturation does not reduce morbidity or mortality among critically ill patients. (N Engl J Med 1995;333:1025-32.)

RECENTLY, increasing attention has been directed to the hemodynamic treatment of critically ill patients, because it has been observed in several studies that patients who survived had values for the cardiac index and oxygen delivery that were higher than those of patients who died and, more important, higher than standard physiologic values.¹⁻³ Cardiac-index values greater than 4.5 liters per minute per square meter of body-surface area and oxygen-delivery values greater than 650 ml per minute per square meter — derived empirically on the basis of the median values for patients who previously survived critical surgical illness — are commonly referred to as supranormal hemodynamic values.⁴

However, there is no agreement about the clinical benefit of a treatment strategy intended to achieve supranormal values, since the few randomized studies

available have produced conflicting results. Two studies of surgical patients^{5,6} have shown significant decreases in mortality associated with such therapy, whereas studies of patients with sepsis⁷ and mixed groups of critically ill patients^{8,9} have failed to show significant differences in mortality. In addition, because mixed venous oxygen saturation (SvO₂) reflects the balance between oxygen delivery and oxygen consumption^{10,11} and because it can be monitored continuously, we thought that targeting therapy to achieve a normal SvO₂ (≥ 70 percent) could result in a hemodynamic treatment better tailored to the oxygen needs of the patient.

We therefore designed a multicenter, randomized trial to determine whether targeting hemodynamic treatment to achieve either supranormal values for the cardiac index or normal values for SvO₂ would improve morbidity and mortality among critically ill patients.

METHODS

Patients were recruited from 56 intensive care units and centrally assigned to treatment groups in a random fashion by telephone (on a 24-hour-a-day, 7-day-a-week basis). Central randomization was based on a random permuted-block algorithm, which permitted stratification according to intensive care unit. The study protocol was approved by the Human Experimentation Committee of the Lombardia Regional Health Authority, and an independent, external safety and efficacy monitoring committee monitored the trial. Both committees

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recommended a consent procedure that had already been used in patients with severe acute disease,^{12,13} by which the patients are to be informed of the study as soon as their clinical condition allows them to understand it clearly.

Since the details of the study protocol have been published elsewhere, together with the results of a pilot phase involving 98 patients,¹⁴ only the essential features of the study design are outlined here.

Outcome Measures

The primary end points of the study were mortality up to discharge from the intensive care unit, mortality six months after randomization (data were obtained through the census offices in the patient's place of residence), and morbidity among surviving patients, as estimated by the number of dysfunctional organ systems.

Criteria for Inclusion and Therapeutic Goals

All patients admitted to the 56 participating intensive care units between July 1991 and August 1993 who had simplified acute physiology scores¹⁵ of 11 or higher when the score was modified to cover the first 48 hours after admission were considered eligible if they had one of the following: a high risk after surgery,⁵ massive blood loss,⁵ septic shock or sepsis syndrome,^{16,17} acute respiratory failure,⁵ acute respiratory failure with chronic obstructive pulmonary disease (COPD), or multiple trauma. Each patient was classified only with regard to the principal diagnostic category that led to admission to the intensive care unit, as judged by the attending physician.

All eligible patients were randomly assigned to one of three treatments designed to achieve different hemodynamic goals: a normal cardiac index (between 2.5 and 3.5 liters of blood per minute per square meter of body-surface area; the control group), a supranormal cardiac index (above 4.5 liters per minute per square meter; the cardiac-index group), and a normal SvO₂ (≥ 70 percent) or a difference of less than 20 percent between the arterial oxygen saturation and the SvO₂ (in patients with severe arterial hypoxemia; the oxygen-saturation group).

Clinical Care

In addition to the therapeutic objectives assigned by randomization, certain clinical variables were required to be maintained within physiologic limits, as follows: a mean arterial pressure of 60 mm Hg or above, a mean pulmonary-artery occlusion pressure of 18 mm Hg or below, a central venous pressure of 8 to 12 mm Hg, a urinary output of 0.5 ml or more per hour per kilogram of body weight, and an arterial pH of 7.3 to 7.5.

The hemodynamic therapy in the three groups consisted of volume expansion (with packed red cells, crystalloid, and colloid) followed by treatment with inotropic agents (dobutamine and dopamine), vasodilator agents (nitroprusside and nitrates), and vasopressor agents (epinephrine and norepinephrine), as suggested by Shoemaker et al.¹⁸ Hemodynamic treatment aimed at achieving the study target was mandatory for five days (the study period) and recommended but not required thereafter.

Patients were considered to have reached the target if their average cardiac index or SvO₂ during the treatment period was equal to or in excess of the assigned target.

Measurements

Hemodynamic measurements, arterial- and venous-blood gas measurements, rates of urinary output, and the use of therapeutic interventions were recorded every 12 hours during the treatment pe-

Table 1. Base-Line Characteristics of the Study Patients.

CHARACTERISTIC*	CONTROL GROUP	CARDIAC-INDEX	OXYGEN-SATURATION	P VALUE†
	(N = 252)	GROUP (N = 253)	GROUP (N = 257)	
	<i>mean \pm SD</i>			
Age (yr)	61.3 \pm 16.2	59.8 \pm 16.8	62.4 \pm 15.4	0.198
Acute physiology score‡	15.0 \pm 3.3	14.8 \pm 3.1	15.4 \pm 3.9	0.088
Mean organ dysfunction (no. of systems)	1.6 \pm 1.0	1.6 \pm 1.0	1.7 \pm 1.0	0.669
Cardiac index (liters/min/m ²)	3.7 \pm 1.5	3.7 \pm 1.6	3.8 \pm 1.6	0.681
Oxygen transport (ml/min/m ²)	536 \pm 220	536 \pm 230	548 \pm 230	0.786
Oxygen consumption (ml/min/m ²)	152 \pm 57	148 \pm 53	141 \pm 54	0.100
SvO ₂ (%)	67.3 \pm 10.5	68.2 \pm 9.7	69.7 \pm 10.5	0.042
PaO ₂ /FiO ₂ §	213 \pm 108	221 \pm 103	207 \pm 97	0.344
Oxygen-extraction ratio (%)	30 \pm 11	30 \pm 9	28 \pm 10	0.028
Pulmonary arterial pressure (mm Hg)	27.0 \pm 9.4	24.2 \pm 7.7	25.9 \pm 8.1	0.001
Pulmonary-artery occlusion pressure (mm Hg)	14.9 \pm 6.3	13.3 \pm 5.9	14.1 \pm 6.1	0.013
Central venous pressure (mm Hg)	10.5 \pm 4.6	10.1 \pm 4.7	10.6 \pm 4.7	0.429
Mean arterial pressure (mm Hg)	85.6 \pm 18.1	85.0 \pm 19.1	84.4 \pm 19.7	0.791
Serum creatinine (mg/dl)	2.2 \pm 1.7	2.1 \pm 1.7	2.0 \pm 1.8	0.614
Serum bilirubin (mg/dl)	1.9 \pm 2.8	2.2 \pm 2.9	2.0 \pm 3.2	0.636
Serum aspartate aminotransferase (IU/liter)	175 \pm 416	241 \pm 679	199 \pm 507	0.427
Serum alanine aminotransferase (IU/liter)	125 \pm 372	160 \pm 380	149 \pm 332	0.574
White cells ($\times 10^{-3}$ /mm ³)	13.0 \pm 7.0	14.9 \pm 9.6	13.0 \pm 7.6	0.009
Platelets ($\times 10^{-3}$ /mm ³)	157 \pm 107	173 \pm 122	156 \pm 101	0.130

*To convert values for creatinine to micromoles per liter, multiply by 88.4; to convert values for bilirubin to micromoles per liter, multiply by 17.1.

†By analysis of variance. P values indicating a statistically significant difference are shown in boldface type.

‡Denotes the modified simplified acute physiology score.

§Denotes the partial pressure of arterial oxygen (in millimeters of mercury) divided by the fraction of inspired oxygen.

riod. Variables defining organ dysfunction were recorded every 24 hours.

Dysfunction of organ systems was defined as follows: respiratory dysfunction, by the need for assisted mechanical ventilation or continuous positive airway pressure for more than 24 hours (or less, if the patient died during the first 24 hours); renal dysfunction, by a serum creatinine concentration of 2 mg per deciliter (177 μ mol per liter) or higher, the presence of artificial kidney support, or both; hepatic dysfunction, by either (1) serum alanine and aspartate aminotransferase concentrations of 80 IU per liter or higher and a serum total bilirubin concentration of 2 mg per deciliter (34.2 mmol per liter) or higher, (2) serum aminotransferase concentrations of 200 IU per liter or higher, or (3) a serum total bilirubin concentration of 3 mg per deciliter (51.3 mmol per liter) or higher; and central nervous system dysfunction, by a score on the Glasgow coma scale lower than 7.

Statistical Analysis

The incremental area under the curve¹⁹ divided by the time each patient spent in the study was used as a summary statistic to compare hemodynamic values and clinical data. The primary analyses were carried out on an intention-to-treat basis; a subgroup analysis was also performed using data from the patients in whom the targets were reached. Data are presented as means \pm SD. Discrete data were analyzed by the chi-square test. A one-way analysis of variance with the Bonferroni correction for multiple comparisons was used to test for differences among the groups in continuous variables. A P value of less than 0.05 by a two-tailed test was considered to indicate statistical significance.

RESULTS

Study Population

Of 10,726 screened patients, 762 patients (564 men and 198 women) met the criteria for entry into the study and were randomly assigned to the three groups

(252 to the control group, 253 to the cardiac-index group, and 257 to the oxygen-saturation group). The characteristics of the patients at entry are shown in Table 1.

Changes in the cardiac index and in the delivery and consumption of oxygen during the five days of treatment are shown in Figure 1. When the cardiac-index group was compared with the other two groups, that group had significantly higher incremental areas under the curve for the cardiac index ($P<0.001$), oxygen delivery ($P<0.001$), and oxygen consumption ($P=0.006$). The characteristics of the patients during treatment are shown in Table 2.

Achievement of Hemodynamic Goals

Twenty-seven of the 762 study patients (6 in the control group, 10 in the cardiac-index group, and 11 in the oxygen-saturation group; $P=0.466$) could not be classified according to whether the target hemodynamic values were reached, because only their base-line values were available. Among the remaining 735 patients, 94.3, 44.9, and 66.7 percent of those in the respective groups reached their target values ($P<0.001$). The percentage of patients in whom the therapeutic target was reached was significantly lower in the cardiac-index group than in the other two groups ($P<0.001$ for both comparisons). The percentage who reached the target was lower in the oxygen-saturation group than in the control group ($P<0.001$).

The patients in each group in whom the target hemodynamic values were reached had similar acute physiology scores at entry ($P=0.377$), but their mean (\pm SD) ages were significantly different (61 ± 16 years in the control group, 52 ± 18 years in the cardiac-index group, and 61 ± 16 years in the oxygen-saturation group; $P<0.001$).

Therapeutic Interventions

The percentages of patients who received volume-expansion treatment, dobutamine infusion, or both during the study period differed significantly among the three groups (volume expansion: 55.2 percent in the control group, 66.8 percent in the cardiac-index group, and 60.7 percent in the oxygen-saturation group [$P=0.027$]; dobutamine infusion: 46.0, 65.6, and 50.6 percent, respectively [$P<0.001$]). The dose of dobutamine in the patients who received that drug did not differ significantly among the three groups ($P=0.139$). Dopamine was used in the three groups with similar frequency ($P=0.402$) and at similar doses ($P=0.378$).

Overall, 505 patients reached their therapeutic targets, whereas 230 did not. When patients who did not reach either their assigned cardiac index or their assigned SvO_2 were compared with patients who reached one of those targets, volume expansion was used more often among those whose targets were not reached (69.6 percent vs. 60.0 percent, $P=0.013$); dopamine was given more often (36.5 percent vs. 26.9 percent, $P=0.008$) and at similar doses (10.1 ± 6.1 vs. 9.1 ± 4.7 μ g per kilogram per minute, $P=0.163$); and dobutamine

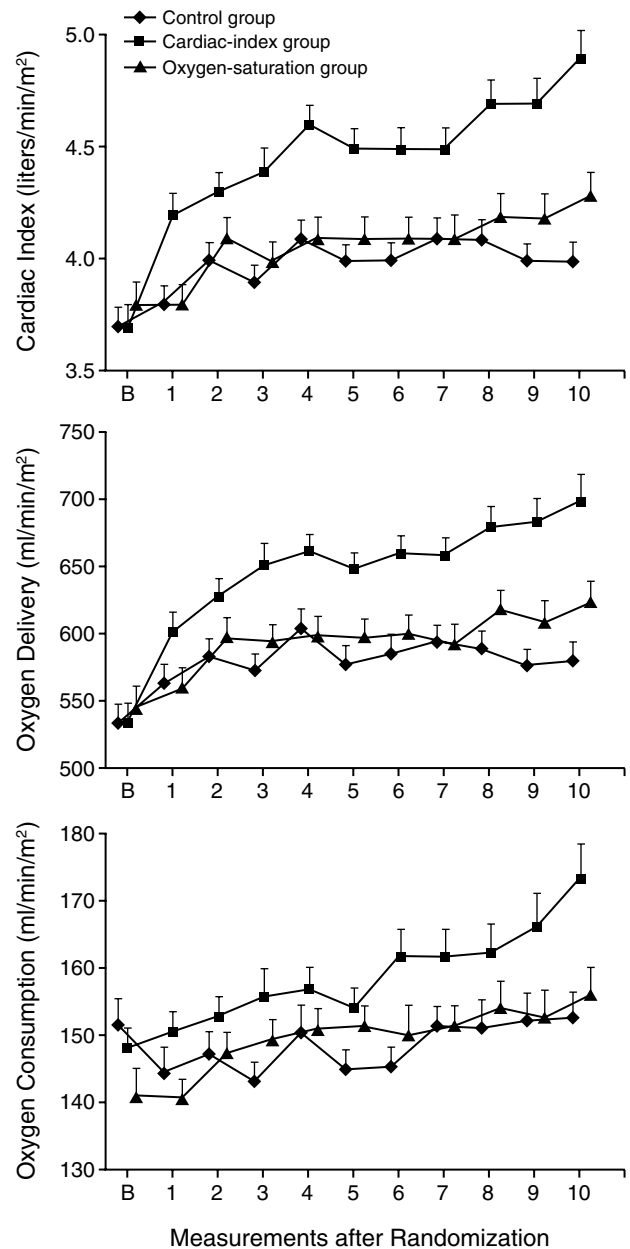


Figure 1. Mean (\pm SE) Cardiac Index, Oxygen Delivery, and Oxygen Consumption in the Three Study Groups.

For each variable, the incremental area under the curve differed significantly among the three groups ($P<0.001$). B denotes base line. Measurements were made twice a day for five days after randomization.

was given more often (71.7 percent vs. 48.3 percent, $P<0.001$) and at higher doses (9.1 ± 5.5 vs. 6.9 ± 4.3 μ g per kilogram per minute, $P<0.001$). The data indicate that patients who did not reach either assigned target had a greater intensity of treatment. However, these patients were older (age, 66 ± 14 vs. 59 ± 17 years, $P<0.001$) and presented with higher acute physiology scores (15.7 ± 3.7 vs. 14.7 ± 3.3 , $P<0.001$) than the patients who reached their target hemodynamic values.

These differences between those who reached and those who did not reach the target values were consistent

Table 2. Characteristics of the Patients during the Five-Day Study Period.

CHARACTERISTIC*	CONTROL GROUP	CARDIAC-INDEX	OXYGEN-SATURATION	P VALUE†
	(N = 252)	GROUP (N = 253)	GROUP (N = 257)	
	<i>mean ±SD</i>			
Cardiac index (liters/min/m ²)	3.9±1.0	4.4±1.3‡§	4.1±1.2	<0.001
Oxygen delivery (ml/min/m ²)	575±164	641±184‡§	591±165	<0.001
Oxygen consumption (ml/min/m ²)	148±34	158±40‡¶	149±38	0.006
SvO ₂ (%)	70.7±7.3	72.1±6.5	71.7±5.9	0.062
PaO ₂ /FiO ₂	452±179	462±167	447±167	0.608
Mechanical ventilation (days)	3.5±1.8	3.2±1.9	3.6±1.8	0.092
Oxygen-extraction ratio (%)	27.1±6.9	25.8±6.3	26.2±5.4	0.056
Pulmonary arterial pressure (mm Hg)	27.7±7.5	26.4±6.4¶**	27.8±6.8	0.042
Pulmonary-artery occlusion pressure (mm Hg)	14.6±4.4	14.1±4.1	14.6±4.7	0.374
Central venous pressure (mm Hg)	10.7±3.5	10.8±3.5	11.2±3.8	0.280
Mean arterial pressure (mm Hg)	88.8±13.6	90.9±12.8	89.4±14.2	0.239
Urinary output (ml/hr)	95.8±50.1	102.0±49.5	95.5±49.5	0.274
Serum creatinine (mg/dl)	2.1±1.8	2.1±1.9	2.0±1.8	0.846
Serum bilirubin (mg/dl)	3.9±4.2	4.5±5.6	4.2±5.1	0.474
Serum aspartate aminotransferase (IU/liter)	130±236	156±312	201±524	0.120
Serum alanine aminotransferase (IU/liter)	89±167	116±229	134±294	0.119
White cells (×10 ⁻³ /mm ³)	13.2±6.0	13.7±6.5	12.8±6.1	0.289
Platelets (×10 ⁻³ /mm ³)	132±89	138±85	128±78	0.404

*To convert values for creatinine to micromoles per liter, multiply by 88.4; to convert values for bilirubin to micromoles per liter, multiply by 17.1.

†By analysis of variance. Statistically significant values are shown in boldface type.

‡P<0.01 for the comparison with the control group.

§P<0.01 for the comparison with the oxygen-saturation group.

¶P<0.05 for the comparison with the oxygen-saturation group.

||Denotes the partial pressure of arterial oxygen (in millimeters of mercury) divided by the fraction of inspired oxygen.

**P<0.05 for the comparison with the control group.

within each of the three groups, with the patients who did not reach the target being significantly older and having a significantly greater intensity of treatment than the patients who reached the target values. On the whole, the data suggest that background conditions, rather than intensity of treatment, were the factors governing the achievement of the target hemodynamic status.

Primary Outcomes

Mortality

No differences in mortality rates were apparent among the three groups up to discharge from the intensive care unit (48.4, 48.6, and 52.1 percent of patients died in the control group, the cardiac-index group, and the oxygen-saturation group, respectively; $P=0.638$) or six months after entry into the study (62.3, 61.7, and 63.8 percent; $P=0.875$) (Fig. 2). Of the 762 patients enrolled, 4.6 percent were lost to follow-up within six months. The relative risks of death in the cardiac-index group and the oxygen-saturation group, as compared with the control group, were 1.01 (95 percent confidence interval, 0.71 to 1.43) and 1.16 (95 percent confidence interval, 0.82 to 1.64), respectively, up to the time of discharge from the intensive care unit and 0.97 (95 percent confidence interval, 0.68 to 1.39) and 1.07 (95 percent confidence interval, 0.74 to 1.53) at six months.

Figure 3 shows that outcomes in the three treatment groups were also similar for each diagnostic category.

Organ Dysfunction

For patients who survived to discharge, there was no difference among the three study groups in the num-

ber of dysfunctional organs at the end of the five-day study period ($P=0.660$). This indicates that the three hemodynamic strategies did not influence morbidity, an inference that was also reflected in the similar lengths of stay in the intensive care unit (26 ± 50 days in the control group, 22 ± 20 days in the cardiac-index group, and 24 ± 27 days in the oxygen-saturation group; $P=0.502$). None of the three treatment strategies appeared to have significantly influenced the rates of dysfunction of specific organ systems (Table 3).

Interruption of the Study Protocol

The study protocol was suspended for technical reasons in 33 patients in the control group, 25 patients in the cardiac-index group, and 26 patients in the oxygen-saturation group ($P=0.437$). Protocol interruptions resulted primarily from malfunctions of the pulmonary-artery catheters. Because of electrocardiographic alterations suggestive of myocardial hypoperfusion, the study protocol was discontinued in two, nine, and three patients in the respective groups ($P=0.043$).

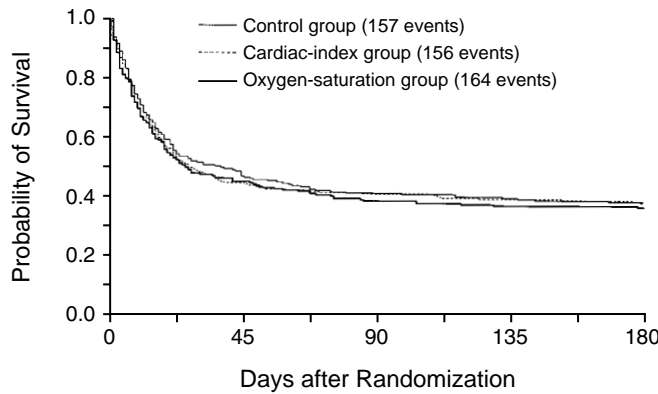
Subgroup Analyses

Mortality and Success in Reaching Hemodynamic Goals

In accordance with the study protocol, we also assessed outcome in relation to whether or not the hemodynamic goals had been achieved. The patients who reached their target values (232 in the control group, 109 in the cardiac-index group, and 164 in the oxygen-saturation group) had similar mortality rates (44.8, 40.4, and 39.0 percent, respectively; $P=0.478$), although they had different values for the cardiac index averaged over time (4.0 ± 1.0 , 5.4 ± 1.1 , and 4.2 ± 1.2 liters per minute per square meter; $P<0.001$). Similarly, no differences in mortality were observed among the three strategies in subgroups of patients who reached their hemodynamic goals within 24 hours of randomization (209, 77, and 139 patients, respectively); the mortality rates in these patients were 44.0, 35.1, and 45.3 percent ($P=0.306$) and their mean ages were 60 ± 16 , 51 ± 18 , and 61 ± 16 years ($P<0.001$).

Outcome Measures and Characteristics of the Intensive Care Unit

Four intensive care units did not randomly assign patients to the cardiac-index group. When the remaining 52 intensive care units were grouped according to their success rates in reaching the goal established for the supranormal cardiac-index values (20 units had rates below 30 percent, 18 had rates between 31 and 60 percent, and 14 had rates above 60 percent), we found no



PATIENTS AT RISK (NO. OF EVENTS)					
Control group	252 (129)	108 (13)	94 (4)	90 (3)	87
Cardiac-index group	253 (133)	102 (8)	90 (4)	86 (3)	83
Oxygen-saturation group	257 (133)	106 (16)	89 (4)	85 (1)	84

Figure 2. Survival Curves from Study Entry to the Six-Month Follow-up in the Three Study Groups.

The numbers of events listed in the key include events that occurred after the six-month follow-up, whereas the survival curve was truncated at six months. No significant differences were found between the groups.

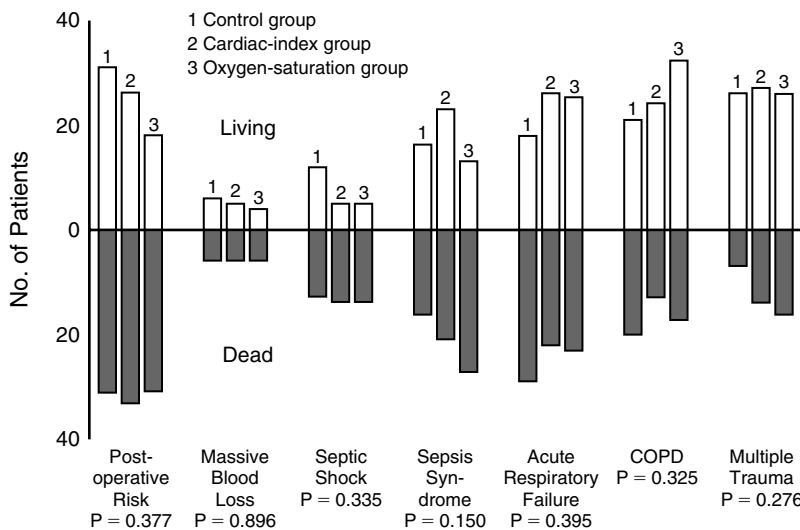


Figure 3. Patients Randomly Assigned to Each Study Group Who Died and Who Survived to Discharge from the Intensive Care Unit, According to Diagnostic Category.

No significant differences in mortality rates were found in any subgroup. COPD denotes exacerbated chronic obstructive pulmonary disease. P values are for the comparison of mortality rates among the three groups.

significant differences in outcome. Overall mortality was similar among units with low, intermediate, and high success rates ($P=0.087$), as well as among study groups in each category of the success rate.

When we grouped the 56 participating intensive care units arbitrarily according to the number of patients enrolled (fewer than 10, between 11 and 20, and more than 20 patients), we defined 25 units as having low, 22 as having intermediate, and 9 as having high rates of recruitment. There were 146, 328, and 288 patients enrolled in the low, intermediate, and high recruitment-rate categories, respectively, with similar overall mortality rates (54.1, 52.1, and 44.8 percent; $P=0.096$). In each

category of intensive care unit, the mortality rates in the three study groups were similar (rates in low-recruitment units, 61.2 percent in the control group, 47.8 percent in the cardiac-index group, and 52.9 percent in the oxygen-saturation group [$P=0.415$]; in intermediate-recruitment units, 50.9, 54.6, and 50.9 percent, respectively [$P=0.818$]; in high-recruitment units, 38.7, 42.4, and 53.1 percent [$P=0.116$]). We found no significant differences in hemodynamic treatment among the units with low, intermediate, or high recruitment-rate status, suggesting that the hemodynamic therapy in intensive care units that were more active was similar to that in intensive care units that were less active.

DISCUSSION

In this study, we found that achieving a supranormal cardiac index was more difficult than achieving a normal cardiac index or a normal SvO_2 . In fact, the supranormal hemodynamic target was reached in only a minority of patients in the cardiac-index group (44.9 percent), whereas normal values for cardiac index and SvO_2 were reached in 94.3 and 66.7 percent of the control group and the oxygen-saturation group, respectively.

Other authors have reported similar difficulties. In the study by Hayes et al.,⁹ 70 percent of patients did not reach the supranormal value (average dose of dobutamine, 25 μg per kilogram per minute). Similarly, 34 percent of the patients in the study by Yu et al.⁸ (who received 5 to 20 μg of dobutamine per kilogram per minute) and 27 percent of the patients in the study by Tuchschiidt et al.⁷ (average dose of dobutamine, 30 μg per kilogram per minute) did not reach the supranormal value. Failure to achieve the target appears, therefore, to be a common problem. In our cardiac-index group, the average dose of dobutamine (7.8 μg per kilogram per minute) was lower than those reported in the previous studies. However, the average cardiac index was the same as those reported by Shoemaker et al.⁵ and Hayes et al.⁹ (4.4 liters per minute per square meter), higher than that of Boyd et al.⁶ (3.2 liters per minute per square meter), but lower than that of Tuchschiidt et al.⁷ (5.1 liters per minute per square meter).

The discrepancies among studies in dobutamine doses and resulting cardiac indexes may be explained by differences in the characteristics of the patients. Our

Table 3. Dysfunction of Organ Systems at Base Line and during the Five-Day Treatment Period.

VARIABLE*	PATIENTS WHO SURVIVED				PATIENTS WHO DIED			
	CONTROL GROUP	CARDIAC-INDEX GROUP	OXYGEN-SATURATION GROUP	P VALUE	CONTROL GROUP	CARDIAC-INDEX GROUP	OXYGEN-SATURATION GROUP	P VALUE
Respiratory dysfunction								
No. of patients/total no.	120/238	117/236	116/248	0.631	118/238	119/236	132/248	0.191
PaO ₂ /FiO ₂ †								
Base line	233±116	239±112	219±98	0.371	191±99	203±94	197±97	0.661
Treatment	248±91	253±85	241±77	0.526	200±83	207±76	206±86	0.781
Mechanical ventilation during treatment (days)	3.6±1.7	3.5±1.8	3.9±1.5	0.180	3.8±1.7	3.4±1.8	3.5±1.8	0.322
Renal dysfunction								
No. of patients/total no.	46/138	47/134	37/134	0.504	92/138	87/134	97/134	0.705
Serum creatinine (mg/dl)								
Base line	2.9±1.6	3.2±1.9	2.8±2.1	0.614	3.0±2.0	2.9±1.8	2.8±2.2	0.742
Treatment	2.8±1.8	3.3±2.1	2.7±2.2	0.418	3.2±2.0	3.0±2.0	3.1±1.9	0.846
Urinary output during treatment (ml/hr)	110±59	88±55	105±55	0.139	75±49	91±56	75±56	0.092
Hepatic dysfunction								
No. of patients/total no.	50/116	50/130	43/123	0.770	66/116	80/130	80/123	0.213
Serum bilirubin (mg/dl)								
Base line	2.3±2.4	3.0±2.9	3.6±6.3	0.383	3.2±4.7	3.2±4.2	2.7±2.3	0.626
Treatment	2.5±2.0	3.1±2.7	3.5±4.5	0.256	3.4±3.1	3.6±4.0	3.2±2.3	0.693
Serum aspartate aminotransferase (IU/ml)								
Base line	254±410	307±530	388±805	0.565	346±676	455±1078	301±624	0.515
Treatment	177±197	213±371	285±778	0.568	239±384	271±431	385±686	0.226
Serum alanine aminotransferase (IU/ml)								
Base line	137±203	280±437	244±358	0.131	276±665	241±538	247±499	0.932
Treatment	127±213	200±315	196±395	0.441	159±235	176±293	237±404	0.334
CNS dysfunction								
No. of patients/total no.	14/42	10/46	14/49	0.597	28/42	36/46	35/49	0.530
Glasgow coma score								
Base line	5.9±4.1	8.2±3.0	8.1±4.1	0.252	9.8±4.3	9.3±4.6	9.4±4.5	0.898
Treatment	7.7±4.1	9.6±2.7	9.2±3.7	0.383	10.5±4.1	9.0±4.1	10.6±3.7	0.246

*Plus-minus values are means ±SD. To convert values for creatinine to micromoles per liter, multiply by 88.4; to convert values for bilirubin to micromoles per liter, multiply by 17.1. CNS denotes central nervous system.

†Denotes the partial pressure of arterial oxygen (in millimeters of mercury) divided by the fraction of inspired oxygen.

data suggest that age influences the likelihood of achieving the supranormal target value; the patients who reached that value were significantly younger (age, 52 ± 18 years; cardiac index, 5.4 ± 1.1 liters per minute per square meter) than those who did not (age, 66 ± 14 years; cardiac index, 3.6 ± 0.7 liters per minute per square meter; $P < 0.001$). Interestingly, the highest average supranormal values reported among the previous five randomized studies were reached in the study⁷ with the youngest patient population (age 49 ± 3 years; cardiac index, 5.1 ± 2.0 liters per minute per square meter), whereas the lowest values were reached in the study⁶ with the oldest population (median age, 69 years; median cardiac index, 3.2 liters per minute per square meter).

We found no significant differences in mortality among our three treatment groups, either up to the time of discharge from the intensive care unit or at the six-month follow-up. Furthermore, the proportion of patients with organ dysfunction and the type of dysfunction did not differ in the three study groups. These conclusions held true even in post hoc analyses based on achievement of the target value or characteristics of the intensive care unit.

It is noteworthy that the group with a normal cardiac index as the target (the control group) and the

group with normal SvO₂ as the target (the oxygen-saturation group) had indistinguishable hemodynamic values and courses, suggesting substantial equivalency between these strategies. We therefore focus on comparing the supranormal with the normal hemodynamic goals.

Hayes et al.,⁹ like us, dealt with a heterogeneous population of critically ill patients. Their study was stopped because there was significantly higher mortality among the treated patients than among the controls. In our cardiac-index group, which was five times larger than theirs, we observed no trend toward higher mortality as compared with the control group and the oxygen-saturation group. The study by Tuchschild et al.⁷ of patients with sepsis and that by Yu et al.⁸ of a mixed group of patients did not show differences in mortality between the treated and the control groups. Nevertheless, both studies suggested that supranormal hemodynamic values were effective in improving survival. These conclusions were reached by stratifying the patients a posteriori and comparing those who reached supranormal values with those who did not. In our opinion, this approach is misleading, since it confounds what is to be proved (i.e., that increasing hemodynamic values to supranormal levels improves survival) with what has been observed (i.e., that patients with a high cardiac in-

dex survive at a higher rate than patients with a low cardiac index). In summary, all available studies dealing with patients randomized after admission to an intensive care unit found no real differences in mortality with supranormal hemodynamic values.

Shoemaker et al.⁵ and Boyd et al.⁶ found a striking decrease in mortality in perioperative patients randomly assigned to supranormal targets. Among our high-risk postoperative patients, however, there were no differences in mortality according to study group. It is important, however, to stress that the treatments used by Shoemaker et al. and Boyd et al. were mainly preventive — i.e., preoperative and perioperative — so it is hard to compare their results directly with ours.

We were not able to confirm the results previously reported in nonrandomized studies. Unlike Fleming et al.,²⁰ we did not find differences in the mean number of organ failures or in the length of stay in the intensive care unit between patients given treatment intended to achieve a supranormal cardiac index and those whose target was a normal SvO₂. Furthermore, we found no advantage to the use of supranormal target values for patients in diagnostic categories for which such values have been said to be effective in decreasing mortality, as in postoperative patients^{3,21} or patients with trauma²⁰ or sepsis.^{22,23}

We conclude that therapy intended to achieve a supranormal cardiac index or a normal SvO₂ does not reduce morbidity or mortality in a general population of critically ill patients.

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APPENDIX

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