The Use of a Postoperative Morbidity Survey to Evaluate Patients with Prolonged Hospitalization After Routine, Moderate-Risk, Elective Surgery

E. Bennett-Guerrero, MD*, I. Welsby, FRCA§, T. J. Dunn, MD†, L. R. Young, MD†,
T. A. Wahl, MD†, T. L. Diers, MD†, B. G. Phillips-Bute, PhD‡, M. F. Newman, MD†, and
M. G. Mythen, MD§

*Department of Anesthesiology, The Mount Sinai Medical Center, New York, New York; Departments of †Anesthesiology and ‡Biostatistics, Duke University Medical Center, Durham, North Carolina; and §Department of Anaesthesia, University College London Hospitals, London, England

Vital healthcare resources are devoted to caring for patients with prolonged hospitalization after routine, moderate-risk surgery. Despite the significant cost, little is known about the overall incidence and pattern of complications in these patients. Four hundred thirty-eight patients undergoing a diverse group of routine, moderate-risk, elective surgical procedures were enrolled into a prospective, blinded, cohort study. Complications were assessed using a postoperative morbidity survey. The main outcome was postoperative complication, defined as either in-hospital death or prolonged postoperative hospitalization (>7 days). The mortality rate was 1.6%. Postoperative complications occurred in 118 patients (27% [95% CI 23–31]). Complications frequently observed in these patients included: gastrointestinal 51% (42–60), pulmonary 25% (17–33), renal 21% (14–28), and infectious 13% (7–19). Most complications were not directly related to the type/site of surgery. Indices of tissue trauma (blood loss [$P < 0.001$], surgical duration [$P = 0.001$]) and tissue perfusion (arterial base deficit [$P = 0.008$], gastric pHi [$P = 0.02$]) were the strongest intraoperative predictors of complications. Despite a low mortality rate, we found that complications after routine, moderate-risk, elective surgery are common and involve multiple organ systems. Our 9-point survey can be used by healthcare providers and payers to characterize postoperative morbidity in their respective settings. **Implications:** Little is known about the overall incidence and pattern of complications in patients with prolonged hospitalization after routine, elective surgery. We prospectively assessed these complications using a novel postoperative morbidity survey. The postoperative morbidity survey can be used in future clinical outcome trials, as well as in routine hospital-based quality assurance.

(Anesth Analg 1999;89:514–9)

Significant healthcare resources are used to provide care to patients with prolonged postoperative hospitalization (1). Clinicians, hospitals, and healthcare payers are increasingly focused on reducing "unnecessary" days of hospitalization after surgery. Despite the need for scientific data, no published studies have prospectively ascertained the incidence and pattern of complications in a diverse group of surgical patients with prolonged hospitalization.

Previous efforts at characterizing postoperative morbidity have been limited to very high-risk surgical procedures (e.g., cardiac surgery) (2,3), intensive care unit patients (4), complications specific to a particular surgical procedure or study objective (5–12), or severe life-threatening complications (3,13). No previous study was designed to prospectively evaluate the overall pattern and incidence of postoperative complications in patients with prolonged hospitalization.

We prospectively observed a diverse group of surgical patients and systematically assessed them for morbidity using predefined criteria. As a secondary objective, we tested the hypothesis that intraoperative indices of tissue hypoperfusion (e.g., gastric pHi, analysis of arterial blood gas) are good predictors of postoperative morbidity.

Methods

After institutional review board approval and informed consent, patients scheduled to undergo major,

elective, noncardiac surgery were enrolled at Duke University Medical Center, Durham, NC, in a prospective, blinded cohort study from January through May 1996.

Inclusion criteria were patients undergoing the following elective surgical procedures under general anesthesia: orthopedic (revision hip arthroplasty, fusion/instrumentation of multiple lumbar or thoracic vertebrae), general (any laparotomy expected to exceed 2 h duration, including partial hepatectomy, pancreatic surgery, reoperative colon surgery), urological (radical prostatectomy, radical cystectomy, radical nephrectomy), vascular (abdominal aortic aneurysm repair), and gynecological (cancer debulking procedure, abdominal hysterectomy). These procedures were selected for several reasons: 1) they are routinely performed surgeries, 2) they represent a diverse group of procedure types, and 3) a retrospective analysis at Duke University Medical Center found these procedures to be associated with prolonged hospitalization.

Exclusion criteria included age <18 yr, emergency surgery, regional anesthesia, any religious/ethical prohibition from receiving blood products, or contraindication to the placement of a naso- or orogastric tube.

Patients were cared for by clinicians who were blinded to study measurements and were not part of the investigative team. At the conclusion of surgery, clinically available cardiovascular variables and indices of tissue perfusion were recorded. Gastric tonometry was performed in a manner consistent with the manufacturer's guidelines and package insert. Briefly, after the induction of anesthesia and insertion of a gastric tonometer (TRIP NGS Catheter; Tonometrics, Tewksbury, MA), saline was introduced into the tonometer's balloon and allowed to equilibrate for at least 90 min. The saline was removed at the conclusion of surgery, and PCO_2 was measured using a blood gas analyzer. pHi was calculated according to the gastric tonometer's manufacturer's guidelines.

As a secondary study objective, we tested the hypothesis that intraoperative indices of tissue hypoperfusion (e.g., gastric pHi, arterial base excess) are good predictors of postoperative morbidity. Several indices of regional and global tissue hypoperfusion were collected at the end of surgery and compared with routinely measured and clinically available hemodynamic variables (e.g., heart rate) and indices of oxygen delivery (e.g., hematocrit, oxygen saturation). These variables were viewed as potential predictors of postoperative morbidity and were not used as an end point of how patients had fared during surgery.

Patients were prospectively observed from the day of surgery until either discharge from the hospital or death. Postoperative length of stay was defined as the number of days from the day of operation (Day 0) until hospital discharge or death. Postoperative complication was the primary outcome of this study and was defined as either in-hospital death or postoperative length of stay >7 days. Seven days was chosen as a reasonable cutoff because a pilot retrospective analysis of these same surgical procedures at Duke University Medical Center revealed that the median postoperative duration of hospitalization for each of the individual procedures was ≤7 days. Furthermore, this same analysis revealed that most patients whose postoperative hospitalization exceeded 7 days had evidence of persistent organ dysfunction.

Hospitalized patients were evaluated on Postoperative Days 5, 8, and 15 using the predefined criteria listed in Table 1. Each assessment was conducted by speaking with the patient, examining the patient, reviewing the medical record, and/or consulting with the patient's caregivers. The criteria used in this postoperative morbidity survey (POMS) were selected to identify both severe complications (e.g., pulmonary failure/acute respiratory distress syndrome) and more subtle morbidity that could delay discharge from the hospital (e.g., moderate pulmonary dysfunction necessitating supplemental oxygen therapy). These criteria were not intended to represent the "gold standard" for assessing a given complication. Our goal was to design a survey that was not cumbersome, not complicated, and could be used routinely to screen thousands of patients for multiple complication types. In addition, other possible reasons for delay in hospital discharge were recorded as a free text entry. We included a free text entry space on the data sheet to avoid a bias toward recording only predefined complications.

Statistical calculations and analyses were performed using the SAS software system version 6.12 (SAS Institute Inc, Cary, NC). Statistical significance was set at $\alpha = 0.05$. Given an estimated incidence of 25% for the primary end point from pilot data, a sample size of at least 400 patients was estimated to generate enough events (100) to allow for relatively narrow (approximately 10%) 95% CIs for the specific complication types observed. Relationships among continuous variables were tested by using linear regression, and associations among categorical variables were tested using the contingency table χ^2 test. This study was not designed to rigorously assess all of the possible perioperative predictors of postoperative complications; therefore, a full multivariate analysis was not deemed appropriate. Nevertheless, as a secondary study objective, we tested for univariate associations between clinically available predictors and the primary outcome, i.e., postoperative complications, using a series of univariate (unadjusted) logistic regression models.

Table 1. Postoperative Morbidity Survey

Morbidity type	Criteria
Pulmonary	*De novo* requirement for supplemental oxygen or other respiratory support (e.g., mechanical ventilation or CPAP)
Infectious	Currently on antibiotics or temperature >38 °C in the last 24 h
Renal	Presence of oliguria (<500 mL/d), increased serum creatinine (>30% from preoperatively), or urinary catheter in place for a nonsurgical reason
Gastrointestinal	Unable to tolerate an enteral diet (either by mouth or via a feeding tube) for any reason, including nausea, vomiting, and abdominal distention
Cardiovascular	Diagnostic tests or therapy within the last 24 h for any of the following: *de novo* myocardial infarction or ischemia, hypotension (requiring pharmacological therapy or fluid therapy >200 mL/h), atrial or ventricular arrhythmias, or cardiogenic pulmonary edema
Neurological	Presence of a *de novo* focal deficit, coma, or confusion/delirium
Wound complication	Wound dehiscence requiring surgical exploration or drainage of pus from the operation wound with or without isolation of organisms
Hematological	Requirement for any of the following within the last 24 h: packed erythrocytes, platelets, fresh-frozen plasma, or cryoprecipitate
Pain	Surgical wound pain significant enough to require parenteral opioids or regional analgesia

CPAP = continuous positive airway pressure.

Results

Four hundred thirty-eight patients were enrolled in the study over the 5-mo period. Preoperative demographics and intraoperative characteristics for the study population are presented in Table 2. Within the first week after surgery, 320 patients (73%) had been discharged to home alive (median length of stay of 5 days). In contrast, postoperative complication (death or prolonged hospitalization) occurred in 118 patients (27%). In-hospital death occurred in 7 patients (1.6%) and 114 patients had a postoperative hospital length of stay >7 days.

Of patients with prolonged hospitalization (>7 days), 98% (95% CI 96–100) exhibited persistent dysfunction of at least one organ system. Two patients did not fulfill any of the predefined morbidity criteria but had a prolonged hospitalization. Delay of discharge in these patients resulted from awaiting the start of chemotherapy ($n = 1$) and awaiting diagnostic tests for the problem for which the patient had undergone surgery ($n = 1$). Complications in hospitalized patients on Postoperative Days 5, 8, and 15 are listed in Table 3. Gastrointestinal dysfunction was the most common type of complication observed on Postoperative Days 5, 8, and 15. We found no direct relationship between surgical procedure type and the presence of postoperative complication or the incidence of specific types of complications.

In a univariate analysis (Table 2), ASA physical status was associated with postoperative complications ($P = 0.001$). For intraoperative variables collected at the end of surgery, several indices of tissue trauma (e.g., surgical duration [$P = 0.001$], estimated blood loss [$P < 0.001$]) and tissue perfusion (e.g., arterial base deficit [$P = 0.008$], arterial pH [$P = 0.01$], gastric pHi [$P = 0.02$]) were associated with postoperative complication. In contrast, cardiovascular variables at the end of surgery (e.g., heart rate, blood pressure, hematocrit, oxygen saturation) were either less predictive or not predictive of postoperative complication.

Discussion

This is a large, descriptive study characterizing the incidence and pattern of postoperative complications in a diverse group of patients undergoing routine, moderate-risk, elective surgery. Postoperative morbidity seems to be common and involves multiple organ systems.

Several previous studies have focused on specific "anesthetic-related" complications occurring immediately after surgery; for example, hypoxemia in the recovery room (14) and postoperative nausea and vomiting (15). Other studies have focused on selected high risk surgeries (e.g., cardiac surgery) (2,3), or focused on a specific type of complication, e.g., infection (10–12). Studies of complications have also been retrospective, have limited their scope to life-threatening severe complications, or have not specifically examined complications in patients with prolonged hospitalization (9,13,16,17). In one example, "severe perioperative adverse outcomes" were studied in 17,201 patients undergoing minor or intermediate-risk elective surgery (13). In that study, several complications that are known to occur after surgery, such as renal dysfunction and wound infection, were not mentioned. In a separate retrospective study ($n = 8,126$), only two types of noncardiac surgery were included, and the definitions for most adverse events were limited to organ failure (16).

We observed a more frequent incidence of morbidity than has been reported in previous studies. This

Table 2. Patient Characteristics

Characteristics	Total	P value	Odds ratio (95% CI)[a]	Units for OR
Age (yr)	59 ± 14	NS		
Sex (% male)	47	NS		
Preoperative weight (kg)	80 ± 20	NS		
ASA physical status I/II/III/IV (%)	5/52/38/5	0.001	2.87 (1.80–4.60)	≥III
Duration of surgery (min)	256 ± 112	0.001	1.43 (1.29–1.63)	30
Estimated blood loss (mL)	910 ± 1096	<0.001	1.34 (1.17–1.56)	500
Mean arterial pressure (mm Hg)	78 ± 13	0.03	1.18 (1.02–1.37)	−10
Heart rate (bpm)	93 ± 17	NS		
Hematocrit (proportion of 1.0)	0.31 ± 0.06	NS		
Spo_2 (%)	98 ± 2	NS		
Pao_2 (mm Hg)	150 ± 40	NS		
Gastric mucosal pHi	7.38 ± 0.08	0.02	1.28 (1.04–1.58)	−0.03
pHa	7.40 ± 0.05	0.01	2.12 (1.22–3.90)	−0.03
Arterial base excess (mmol/L)	−1.4 ± 2.4	0.008	1.18 (1.05–1.35)	−2
Urine output (mL · kg^{-1} · hr^{-1})	1.2 ± 1.0	NS		
Crystalloid administered (L)	5.0 ± 2.9	0.0001	1.25 (1.15–1.37)	0.5
Temperature (°C)	37.4 ± 0.7	NS		

Values are mean ± SD.
All measurements were made at the end of surgery unless indicated.
NS = not significant.
[a] Effect per unit increase.

Table 3. Postoperative Complications

	Patients hospitalized with specified complication		
Complication type	POD 5 (n = 176)	POD 8 (n = 114)	POD 15 (n = 21)
Gastrointestinal	55 (48–62)	51 (42–60)	52 (34–70)
Pulmonary	17 (11–23)	25 (17–33)	29 (12–46)
Renal	26 (20–32)	21 (14–28)	19 (5–33)
Infectious	12 (7–17)	13 (7–19)	43 (25–61)
Wound complication	3 (0–6)	12 (7–17)	24 (8–40)
Pain	23 (17–29)	22 (15–29)	10 (0–21)
Cardiovascular	9 (5–13)	9 (4–14)	14 (1–27)
Neurological	14 (9–19)	10 (5–15)	5 (0–13)
Hematological	8 (4–12)	16 (10–22)	14 (1–27)

Results are expressed as % (95% CI).
POD = Postoperative Day.

difference arose because we did not limit our scope to severe life-threatening complications such as organ failure. Instead, we included less severe forms of morbidity that may not result in death but can nevertheless increase hospital length of stay and healthcare costs.

Our study was not designed or powered to determine the exact incidence of complications. For example, it was not designed to prove that pulmonary complications (25%, 95% CI 17–33) are more common than renal complications (21%, 95% CI 14–28). Our study was instead designed to elucidate the overall incidence and pattern of postoperative morbidity. The high incidence of organ dysfunction observed in the present study contradicts anecdotal claims that prolonged hospitalization is due to errors in surgical technique or to the underlying surgical pathology. Several

of the complications observed warrant discussion.

Gastrointestinal dysfunction was the most common type of postoperative complication in all surgery types. This finding is consistent with those of previous studies that suggest that the gastrointestinal tract is extremely sensitive to hypovolemia, catecholamines, and other insults (18–20). Patients undergoing procedures involving a laparotomy had approximately twice the incidence of postoperative gastrointestinal dysfunction, which confirms the notion that mechanical trauma is an important determinant of this complication. However, our findings demonstrate that mechanical trauma cannot be the only cause of gastrointestinal dysfunction because 32% of patients with prolonged hospitalization exhibited this complication after extraabdominal procedures (e.g., revision hip arthroplasty).

Also of note was our finding that cardiac morbidity was less common than other types of morbidity, such as pulmonary, renal, and infectious complications. It was previously suggested that cardiac complications are the most relevant type of morbidity after noncardiac surgery (1,17). Studies reporting a high incidence of cardiac complications included predominantly high-risk patients, e.g., Veterans Administration hospitalized patients undergoing vascular surgery (17). In contrast, our study enrolled a diverse group of patients undergoing varying surgical procedures, which is a likely reason for the differences observed. Because studies reporting a high incidence of cardiac complications also did not rigorously assess patients for noncardiac morbidity, it is possible that patients in those studies exhibited a high degree of noncardiac morbidity that went unreported.

Several plausible theories could account for our finding of diffuse, multisystem complications unrelated to the type of surgery. It is clear from the critical care literature that a massive injury or insult often results in multiple organ dysfunction syndrome that is often not directly related to the site of the initial injury (21–23). Organ dysfunction in these patients is thought to be due to a systemic process, perhaps excessive systemic inflammation induced by endotoxin, cytokines, and/or other mediators (20–24). Our study's findings support the theory that a large proportion of postoperative morbidity is similar in pattern, and perhaps pathophysiology, to complications observed in intensive care unit patients (18), albeit of a less severe form.

As a secondary study objective, we tested the hypothesis that intraoperative indices of tissue hypoperfusion (e.g., gastric pHi, arterial base excess) are good predictors of postoperative morbidity. We chose to exclude most of the preoperative "predictors" previously studied for the following reasons. It is already known that patients who have a major preoperative comorbidity (e.g., left ventricular ejection fraction of 10%) are more likely to have postoperative complications. In general, very little can be done to alter these preoperative variables (e.g., age) so as to alter outcome.

Several indices of regional and global tissue hypoperfusion were collected at the end of surgery and compared with routinely measured and clinically available hemodynamic variables (e.g., heart rate) and indices of oxygen delivery (e.g., hematocrit, oxygen saturation). This study was not designed to rigorously assess all of the possible perioperative predictors of postoperative complications; therefore, a full multivariate analysis was not deemed appropriate. Nevertheless, as a secondary study objective, we tested for univariate associations on clinically available predictors. The strongest predictors of complications were characteristics reflective of a more traumatic operation (e.g., greater blood loss and longer duration of surgery) and indices of inadequate resuscitation and tissue hypoperfusion (e.g., acute global metabolic acidosis). This finding is consistent with those of numerous studies that have demonstrated an association between organ hypoperfusion and organ dysfunction (4,25–28). In fact, several randomized clinical trials in surgical patients have shown reductions in postoperative complications by using prophylactic strategies aimed at optimizing tissue perfusion in the immediate perioperative period (29–32). Although not conclusive, results from these trials suggest that some complications observed in surgical patients may be preventable by using prophylactic strategies that optimize tissue perfusion.

In our study, patients who had been discharged home were not observed by our study team. This limitation in no way invalidates our findings with respect to the pattern and high incidence of complications in hospitalized patients. The complications we observed are the likely cause for the prolonged length of hospitalization in these patients for two reasons. First, the complications were defined by the need for some specific acute medical therapy or intervention. For example, pulmonary complication was defined as the need for supplemental oxygen. It is unlikely that a physician would discharge a patient home on supplemental oxygen if the patient did not require home oxygen therapy preoperatively. Second, we included a free text entry in the trial data sheet to record other potential reasons for delay of discharge. Fewer than 2% of patients had a reason for delay of discharge not covered by our POMS.

Our results can be used in several ways. Our nine-point POMS can be easily used by healthcare providers and payers (e.g., clinicians, hospitals, health maintenance organizations) to characterize postoperative morbidity in their respective settings. The high incidence and cost of these complications have significant medical and economic consequences, given the millions of patients undergoing moderate-risk surgery in the United States annually (1). Our findings and the use of our POMS may be useful in future studies involving surgical patients. In fact, we believe that surgical patients represent an ideal group to show effectiveness for interventions that may also be useful in critically ill patients. An intervention that is not effective when administered prophylactically to surgical patients is unlikely to be effective when administered to critically ill patients who usually present to the intensive care unit many hours or days after the inciting injury.

Our study demonstrates that, despite a low mortality rate, complications involving multiple organ systems are common after routine, moderate-risk, elective surgery. Many of these complications are not directly related to the type/site of surgery, which supports the theory that a systemic inflammatory response may be responsible for much of this morbidity.

References

1. Mangano DT. Perioperative cardiac morbidity. Anesthesiology 1990;72:153–84.
2. Rady MH, Ryan T, Starr NJ. Perioperative determinants of morbidity and mortality in elderly patients undergoing cardiac surgery. Crit Care Med 1998;26:225–35.
3. Michalopoulos A, Stavridis G, Geroulanos S. Severe sepsis in cardiac surgical patients. Eur J Surg 1998;164:217–22.
4. Maynard N, Bihari D, Beale R, et al. Assessment of splanchnic oxygenation by gastric tonometry in patients with acute circulatory failure. JAMA 1993;270:1203–10.
5. Mangano DT, Layug EL, Wallace A, et al. Effect of atenolol on mortality and cardiovascular morbidity after noncardiac surgery. N Engl J Med 1996;335:1713–20.

6. Christopherson R, Beattie C, Frank SM, et al. Perioperative morbidity in patients randomized to epidural or general anesthesia for lower extremity vascular surgery. Anesthesiology 1993;79:422–34.

7. Yeager MP, Glass DD, Neff RK, Brinck-Johnsen T. Epidural anesthesia and analgesia in high-risk surgical patients. Anesthesiology 1987;66:729–36.

8. Kurz A, Sessler DI, Lenhardt R, et al. Perioperative normothermia to reduce the incidence of surgical-wound infection and shorten hospitalization. N Engl J Med 1996;334:1209–15.

9. Frank SM, Fleisher LA, Breslow MJ, et al. Perioperative maintenance of normothermia reduces the incidence of morbid cardiac events: a randomized clinical trial. JAMA 1997;277:1127–34.

10. Mehta G, Khanna SK, Trehan H, Gupta V. Postoperative infection in cardiac surgery: the influence of a change in prophylactic antibiotic regimen. J Hosp Infect 1990;15:353–62.

11. Garibaldi RA, Cushing D, Lerer T. Risk factors for postoperative infection. Am J Med 1991;91:158S–63S.

12. Culver DH, Horan TC, Gaynes RP, et al. Surgical wound infection rates by wound class, operative procedure, and patient risk: National Nosocomial Infections Surveillance System. Am J Med 1991;91:152S–7S.

13. Forrest JB, Rehder K, Cahalan MK, Goldsmith CH. Multicenter study of general anesthesia: predictors of severe perioperative adverse outcomes. Anesthesiology 1992;76:3–15.

14. Moller JT, Johannessen NW, Espersen K, et al. Randomized evaluation of pulse oximetry in 20,802 patients: perioperative events and postoperative complications. Anesthesiology 1993;78:445–53.

15. Pallazzo M, Evans R. Logistic regression analysis of fixed patient factors for postoperative sickness: a model for risk assessment. Br J Anaesth 1993;70:135–40.

16. Rosen AK, Geraci JM, Ash AS, et al. Postoperative adverse events of common surgical procedures in the Medicare population. Med Care 1992;30:753–65.

17. Mangano DT, Browner WS, Hollenberg M, et al. Association of perioperative myocardial ischemia with cardiac morbidity and mortality in men undergoing noncardiac surgery. N Engl J Med 1990;323:1781–8.

18. Mythen MG, Webb AR. The role of gut mucosal hypoperfusion in the pathogenesis of post-operative organ dysfunction. Intensive Care Med 1994;20:203–9.

19. Hamilton-Davies C, Mythen MG, Salmon JB, et al. Comparison of commonly used clinical indicators of hypovolemia with gastrointestinal tonometry. Intensive Care Med 1997;23:276–81.

20. Fink MP. Effect of critical illness on microbial translocation and gastrointestinal mucosa permeability. Sem Resp Infect 1994;9:256–60.

21. De Camp MM, Demling R. Posttraumatic multisystem organ failure. JAMA 1988;260:530–4.

22. Goris RJA, Boekhorst TPA, Nuytinck JKS, Gimbrère JSF. Multiple-organ failure: generalized autodestructive inflammation? Arch Surg 1985;120:1109–15.

23. Bone RC, Balk RA, Cerra FB, et al. Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis: ACCP/SCCM consensus conference. Chest 1992;101:1644–55.

24. Danner RL, Elin RJ, Hosseini JM, et al. Endotoxemia in human septic shock. Chest 1991;99:169–75.

25. Marik PE. Gastric intramucosal pH: a better predictor of multi-organ dysfunction syndrome and death than oxygen-derived variables in patients with sepsis. Chest 1993;104:225–9.

26. Fiddian-Green RG, Baker S. Predictive value of the stomach wall pH for complications after cardiac operations: comparisons with other monitoring. Crit Care Med 1987;15:153–6.

27. Chang MC, Cheatham ML, Nelson LD, et al. Gastric tonometry supplements information provided by systemic indicators of oxygen transport. J Trauma 1994;37:488–94.

28. Mythen MG, Webb AR. Intra-operative gut mucosal hypoperfusion is associated with increased post-operative complications and cost. Intensive Care Med 1994;20:99–104.

29. Boyd O, Grounds RM, Bennett ED. A randomized clinical trial of the effect of deliberate perioperative increase of oxygen delivery on mortality in high-risk surgical patients. JAMA 1993;270:2699–707.

30. Mythen MG, Webb AR. Perioperative plasma volume expansion reduces the incidence of gut mucosal hypoperfusion during cardiac surgery. Arch Surg 1995;130:423–9.

31. Sinclair S, James S, Singer M. Intraoperative intravascular volume optimization and length of hospital stay after repair of proximal femoral fracture: randomized controlled trial. BMJ 1997;315:909–12.

32. Shoemaker WC, Appel PL, Kram HB, et al. Prospective trial of supranormal values of survivors as therapeutic goals in high-risk surgical patients. Chest 1988;94:1176–86.