Goal-oriented hemodynamic treatment in high-risk surgical patients
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Chapter 6

Goal-oriented Hemodynamic Treatment in Patients Undergoing Major Surgery.

Conclusions and Perspectives in the Context of Perioperative Medicine.
Introduction

Heart rate (HR) and blood pressure (BP) are classical variables that can be monitored continuously for evaluation of the hemodynamic condition of critically ill patients. The introduction of the pulmonary artery catheter (PAC) allows clinicians to be informed about central hemodynamic pressures and cardiac performance. PAC-derived values of global perfusion (CI, DO$_2$I, VO$_2$I) significantly discriminated surviving from nonsurviving patients. The pathophysiology of oxygen transport and utilization was conceptualized as an oxygen debt that should be timely corrected. The effect of this treatment was studied in prospective studies, in high-risk surgical patients and also in other groups, such as patients suffering from septic shock or trauma.

The study published by the group of Shoemaker in 1988 became a reference for identification and treatment of surgical patients who could benefit from goal-oriented hemodynamic treatment (GOHT). During the early nineties of the twentieth century promising results of perioperative GOHT were published. Others criticized these studies for weaknesses in design and bias from case mix and other potential confounding variables (Chapter 1).

The Groningen University Tune-up Study (GUTS) was designed to study the impact on clinical outcome of GOHT in patients undergoing major elective noncardiac surgery. Standard preoperative management was compared with GOHT, starting at the ICU preoperatively.

Conclusions from the thesis

The major problem that had to be faced was that the study could not be completed for logistic reasons. The study is now underpowered. Therefore, firm conclusions cannot be drawn. Nevertheless, the analyses performed suggest that GOHT does not improve outcome.

The study was focused on a reduction of complications. Although at first sight GOHT seemed to reduce postoperative complications, a more thorough analysis showed that these results were confused by clinical variables. The same conclusions were made regarding secondary endpoints: ICU length of stay (LOS) and hospital LOS. Also, the hospital mortality was very low in the GUTS (2.4%).

A large group of patients eligible for the GUTS and planned for postoperative ICU-admission was not randomized. This group was comparable regarding preoperative scoring and underwent similar surgical procedures as randomized patients who were admitted to the ICU postoperatively (n=110; hospital mortality 2.7%). Mortality was somewhat higher in this group (6.8%), but no differences were found regarding ICU and hospital LOS when corrected for potential confounding variables.

Costs for patients enrolled in the GUTS were calculated, using a model of overall hospital costs that mainly accounted for costs of ICU and hospital days. In the GUTS, overall costs in both groups were similar. Costs of patients admitted to the ICU postoperatively were calculated separately for patients of the GUTS and nonrandomized patients. Costs of the GUTS-groups were significantly higher.

Mortality, ICU LOS and hospital LOS of high-risk patients were evaluated and the results compared to those described by others in similar patients. In our (underpowered) study GOHT did not significantly improve the outcome in high-risk patients.

A critical review of the literature shows that GOHT only improved clinical outcome in a few prospective studies of mixed groups of high-risk patients. These studies have in common an unusual high mortality (15-20%) in the control group. The efficacy of GOHT in the reduction of mortality and faster postoperative recovery may have been caused by an undertreatment of the control groups. However, the conclusion that GOHT is efficacious in high-risk patients
has faded with time. Nevertheless, it can not be excluded that some high-risk patients indeed may benefit clinically from any kind of preoperative GOHT. These patients and their appropriate hemodynamic management, however, still need to be identified.

**Perspectives – the problem of defining ‘high-risk’**

The definition of ‘high-risk’ in surgery has been poorly defined. It is unclear whether the risk refers to the patient’s condition, the surgical procedure or both. The content of risk may be specialty-related. From an anesthesiologic perspective, perioperative cardiorespiratory function, airway management, metabolic changes and pain management are key issues. From the surgical perspective the emphasis lays on postoperative complications of the surgical site and detrimental effects on organ function and recovery that may lengthen hospital stay or even increase the risk of death. Some postoperative complications are related to specific surgical procedures, i.e. anastomotic leakage in surgery of the intestinal tract or ischemia of the colon after abdominal aortic surgery. The ACC-guidelines for perioperative management are confined to the cardiac risk. Limitations in other organ systems and its related risk for postoperative morbidity and mortality are reflected in the physiologic part of the POSSUM-score. Factors that are associated with the postoperative pulmonary complications have recently been identified and validated in a large study. Major noncardiac surgery is usually labeled as high-risk, yet many patients uneventfully undergo major surgical procedures. These issues at least make it necessary to redefine, qualify and quantify the content of ‘high-risk’ in the future.

**Perspectives – defining endpoints in strategies of perioperative medicine to improve postoperative outcome**

In case of management of disease, disease-free survival and survival rates are primary outcome measures. In perioperative medicine the focus in high-risk surgical patients is on improving outcome by reducing hospital mortality and morbidity. Mortality is expressed mostly as surgical mortality (30-day mortality) or hospital mortality; in some studies the window of follow-up extends to a postoperative period up to 12 months or even more. In this thesis problems are discussed by measuring the quantity and quality of perioperative morbidity. Different studies use different lists of complications. When a significant reduction in complications is found, this may be a result of a narrowed focus on the overall clinical image. The selection of complications may result in biased conclusions in advantage of new therapeutic strategies, while the clinical relevance of the selected complications is not taken into consideration. The clinical impact of complications should be accounted for, especially when complications result in ICU-readmission or lengthen hospital stay. A single complication may vary extensively in severity and clinical impact. It is of note that a majority of complications occur in a minority of patients. The percentage of patients without complications has been presented as an alternative endpoint. The clinical impact of complications is best reflected in hospital mortality, ICU LOS and hospital LOS.

**Improving outcome in high-risk patients – the perspective beyond GOHT**

The problem of postoperative mortality and morbidity in major noncardiac surgery has been approached by other strategies than GOHT. Combining such strategies was shown to be highly effective in reducing mortality, morbidity and LOS in specific categories of patients undergoing major noncardiac surgery, or so called ‘high-risk’ patients. Implementing
clinical pathways in elective abdominal aortic surgery was successful in reducing ICU LOS, hospital LOS and costs.\textsuperscript{8-10} Modification of perioperative medicine in colon surgery and other major abdominal procedures has also been shown to be effective in reducing postoperative hospital LOS and/or costs and appeared to be safe.\textsuperscript{7,11-15} In none of these studies GOHT was part of the overall strategy to accelerate and improve postoperative recovery. First, this shows that other factors than GOHT can significantly improve postoperative outcome.\textsuperscript{6,16} Secondly, this shows that many of those factors may interfere with postoperative outcome in studies specifically designed to test the efficacy of GOHT. Whether postoperative outcome represents the quality of perioperative medicine is still a matter of discussion.\textsuperscript{17,18} But identification of the factors involved may result in modified patient care to improve outcome. Preoperative nutritional condition has been established as a patient factor that determines postoperative outcome\textsuperscript{19,20}; treatment in selected patients (weight loss $\geq 10\%$) improved outcome.\textsuperscript{21} Patients with increased cardiovascular risks may benefit from medical treatment by beta- and calcium blockers or alpha-2-agonists.\textsuperscript{22} Other items have become key issues in major surgery. Maintenance of normothermia has beneficial effects on postoperative outcome.\textsuperscript{23} New developments in blood transfusion strategies have been suggested to improve postoperative outcome.\textsuperscript{24} Postoperative pain treatment by epidural anesthesia\textsuperscript{25,26}, early postoperative enteral feeding\textsuperscript{27} and early mobilization are beneficial, i.e. improve postoperative outcome. Combining such strategies into one multimodal approach has been strongly advocated in patients undergoing major noncardiac surgery.\textsuperscript{9} Careful postoperative clinical monitoring for early detection of postoperative abnormal or detrimental course may further reduce the impact of postoperative complications.\textsuperscript{28} Postoperative admission to different levels of care was shown to reduce postoperative ICU-admissions\textsuperscript{29} For esophageal resections and pancreaticoduodenectomies in cancer surgery, modification of the surgical procedure significantly reduced postoperative morbidity, ICU los and/or hospital LOS.\textsuperscript{30,31} Introduction of new surgical techniques to minimize the extent of the surgical procedure have now reached procedures in vascular and intestinal surgery that were formerly described as major and high-risk surgery. Endovascular repair of the abdominal aortic aneurysm and laparoscopic major abdominal resections have now been shown to improve postoperative outcome significantly.\textsuperscript{32,33} Surgically technical imperfections have a significant and large impact on postoperative outcome in esophageal surgery.\textsuperscript{34} In general, increased surgeon volume and hospital volume of a certain treatment are associated with reduced postoperative morbidity and mortality in major surgery.\textsuperscript{35-39} The experience of the surgeon and the surgical team involved in all aspects of perioperative medicine account both for half of beneficial postoperative outcome.\textsuperscript{40} Concentrating major surgical procedures in high volume hospitals have become the target of further improving postoperative outcome in the Leapfrog Initiative.\textsuperscript{41} New standards were defined for a set of five major surgical procedures to change the health care system, including abdominal aortic aneurysm repair and esophageal surgery for cancer. Leapfrog standards have been shown to be more efficacious than solely concentrating specific surgical procedures in high volume hospitals.\textsuperscript{42} It is in this wide context of improving postoperative outcome by different strategies in (high-risk) patients undergoing major noncardiac surgery that the clinical relevance of any kind of GOHT has to be evaluated. It was concluded that the majority of such patients do not benefit from GOHT. However, when the factors are considered that are related to postoperative outcome, it cannot be excluded that a subgroup of patients formerly characterized as high-risk still may benefit from continuous perioperative hemodynamic monitoring and treatment.
Chapter 6

Improving surgical outcome by GOHT; matching the right treatment to the right patient

When GOHT may have a crucial role in the outcome of a selected group of patients, the first and major task is to identify these patients accurately. Risk scoring systems may help to identify these patients. However, these systems are based on population-based data and supply insufficient information on the risk of circulatory deficiencies for individual patients. In the GUTS nearly all patients performed a simple exercise test preoperatively. HR, respiration frequency (RF) before and after exercise were measured, the increase in HR and/or RF was calculated and these values were also combined. However, none of the values could be correlated to postoperative outcome variables, such as the number of (postoperative) complications, ICU LOS and hospital LOS. In chapter 5 the work of Older et al. was described. They measured the anaerobic threshold (AT) in high-risk patients by preoperative bicycle testing. A level of VO$_2$I $< 11$ mL/min helped to accurately identify patients who are at risk of poor postoperative outcome. Identification of these patients may have an important implication when their (hemodynamic) condition can be modified. When postoperative outcome of these patients with a limited exercise capacity is related to conditions of general hypoperfusion, a rationale for hemodynamic treatment may emerge. The major goal in such patients is then characterized by prevention of a slide down to conditions of general hypoperfusion, eventually resulting in organ dysfunction or organ failure. The goal of GOHT needs to be clearly defined. Older et al. did not provide information on hemodynamic goals and hemodynamic results of PAC-guided treatment. The classical ‘supranormal’ values of general perfusion have been shown not to be effective in large populations. Moreover, in patients with limitations of the cardiorespiratory system, such high values may not be attainable and may even be accompanied by serious (cardiac) adverse events. For example, in 1988 Older et al. suggested that the increase of VO$_2$I from $100$ mL/min to $140$ mL/min could be of major importance. This value is still far below the desired classical endpoint of $170$ mL/min. It is of note that a condition of $100$ mL/min may be sufficient for daily life activities; in this hypothetical patient the increase of this value by $40\%$ may be crucial for surviving the insults of perioperative stress during major surgery. In 2004, however, Older commented that striving for high values of VO$_2$ does not seem to be logical – “One does not tune a car to obtain the highest use of petrol that is possible”. In this thesis it is suggested that the best value of GOHT is the patient’s maximum attainable cardiac performance as expressed by CI or SVI, while at the same time tachyarrhythmias are prevented. These maximum attainable cardiac values may help to prevent a complicated postoperative course as reflected by postoperative organ-dysfunction, -failure or even death. To attain maximum attainable values, preloading by fluids is the first choice of potential interventions. Older et al. used the PAC as instrument to optimize patients hemodynamically. He suggested focusing on adequate postoperative DO$_2$I as reflected by a stable O$_2$ER, stable and low lactate concentration and adequate urine volume. The heart plays a keyrole in providing an adequate DO$_2$I. SVI-measurements by echo Doppler during fluid loading is highly informative of the maximum attainable values by preloading and were shown to be of clinical relevance in elderly patients undergoing hip surgery and patients undergoing major abdominal surgery. Continuous monitoring of cardiac output has become available without dependency of instruments, such as the transesophageal ED, and may even be more accurate in monitoring cardiac performance than the PAC. Inotropic support may further help to improve general perfusion. The use of phosphodiesterase inhibitors instead of dobutamine may be beneficial for improving hepatosplanchnic perfusion and in patients with congestive heart failure.
The correction of ‘pre-shock’ states, however, will not be attainable in all patients. Hemodynamic management may elucidate the existence of severe restrictions of the cardiorespiratory system. In clinical practice such monitoring results may help to decide whether to limit the extent or even abandon a surgical procedure. This has a close relation with the finding by Del Guercio et al. that was described in Chapter 1. They advised not to perform major surgery in patients with uncorrectable deficiencies. Nevertheless, some of these patients underwent major surgery. Uncorrectable hemodynamic conditions appeared to be highly predictive for an increased mortality rate. In the future the value of GOHT should be tested in randomized controlled trials, in which only patients are included who have an AT < 11 mL/kg/min and are planned for major (abdominal) noncardiac surgery. Identification of patients and/or testing of the AT in such patients may be a task of the preoperative anesthesiologic assessment clinic. The target of treatment should be the maximum attainable value of SVI of the individual patient in response to fluid challenges. The SVI should be monitored continuously. The use of inotropics in such patients needs careful evaluation, as due to the side effects their use may be more harmful for the patient than beneficial. Lower and upper limits for HR have to be strictly defined for reasons of safety, especially in patients with cardiac failure or (reversible) ischemic heart disease.

Increasing general perfusion may be beneficial for overall improved outcome in patients with a reduced AT. However, this does not exclude the occurrence of regional hypoperfusion. Direct measuring and treatment of regional blood flow during esophageal and abdominal aortic surgery may have implications for future intraoperative hemodynamic management, not only in patients with a low AT.

Pathophysiology of organ dysfunction and organ failure in major surgery

Prevention seems to be more effective than treatment of postoperative morbidity. A reduction of morbidity may also reduce hospital mortality. Regional hypoperfusion is presumed to result in an insufficient oxygen supply. This may induce organ dysfunction, which under severe and long-lasting conditions may progress to multi organ failure (MOF) -see Introduction-. Although this is the main pathway that causes organ dysfunction, alternative mechanisms at cellular level have been proposed. The systemic inflammatory response syndrome (SIRS) and sepsis responses have been thoroughly investigated. However, the complexity of the inflammatory response and its genetic backgrounds make it difficult to find a rationale for the best possible treatment. In major surgery the correlation between the type and severity of SIRS and postoperative outcome has been established. It is unknown whether these mechanisms can be triggered by surgical trauma independent of circulatory conditions. They may be augmented by hypoperfusion or hypoxemia. The interaction between both is a hypothetical one. When the surgical patient has become a critically ill patient, characterized by one or more postoperative complications or organ dysfunction, removal of causative (surgical) problems does not automatically reverse the dysfunction. Efforts to improve outcome by GOHT (increasing \( \text{DO}_2 \)) in critically ill (surgical) patients with established organ dysfunction, have not been successful in reducing morbidity or mortality. Early hemodynamic interventions in severe sepsis may be beneficial. However, if the detrimental course is not timely interrupted, organ dysfunction and/or failure become unavoidable. Attempts to reverse such a condition by any type of GOHT may be in vain. Singer et al. recently described MOF as an adaptive response to overwhelming inflammation. This is in close comparison with the cellular mechanisms that result in stunning and hibernation of the heart during and after conditions of hypoxia/reperfusion. Here we are at the edge of different cell responses after reperfusion:
necrosis, apoptosis or regeneration. The elucidation of the molecular basis of these mechanisms may help to understand disease from a pathophysiologic point of view. Until now a gap remains between understanding and treatment of conditions that are effective in the reversal of organ dysfunction and failure. Baue made considerations about the pathophysiology of MOF and its treatment in critical care; modification of the SIRS has not yet resulted in improved clinical outcome. When ‘hibernating-like responses’ play a role in survival of cells and organs, manipulation of these mechanisms may be deleterious. Tight regulation of glucose and treatment by recombinant activated protein C improves postoperative outcome in critically ill patients. Till now, after the causes of critical illness have been neutralized, in general we have nothing more to offer than supportive treatment of critically ill (surgical) patients.

**Conclusion**

GOHT as a preventive strategy may improve postoperative outcome in a limited group of formerly denoted ‘high-risk’ surgical patients. A well-designed prospective randomized controlled trial of selected patients is needed to assess the additional value of GOHT amongst other non-GOTH perioperative strategies that have been shown to be efficacious in improving postoperative outcome as reflected in reductions of mortality, complications, ICU LOS and hospital LOS. When (serious) postoperative complications occur, resulting in organ dysfunction or organ failure, no data are available indicating that treatment directed at enforced and/or accelerated recovery of function improves outcome. First the cause of organ dysfunction/failure has to be eliminated. Thereafter, supportive treatment will help to achieve the best possible outcome. Elucidating pathophysiologic mechanisms of disease at cellular and organ level may hopefully result in novel therapies that help to improve a complicated postoperative course in major noncardiac surgery.
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