Targeting skeletal muscle tissue oxygenation (StO\textsubscript{2}) in adults with severe sepsis and septic shock: a randomised controlled trial (OTO-StS Study)

Olivier Nardi,\textsuperscript{1} Elizabeth Zavala,\textsuperscript{2} Claude Martin,\textsuperscript{3} Serafim Nanas,\textsuperscript{4} Thomas Scheeren,\textsuperscript{5,6} Andrea Polito,\textsuperscript{1} Xavi Borrat,\textsuperscript{2} Djillali Annane\textsuperscript{1}

ABSTRACT

Objective Evaluation of the ratio of oxyhaemoglobin to total haemoglobin in skeletal muscle (StO\textsubscript{2}) using near-infrared spectroscopy may aid in the monitoring of patients with sepsis. This study assessed the benefits and risks of targeting StO\textsubscript{2} in adults with severe sepsis or septic shock.

Design A European randomised controlled trial was performed on two parallel groups.

Setting Five intensive care units (ICU) in France, Greece, Spain and Germany were used for the study.

Participants A total of 103 adults with severe sepsis or septic shock on ICU admission were randomised (54 subjects in the experimental arm and 49 subjects in the control arm).

Interventions Haemodynamic management using an algorithm that was adapted from the 2004 Surviving Sepsis Campaign guidelines with (experimental arm) or without (control arm) targeting an StO\textsubscript{2} value greater than 80\% at a minimum of two different sites.

Outcomes The primary outcome was a composite: 7-day all-cause mortality or worsening of organ function, defined as a positive difference in Sepsis-related Organ Failure Assessment (SOFA) score between day 7 and randomisation (ie, delta SOFA >0). Secondary endpoints: 30-day mortality, duration of mechanical ventilation and vasoressor therapy up to 30 days from randomisation.

Results The study ended prematurely due to lack of funding after enrolment of 103/190 patients. Eighteen patients (33.3\%) in the experimental arm and 14 (28.6\%, \textit{P}=0.67) in the control arm died or exhibited delta SOFA >0 on day 7. The mean number of days on mechanical ventilation was 12.2±10.6 in the experimental group and 7.6±7.9 in the control group (\textit{P}=0.03). Thirty-one (57\%) patients in the experimental group and 7.6±7.9 in the control group (\textit{P}=0.03). Thirty-one (57\%) patients in the experimental arm and 14 (29\%) patients in the control arm received red cells by day 7 (\textit{P}=0.01).

Conclusion Despite the limitation related to premature termination, this study provides no data to support the routine implementation of resuscitation protocols incorporating StO\textsubscript{2} >80\% at two or more muscle sites as a target. StO\textsubscript{2}-guided therapy may be associated with prolonged use of mechanical ventilation and an increased number of red blood cell transfusions.

Trial registration number NCT00167596; Results.

INTRODUCTION

Near-infrared spectroscopy (NIRS) is based on the capacity of different chromophores in tissues to absorb light in the 700–1000 nm wavelength range. Analysis of the light emitted and received provides a non-invasive and continuous semiquantitative calculation of the ratio of oxyhaemoglobin to total haemoglobin in skeletal muscle (ie, the tissue oxygen saturation or skeletal muscle tissue oxygenation). Basal StO\textsubscript{2} values of 86\%±6\% were reported in the thenar prominence (Thenar-StO\textsubscript{2}) in healthy volunteers. Evaluation of StO\textsubscript{2} using NIRS may aid in the monitoring of patients with sepsis or septic shock.\textsuperscript{12} A low StO\textsubscript{2} value during sepsis may be associated with poor clinical outcomes\textsuperscript{3–6} and reflect altered microcirculatory perfusion.\textsuperscript{7} StO\textsubscript{2} values under 75\% in septic patients were associated with poor outcomes.\textsuperscript{1,3–5} However, there is important overlap between pathological values and the values obtained under normal conditions.\textsuperscript{1} The 2004 guidelines for the management of sepsis recommended early quantitative resuscitation protocolised care based on a set of central haemodynamic...
targets, including mean arterial pressure (MAP), heart rate, urinary output, central venous pressure (CVP) and global indices of tissue hypoperfusion (ie, central venous oxygen saturation and/or lactate clearance).\textsuperscript{3, 9} The Surviving Sepsis Campaign guidelines do not include recommendations for monitoring or targeting the microcirculation, but interventions, such as inotropes and blood products transfusion, may affect sepsis survival.\textsuperscript{4-11} Some patients continue to exhibit altered microcirculation, for example, low StO\textsubscript{2} associated with poor clinical outcomes, despite completion of early quantitative protocolised care.\textsuperscript{6} Our previous pilot study evaluated the feasibility of targeting the microcirculation via monitoring of StO\textsubscript{2} at multiple sites in patients who completed a 6-hour bundle of the Surviving Sepsis Campaign.\textsuperscript{12} The present European, multicentre, randomised trial (the Optimization of Tissue Oxygenation-StO\textsubscript{2} in Sepsis Study) assessed the benefits and risks of targeting StO\textsubscript{2} in adults with severe sepsis who were managed according to the 6-hour bundle of the 2004 Surviving Sepsis Campaign. Our hypothesis was that StO\textsubscript{2} evaluation would aid in the detection of patients who remained under-resuscitated after completion of early goal-directed therapy, and further StO\textsubscript{2}-guided haemodynamic treatment may improve their clinical outcomes.

MATERIALS AND METHODS

Study design

The ethics committees of the participating institutions in France (n=2), Greece (n=1), Spain (n=1) and Germany (n=1) approved the protocol for this multicentre, randomised, non-blinded phase II/III trial. Recruitment into the trial began in February 2006 and ended in May 2009. An independent safety, efficacy and data-monitoring committee reviewed the study protocol prior to the initiation of recruitment and periodically reviewed the accumulated study data. All authors contributed to the design of the study, recruitment of patients, and data collection and interpretation. The sponsor had no role in the design or conduct of the study, in the collection, management, analysis, or interpretation of the data, or the preparation, review, approval or submission of the manuscript. This trial is registered at ClinicalTrials.gov under NCT00167596.

Patients

Patients with suspected or confirmed sources of infection were considered for enrolment in this study if they were 18 years of age or older, admitted to the intensive care unit (ICU), met two or more of the Systemic Immune Response Syndrome criteria\textsuperscript{13} and exhibited at least one of the following signs of tissue hypoperfusion: (1) a systolic blood pressure of 90 mm Hg or less; (2) arterial lactate level of 4 mmol/L or more; (3) mottled skin; (4) urine output below 30 mL/hour for at least 1 hour; and (5) altered mental status. The time window for inclusion was less than 8 hours from the onset of the first sign of hypoperfusion. Patients younger than 18 years, pregnant women, brain-dead patients and patients who decided to withhold or withdraw from life-supporting treatments were not eligible.

Randomisation (1:1 ratio) was stratified according to the study centre and balanced by blocks of 4 using a computerised random number generator list provided by an independent statistician. Sequentially numbered, sealed and opaque envelopes were used. Each envelope was assigned to a patient and opened only after the investigator wrote the patient’s information on it and faxed the signed inclusion sheet with the patient’s randomisation details to the coordinating centre. This procedure allowed for the monitoring of treatment allocation to unique patients in an appropriate order.

Interventions

Subjects were managed using an algorithm that was adapted from the 2004 Surviving Sepsis Campaign guidelines. Briefly, patients received 500 mL of crystalloids or colloids every 30 min until their CVP was between 8 and 12 mm Hg. Vasopressor therapy (norepinephrine or epinephrine) was initiated if the MAP remained lower than 65 mm Hg, using titration until an MAP of 65–80 mm Hg was reached. Packed red blood cells were transfused if the central venous oxygen saturation (ScvO\textsubscript{2}) was lower than 70% and haematocrit levels were lower than 30%. Dobutamine was initiated at a dose of 2.5 µg/kg/min if the ScvO\textsubscript{2} was lower than 70% and the haematocrit levels were higher than 30%. Dobutamine was titrated in incremental steps of 2.5 µg/kg/min every 30 min until the ScvO\textsubscript{2} was 70% or greater without exceeding an infusion rate of 20 µg/kg/min. The dobutamine infusion rate was kept constant as soon as all of the haemodynamic goals were achieved or decreased whenever the heart rate exceeded 120/min. The CVP, MAP and ScvO\textsubscript{2} were optimised in the StO\textsubscript{2} arm, and the interventions (figure 1) targeted StO\textsubscript{2} values of 80% or greater in at least two muscular sites in the thenar, masseter and deltoid areas.

ScvO\textsubscript{2} and StO\textsubscript{2} recordings

All patients had an arterial line placed in the radial or femoral artery and a catheter in the superior vena cava. The ScvO\textsubscript{2} and StO\textsubscript{2} levels were recorded at baseline (H0) and at H2, H4, H6 and H24 following randomisation. StO\textsubscript{2} was recorded using an InSpectra Tissue Spectrometer (InSpectra 650 StO\textsubscript{2} Tissue Oxygenation Monitor, Hutchinson Technology, MN, USA) and 25 mm probes placed over the left thenar eminence (Thenar-StO\textsubscript{2}), left masseter muscle (Masseter-StO\textsubscript{2}) and left deltoid muscle (Deltoid-StO\textsubscript{2}) as described by Colin \textit{et al.}\textsuperscript{3} Measurements of the Thenar-StO\textsubscript{2} ipsilateral to a radial arterial line were collected. The StO\textsubscript{2} values were sequentially collected after 2 min of stable recording in the masseter, deltoid and thenar areas. Calibration of the spectrometer was performed once before monitoring as recommended by the
manufacturer. Adhesive shields were kept in place throughout the duration of the experiments. The StO₂ was recorded in the control group and masked throughout the study period to the investigators and medical and nursing staff members.

**Data collection and follow-up**

The patients’ prior locations (ie, community, hospital or long-term care facility), Knaus categorisation of health status, McCabe class, severity of illness as assessed by vital signs, Simplified Acute Physiology Score II, Sepsis-related Organ Failure Assessment (SOFA) score, type and dose of any intervention, routine laboratory data, arterial blood lactates and cultures of samples collected at any suspected site of infection were recorded on admission.

The vital status of the patients was followed up to 30 days from randomisation. The type and dose of any intervention, ScvO₂, and StO₂ at H0, H2, H4, H6 and H24 were systematically recorded during the first 24 hours after randomisation. The SOFA score was recorded each morning from randomisation to day 7 of the study.
Endpoints
The primary outcome was a composite endpoint of all-cause mortality on day 7 and deterioration in organ function as defined by a positive difference in the SOFA score between study day 7 and baseline (ie, delta SOFA >0).

The secondary endpoints included 30-day all-cause mortality, duration of mechanical ventilation and the use of vasopressors within 30 days after randomisation. Outcomes were assessed in a non-blinded manner.

Statistical analysis
Sample size
A total of 95 patients must be included in each arm to achieve a statistical power of 80%, considering that an absolute 20% difference in the main criterion would be clinically significant and the main criterion would be reached in 50% of the patients in the control group. However, the study ended after inclusion of 54 patients in the experimental group and 49 patients in the control group, which reduced the study power. The corresponding power to detect a 20% absolute difference if the main criterion was reached in 50% of the patients in the control group was only 54%.

Descriptive statistics
Continuous variables are reported as the means plus or minus SD or medians and IQR in cases of non-normality in variable distribution. Categorical variables are reported as numbers and percentages.

Comparative analyses
We performed intent-to-treat analysis after completion of the last follow-up of the last recruited patients. We did not plan interim analyses. We did not plan formal statistical comparisons of baseline characteristics because of the randomisation of treatment allocation. The primary outcome (composite endpoint of all-cause mortality on day 7 and deterioration in organ function as defined by a delta SOFA >0) was compared between groups by χ² tests, and relative risk and absolute difference with 95% CIs were computed. Comparisons of secondary outcomes (duration of treatment with vasopressors, duration of mechanical ventilation and mortality on day 30) were performed using χ² tests, and relative risks with 95% CIs were computed. Survival curves until day 30 were created using the Kaplan-Meier method and compared using the log-rank test. We also performed post hoc statistical analyses to compute univariate and multivariate ORs of mechanical ventilation on day 7. All tests were two sided, and the differences were significant when P values were lower than 0.05.

Results
Patients
The sponsor of this study withdrew support for the trial in May 2009 as a consequence of the global economic crisis. The trial was stopped as a result of the cessation of funding. A total of 103 patients (54% of the 190 planned) were enrolled at the study termination.

A total of 555 patients were screened for enrolment in this study from February 2006 to May 2009. A total of 103 of the 143 eligible patients, or their next of kin, provided written informed consent. Fifty-four patients were randomly assigned to the experimental arm, and 49 patients were assigned to the control arm (figure 2). Patient characteristics and demographics of the two groups were well matched at baseline (table 1). The lungs were the most common source of infection (52.5%), and 16% of the patients exhibited positive blood cultures. Eighty-six per cent of the patients in the StO₂ group and 85% in the control group were on mechanical ventilation at inclusion.

Resuscitation endpoints
Only 27 (26%) patients, 15 in the experimental arm and 12 in the control arm, exhibited ScvO₂ values below 70% at baseline (table 2). In contrast, 67 (65%) patients, 32 in the experimental arm and 35 in the control arm, exhibited StO₂ values less than 80% at two or more muscular sites. No significant differences between the two study groups were observed in any of the haemodynamic variables or lactate levels during the first 6 hours after randomisation (table 2). The interventions delivered to the patients in the experimental arm did not produce the intended effect on StO₂, with almost one-fourth of the patients unable to achieve the target of StO₂ >80% at ≥2 sites (table 2).

Primary endpoint
There were 18 (33.3%) patients who died or had a delta SOFA >0 in the experimental arm on day 7 compared with 14 (28.6%) patients in the control arm (absolute difference 4.8%; 95% CI −0.13 to 0.226; P=0.67) (table 3). There were nine (16.7%) deaths in the experimental arm and nine (18.4%) deaths in the control arm (absolute difference: 17%; 95% CI −0.13 to 0.17; P=0.69).

Secondary endpoints
There were 32 (31.1%) deaths at study day 30, 17 (31.5%) in the experimental arm and 15 (30.6%) in the control arm (P=0.90) (table 3 and figure 3). There were no significant differences in the time in vasopressor therapy between groups (5.8±13.5 days in the experimental group vs 4.1±5.8 days in the control group, P=0.40). Thirty-one (57%) patients in the experimental arm and 14 (29%) in the control arm received red cells by day 7 (P=0.01, table 3). There was a trend towards higher doses of dobutamine in the experimental group at day 1 (P=0.08, table 3). The mean number of days on mechanical ventilation up to 30 days was 12.2±10.6 days in the experimental group and 7.6±7.9 days in the control group (P=0.03) (online supplementary figure 1). Thirty-six (66.7%) and 17 (35.5%) patients were on mechanical ventilation in the experimental and control groups, respectively, on
day 7 (P<0.01, OR 3.3, 95% CI 1.2 to 8.7). This difference remained significant after adjustments for age and red cells transfusion (OR 2.9, 95% CI 1.1 to 8.1). There was no significant difference between groups for CVP, systolic blood pressure or heart rate at H6 (table 2).

**DISCUSSION**

This trial did not find any evidence for a benefit in survival or organ function from an NIRS-derived StO2-guided early goal-directed therapy. There was some evidence that the experimental algorithm of resuscitation was associated with prolonged mechanical ventilation, more blood transfusion and more use of inotropes.

The trial was terminated after the enrolment of 103 patients because of cessation in financial support. This decision was made because the 2009 global economic crisis strongly affected the trial sponsor, Hutchinson Technology. Thereafter, it was not possible to obtain the appropriate probes for StO2 monitoring, and the clinical research personnel who assisted with data management were not available. We obtained access to the database in March 2010, and the final statistical report was available before the end of 2011. Thereafter, the study chair (DA) worked for the French government as chief counsellor for the Minister of Health from May 2012 to May 2017, and he could not publish any paper in partnership with health product companies. The direction of the point estimate for the primary outcome did not favour the experimental intervention, and there was a strong indication for harm in the analysis of the secondary outcomes, despite the premature termination of the trial. Trials stopped prematurely for efficacy may result in an overestimation of the effects of an experimental intervention, but this trial was stopped as a consequence of the global economic crisis and not because of treatment efficacy.

This study was the first multicentre randomised trial of NIRS-derived StO2-guided resuscitation in sepsis or septic shock. We found no evidence to support the addition of muscle StO2 as a surrogate of microcirculation evaluation in the early phase of haemodynamic management of patients with sepsis. There was no gold standard for microcirculation available to compare our StO2-guided strategy. The experimental strategy of targeting muscle StO2 produced no survival benefit and no evidence in favour of the prevention or hastening of the resolution of organ dysfunction.

Figure 2  Study flow diagram.
interventions other than dobutamine and blood products. However, the aggressive use of dobutamine and red cell transfusion failed to normalise muscle StO2 in most patients.


The experimental algorithm was associated previously described algorithms for early goal-directed therapy. The results reflect that the global management of patients has substantially changed since the landmark study of Rivers et al. However, the treatment strategies tested in these trials did not include microcirculation as a target. Therefore, the recent challenge of early goal-directed therapy may not affect the results of our study.

The inclusion of muscle StO2 targets in the quantitative resuscitation protocolised care was associated with prolonged mechanical ventilation, which may have at least partially resulted from increased blood transfusions. Notably, the weaning of patients from mechanical ventilation followed current guidelines in both trial arms. This result encourages the monitoring of ventilation length in further studies.

We chose to target skeletal muscle StO2 values of 80% or greater because this cut-off corresponded to the lower limit of the 95% CI in healthy volunteers and discriminated between sepsis survivors and non-survivors.

We used the commonly accepted NIRS technology to measure StO2 and recorded StO2 from the three different areas to obtain a broader evaluation of tissue oxygenation. We used steady-state StO2 values rather than values obtained during vascular occlusion tests. The assessment of dynamic changes in StO2 during and immediately after limb ischaemia may be more sensitive than steady-state StO2 values to detect the extent of microcirculation dysfunction during sepsis. However, vascular occlusion test results may depend on the probe and site of measurement, and these measurements are cumbersome and inconvenient for serial assessments at very short intervals. The vascular occlusion test cannot be used to assess muscle StO2 at multiple sites.

A major objective of the initial resuscitation of patients with sepsis is to prevent the deterioration of organ function. The SOFA score is an effective method to describe organ dysfunction/failure. The delta SOFA score may be used to quantify the degree of dysfunction/failure already present on ICU admission, the degree of dysfunction/failure that appears during the ICU stay, and the cumulative insult suffered by the patient. These properties make it a good instrument in the evaluation of organ dysfunction/failure.

Patients who exhibit a 1-point increase in SOFA score during the first days of ICU had death rates >50%, which is markedly higher than patients in whom the SOFA score decreased by 1 point (mortality 23%) or remained unchanged (mortality 31%).

The overall recruitment rate of this study was low, primarily because most patients entered the ICU beyond the 8-hour time window from sepsis onset. This trial found that approximately two-thirds of patients with sepsis/septic shock exhibited baseline StO2 levels <80% at two sites, and deserve further investigation. The concept of early goal-directed therapy was challenged in three large sepsis trials. The results reflect that the global management of patients has substantially changed since the landmark study of Rivers et al. However, the treatment strategies tested in these trials did not include microcirculation as a target. Therefore, the recent challenge of early goal-directed therapy may not affect the results of our study.

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</tr>
<tr>
<td>Control arm</td>
<td>95</td>
<td>49</td>
<td>77</td>
<td>72</td>
</tr>
<tr>
<td>P value</td>
<td>0.4</td>
<td>0.8</td>
<td>0.7</td>
<td>0.9</td>
</tr>
</tbody>
</table>
the vast majority exhibited ScvO₂ over 70%. These findings confirm that abnormal StO₂ may be a common feature in sepsis/septic shock. This trial found that the inclusion of StO₂ >80% as a target in the algorithm for early goal-directed therapy likely provided no value in clinical outcomes. However, these findings do not exclude a potential benefit of targeting StO₂ in a different protocol using different cut-off values or treatment strategies. These findings do not exclude a potential benefit of targeting other surrogates of microcirculation. The Surviving Sepsis Campaign guidelines were updated twice,8 9 and the definition of sepsis was updated once,36 since our trial was performed. The 2016 updated guidelines still include no statement about targeting the microcirculation in sepsis. There are several techniques to

### Table 2

<table>
<thead>
<tr>
<th>Variable and treatment group</th>
<th>Expected number of patients</th>
<th>Actual number of patients</th>
<th>Baseline 0</th>
<th>Hours after start of therapy 2</th>
<th>Hours after start of therapy 4</th>
<th>Hours after start of therapy 6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thenar-StO₂ (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Experimental arm</td>
<td>95</td>
<td>54</td>
<td>83±10</td>
<td>83±11</td>
<td>81±16</td>
<td>81±16</td>
</tr>
<tr>
<td>Control arm</td>
<td>95</td>
<td>49</td>
<td>81±10</td>
<td>79±9</td>
<td>77±14</td>
<td>78±13</td>
</tr>
<tr>
<td>P value</td>
<td></td>
<td></td>
<td>0.3</td>
<td>0.11</td>
<td>0.17</td>
<td>0.25</td>
</tr>
<tr>
<td>Thenar-StO₂ &lt;80% (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Experimental arm</td>
<td>95</td>
<td>54</td>
<td>31</td>
<td>32</td>
<td>26</td>
<td>31</td>
</tr>
<tr>
<td>Control arm</td>
<td>95</td>
<td>49</td>
<td>37</td>
<td>43</td>
<td>43</td>
<td>54</td>
</tr>
<tr>
<td>P value</td>
<td></td>
<td></td>
<td>0.5</td>
<td>0.4</td>
<td>0.08</td>
<td>0.02</td>
</tr>
<tr>
<td>StO₂ &gt;80% over two sites (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Experimental arm</td>
<td>95</td>
<td>54</td>
<td>28</td>
<td>39</td>
<td>40</td>
<td>34</td>
</tr>
<tr>
<td>Control arm</td>
<td>95</td>
<td>49</td>
<td>29</td>
<td>33</td>
<td>36</td>
<td>23</td>
</tr>
<tr>
<td>P value</td>
<td></td>
<td></td>
<td>0.7</td>
<td>0.6</td>
<td>0.5</td>
<td>0.2</td>
</tr>
</tbody>
</table>

### Table 3

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Experimental arm</th>
<th>Control arm</th>
<th>Incremental effect (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary outcome: death at day 7 or DSOF &gt;0, n (%)</td>
<td>18 (33.3)</td>
<td>14 (28.6)</td>
<td>1.17 (0.58 to 2.34)</td>
<td>0.67</td>
</tr>
<tr>
<td>Relative risk</td>
<td></td>
<td></td>
<td>1.17 (0.58 to 2.34)</td>
<td>0.67</td>
</tr>
<tr>
<td>Absolute risk reduction</td>
<td></td>
<td></td>
<td>−4.7 (−22.6 to 13.1)</td>
<td></td>
</tr>
<tr>
<td>Unadjusted OR</td>
<td></td>
<td></td>
<td>1.25 (0.54 to 2.89)</td>
<td>0.64</td>
</tr>
<tr>
<td>Adjusted OR (on age and gender)</td>
<td></td>
<td></td>
<td>1.22 (0.52 to 2.87)</td>
<td>0.64</td>
</tr>
</tbody>
</table>

For one patient without a day 7 SOFA score, the last known SOFA score value (day 6 SOFA score) was used for the calculation of the difference (last value carried forward method). Eight patients did not have a baseline SOFA score, so the day 1 value was used as the baseline score.

*Unadjusted OR.
†Wilcoxon test.
SOFA, Sepsis-related Organ Failure Assessment.
measure/monitor microcirculation, but no trials have investigated their usefulness in guiding patient resuscitation.37

CONCLUSIONS
The present study ended prematurely due to lack of funding. Nevertheless, the current findings provide no evidence for any potential benefit from targeting muscle StO2 in addition to CVP, MAP and ScvO2. The targeting of muscle StO2 for early goal-directed therapy failed to significantly increase muscle StO2 in most patients, and it was associated with prolonged mechanical ventilation, increased blood transfusions and increased doses of dobutamine.

Author affiliations
1Intensive Care Unit, Raymond Poincaré Hospital, Assistance Publique Hôpitaux de Paris and Laboratory of Inflammation and Infection UMR 1173, University of Versailles SOY and INSERM, Garches, France
2Department of Anesthesiology and Intensive Care Medicine Hospital Clinic, University of Barcelona, Barcelona, Spain
3Department of Anesthesiology and Intensive Care Medicine, Hôpital Nord, Assistance Publique Hôpitaux de Marseille, University of the Mediterranean, Marseille, France
4Critical Care Department, Evangelismos General Hospital, Athens, Greece
5Department of Anesthesiology and Intensive Care Medicine, University Hospital Rostock, Rostock, Germany
6Department of Anesthesiology, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands

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Contributors ON and DA designed the study, performed the statistical analysis and interpretation of data, and drafted the manuscript. EZ, CM and SN designed the study, and participated in patient recruitment and data acquisition. TS designed the study, and participated in data analysis, patient recruitment, data acquisition and revision of the manuscript. AP and XB participated in patient recruitment, study design and data acquisition. All authors read and approved the final manuscript.

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Competing interests None declared.

Patient consent Obtained.

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Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement The data cannot be deposited in public repositories since the agreement of the Ethics Committee did not cover this aspect. However, we fully agree to discuss and share key data with interested individuals (djillali.annane@aphp.fr).

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Olivier Nardi, Elizabeth Zavala, Claude Martin, Serafim Nanas, Thomas Scheeren, Andrea Polito, Xavi Borrat and Djillali Annane

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