Optimizing patients undergoing surgery: a matter of 'eminence-based medicine'?

Andreas Hoeft, Georg Baumgarten, and Olaf Boehm

Anaesthesia has become very well tolerated with a very low anaesthesia-related mortality, despite the fact that the surgical population has become older and sicker over the last decades [1,2]. An 'exitus in tabula' has become very rare. Still, patients die after surgery, but not in the operating room rather in the ICU or to a surprisingly large proportion on the normal ward [3]. There is growing evidence that postoperative death derives mainly from complications. This phenomenon has more recently been called 'failure to rescue (FTR)', which has been defined as death after complications. FTR mainly occurs in patients with comorbidities who are naturally prone to develop all kinds of complications [4]. This issue of *Current Opinion in Anesthesiology* aims to shed a little light on various comorbidities and how these patients can be better managed to avoid FTR. It is a selection of the most common comorbidities, but by far not covering all.

Unfortunately, there is little evidence-based knowledge how to deal with high-risk patients and in almost all of the reviews we find a sentence like: 'There is a lack of solid randomized controlled trials…'. Many of the recommendations given in the reviews are therefore more opinion based or 'eminence based' than 'evidence based'. However, this lack of evidence should not lead to therapeutic nihilism. In fact, it is questionable whether ever controlled randomized studies can be performed to answer the numerous questions like how to optimally manage patients undergoing surgery. Most likely not. Single measures to improve perioperative management of high-risk patients might have only minor effects, and it will be difficult to demonstrate in a clinical trial a benefit with reasonable numbers of randomized patients. Moreover, some trials might not be possible in a randomized fashion because of ethical concerns. Nevertheless, we should always strive to improve patients care and the sum of many small optimization measures might make a difference for the benefit of the patient.

Surgery is a trauma to the patient and as any trauma especially major surgery massively alters the immune response of the body [5]. Usually, we think in terms of inflammation and anti-inflammation, maybe a mixed response. Some inflammation will be definitely necessary for the healing process following the trauma. But how much? Whereas evolution has developed defence mechanisms for physical trauma, Mother Nature has not foreseen surgery. On the other hand, activation of inflammatory genes is generally followed by activation of an anti-inflammatory response, which might predispose for nosocomial infections as well as impaired defence against seeding of tumour cells. Thus, should we accelerate the immune response or step on the brakes? There is currently no answer to this question and it might be different for the individual patient depending on his individual immune response to surgery. Moreover, the paradigm of inflammation vs. anti-inflammation may be by far too simplistic. We are just at the beginning of understanding the complex network of the immune response to surgery. Hundreds of genes are activated and the time course is even more complex [5]. It is questionable whether we ever will be able to analyse the immune status of a patient and draw therapeutic conclusions from it based on our current simplistic view on it. Maybe in the future 'big data' tools and computer-aided diagnoses, more or less as a form of artificial intelligence and advanced decision support systems, might help to enter an era of perioperative immunologic management.

So far, we have to accept that 'postoperative infections are an extremely common cause of postoperative complications and lead to poor outcomes …'. Torance *et al.* (pp. 376–383) in their review on this subject come to the opinion that 'perioperative immune monitoring, through either the analysis of perioperative cytokine gene expression patterns or

Department of Anesthesiology and Intensive Care Medicine, University Hospital Bonn, Bonn, Germany

Correspondence to Professor Andreas Hoeft, MD, Department of Anesthesiology and Intensive Care Medicine, University Hospital Bonn, Sigmund-Freud-Straße 25, 53105 Bonn, Germany. Tel: +49 0 228 287 14110; fax: +49 0 228 287 14115;
e-mail: Andreas.Hoeft@ukb.uni-bonn.de

Curr Opin Anesthesiol 2016, 29:372–375
DOI:10.1097/ACO.0000000000000347

postoperative changes in cell surface characteristics of specific immune cells, holds the greatest promise in terms of predicting the occurrence of postoperative infections'. In our opinion, it still will be a long way as we do not know yet, which patterns really predispose for postoperative infections and possibly simple clinical risk factors such as known comorbidities might be even more predictive for postoperative infections (diabetes, age, site of surgery, fragility, nutritional status, etc.), and lab tests are futile if the results will not lead to a therapeutical consequence. As long as we cannot interpret immune status lab results, which would then lead to an explicit therapeutical intervention, it seems unnecessary to perform these. We already apply antibiotic prophylaxis in most patients. Postoperatively screening and early detection of infection by modern quick and sensitive PCR-based techniques [6] might be more helpful, at least in the near future.

The other reviews deal with a mixed bag of comorbidities, some of them related to each other. Obesity will become more prevalent, and with the aging population also diabetes, hypertension, heart failure, coronary heart disease, chronic renal failure, anaemia, and patients prone to develop postoperative delirium. For most of these problems, there are no evidence-based 'magic bullets'. Mostly, a bundle of various measures might help to avoid adverse postoperative outcomes.

'Higher age and cognitive impairment ...' (the latter is often not recognized as such before surgery) '... are the most significant factors for postoperative delirium'. There is no drug against delirium, it is rather the avoidance of some drugs, in particular benzodiazepines and overdose of anaesthetics, which might help. Interestingly, the only drugs, which seem to be protective are statins, presumably because of their anti-inflammatory effect. A bundle of measures to avoid delirium are recommended by Guenther *et al.*(pp. 384–390). First, delirium is often undiagnosed as it occurs more often in its hypoactive variant. A tool for routine postoperative delirium screening as well as a test for preoperative assessment of mild cognitive impairment should therefore be established. Second, according to the currently available evidence, too deep anesthesia as revealed by burst suppression patterns in the electroencephalogram should be avoided. This is most likely one of the strongest arguments for applying bispectral index (BIS) monitoring, even more important than avoidance of awareness by BIS monitoring. Most effective against delirium seems to be a multicomponent intervention programme with early mobilization being one of the key components. Taken together, prophylaxis and treatment of delirium does not come at no cost. It costs time and personnel for pre and postoperative screening as well as for additional intraoperative monitoring of depth of anaesthesia. This will be a major handicap to introduce appropriate delirium management in clinical practice, even if in theory the additional costs might be offset by savings because of decreased complications and decreased length of stay in the hospital.

Cardiovascular comorbidities are another focus of the reviews in this issue. Since years, it is known that the postoperative mortality in patients with chronic heart failure is even higher than in patients with known coronary artery disease [7]. It is also known for years that systemic inflammation (as caused by surgery) is associated with cardiodepression [8]. It is therefore not surprising that 25% of patients with heart failure suffer from an acute exacerbation in the perioperative period. With brain natriuretic peptide and N-terminal-pro B-Type natriuretic peptide, we now seem to have an appropriate biomarker for preoperative assessment of patients with heart failure. Clearly, patients with newly diagnosed heart failure should be preoperatively optimized and a cardiology consult might be indicated. In general, medication in patients with known heart failure should be maintained perioperatively and the crucial question might be whether medical therapy can be still improved preoperatively. However, surprisingly little research is available on how to deal with heart failure patients intra and postoperatively. There is neither guidance in which patients' enhanced haemodynamic monitoring should be applied nor what the main haemodynamic goals should be. Furthermore, there are no recommendations how to deal the balance between fluids and inotropic support or vasopressors. Should fluid management be restrictive with more positive inotropic support or should fluids always be given until maximal filling of the heart with maximal stroke volume is achieved? Even the choice of vasopressors and catecholamines is unclear. How about levosimendan, a 'hit and run' drug, which based on its pharmacokinetics, would cover the most difficult first 3 days after surgery? And, are there different approaches to systolic and diastolic heart failure? Still more questions than answers. Smit-Fun and Buhre (pp. 391–396) strongly recommend the intraoperative use of echocardiography. This might be realistic in a privileged university hospital, but it might currently be unrealistic in many 'normal' hospitals, not only because of the required equipment but also because of a lack of adequately trained personnel.

The patient with hypertension is very common and is covered in the review by Lapage and Wouters (pp. 397–402). Again, the approach to

the hypertensive patient is more 'eminence based' than evidence based. Hypertension itself might be a less risk factor for surgery than the other comorbidities often associated with it, like heart failure, diabetes, and renal impairment. Today, Lapage and Wouters (pp. 397–402) recommend to be somewhat more liberal regarding acceptance of hypertensive patients for surgery as it might have been common practice years ago. Only grade 3 hypertension, which is systolic blood pressure above 180 mmHg or a diastolic blood pressure of more than 110 mmHg, should be postponed. How should we manage hypertensive patients intraoperatively? Again, there exists no clear answer except to avoid β-blocker withdrawal. Also, there is now cumulating evidence that intraoperative hypotension is associated with adverse outcomes. In patients who receive angiotensin-converting-enzyme (ACE) inhibitors this might become problematic: On the one hand these patients have a higher incidence of hypotension, on the other hand perioperative withdrawal of ACE inhibitors might be harmful. So what should be the consequences? Lapage and Wouters (pp. 397–412) come to the somewhat weak conclusion: '... an individualized and pathophysiology-based approach to control intraoperative blood pressure may be the best option to guide hypertensive patients through the perioperative period'. This conclusion is not really satisfying, but we also cannot offer a better one.

Myocardial injury after noncardiac surgery (MINS) is a relatively new pathophysiologic entity, which has been unrevealed by the Vascular Events in Noncardiac Surgery Patients Cohort Evaluation (VISION) study [9] and which is covered by Mauerman *et al.* (pp. 403–412). It has been recognized now that many more patients have clinically silent troponin elevations after surgery than formerly thought. MINS is not necessarily a myocardial necrosis similar to myocardial infarction. It might only be a risk marker, and surgery in this context is basically a stress test. However, MINS is not just a 'troponinitis' but it is associated with significantly worse outcomes. As this entity is new, nobody really knows how to deal with these patients as the clinical trials appropriately addressing possible treatment options for MINS are still underway. However, little or only weak evidence cannot be an argument to ignore MINS, that is, not to measure it (What I do not know does not bother me ...). High-risk patients should be screened postoperatively and should be treated according to our current best knowledge, which is basically with statins and aspirin. Mauerman *et al.* (pp. 403–412) nicely give very practical recommendations to those who currently handle this issue in their clinical practice. In my own experience, it is not so easy to introduce postoperative troponin screening. Often, surgeons do not want to bother with it, and costs might also be an issue. As a result, only few currently do postoperative troponin screening, despite 'eminence-based' recommendations.

Acute kidney injury (AKI) is one of the major postoperative deadly complications. As with the other comorbidities, the prevalence of patients with chronic kidney disease and therefore prevalence of patients at risk for developing postoperative AKI will increase over the next years. Again, no evidence-based 'magic bullet' to protect these patients is available. Zarbock *et al.* (pp. 413–420) in their review recommend another bundle of measures for perioperative renal protection, and again it is mainly based on pathophysiologic rationale. They clearly point out, which patients should be preoperatively screened for impaired kidney function and serum creatinine remains to be the mainstay for this screening. Zarbock *et al.* (pp. 413–420) also give recommendations for perioperative nephroprotective measures. Appropriate haemodynamic management is important and they therefore favour enhanced haemodynamic monitoring using stroke volume variation or another functional parameter for fluid optimization. In principle, this is not much different from 'decent' haemodynamic management of any high-risk patients in any type of surgery, and therefore not really specific for the patient with chronic kidney disease. Of course, radiocontrast agents and starches should be avoided. We personally doubt whether the suggested hourly monitoring of urine output is helpful. Intraoperatively, urine output is not related to postoperative AKI, and postoperatively hourly urine output will only be measured on intermediate or ICUs.

Obese patients can be very challenging. Obesity is often associated with other comorbidities in particular diabetes and hypertension, which are covered by other reviews in this issue. Bluth *et al.* (pp. 421–429) focus in their review on the respiratory and ventilatory challenges associated with obesity. A significant proportion of these patients also have obstructive sleep apnoea. Frankly, the existence of 'obesity-associated asthma' and an 'obese hypoventilation syndrome' was new for us. The question whether obese patients will benefit from higher levels of positive end-exspiratory pressure (PEEP) is still unsolved and under investigation. Until these results are available, the authors recommend low tidal volumes, only, and leave the question PEEP and recruitment maneuver open.

What is new for the management of patients with diabetes? First, glucose is not necessarily

the gold standard for preoperative assessment anymore. It has been superseded by hemoglobin A1c (HbA1c), which is more reliable and does not require nil per os (NPO) status. Unfortunately, it is more expensive. Which patients should have a preoperative HbA1c measured? Of course those with a known diabetes mellitus! An Hb1Ac greater than 8.5% indicates an insufficient glucose control, and if possible, these patients should be referred to a diabetes specialist team. The area of tight intensive insulin therapy with physiologic target levels for glucose is over. Too many studies have proven that the danger of hypoglycaemia is too high and that the benefits are not as pronounced as hoped in the initial enthusiastic studies. It seems to be sufficient to keep glucose levels between 110 and 180 mg/dl (or 5–10 mmol/l). Maybe in the near future this will change again with the availability of new glucose sensors and smarter insulin delivering devices. Dhatariya *et al.* (pp. 430–437) point out in their review that day of surgery admission is of course possible in diabetic patients, but still too often it is used as an argument for earlier admission in current clinical routine.

Finally, the patient with anaemia is the topic of the review by Shander and Javidroozi (pp. 438–445). The evidence that anaemia is associated with poor outcomes is clearly overwhelming. However, it is not so clear what the underlying reasons are. Of course, anaemia is the major risk factor for transfusion and transfusion itself is associated with worse outcomes. Still, it is unclear what is the chicken and what is the egg. Transfusions clearly alter the immune system but they might also be just a marker for major surgery. On the other hand, a more restrictive transfusion strategy does not seem to be harmful for most patients, except perhaps those with cardiac diseases. Similarly, anaemia might just be a marker for fragility, poor nutritional status, or other comorbidities. Nevertheless, we introduced in our hospital a successful 'patient blood management' programme, including preoperative iron therapy in patients in whom it is indicated. In fact, we saved transfusions without any recognizable change in outcome, neither to the good nor to the bad. Despite the lack of a clinical benefit, there has been a significant reduction in costs.

In summary, the reviews presented in this issue cover the most prevalent comorbidities and give some practical advice how to manage these. Even if most of the recommendations are 'eminence based', they might help optimizing patients undergoing surgery. Maybe these reviews motivate some readers to start their own optimizing patients undergoing surgery campaign in their hospital.

Acknowledgements

None.

Financial support and sponsorship

None.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Li G, Warner M, Lang BH, *et al.* Epidemiology of anesthesia-related mortality in the United States, 1999-2005. Anesthesiology 2009; 110:759–765.
2. Lienhart A, Auroy Y, Pequignot F, *et al.* Survey of anesthesia-related mortality in France. Anesthesiology 2006; 105:1087–1097.
3. Pearse R, Moreno RP, Bauer P, *et al.* Mortality after surgery in Europe: authors' reply. Lancet 2013; 381:370–371.
4. Ghaferi AA, Birkmeyer JD, Dimick JB. Variation in hospital mortality associated with inpatient surgery. N Engl J Med 2009; 361:1368–1375.
5. O'Dwyer MJ, Owen HC, Torrance HD. The perioperative immune response. Curr Opin Crit Care 2015; 21:336–342.
6. Lehmann LE, Hunfeld KP, Steinbrucker M, *et al.* Improved detection of blood stream pathogens by real-time PCR in severe sepsis. Intensive Care Med 2010; 36:49–56.
7. Hammill BG, Curtis LH, Bennett-Guerrero E, *et al.* Impact of heart failure on patients undergoing major noncardiac surgery. Anesthesiology 2008; 108:559–567.
8. Mann DL. Innate immunity and the failing heart: the cytokine hypothesis revisited. Circ Res 2015; 116:1254–1268.
9. Vascular Events In Noncardiac Surgery Patients Cohort Evaluation (VISION) Study Investigators. Devereaux PJ, Chan MT, Alonso-Coello P, *et al.* Association between postoperative troponin levels and 30-day mortality among patients undergoing noncardiac surgery. JAMA 2012; 307:2295–2304.