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Goal-Directed Intraoperative Therapy Reduces Morbidity and Length of Hospital Stay in High-Risk Surgical Patients*

Abele Donati, MD; Silvia Loggi, MD; Jean-Charles Preiser, MD, PhD; Giovanni Orsetti, MD; Christopher Münch, MD; Vincenzo Gabbanelli, MD; Paolo Pelaia, MD; and Paolo Pietropaoli, MD†

Background: Postoperative organ failures commonly occur after major abdominal surgery, increasing the utilization of resources and costs of care. Tissue hypoxia is a key trigger of organ dysfunction. A therapeutic strategy designed to detect and reverse tissue hypoxia, as diagnosed by an increase of oxygen extraction (O_2ER) over a predefined threshold, could decrease the incidence of organ failures. The primary aim of this study was to compare the number of patients with postoperative organ failure and length of hospital stay between those randomized to conventional vs a protocolized strategy designed to maintain $O_2ER < 27\%$.

Methods: A prospective, randomized, controlled trial was performed in nine hospitals in Italy. One hundred thirty-five high-risk patients scheduled for major abdominal surgery were randomized in two groups. All patients were managed to achieve standard goals: mean arterial pressure > 80 mm Hg and urinary output > 0.5 mL/kg/h. The patients of the “protocol group” (group A) were also managed to keep $O_2ER < 27\%$.

Measurements and main results: In group A, fewer patients had at least one organ failure ($n = 8$, 11.8%) than in group B ($n = 20$, 29.8%) [$p < 0.05$], and the total number of organ failures was lower in group A than in group B (27 failures vs 9 failures, $p < 0.001$). Length of hospital stay was significantly lower in the protocol group than in the control group (11.3 ± 3.8 days vs 13.4 ± 6.1 days, $p < 0.05$). Hospital mortality was similar in both groups.

Conclusions: Early treatment directed to maintain O_2ER at $< 27\%$ reduces organ failures and hospital stay of high-risk surgical patients.

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Key words: central venous saturation; goal-directed therapy; high-risk surgical patient; oxygen extraction ratio

Abbreviations: ASA = American Society of Anesthesiologists; CVP = central venous pressure; HR = heart rate; MAP = mean arterial pressure; NS = not significant; O_2ER = oxygen extraction ratio; O_2ERe = oxygen extraction ratio estimated; PRBC = packed RBC; SaO_2 = arterial oxygen saturation; $ScvO_2$ = central venous saturation

The development of postoperative organ failures severely affects the prognosis of surgical patients and substantially increases the utilization of resources and cost of care. The prevalence of organ failures ranges from 27 to 77%. Length of stays in the ICU and in the hospital as well as postoperative mortality are largely increased in “high-risk” patients, for whom preoperative risk factors are unavoidable.^{1,2} Therefore, the use of early and efficient therapeutic strategies able to detect and to treat potential triggers of organ failures, such as tissue

hypoperfusion, is particularly important in this high-risk population. If hypoperfusion is not adequately managed, tissue hypoxia could occur, resulting from an impairment of the adaptive mechanisms of myocardial contractile function, under the influence of inflammatory mediators, and the peripheral tissues will then increase their oxygen extraction (O_2ER).^{1–4} When O_2ER increases over a threshold value, venous oxygen saturation will decrease and lactic acidosis can ultimately occur.⁵ Hence, the use of O_2ER calculated from arterial and mixed venous oxygen

saturation as a therapeutic goal is appropriate to monitor goal-directed hemodynamic strategies because it reflects the balance between oxygen delivery and consumption.^{6,7} The ensuing therapeutic approach will then imply the application of a standardized algorithm as soon as O_2ER reaches a predefined threshold. This concept, which differs from the “preoperative optimization of oxygen delivery”^{8,9} or the strategies aiming at the maintenance of stroke volume,¹⁰ was already assessed in mixed populations of critically ill patients^{11,12} and patients with early sepsis.¹³

The interpretation of venous oxygen saturation is eventually similar when mixed venous blood drawn from a pulmonary artery catheter is replaced by venous blood drawn from a central venous line.¹⁴ Indeed, evidence suggests that a multifaceted goal-directed strategy, including fluid challenge, blood transfusion, and inotropes titrated to keep central venous oxygen saturation higher than a predetermined threshold of 70%, was associated with decreased mortality and rate of organ failures when applied from the early phase of septic shock or severe sepsis.¹³ The aim of the present multicenter, prospective, randomized study was to compare the outcomes of patients randomized to a conventional management or to a therapeutic strategy guided by O_2ER estimate (O_2ERe) calculated from the arterial oxygen saturation (SAO_2) and central venous saturation ($ScvO_2$). Specifically, we hypothesized that the use of a goal-directed protocol aimed at maintaining the O_2ERe below a previously defined “critical” (able to discriminate survivors from nonsurvivors) value of 27%¹⁵ during surgical interventions in high-risk patients will reduce the rate of postoperative organ failures, hospital length of stay, and mortality, as compared with the standard management based on the monitoring of mean arterial pressure (MAP), central venous pressure (CVP), and urinary output.^{16,17}

*From the Department of Neuroscience, Anesthesia, and Intensive Care Unit (Drs. Donati, Loggi, Orsetti, Münch, Gabbanelli, and Pelaia), Marche Polytechnic University, Ancona, Italy; Department of Intensive Care (Dr. Preiser), University Hospital of Liege, Belgium; and Department of Anesthesia and Intensive Care (Dr. Pietropaoli), University “La Sapienza,” Rome, Italy. †A list of participating hospitals is given in the Appendix. The authors have no conflicts of interest to disclose. Manuscript received March 9, 2007; revision accepted September 10, 2007.

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Correspondence to: Abele Donati, MD, Clinica di Anestesia e Rianimazione Clinica, Ospedali Riuniti Umberto I, Lancisi, Salesi-Università Politecnica delle Marche, Via Conca 71, 60020 Torrette di Ancona, Italy; e-mail: donati.abele@tiscali.it
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MATERIALS AND METHODS

This prospective, randomized, controlled, multicenter study was approved by the Hospital Ethical Committee of Ancona for all the institutions involved in the trial. Written informed consent was obtained preoperatively from the patients. The study was performed in nine Italian hospitals during 48 months. In these hospitals, major abdominal surgery and abdominal aortic surgery were routinely performed, and these patients were usually admitted after surgery in the ICUs (5 to 12 beds).

Inclusion and Exclusion Criteria

Patients scheduled for elective abdominal extensive surgery or abdominal aortic surgery were eligible. After enrollment, the patients were randomized to one of the two groups of treatment (group A or group B) by a telephone system on a 24 h/d, 7 d/wk basis. Randomization was based on a permuted-block algorithm, allowing stratification for each center. The exclusion criteria from the study were age < 16 years and preexistent neurologic or malignant hematologic diseases.

Study Protocol

In preparation for surgery, the patients were equipped with central and peripheral venous and arterial catheters, respectively. Standard monitoring included continuous recording of ECG, body temperature, heart rate (HR), pulse oximetry, and arterial BP. CVP, $ScvO_2$, arterial blood gas levels, lactate concentration, body temperature, and urinary output were recorded hourly. Hemoglobin concentration was measured when deemed necessary by the anesthesiologist. For the purpose of the study, blood gas levels measured on arterial and central venous samples, arterial lactate, and O_2ERe ($SAO_2 - ScvO_2/SAO_2$) were recorded after induction of anesthesia, hourly after cutaneous incision, throughout surgery, half an hour after the end of anesthesia, hourly during the first 6 h of the postoperative period, and on postoperative day 1 (Fig 1).

In both groups, the patients were managed to achieve predefined standard goals: MAP > 80 mm Hg, urinary output > 0.5 mL/kg/h, and CVP from 8 to 12 cm H_2O until the first postoperative day. The patients of the “protocol group” (group A) were managed to keep O_2ERe < 27%, following algorithms detailed in Figure 1. In brief, a fluid challenge (colloids, 250 to 1,000 mL infused over 30 min to restore CVP to at least 10 mm Hg), dobutamine (incremental doses of 3 μ g/kg/min up to 15 μ g/kg/min), and/or packed RBCs (PRBCs) [in cases of hemoglobin concentration < 10 g/dL or intraoperative hemorrhage > 1,000 mL] could be administered. Colloids were preferred to crystalloids because this is consistent with standard practice at our institutions. There was no specific requirement regarding the type of anesthesia in any of the groups.

Outcome Measures

The primary end point of this study was the number of patients who had at least one new postoperative organ failure described using the sequential organ failure assessment score recorded daily during the stay in the ICU (Table 1), with the expectation of a 50% reduction with the use of the tested therapeutic protocol. Secondary end points included the number of organ failures during the ICU stay, length of hospital stay, and hospital mortality.

Statistical Analysis

A total of 130 patients was the calculated sample size needed to detect, in a one-sided test performed with a 0.05 type I

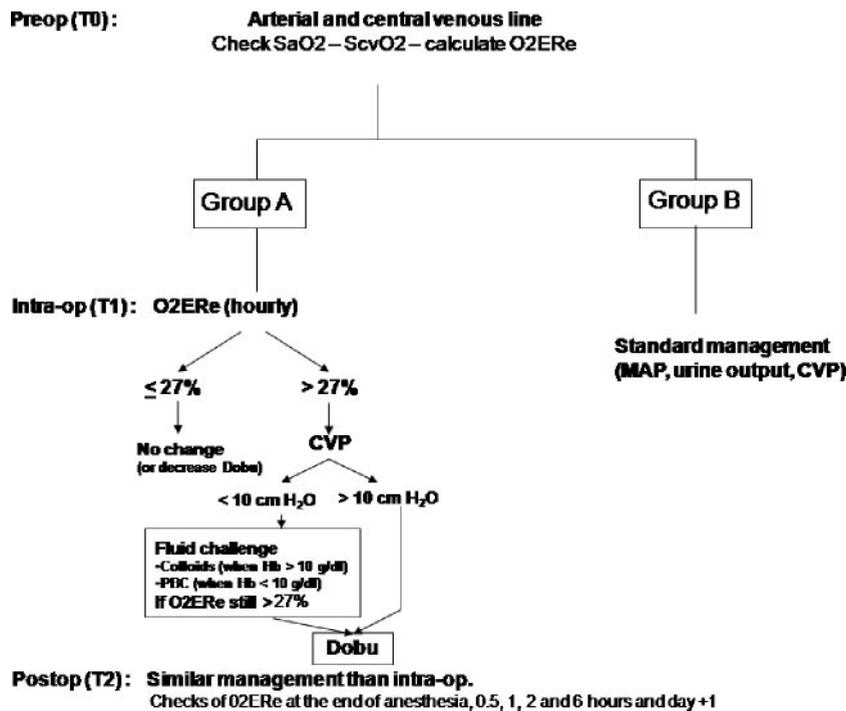


FIGURE 1. Therapeutic protocol. In addition to the standard management (group B), a standardized therapeutic protocol designed to restore and/or keep O₂ERe < 27% was applied to patients randomized to group A. Intra-op = intraoperative; Preop = preoperative; Postop = postoperative.

error, an absolute difference between the two groups on the number of patients who had at least one new postoperative organ failure of 20% with a 80% power, assuming a 40% of patients with complications in the control group (based on an historical database). A one-sided formulation was chosen to compute the

sample size because the trial was designed to test whether therapy in the protocol group (group A) was more effective than therapy in the control group (group B), and we had no interest in formally demonstrating the opposite alternative hypothesis. At each time point, means and SDs for continuous variables were calculated for both groups of patients and were compared using two-way analysis of variance, with Bonferroni posttest for multiple comparisons to assess differences at each time between group A and group B. Fisher exact test was used to test differences in therapeutic interventions and in outcome, measured as death and organ failures. Student *t* test was used to test differences between groups and differences in the length of hospital stay; *p* values were considered significant if < 0.05 (GraphPad 2.0; GraphPad; San Diego, CA).

Table 1—Definition of Organ Failures*

Cardiocirculatory: MAP < 80 mm Hg and CVP > 18 mm Hg and urinary output < 0.5 mL/kg/h; acute myocardial infarction†; myocardial ischemia defined as an ST-segment depression or elevation > 1 mm‡
Respiratory: mechanical ventilation or requirement for continuous positive airway pressure for > 24 h
Renal: serum creatinine concentration > 2 mg/dL or need for renal replacement therapy
Hepatic: ALT and AST > 80 UI and total bilirubin > 2 mg/dL or AST and ALT > 200 or total bilirubin > 3 mg/dL
Hematology: platelets < 50,000 × 10 ³ /μL; leukocytosis < 2,500 or > 30,000 × 10 ³ /μL; disseminated intravascular coagulation, defined as fall of platelet count > 50% with increase of prothrombin time ≥ 50% or increase of partial thromboplastin time > 20% and increase d-dimer > 500 ng/mL
CNS: Glasgow coma scale score < 7

*Modified from Gattinoni et al.¹¹ ALT = alanine aminotransferase; AST = aspartate aminotransferase.

†Myocardial infarction was defined when ECG (ST-segment elevation, new bundle-branch block, 20% have other changes, eg, ST-segment depression or T-wave inversion), and an increase of troponin levels > 0.2 ng/mL were both present.

‡ECG was performed every day for the first 3 postoperative days, then after 3 days and when the clinician judged necessary.

RESULTS

Three hundred twenty-four patients were assessed for eligibility, but 189 patients were excluded: 153 patients because they did not meet inclusion criteria, and 36 patients because they refused to participate in the study. One hundred thirty-five patients were eventually enrolled in the study: 68 patients in group A, and 67 patients in group B. All the patients enrolled concluded the study and were included in the analysis.

The patients of both groups did not differ in terms of demographic variables: age, male/female ratio, American Society of Anesthesiologists (ASA) class,¹⁸ type and duration of surgical procedures, and blood

Table 2—Patient Characteristics*

Characteristics	Group A	Group B	p Value
Patients, No.	68	67	
Age, yr	66.0 ± 7.7	66.1 ± 7.1	NS
Male/female gender, No.	45/23	43/24	NS
Patients subclassified according to ASA class			
ASA class II	9	11	NS
ASA class III	49	45	NS
ASA class IV	10	11	NS
Type of surgery			
Abdominal aortic aneurysm	21	19	NS
Intestinal resection for cancer	32	38	NS
Duodenopancreatectomy	7	5	NS
Aortoiliac bypass	8	5	NS
Total	68	67	NS
Operative time, h	3.4 ± 1.1	3.3 ± 1.0	NS
Blood loss, mL	340 ± 178	354 ± 196	NS

*Data are presented as mean ± SD unless otherwise indicated.

loss (Table 2). The assigned intervention could be performed and follow-up was complete for each randomized patient. There was no patient excluded from the analysis.

Therapeutic Interventions

Fluid challenge with colloids was administered to 27 patients in each group (1,940 ± 673 mL vs

1,805 ± 611 mL and 2,191 ± 377 mL vs 2,209 ± 381 mL, during and after surgery, for groups A and B, respectively; $p =$ not significant [NS]) [Fig 2]. Remarkably, patients in group A received the fluid challenge earlier than the patients in group B (during operation, 10 patients vs 8 patients; during and after operation, 9 patients vs 6 patients; only after surgery, 8 patients vs 13 patients of groups A and B, respectively). Similarly, 10 patients in each group received PRBCs (260 ± 130 mL per patient vs 271 ± 173 mL per patient for groups A and B, respectively; $p =$ NS), but earlier in group A (more transfusions during operation) than in group B (more transfusions after operation). In contrast, dobutamine was administered much more often in group A (30 patients, 44.1%) than in group B (3 patients, 4.5%) [$p < 0.01$], during (10 patients vs 1 patient), during and after (11 patients vs 1 patient), or only after surgery (9 patients vs 1 patient). The mean dose of dobutamine was also higher in group A (2.6 ± 4.0 µg/kg/min vs 0.4 ± 2.2 µg/kg/min and 2.1 ± 3.7 vs 0.3 ± 1.7 µg/kg/min during and after surgery for groups A vs B, respectively; $p < 0.001$). Both fluid challenge and dobutamine infusion were used in more patients of group A than group B (9 patients vs 0 patients and 6 patients vs 1 patient during and after surgery, respectively; $p < 0.001$).

Hemodynamic and Oxygen-Derived Variables

Importantly, most of the standard variables used to monitor the hemodynamic status (MAP, urinary

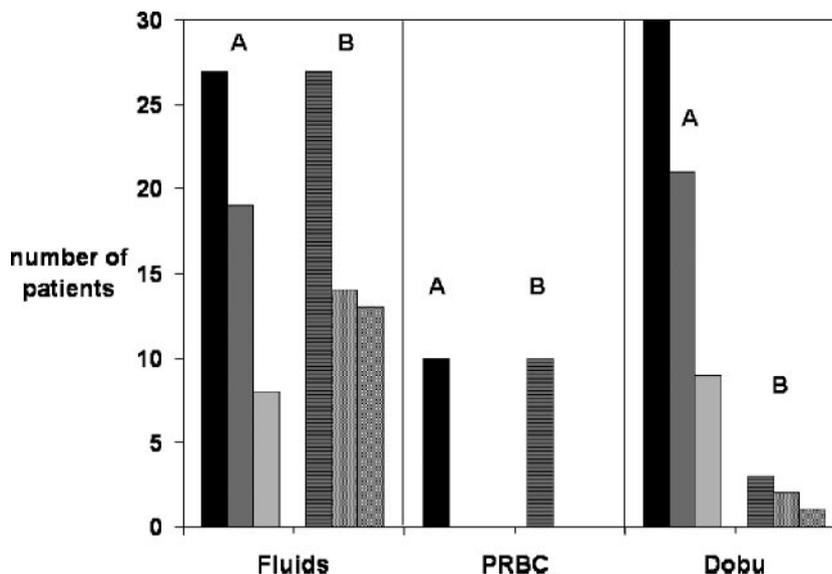


FIGURE 2. Therapeutic interventions. Total fluids, PRBC, and dobutamine (Dobu) administered to the patients randomized to standard care (group B [B]) and to patients assigned to a standardized therapeutic protocol designed to restore and/or keep $O_2ERe < 27\%$ (group A [A]). The number of patients receiving fluid challenges (left panel), PRBCs (middle panel), and dobutamine (right panel) are shown. For each set of data, the number of patients recorded during the total period of observation (left bars), the intraoperative period (middle bars), and the postoperative period (right bars) are shown.

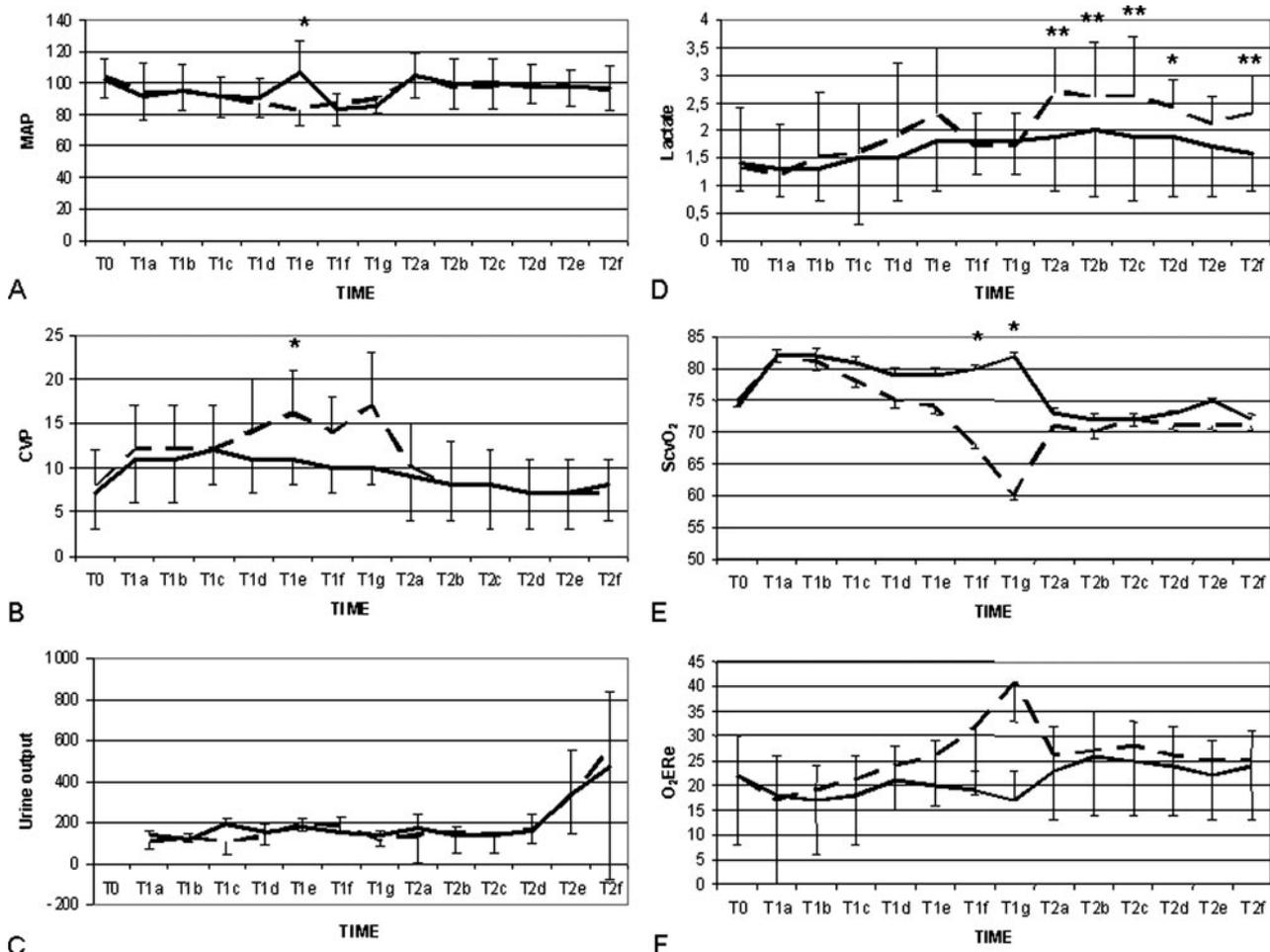


FIGURE 3. Time course of MAP (mm Hg), CVP (mm Hg), urinary output (mL/h), blood lactate (mmol/L), ScvO₂ (%), and O₂ERe recorded after induction of anesthesia (T0), hourly after cutaneous incision (T1a–f), throughout surgery, during the first 6 h of the postoperative period (T2a–f), and on postoperative day 1. Group A (O₂ERe group) is represented by solid line, and group B (standard management group) is represented by dotted line. Data are shown as mean ± SD. *p < 0.05 and **p < 0.01 between groups.

output [Fig 3, top left, A, and bottom left, C)], HR, PaO₂/fraction of inspired oxygen, and body temperature were similar in both groups. Importantly, CVP was higher in group B than in group A during the late postoperative time (Fig 3, center left, B). O₂ERe and lactate were higher in group B than group A, and conversely ScvO₂ was higher in group A than group B (Fig 3, top right, D, to bottom right, F).

Rate of Organ Failures and Outcome

Dramatic differences in the rate of organ failures and in the length of hospital stay were seen (Fig 4). In group A, fewer patients had at least one organ failure (n = 8, 11.8%) than in group B (n = 20, 29.8%) [p < 0.05], and the total number of organ failures was lower in group A than in group B (27 failures vs 9 failures, p < 0.001). The incidence of

each type of organ failure was decreased, with the exception of respiratory failure. There was no dysfunction of the CNS noted in any group. These impairments in organ function were mostly transient. However, the length of hospital stay was significantly lower in group A than in group B (11.3 ± 3.8 days vs 13.4 ± 6.1 days, p < 0.05), but hospital mortality was similar in both groups (2.9% and 3.0% for groups A and B, respectively), and this mortality rate was actually expected from the preoperative status of the patients.

DISCUSSION

This study clearly confirms that a goal-directed therapy titrated to keep O₂ER ratio calculated from central venous sample (O₂ERe) value lower than a

Type of organ failures

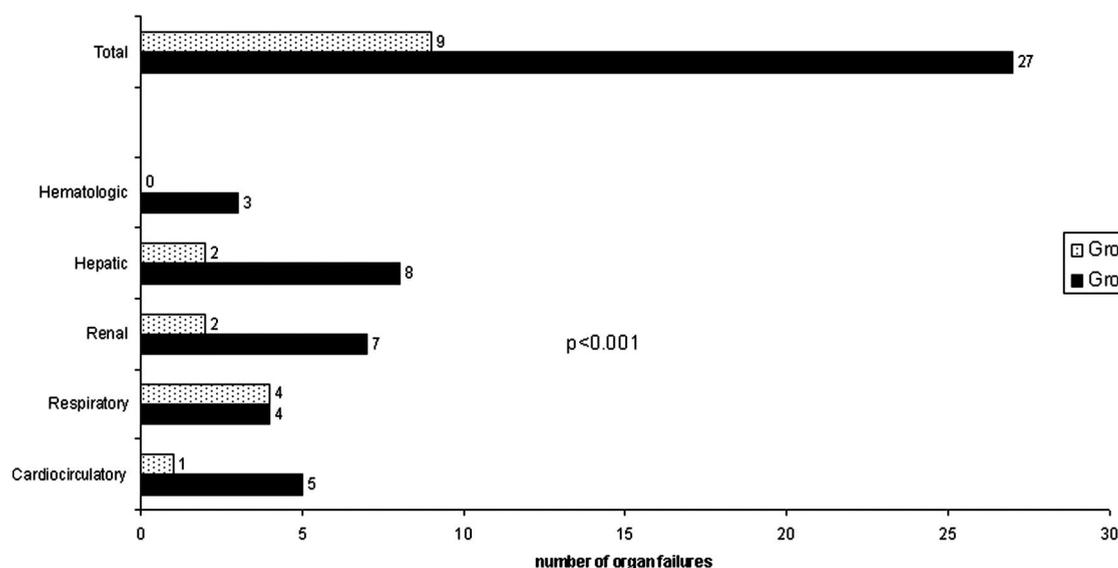


FIGURE 4. Number and type of organ failures observed in group A (O₂ERe group, dotted column) and in group B (standard management group, black column). The total number of organ failures was lower in group A than in group B ($p < 0.01$). The incidence of each type of organ failure was decreased, with the exception of respiratory failure.

predefined threshold of 27% reduces the incidence of postoperative organ failures and length of hospital stay. The critical value of 27% for O₂ERe, as representative of the hypoxic threshold, was already reported by previous investigators¹⁵ as a predictor of survival in high-risk surgical patients. These encouraging results have been simply achieved by an earlier and more aggressive hemodynamic management, which does not require any additional invasive or expensive equipment or procedures and is operator independent. Importantly, the feasibility of the tested protocol was confirmed in the present trial because each patient randomized to the “aggressive” therapeutic strategy was treated as initially assigned, and because O₂ERe was always maintained below the critical value in patients randomized to the group A, as recommended. Due to the close monitoring, there was less concern for the incidence of adverse events such as pulmonary edema, arrhythmia, and increase of HR in spite of dobutamine infusion.

The preoperative and postoperative characteristics of patients studied here were very usual in the setting of scheduled major abdominal surgery in terms of age, gender, duration of surgical procedure, ASA class, and incidence of postoperative organ failures with conventional management.^{2,8,9,19–21} The issue of whether the therapeutic approach tested here may decrease postoperative mortality would require a much larger sample of patients. However, as the organ failures are usually transient and as the

crude mortality is low, we would not expect a major impact of this therapeutic strategy on vital outcome. In contrast, the cost-effectiveness ratio of this therapeutic strategy, although not assessed, is probably very advantageous. Pearse and colleagues²² found that early-goal directed therapy was effective to reduce complications after major surgery. In any case, they used hemodynamic monitoring to assess oxygen availability, but this is not always available in all hospitals.

We speculate that the prevention of tissue hypoxia as soon as a warning signal is detected (*ie*, increase in O₂ERe) in patients for whom oxygen utilization cannot be adapted explains these results and may also help to prevent postoperative organ failures in high-risk patients surgical patients.^{1,3,23} Although not investigated in the present trial, the underlying mechanisms of tissue hypoxia could involve an impairment in myocardial contractility, a loss of vaso-genic peripheral control leading to a large heterogeneity in perfusion, coagulation abnormalities, vascular permeability, endothelial dysfunction,²⁴ and a reduction of the capacity of tissues to adapt the oxygen utilization to the supply due to anesthetic drugs and hypothermia.^{24,25} In any case, increasing oxygen availability by correcting hypovolemia and/or an inadequately low cardiac output is the only possibility to reverse ongoing tissue hypoxia. The timing of therapeutic intervention is definitely a key issue, as shown by the data of the present trial, when the same

amount of fluids and PRBC was administered earlier in group A than in group B. Only the dose and the frequency of use of dobutamine were higher in group A than in group B. However, the dose was much lower than in some previous studies,^{12,15,19,26} where the hemodynamic target could not be achieved with 20 to 25 $\mu\text{g}/\text{kg}/\text{min}$ of dobutamine. As cardiac function was often compromised in the patients studied here, the frequent use of dobutamine was actually expected. As the preoperative use of beta-blockers was similar in both groups (data not shown), the absence of difference in HR rate in spite of a more frequent use of higher doses of dobutamine in group A than group B is somewhat surprising. A partial explanation could be related to the earlier fluid load in group A, thereby preventing the need for a compensatory increase in HR. The doses of dobutamine required were lower than in other studies,^{2,12} in which the therapeutic goal was cardiac output and oxygen delivery, that we did not record. The present data suggest that the optimization of O_2ER could be achieved with low doses of dobutamine in conjunction with appropriate fluid loading. Dobutamine was preferred over other tested agents such as adrenaline or dopexamine⁸ because we hypothesized that a transient myocardial dysfunction was a significant and correctable causative factor of tissue hypoxia unresponsive to fluid loading. However, we cannot anticipate the effects of other agents with positive inotropic effects.

The efficacy of therapies guided to reach a hemodynamic goal was usually confirmed in conditions of tissue hypoperfusion and possible early and reversible tissue hypoxia such as the initial phases of trauma, severe sepsis, and surgery,^{2,8-10,13,15,21-23,27} but was no longer confirmed in protracted conditions, likely associated with irreversible organ dysfunctions perhaps related to cell death.^{11,12,26} We might explain the discrepancy between these latter findings and the success of the approach tested here by the control and rapid prevention of tissue hypoxia as soon as a warning signal was believed, in contrast to the indiscriminate use of a standard therapy with its potential side effects regardless of the presence or the stage of tissue hypoxia. Therefore, the data presented here cannot be extrapolated to conditions where more complex impairments of oxygen utilization and other mechanisms of cell injury can occur. Indeed, the interpretation of O_2ERe can then become much more complex than during surgery. In any case, also a metaanalysis²⁸ showed that interventions aimed to hemodynamic optimization of high risk surgical patients reduce mortality, with an odd ratio of 0.61 (95% confidence interval, 0.46 to 0.81).

In this study, we compared two potential indexes of tissue level oxygenation: $\text{ScvO}_2/\text{O}_2\text{ERe}$ and arterial

lactate. Consistently, lactate rose later than ScvO_2 and O_2ERe and only when these were not corrected aggressively (in group B). Interestingly, organ failures were observed much more often in patients with at least one elevated lactate value (24 organ failures in 53 patients) than in patients without any elevation of lactate (6 organ failures in 82 patients) [$p < 0.001$]. The changes in ScvO_2 and O_2ERe are transient, however, while the later increase in lactate lasts longer. Taken together, these findings are consistent with the basic assumption of tissue hypoperfusion that leads to hypoxia, decreased oxygen consumption, and eventual production of lactate, cell injury, and organ failure.

CONCLUSIONS

In conclusion, during major abdominal surgery, the findings presented here argue for a close monitoring of O_2ER calculated from central venous blood sample and for the routine use of a therapeutic algorithm designed to correct an increase in $\text{O}_2\text{ER} > 27\%$.

APPENDIX

Hospitals Participating the Study

Ancona University Hospital; Fano Hospital; Perugia University Hospital; Varese University Hospital; "Porta Roma" Hospital, Verona; San Salvatore Hospital, Pesaro; "Galliera" Hospital, Genova; Jesi Hospital; and Senigallia Hospital.

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