Fit for Surgery?

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In this issue of *Anesthesia & Analgesia*, Banz et al. "…provide a survey of fields of opportunities for improving outcome after major surgery."[1] In particular, they review the pathophysiologic considerations. They start by reminding us that despite patients having worse clinical and pathologic characteristics, outcomes are improving. Elective surgical patients are not sick and there is no need for them to get sick. Postoperative complications can be and should be completely avoided. An elective surgical procedure is not an illness but rather a marathon or a big hill. Patients are physiologically and emotionally challenged by trauma, inflammation, immunomodulation, pain, and any iatrogenic harm. A major determinant of outcome is their ability to rise to the challenge that they are presented with. We now have increasingly sophisticated strategies to minimize the challenges (i.e., shorten the marathon or reduce the size and slope of the hill).

Modern perioperative care pathways have 3 broad strategic aims: (a) to modulate inflammation, (b) to minimize pain, and (c) to avoid iatrogenic harm. Over the last few decades, we have amassed an increasing understanding of the importance of balancing pro- and antiinflammatory responses to pathologic insults such as trauma or infection. We understand that excessive inflammation causes harm, but some inflammation is absolutely necessary to enable effective healing. As detailed in the article by Banz et al., modulating and immunomodulating strategies are now routinely used, such as the increasing use of minimally invasive surgery and optimizing oxygen delivery and tissue perfusion by using a goal-directed approach.[2] A grayer area is the use of antiinflammatory drugs such as steroids. As our understanding of biology grows, options for therapeutic intervention and particularly drug intervention will increase. We can anticipate accelerated developments in this area, because a link has now clearly been demonstrated between systemic inflammation and postoperative cognitive dysfunction.[3] Other potential areas for immune-modulation include the possibility of preemptive active or passive immunization of patients who have weakened or impaired natural immunity.[4,5]

Minimization of pain has always been at the heart of perioperative care, but the choice of therapeutic drugs has in reality changed little over the last 40 years. What has changed is the way in which we use the drugs. The increasing use of a multimodal approach and regional techniques that use ultrasound-guided catheter placements have improved the provision of postoperative pain relief. However, the biggest change has been the use of effective pain minimization to facilitate immediate postoperative mobilization. There is no doubt that achieving effective pain relief is much easier with minimally invasive surgical techniques such as laparoscopic and/or robotic surgery.

Probably the biggest change in perioperative care in the last decade has been the increased awareness of, and avoidance of, iatrogenic harm. We now recognize that many of the traditions of perioperative care were not evidence based and caused more harm than good, approaches such as dehydration and starvation, the use of bowel preparation, the use of premedicating drugs and long-acting anesthetic drugs, enforced bed rest and nil-by-mouth postoperatively, routine placement of nasogastric tubes and percutaneous drains, salt and water overload, and the use of long-acting opiate drugs to relieve pain. We can add to this list the use of long midline incisions when smaller lateral incisions or laparoscopic techniques can be used to achieve the same goals.

As concluded by Banz et al., bundles of care and pathways are undoubtedly the way forward. Much progress has been seen in this area, and the exemplar is the so-called "Enhanced Recovery" or "fast-track" approach to major surgery.[6] Pioneered by Prof. Henrik Kehlet and now increasingly widely adopted throughout the world, Enhanced Recovery is a multimodal, multiprofessional, best-evidence-based approach to the care of the patient undergoing elective and increasingly emergency major surgery. Many of the pathophysiologic issues presented by Banz et al. can be addressed by using the Enhanced Recovery approach. The process is driven by a more detailed understanding of the pathophysiology of postoperative morbidity; interventions that may improve outcome have been adopted piecemeal as they become available and have been packaged in the care process.

In some places, an Enhanced Recovery program has become the norm rather than the exception. Many people now ask themselves, "Why wouldn't I use an Enhanced Recovery approach for this patient?" as opposed to "Why

should I?" In England, the National Health Service supported a national program to rollout "Enhanced Recovery" starting in 2009 and an accelerated rollout in 2010.[a] The program is continuously refined and monitored, and the preliminary results are already demonstrating significant reductions in complications and length of stay in the 4 surgical areas in which it is primarily being tested (colorectal, musculoskeletal, gynecologic, and neurologic). We are currently aware of >100 programs running in England.

The final major change that we have seen in recent years is a more sophisticated approach to the postoperative care environment, with patients being triaged depending on the size of the challenge they face and their ability to rise to that challenge. In many countries, we have seen increased use of intensive care facilities, targeted at the higher-risk patients, to allow the continued use of the strategies introduced in the intraoperative period. The increased use of postanesthesia care units or overnight enhanced recovery wards has allowed 6 to 24 hours of continuation of everything that has been described above. Certainly in our own institution, after a long battle, we were given the green light to open a larger postanesthesia care unit, and we have clearly demonstrated a decrease in both morbidity and mortality, thus reduced length of stay and overall intensive care unit bed utilization.

For most of us, what I have described thus far is now routine practice and thus a "normal day at the office." Therefore, for many of us, the area that offers the greatest potential for improving outcome after major surgery is determination and modulation of fitness for surgery, i.e., carefully matching patients' ability to rise to the challenge with the challenge they are presented with. It has been said that morbidity and mortality after elective surgery are simply manifestations of the failure to accurately identify and then modify risk. We must remind ourselves that the patient presenting for elective surgery still has 3 options:

1. To proceed with the planned surgery, with the effective application of the risk minimization strategies detailed above.
2. To go for a lesser operation and thus to try and minimize the challenge to a level that allows the patient to survive, or rather to provide a challenge that is appropriate for the individual patient. We cannot all run a marathon, but many of us could walk one.
3. The third and most important option to consider is that no surgery takes place at all.

The ability of an individual to tolerate the surgical challenge is what we have traditionally referred to as "Fitness for Surgery." For a long time, we have recognized that there are 3 major determinants of an individual's ability to tolerate major surgery: their age, their comorbidities, and their functional capacity. Their age, per se, does not mean patients are less fit for major surgery, but with increasing age there is, inevitably, an increasing incidence of comorbidities and reduced functional capacities, but with highly

individual variations. As Banz et al. point out: "While a patient's age cannot be changed, an in-depth understanding of the altered physiology associated with increased age may help to develop better care …" What is less well understood, or routinely evaluated, is an individual's reaction to an inflammatory stimulus and/or their immune status, e.g., baseline levels of inflammation as determined by high-sensitivity C-reactive protein or markers of innate immunity such as the measurement of natural antibodies.[4,5,7]

There are increasingly sophisticated efforts to determine risk in the preoperative period. However, at least in the National Health Service in England, I think the timing of preoperative evaluation is misplaced if we are to act on what is already known about factors that determine outcome. A typical pathway for our patients would be that they would be referred for a surgical opinion by a community doctor. The surgeon would make a decision as to whether surgery could help, and then a date would be booked; after this, the patient would be referred to the preoperative assessment clinic. There is a possibility that the community doctor may have performed some form of triage, i.e., may not be referring some patients for a surgical opinion because they appear to be unfit for surgery, thus denying them expert preoperative assessment.

There is no doubt that specialist preoperative clinics have proven to be effective in reducing the number of same-day cancellations; what is less clear is whether they have effectively improved overall outcome. Our own clinic routinely uses risk scores and objective determination of fitness using cardiopulmonary exercise testing, and has demonstrated that it can improve triage and the use of postoperative resources and thus reduce complications and length of stay. But, overall, I believe the timing is wrong. Because preoperative assessment occurs after the initial surgical evaluation and offer of an elective procedure, the patient is already on a path to surgery that is much harder to deviate from. There is now little time to modify risk in ways proposed by Banz et al. or to easily change course. I think we should change the timelines, as has already happened in some places. I think the initial referral should be to a specialist clinic that evaluates risks and sets out a plan for the modification of risk. A simple risk evaluation tool can be used to triage patients in the first instance, then all but the young, comorbidity-free individuals could undergo objective determination of fitness and be prescribed lifestyle changes, such as exercise and diets, with counseling regarding stopping smoking and reducing alcohol use. Anemia, hypertension, and diabetes could all be investigated and modifications made before referral to the surgeon. The surgeon would then be able to review a patient with all the information necessary to counsel them with regard to the 3 major options: the ideal surgery for fit patients, modified surgery, or no surgery for the "unfit." If the final outcome was to be no surgery, the screening efforts with regard to determination of fitness and lifestyle changes and investigation and treatment of common abnormalities would not be wasted. Indeed, over time, these evaluations and interventions could and probably should take place in the family doctor's office. Using this model, once the patient has seen the surgeon, he or she can start

down the path of a truly informed consent process. The 3 options could be offered from the outset, and patients can consider the 3 options within the context of a true understanding of their own potential risks and their determination and willingness to modify risk factors (e.g., lose weight, get more exercise, and stop smoking), as detailed by Banz et al.[1,8] ■

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Improving Outcome After Major Surgery: Pathophysiological Considerations

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Surgical and anesthesia-related techniques may reduce physical stress for patients undergoing high-risk surgery, but major surgery is increasingly performed in patients with substantial comorbidities. Strategies for improving the outcome for such patients include approaches that both increase tissue oxygen delivery and reduce metabolic demand. However, these strategies have produced conflicting results. To understand the success and failure of attempts to improve postoperative outcome, the pathophysiology of perioperative hemodynamic, metabolic, and immunological alterations should be analyzed. Our aim in this review is to provide a survey of fields of opportunities for improving outcome after major surgery. The issues are approached from 3 different angles: the view of the patient, the view of the surgical intervention, and the view of the anesthesia. Special attention is also given to what could be considered the result of the interaction among the 3: perioperative inflammation and immune response. (Anesth Analg 2011;112:1147–55)

High-risk surgery is a term rarely explicitly defined in scientific articles. There seems to be a common understanding among surgeons and anesthesiologists of what major surgery means. It can be defined as a surgical procedure that is extensive, involves removal of whole or parts of organs, and/or is life-threatening. It has also been defined as a surgical procedure with >1% mortality.[1]

One possibility for evaluating the perioperative risk is the use of 1 of several risk scores. These include, e.g., the Estimation of Physiological Ability and Surgical Stress,[2] the Physiological and Operative Severity Score for the enUmeration of Mortality and Morbidity,[3] and derivatives. These attempt to incorporate patient age and severity of the operative procedure into the risk stratification. The American Society of Anesthesiologists score[4] is widely used and easy to apply, but excludes age from its risk analysis. As with all risk scores, they cannot and must not be used to predict the individual risk of a patient.

Progress in the treatment of chronic diseases such as diabetes, hypertension, and coronary artery disease is increasing the prevalence of heart failure.[5–8] This is important considering that >75% of all patients with heart failure are >65 years old, and these older patients have the highest incidence of major noncardiac operations.[9,10] Furthermore, the prevalence of obesity is rapidly increasing.[11] Despite this, improved postoperative outcomes have been documented over the last several decades. Left ventricular dysfunction as a risk factor for hospital mortality after aortic valve surgery for chronic aortic regurgitation was neutralized between 1972 and 2000,[12] and the incidence of pneumonia in postoperative patients without epidural analgesia decreased from 34% to 12% between 1971 and 2006.[13] A meta-analysis of all English-language literature reporting operative mortality of ruptured abdominal aortic aneurysm (AAA) repair between 1955 and 1998 found a constant mortality reduction of approximately 3.5% per decade.[14] In addition, postoperative death rates after surgery for rectal cancer have shown improvement in recent years. A systematic review including all prospective studies of rectal cancer patients receiving radical surgery published between 1990 and 2008 (24,845 patients) identified year of publication as the only statistically significant variable to explain postoperative death rate in a multivariable model.[15] Similarly, using longitudinal analyses of cancer registries, improved outcomes for surgically treated gastrointestinal cancers were documented between 1973 and 2000.[16] Despite worse clinical and pathological characteristics, survival rates after hepatic resection for colorectal metastases increased between 1985 and 2004.[17] Likely contributing factors to a better outcome are improvements in patient selection and perioperative management. This review provides a basis for the evaluation of factors with the potential to further improve outcome in high-risk surgery.

Patients: Comorbidities and Risk Factors

Impact of Age

Age was previously identified as one of the most important, if not the single most predictive, risk factors for morbidity and mortality after high-risk interventions, including but not limited to cardiac surgery,[18] major pancreatic surgery,[19] and gastric cancer surgery.[20] In a recent retrospective cohort study, 121 hospitals participated in the American College of Surgeons National Surgical Quality Improvement Program.[21] A total of 24,747 patients requiring upper and lower abdominal surgery were evaluated. Overall perioperative morbidity was 1.2 to 2 times higher and mortality 2.9 to 6.7 times higher in elderly patients (defined as >75 years) than in younger patients after adjusting for differences in preoperative comorbidities. Irrespective of procedure type, the elderly were significantly more likely to experience cardiac, pulmonary, and

renal complications, whereas surgical site infections, post-operative bleeding events, deep venous thromboses, and rates of return to the operating room did not differ.

Although a patient's age cannot be changed, an in-depth understanding of the altered physiology associated with increased age may help to provide better care and lead to adapted treatment strategies. Young patients can readily increase their cardiac output, by an increase in stroke volume and/or heart rate, but the older heart has an altered muscle wall that limits the heart's mechanical and contractile abilities.[22] In addition, diastolic dysfunction is common in the older patient.[23] Accordingly, the stroke volume is limited under stress, and thus the elderly patient has a decreased cardiac reserve. Increased chest wall rigidity, weakening of the respiratory muscles due to loss of muscle mass, and reduced surface area for alveolar gas exchange give rise to a reduced ability to adapt to hypoxia. Any respiratory challenge can thus put older patients at risk for perioperative and postoperative hypoxemia.[24] Moreover, sleep apnea syndrome may aggravate hypoxia.[25] Elderly patients also seem to have a particularly high risk of arterial and venous thromboembolism.[26] Altered pharmacokinetics and pharmacodynamics put these patients at risk for inadequate drug dosing and adverse drug effects.[27] As an example, a decreasing proportion of cardiac output directed to vessel-rich tissues,[28] and increasing tissue and blood solubility of inhaled anesthetics with age[29] may result in progressively slower onset and offset of their effects. Indeed, it has been shown that age significantly reduces the requirements of sevoflurane.[30]

Finally, protein energy malnutrition and involuntary weight loss are common problems in the elderly patient population. As an example, a retrospective review of 123 patients older than 65 years with major burns reported malnutrition to be present in 61%.[31] There was a significant increase in infection rate, a decrease in the rate of healing of a standard skin graft donor site, and an increase in length of stay in the malnourished group compared with an adequately nourished elderly burn population. Mortality in malnourished patients was 17%, compared with 9% in the well-nourished patients. Elderly patients are also at high risk of abnormal hematocrit values.[32] In a retrospective study including 310,311 patients aged >65 years undergoing major noncardiac surgery between 1997 and 2004, 30-day mortality and cardiac event rates increased monotonically, with either positive or negative deviations from normal hematocrit levels.[32] Postoperative cognitive dysfunction occurs in a significant proportion of patients in the early weeks after major noncardiac surgery, with the elderly being more at risk.[33] In 110 prospectively studied patients aged >65 years undergoing major surgery, preoperative markers related to 6-month mortality included impaired cognition, recent falls, low albumin, anemia, functional dependence, and increased comorbidities.[34] Logistic regression identified any functional dependence as the strongest predictor of 6-month mortality (odds ratio 14).

From the available evidence, it can be concluded that attempts to improve preoperative nutritional status, preoperative assessment using geriatric-specific markers, better perioperative organ function monitoring and support, and postoperative measures to reduce delirium and increase patient autonomy may all have potential or at least provide options for improving outcome for the elderly patient group.

Impact of Smoking

Patients who smoke have an increased risk of intra- and postoperative complications, particularly of a pulmonary or cardiovascular nature, compared with nonsmoking patients.[35,36] As carbon monoxide (CO) preferentially binds to hemoglobin in place of oxygen, the short-term effects of cigarette smoking include elevated blood CO levels that result in a 3% to 12% reduction of oxygen availability in the periphery.[37] Moreover, nicotine stimulates a surgical stress response that resembles a "cardiac workout," with increases in heart rate, arterial blood pressure, and peripheral vascular resistance. These effects may not negatively influence an otherwise fit patient, but the imbalance between oxygen availability and oxygen consumption in a smoker may produce a detrimental effect. In the setting of a surgical intervention, particularly in high-risk surgery, the surgery and anesthesia place a certain unavoidable strain on the patient's cardiovascular functions; thus, additional stress related to smoking may tip the balance and result in hypoxemia in the vital organs.

The short-term benefits of smoking cessation before surgery (decreases in CO and nicotine levels) are observed as early as 24 to 48 hours after the last cigarette.[37] However, a substantially longer smoking abstinence of several weeks before surgery is required for a reduction in pulmonary complications.[38] In a randomized controlled trial including 117 patients undergoing different types of surgery such as cholecystectomy and hip or knee prosthesis, smoking cessation therapy with individual counseling and nicotine substitution was started 4 weeks before surgery and continued 4 weeks postoperatively.[39] The control group received standard care. The overall complication rate in the control group was significantly higher (41% vs 21%). Relative risk reduction for the primary outcome of any postoperative complication was 49% and number needed to treat was 5. An analysis per protocol showed that abstainers had fewer complications (15%) than those who continued to smoke or only reduced smoking (35%).

In a recent meta-analysis including 11 randomized controlled trials with 1194 patients, smoking interventions significantly reduced the occurrence of complications (pooled risk ratio 0.6; 95% confidence interval 0.4–0.8).[40] Intensive interventions increased smoking cessation rates both before operation and up to 12 months thereafter. The effects of medium to less intensive interventions were not significant.

The available data suggest, therefore, that surgical patients may benefit from intensive preoperative smoking cessation interventions. These include individual counseling, initiated at least 4 weeks before the scheduled operation, and nicotine replacement therapy.

Impact of Obesity

The literature is full of reports pointing out the disadvantages of obesity in the preoperative setting; increases in morbidity and mortality are only 2 of the many aspects

evaluated.[41] The association between obesity and the inflammatory response and the pathogenesis of obesity-related comorbidities, such as Type 2 diabetes, have been well documented.[42] Obese patients have high levels of C-reactive protein (CRP) and tumor necrosis factor (TNF)-α[43] in addition to an increased white cell count.[44] More recently, several studies have focused on the effect of obesity on the innate immune system, showing that overweight people have elevated neutrophil activation compared with normal-weight subjects.[45] Elevated CRP and white blood cell counts (especially high neutrophil counts) have been identified as significant risk factors for stroke[46] and cardiac events, including cardiac death.[47] Thus, elevated inflammatory markers in obese patients act as surrogate markers for postoperative complications.

Recently, Tokunaga et al.[48] evaluated the effects of general obesity on postoperative complications in extensive abdominal surgery (open gastrectomy). In particular, they identified visceral fat as a risk factor for postoperative intraabdominal infection, prolonged hospital stay, and death.

In a prospective, multicenter, observational study of 30-day outcomes in consecutive patients undergoing bariatric surgical procedures at 10 clinical sites in the United States from 2005 through 2007, 4.3% of patients had at least 1 major adverse outcome.[49] A history of deep vein thrombosis or pulmonary embolus, a diagnosis of obstructive sleep apnea, impaired functional status, and extreme values of body mass index (BMI) were each associated with an increased risk of the composite end point.

The authors of a review found good evidence that obesity is a risk factor for wound infection after colorectal surgery.[50] Obesity may increase the risk of wound dehiscence, incisional site herniation, and stoma complications. Obesity is linked to anastomotic leak, and obese patients undergoing rectal resections may be at particular risk.[50] Furthermore, operation times are longer for rectal procedures in obese patients, and obese patients undergoing laparoscopic colorectal surgery are at increased risk of conversion to an open procedure. However, hospital stay does not seem to be prolonged.

Although it is evident that obesity increases perioperative complications, the effect of weight reduction before scheduled surgery remains to be determined.

Perioperative Nutritional Support: Pro or Con?

Previously published data clearly show that malnourished patients who require major operations are predisposed to infectious complications and poor outcome.[51,52] Adequate perioperative nutritional support resulted in a reduction of postoperative complications.[53] A low preoperative BMI (kg/m^2) may be regarded as an overall indicator of the size of the patient's reserves; a BMI <20 kg/m^2 is an accepted indicator of malnutrition. However, it has been recognized that acutely malnourished patients may still have a normal or even elevated BMI. In an increasingly obese population, BMI alone is insufficient to assess an individual's nutritional status. More useful assessments of malnutrition consider the rate of weight loss or the percentage loss of usual body weight; an example is the Nutritional Risk Screening developed by Kondrup et al.[54]

Nutritional status was assessed between 1999 and 2002 in a cohort of 460 patients undergoing major elective surgery using the Nutritional Risk Index, Maastricht Index, Subjective Global Assessment, and Mini Nutritional Assessment.[55] Twenty patients died during the study period and 42 patients had 2 or more complications. The frequency of malnutrition was 58%, 64%, and 67% as assessed by the Subjective Global Assessment, Nutritional Risk Index, and Maastricht Index, respectively. Morbidity rates, especially severe infectious and noninfectious complications, were significantly higher in malnourished patients in all nutritional indices.

Serum protein markers such as albumin (for evaluating long-term nutritional status) and prealbumin (for evaluating acute responses to nutritional support) have been shown to be useful additional measurements for assessing nutritional status. Low albumin levels have been identified as an independent risk factor for postoperative morbidity and mortality.[52,56] For starving, malnourished patients, nutritional support leads to an improved postoperative course that outweighs any theoretical risks of potentially increased tumor growth. However, it should be emphasized that, although preoperative enteral or parenteral nutritional support clearly benefits surgical cancer patients,[57] a systematic review showed that "preventive" administration of parenteral support in nonmalnourished patients did not positively influence outcome and may even be potentially harmful for certain patient subgroups.[58]

More recently, the concept of immunonutrition has evolved, in which enteral formulas are supplemented with arginine and glutamine, nucleotides, or omega-3 fatty acids in an attempt to positively modulate the immune system. The notion that immunomodulation can improve the immune response was supported in certain studies that showed reduced overall and, in particular, infectious complications.[59] In a double-blind study, esophageal cancer surgery patients were randomized to a standard enteral nutrition formula or a formula enriched with 2.2 g eicosapentaenoic acid (EPA)/d for 5 days preoperatively (orally) and 21 days postoperatively (jejunostomy).[60] The EPA group maintained all aspects of body composition postoperatively, whereas patients in the standard enteral nutrition group lost significant amounts of fat-free mass compared with the EPA group. The EPA group had a significantly attenuated stress response to TNF-α, interleukin (IL)-10, and IL-8. However, this did not translate into a reduced incidence of major complications.

In another study, 196 well-nourished patients undergoing resection for pancreatic or gastric cancer between 2004 and September 2007 were randomized to receive postoperative enteral nutrition with immunostimulating diet or standard oligopeptic diet.[61] Complications were observed in 23% and 25%, respectively (not significant). There were no differences in liver and kidney function, visceral protein turnover, or treatment tolerance between the groups.

The benefits of immunonutrition, therefore, remain debatable. A major drawback is the significantly higher costs involved with the administration of immunonutrition.

Whereas perioperative nutrition in the malnourished patient can improve postoperative outcome, immunonutrition seems to attenuate the inflammatory response and interferes with certain immune functions in selected patient groups.

Consequences of Major Surgery

Effects of Surgery on Inflammation and Immune Response

Major abdominal surgery causes a hyperdynamic and hypermetabolic host response that seems to be more pronounced in older patients.[62] Tissue injury during major surgery is aggravated by repeated ischemia-reperfusion events, particularly during vascular surgery. Both tissue injury and ischemia-reperfusion may lead to systemic effects. Even in the 1970s, we understood that major surgical interventions resulted in immune cell alterations, with reductions in total T lymphocytes, cytotoxic T cells, and natural killer cells.[63] The surgery-induced postoperative inflammatory response combined with paralysis of the cell-mediated immune system has since been confirmed in numerous other studies.[64,65] It has been shown that genes encoding IL-6 and components of the local renin-angiotensin system are activated early during aortic surgery.[66] The resulting systemic inflammatory reaction is followed by impaired pulmonary function.[66] In contrast, systemic inflammation seems to be less severe or even absent during abdominal surgery without tissue ischemia. Major surgery also causes the depression of macrophage antigen presentation capacity, a factor that contributes significantly to cell-mediated immunity.[67]

When visceral ischemia is prolonged during major surgery, the levels of TNF-α, IL-6, IL-8, and IL-10 become elevated.[68] The magnitude of this inflammatory reaction seems to correlate with the frequency and magnitude of postoperative organ dysfunction.[68,69] Postoperative organ failures and infection are complications associated with a bad outcome, particularly after major surgery for cancer. It has been shown that prolonged operation times, the presence of remote infection at the time of the operation, and long preoperative hospital stays are important risk factors for infectious complications after surgery.[70] In a large database including 4700 patients who underwent noncolorectal abdominal surgery, independent risk factors for postoperative infection included age, a very low or high BMI, liver cirrhosis, vertical abdominal incision, and suturing or anastomosis of the bowel.[71]

To combat postoperative immunodepression, perioperative IL-2 administration was tested in a phase II randomized trial to analyze its effect on patients with radically operable gastric cancer.[72] Compared with patients who received no IL, patients who received IL-2 had a significant increase in total and CD4-positive lymphocytes and did not experience any anesthesia-related or surgical complications.[73]

There are some recent studies evaluating perioperative antiinflammatory therapies in patients. In a prospective, randomized, double-blind, placebo-controlled trial involving 36 high-risk patients undergoing cardiac surgery, the effects of stress doses of hydrocortisone on markers of systemic inflammation were investigated.[73] Patients treated with hydrocortisone had significantly lower levels of IL-6 and higher levels of IL-10, resulting in an attenuated change in IL-6/IL-10 ratio 4 hours after cardiopulmonary bypass. Patients in the hydrocortisone group also had a shorter duration of catecholamine support, a shorter length of stay in the intensive care unit (ICU), and a lower incidence of postoperative atrial fibrillation. Oxidative stress is involved in the development of secondary tissue damage and organ dysfunction, and "micronutrients" could theoretically contribute to the antioxidant defense. In a prospective, double-blind trial, 200 patients admitted to an ICU with organ failure after complicated cardiac surgery, major trauma, or subarachnoid hemorrhage were randomized to receive IV supplements of selenium, zinc, vitamin C, and vitamin B_1 for 5 days versus placebo.[74] The incidence of postoperative acute kidney failure and subsequent decrease in sequential organ failure assessment score were similar between the groups. Although CRP decreased more quickly in the intervention group, neither infectious complications nor length of hospital stay differed between groups.

Cardioprotection with β receptor antagonists can improve the outcome in high-risk patients undergoing elective surgery. In a randomized, controlled trial, 42 ICU patients aged >55 years were randomized to receive continuous β-blockers or standard care.[75] Levels of IL-6, but not IL-1β, decreased over time in patients receiving a β-blocker, whereas levels in controls remained unchanged. There were no complications related to the use of β-blockers.

Perioperative hypothermia may contribute to intraoperative and postoperative complications. A recent systematic review of the literature found 25 studies encompassing 3599 patients in various surgical disciplines.[76] Of these, 19 were randomized trials involving 1785 patients. Not warming the patient during surgery was associated with significant hypothermia. Normothermic patients had significantly less pain, a lower incidence of wound infection, and reduced blood loss, most likely because of the prevention of hypothermia-induced coagulopathy.

Further studies are needed to evaluate the effect of immunomodulating and antiinflammatory compounds on postoperative outcome in high-risk surgery patients. "Low-dose" antiinflammatory drugs may have the potential to reduce inflammation and lead to faster organ recovery in selected patient groups.[73]

Effects of Hemorrhage

Several studies have shown that, after hemorrhagic shock, lymphocyte function is severely depressed for up to 5 days postoperatively.[77,78] In addition to the effects on T cell populations, the splenic B cell capacity for antibody production is also significantly reduced.[79] Significant blood loss during surgery is associated with a cascade of inflammatory responses, with circulating TNF-α levels increasing as early as 30 minutes after the initial injury.[80] Together with TNF-α, increases in other proinflammatory cytokines, including IL-6 and IL-1,[81] may contribute to initiating the development of multiple organ dysfunction after severe hemorrhagic shock.

In trauma patients, the release of proinflammatory cytokines seems to be related to the magnitude of surgery, rather than to the duration of the procedure.[82] However, the cytokine release is also associated with the degree of blood loss.

The Surgical Approach

In an attempt to maximally reduce surgical trauma, standard laparotomy has now been routinely replaced by far

less invasive laparoscopic techniques. The latter include a wide variety of surgical interventions, including the "gold standard" laparoscopic cholecystectomy,[83] laparoscopic colorectal resections, and gastric bypass operations for morbid obesity or antireflux surgery, to name but a few minimally invasive interventions. Laparoscopic surgery reduces postoperative pain, accelerates postoperative recovery, and shortens hospital stay[84]; in addition, it provides potential solutions for particularly fragile, high-risk patients by reducing overall surgical trauma.

In a prospective, multicenter, double-blind trial, patients were randomized to either laparoscopic or open sigmoid resection between 2002 and 2006. Although laparoscopic resection took longer, it was associated with a 15% reduction in major complication rates, less pain, improved quality of life, and shorter hospitalization time.[85]

Interestingly, sometimes patients with high-risk and major comorbidities are denied laparoscopic interventions. Contraindications for these patients include the necessary abdominal insufflation, the patient positioning (sometimes prolonged periods in Trendelenburg or anti-Trendelenburg positioning), and potentially longer operating times. Yet, an observational cohort study found some evidence that these patients are likely to benefit from minimal trauma and reduced blood loss.[86]

Reduced intraoperative bleeding has been documented with laparoscopic hepatic resection,[87] and a Cochrane analysis examining short-term postoperative outcome after laparoscopic colorectal surgery also showed reduced blood loss, reduced local (wound) complications, and improved postoperative lung function compared with open surgery.[84]

In the last 2 decades, endovascular repair as an alternative to open vascular surgery has become popular. In a multicenter clinical trial of 881 veterans, postoperative outcome of endovascular and open repair of AAA was compared between 2002 and 2008.[88] Whereas perioperative mortality was lower for endovascular repair, 2-year mortality was similar in both groups. Patients in the endovascular repair group had reduced median procedure time, blood loss, transfusion requirements, duration of mechanical ventilation, hospital stay (3 vs 7 days), and ICU stay (1 vs 4 days). There were no differences between the 2 groups in major morbidity, procedure failure, secondary therapeutic procedures, aneurysm-related hospitalizations, health-related quality of life, or erectile function.

Endovascular aneurysm repair was also compared with open repair of inferior AAAs in a single-center retrospective study including 677 patients between 1996 and 2005.[89] Endovascular repair was associated with reduced blood loss, reduced length of ICU and hospital stay, and increased number of patients discharged home compared with open repair.

Accordingly, less-invasive procedures seem to have clinically significant advantages and can be recommended, especially for high-risk patients.

The Effect of Anesthetic Management

All anesthetic drugs may alter the hemodynamic status by blunting the sympathetic output of the central nervous system or by directly causing peripheral vasodilation. Anesthetics may also affect cellular functions of other organs. Whereas there is evidence that neither total IV nor inhaled anesthesia has significant effects on mesenteric perfusion in the absence of surgical stimulation,[90] hepatocellular disintegrity and subclinical liver dysfunction have been demonstrated with both forms of anesthesia[91,92] during open surgery and laparoscopic surgical interventions.[93]

The time-dependent expression of alveolar macrophage genes for proinflammatory cytokines was evaluated in patients during propofol and isoflurane anesthesia.[94] Gene expression for IL-1β, IL-6, IL-8, interferon γ (IFN-γ), and TNF-α increased 10-fold during surgery and anesthesia. The increases in IL-8 and IFN-γ were up to 3 times larger during isoflurane than propofol anesthesia.

To separate the effects of mechanical ventilation and general anesthesia, rats were allocated to spontaneous or mechanical ventilation with and without exposure to halothane, enflurane, isoflurane, or sevoflurane.[95] TNF-α gene expression from pulmonary lavage cells was greater during mechanical than spontaneous ventilation and in nonventilated controls. During exposure to volatile anesthetics, gene expression for IL-1β, IFN-γ, and TNF-α all increased significantly compared with mechanical ventilation alone.

Alveolar macrophages' phagocytosis and microbicidal activity was also measured in patients anesthetized with isoflurane or propofol for orthopedic surgery.[96] The fraction of alveolar macrophages ingesting particles, the number of particles ingested, and microbicidal function decreased significantly over time, with a greater decrease during isoflurane compared with propofol anesthesia. These data suggest that pulmonary defenses are modulated by the type (and duration) of anesthesia. Other effects of anesthetics include oxidant and antioxidant properties.[97]

Anesthetics may have further effects with the potential to interfere with postoperative outcome. One example is the inhibition of the response to adrenocorticotrophic hormone stimulation. This is best known for etomidate,[98] but may also occur after propofol and thiopental anesthesia,[99] albeit less consistently.

Thoracic, but not lumbar, epidural anesthesia appears to increase liver blood flow after major abdominal surgery.[100,101] However, there are also studies demonstrating a selective decrease in hepatic blood flow.[102] This fact precludes recommendation of epidural anesthesia for potential improvement of liver perfusion. Nevertheless, thoracic epidural anesthesia may blunt the reduction in subcutaneous tissue oxygen tension caused by surgical stress and adrenergic vasoconstriction during surgery,[103] and may prevent stress-induced perioperative impairment of proinflammatory lymphocyte function.[104] The potential of epidural anesthesia/analgesia to improve postoperative outcome and attenuate the physiological response to surgery has been documented. Reviews including retrospective, prospective, and meta-analysis studies found improvement in surgical outcomes through beneficial effects on perioperative pulmonary function, surgical stress response, and analgesia.[105,106] Nevertheless, in unselected patients undergoing gastrointestinal surgery, epidural analgesia does not seem to reduce anastomotic leakage, intraoperative blood loss, transfusion requirement, risk of thromboembolism, cardiac morbidity, or hospital stay compared with conventional analgesia.[106] Complications of

epidural anesthesia/analgesia range from transient paresthesias to potentially devastating epidural hematomas in rare cases.

Accordingly, the beneficial effects of epidural analgesia seem largely to be related to improved lung functions and better maintained analgesia with an acceptable risk/benefit ratio.

Fluid Management

Although the importance of perioperative fluid restriction has been emphasized, fluid restriction regimens may increase the likelihood of perioperative hypovolemia and splanchnic ischemia. In a group of patients who underwent major (mainly cardiovascular) surgery, it was shown that low gastric pH measured during the intraoperative period was associated with increased postoperative complications and costs.[107] Gastrointestinal perfusion is often compromised earlier than perfusion in other vascular beds under conditions of imbalanced tissue oxygen delivery and needs, e.g., hypovolemia, stress, and increased metabolic demand.[108] There is a strong association between relative gastric luminal hypercarbia (suggesting relative gastrointestinal hypoperfusion) and postoperative organ dysfunction, including the gastrointestinal tract.[109–111] Therefore, restoration of oxygen delivery, especially to the splanchnic bed, is of critical importance. However, the characteristics of optimal perioperative fluid management remain controversial.

Until recently, the general approach to perioperative intravascular volume management was the administration of large amounts of fluids and sodium, with the goal of maintaining organ perfusion, preserving function, and thus improving patient outcome. During the last few years, an alternative approach has been suggested and explored (reviewed in an article by Walsh et al.[112] in 2008). A series of trials demonstrated that postoperative patients could be managed successfully with quantities of fluid that previously would have been considered inadequate.[113–115] In these trials, fluid-restricted groups had fewer complications, less edema, and earlier return of bowel function. Renal impairment was a rare event in the fluid-restricted group. In contrast, in another study, there were no differences in complication rates or the return of bowel function in patients with restricted versus liberal volume management.[116] It has been suggested that the lack of effect in that trial may have been attributable to the restriction of intraoperative fluid administration in both arms of the trial.[114] Another study showed that when transesophageal echocardiography was used to maintain preoperative left ventricular end-diastolic volume and cardiac output during colorectal surgery, the patients required lower than commonly recommended crystalloid solution delivery rates, especially during laparoscopic surgery.[117]

In patients undergoing elective major abdominal surgery, a restricted (1.5 L/24 hours) versus standard (2.5 L/24 hours) postoperative IV fluid regime increased postoperative hospital stay by 4 days and increased major complications.[118] No differences were found in time to restore gastric functions between the groups. In contrast, in patients after elective abdominal vascular surgery, a restricted fluid regime resulted in shorter postoperative hospital stay (8 days vs 12 days).[119] In patients undergoing elective major abdominal surgery, intraoperative fluid management using systolic pressure variation versus routine care increased the amount of administered fluid but did not alter organ perfusion and function.[120] In another prospective randomized study in patients undergoing open AAA repair, standard fluid management resulted in a cumulative fluid balance of 8.2 L on postoperative day 5 vs 2.6 L for restricted management.[121] Total and postoperative length of stay in hospital was reduced by 50% in the restricted group. In a randomized study in patients aged >50 years undergoing emergency abdominal surgery, use of pulse pressure variation measurements to guide fluid boluses was not associated with a change in postoperative renal function.[122]

In a recent review of prospective, randomized studies comparing the effect of 2 different fixed fluid volumes on postoperative clinical outcome in major surgery ($n = 7$), it was determined that a liberal intraoperative fluid regimen ranged from 2.8 to 5.4 L and a restrictive regimen from 1 to 2.7 L.[123] The period for fluid therapy and outcome end points were inconsistently defined and only 2 studies reported perioperative care principles and discharge criteria. Whereas 3 studies found an improved outcome in terms of morbidity and/or hospital stay with a restrictive fluid regimen, 2 studies found no difference and 2 studies found differences in other selected outcome variables. We conclude with the authors that differences in definitions and methodology and conflicting results preclude evidence-based guidelines for procedure-specific perioperative fixed-volume regimens so far.[123]

CONCLUSIONS

Cancer, organ dysfunction, and individual specific risk factors contribute to increased risk after major surgery. Adequate nutritional support, reduction of invasiveness, shorter operation times, regional or combined regional/general anesthesia, and target-controlled fluid management are options for reducing postoperative morbidity.

Despite all efforts to improve outcome and the many available risk stratification scores, an individual's actual risk cannot be precisely predicted. Further studies are needed to evaluate the value of "bundles" of interventions and whether they can improve outcome after major surgery. ■

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