CHEST

From Early Goal-Directed Therapy to Late(r) $Scvo_2$ Checks

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Septic shock is the typical form of distributive shock, characteristically associated with a hyperkinetic (high cardiac output) state and normal or high mixed venous oxygen saturation (Svo_2).[1] Rivers et al[2] introduced the concept of early goal-directed therapy in septic shock, made on the basis of measurements of central venous oxygen saturation ($Scvo_2$), which are more easily obtained than Svo_2, especially in an ED. This strategy, which included giving more fluids, transfusions, and dobutamine when the $Scvo_2$ was $< 70\%$, was associated with a reduction in mortality from 46.5% in the control group to 30.5% in the early goal-directed therapy group. Of importance, the patients included in the study by Rivers et al[2] had an initial $Scvo_2$ of 49%. Three large prospective, randomized, controlled trials showed no differences in mortality when $Scvo_2$-targeted strategies were used, but the patients enrolled in these trials were not severely ill and had a mean initial $Scvo_2$ of at least 70%.[3] Nevertheless, the clear message from these studies was that protocols that target $Scvo_2$ only do not improve outcomes in heterogeneous populations of patients with septic shock. Indeed, this would be too simple.

This finding does not mean that physiology is wrong, however, and that Svo_2/$Scvo_2$ does not matter. Svo_2 reflects the balance between oxygen consumption and oxygen delivery (Do_2), so that a low Svo_2 is an important signal in patients who are hemodynamically unstable. In this issue of *CHEST*, Protti et al[4] reevaluated the prognostic value of $Scvo_2$ in a retrospective analysis of data from their large Albumin Italian Outcome Sepsis study on albumin administration in 1,818 patients with sepsis. Mortality rates at 90 days were higher in the 514 (35%) patients who initially had a low $Scvo_2$ ($<70\%$) than in other patients (44% vs 38%; $P = .03$), but the differences were no longer statistically significant in a multivariable analysis. The majority (54%) of these patients still had a low $Scvo_2$ after 6 h of resuscitation; these patients also had a higher 90-day mortality rate than those in whom $Scvo_2$ was only transiently $< 70\%$ (50% vs 37%; $P = .005$). This higher mortality may reflect greater severity of disease but this was not clearly the case, with the simplified acute physiology score II and sequential organ failure assessment similar in the two groups and, unlike the situation for initial $Scvo_2$, the differences between patients with persistent $Scvo_2$ and transient $Scvo_2$ remained statistically significant in multivariable analysis. Importantly, the higher mortality may, in part, have been related to under resuscitation (in 36% of these patients), especially because these patients appeared to have more severe cardiac dysfunction than the others. The higher mortality rates were not clearly related to the severity of the shock, implying that even careful clinical examination cannot reveal underlying $Scvo_2$ values. Fortunately, $Scvo_2$ can be easily measured by blood sampling through a central venous catheter, which is required in any case for safe administration of vasopressors and to guide fluid challenges.[5]

The implications of these results are as follows. In the very early stages of resuscitation, consisting of fluids and vasopressors, a $Scvo_2$ measurement may not be needed, and it may not be needed later either if the patient improves rapidly. In cases of persistent septic shock, however, if vasopressor support remains indicated, $Scvo_2$ should be checked to evaluate whether strategies should be used to further increase Do_2. If $Scvo_2$ is $\geq$ 70%, and especially if the venoarterial partial pressure of carbon dioxide gradient is < 6 mm Hg,[6] the benefits of increasing Do_2 further are doubtful. An $Scvo_2$ value

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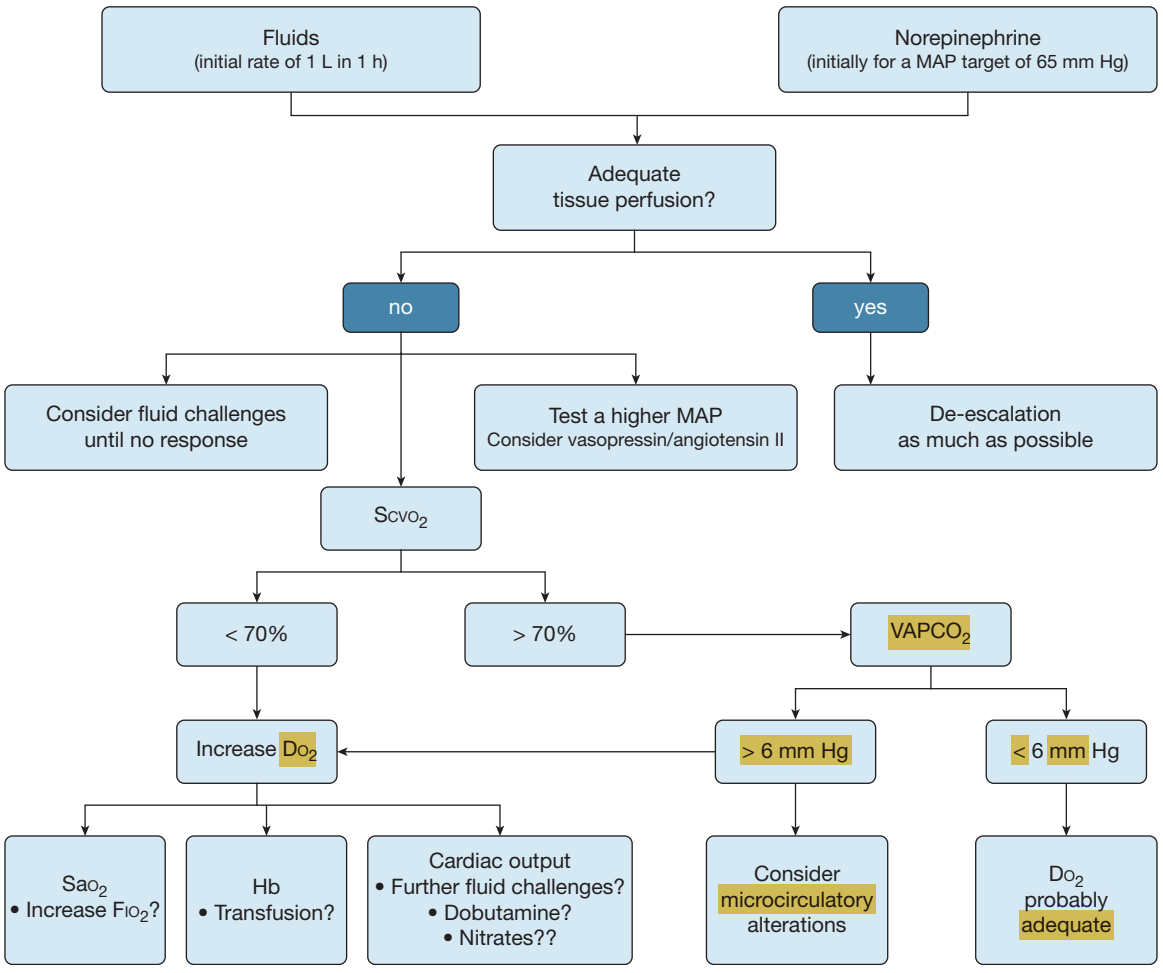

Figure 1 – *Suggested algorithm for hemodynamic management of septic shock using* S_{CVO_2}. D_{O_2} = *oxygen delivery; Hb = hemoglobin; MAP = mitogen-activated protein;* S_{aO_2} = *oxygen saturation;* S_{CVO_2} = *central venous oxygen saturation;* $VAPCO_2$ = *venoarterial partial pressure of carbon dioxide.*

< 70% should, however, encourage use of strategies to increase D_{O_2}. If the patient is no longer responding to fluids, a small dose of dobutamine can significantly improve tissue perfusion, as assessed clinically. This approach was proposed almost 30 years ago[7] and is suggested in the Surviving Sepsis Campaign guidelines for management of sepsis.[8] S_{CVO_2} is actually more informative than cardiac output in circulatory shock. Before giving dobutamine, an assessment of cardiac function may be helpful, although dobutamine administration should not be restricted to cases of severe cardiac depression. Even though blood transfusions are not indicated routinely in all patients with septic shock,[9] a blood transfusion should be considered in the presence of anemia when the situation is severe.[10] Repeated measurements of blood lactate levels can help to ascertain the patient's response to therapy.[8] It is important that attempts to normalize S_{CVO_2} in the absence of shock should not be attempted because this may result in fluid overload, excessive transfusions, and inappropriate use of inotropic agents. We propose a management algorithm in Figure 1.

Do we need a randomized, controlled trial to validate this approach? We do not think so, because it would be difficult, and hardly ethical, to simply observe a patient in the control group without attempting to treat further if the S_{CVO_2} decreases to < 70%. These suggestions are just good medicine, made on the basis of well-known physiology.

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Persistence of Central Venous Oxygen Desaturation During Early Sepsis Is Associated With Higher Mortality

A Retrospective Analysis of the ALBIOS Trial

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BACKGROUND: Relevance of low (< 70%) central venous oxygen saturation ($Scvo_2$) during early sepsis has been recently questioned by three negative trials (Protocol-Based Care for Early Septic Shock, Australasian Resuscitation in Sepsis Evaluation, and Protocolized Management in Sepsis) on early goal-directed therapy; however, subjects included in those trials had $Scvo_2$ at enrollment as high as 71 ± 13%, 73 ± 11%, and 70 ± 12%. Here we assess the association between $Scvo_2$ < 70% at 6 h and 90-day mortality in subjects enrolled in the Albumin Italian Outcome Sepsis (ALBIOS) trial, focusing on those with initial $Scvo_2$ < 70%.

METHODS: Regardless of treatment assignment (to receive albumin or not), all subjects enrolled in the ALBIOS trial received early goal-directed therapy aiming for $Scvo_2$ ≥ 70% at 6 h. Using multivariable logistic regression analyses, we tested the association between $Scvo_2$ < 70% at 6 h and 90-day mortality in those with initial $Scvo_2$ < 70% (n = 514) or ≥ 70% (n = 961).

RESULTS: $Scvo_2$ < 70% at 6 h was independently associated with higher 90-day mortality in subjects with initial $Scvo_2$ < 70% (OR, 1.84; 95% CI, 1.19-2.85; P = .007) but not in those with initial $Scvo_2$ ≥ 70% (OR, 1.25; 95% CI, 0.79-1.95; P = .357). $Scvo_2$ < 70% at enrollment and at 6 h was associated with history and/or signs of cardiac dysfunction but not with greater severity of disease or more aggressive resuscitation (required per protocol).

CONCLUSIONS: In the ALBIOS trial, persistence of low $Scvo_2$ was associated with higher 90-day mortality, possibly because it reflected underlying cardiac dysfunction. Subjects with $Scvo_2$ < 70% may benefit most from individually tailored interventions aimed at normalizing the balance between systemic oxygen delivery and consumption.

TRIAL REGISTRY: ClinicalTrials.gov; No. NCT00707122; URL: www.clinicaltrials.gov.

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ABBREVIATIONS: hs-cTnT = high-sensitivity cardiac troponin T; NT-proBNP = N-terminal pro-B-type natriuretic peptide; SAPS = Simplified Acute Physiology Score; $Scvo_2$ = central venous oxygen saturation; SOFA = Sequential Organ Failure Assessment

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Central venous oxygen desaturation (central venous oxygen saturation [$Scvo_2$] < 70%) signals a mismatch between oxygen delivery and consumption in the upper, and possibly even in the lower, part of the human body.[1] If severe or prolonged enough, inadequate oxygen supply will limit cellular aerobic energy production and cause cellular dysfunction or death.[2] According to this model, $Scvo_2$ < 70% has been associated with poor prognosis.[3,4]

Approximately 15 years ago, one single-center randomized controlled trial showed that (early goal-directed) therapy aiming for prompt reversal of $Scvo_2$ < 70% could reduce in-hospital mortality of subjects with systemic inflammatory response to infection and either hypotension or blood lactate concentration ≥ 4 mmol/L.[5] Since then, targeting $Scvo_2$ ≥ 70% during initial resuscitation from severe sepsis or septic shock has been strongly encouraged.[6] Subsequent large retrospective and prospective studies further supported this recommendation.[7,8]

More recently, three multicenter randomized controlled trials did not confirm those previous findings:[9-11] assignment of subjects with severe sepsis or septic shock to early goal-directed therapy did not reduce 60- or 90-day mortality.[12] On the basis of these results, Surviving Sepsis Campaign Guidelines no longer recommend monitoring and targeting $Scvo_2$ during early management of sepsis.[13]

One reason for this inconsistency may be the marked difference in $Scvo_2$ at enrollment between the first positive trial (49 ± 11%)[5] and the other three negative trials (71 ± 13%,[9] 73 ± 11%,[10] and 70 ± 12%[11]). It seems that harms of $Scvo_2$ < 70%, when cellular aerobic energy production is limited by (inadequate) oxygen supply, become clear only if initial $Scvo_2$ is really < 70%.

On the basis of this hypothesis, we investigated the incidence, risk factors, and association with 90-day mortality of $Scvo_2$ < 70% during the first 6 h of treatment in subjects included in the Albumin Italian Outcome Sepsis (ALBIOS) trial,[14] separating those with initial $Scvo_2$ < 70% (who were more represented in the study in which early goal-directed therapy was beneficial)[5] from those with initial $Scvo_2$ ≥ 70% (who were more represented in the other three studies in which early goal-directed therapy was not beneficial).[9-11]

Methods

This is a retrospective analysis of the ALBIOS trial, a multicenter randomized controlled study on the efficacy of albumin replacement during severe sepsis or septic shock. The ALBIOS trial complied with the 1975 Declaration of Helsinki as revised in 2008 and was approved by the institutional review boards of the participating centers. Written informed (deferred) consent was obtained from each subject enrolled, according to the Italian legislation.

Study protocol and main results of the trial have been reported elsewhere.[14] Briefly, the trial enrolled 1,818 adults who received a diagnosis of severe sepsis or septic shock from < 24 h, at any time during their stay in 100 Italian ICUs. As recommended at the time of designing the study, severe sepsis was defined as proven or suspected infection; two or more signs of the systemic inflammatory response syndrome; and at least one acute, sepsis-related organ dysfunction as measured with the Sequential Organ Failure Assessment (SOFA) score (Table 1).[15-18] Septic shock was defined as a score ≥ 3 for the cardiovascular component of the SOFA score.[16] Subjects fulfilling these criteria were randomly assigned to receive either 20% albumin and crystalloid solutions (study group) or crystalloid solutions alone (control group) for fluid resuscitation, from randomization until day 28 or ICU discharge, whichever came first.

Regardless of treatment assignment, all subjects had to receive fluids, catecholamine(s), RBC, sedation, and/or mechanical ventilation according to a standardized protocol to reach the following targets within the first 6 h: mean arterial pressure, 65-90 mm Hg; central venous pressure, 8 to 12 mm Hg; and $Scvo_2$, ≥ 70% (early goal-directed therapy).[5]

In the present analysis, we included only subjects with $Scvo_2$ recorded both at enrollment and at 6 h (Fig 1). Some of these subjects also had plasma levels of biomarkers of cardiac injury N-terminal pro-B-type natriuretic peptide (NT-proBNP) and high-sensitivity cardiac troponin T (hs-cTnT) measured at day 1 as part of a predefined substudy.[19]

Statistical Analysis

Continuous variables are reported as mean (SD) or median (interquartile range), whereas categorical variables are reported as proportions. Groups were compared with Student *t* or Mann-Whitney rank sum test, χ^2 or Fisher exact test, as appropriate.

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TABLE 1] Comparison of Baseline Characteristics, Physiological Variables, and Laboratory Variables at Enrollment Between Subjects With or Without Initial $Scvo_2 < 70\%$

Variables	Entire Study Population	With Initial $Scvo_2 < 70\%$	With Initial $Scvo_2 \geq 70\%$	*P*
No. (%)	1,475 (100)	514 (35)	961 (65)	
$Scvo_2$ at enrollment (%)	72 ± 10	61 ± 8	78 ± 5	< .001
Age, y	66 ± 14	68 ± 14	65 ± 15	< .001
Women	583 (40)	201 (39)	382 (40)	.809
BMI, kg/m^2	27 ± 6	26 ± 5	27 ± 6	.713
Reason for admission to ICU				< .001
Medical	830 (56)	288 (56)	542 (56)	
Elective surgery	105 (7)	55 (11)	50 (5)	
Emergency surgery	540 (37)	171 (33)	369 (38)	
Preexisting conditions				
Liver disease	20 (2)	2 (0)	18 (2)	.019
COPD	172 (12)	57 (11)	115 (12)	.617
Chronic renal failure	55 (4)	25 (5)	30 (3)	.093
Immunodeficiency	192 (13)	62 (12)	130 (14)	.426
Congestive or ischemic heart disease	259 (18)	129 (25)	130 (14)	< .001
SAPS II score	48 (37-59)	50 (38-61)	47 (36-58)	.002
SOFA score	8.00 (6.00-10.00)	8.00 (6.00-10.00)	8.00 (6.00-10.00)	.193
Physiological variables at enrollment				
Arterial oxygen saturation (%)	97 (95-98)	96 (93-98)	97 (96-99)	< .001
Heart rate, beats/min	106 ± 21	106 ± 22	106 ± 20	.965
Mean arterial pressure, mm Hg	73 ± 15	71 ± 16	74 ± 15	< .001
Central venous pressure, mm Hg	10 ± 5	10 ± 5	10 ± 5	.125
Urine output, mL/h	50 (25-100)	50 (20-100)	60 (30-100)	.003
Laboratory variables at enrollment				
Leukocytes, $10^3/mm^3$	11.8 (5.2-18.3)	12.2 (4.8-18.8)	11.4 (5.4-17.9)	.907
Hemoglobin, g/dL	11.0 ± 2.0	10.8 ± 2.0	11.1 ± 2.0	< .001
Lactate, mmol/L	2.5 (1.5-4.2)	2.5 (1.6-4.7)	2.5 (1.5-4.0)	.128
Serum albumin, g/L	24 ± 6	24 ± 6	24 ± 6	.064
NT-proBNP on day 1, ng/L	4,393 (1,271-13,444)	6,464 (2,521-21,777)	3,467 (1,036-9,607)	< .001
hs-cTnT on day 1, ng/L	51 (21-133)	68 (33-206)	43 (18-116)	< .001
Organ(s) dysfunction				.444
1 organ	304 (21)	93 (18)	211 (22)	
2 organs	553 (37)	200 (39)	353 (37)	
3 organs	404 (27)	144 (28)	260 (27)	
4 organs	160 (11)	60 (12)	100 (10)	
5 organs	54 (4)	17 (3)	37 (4)	
Septic shock	943 (64)	311 (61)	632 (66)	.045
With mechanical ventilation at enrollment	1,173 (80)	369 (72)	804 (84)	< .001

(Continued)

TABLE 1] *(Continued)*

Variables	Entire Study Population	With Initial $Scvo_2$ < 70%	With Initial $Scvo_2$ ≥ 70%	*P*
Albumin in previous 24 h	259 (18)	73 (14)	186 (19)	.013
Synthetic colloids in previous 24 h	799 (54)	269 (52)	530 (55)	.301
With ≥2 catecholamines at enrollment	402 (27)	128 (25)	274 (29)	.138
With antibiotic(s)	1,379 (93)	475 (92)	904 (94)	.219
With adequate antibiotic(s) on day 1	647 (77)	238 (79)	409 (76)	.294
Enrolled within 6 h	485 (33)	194 (38)	291 (30)	.004

Data are presented as No. (%) unless otherwise indicated. Variables were defined as in the original study protocol.[14] BMI was the ratio between body weight and the square of body height. Liver disease denoted the presence of cirrhosis, portal hypertension, or previous episodes of liver insufficiency. Immunodeficiency denoted the presence of immunosuppressive diseases or receipt of immunosuppressive therapies. Congestive or ischemic heart disease was defined as New York Heart Association class II (class III and class IV were original exclusion criteria). SAPS II was used to assess the severity of systemic illness at baseline. Scores range from 0 to 163, with higher scores indicating more severe illness.[17] The SOFA score includes subscores ranging from 0 to 4 for each of 6 components (neurological, respiration, coagulation, liver, cardiovascular, and renal components), with higher scores indicating more severe acute organ dysfunction.[15] In the original Albumin Italian Outcome Sepsis trial, and here, this scoring system was slightly modified by excluding the assessment of the neurological component (with the Glasgow Coma Scale), which was not performed in these subjects, and by decreasing to 65 mm Hg the mean arterial pressure threshold for a cardiovascular subscore of 1, for consistency with the target of early goal-directed therapy. Organ dysfunctions were defined as a SOFA score ≥ 2 for the respiratory component; ≥ 2 for the coagulation component; ≥ 2 for the liver component; 1, 3, or 4 for the cardiovascular component; and ≥ 2 for the renal component. Shock was defined as a SOFA score ≥ 3 for the cardiovascular component, that is need of dopamine (> 5 μg/kg/min), epinephrine, or norepinephrine.[16] Antibiotic(s) were considered appropriate if all pathogenic microorganisms isolated at the site of infection were susceptible to at least 1 of the drugs administered by day 1, as judged by a local microbiologist.[18] Data on SOFA score were available for 1,434 subjects; data on arterial oxygen saturation for 1,461; data on central venous pressure for 1,450; data on leukocytes for 1,468; data on hemoglobin for 1,458; data on lactate for 1,419; data on albumin for 1,349; data on NT-proBNP for 771; data on high-sensitivity cardiac troponin T on 772; and data on adequacy of antibiotic(s) on day 1 for 837. hs-cTnT = high-sensitivity cardiac troponin T; NT-proBNP = N-terminal pro-B-type natriuretic peptide; SAPS = Simplified Acute Physiology Score; $Scvo_2$ = central venous oxygen saturation; SOFA = Sequential Organ Failure Assessment.

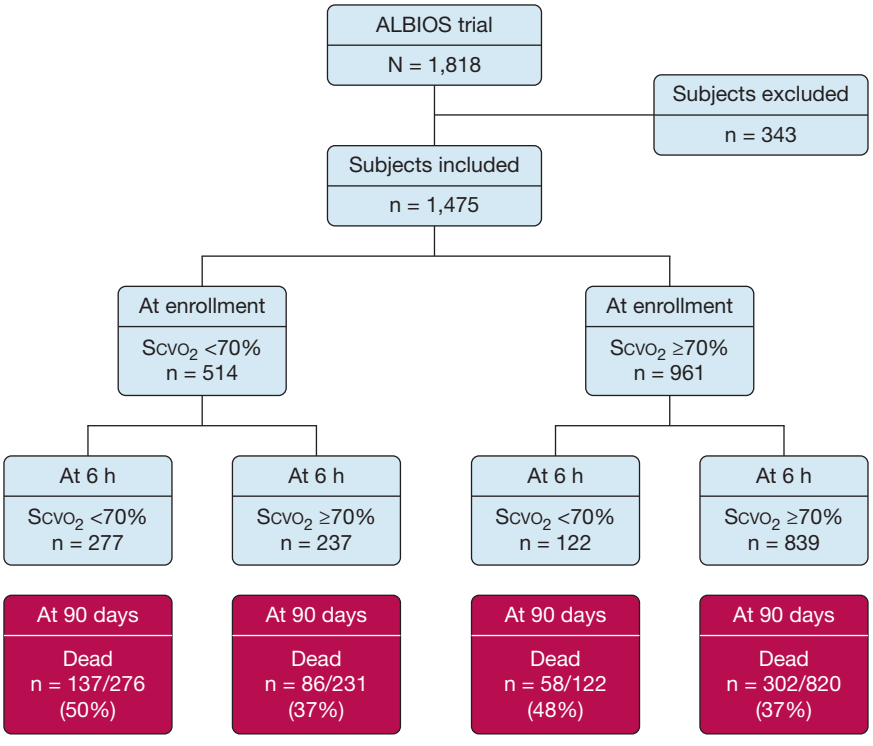


Figure 1 – *Study design of the present analysis and crude 90-day mortality rates in the identified subgroups.* ALBIOS = Albumin Italian Outcome Sepsis; $Scvo_2$ = central venous oxygen saturation.

Multivariable logistic regression analyses were applied to identify risk factors for 90-day mortality. Variables recorded at enrollment or at 6 h associated with 90-day mortality at univariate analyses ($P < .05$), were included in multivariable models. For multivariable analyses only, missing data were handled depending on their frequency:[20] if < 5%, they were imputed with median (by subgroup) values; if 5% to 10% (as for serum albumin at enrollment), subjects were excluded from the analysis. This rule did not apply to the variable "with adequate antibiotic therapy at day 1" (yes or no) because it reasonably affected outcome.[21] This variable was always included in multivariable models, and missing values (culture-negative samples) were replaced with a dummy indicator. Backward selection was used to define final models. Results are reported as OR and 95% CI.

Statistical analyses were performed with SAS software 9.3 (SAS Institute) and Sigma Plot software 11.0 (Jandel Scientific Software).

Results

Incidence, Risk Factors, and Association With 90-Day Mortality of Initial $Scvo_2$ < 70%

Eight subjects were excluded from the original analysis because of withdrawal of consent (n = 2) or randomization error (n = 6); 335 subjects were excluded from this present analysis because of missing $Scvo_2$ at enrollment (n = 218) and/or at 6 h (n = 268). Among the remaining 1,475 subjects, 514 (35%) had an initial $Scvo_2$ < 70% (61 ± 8%; range, 28%-69%) (Fig 1).

Subjects with initial $Scvo_2$ < 70% differed in several aspects from those with initial $Scvo_2$ ≥ 70% (Table 1). More commonly, they had undergone elective surgery, had a history of cardiac disease, and were enrolled early after fulfillment of inclusion criteria. Less commonly, they had undergone emergency surgery, suffered from septic shock, were treated with mechanical ventilation, and had received albumin in the previous 24 h. On average, they were older, had higher Simplified Acute Physiology Score (SAPS) II and lower, but still quite normal, arterial oxygenation, mean arterial pressure, urine output, and hemoglobin concentration. Initial $Scvo_2$ < 70% was also associated with higher plasma levels of biomarkers of cardiac injury at day 1.

Ninety-day mortality was higher in subjects with initially low, compared with normal, $Scvo_2$ (44% vs 38%; $P = .033$) (Fig 2). However, at multivariable analysis, initial $Scvo_2$ < 70% did not emerge as a significant risk factor for death (OR, 0.98; 95% CI, 0.75-1.28; $P = .877$) (e-Tables 1 and 2).

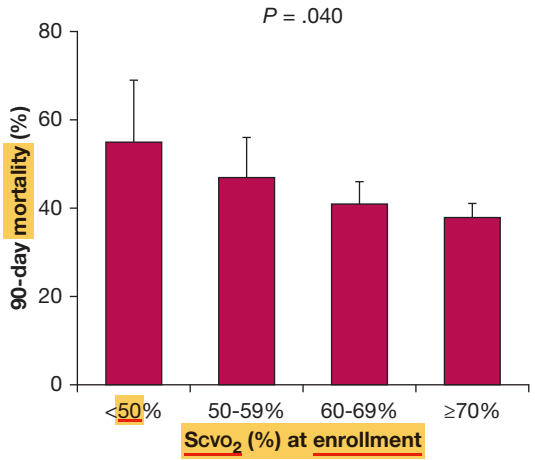
Incidence, Risk Factors, and Association With 90-Day Mortality of $Scvo_2$ < 70% at 6 h

Among 514 subjects with initial $Scvo_2$ < 70%, 277 (54%) had $Scvo_2$ < 70% even at 6 h ("persistent" $Scvo_2$ < 70%) (Fig 1). As shown in Table 2, these latter subjects more commonly had undergone elective, but not emergency, surgery and more frequently had chronic cardiac disease than those with $Scvo_2$ < 70% at enrollment but not at 6 h ("transient" $Scvo_2$ < 70%). On average, they also had lower initial $Scvo_2$ at enrollment, lower arterial oxygenation, mean arterial pressure and hemoglobin concentration at 6 h, and higher plasma levels of biomarkers of cardiac injury at day 1 than the others.

Mortality at 90 days was higher in subjects with persistent, compared with transient, $Scvo_2$ < 70% (50% vs 37%; $P = .005$) in spite of similar scores of severity of disease (SAPS II score) and organ dysfunction (SOFA score). When this analysis was adjusted for possible confounders, persistence of $Scvo_2$ < 70% appeared to increase the risk of death (Fig 3 and e-Tables 1, 3-5).

Among 961 subjects with initial $Scvo_2$ ≥ 70%, 122 (13%) had $Scvo_2$ < 70% and 839 (87%) had $Scvo_2$ ≥ 70% at 6 h (Fig 1). Mortality at 90 days differed between these two groups at univariate (48% vs 37%; $P = .023$) but not at multivariable analyses (Fig 3 and e-Tables 1, 3-5).

Finally, when we extended the multivariable analyses to the entire study population (514 subjects with initial $Scvo_2$ < 70% and 961 subjects with initial



Events – n	26	56	141	360
At risk – n	47	120	340	942

Figure 2 – *The 90-day mortality of subjects enrolled in the ALBIOS trial, stratified according to their initial $Scvo_2$. Error bars indicate 95% CI. See Figure 1 legend for expansion of abbreviations.*

TABLE 2] Comparison of Baseline Characteristics, Physiological and Laboratory Variables at 6 h, and Treatments Administered During the First 6 h Between Subjects With $Scvo_2 < 70\%$ at Enrollment and at 6 h (as for Nonsuccessful Early Goal-Directed Therapy), and Subjects With $Scvo_2 < 70\%$ at Enrollment but Not at 6 h (as for Successful Early Goal-Directed Therapy)

Variables	$Scvo_2 < 70\%$ at 6 h	$Scvo_2 \geq 70\%$ at 6 h	*P*
No. (%)	277 (54)	237 (46)	
$Scvo_2$ at 6 h, %	60 ± 9	76 ± 5	< .001
$Scvo_2$ at enrollment, %	59 ± 8	63 ± 7	< .001
Age, y	68 ± 13	68 ± 14	.998
Women	113 (41)	86 (37)	.396
BMI, kg/m^2	26 ± 5	26 ± 5	.726
Reason for admission to ICU			.022
Medical	153 (55)	135 (57)	
Elective surgery	39 (14)	16 (7)	
Emergency surgery	85 (31)	86 (36)	
Preexisting conditions			
Liver disease	1 (0)	1 (0)	.912
COPD	29 (10)	28 (12)	.628
Chronic renal failure	16 (6)	9 (4)	.299
Immunodeficiency	35 (13)	27 (11)	.666
Congestive or ischemic heart disease	82 (30)	47 (20)	.011
SAPS II score	49 (38-63)	50 (38-60)	.757
SOFA score	8 (6-10)	8 (6-10)	.752
Physiological variables at 6 h			
Arterial oxygen saturation (%)	97 (94-98)	98 (96-99)	< .001
Heart rate, beats/min	100 ± 21	98 ± 21	.482
Mean arterial pressure, mm Hg	75 ± 13	80 ± 14	< .001
Central venous pressure, mm Hg	11 ± 5	11 ± 5	.763
Urine output, mL/h	83 (33-150)	85 (42-167)	.442
Laboratory variables at 6 h			
Leukocytes, $10^3/mm^3$	NA	NA	
Hemoglobin, g/dL	10.3 ± 1.6	10.7 ± 1.7	.028
Lactate, mmol/L	NA	NA	
Serum albumin, g/L	NA	NA	
NT-proBNP on day 1 (ng/L)	6,463 (2,167-19,341)	5,230 (2,340-15,265)	.024
hs-cTnT on day 1 (ng/L)	80 (37-269)	56 (28-134)	< .001
Organ(s) dysfunction			.790
1 organ	53 (19)	40 (17)	
2 organs	102 (37)	98 (41)	
3 organs	81 (29)	63 (27)	
4 organs	33 (12)	27 (11)	
5 organs	8 (3)	9 (4)	
Septic shock	165 (60)	146 (62)	.638
With mechanical ventilation at 6 h	206 (74)	195 (82)	.031
Albumin in previous 24 h	37 (13)	36 (15)	.553
Synthetic colloids in previous 24 h	139 (50)	130 (55)	.291
With two or more catecholamines at 6 h	98 (35)	68 (29)	.106
With antibiotic(s)	255 (92)	220 (93)	.743

(Continued)

TABLE 2] *(Continued)*

Variables	$Scvo_2$ < 70% at 6 h	$Scvo_2$ ≥ 70% at 6 h	*P*
With adequate antibiotic(s) on day 1	131 (80)	107 (78)	.629
Enrolled within 6 h	102 (37)	92 (39)	.642
Randomized to albumin	144 (52)	130 (55)	.516
Fluids administered from enrollment to 6 h			
20% albumin (mL)	0 (0-300)	100 (0-300)	.295
RBC units (n)	0 (0-0)	0 (0-0)	.589
Fresh frozen plasma (mL)	0 (0-0)	0 (0-0)	.819
Platelets (mL)	0 (0-0)	0 (0-0)	.565
Crystalloids (mL)	1,000 (600-2,000)	1,500 (725-2,120)	.028
Other fluids (mL)	200 (0-500)	100 (0-500)	.118
Total (mL)	1,860 (1,250-2,750)	2,080 (1,490-2,900)	.039

Data are presented as No. (%) unless otherwise indicated. These data refer to 514 subjects with initial $Scvo_2$ < 70% (see Fig 1). Data on SOFA score were available for 500 subjects; data on arterial oxygen saturation for 510; data on central venous pressure for 504; data on hemoglobin for 510; data on NT-proBNP for 250; data on hs-cTnT on 251; and data on adequacy of antibiotic(s) on day 1 for 300. NA = not available. See Table 1 legend for expansion of other abbreviations.

$Scvo_2$ ≥ 70%; n = 1,475), $Scvo_2$ < 70% at 6 h emerged as an independent risk factor for death (Fig 3 and e-Tables 1, 3-5).

Clinical Characteristics and Interventions Associated With Persistence of $Scvo_2$ < 70%

Among 514 subjects with initial $Scvo_2$ < 70%, those with or without $Scvo_2$ < 70% even at 6 h were similar for age, SAPS II score, SOFA score, initial arterial lactate concentration (2.4 [1.6-4.7] vs 2.8 [1.6-4.6] mmol/L; *P* = .666) and prevalence of shock (Table 2). As for the first 6 h of treatment, subjects with persistent $Scvo_2$ < 70% received fewer crystalloids and fluids in general, no more blood transfusions, no more catecholamine(s), and less mechanical ventilation than those with transient $Scvo_2$ < 70% (Table 2).

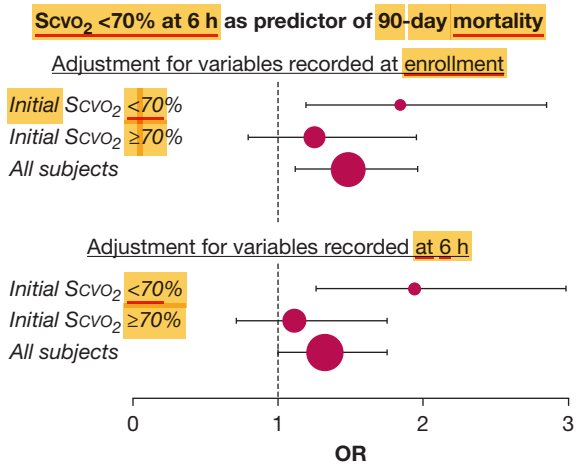


Figure 3 – *Association between baseline characteristics, physiological and laboratory variables, $Scvo_2$ at 6 h, and 90-day mortality in subjects enrolled in the ALBIOS trial. The results of multivariable analyses are applied to identify predictors of 90-day mortality, including presence or absence of $Scvo_2$ < 70% at 6 h. Upper, Results adjusted for baseline characteristics, physiological variables recorded at enrollment, and laboratory variables recorded at enrollment (Table 1). Lower, results adjusted for baseline characteristics, physiological variables recorded at 6 h, and laboratory variables recorded at 6 h (Table 2). Dot size reflects sample size. Error bars indicate 95% CI. See Figure 1 legend for expansion of abbreviations.*

Biomarkers of Cardiac Stress and Injury

Circulating levels of NT-proBNP and hs-cTnT were measured in 772 subjects at day 1 (Table 3). Among subjects with initial $Scvo_2$ < 70%, these biomarkers were higher in those with persistent, compared with transient, $Scvo_2$ < 70%. According to multivariable analyses reported previously, these were the subjects with an increased risk of death. By contrast, among subjects with initial $Scvo_2$ ≥ 70%, circulating levels of NT-proBNP and hs-cTnT did not differ between those with $Scvo_2$ < 70% or ≥ 70% at 6 h. According to multivariable analyses, these two groups also had a similar risk of death.

Discussion

In this retrospective analysis of a multicenter randomized trial, nonresolution of initially low $Scvo_2$ was associated with higher 90-day mortality of severe sepsis or septic shock, independently from other risk factors for death.

Initial $Scvo_2$ < 70% was associated with higher 90-day mortality at univariate, but not at multivariable, analysis. By contrast, $Scvo_2$ < 70% at 6 h in spite of early

TABLE 3] Biomarkers of Cardiac (Dys)function in 772 Subjects Enrolled in the ALBIOS Trial, Divided in Groups on the Basis of Their $Scvo_2$ at Enrollment and at 6 h

Variable	$Scvo_2$ at 6 h < 70%	$Scvo_2$ at 6 h ≥ 70%	*P*
Initial $Scvo_2$ < 70%	NT-proBNP (ng/L): 8,485 (2,902-23,405) hs-cTnT (ng/L): 80 (37-269)	NT-proBNP (ng/L): 5,230 (2,340-15,265) hs-cTnT (ng/L): 56 (28-134)	.024 .024
Initial $Scvo_2$ ≥ 70%	NT-proBNP (ng/L): 3,467 (1,021-9,603) hs-cTnT (ng/L): 43 (18-116)	NT-proBNP (ng/L): 3,324 (1,036-11,057) hs-cTnT (ng/L): 42 (21-127)	.842 .567

See Table 1 legend for expansion of abbreviations. Refer to Masson et al[19] for details on methods.

goal-directed therapy remained associated with higher mortality even after adjusting for possible confounders, including initial diagnosis (severe sepsis or septic shock). According to subgroup analysis, this result was valid only for subjects with initial $Scvo_2$ < 70% (and $Scvo_2$ < 70% at 6 h); that is, those with persistent $Scvo_2$ < 70%. These could be the subjects with an oxygen deficit profound enough and/or prolonged enough to trigger cellular dysfunction or death.[22,23]

There are several possible explanations for persistence of $Scvo_2$ < 70% in spite of early goal-directed therapy and the associated higher risk of death. First, this persistence reflected higher severity of disease; however, at univariate analysis, many other well-validated prognostic factors such as age, SAPS II score, SOFA score, initial arterial lactate concentration, and prevalence of shock did not differ between subjects with or without $Scvo_2$ < 70% even at 6 h. More important, at multivariable analysis, persistence of $Scvo_2$ < 70% predicted death independently from several covariates (e-Tables 3 and 5), including all those cited here previously. Similar resuscitation efforts (Table 2) suggest similar severity of disease, as perceived by attending physicians.

Second, this persistence depended on low compliance to resuscitation protocol. In fact, 99/277 (36%) subjects with persistently low $Scvo_2$ did not receive more fluids and/or norepinephrine, although their central venous pressure was <8 mm Hg and/or mean arterial pressure was <65 mm Hg at 6 h; 70/277 (25%) did not receive more red blood cells although their arterial hemoglobin concentration was < 10 g/dL at 6 h; 90/277 (32%) were not treated with dobutamine, as expected, at 6 h; and 71/277 (26%) were not sedated and mechanically ventilated at 6 h. Low adherence to early goal-directed therapy has been previously reported[7,8]; being a pragmatic trial, the ALBIOS trial confirms this finding. It is possible that stronger adherence to the resuscitation protocol, as in the Rivers' study, where, for example, 64% of the subjects assigned to early goal-directed therapy received red blood cells, would have resulted in more subjects with $Scvo_2$ ≥ 70% at 6 h and higher survival rate.

Third, this persistence reflected cardiac dysfunction that was probably not recognized and not adequately treated. In fact, it was associated with history of heart disease and higher circulating levels of markers of myocardial stress and injury (NT-proBNP and hs-cTnT),[24] but no other sign of higher severity of disease. Subjects with $Scvo_2$ < 70% even at 6 h mainly failed to respond to fluid resuscitation; few of them received norepinephrine (4%), RBC (22%), dobutamine (9%), and/or mechanical ventilation (5%) after study entry, with the aim of normalizing $Scvo_2$. If persistence of low $Scvo_2$ predominantly depended on cardiac dysfunction, some of the other interventions would have been (more) indicated.[25,26] Protocol-based resuscitation may provide no benefit, or even cause harm, when applied equally to all subjects without considering the individual hemodynamic phenotype.[27] On the one hand, cardiac dysfunction reasonably contributed at lowering $Scvo_2$; on the other, it possibly directly affected outcome, even more strongly than $Scvo_2$ < 70% at 6 h per se. In fact, according to multivariable analyses, $Scvo_2$ < 70% at 6 h was associated with an increased risk of death only in subjects with initial $Scvo_2$ < 70% (Fig 3), exactly those with highest plasma levels of NT-proBNP and hs-cTnT at day 1 (Table 3).

The first, positive, trial on early-goal directed therapy was quite small and with unexpectedly high mortality among control patients.[5] Trials published more recently that were consistently negative addressed most of these issues; however, they all enrolled many subjects with $Scvo_2$ ≥ 70%,[9-11] who could have hardly benefited from early goal-directed therapy because they lacked the condition that was meant to be treated. Our own results were positive when referring to subjects with initial $Scvo_2$ < 70%, just as in the first positive trial. At the same time, they were negative (no better outcome) when referring to subjects with initial $Scvo_2$ ≥ 70%, just as in the subsequent three negative trials.[9-11]

Our study is novel in that it examines the prognostic value and the underlying reasons for persistence of low $Scvo_2$ in 1,475 subjects, including 514 with initial $Scvo_2 < 70\%$, with severe sepsis or septic shock, all treated with early goal-directed therapy. In the three most recent trials, $Scvo_2$ was not recorded in control patients.[9-11] Therefore, these studies do not provide any evidence for or against early-goal directed therapy in subjects presenting with $Scvo_2 < 70\%$. It also has some limitations. First, it is a retrospective analysis of a trial that was not designed to investigate benefits or harms of targeting $Scvo_2$ during the early phase of sepsis. Causality cannot be established by statistics alone; it should be tested in prospective trials enrolling subjects with initial $Scvo_2 < 70\%$. Second, arterial lactate was not measured at 6 h; therefore, we cannot establish whether normalization (or decrease) of lactate is a better initial end point than normalization of $Scvo_2$.[28] Third, circulating biomarkers of cardiac dysfunction were measured only in a subgroup of subjects. Nonetheless, this subgroup was highly representative of the entire study population of the ALBIOS trial.[29]

Conclusions

This analysis suggests that persistence of initial $Scvo_2 < 70\%$ is associated with increased 90-day mortality of severe sepsis or septic shock, possibly because it reflects cardiac dysfunction. Subjects with $Scvo_2 < 70\%$ may benefit most from individually tailored interventions aimed at normalizing the balance between systemic oxygen delivery and consumption.

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