Reducing Mortality in the Perioperative Period

Second Edition

Giovanni Landoni
Laura Ruggeri
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Rinaldo Bellomo

1.1 Introduction

Perioperative care is extremely complex and dynamic due to several factors. First, it typically involves doctors from different specialties either sequentially or simultaneously: surgeons, cardiologists, internists, anesthetists, and intensivists. These specialty groups have different (and sometimes competing) clinical and physiological priorities as well as different non-evidence-based belief systems. Second, these priorities, belief systems, and their application to patient care change from the preoperative period to the surgery itself and the postoperative period. They vary from premedication, to induction, to surgery itself, to the immediate period of emergence from anesthesia to the immediate control of pain after awakening to the period after awakening (or, in intubated patients, after transfer to the postoperative care area or intensive care) to the need to maintain cardiorespiratory physiological safety and relieve pain. Third, comorbidities affect the way in which these interventions are prioritized or delivered in ways that are unpredictable and also poorly supported by high-level evidence. These interventions are then typically adjusted hour to hour, sometimes minute to minute, in order to meet perceived biochemical, physiological, and clinical needs and to achieve variable intermediate and then longer-term biochemical, physiologic, and clinical goals.

The way clinicians choose, time, and modulate the intensity and duration of these interventions is typically driven by a poorly understood and perhaps impossible to understand mix of evidence, inductive physiological reasoning, local culture, previous mentorship, resource availability, heuristic bias, fashion, technology, medicolegal concerns, and random and unpredictable other forces and events.

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All of the above extraordinarily complex human activity falls under the term of "perioperative medicine" [1]. Much evidence suggests that surgical volume (a surrogate of surgical skill) conditions the outcome of major surgery [2]. Yet other studies also suggest that perhaps 50 % of the variance in surgical mortality relates to factors beyond surgical volume, skill, and performance [3]. If these studies are correct, then perioperative medicine is likely to matter, and its quality, safety, and the interventions it delivers may be an important determinant of morbidity and even mortality.

If interventions exist which, if applied as part of perioperative care, can decrease mortality, then such interventions should surely be applied throughout the world to decrease perioperative mortality. Conversely, if interventions exist which, if applied as part of perioperative care, can increase mortality, then such interventions should surely be avoided throughout the world to decrease perioperative mortality. This imperative should be true even when only relatively small improvements can be achieved. For example, even a 1 % absolute reduction in mortality with a number needed to treat of 100 will save thousands of lives worldwide given the massive number of patients who undergo major surgery and, therefore, receive perioperative care.

Furthermore, the cost of perioperative interventions is typically small because they last for short time (the perioperative period). If each intervention cost 1,000 dollars, then $100,000 would save a life. If that patient lived, for example, on average 5 more years after that surgery, the cost of such care would have only been $ 20,000 per year of life saved. This amount would be 50 % of the yearly cost of dialysis, a widely accepted benchmark as sufficient to socially and to financially justify an intervention. Thus, there is a strong case for implementing perioperative interventions that can decrease mortality and for avoiding those that increase mortality and morbidity. Yet, what are these interventions? The search for these interventions begins with the identification of all perioperative interventions that have been reported *at least once* to either decrease or increase mortality. This does not imply that such interventions need to be implemented (the robustness of trial findings, their biological plausibility, their fragility index, the chance of type I or type II error, and their reproducibility all would need assessment), but simply that they should take priority as targets for level I trials or, if appropriate, they should be translated into improved practice.

A recent study identified 14 of such interventions: 11 that had reported at least once a decrease in mortality in a randomized controlled trial or after meta-analysis and two that reported an increase in mortality. Yet the fact that a particular intervention has been shown to change mortality in a particular study does not say anything about the quality of such a study [4]. A comprehensive assessment is crucial to evaluate whether the evidence justifies recommendations or suggestions or should be dismissed as of little relevance [5]. Without such a thoughtful and systematic assessment, one might otherwise equate the finding of a single-center non-blinded 40-patient study to those of 4,000-patient multicenter randomized double-blind, placebo-controlled trial. Such implied equivalence would be a travesty of common sense, a subversion of clinical and statistical science, and a betrayal of the meaning of evidence. Perhaps more importantly, it may mislead clinicians to deliver unproven

and, often enough, potentially dangerous interventions. However, who is to perform such an assessment? Who is to issue such recommendations or suggestions? How is such a process to be undertaken? When should it be done? Where should it be done? The global response to these questions has, so far, broadly been based on the development of consensus conferences and the issuing of consensus guidelines.

1.2 The Current Consensus Process

The above consensus approach seems a reasonable response to the need of assessing evidence in a systematic manner. Yet, it is currently achieved by first putting together a group of so-called experts. This is a problem, because no systematic assessment exists to quantify what defines a person as an expert. Dealing with the topic under discussion, should it be the number of postoperative patients treated? This is a problem as such data are typically not available. Should it be based on the number of publications in the field of perioperative medicine or in the subdivisions of it under scrutiny? Should such publications be weighted according to journal of publication and impact factor or should they be weighted according to number of citations? Such information is typically available but never used. The process of expert selection relies on personal contact, availability, connections, and political or hierarchical imperatives.

Because of all the factors above, the current consensus process implies that a group of perhaps 10–20 "experts" is in position to hold sufficient wisdom and knowledge to tell the practicing community of thousands of perioperative medicine clinicians what to do. Should these thousands of clinicians not be rather left alone to make the necessary judgments independently? They can presumably read and think. They can presumably make informed judgments. Consensus statements and guidelines may well be lacking in any utility as well as being potentially misguided because they are issued by a small group of acolytes with limited worldwide perspective. The example of the surviving sepsis campaign guidelines issued in 2008 is an illustrative demonstration of the flaws of this system [6]. Rejected by the Australian and New Zealand Intensive Care Society [7] because of perceived biases and lack of rigor, it recommended two interventions which were supported by dubious scientific data and which were subsequently challenged by two major trials: one found that the intervention increased mortality, while the other lead to the removal of the drug in question form the market [8, 9]. Even more spectacular, there has been the recent demise of yet another strong recommendation by experts: the use of early goal-directed therapy in the early treatment of sepsis [10–12].

In response to the above concerns, the oligarchy of experts who control the consensus process will immediately point that many clinicians do not understand the flaws of published studies, the details of randomization, the impact of lack of blinding, the issues of power and type I or type II error, the presence of bias [13], the limitations of single-center studies [14], the concept of biological plausibility [15], and the impact of confounders [16]. Unless a group of wise men (and they are, almost always, mostly men) tells them, clinicians will continue to deliver

suboptimal perioperative care. Yet, there is no empirical evidence to confirm this dominant paradigm. It is also of interest that there is no level 1, randomized controlled empirical evidence that the issuing of consensus guidelines leads to changes in practice or outcome. There is also no randomized evidence that allocation of clinicians to guideline implementation as opposed to standard care changes patient outcomes.

1.3 New Approaches to Consensus Development

Are there alternatives to the oligarchy-based consensus process? A web-enabled approach may offer the beginning of an alternative and more democratic definition of "consensus." Through such an approach, anybody can see the self-reported position of many more doctors from many more countries [17, 18]. This type of response and consensus does not indicate that the physicians in questions actually apply interventions they believe might be beneficial or that they think they should be given to all patients. It simply indicates that they believe that some of them might be of higher priority or higher likelihood of success than others [19].

Would such a web-enabled approach offer some kind of salvation or relief from the cacophony of opinions, expert views, sponsored academic consensus conferences, debates, symposia, webinars, and guidelines that increasingly torment the lives of busy clinicians? Or is this kind of web-enabled consensus yet another pernicious metastasis into the field of medicine of the ever-spreading "social network" disease currently afflicting teenagers? Only time will tell.

However, this approach represents the beginning of a new way to achieve a consensus process that is likely to evolve further in the next decade. If we can capture the self-reported views of hundreds of physicians, then the next step might be to capture what they do on a given day. Just following up on the initial response with questions like "Did you apply treatment X to the care of any of your postoperative patients in the last 48 hours?" might provide us with a unique insight into actual clinical practice among the cohort of physicians with an interest in postoperative medicine and web-enabled expression.

We might ask such clinicians whether they practice perioperative hemodynamic optimization and what they did (fluids? vasopressors? both? what physiological targets? and so on) in their last postoperative three patients to achieve such optimization. Such information might provide us with a unique sense of current practice in this field from a more global perspective. Finally, they might agree to implement interventions and collect simple data for patients treated over a 24-h cycle. The ethics of such interaction might prove complex but not insoluble. The use of the web for the purpose of research and consensus development is in its infancy and the possibilities are vast. More provocatively, one could conduct randomized controlled trials comparing "expert-based consensus therapy" with "web-enabled consensus therapy." If differences were found, it would be fascinating to see web-enabled consensus therapy deliver better outcomes than self-appointed expert-based consensus.

Table 1.1 Advantages and disadvantages of traditional approach to consensus development and a new web-based approach to consensus development

Traditional approach to consensus	Web-based approach to consensus
Advantages	**Advantages**
Widely used and well known	Democratic
Logistically easy to implement	Inclusive and open
Often supported by learned societies	Consensus could be dynamic and evolve
Politically powerful	Extends beyond "Western" countries
Typically includes some key investigators in the field	Once website setup, cheap to maintain and apply to multiple issues
Typically results in generation of document	Not linked to political agenda of a given society
Typically results in suggestions or recommendations	No experts are self-appointed and multiple investigators could offer preparatory comments
Disadvantages	**Disadvantages**
Exclusive and non-democratic	May be unable to issue suggestions or recommendations
Typically only expresses "Western" views	Web responders may not be sufficiently representative
Carries significant costs	Lack of support from learned societies will inhibit distribution of findings and political impact
Often only includes society members and is parochial	May be unable to develop and deliver guidelines
May have unstated political aims as well as scientific ones	Novelty may generate confusion in relation to expectations
Experts may be "self-appointed" and have limited clinical experience	Controversy regarding who controls the website and the issues to be addressed
Key investigators with contrary views may be excluded	Possibility of multiple competing consensus websites creating conflict and confusion
Suggestions and recommendations may prove biased and misleading	

It is impossible to know now whether the Internet will become the electronic cradle of a new clinical consensus democracy or simply produce a chaotic cacophony of views, a Babel of personal preference-driven behavior. Many health workers will be skeptical about the amount of impact that they can make through online participation. Yet, the massive spread of medical information through the Internet will become a central networking hub for our clinical world. This initial approach has now been tried and may evolve to more sophisticated levels asking physicians to agree or disagree with statements and using a Likert scale to obtain such information. It might also allow more complex votes including not only a quantitative aspect of support but also the possibility of expressing uncertainty or offering alternative views. It may consider comparisons of the opinion and voting of experts versus that of the web participants and so on. Some of the advantages and disadvantages of the current approach and the potential new approach are presented in Table 1.1.

Although these are the first steps and there is uncertainty about the future evolution of this process, this new consensus methodology has the potential to increase our understanding of global practice and to help us better define research priorities. If the Internet is to become a new international tool of clinical consensus decision-making, through which clinicians can participate in and influence perioperative processes, it is vital that all health workers irrespective of specialty and geographical location have physical access to it and the skills and confidence to use it. It must be collaborative, cooperative, inclusive, and egalitarian. This is quite different from the current dominant approach, which is often competitive, exclusive, non-egalitarian, and based on academic prestige. Whether this can be achieved remains uncertain.

Conclusion

The development of consensus and the issuing of consensus guidelines in medicine and in perioperative medicine in particular appear to be potentially useful activities whose impact on patient outcome, however, remains unclear. The current approach based on the creation of semi-arbitrary groups of so-called experts who meet for a period of time and issue statements, guidelines, suggestions, and recommendations has several potential flaws but has not, until recently, been challenged by another approach. The arrival of a web-based consensus process provides the first challenge to the current model and overcomes some of its limitations while potentially creating others. Which one of the two models will prove empirically superior and will become the dominant paradigm in within a decade or two remains uncertain.

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The Process of Consensus Building

2

Massimiliano Greco, Pier Carlo Bergonzi, and Luca Cabrini

2.1 General Principles

Surgery is one of the most common medical procedures in the world, with up to 280 million surgical procedures performed every year [1], a large part of those performed in middle- and high-income countries. Consequently, perioperative care absorbs a large part of economic resources of healthcare systems in the western world.

However, the amount of high-quality evidence underlying perioperative care is surprisingly low. The majority of drugs and techniques employed in the perioperative period have never been proved to be helpful or detrimental in terms of survival, and they are usually employed according to local "traditions," or their efficacy is based on surrogate outcomes only, which are more frequently used to reduce costs and sample size [2].

Moreover, perioperative mortality has been found in large prospective studies to be lower than 4 %. Consequently, with millions of patients undergoing surgery each year, even a small difference in mortality for each drug could affect the lives of thousands of patients each year.

To rationalize and to help clinician improve perioperative care, several guidelines have been published by scientific societies. Guidelines are traditionally built on expert-based knowledge more than on randomized evidence, due to a shortage

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of the latter. Accordingly, most of the recommendations included in guidelines are considered in the lower part of the hierarchical pyramid of evidence-based medicine [3], and such is the standard of medical care.

To solve these issues, the Democratic Consensus Conference methodology was developed [4, 5] and successfully employed in a previous Consensus Conference on perioperative medicine in 2012 [6] and in other settings [7–10]. We performed a new study on perioperative mortality using the same methodology, to update the previous Consensus Conference with the best randomized evidence published in the perioperative setting in the last 3 years.

The Consensus Conference was based on the previously described five-step model: the first phase of systematic review is to identify eligible articles, followed by the first web-based polling (second phase) and by the Consensus meeting (third phase). Meeting results were again validated through a new web polling (fourth phase). The last step is dedicated to reanalysis and publication of results [4] (Fig. 2.1).

2.2 The New Systematic Review

A systematic review was conducted ex novo, with no time limits. The systematic review started in September 2014 and was concluded in January 2015 by a trained team of physicians.

Studies were retained in the Consensus process if the following criteria were met:

- Based on randomized evidence (RCTs or meta-analyses of RCTs)
- Focused on ancillary/non-surgical interventions (drugs, strategy, or techniques)
- Reporting on mortality, with a statistically significant difference between cases and controls
- Published in a peer-reviewed journal
- Including adult patients undergoing surgery in any setting

Every participant to the Consensus could propose new articles, fulfilling these criteria, at any moment until the end of the consensus meeting.

From a total of 19,633 papers identified by research on PubMed and by expert advice, 85 were retained for detailed assessment (19,548 were excluded at title-abstract level). Ten papers were further excluded after detailed assessment, and 75 were proposed in the first online poll and discussed in the in-person meeting.

2.3 First Web Vote

According to the well-validated democracy medicine approach, two international web polls were conducted, before and after the consensus meeting. A total of 500 physicians, from different medical specialties, took part into the online poll from 61 countries, on the dedicated website www.democracybasedmedicine.org. Participants covered a large area of medical specialties involved in the perioperative care. The upcoming consensus was advertised via web and e-mail and through scientific networks.

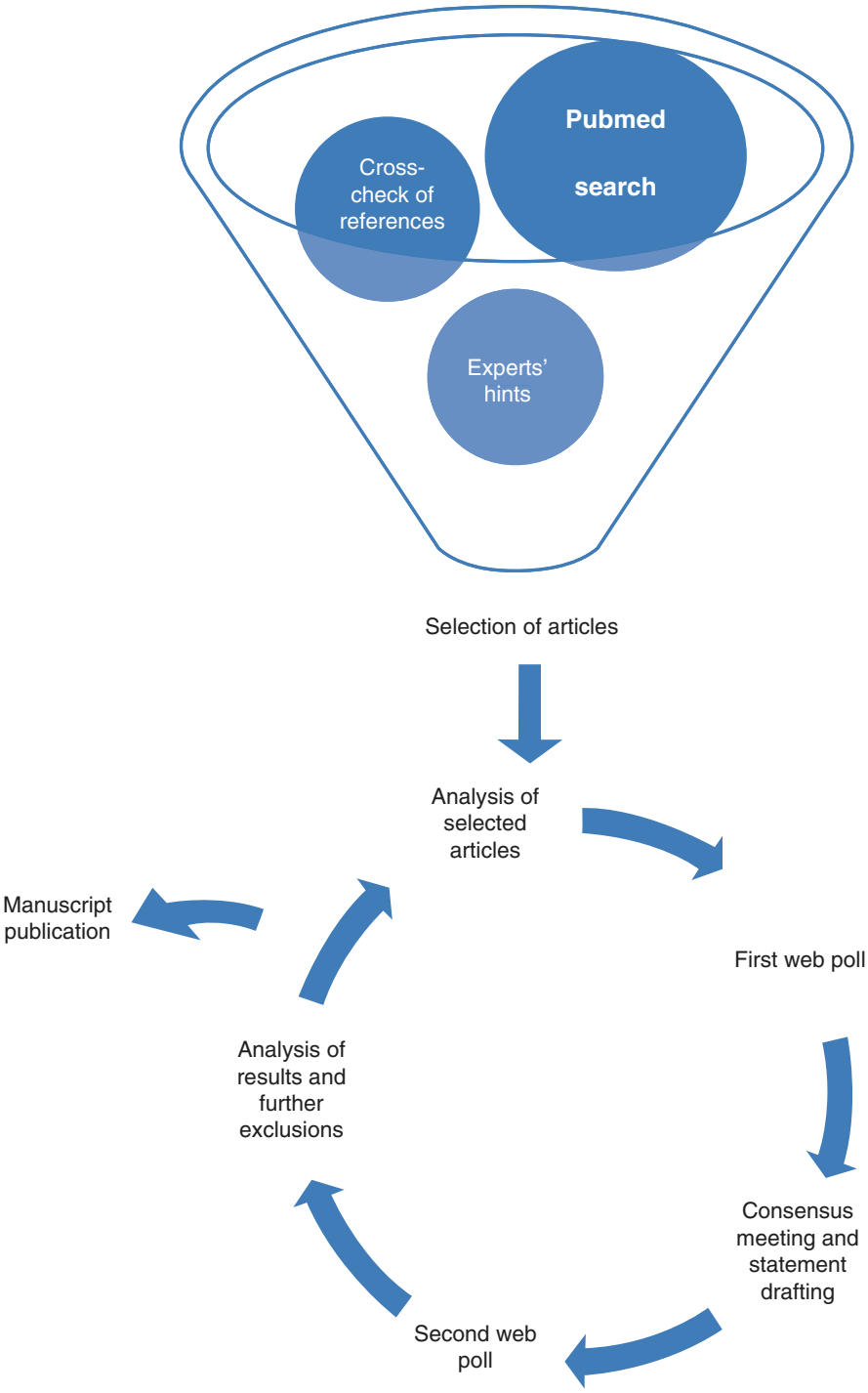

Fig. 2.1 Consensus Conference process

The first web poll was conducted from March 1 to March 5, 2015, and participants were asked to vote in favor or against the identified topics and to submit further articles to the consensus. For each intervention participants were actively encouraged to express their opinion in a separate open panel. All opinions were collected and presented within the meeting.

Web participants were required to disclose any potential conflict of interest for each proposed intervention, and they were invited to suggest new articles up to the date of the Consensus meeting.

2.4 Step 3 Consensus Meeting

A face-to-face meeting was held on March 6, 2015, at the Vita-Salute University of Milan among a task force composed by anesthesiologists, intensivists, surgeons, cardiologists, and epidemiologists.

Each consensus topic was presented by a rapporteur and commented by one or two discussants. Through argumentation, a meeting position statement was approved describing the reasons for the inclusion or for exclusion.

Excluded papers with reasons for exclusion are reported in Table 2.1.

From this web poll, two papers were excluded as screening failures; 16 papers (13 topics) were considered major exclusion due to methodological limitations or inconclusive findings.

Sixteen topics (46 papers) were finally selected by the Consensus Meeting as substantially proven to affect mortality in the perioperative period.

Table 2.1 Topics excluded by the consensus process

Topics reducing mortality excluded during the consensus meeting	Topics increasing mortality excluded during the consensus meeting	Topics excluded due to low agreement after the second web poll
Ticarcillin	Oxygen	Minimal extracorporeal circulation
		Liberal transfusion strategy
Abdominal compression in cardiopulmonary resuscitation		Statins[a]
N-Acetylcysteine	Deep sedation worse than light sedation	
Hypotensive resuscitation	Urinary alkalization with sodium bicarbonate	
Active negative pressure peritoneal therapy		
Chlorhexidine oral rinse		
Alpha-2 adrenergic agonists		
Nesiritide		
Antifungal prophylaxis amphotericin		
Dopexamine		

[a]Removed after publication of new high-quality evidence against the intervention

2.5 Second Web-Based Polling

The statements produced in the consensus meeting were again subjected to peer review in a second online poll between March and August 2015. Participants voted again to support or dispute the topics and statements that were proposed by the Consensus.

Questions included in the second web survey are reported in Table 2.2.

Topics with statements that obtained a low percentage of agreement (<67 %) were excluded at this step. Two topics were excluded for low agreement and are reported in Table 2.1. One topic (statins) was further excluded, with the consensus of the majority of participants, during the article drafting phase, when a new high-quality evidence against this intervention was published.

In conclusion, the second Democracy-based Consensus Conference on the perioperative medicine identified 13 topics, 11 reducing mortality and 2 increasing mortality. These are reported in Table 2.3 and extensively explained in the other chapter of this book.

Table 2.2 Structure of the second web survey

Interventions reducing mortality	Interventions increasing mortality
1. Do you agree with this sentence? (*Yes*; *No*; *Do not know*)	1. Do you agree with this sentence? (*Yes*; *No*; *Do not know*)
2. Do you routinely use this intervention in your clinical practice? (*Yes*; *No*; *Does not apply*)	2. Do you routinely avoid this intervention in your clinical practice? (*Yes*; *No*; *Does not apply*)
3. Would you include this intervention into future international guidelines to reduce perioperative mortality? (*Yes*; *No*; *Do not know*)	3. Would you suggest that future international guidelines should contraindicate this intervention to reduce perioperative mortality? (*Yes*; *No*; *Do not know*)

Table 2.3 Drugs/techniques influencing perioperative survival

Topic	Type of evidence
Reduces perioperative mortality	
Perioperative hemodynamic optimization	5 meta-analyses of RCTs
Insulin for glycemic control	2 RCTs and a meta-analysis of RCTs
Noninvasive ventilation	3 RCTs
Levosimendan	4 meta-analyses and a RCT
Leukocyte-depleted red blood cell transfusion	2 RCTs
Preoperative IABP (intra-aortic balloon pump) in high-risk CABG	4 meta-analyses and a RCT
Volatile agents	2 meta-analyses
Tranexamic acid	A meta-analysis
Neuraxial anesthesia	4 meta-analyses
Remote ischemic preconditioning	A RCT
Selective decontamination of the digestive tract	A meta-analysis
Increases perioperative mortality	
Beta-blockers	3 meta-analyses and a RCT
Aprotinin	A RCT

2.6 A Glance to the Future

The second Consensus Conference in perioperative medicine identified only 13 items as able to affect mortality in the perioperative period. This number is astonishing low, when compared to the vast number of drugs and techniques that are employed in the perioperative care.

As the population of patients undergoing surgery is becoming increasingly aged and morbidly ill, any intervention in perioperative medicine should be evaluated according to the principles of evidence-based medicine. We believe that drugs and techniques employed in the perioperative medicine should be evaluated using survival as main outcome, in place of surrogate outcomes. Multicenter RCTs should be used instead of lower-quality evidence [11]. It is mandatory for the society that research funding increases in perioperative medicine, from both private and institutional donors, to stimulate research in this area. This process has certainly already begun, but needs to be magnified to further extent to improve surgical safety and reduce the burden of mortality in perioperative care. As more and more will be published in the next years in this setting, we plan to perform other updates of the Consensus Conference using the innovative Democracy Medicine approach, to allow it to remain a valuable help for clinicians in their daily clinical practice.

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Noninvasive Ventilation and Perioperative Mortality

3

Paolo Feltracco, Daniela Pasero, and Laura Ruggeri

3.1 Background

Postoperative pulmonary complications (PPCs) are caused by a variable impairment of respiratory function, whose common responsible are the dysfunction of the abdominal, thoracic, and diaphragmatic muscles, along with reduction in lung parenchyma excursion and derecruitment occurring after anesthesia and surgery. These abnormalities are frequent, following long and high-risk surgical procedures, and may persist for days. Patients affected by any pulmonary abnormality occurring in the postoperative period are at increased risk of developing ventilation perfusion mismatch, hypoxemia, carbon dioxide retention, and respiratory failure. Moreover, PPCs may be associated with prolonged hospital length of stay, long-term poor outcome, and reduced survival rate [1].

As described by the EUSOS study ($N=46{,}539$) [2], including adult patients undergoing noncardiac surgery, postoperative acute respiratory failure is one of the main causes of increased morbidity and mortality. It affects 5–10 % of all surgical patients and up to 40 % of those undergoing abdominal surgery [3, 4].

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Invasive mechanical ventilation has been considered for many years the unique ventilatory strategy for acute PPCs, despite the associated complications and mortality rate [5]. Nevertheless, in recent years noninvasive ventilation (NIV) has increasingly been considered a simpler and safer alternative to invasive mechanical ventilation to extend optimal respiratory care into the postoperative period. Meta-analysis and original works in this area [6, 7] have demonstrated that NIV in the prevention or treatment of perioperative respiratory failure is associated with a reduction in the rates of pneumonia, reintubation, and overall morbidity. NIV effects on survival come mainly from few works presenting a small number of patients and/or a poor quality, as recently confirmed by the update of the web-based International Consensus Conference on mortality reduction after adult surgery [8, 9]. Notably, NIV is currently underutilized in the perioperative setting as few centers have the possibility to employ NIV in the surgical wards [10] or even in the surgical ICU.

3.2 Published Evidence

NIV is increasingly used either to prevent acute respiratory failure after surgery (prophylactic use) or to treat acute respiratory failure once it has occurred (therapeutic use). Two recent meta-analyses [7, 11] of randomized clinical trials on NIV in the perioperative period were performed in the setting of abdominal surgery (nine studies), thoracic surgery (three), cardiac surgery (eight), thoracoabdominal surgery (three), bariatric surgery (four), and solid organ transplantation surgery (two). They found that both prophylactic and therapeutic NIV is beneficial in reducing in-hospital stay and incidence of pneumonia and reintubation. ICU stay was reduced in postsurgical patients who received NIV after extubation. However, there was insufficient data to assess whether NIV affected patients' survival when compared with standard therapy.

3.2.1 Thoracic Surgery

Evidences of benefit in terms of gas exchange and lung volumes are well established when NIV is employed as preventive or therapeutic treatment after lung surgery, even in the case of high-risk patients [12, 13]. Lefebvre et al. analyzed the preventive approach showing how NIV approach for acute respiratory failure after lung surgery presents a reduction in the need for invasive mechanical ventilation and overall severe complications, as those affecting the surgical site (bronchial stump disruption, bronchopleural fistula, persistent air leakage, and pneumonia) [14]. However, these data was not confirmed by Lorut et al. [15] who focused on COPD patients in a randomized trial of early prophylactic NIV vs. conventional postoperative treatment following major lung surgery. They found no difference between the groups in the rate of acute respiratory events, intubation rate, infectious and noninfectious complications, duration of ICU and hospital stay, and 30-day mortality rate.

The only evidence of reduction in mortality comes from a randomized single-center trial (48 patients) in which patients with acute hypoxemic respiratory failure

after lung resection were randomly assigned to NIV or standard treatment [16]. NIV was provided with nasal mask in pressure support mode to achieve an 8–10-mL/kg exhaled tidal volume and to obtain a saturation of peripheral oxygen (SpO2) above 90 %. Standard treatment consisted of oxygen supplementation to achieve SpO2 >90 %, bronchodilators, patient-controlled analgesia, and chest physiotherapy. Nine patients in the standard treatment group (37.5 %) versus three (12.5 %) in the NIV group died ($p = 0.045$). A significant decrease in in-hospital stay and 3-month mortality rate in the NIV group emerged. Intubation and invasive ventilation was significantly lower in the NIV group.

3.2.2 Cardiac Surgery

A recent systematic review and meta-analysis of randomized trials [17] included 14 studies and 1,211 patients, mainly after cardiac or vascular surgery. NIV reduced the reintubation rate (risk ratio [RR], 0.29; 95 % CI, 0.16–0.53; P for efficacy <0.0001; I 2 = 0), hospital length of stay, and mortality. Subgroup analyses suggested that the benefits of NIV are more important in patients with ongoing acute respiratory failure and in those at high risk of developing postoperative pulmonary complications. Analyses including prophylactic studies in patients at low risk did not show a significant effect of NIV on reintubation rate nor on any of the outcomes considered except for oxygenation. Despite a growing amount of data, adequately powered randomized trials on NIV are still limited. NIV seems effective both in early and in severe Acute Respiratory Failure (ARF), improving hospital length of stay and survival. NIV efficacy when applied as a preventive tool in unselected patients is not demonstrated, and it is likely that NIV should be reserved to patients who are at high risk for postoperative ARF.

Thereafter, Al Jaaly et al. [18] randomized 129 patients to NIV versus standard care to prevent PPC after coronary artery bypass. Respiratory complications were significantly lower in the NIV group although length of stay and mortality were not different.

In a recent randomized controlled trial (RCT) by Zhu et al. [19], 95 patients who developed acute respiratory failure after cardiac surgery were randomized to positive pressure NIV vs. standard medical care and oxygen therapy as needed. The group undergoing NIV therapy displayed a lower rate of reintubation, tracheotomy, ventilation-associated pneumonia, and a reduced duration of both mechanical ventilation and ICU stay. The mortality rate in this group was significantly lower than in the standard treatment group: 18.8 % vs. 38.3 %, respectively.

3.2.3 Abdominal Surgery

The benefits of prophylactic NIV are well described in abdominal surgery. Therapeutic NIV is associated with better gas exchange, lower intubation rate, and reduction in ICU length of stay [20–25]. Squadrone et al. [26] conducted a large randomized controlled study across 15 ICUs in Italy: 209 patients who underwent laparotomy

and developed postoperative hypoxemia were randomized in two groups (CPAP 7.5 cm H_2O via helmet vs. standard care). CPAP was associated with a lower intubation rate (1 % vs. 10 %; $p=0.005$) and a lower occurrence rate of pneumonia, sepsis, anastomotic leaks, and infections. None of the patients treated with CPAP died in the hospital, while three deaths occurred among those treated with oxygen alone.

Narita and coworkers [25] applied NIV in 16 patients who developed respiratory failure and/or a massive atelectasis after liver resection. In the NIV group, respiratory-cause mortality was significantly lower (0.0 % vs. 40.0 %; $p=0.007$) than in conventional treatment without NIV (oxygen supplementation to achieve SpO2 above 90 %, inhaled bronchodilators, continuous epidural analgesia, physiotherapy). Rate of reintubation was significantly lower in the NIV group (12.5 % vs. 50.0 %; $p=0.040$), and all-cause mortality was lower after NIV treatment (18.8 % vs. 50.0 %; $p=0.100$).

3.2.4 Solid Organ Transplantation

Acute respiratory failure still represents the most frequent cause of postoperative mortality after solid organ transplantation.

Antonelli et al. [27] enrolled 40 consecutive adults recipients of solid organ transplantation, admitted to the ICU because of acute respiratory distress. Twenty patients were assigned to receive NIV through a face mask and 20 to standard treatment with oxygen supplementation via a Venturi mask. The use of NIV was associated with a significant reduction in the rate of endotracheal intubation (20 % vs. 70 %; $p=0.002$) and length of stay in the intensive care unit (mean days, 5.5 vs. 9; $p=0.03$). Moreover, a significant reduction in ICU mortality was observed with early NIV implementation, while in-hospital mortality was similar in the two groups.

3.3 Therapeutic Use

The positive pressure can be delivered as continuous positive end-expiratory pressure (CPAP) or, if an inspiratory pressure is added, as pressure support ventilation (PSV).

3.3.1 Ventilation Strategies

NIV increases functional residual capacity and oxygenation and reduces the respiratory work by increasing intrathoracic pressure. A progressive increase of pressure support and PEEP level is a good strategy to relieve dyspnea and improve gas exchange. The duration of NIV trial in the postoperative setting is difficult to standardize; practical experience and individual tolerance may determine the total daily use. Overall, the length of NIV cycles (1 to 3–4 h) is progressively reduced as gas

exchange, respiratory patterns, and clinical conditions improve. Optimal noninvasive approach is based on individual patients and local feasibility and protocols, available devices, and expertise. Notably, postoperative lung dysfunction should also be treated with a proper pain control (i.e., epidural analgesia).

3.3.2 Patient Ventilator Interface

Nasal masks, oronasal (full-face) masks, and the "total face" helmets remain the most common interfaces for postoperative NIV. The advantages of nasal masks include less dead space, less claustrophobia, and minimum complications especially if vomiting occurs. Full-face masks are nowadays more common and more suitable for a moderately dyspneic patient. However, they tend to lead to discomfort and intolerance in case of prolonged use and to be more claustrophobic. Although it has been stated that helmets are less effective than face masks in delivering NIV, the very high tolerability of the helmet makes it a better interface when prolonged and continuous assistance is needed or in case of claustrophobic patients [23].

3.3.3 Complications

Failure of NIV therapy can be considered the worst complication due to the risk of prolonged time to intubation. Lefebvre et al. [14] described a successful rate after lung resection of 85.3 %. The mortality rate in "nonresponders" to NIV was 46.1 %. Factors significantly associated with NIV failure were previous cardiac comorbidities, postoperative pneumonia, and no initial response to NIV. Other predictive factors of NIV failure were age, admission in the surgical intensive care unit (ICU), and occurrence of noninfectious complications. Riviere et al. [28] reported a rate of 30 % of NIV failure after thoracic surgery. According to the authors, four independent variables were associated with NIV failure during the first 48 h of application: an increased respiratory rate, an increased Sequential Organ Failure Assessment (SOFA) score, an increased number of fiber-optic bronchoscopies performed, and the number of hours spent on NIV. Similarly, Wallet et al. [29] found that 58 % of patients with postsurgical respiratory failure treated with NIV avoided intubation. Factors associated with postoperative NIV failure were a decrease in the paO2/FiO2 ratio after 1 h of NIV, the need for tracheal intubation because of nosocomial pneumonia, and an increased Simplified Acute Physiology Score (SAPS).

Major NIV complications as barotrauma and hemodynamic effects, although uncommon, may be potentially life-threatening and are usually correlated with pulmonary and cardiovascular involvement. Minor complications are usually related to NIV interfaces or airflow patterns. Besides the shortcomings related to mask, pressure, and airflow, NIV requires caution regarding aspiration risk. Arm edema, deep venous thrombosis, discomfort, facial skin lesions, nasal or oral dryness, nasal congestion and gastric insufflation are common after prolonged use [30].

Conclusion

NIV is a safe and effective mean of reducing postoperative pulmonary complications, improving alveolar ventilation and gas exchange, decreasing infectious complications and even improving survival in selected patient populations with acute postoperative respiratory failure.

Summary Table

Clinical summary					
Technique	Indications	Cautions	Side effects	Dosage	Notes
Noninvasive ventilation	Postoperative acute respiratory failure	Failure of NIV therapy can be considered the worse complication due to the risk of prolonged time to intubation and should be early detected	Major complications (uncommon): barotrauma and hemodynamic effects Minor complications (common after prolonged use): aspiration risk, arm edema, deep venous thrombosis, discomfort, facial skin lesions, nasal or oral dryness, nasal congestion, and gastric insufflations	Progressive increase of pressure support and PEEP level to relieve dyspnea and improve gas exchange Optimal duration of NIV trial is unclear	Evidences of survival benefits come from lung resection surgery [16], liver resection surgery [24], solid organ transplantation [26]

NIV noninvasive ventilation, *PEEP* positive end-expiratory pressure

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Role of Inhalational Anesthetic Agents in Reducing Perioperative Mortality

4

Murali Chakravarthy and Laura Ruggeri

4.1 General Principles

In a recent Consensus Conference, among the 12 maneuvers that led to improved outcome in the perioperative period, inhalational anesthetic agents were the only anesthetic agents identified as contributing to reduced postoperative surgical mortality [1, 2]. Inhalational anesthetic agents have been shown to provide short-term as well as long-term protection [3, 4]. The evidence supporting mortality reduction via inhalational anesthetic agents seems to be growing.

4.2 Published Evidence

Several randomized controlled trials suggested a reduction in cardiac troponin release in patients receiving volatile anesthetics in cardiac surgery when compared to patients receiving a total intravenous anesthesia (TIVA). A meta-analysis of randomized trials summarized these findings and also suggested a beneficial effect of volatile agents on myocardial infarction and survival [5]. Based on these results, the American College of Cardiology and the American Heart Association suggested that the use of inhalational anesthetic agents might be cardioprotective [6]. A recent meta-analysis confirmed that mortality was doubled in patients receiving TIVA in contrast to volatile agents (1.3 % in the volatile group vs 2.6 % in TIVA group, $p = 0.004$) [7].

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4.3 Pharmacological Properties

Inhalational anesthetic agents seem to protect myocardium by a mechanism known as "ischemic preconditioning," which is defined as "adaptive response to brief sublethal episodes of ischemia leading to a pronounced protection against subsequent lethal ischemia." Ischemic preconditioning provides two "protective windows": the first occurs immediately after restoration of circulation and lasts about 2 h and the second appears after 24 h, lasting up to 72 h. Intracellular signaling pathways resulting in the opening of sarcolemmal and mitochondrial adenosine-triphosphate-regulated potassium channels have now been identified to be responsible for myocardial protection, which is dose dependent. The reactive oxygen species, apoptotic cascade, nitric oxide, and calcium intracellular overload appear to play a major role in preconditioning. Myocardial protection by isoflurane triggers partial mitochondrial uncoupling and reduces mitochondrial Ca2+ uptake [8]. Availability of gene chips enabled researchers to show that ischemic preconditioning and isoflurane cardioprotection appear to modulate gene expression in rat hearts, suggesting trigger-dependent transcriptome variability [9]. However, recently a multicentric trial on remote ischemic preconditioning during cardiac surgery did not show beneficial effect [10].

4.4 Therapeutic Use

Therapeutic use of inhalational anesthetic agents for myocardial protection during cardiopulmonary bypass, beating heart surgery, percutaneous coronary interventions and noncardiac surgery is known. This protective phenomenon is predominantly pronounced during cardiac surgery using cardiopulmonary bypass and to a lesser extent during off-pump coronary artery bypass (OPCAB) surgery. Its role during percutaneous coronary interventions and noncardiac surgery appears to be even lesser.

4.4.1 Myocardial Protection in Patients Undergoing Surgery Under Cardiopulmonary Bypass

It was suggested that "a combination of alteration in contractility and metabolism, as well as a preconditioning-like effect, appears to be responsible for the protective properties against ischemia and reperfusion damage" [11].

4.4.1.1 Isoflurane

In a recent meta-analysis of role of isoflurane in comparison to propofol, Bignami and coworkers showed a trend ($p = 0.05$) toward a reduction in mortality in a subgroup of well-conducted studies [12]. Isoflurane protection activates the pro-survival signaling pathways even if the combination of ischemic preconditioning and anesthetic preconditioning by isoflurane merely increases the intracellular ATP concentration without additional benefits [13]. A recent meta-analysis of

randomized trials identified 37 studies and 3,539 patients in cardiac (16 studies) and in noncardiac surgery (21 studies). The authors found a reduction in mortality only when studies with a low risk of bias were included in the analyses (0 % in the isoflurane group versus 0.7 % in the comparator group, OR 0.13, 0.02–0.76, $p = 0.02$) with four cardiac and six noncardiac trials included and five non-inhalation and five inhalation agents as the comparator. A trend was noted when a subanalysis was performed with propofol as a comparator (0.2 % versus 1.1 %, $p = 0.05$, with 16 studies included) [12].

4.4.1.2 Sevoflurane and Desflurane

Recent data suggest that sevoflurane/desflurane use resulted in improved cardiac outcome [7]. In this meta-analysis, the authors stated that "Volatile agents were associated with a reduced time of mechanical ventilation, and duration of ICU and hospital stay. Furthermore, of 17 studies with troponin I analysis, 7 significantly favored the volatile regimen, in 6 we observe a trend in favor of volatile agents, and in 4 a trend in favor of TIVA." Landoni and coworkers also maintained that "Anesthesia with volatile agents appears to reduce mortality after cardiac surgery when compared with TIVA, especially when sevoflurane or desflurane is used. A large, multicentre trial is warranted to confirm that long-term survival is significantly affected by the choice of anesthetic" [7]. The same study group recently planned a large randomized trial to confirm the findings. [NCT02105610] The use of inhalational agents was shown to reduce 1-year mortality when compared to the TIVA group, although the markers of myocardial injury were not different between groups [14].

4.4.2 Myocardial Protection in Patients Undergoing OPCAB Surgery

It is but logical to expect a similar myocardial protection to be offered by inhalational anesthetic agents during OPCAB. Hemmerling and coworkers showed less myocardial injury during the first 24 postoperative hours in patients receiving sevoflurane for OPCAB surgery in contrast to those receiving propofol [15]. Wang and coworkers recently showed that, in a group of 48 patients, >1 MAC sevoflurane could exert a significant myocardial protective effect during OPCAB surgery [16]. However, in a large randomized controlled study, we could not demonstrate short-term benefits by the use of inhalational agents [17]. The data on this topic are still not forthcoming.

4.4.3 Myocardial Protection in Patients Undergoing Noncardiac Surgery or Percutaneous Coronary Interventions

Data about anesthetic agents in noncardiac surgery and percutaneous interventions are not supportive of the protective action [18, 19].

Conclusion

Volatile anesthetic agents decrease mortality and morbidity among cardiac surgical patients whether they undergo surgery under cardiopulmonary bypass or off-pump. The level of evidence for protection by TIVA seems lacking. Superiority of one volatile over the other has not been established, but in general, they all seem to provide clinically relevant protection. Nevertheless the dose route, duration, and type of volatile agents that might offer maximum protection with minimal side effects are still under investigation. It has now become all the more relevant to perform a large multicentric randomized control trial to better understand these intricacies.

Summary Table

Clinical summary					
Drug	Indications	Cautions	Side effects	Dosage	Notes
Inhalational agents	Myocardial protection during general anesthesia for cardiac surgery	Myocardial protection is dose and duration of inhalational anesthetic agent dependent	Common side effects of inhalational agents such as hypotension, myocardial depression, arrhythmias and effects on other solid organs	Unclear at the moment	Myocardial protection, decrease in infarct size and reduction in mortality during cardiac surgery have been well documented

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Can Neuraxial Anesthesia Reduce Perioperative Mortality?

5

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5.1 Introduction

Neuraxial anesthesia results from injection of local anesthetics into the subarachnoid space (spinal anesthesia) and/or into the epidural space (epidural anesthesia). According to two recent systematic reviews, neuraxial anesthesia compared with general anesthesia may reduce postoperative mortality in surgical procedures, especially in patients with intermediate-to-high cardiac risk [1, 2]. In the first analysis, Guay et al. summarized nine Cochrane systematic reviews in order to assess whether anesthetic technique influences mortality after surgery [1]. Compared with general anesthesia, neuraxial anesthesia alone reduced perioperative mortality up to 30 days after surgery (risk ratio 0.71; 95 % confidence interval 0.53–0.94: analysis of 20 studies with a cumulative $N = 3006$) [1]. Compared with general anesthesia alone, combined neuraxial and general anesthesia had no significant effect on perioperative mortality up to 30 days after surgery (relative risk 1.07; 95 % confidence interval 0.76–1.51: analysis of 18 studies with a cumulative $N = 3228$) [1]. In the second analysis, Pöpping et al. evaluated the impact on mortality of concomitant epidural analgesia, compared with systemic analgesia, in adults having surgery under general anesthesia (cumulative $N = 2201$: ten randomized controlled

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trials published up until July 2012) [2]. The results showed that there was a significant reduction in mortality risk associated with epidural analgesia (3.1 % vs 4.9 %; odds ratio 0.60; 95 % confidence interval 0.39–0.93) [2]. The results obtained in these two recent systematic reviews were in agreement with the findings from earlier analyses published in 2000 [3, 4]. Despite these recent publications, there is ongoing debate about whether neuraxial blockade can reduce perioperative mortality. Recent large high-quality trials have focused on this important question. This chapter will review the main recent trials in this area and develop an evidence-based answer to this debate.

5.2 Main Evidence

5.2.1 Orthopedic Surgery

The principal paper on this field was published by Urwin et al. [4]. They performed a meta-analysis of 15 randomized trials that compared mortality associated with general versus regional anesthesia for hip fracture patients and found a reduced 1-month mortality in the regional anesthesia group (odds ratio 0.66; 95 % confidence interval 0.47–0.96) [4]. A subsequent Cochrane systematic review published in 2004 ($N = 2567$: 22 trials) demonstrated that there was insufficient evidence to rule out clinically important effects on perioperative mortality due to neuraxial blockade in the setting of adult hip fracture surgery [5]. A single-center study ($N = 298$) also failed to demonstrate any survival advantage associated with anesthetic technique in geriatric patients undergoing surgery for hip fracture [6]. A recent large database analysis ($N = 18{,}158$; 126 medical centers during 2007 and 2008 throughout New York State, USA) found that neuraxial anesthesia significantly reduced mortality in adult hip fracture surgery (odds ratio 0.710; 95 % confidence interval 0.541–0.932; $P = 0.014$) [7]. In primary adult lower-extremity joint arthroplasty, general anesthesia as compared with neuraxial anesthesia also has recently been associated with increased mortality in multivariate analysis (odds ratio 1.83; 95 % confidence interval 1.08–3.1; $P = 0.02$) in a massive observational cohort ($N = 382{,}236$ in 400 medical centers around the USA from 2006 to 2010) [8]. The increased mortality risk associated with general anesthesia in this clinical setting persisted when compared to patients undergoing neuraxial blockade combined with general anesthesia (odds ratio 1.70; 95 % confidence interval 1.06–2.74; $P = 0.02$) [8]. In a large observational cohort of adult primary knee arthroplasty ($N = 14{,}052$ from 2005 to 2010), neuraxial anesthesia significantly reduced perioperative complications, including mortality [9].

In summary, the current evidence base suggests that there may be a survival advantage associated with neuraxial anesthesia in lower-extremity major joint procedures [4–9]. Although these data are suggestive, they are not conclusive [10, 11]. They serve as hypothesis generating in the planning and execution of appropriately powered randomized clinical trials to test whether anesthetic technique reduces mortality in this clinical setting.

5.2.2 Vascular Surgery

A recent multicenter observational trial ($N=6009$ in medical centers around the USA from 2005 to 2008) compared neuraxial anesthetic techniques with general anesthesia and monitored anesthesia care in elective endovascular aortic aneurysm repair [12]. Although general anesthesia compared to neuraxial blockade was significantly associated with pulmonary morbidity (odds ratio 4.0; 95 % confidence interval 1.3–12.5; $P=0.020$) and a 10 % increase in hospital length of stay (95 % confidence interval 4.8–15.5 %; $P=0.001$), neuraxial blockade did not offer any survival advantage in this setting [12]. A large international observational study ($N=1271$: 79 medical centers in 30 countries) also demonstrated no survival advantage related to anesthetic technique, although neuraxial anesthesia significantly reduced the risk of admission to the intensive care unit (odds ratio 0.71; 95 % confidence interval 0.53–0.97; $P=0.030$) and the duration of hospital stay ($P=0.003$) [13]. A recent meta-analysis highlighted the lack of high-quality randomized data to guide decision-making about which anesthetic technique reduces perioperative mortality in this major vascular surgical procedure [14].

In lower-extremity vascular surgery, recent observational database analysis ($N=5462$ in multiple medical centers across the USA from 2005 to 2008) documented a perioperative mortality rate of 3 %: multivariate analysis demonstrated no significant effect of neuraxial anesthesia on mortality [15]. Contemporary meta-analysis from the Cochrane group on this question ($N=696$: four studies) demonstrated no conclusive effect on mortality from neuraxial anesthetic techniques, but also noted that that insufficient high-quality evidence was available [16]. A recent review has noted that while neuraxial blockade has significant clinical application in vascular surgical patients, the current evidence base does not permit a definite conclusion about its effects on perioperative mortality [17]. In summary, future appropriately powered randomized trials should evaluate this question, as has already been done for local anesthesia in carotid endarterectomy [18].

5.2.3 Cardiac Surgery

A recent series of three meta-analyses have explored the effects of neuraxial anesthetic techniques on outcomes after cardiac surgery, including perioperative mortality [19–21]. The first two demonstrated no beneficial effect on mortality due to neuraxial blockade [19, 20]. The third meta-analysis ($N=2366$: 33 trials) suggested that epidural anesthesia in cardiac surgery reduces the composite endpoint of mortality and myocardial infarction (odds ratio = 0.61; 95 % confidence interval 0.40–0.95; $p=0.03$ number needed to treat = 40) [21]. Recent randomized trials of neuraxial blockade in cardiac surgery have been underpowered to rule out a clinically meaningful beneficial effect on perioperative mortality in cardiac surgery [22–24]. The clinical concern about the risk of neuraxial hematoma in this anticoagulated surgical patient cohort will likely remain a significant barrier to recruitment for large adequately powered clinical trials to effectively address this question.

5.2.4 Cancer Surgery

A recent meta-analysis has suggested that neuraxial anesthesia may significantly improve survival after surgery for urologic and colorectal cancer [25, 26]. Although the evidence favors a reduction in mortality associated with neuraxial anesthesia in these settings, it appears inadequate to ascertain whether the risk of tumor recurrence is also reduced [27]. In summary, appropriately powered randomized trials are indicated to test these associations detected in meta-analysis yet further.

Conclusion

The current evidence base suggests that the real effect of neuraxial blockade on perioperative mortality, despite extensive meta-analyses both in cardiac and non-cardiac surgery, is still uncertain. Nevertheless, the Consensus Conference by Landoni et al. included neuraxial anesthesia among the interventions which may provide a survival benefit in the perioperative period [28, 29]. Future trials should explore this enduring question with adequate power, ideally in the setting of high-quality multicenter randomized trials.

Summary Table

Clinical summary			
Technique	Indications	Cautions	Notes
Neuraxial anesthesia	Lower-extremity major joint procedures	Neuraxial hematoma	Suggestive reduction in mortality
Neuraxial anesthesia/ analgesia	Cardiac surgery	Neuraxial hematoma	No conclusive effect on mortality
Neuraxial anesthesia	Lower-extremity vascular surgery	Neuraxial hematoma	No conclusive effect on mortality
Neuraxial anesthesia	Elective endovascular aortic aneurysm repair	Neuraxial hematoma	No conclusive effect on mortality
Neuraxial anesthesia	Cancer surgery	Neuraxial hematoma	Suggestive reduction in mortality

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Role of Hemodynamic Optimization in Reducing Perioperative Mortality

6

Agostino Roasio and Piero Mussa

6.1 General Principles

More than 300 million surgical procedures are undertaken each year worldwide. As perioperative mortality is still greater than the expected value (10 % in high-risk surgical patients) [1, 2], nonsurgical interventions supported by high-quality studies that have shown a significant reduction in perioperative mortality after surgery have been collected and recently updated [3, 4]. Among them, we include perioperative hemodynamic optimization, also known as goal-directed hemodynamic therapy (GDHT), which is based on the titration of fluids and inotropic drugs according to physiological flow-related end points [5].

6.2 Main Evidences

The effect of hemodynamic monitoring on the perioperative outcome has long been debated. In fact, despite the use of pulmonary catheter has proven to be effective in reducing perioperative mortality in high-risk surgical patients in a number of cases [6], subsequent data showed conflicting results [7].

Also, in an older study, a "paradoxical" increase in mortality was observed in a heterogeneous group of critically ill patients when supranormal oxygen delivery values (DO_2) were obtained through very high doses of dobutamine [8]. This suggested that, in some cases, aggressive efforts to boost oxygen consumption may be detrimental, particularly when organ failure has occurred. In a successive study,

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Kern et al. assessed the effects of hemodynamic optimization on mortality in high-risk patients: the most significant results were seen in the perioperative setting where the preemptive hemodynamic monitoring showed an improved outcome in high-risk surgical patients before the occurrence of organ damage (23 % mortality difference between the control and protocol groups with early optimization, $p<0.05$ in six studies with mortality rate in control groups over 20 %) [9].

The International Consensus Conference by Landoni et al. showed a significant reduction in perioperative mortality after cardiac surgery [3] and noncardiac surgery [4] upon inclusion only of high-quality evidence (RCTs or meta-analysis of RCTs). Moreover, according to the recently updated results, hemodynamic optimization is the intervention with a positive effect on outcome showing the greater worldwide agreement (95 % of participants to the updated web vote).

About the GDHT in noncardiac adult surgery, five meta-analyses of RCTs were collected in the recent International Consensus Conference (Table 6.1) [11–15]. Poeze et al. demonstrated a positive effect on mortality rate (RR 0.75, 95 % CI 0.62–0.90, $p=0.002$), particularly when achieving supraphysiological level of oxygen delivery (DO_2>600 mL/min/m^2) in the perioperative setting (RR 0.66, 95 % CI 0.54–0.81, $p<0.0001$) [11]. Three of the following studies pointed out that prevention of perioperative multiorgan failure, achieved by maintenance of adequate tissue perfusion, is paramount to reduce perioperative mortality [12–14]. Brienza et al. showed a positive effect on renal function and consequently on perioperative mortality with the use of pulmonary artery catheter to titrate the administration of fluids and inotropes to physiological DO_2 levels (pooled OR 0.50, 95 % CI 0.31–0.80, $p=0.004$) [12]. Moreover, Gurgel et al., analyzing 5056 high-risk surgical patients (32 RCTs), confirmed that maintaining an adequate tissue perfusion with a protocol driven by hemodynamic criteria significantly decreases perioperative mortality (pooled OR 0.67, 95 % CI 0.55–0.82, $p<0.001$); further reduction was seen when the mortality rate in the control group was >20 % (OR 0.32, 95 % CI 0.21–0.47, $p<0.00001$) [13]. A review by Hamilton et al. showed that the preemptive strategy of hemodynamic monitoring reduces perioperative mortality [14] and concluded that an adequate tissue perfusion with an early monitoring in the right patient cohort (high-risk patients) through a defined protocol improves survival (pooled OR 0.48, 95 % CI 0.33–0.70, $p=0.0002$). Cecconi et al. analyzed 32 RCTs and confirmed that a well-protocolized GDHT significantly reduced the perioperative mortality (pooled OR 0.52 95 % CI 0.36–0.74 $p=0.0003$), particularly in very high-risk patients with a mortality risk >20 % (OR 0.20 95 % CI 0.09–0.41 $p<0.0001$) [15]. Finally, a recent meta-analysis of ten RCTs (1527 enrolled patients) confirmed that the GDHT has a beneficial effect on perioperative mortality if early performed in perioperative setting and titrated on supraphysiological DO_2 (RR 0.63; 95 % CI, 0.42-0-94; $P=0.02$) [16] (Table 6.1).

However, the recent studies do not completely overcome the "gray area" regarding the perioperative GDHT for many reasons:

- Many outdated studies.
- Mortality in the control group significantly decreased over the years due to an overall improving in anesthesiological and surgical techniques.

Table 6.1 Summary of main evidences in literature

Source	RCTs (patients)	Setting	Evidence on mortality	Main conclusion
Poeze et al. [11]	All studies, 30 RCTs (5733). Perioperative and trauma, 21 RCTs (4174)	Adult critically ill, surgical perioperative, and trauma patients	Overall mortality reduction was seen in adult critically ill population	Hemodynamic optimization significantly reduces mortality especially in perioperative and trauma setting. In this subgroup 31 patients had to be treated to save 1 life
			(RR 0.75 95 % CI 0.62–0.90 p 0.002)	Overall quality of single studies is only moderate
			Perioperative and trauma setting	
			(RR 0.66 95 % CI 0.54–0.81 $p<0.0001$)	
Brienza et al. [12]	20 RCTs (4220)	Adult surgical patients	A significant mortality reduction was seen OR 0.50 (95 % CI 0.31–0.80) $p=0.004$	Hemodynamic optimization reduces postoperative renal failure and significantly improves survival in high-risk patients. Although the strength of evidence is reduced by the poor quality of single studies
Gurgel et al. [13]	32 RCTs (5056)	Adult surgical patients with no organ failure before surgery	Global morality reduction (OR 0.67 95 % CI 0.55–0.82 $p<0.001$). Reduction in mortality in high-risk surgical patients (OR 0.32 95 % CI 0.21–0.47 $p<0.0001$)	Maintaining tissue perfusion with a specific protocol improves outcome and reduces mortality in high-risk surgical patients. More significant results are achieved, monitoring DO_2 and VO_2 by PAC. Methodological trial quality presents some important deficiency

(continued)

Table 6.1 (continued)

Source	RCTs (patients)	Setting	Evidence on mortality	Main conclusion
Hamilton et al. [14]	29 RCTs (4805)	Moderate- and high-risk surgical adult patients	Mortality reduction OR 0.48 95 % CI 0.33–0.70 $p=0.0002$	Preemptive hemodynamic intervention reduces mortality in moderate- and high-risk patients. More significant treatments are related to pulmonary artery catheter, fluids and inotrope administration, monitoring of DO_2 and cardiac index, and reaching a supraphysiological values. Very few studies were performed in high-quality design
Cecconi et al. [15]	32 RCTs (2808)	Adult general surgical population	Overall benefit on mortality OR 0.52 95 % CI 0.36–0.74 $p=0.003$; very high-risk patients OR 0.20 95 %CI 0.09–0.41 $p<0.0001$	Hemodynamic optimization is likely to have the greatest benefit if applied early, in the right patient cohort (extremely high-risk patients), and with a clearly defined protocol (combining fluids and inotropes and using PAC)
Rippoles et al. [16]	10 RCTs (1527)	Adult patients undergoing noncardiac surgery	GDHT significantly reduced mortality RR 0.63; 95 %CI,0.42–0.94; $p=0.02$	Perioperative GDHT significantly reduces mortality; greatest benefits are seen when GDHT is used in perioperative period not only postoperative, using supraphysiological values as target

CI confidence interval, DO_2 oxygen delivery, *GDHT* goal-directed hemodynamic therapy, *PAC* pulmonary artery catheter, *OR* odds ratio, *RCTs* randomized controlled trials, *RR* risk ratio, VO_2 oxygen consumption indexed

- Pulmonary artery catheter, used in many clinical trials, superseded by less invasive monitoring systems.
- Heterogeneous treatment between the studies (different types and amount of fluids and inotropic drugs).
- Low methodological quality of single papers (often monocentric, underpowered for mortality reduction, few double blind).

6.3 Physiopathology

In the most significant studies revised by Landoni et al., the common physiopathological background is to maintain an adequate perioperative tissue oxygenation [4]. The oxygen consumption increases in the postoperative period resulting in oxygen debt, which is more severe in non-survivors (Fig. 6.1) [5]. Oxygen debt is the underlying cause of tissue hypoxia that is deeper and more prolonged in high-risk patients with reduced cardiac reserve. In the bowel, this situation damages the endothelial barrier releasing endotoxins into the blood circulation, activating and stimulating an inflammatory response. The subsequent multiorgan dysfunction syndrome (MODS) causes death in the most severe cases [17, 18]. Prevention of tissue hypoxia involves a balance between DO_2 and oxygen consumption (VO_2) (Fig. 6.2) [19]. While VO_2

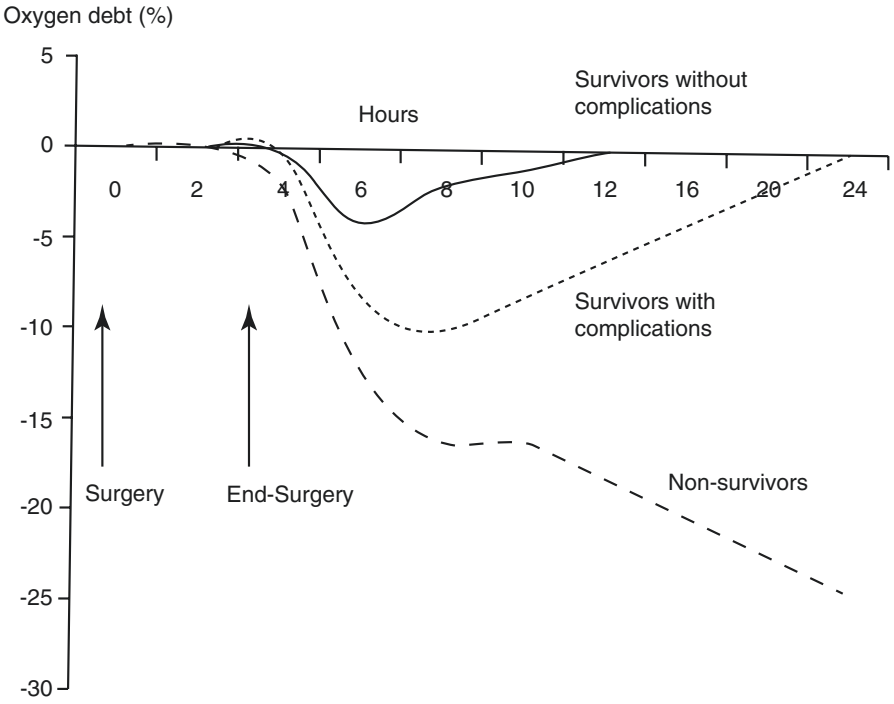

Fig. 6.1 Trend of perioperative oxygen debt during surgery (From Marik et al. [5])

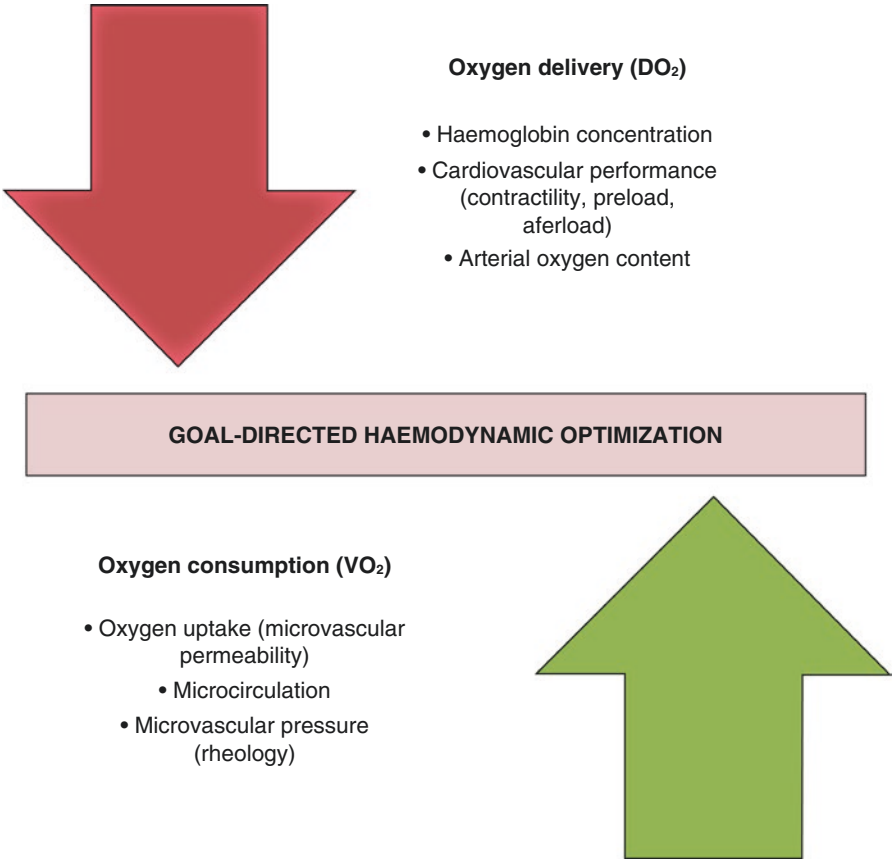

Fig. 6.2 Concept of perioperative hemodynamic optimization. *CVVH* continuous veno-venous hemofiltration (From Kirov et al. [18])

can be only minimally optimized, its delivery (DO_2) is the key element for hemodynamic optimization.

DO_2 depends on the following parameters:

$$\text{Oxygen delivery } DO_2 \ (\text{mL/min}) = \text{cardiac output } (CO)\ (\text{L/min}) \times \text{arterial oxygen content } (CaO_2)$$

The components of oxygen delivery (DO_2) are the arterial oxygen content (depending on hemoglobin and oxygenation) and cardiac output (CO). Cardiac output can be rapidly monitored and adapted to the patient's bedside, as many monitoring devices allow, with different methods depending on their technology and invasiveness, to estimate the stroke volume (SV) and thus to obtain the CO value:

$$\text{Cardiac output } (CO)\ (\text{mL/min}) = \text{stroke volume } (SV)\ (\text{mL/beat}) \times \text{heart rate } (HR)\ (\text{beat/min})$$

Table 6.2 Clinical criteria for high-risk surgical patients

Patient-related criteria	Surgery-related criteria
Severe cardiac or respiratory illness resulting in severe functional limitation	Extensive noncardiac surgery (e.g., carcinoma involving bowel anastomosis, pneumonectomy, complex traumatological and orthopedic procedures)
Aged over 70 years with moderate functional limitation of one or more organ systems	Major/combined cardiovascular surgery (e.g., aortic aneurysm, combined valve repair, coronary surgery, and carotid endarterectomy)
Acute massive blood loss (>2.5 l)	Surgery prolonged >2 h (e.g., neurosurgical interventions, combined gastrointestinal surgery)
Severe sepsis	Emergency surgery
Shock or severe hypovolemia of any origin	
Respiratory failure (paO_2 <60 mmHg or SpO_2 <90 % in spontaneously breathing patients receiving oxygen or paO_2/FiO_2	
<300 in mechanically ventilated patients or ventilation >48 h)	
Acute gastrointestinal failure (e.g., intra-abdominal compartment syndrome, pancreatitis, perforated viscus, gastrointestinal bleeding)	
Acute renal failure (urea >20 mmol/l, creatinine >260 mmol/l)	

From Kirov et al. [19]

Table 6.2 summarizes the main characteristics of different devices [20]. Besides the perfusion parameters (SV and CO), many current devices allow for a more precise and focused hemodynamic management through the measurement of other parameters:

- Static preload data: global end-diastolic volume (GEDV), intrathoracic blood volume (ITBV), and extravascular lung water (EVLW)
- Functional hemodynamic variables: systolic volume variation (SVV), pulse pressure variation (PPV), or response to passive leg raising test (PLR test)
- Oximetry data: central venous ($ScvO_2$) or mixed venous (SvO_2) oxygen saturation showing the balance between oxygen delivery and consumption

Monitoring the above parameters allows to complete the hemodynamic management, despite not having direct correlations with the perioperative outcome. In particular, monitoring venous oximetry, an index of oxygen debt, does not have a significant impact on perioperative mortality, probably due to the deep metabolic alterations that occur as a result of the anesthesia itself [21].

6.4 Therapeutic Use

The first step is the identification of high-risk surgical patients (Table 6.2). Among the clinical criteria, metabolic equivalents (METs) are the most useful in predicting poor cardiorespiratory function [17].

The right timing of hemodynamic optimization is crucial as all significant studies indicated that GDHT must be applied early (pre-/intraoperative or postoperative within 8 h) [19].

Monitoring systems available, albeit different from each other according to their invasiveness, measuring methods and monitored data, are based on the measurement of the flow and can provide the necessary parameters for a correct goal-directed therapy (Fig. 6.3). However, only the use of pulmonary catheter led to a significant mortality reduction, while literature does not support less invasive systems applied to lower-risk patients. Recently, a "modular" approach has been implemented, where the different monitoring systems can be chosen according to the degree of perioperative risk (Fig. 6.4) [22].

In the considered studies, only flow parameters (DO_2, CI, and VO_2) correlate significantly with the reduction in mortality. This confirms what experimental studies have shown: a significant improvement in tissue flow and oxygenation after major surgery was obtained titrating fluids and inotropes on SV [23].

The best results in reducing perioperative mortality are obtained with a "proactive" management, as recently defined [22], which consists in maximizing SV and maintaining CI or DO_2 in a desired range ($DO2>600$ mL/min/m^2) avoiding any hemodynamic imbalance. Firstly, hypovolemia should be evaluated and corrected as possible cause of death in the most severe cases. Then optimization of circulating volume must be patient tailored using dynamic preload data and fluid responsiveness parameters (SVV or PPV<12 %). After optimizing volemia, inotropic support must be taken in consideration (Fig. 6.5) [24]. For this matter, drugs with inodilator function as dobutamine and dopexamine gave the best results in reducing mortality. Finally, the clinicians have to maintain an adequate Hb level (over 7 g/dL, higher in ischemic heart disease) and an adequate oxygenation level.

	Methodology	Devices	Stroke volume	Cardiac output	Contractility	Systemic vascular resistence	Stroke volume variation	Pulse pressure variation	Other data	Note
Non invasive	Ultrasound	TTE	☑	☑	☑	-	☑	-	-	
		Suprasternal doppler (USCOM)	☑	☑	☑	☑	☑	-	Cardiac power	Rapid technique. Conflicting results in different clinical studies.
	Bioimpedance – bioreactance	Bioimpedance (BioZ)	☑	☑	☑	☑	-	-	TFC LCWI	Poor reliability of this system
		Bioreactance (Cheetah NICOM)	☑	☑	☑	☑	☑	-	TFC DO2I	Less accurate in diseased lung. Validation studies disposable
	Volume clamp method	Clearsight	☑	☑	-	☑	☑	-	-	Acceptable agreement in CO measured by PAC in critical care and cardiac surgical setting.
		CNAP	☑	☑	-	☑	☑	☑	-	
		Finapres	☑	☑	☑	☑	-	-	-	
	Radial artery applanation technique	Tensys	-	-	-	-	-	-	-	
	Non invasive arterial blood pressure	Nexfin	☑	☑	☑	-	-	☑	-	
	Photoplethysmography	Masimo Radical 7	-	-	-	-	-	-	PVI	
Minimally invasive	Ultrasound	TEE	☑	☑	☑	-	☑	-		
		Esophageal Doppler (CardioQ)	☑	☑	☑	☑	☑	-	FTc	Probe position and use of normograms have raised some doubts
	Uncalibrated arterial waveform analysis	ProQt	☑	☑	☑	☑	☑	_		
		PulsioFlex	☑	☑	☑	☑	☑	-		Dedicated addition sensor connected to a regular arterial catheter
		LIDCO rapid	☑	☑	☑	☑	☑	☑		Use the same algorithm as the LiDCO plus.
		Flotrac/Vigileo	☑	☑	☑	☑	☑	-		Useful in perioperative optimizing protocols
		MostCare system	☑	☑	☑	☑	☑	-		Promising clinical data are available, other validation studies are needed.
	Applied Fick principle	NICO System	☑	☑	☑	-	-	-		Assessment of CO possible in fixed ventilator setting, good respiratory function without relevant pulmonary shunt.
	Dye dilution	DDG-30 pulsed dye densitometry	-	-	-	-	-	-		A signal compromised by vasoconstriction, movement, interstitial edema can limit the reliability of CO
Invasive	Pulmonary catheter	PAC (Ccombo PAC®)	☑	☑	☑	☑	-	-	PAP, PVR SvO2	Considered as gold standard. Required adequately trained clinicians
	Calibrated arterial waveform analysis	PICCO plus $PICCO_2$ system	☑	☑	☑	☑	☑	-	ScvO2 GEDV ITBV GEF EVLW	Frequently recalibrated, at least every 8 hours in stable patients
		LIDCO plus	☑	☑	☑	☑	☑	☑	ScvO2 ITBV	Calibration with a transpulmonary lithium indicator. Validated in critically ill patients
		EV1000/ Volumeview	☑	☑	☑	☑	☑	-	EVLW GEDV GEF	Validated against the PICCO and transpulmonary thermodilution

TTE – Trans-thoracic-echocardiography, TEE Trans-esophageal echocardiography, TFC Thoracic Fluid Content, LCWI- Left Cardiac Work Index, DO2I- Oxygen Delivery, PVI-Pleth Variability Index, Ftc-Flow Time corrected, SvO2-mixed venous saturation, ScvO2-central mixed venous saturation, GEDV-Global End Diastolic Volume, ITBI-Intrathoracic Blood Index, GEF-Global Enjection Fraction, EVLW-Extravascular Lung Water, ITBV Intrathoracic Blood Volume, CO cardiac output. PAP-pulmonary artery pressure, PVR pulmonary vascular resistence

Fig. 6.3 Overview of different hemodynamic monitors

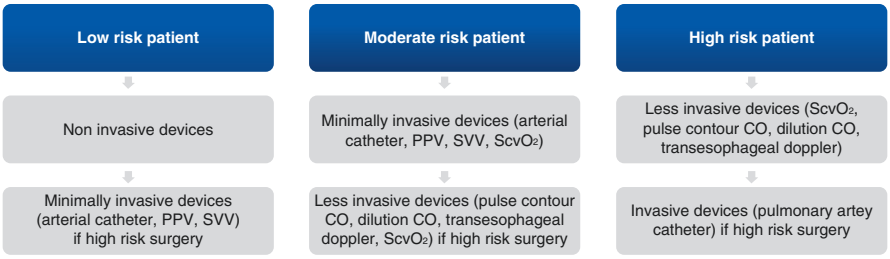

Fig. 6.4 Choice of monitoring system in relation to perioperative risk. *CO* cardiac output, *PAC* pulmonary artery catheter, *PPV* pulse pressure variation, $ScvO_2$ central venous oxygen saturation (From Vincent et al. [22])

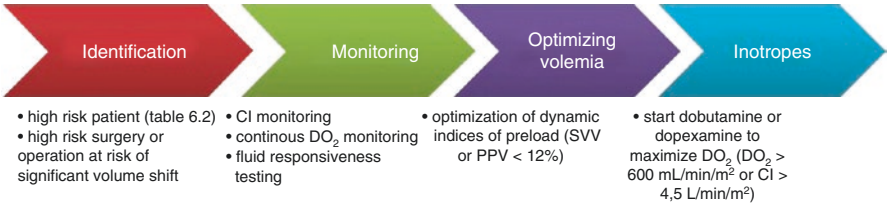

Fig. 6.5 Management of goal-directed hemodynamic therapy. DO_2 oxygen delivery, *CI* cardiac index, *SVV* stroke volume variation, *PPV* pulse pressure variation

Conclusion

The web-based Consensus Conference, updated in 2015, agrees on the positive effect of hemodynamic optimization on perioperative mortality in high-risk patients [10]. To consider hemodynamic optimization as a mere achievement of certain targets can be overly simplistic and potentially dangerous. On the contrary, this approach proves to be effective in significantly reducing the mortality when perioperative tissue perfusion is maintained through a broader management practice that involves the patient before, during, and after surgery.

6.5 Summary Table

Clinical summary					
Technique	Indications	Cautions	Side effects	Hemodynamic target	Notes
Perioperative hemodynamic optimization	High-risk surgical patients or high-risk surgery. Hemodynamic monitoring is mandatory pre-/intraoperative or within 8 postoperative hours	Clinicians should choose hemodynamic monitoring according to perioperative risk. They have to consider patient's comorbidities and disease that can limit the use of some devices (arrhythmias, spontaneous breathing, cardiac disease). Treatment should be titrated on individual goals	Excessive fluid administration may result in fluid overload worsening outcome. High doses of inotropic drugs can be detrimental, compromising myocardial function, especially in patients with coronary artery disease	Flow-based hemodynamic monitoring gives best results, first optimizing volemia with dynamic indices (SVV or PPV <12 %) and then maximizing stroke volume (CI >4.5/min/m^2) and oxygen delivery (DO_2 >600 mL/min/m2) and maintaining $ScvO_2$ >65 %	Hemodynamic optimization improves postoperative outcome reducing tissue hypoperfusion and renal failure. Effects on mortality in low-risk patients need more proofs

CI cardiac index, DO_2 oxygen delivery, *PPV* pulse pressure variation, $ScvO_2$ central venous oxygen saturation, *SVV* stroke volume variation

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Levosimendan

7

Massimiliano Greco, Gianluca Paternoster,
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7.1 General Principles

Cardiac dysfunction, with hemodynamic compromise and need for inotropic support, may complicate cardiac surgery as well as general surgery, leading to unfavorable outcomes [1].

Levosimendan is an inodilator with specific properties, belonging to the class of calcium sensitizers. Levosimendan improves heart contractility without increasing calcium concentration or affecting lusitropy, nor increasing myocardial oxygen consumption [2]. Due to these favorable features, levosimendan is gaining more and more prominence in acute or chronic heart failure, or cardiac complication after surgery, and in critically ill patients [3, 4]. In 2012 the first international consensus conference on perioperative medicine identified levosimendan as one of the drugs that can increase survival after surgery [5]. Recently, a new and updated consensus conference was conducted to include all the new randomized evidence produced since. The new consensus confirmed that levosimendan is 1 of the 11 drugs/techniques that have been proved, with high-quality evidence, to reduce mortality in the perioperative period [6].

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7.2 Main Evidences

Levosimendan has been extensively studied in cardiac anesthesia, intensive care, and in the heart failure setting. Its positive action on critically ill patients was recently supported by results from a meta-analysis by Landoni et al. [4] reporting a significant reduction in mortality for levosimendan with a number needed to treat as low as 17. In the perioperative setting, most of the high-quality evidence derives from cardiac surgery. The first meta-analysis of randomized controlled studies to suggest that levosimendan reduces 30-day mortality (odds ratio 0.35 [95 % CI 0.18–0.71]) when compared to classic inotropes or placebo was published in 2010 [3]. Levin et al. conducted a randomized controlled study confirming that levosimendan was superior to dobutamine to treat postoperative low cardiac output syndrome [7]. In patients undergoing coronary revascularization, levosimendan was found to be superior to any other comparator, with a 60 % [95 % CI 0.21–0.76] reduction in odds ratio for mortality, and improvements in several ancillary perioperative outcomes [8]. In a meta-analysis of RCT by Harrison et al., levosimendan reduced cardiac surgery mortality in high-risk patients with low ejection fraction (7 % [3–11 %] risk difference for mortality) [9].

These studies confirm the results of the first International Consensus Conference in cardiac anesthesia, which enthroned levosimendan among the drugs that might reduce mortality in this perioperative setting [10]. The superiority of levosimendan in cardiac surgery is evident not only versus classic inotropes but also when confronted to intra-aortic balloon pump [11].

In noncardiac surgery, the effect of levosimendan on mortality has not yet been cleared. However, given its prolonged action and its effects in cardiac surgery and in heart failure patients, a preoperative administration of levosimendan has been proposed as a possible technique to optimize cardiac function in patients with heart failure undergoing noncardiac surgery [12].

Levosimendan has been first and thoroughly investigated in patients with decompensated heart failure. In the RUSSLAN study, patients with cardiac insufficiency randomized to levosimendan showed an increased survival when compared to placebo (hazard ratio 0.56 [95 % CI 0.33–0.95]) [13]. In the LIDO study, severe low-output heart failure patients receiving levosimendan achieved the composite endpoint of improvement in hemodynamic values (30 % increase in cardiac output and 5 % decrease in pulmonary capillary wedge pressure) significantly more than patients receiving dobutamine [14]. The CASINO trial confirmed these results against dobutamine and placebo, with the study interrupted prematurely by the ethical committee due to the clear survival advantage for levosimendan [15], similarly to REVIVE I and II trials where dobutamine was confirmed to reduce symptoms, hospital stay, and levels of brain natriuretic peptide (BNP) [16]. The reduction in BNP levels was confirmed in the SURVIVE study, although a similar rate of mortality was found at 6 months between cases and controls [17].

7.3 Pharmacologic Properties

Classic inotropic drugs function through stimulation of beta-receptors, increasing intracellular cyclic adenosine monophosphate (cAMP) levels, leading to sarcoplasmic reticulum calcium release. The elevation in plasmatic calcium concentration enhances contractility and improves stroke volume. Phosphodiesterase 3 inhibitors (PDE-3 inhibitors) exert a similar action that directly increases cAMP levels through inhibition of the enzyme catalyzing its breakdown, leading to an increased intracellular calcium concentration.

Both beta-receptor agonists and PDE-3 inhibitors increase cardiac stroke volume at the expenses of higher myocardial oxygen demand and jeopardize cardiac relaxation (lusitropy) and diastolic function. These side effects are directly related to cytoplasmic calcium content, and they are considered the origin of the detrimental effects of PDE-3 inhibitors and beta-adrenergic inotropes [18].

On the contrary, levosimendan uniquely increases troponin C affinity for calcium stabilizing its conformation, without increase in intracellular calcium concentration. Cardiac contractility thus improves without increasing oxygen consumption [19]. Moreover, the binding of levosimendan to troponin C is dependent on cytosolic calcium content, and it consistently reduces during diastole, when cytoplasmic calcium content is low (Fig. 7.1). This action avoids the detrimental effects of traditional inotropes: lusitropy reduction and increase in arrhythmias [2]. As other inodilators, levosimendan induces vasodilation in the peripheral smooth musculature but exerts its action through binding of potassium channels.

Levosimendan has anti-apoptotic and anti-inflammatory properties that have been recently demonstrated and that may further improve long-term outcomes in the failing heart [20]. The beneficial effect of levosimendan on mortality is probably due to the sum of these unique actions.

7.4 Therapeutic Use

Levosimendan is administered through continuous infusion with or without an initial bolus. It has a 60-min half-life, with steady-state concentration reached within 4 h and active metabolite plasma concentration peaking at 2 days after infusion. Levosimendan clearance is about 3 mL/kg/h, largely through liver metabolism and with a smaller proportion metabolized through the intestine, and it is eliminated through renal and fecal excretion. Its main metabolites are OR-1855 and OR-1986. The former is an intermediate compound, extracted in the bowel through the biliary route. The latter is formed by N-acetylation of OR-1855 and is the most clinical relevant metabolite, with an 80-h half-life that is probably responsible for the prolonged effect of drug, which persists for many days after administration.

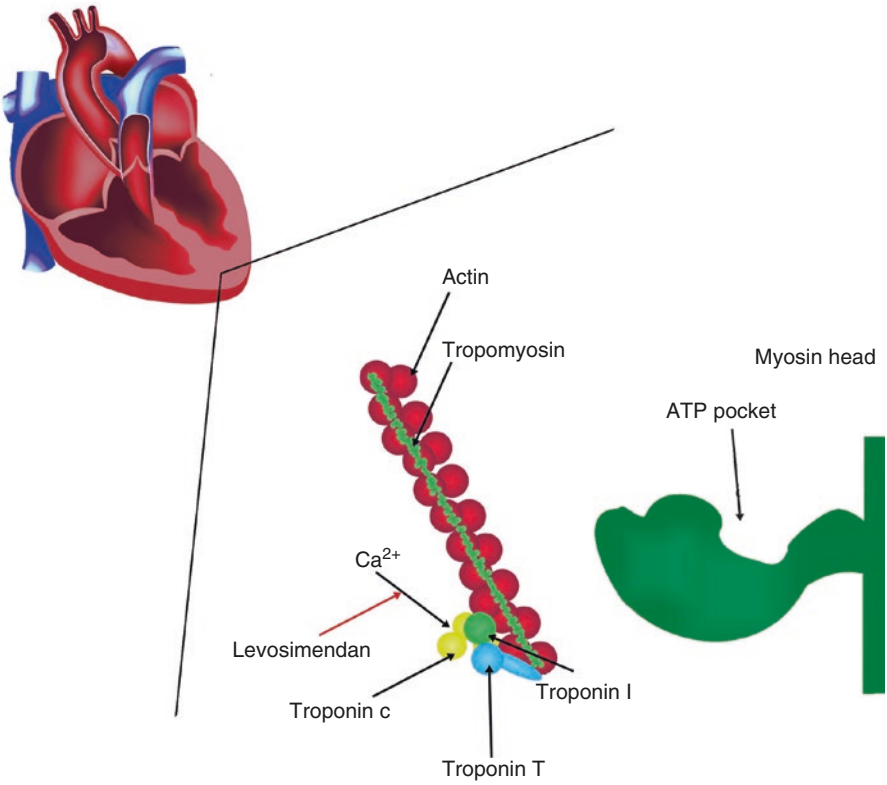

Fig. 7.1 Levosimendan myocardial mechanism of action

Levosimendan dosage should be cautious in patients with end-stage renal disease, as data on patients with renal dysfunction suggest that the elimination half-life of OR-1986 (but not levosimendan half-life) is prolonged in these patients. Hepatic insufficiency directly increases levosimendan concentration, and dosing should be reduced in patients with liver failure. Other relative contraindications are left ventricular outlet obstruction that may be worsened by levosimendan, severe hypotension and tachycardia, or history of torsades de pointes.

No risk of tolerance or rebound has been documented after prolonged infusion. Due to its distinct action, levosimendan can be safely used with other cardioactive drugs, including beta-adrenergic inotropes and PDE-3 inhibitors. Moreover, beta-blockers do not reduce levosimendan action, leading to new potential therapeutic synergism in heart failure patients [21].

Levosimendan is administered through continuous infusion ranging from 0.05 to 0.2 μg/kg/min. A loading dose of 6–12 μg/kg was suggested to anticipate the target

concentration, but a significant increase in rate of hypotension has been demonstrated for bolus doses. Thus, bolus administration of this drug should be probably avoided [4].

7.4.1 Intermittent Administration

Promising results have also been achieved in outpatients with end-stage heart failure, using an intermittent monthly intravenous administration of levosimendan. A trial documented an increased survival as well as hemodynamic improvements for levosimendan intermittent administration when confronted to dobutamine or other controls [22]. This positive action is probably related with the long-lasting effects of levosimendan metabolites.

Outpatients with chronic severe heart failure will be the target of this treatment, probably reducing hospitalization, morbidity, and mortality and reducing healthcare costs.

7.4.2 Possible Future Targets

Diaphragm muscle weakness is a prominent finding in critically ill patients, and it is due to various conditions, such as mechanical ventilation, chronic obstructive pulmonary disease (COPD), and cachexia. In these patients, specifically in COPD patients, a higher level of intracellular calcium concentration is needed to obtain normal muscular contraction [23]. Moreover, results from animal studies document impaired contractility and reduced efficiency of the diaphragm in congestive heart failure and prolonged mechanical ventilation animal models. No therapeutic options are available to improve diaphragm function. However, levosimendan showed a beneficial effect in isolated diaphragm test, enhancing contractility, possibly suggesting a new therapeutic approach in patients with respiratory failure and difficult weaning from mechanical ventilation.

Conclusion

Levosimendan has been introduced in clinical practice a decade ago and has been proven to be superior to other inodilators in various clinical settings. Its beneficial effect is probably due to its peculiar mechanism of action. Levosimendan should be preferred in perioperative medicine in patients with cardiac dysfunction, after cardiac and noncardiac surgery. Further trials in critically ill patients with sepsis or septic shock or in ambulatory patients with chronic heart failure are ongoing and may lead to further application of levosimendan in new settings.

Summary Table

Clinical summary					
Drug	Indications	Cautions	Side effects	Dose	Notes
Levosimendan	Acutely decompensated heart failure Low output syndrome in cardiac surgery Critically ill patients (evidence mostly from above reported settings) Sepsis-related cardiac dysfunction (unconclusive but promising results) Intermittent levosimendan administration in chronic heart failure	Monitor for hypotension and tachycardia Loading dose has been associated with adverse effects and hypotension and should be avoided whenever possible Should be used with caution in patients with renal or hepatic impairment	Hypotension (dose dependant) Tachycardia Headache Atrial/ventricular arrhythmias	[Loading dose: 6–12 μg/kg, see cautions] Continuous infusion of 0.05–0.1 μg/kg/min, if tolerated can be increased up to 0.2 μg/kg/min	Hemodynamic effect persist for at least 24 h, and has been reported to last for 7–10 days No adjustment is required for age Can be used in patients receiving β-blocking agents without loss of efficacy. Synergistic effects with classic inotropes

New indications like prevention of decompensation in chronic heart failure through oral or intermittent intravenous administration are currently under investigation and are showing promising results in preliminary data

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Perioperative β-Blocker Therapy

8

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8.1 General Principles

We have previously identified 13 interventions that might change perioperative mortality in adult surgery [1, 2], among them are perioperative β-blockers (BB). The increased prevalence of cardiovascular (CV) disease together with the awareness of the survival benefit of BB in various cardiac pathologies, promoted a dramatic increase in its utilization. A decrease in the myocardial oxygen consumption to avoid supply/demand mismatch in addition to their anti-arrhythmic properties and known coronary plaque stabilizing effect are the main benefits. Nevertheless, in instances of hypotension during anesthesia or blood loss, failure to sufficiently augment the cardiac output (while on BB) is concerning. The use of perioperative BB to improve cardiac outcomes and mortality before noncardiac surgery continues to be debated, and over the past two decades, several randomized controlled studies showed conflicting results. Due to guideline and institutional recommendations, physicians in charge of the surgical patient have become more liberal with administering BB and are ready to accept the accompanying intraoperative hypotension and bradycardia in favor of possibly improving the cardiac outcome. In 2008, the largest multicenter randomized trial "POISE" [3] demonstrated a significant reduction in CV death but at the cost of an increased mortality and an additional risk of stroke in the BB-treated patients and has raised more questions than answers. Because the

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evidence from the Dutch Echocardiographic Cardiac Risk Evaluation Applying Stress Echocardiography (DECREASE) family of trials for the value of perioperative BB is no longer secure, further trials and meta-analyses were performed to investigate its benefit.

8.2 Main Evidence

8.2.1 Randomized β-Blocker Studies Outcome

Table 8.1 is a compilation of the major studies evaluating the outcome of perioperative BB with emphasis on the number of patients, type of BB used, onset and duration of administration, type of surgery and outcome. While the initial three studies by Mangano et al. [4], Poldermans et al. [5, 6], and Lindenauer et al. [7] showed a statistically significant benefit for BB over placebo, the POBBLE [8], MAVS [9], DIPOM [10], BBSA [11], Yang and colleagues' [12], and POISE [3] trials did not conform to the same findings. In the latter six studies, BB administration was started 2 h to 1 day before surgery without any titration to achieve the desired heart rate. The extensive work of Poldermans in perioperative medicine represents the main evidence that promoted a more liberal use of perioperative BB. This has significantly influenced the European Society of Cardiology (ESC) guidelines; however, this data is now under question. In 2008, the POISE trial randomized 8,331 patients to either extended release metoprolol or placebo. Although there was a reduction in primary end points, a composite of cardiovascular death, nonfatal MI, and nonfatal cardiac arrest, with metoprolol (5.8 % vs. 6.9 %, $P = 0.399$), there was a significant 33 % increase in the total mortality and a twofold increased risk of stroke. The design and outcome of POISE trial were later questioned as it was not reflective of the optimal way to use perioperative BB. The large dose of metoprolol (200 mg) was given 2–4 h before surgery without any titration.

Several meta-analyses were performed. Bouri et al. Conducted a meta-analysis of secure data from randomized controlled trials effect of BB on perioperative mortality, nonfatal myocardial infarction, stroke, and hypotension in noncardiac surgery and found that initiation of BB before surgery although reduced nonfatal myocardial infarction (RR 0.73, $p = 0.001$) yet caused a 27 % risk increase in 30-day all-cause mortality ($p = 0.04$) and increased stroke (RR 1.73, $p = 0.05$) and hypotension (RR 1.51, $p < 0.00001$) [13]. In a systematic analysis by Wijeysundera et al. [14], BB decreased nonfatal myocardial infarction (RR, 0.69; 95 % CI, 0.58–0.82) but increased nonfatal stroke (RR, 1.76; 95 % CI, 1.07–2.91), hypotension (RR, 1.47; 95 % CI, 1.34–1.60), and bradycardia (RR, 2.61; 95 % CI, 2.18–3.12), and these findings were unchanged after excluding the DECREASE and POISE trials. Nonetheless, effects on mortality differed significantly between the DECREASE and other trials. While BB were associated with a trend toward reduced all-cause mortality rate in the DECREASE trials (RR, 0.42; 95 % CI, 0.15–1.22), it was associated with increased all-cause mortality rate in other trials (RR, 1.30; 95 % CI, 1.03–1.64) [14].

Table 8.1 Major studies describing the outcome of perioperative β-blocker use

Study	*N*	Drug	Onset and duration	Surgery	Results
Mangano/1966	200	Atenolol 50–100 mg	Before induction–7 days postop	Noncardiac surgery	Reduced mortality at 6 months (0% vs. 8%, $p<0.001$), at 1 year (3% vs. 14%, $p=0.005$), and at 2 year (10% vs. 21% $p=0.019$)
Decrease1/1999	112	Bisoprolol 5−10 mg	1 week preop–30 days postop	Major vascular surgery	Decreased cardiac mortality (3.4% vs. 17%, $p=0.02$) and nonfatal MI (0% vs. 17%, $p<0.001$) in the BB group
Lindenauer/2005	122,338	Undetermined	Hospital day 2	Major noncardiac surgery	RCRI score 0 or 1, no benefit and possible harm. Score 2, 3, or 4 or more, adjusted OR for in-hospital death is 0.88, 0.71, 0.58, respectively
POBBLE/2005	103	Metoprolol 50 mg BID	1 day before surgery–7 days postop	Infrarenal vascular surgery	No difference in 30-day CV events (32% vs. 34%) in the BB and placebo group, respectively
MAVS/2006	496	Metoprolol 25–100 mg	2 h preop–5 days or discharge	Vascular surgery	No significant difference in primary outcome[a] at 30 days (10.2% vs. 12.0%) in BB and placebo groups, respectively, ($p=0.57$) and at 6 m ($p=0.81$)
DIPOM/2006	921	Metoprolol 100 mg ER	1 day preop–8 days postop	Major noncardiac surgery	Primary outcome[b] occurred in 21% and 20% in BB and placebo, respectively (CI 0.80–1.41). All cause mortality was 16% in both groups (CI 0.74–1.42 $p=0.88$)

(continued)

Table 8.1 (continued)

Study	*N*	Drug	Onset and duration	Surgery	Results
BBSA/2007	219	Bisoprolol 5 mg	3 h preop–10 days or discharge	Surgery with spinal block	Primary outcome[c] was 22.7 % vs. 22.0 % in BB and placebo group, respectively, at 1 year ($p=0.90$)
Yang/2008	102	Metoprolol	Oral or IV metoprolol from 2 h before surgery to 30 days after surgery	Intrathoracic or intra-abdominal surgery	Cardiovascular events occurred in 9.8 % of control vs. 2 % in BB group (P = NS)
Poise/2008	8,331 Metoprolol ER 200 mg	2–4 h preop–30 days postop	Noncardiac surgery	MI occurred in 4.2 % vs. 5.7 % in BB and placebo, respectively, $p=0.017$. Mortality was higher in the metoprolol group (3.1 % vs. 2.3 %, $p=0.0317$). Stroke was more in the metoprolol group (1 % vs. 0.5 %, $p=0.0053$)	
Decrease IV/2009	1066	Bisoprolol 2.5–10 mg	3–4 days presurgery and continued for 30 days post surgery	General; urological; orthopedic; ear, nose, and throat; gynecological plastic; or other surgeries	Patient randomized to bisoprolol had lower perioperative mortality and nonfatal MI (2.1 % vs. 6.0 % events; hazard ratios, 0.34; 95 % confidence intervals, 0.17–0.67; $P=0.002$)

Look to references for expansion of study abbreviations. *ER* extended release, *preop* preoperative, *postop* postoperative, *d* day, *m* month, *y* year, *RCRI* Revised Cardiac Risk Index, *MI* myocardial infarction, *CV* cardiovascular, *BB* β-blocker, *OR* odds ratio, *BID* twice a day

[a]Primary outcome was postoperative 30-day composite incidence of nonfatal myocardial infarction, unstable angina, new congestive heart failure, new atrial or ventricular dysrhythmia requiring treatment, or cardiac death

[b]Primary outcomes were time to all-cause mortality, acute myocardial infarction, unstable angina, or congestive heart failure

[c]Primary outcomes were cardiovascular mortality, nonfatal myocardial infarction, unstable angina, congestive heart failure, and cerebrovascular insult

8.2.2 AHA Guidelines for Perioperative Beta-Blockers

In 2014, the ACC/AHA released guidelines on perioperative cardiovascular evaluation and management of patients undergoing noncardiac surgery including recommendations on perioperative beta-blocker therapy [15]. Table 8.2 summarizes these recommendations.

8.3 Therapeutic Use

8.3.1 Titration of Beta-Blockers and Which Class to Use

There are insufficient data regarding perioperative titration of BB and whether this is more beneficial than fixed-dose regimens. Although several studies suggested that titration is important to achieving appropriate anti-ischemic effects [13], many patients in the original trials remained on their starting medication dose at the time of surgery. Studies that titrated BB started therapy >1 day before surgery, making it difficult to confirm whether dose titration or preoperative timing was more important to produce benefit from BB. Several studies have evaluated the intraclass differences in BB according to duration of action and beta-1 selectivity [16–19], but no head-to-head comparisons were performed. In addition these intraclass differences may be driven by differences in beta-adrenoceptor type rather than the medication itself [20]. Table 8.3 summarizes the pharmacokinetics and pharmacodynamics of BB used in the perioperative period.

Table 8.2 Summary of recommendations by the ACC/AHA on perioperative β-blocker therapy before noncardiac surgery

T1 ACC/AHA guideline (2014) (column 1–2)	
Class I	Beta-blockers are recommended in patients undergoing surgery who have been on beta-blockers chronically (level of evidence B)
Class IIa	It is reasonable for the management of beta-blockers after surgery to be guided by clinical circumstances, independent on when the agent was started (level of evidence B)
Class IIb	1. In patients with intermediate- or high-risk myocardial ischemia noted in preoperative risk stratification tests, it may be reasonable to begin perioperative beta-blockers (level of evidence C)
	2. In patients with 3 or more RCRI risk factors (e.g., diabetes mellitus, HF, CAD, renal insufficiency, cerebrovascular accident), it may be reasonable to begin beta-blockers before surgery (level of evidence B)
	3. Patients with a compelling long-term indication for beta-blocker therapy but no other RCRI risk factors, initiating beta-blockers in the perioperative setting as an approach to reduce perioperative risk is of uncertain benefit (level of evidence B)
	4. In patients in whom beta-blocker therapy is initiated, it may be reasonable to begin perioperative beta-blockers long enough in advance to assess safety and tolerability, preferably more than 1 day before surgery (level of evidence B)
Class III	Beta-blocker therapy should not be started on the day of surgery (level of evidence B)

Table 8.3 Summary of pharmacokinetics and pharmacodynamics of ß-blockers in the perioperative period

Clinical summary (column 1–6)					
Drugs[a]	Indications	Cautions	Side effects	Dosage	Notes
1. Metoprolol 2. Atenolol 3. Bisoprolol	1. Patients on chromic BB therapy 2. Patients with evidence of myocardial ischemia on preoperative testing	1. Severe bradycardia or high grade AV block 2. Hypotension (SBP < 90 mmHg) 3. Decompensated heart failure or cardiogenic shock 4. Severe bronchospasm Symptomatic PAD (rest pain or gangrene)	1. Bradycardia 2. Hypotension 3. Bronchospasm 4. Risk of stroke if started perioperative in high dose without titration	Metoprolol Start 25 mg PO BID, maximum dose 200 mg qd[b] Atenolol Start 25 mg PO qd, maximum 100 mg qd Bisoprolol Start 5 mg daily, maximum 10 mg qd	1. In those on chronic BB therapy resume the same regimen and titrate if needed to achieve target HR 2. In those not a BB, titration should be started slowly, preferably 1 week earlier 3. Half-dose BB can be used in small, elderly or frail patients or if SBP is <110 mmHg or HR <65/min

BB ß-blockers, *SBP* systolic blood pressure, *HR* heart rate, *PAD* peripheral arterial disease

[a]Carvedilol is not included as it is not well studied in the perioperative period

[b]For patients unable to tolerate oral medications, metoprolol can be given in a dose of 2.5–5 mg IV q 6 h (initial dose can be repeated after 5 min to achieve target HR)

8.3.2 Discontinuing β-Blockers

In the perioperative period, discontinuation of BB is occasionally observed in the surgical patient when oral BB therapy is either not changed to its equivalent intravenous dose or when it is prescribed as a PRN order to be given only when blood pressure increase. Discontinuation of BB is associated with a rebound increase in the heart rate and blood pressure and an increased risk of myocardial ischemia. Wallace et al. concluded that perioperative withdrawal of BB almost quadrupled the 30-day mortality rate (OR, 3.93, 95% CI, 2.57–6.01; $P<0.0001$) and almost doubled the 1-year mortality rate (OR, 1.96; 95% CI, 1.49–2.58; $P<0.0001$) [21]. Similarly, a retrospective analysis of low-risk patients undergoing arthroplasty showed that the discontinuation of BB was significantly associated with postoperative myocardial infarction (OR, 2.0; 95% CI, 1.1–3.9) and death (odds ratio, 2.0; 95% CI, 1.0–3.9) [22]. In case of a clear contraindication to BB, it has been advised to taper therapy gradually. This supports the major rationale for the ACC/AHA Class I recommendation regarding continuation of BB in patients already on the drug.

8.4 Summary of Recommendations

1. The two main groups that will benefit (supported by current evidence) from perioperative BB are those on chronic BB therapy and those with evidence of ongoing ischemia anticipating high-risk surgery.
2. In patients not previously on BB, avoid initiating therapy in the immediate preoperative period unless it is mandatory due to active coronary artery disease.
3. Avoid discontinuing BB in the perioperative period but should rather be changed to an equivalent intravenous dose in patients unable to receive oral medications.
4. Patient receiving perioperative BB should be carefully monitored for hypotension and bradycardia, especially intraoperatively.
5. Resume BB in the postoperative period in those on the drug preoperatively. In patients with contraindications to the drug, gradual rather than abrupt discontinuation is recommended.

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9 Leukocyte Depletion of Transfused Blood May Reduce Mortality in Cardiac Surgery Patients

Antonella Capasso, Federico Masserini, and Antonio Pisano

9.1 General Principles

Allogenic blood transfusions (ABTs) are widely used in the perioperative care of patients undergoing major surgery. According to the last available update of the World Health Organization Global Database on Blood Safety [1], approximately 92 million blood donations are collected annually worldwide, with surgical procedures accounting for consumption of up to 40% of total blood supply in Western countries.

Although transfusions have been proven to have deleterious effects on patients' outcome and efforts have been made accordingly in recent years to reduce the use of blood products in clinical practice, the use of ABTs might even increase in the coming years.

Indeed, three randomized clinical trials (RCTs) published in 2015 found an improved survival with the use of more liberal transfusion triggers in different clinical settings [2–4], the larger of which (TITRe2 trial) [2] was held in cardiac surgery (see Chap. 14). Subsequent meta-analyses confirmed that restrictive transfusion strategies do not seem to offer benefits in terms of mortality [5] and may even be harmful [6]. Although this topic is controversial and no agreement exists on the optimal transfusion trigger to be used in critically ill or surgical patients, a restrictive transfusion strategy appears to be hazardous at least in some clinical settings such as ischemic heart disease and cardiac surgery [2, 7].

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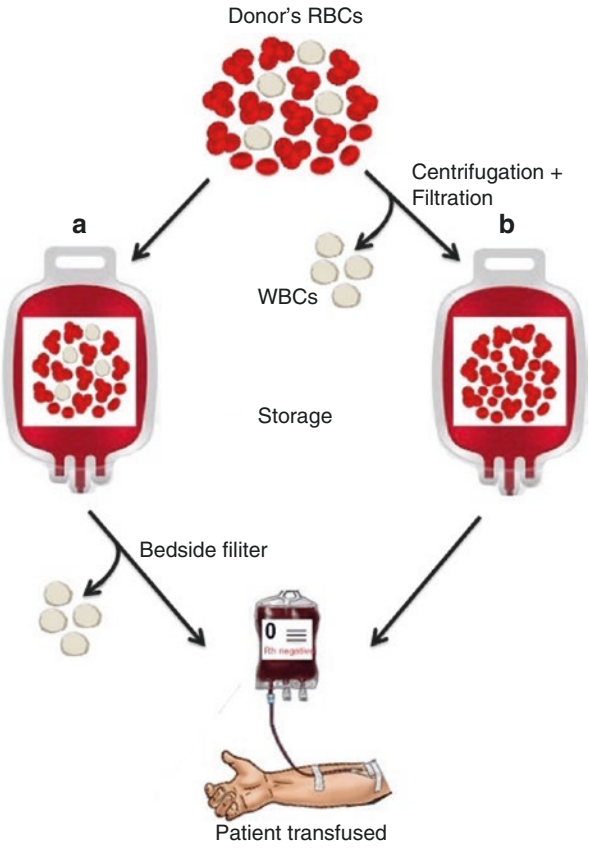

Fig. 9.1 Poststorage (**a**) and prestorage (**b**) leukoreduction. *RBCs* red blood cells, *WBCs* white blood cells

However, several studies on high-risk surgical patients showed a dose-dependent relationship between blood transfusions and both hospital mortality and the development of postoperative complications such as infections and multi-organ failure [8, 9]. One of the possible responsible mechanisms for the increased susceptibility to infections in patients receiving transfusions is a suppression of the immune function, maybe together with inflammatory response, due to the allogenic leukocytes contained in blood transfusions. This transfusion-related immunomodulation (TRIM) effect is, however, still controversial [10].

Leukoreduction (LR) consists in leukocyte removal from blood components with the aim to overcome the putative adverse effects of allogenic leukocytes. This process may occur by centrifugation and subsequent filtration shortly after blood collection (so-called prestorage LR) or by using special filters just prior to transfusion (poststorage LR) (Fig. 9.1).

Prestorage LR is more effective because it prevents the fragmentation of leukocytes and the synthesis of cytokines during the storage, while membrane fragments and cytokines passing through poststorage filters may account for the same adverse effects of intact white blood cells (WBCs). Further agreed-upon indications for LR

are as follows: decrease in the transmission of cytomegalovirus, prevention of HLA alloimmunization in high-risk patients, and reduction in both febrile transfusion reactions and graft versus host disease [9].

In the last few years, several countries have adopted a policy of universal leukoreduction, but its effects on reduction in postoperative infections and mortality are still unclear. Many RCTs and meta-analyses of RCTs have focused on the ability of leukoreduced red blood cells (LR-RBCs) to decrease infections and mortality in the postoperative period, with conflicting results. However, a significant beneficial effect of leukodepletion on mortality is fairly well documented in cardiac surgery patients [11–18].

9.2 Main Evidence

Several RCTs investigated the difference in short-term (up to 3 months) mortality between patients receiving leukodepleted and non-leukodepleted RBCs, both in cardiac surgery [11–16] and in other clinical settings [19–24] (Table 9.1).

9.2.1 Leukocyte Depletion and Mortality in Cardiac Surgery

In the large RCT by van de Watering et al. [11], 914 patients undergoing cardiac surgery were randomized to receive standard buffy-coat-depleted RBCs (BCD-RBCs, $n = 306$) or the same product filtered either before (fresh filtered [FF], $n = 305$) or after storage (stored filtered [SF], $n = 303$). A higher 60-day mortality in the group receiving BCD-RBC as compared with those receiving FF or SF products (7.8 vs. 3.6 vs. 3.3 %, $p = 0.01$) was found. Moreover, a subgroup analysis according to the number of transfusions showed a dose-dependent effect, as the difference in mortality was statistically significant only in cardiac surgery patients who received more than three RBC units.

These authors conducted a further study on 496 cardiac valve surgery patients with high probability of multiple RBC transfusions and higher risk for postoperative complications [12]. The in-hospital mortality was significantly lower in the group receiving prestorage LR-RBC compared with BCD-RBC (5.5 vs. 10.1 %, $p = 0.05$). Leukodepletion was also associated with a significantly reduced infection rate.

In these two investigations [11, 12], the higher mortality rate among patients who received standard buffy-coat-poor RBCs as compared with prestorage leukodepleted RBCs was mainly associated with a combination of infection and multiorgan dysfunction syndrome (MODS) [17].

As reported by the first web-based Consensus Conference on randomized evidence for reduction in perioperative mortality [25], and by its recent update [26], no other investigations to date found a survival benefit of leukodepleted RBCs among cardiac surgery patients (Table 9.1). Connery et al. [13] compared bedside-filtered RBCs with unfiltered RBCs in 69 patients undergoing coronary artery bypass graft (CABG) surgery, and they found no difference in mortality, even if the study was

Table 9.1 RCTs investigating mortality in patients transfused with leukodepleted versus leukocyte-containing red blood cells

Study	Setting	No. patients	Blood products	End points	Results (%)	*p*
van de Watering [11] (1998)	Cardiac surgery	914	BCD-RBC vs. LR (prestorage) vs. LR (post-storage)	60-day mortality	7.8 vs. 3.6 vs. 3.3	0.015
Bilgin [6] (2004)	Cardiac surgery	474	BCD-RBC vs. LR (prestorage)	Hospital mortality	10.1 vs. 5.5	0.05
				90-day mortality	12.7 vs. 8.4	n.s.
Connery [7] (2005)	Cardiac surgery	98	BCD-RBC vs. LR	30-day mortality	3.2 vs .2.6	n.s.
Wallis [8] (2002)	Cardiac surgery	597	BCD or plasma-reduced RBC vs. WBC-filtered RBC	90-day mortality	2.9 vs. 2.5 vs. 0.5	n.s.
Bracey [9] (2002)	Cardiac surgery	443	BCD-RBC vs. LR (prestorage)	Hospital mortality	7.5 vs. 5.9	n.s.
Boshkov [10] (2006)	Cardiac surgery	1,227	BCD-RBC vs. LR	60-day mortality	9.7 vs. 4.9	–
Jensen [13] (1996)	Colorectal surgery	586	BCD-RBC vs. LR (prestorage)	Hospital mortality	2.8 vs. 3.4	n.s.
Titlestad [14] (2001)	Colorectal surgery	279	BCD-RBC vs. LR (prestorage)	30-day mortality	8.5 vs. 3.6	n.s.
Skamberg [15] (2007)	Colorectal cancer surgery	642	BCD-RBC vs. LR	99-month mortality	49.7 vs. 52.5	n.s.
Dzik [16] (2002)	Medical/major surgery	2,780	RBC vs. LR (prestorage)	Hospital mortality	8.5 vs. 9.0	n.s.
Van Hilten [17] (2004)	Gastrointestinal and aortic aneurysm surgery	1,051	BCD-RBC vs. LR (prestorage)	Hospital mortality	8.4 vs. 10.3	n.s.
Nielsen [18] (1999)	Burns/trauma	24	BCD-RBC vs. LR (prestorage)	Hospital mortality	33.3 vs. 16.6	n.s.

ABT allogenic blood transfusion, *TRIM* transfusion-related immunomodulation, *LR* leukoreduction, *RCT* randomized controlled trial, *RBC* red blood cells, *BCD* buffy coat depleted, *MODS* multi-organ dysfunction syndrome, *CABG* coronary artery bypass grafting, *CPB* cardiopulmonary bypass, *SIRS* systemic inflammatory response syndrome, *CARS* compensatory anti-inflammatory response syndrome

stopped early due to an interim analysis showing less respiratory tract infections in the filtered group ($p = 0.048$).

In a study on 597 patients admitted for CABG or valve surgery, Wallis et al. [14] randomized patients to receive plasma-reduced RBCs ($n = 198$), BCD-RBCs ($n = 204$), or WBC-filtered RBCs ($n = 195$) and found similar mortality rates among the patients transfused with WBC-filtered blood products as compared with the other groups.

Overall, however, when the results of the five RCTs [11, 12, 14–16] conducted in cardiac surgery were combined in a meta-analysis, including a total of 2,990 patients, and were analyzed separately from studies conducted in other surgical settings, the mortality rate was significantly higher in patients transfused with leukocyte containing RBC (summary odds ratio [OR] 1.72, 95 % confidence interval [CI] 1.05–2.81) [18].

The benefits of leukocyte depletion of transfused RBCs in patients undergoing cardiac surgery were recently challenged by a large retrospective study involving a cohort of 14,980 patients from 6 teaching hospitals in Australia [27]. Universal leukodepletion (ULD) was introduced in this country in July 2008. McQuilten et al. [27] evaluated mortality, infections, acute kidney injury (AKI), and intensive care unit (ICU) length of stay (LOS) in patients who underwent cardiac surgery before (2005–2008, $n = 8{,}857$) and after (2008–2010, $n = 6{,}123$) the introduction of ULD. No difference in either mortality or infection rate was shown between the two periods. Although ULD was found to be associated with reduced AKI, a similar difference was observed among non-transfused patients, suggesting that it could be attributed to other changes in care over time.

Despite this evidence, the above-discussed survival benefits of leukocyte depletion in cardiac surgery patients have not been disproved by further randomized evidence.

9.2.2 Leukocyte Depletion and Mortality in Noncardiac Surgery

No RCT reported any significant difference in mortality rates in noncardiac surgical settings. Three large RCTs [19–21] on colorectal surgery patients did not show differences in mortality between patients transfused with LR-RBCs as compared with patients transfused with BCD-RBCs. However, the study by Jensen et al. [19] showed a significantly lower rate of wound infections and intra-abdominal abscesses in patients who received leukodepleted blood. Dzik et al. [22] performed an extensive RCT on a heterogeneous population including 2,780 medical and surgical patients. The compared groups received either standard or leukodepleted RBC. These authors found no difference in mortality or in-hospital LOS. Additional analysis of specific surgical subgroups, such as cardiac and colorectal surgery, failed to show any significant difference between the leukodepleted group and the control group. No difference in mortality emerged also from the study by van Hilten et al. [23] on patients undergoing major (gastrointestinal or abdominal aortic) surgery. Nevertheless, hospital LOS and incidence of MODS were lower in the filtered-RBC group. Finally, the aforementioned meta-analysis by Vamvakas et al. [18] considered 11 RCTs,

including the 5 conducted in cardiac surgery cited above, 4 in gastrointestinal surgery, 1 in trauma patients, and 1 in a mixed medical/surgical population. Their results showed no difference in terms of mortality across all clinical settings and transfused RBC products, except, as mentioned, in cardiac surgery.

9.2.3 Leukocyte Depletion and Infections

The hypothesis that WBCs contained in ABTs could have a causative role in postoperative infection was tested in several RCTs, with conflicting results [11–15, 17, 19–23]. In particular, two meta-analyses of RCTs attempted to detect a difference in infection rates related to the use of leukodepleted blood products [18, 28]. Of these, the one using an intention-to-treat analysis did not find association between LR and postoperative infection, while the one restricted to the actually transfused patients (as-treated analysis) [28] reported up to almost 50 % reduction in the relative risk for developing a postoperative infection after transfusion of leukodepleted RBC ($p < 0.005$). However, both have been criticized for the lack of homogeneity between the included trials [29] and for the disagreement between intention-to-treat and as-treated methods [30].

In light of currently available studies, the reduction in mortality observed in the cardiac surgical setting cannot be completely attributed to the ability of LR to prevent postoperative infections. More complex mechanisms have been proposed.

9.3 Pharmacologic Properties

ABTs have considerable impact on the recipient's immune system. This so-called TRIM effect is presumed to result from allogeneic leukocytes and was revealed in the 1970s in patients receiving a kidney allograft, in which pre-transplant blood transfusions improved the graft outcome. The observation of a possible immunosuppressive action also raised concerns about an increased susceptibility to postoperative infection.

Several factors have been suspected to play a role in TRIM, such as leukocytes' activation or soluble factors released by leukocytes during storage.

Cardiac surgery is a model in which additional pathophysiological mechanisms may operate to enhance any effect of ABTs on postoperative infection and mortality. Cardiopulmonary bypass (CPB) leads to a systemic inflammatory response syndrome (SIRS), characterized by a cytokine storm and leukocyte activation, with the release of mediators like interleukin 6 (IL-6), IL-12, and tumor necrosis factor α (TNF-α). A compensatory anti-inflammatory response syndrome (CARS) always counteracts this pro-inflammatory pattern via the release of anti-inflammatory cytokines like IL-10.

Leukocyte-containing RBCs seem to alter the balance between pro- and anti-inflammatory response after CPB, amplifying SIRS response and favoring the progress to MODS. In addition, a pronounced inflammatory response may lead to a more accentuated CARS that is associated with increased susceptibility for postoperative infections.

Bilgin et al. [31] investigated pro- and anti-inflammatory cytokine profiles in cardiac surgery patients randomized to receive LR-RBC or BCD-RBC. They found a significantly higher IL-6 concentration in BCD-RBC group, among patients transfused with more than four RBC units. Moreover, patients who developed postoperative infection and MODS showed increased concentrations of IL-6 and IL-12, respectively, in the BCD-RBC group. These findings suggest that leukocyte-containing RBCs interfere with the postoperative inflammatory response. This "second hit" induced by allogenic leukocytes aggravates the SIRS triggered by cardiac surgery and may be, in combination with a greater susceptibility to infection, the cause of more severe MODS.

9.4 Therapeutic Use

Cardiac surgery patients are a heavily transfused population and show a greater inflammatory activation in response to the surgical procedure. Therefore, this population constitutes a model in which the benefits of leukodepletion can be amplified.

As discussed above, there is consistent evidence supporting the use of leukoreduced blood products in cardiac patients [11–16, 18, 25, 28].

Whether this beneficial effect also concerns other surgical groups with large blood needs remains a matter of debate and will require further research, even though leukocyte depletion results in a reduction in postoperative febrile reactions and consumption of antibiotics. Moreover, as transfusion-related immunomodulation seems to be a real entity, even if its magnitude and its precise mechanism are uncertain, leukoreduction may likely provide an increased level of safety for the majority of transfusion recipients.

Relatively few adverse effects have been reported in association with leukoreduced blood products: the "red eye" syndrome, an allergic conjunctivitis, has been observed in patients who had received red cells filtered through a filter containing cellulose acetate.

Unfortunately, leukocyte reduction is a costly procedure, and cost-effectiveness analyses are poor. Nonetheless, lower medical costs would be expected as a result of reduction in transfusion-related adverse events and improved outcome of patients.

For these reasons, transfusion of leukodepleted blood components is nowadays considered the best practice in most Western countries, where universal leukodepletion is therefore adopted.

Conclusion

Although several studies reported an increased incidence of postoperative infections and multi-organ failure due to red blood cell transfusions and, conversely, a reduction in these complications with the use of leukodepleted products, the effects of leukodepletion are still controversial, and its possible mechanisms of action remain, at least partly, unclear. Most investigations, however, suggest a beneficial effect of leukodepletion among cardiac surgery patients, where both an enhanced inflammatory response and an immunomodulatory effect due to

leukocytes contained in blood products may contribute to a higher rate of infections and multi-organ failure. Particularly, a large randomized controlled trial suggested that cardiac surgery patients receiving at least three blood transfusions might have a survival benefit from leukocyte depletion of transfused blood. This topic deserves further investigation, including cost-effectiveness studies.

Summary Table

Clinical summary					
Technique	Indications	Cautions	Side effects	Dose	Notes
Leukodepletion of transfused RBC by (pre- and post-storage) filtration	Cardiac surgery	None	Generally well tolerated "Red eyes" syndrome High costs	Prestorage filtration, within 2–4 h after collection, is preferred It allows to obtain a WBC count of $1–5 \times 10^6$ per unit	Mortality reduction may be related to reduction in both TRIM and infection rate Allogenic leukocytes result in a pro-inflammatory effect that worsen SIRS triggered by CPB in cardiac surgery

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Reducing Perioperative Mortality with the Intra-Aortic Balloon Pump

10

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10.1 General Principles

The intra-aortic balloon pump (IABP) enhances myocardial performance by minimizing oxygen supply/demand mismatch [1–6]. Balloon inflation during diastole enhances myocardial oxygen delivery due to increased diastolic coronary perfusion pressure [4–6]. Balloon deflation just prior to systole reduces myocardial oxygen demand by unloading the left ventricle [4–6]. Recent evidence has identified the IABP as a therapeutic modality that may reduce perioperative mortality due to these myocardial benefits [1–3].

10.2 Therapeutic Application

The clinical indications for the IABP include acute coronary syndromes, cardiogenic shock, high-risk percutaneous coronary intervention (PCI), and cardiac surgery [1–6]. Perioperative indications also include preoperative stabilization of the cardiac surgery

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patient, postcardiotomy cardiogenic shock, and the high-risk noncardiac surgery in the setting of critical cardiac disease [1–8]. The complications of the IABP include aortic regurgitation, arterial dissection, arterial rupture, atheroembolism, and branch vessel occlusion [9, 10]. Consequently, the contraindications for this therapy include significant aortic insufficiency, aortic dissection, aortic aneurysm, and severe aortic atheroma. Important technical considerations to maximize the benefits of the IABP include meticulous synchronizing of balloon events within the cardiac cycle and imaging to confirm correct placement within the descending thoracic aorta.

10.3 Main Evidences

10.3.1 Cardiac Surgery

The 2011 North American guidelines for coronary artery bypass graft (CABG) surgery recommended the IABP as a consideration in the high-risk patient with a prior sternotomy, a left ventricular ejection fraction ≤30 %, and/or left main coronary disease (Class IIa recommendation; Level B evidence) [11]. The 2014 European guideline for myocardial revascularization (CABG or PCI) highlighted the role of IABP in ischemic cardiogenic shock, especially for mechanical complications including mitral regurgitation and ventricular septal defect (Class IIa recommendation; Level C evidence) [3]. The routine application of the IABP in ischemic cardiogenic shock was not recommended (Class III recommendation; Level A evidence) [4].

A prospective single-center randomized clinical trial ($N = 110$) demonstrated that IABP inserted preoperatively in hemodynamically stable patients with an ejection fraction <35 % did not reduce major morbidity, including mortality after CABG (odds ratio 1.49 95 % confidence interval 0.68–3.33; $P > 0.05$) [12]. A larger multicenter randomized clinical trial (IABP-SHOCK II: $N = 600$) demonstrated that therapy with IABP in ischemic cardiogenic shock did not reduce mortality after PCI or CABG both at 30 days (risk ratio 0.96; 95 % confidence interval 0.79–1.17; $P = 0.69$) and at 1 year (risk ratio 1.01; 95 % confidence interval 0.86–1.18; $P = 0.91$) [13, 14].

Conversely, recent meta-analyses of randomized clinical trials have demonstrated that preoperative therapy with the IABP in high-risk CABG surgery may have a perioperative mortality benefit [1, 15]. In the first meta-analysis (eight trials: cumulative $N = 625$), the preoperative IABP significantly reduced perioperative mortality (risk ratio 0.38; 95 % confidence interval 0.20–0.73; $P = 0.004$) [1]. In the second meta-analysis (nine trials: cumulative $N = 1{,}171$), a preoperative IABP significantly reduced in-hospital mortality (odds ratio 0.381; 95 % confidence interval 0.23–0.69; $P < 0.001$) [15]. Both these meta-analyses omitted from their datasets the IABP-SHOCK II trial since it also included patients for PCI [13, 14]. This important distinction highlights the importance for further multicenter randomized clinical trials adequately powered to test for a survival benefit of the IABP in high-risk patients for CABG [1, 15].

10.3.2 Noncardiac Surgery

Recent European and North American guidelines have highlighted the limited evidence to inform the clinical indications for IABP in high-risk noncardiac surgery [7, 8]. As a group, the case reports and case series have documented the perioperative utility of the IABP in these settings for critical cardiac patients who either require emergency surgery prior to myocardial revascularization or who require intraoperative hemodynamic resuscitation [16, 17]. The IABP therefore can be recommended as a consideration for noncardiac surgery in the setting of acute and severe cardiac dysfunction that cannot be corrected before surgery (Class IIb recommendation; Level C evidence) [7].

10.3.3 Percutaneous Coronary Intervention

Current North American and European guidelines for PCI have recommended that the IABP should be considered in high-risk patients, including cardiogenic shock (Class II recommendation; Level C evidence) [4–6]. Furthermore, these guidelines have also recommended against the routine application of the IABP in these settings (Class III recommendation; Level A evidence), given the high-quality evidence discussed earlier in this chapter [3–6, 13, 14]. These recent recommendations represent a downgrading of the therapeutic role of the IABP in this setting, since previously it enjoyed a class I recommendation [4–6, 18, 19].

A recent meta-analysis of randomized controlled trials (seven trials: cumulative $N=790$) evaluated the effect of the IABP on mortality at 30 days in acute myocardial infarction complicated by cardiogenic shock [18]. This Cochrane meta-analysis included the IABP – SHOCK II landmark trial that enrolled patients both for PCI and CABG [13, 14]. The main finding from this high-quality trial was that therapy with IABP in this high-risk population had no effect on all-cause 30-day mortality (hazard ratio 0.95; 95 % confidence interval 0.75–1.19), despite beneficial effects on hemodynamic parameters [18]. The Cochrane investigators concluded that there is currently no convincing randomized data to support therapy with IABP in infarct-related cardiogenic shock.

These findings were confirmed in two further meta-analyses [20, 21]. The first meta-analysis included randomized trials regardless of hemodynamic status (12 trials: cumulative $N=2{,}123$) and demonstrated no mortality benefit associated with the IABP (odds ratio 0.96; 95 % confidence interval 0.74–1.24) [20]. Furthermore, this lack of mortality benefit persisted with (odds ratio 0.94; 95 % confidence interval 0.69–1.28; $P=0.69$) or without (odds ratio 0.98; 95 % confidence interval 0.57–1.69; $P=0.95$) cardiogenic shock [20]. The second meta-analysis included randomized trials both for PCI and CABG (12 trials: cumulative $N=2{,}155$) and demonstrated no significant mortality effect in the short term (relative risk 0.66; 95 % confidence interval 0.42–1.01) or long term (relative risk 0.79; 95 % confidence interval 0.47–1.35) [21]. Furthermore, in this second meta-analysis, the

high-risk CABG subgroup had reduced mortality with the IABP (relative risk 0.40; 95 % confidence interval 0.25–0.67), a finding consistent with meta-analyses discussed earlier [1, 15, 21].

Conclusion

In perioperative therapy the IABP can assist in the management to stabilize the patient with cardiogenic shock in cardiac surgery and noncardiac surgery, including the cardiac catheterization laboratory [22]. Given this clinical benefit, recent evidence and guidelines support the selective application of this intervention. While the IABP appears to reduce mortality as a preoperative intervention in high-risk CABG, its benefits are less clear in high-risk PCI. Further trials are required to explore its effects on mortality in high-risk cardiac patients both for cardiac surgery and noncardiac surgery [22].

Summary Table

Clinical summary			
Indications	Contraindications	Complications	Monitoring
Cardiogenic shock	1. Aortic regurgitation	1. Aggravation of aortic regurgitation	Imaging is required to confirm correct placement
High-risk CABG	2. Severe aortic atheroma	2. Atheroembolism	Optimal timing for balloon inflation and deflation in the cardiac cycle maximizes hemodynamic benefits
High-risk PCI	3. Aortic dissection	3. Aortic dissection	
Severe myocardial ischemia in noncardiac surgery	4. Aortic aneurysm	4. Arterial rupture	Monitoring for distal ischemia reduces complications
	5. Aortic branch vessel occlusion	5. Aortic branch vessel occlusion	

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Selective Decontamination of the Digestive Tract

11

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11.1 General Principles

Selective decontamination of the digestive tract (SDD) is an antimicrobial prophylaxis using parenteral (e.g. third-generation cephalosporin) and enteral antimicrobials (polymyxin E, tobramycin and amphotericin B) for the control of severe infections in critically ill patients [1].

SDD is based on the observation that critical illness profoundly affects the body flora, both qualitatively and quantitatively, promoting a shift from normal to abnormal carriage and from low to high carriage (overgrowth) of normal and abnormal flora [1]. The efficacy of SDD in controlling infections and in reducing mortality is based on the ability of the chosen antimicrobials to clear the carriage of potentially pathogenic microorganisms (PPMs) in overgrowth concentration.

11.2 Main Evidence

There have been 68 randomized controlled trials (RCT) of SDD in about 15,000 critically ill patients and 12 meta-analyses over a research period of 30 years. However, most RCTs were designed to detect morbidity, i.e. infection of the lower airways and the bloodstream, and were underpowered to detect a survival benefit.

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The most robust meta-analyses showed that SDD, using the full protocol of parenteral and enteral antimicrobials, significantly reduced lower airway infection by 72 % (OR 0.28, 95 % CI, 0.20–0.38), bloodstream infection by 27 % (OR 0.73, 95 % CI, 0.59–0.90) and mortality by 27 % (OR, 0.73, 95 % CI, 0.64–0.84) to 29 % (OR, 0.71, 95 % CI, 0.61–0.82) [1–3].

The largest RCTs on SDD with the end point of mortality were performed in the Netherlands [4, 5]. The first Dutch trial included 934 patients and showed a 35 % reduction of intensive care unit (ICU) mortality (RR 0.65, 95 % CI, 0.49–0.85) in the overall population and a significant reduction of ICU mortality in the subset of surgical patients who underwent emergency surgery (RR 0.48, 95 % CI, 0.26–0.87) [4]. The second Dutch study on SDD included about 6,000 patients and compared SDD, selective oropharyngeal decontamination (SOD), a regimen without intestinal and parenteral components and standard care [5]. SDD reduced ICU mortality compared to standard care [OR 0.81, 95 % CI, 0.69–0.94]. A post hoc analysis in surgical patients showed that SDD reduced 28-day mortality, albeit not significantly (OR 0.86, 95 % CI, 0.69–1.09) [6]. Finally, a third German RCT in 546 surgical patients [7], although not designed to detect a survival benefit, showed a significant mortality reduction in patients with mid-range APACHE II score of 20–29 (RR 0.51, 95 % CI, 0.29–0.87).

Pneumonia, post-operative infections and anastomotic leakage were reduced by SDD in gastrointestinal surgery [8]. There are three meta-analyses in liver transplant recipients receiving SDD (9–11). Two of them [9, 10] found a significantly reduced infection due to aerobic gram-negative bacilli (AGNB) and yeasts (OR 0.16, 95 % CI, 0.07–0.37 and OR 0.41, 95 % CI, 0.23–0.73, respectively), although the mortality reduction was not significant due to the small sample size (OR 0.82, 95 % CI, 0.22–2.45) [9].

SDD has been studied in cardiac surgical patients. All RCTs showed a reduction in rates of infections and reduced levels of endotoxin and inflammation mediators in the post-operative period [11].

Two meta-analyses exploring the efficacy of SDD in critically ill surgical patients showed a significant reduction in morbidity and mortality [11, 12]. Remarkably, SDD reduced mortality in surgical population by 27 % (OR 0.73, 95 CI, 0.55–0.98) [personal data not published] to 40 % (OR 0.60, 95 % CI, 0.41–0.88) [11].

Recently, two Consensus Conferences identified all interventions that might reduce mortality in adult surgical patients [13–15]. Based on evidence from only RCTs and meta-analyses, SDD has been included among the 14 non-surgical interventions that reduce mortality [15].

Additionally, SDD has been included in the 2012 edition of the guidelines for the management of severe sepsis and septic shock, unfortunately with an unaccountable level 2B for strength of recommendation and quality of evidence [16].

11.3 Pharmacologic Properties

The mechanism of action of SDD is the control of critical illness-related carriage in overgrowth (CIRCO) state [1]. Low-grade carriage is defined as $<10^5$ potentially pathogenic microorganisms (PPMs) per gram of digestive tract secretions.

High-grade carriage (i.e. overgrowth) is defined as $\geq 10^5$ PPMs per gram of digestive tract secretions. CIRCO is a risk factor for developing endogenous infection and resistance [1].

The majority of infections developing in ICU patients are endogenous (85 %), i.e. they are preceded by overgrowth in the throat and/or gut [1]. Oropharyngeal carriage of PPMs in overgrowth concentrations is the first step in the pathogenesis of lower airway infections. Similarly, gut carriage of PPMs in overgrowth concentrations is the first stage in the pathogenesis of bloodstream infections. Normal PPMs are the etiological agents in previously healthy individuals requiring intensive care following an acute event, such as trauma, surgery, pancreatitis, acute hepatic failure and burns. They are *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Moraxella catarrhalis, Escherichia coli*, methicillin-sensitive *Staphylococcus aureus* and *Candida albicans*. There are nine abnormal PPMs carried by individuals with underlying diseases: eight AGNB (*Klebsiella*, *Enterobacter*, *Citrobacter*, *Proteus*, *Morganella*, *Serratia*, *Acinetobacter* and *Pseudomonas* species) and methicillin-resistant *S. aureus* (MRSA) [1].

There is a qualitative and quantitative relationship between surveillance cultures of the throat and gut and diagnostic samples of lower airways and blood, i.e. when the potential pathogen reaches overgrowth concentrations in the throat and gut, lower airway secretions and blood may become positive for the same potential pathogen.

Exogenous infections (15 %) are not preceded by overgrowth in the throat and/or gut; they are usually caused by abnormal bacteria and may occur anytime during ICU stay. A high level of hygiene is the controlling manoeuvre and, in tracheostomized patients, may be combined with topical SDD antimicrobials onto the tracheostoma to prevent lower airway infections.

11.4 Therapeutic Use

The full protocol of SDD is based on the following four pillars [1] (Table 11.1):

1. Parenteral antibiotics given immediately on admission for 4 days to control primary endogenous infections due to PPMs already present in the patient's admission flora. Healthy patients with normal flora can be treated with cefotaxime 80–100 mg/kg/day. Patients with a chronic underlying disease or patients transferred from other ICUs or general wards may carry both normal and abnormal flora in the throat and gut, and they may require an antipseudomonas cephalosporin or a glycopeptide if MRSA carriage is expected.
2. Enteral non-absorbable antimicrobials, i.e. polymyxin E (colistin), tobramycin and amphotericin B (PTA), given throughout the treatment in the ICU, to control secondary carriage and subsequent secondary endogenous infections due to PPMs acquired in the ICU. Half a gram of gel or paste containing 2 % PTA is applied to the oropharyngeal mucosa with a spatula or a gloved finger four times a day; additionally, 10 mL of a suspension containing 100 mg of polymyxin E, 80 mg of tobramycin and 500 mg of amphotericin B is administered into the gut

Table 11.1 The four-component protocol of SDD

Target PPM, antimicrobials, manoeuvres	Total daily dose[a] (column 2–4)		
–	<5 years	5–12 years	> 12 years
Parenteral antimicrobials	–	–	–
Cefotaxime, mg	150/kg	200/kg	4000
Enteral antimicrobials	–	–	–
Oropharynx	–	–	–
AGNB: polymyxin E with tobramycin	2 g of 2 % paste or gel (column 2–4)		
Yeasts: amphotericin B or nystatin	2 g of 2 % paste or gel (column 2–4)		
MRSA: vancomycin	2 g of 4 % paste or gel (Column 2–4)		
Gut	–	–	–
AGNB: polymyxin E[b], mg	100	200	400
With tobramycin, mg	80	160	320
Yeasts: amphotericin B, mg	500	1000	2000
Or nystatin units	2×10^6	4×10^6	8×10^6
MRSA: vancomycin, mg	20–40/kg	20–40/kg	500–2000
Hygiene (with topical antimicrobials)	(2 g of 2 % PTA paste/gel or 4 % vancomycin paste/gel) (column 2–4)		
Surveillance swabs of throat and rectum on admission, Monday, Thursday	–	–	–

SDD selective decontamination of the digestive tract, *PPM* potentially pathogenic microorganisms, *AGNB* aerobic gram-negative bacilli, *MRSA* methicillin-resistant *Staphylococcus aureus*, *PTA* polymyxin/tobramycin/amphotericin B, *mg* milligram, *g* gram, *kg* kilogram

[a]Total daily dose must be divided into four doses

[b]Polymyxin E is colistin sulphate; 1 mg of colistin sulphate corresponds to about 20,000 International Unit (IU) of colistin

through the nasogastric tube four times a day. In properly decontaminated patients, surveillance samples of the throat and rectum are free from AGNB, *S. aureus* and yeasts. In case of MRSA endemicity, half a gram of a 4 % vancomycin gel/paste in the oropharynx and/or 500 mg of vancomycin solution in the intestine can be added to the classical PTA regimen to prevent the possible selection of MRSA.

3. High standards of hygiene are needed to control exogenous infections due to transmission of ICU-associated microorganisms. Identical antimicrobials of PTA and/or vancomycin as gel/paste are indicated for topical use on the tracheostomy in tracheostomized patients to control exogenous lower airway infections.
4. Surveillance cultures of the throat and rectum on admission and, afterwards, twice weekly are required to monitor the efficacy of SDD and to detect the emergence of resistance at early stage.

The combination of polymyxin and tobramycin was chosen because it covers most abnormal AGNB including *Pseudomonas* species, and it is synergic in vitro. The use of a polyene, such as amphotericin B or nystatin, eradicates fungal overgrowth.

Experts are concerned that SDD may lead to an ecological catastrophe. In contrast, the best evidence is that the use of SDD is generally safe, and resistance is under control [17, 18]. This is mainly due to the control of gut overgrowth reducing spontaneous mutations, polyclonality and resistance [1, 19]. Two large Dutch RCTs had resistance as end point [4, 5]. Both RCTs showed significantly less resistance in patients receiving SDD than in those receiving standard care. Additionally, the incidence of bacteremia and lower respiratory tract colonization due to highly resistant AGNB was significantly reduced by SDD compared to standard care [18]. Two recent meta-analyses explored the impact of SDD on resistance [19, 20]. In the first meta-analysis, including only RCTs, resistance was reduced in patients receiving SDD compared with controls (OR 0.56, 95 % CI 0.41–0.76) [19]. Another systematic review showed a reduction in polymyxin and third-generation cephalosporin resistance to AGNB in patients receiving SDD compared with those who received no intervention [20].

The enteral antimicrobials of SDD are usually poorly absorbed. However, critical illness may determine a gut barrier failure. Therefore, serum tobramycin levels should be routinely checked in critically ill patients with renal failure and/or receiving renal replacement therapy [21].

Conclusion

SDD, including parenteral and enteral antimicrobials, controls gut overgrowth of potential pathogenic microorganisms, reduces infections of lower airways and blood and provides a survival benefit in critically ill, including surgical patients. SDD is a safe manoeuvre with regard to the emergence of resistance.

Summary Table

Clinical summary					
Drugs	Indications	Cautions	Side effects	Dosage	Notes
Selective decontamination of the digestive tract (SDD)	Critically ill patients requiring mechanical ventilation for ≥72 h Surgical patients scheduled for oesophageal, gastric, intestinal surgery and radical cystectomy with urinary diversion Transplant recipients Other conditions (apart from mechanical ventilation) in which a critical illness-related overgrowth of potentially pathogenic microorganisms is present (e.g. pancreatitis, burns, neurological impairment)	Critically ill patients with renal failure and/or receiving renal replacement therapy should be routinely checked for serum tobramycin levels *Proteus* species are intrinsically resistant to polymyxin E. In this case the efficacy of tobramycin should be checked, and in case of tobramycin resistance, another aminoglycoside should be used (e.g. amikacin, paromomycin)	SDD has not been designed to cover methicillin-resistant *S. aureus* (MRSA) In case of MRSA endemicity, SDD may select this pathogen and vancomycin should be added to the SDD protocol (see next column) Resistance: present data show that SDD does not increase resistance; it may reduce the resistance problem, if present	Parenteral antibiotic (e.g. cefotaxime 80–100 mg/kg/day for 4 days) 0.5 g of 2 % polymyxin E/ tobramycin/amphotericin B paste or gel four times a day in the oral cavity 100 mg polymyxin E + 80 mg tobramycin +500 mg amphotericin B in the gut four times a day 0.5 g of 4 % vancomycin paste or gel 4 times a day in the oral cavity and/ or 500 mg vancomycin in the gut four times a day (in case of MRSA endemicity)	Surveillance cultures of throat and rectum are part of the technique and should be taken on admission and afterwards twice a week to monitor the efficacy of SDD, and to detect resistance in an early stage High level of hygiene is required to control exogenous infections In tracheostomized patients identical antimicrobials of PTA and/or vancomycin as gel/paste are indicated for topical use on the tracheostomy to control exogenous lower airway infections

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Role of Insulin in Reducing Mortality in the Perioperative Period

12

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12.1 General Principles

Hyperglycaemia is a frequently diagnosed metabolic abnormality in the inpatient setting, either related to the case of known diabetes, previously undiagnosed diabetes or as a result of the acute or exacerbation of presenting chronic illness [1, 2]. Stress hyperglycaemia may also be induced by medications including steroids, inotropic agents, immunosuppressants and nutritional support via the enteral or parenteral route [1, 2]. Preoperative glycaemic imbalance and perioperative elevations of blood glucose are directly associated with poor prognosis [1–4], including increase in mortality, decrease in cardiovascular event-free survival, increase in resource utilisation and decrease in quality of life. Hyperglycaemia significantly influences hospital morbidity, including increase in the risk of infections, renal failure, prolonged mechanical ventilation and anaemia requiring blood transfusions, which subsequently extends the length of hospital stay [1–4].

Perioperative glycaemic control and mortality have been recently addressed during two Consensus Conference: the first included 340 physicians from 65 countries and covered interventions affecting mortality in cardiac anaesthesia and intensive care [5], while the second Consensus Conference – devoted to all surgical aspects of mortality reduction in the perioperative setting – included more than 1,000 physicians from 77 countries [6, 7].

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12.2 Main Evidences

In the first randomised study, in critically ill surgical subjects published in 2001, Van den Berghe et al. [8] revealed that intensive insulin therapy (IIT) (i.e. maintenance of blood glucose at a level 80–110 mg/dL) was more effective compared with conventional therapy (i.e. blood glucose 180–200 mg/dL) in reducing short-term mortality (RR = 0.58, 95 % CI 0.38–0.78; $p = 0.01$). In 2006, Van der Berghe et al. [9] published the results of a second randomised study performed in medical ICU subject. They found no impact of IIT on mortality, but in subgroup analysis of patients with an ICU stay longer than 2 days ($n = 386$), IIT was associated with a moderate decrease in mortality (from 53 to 43 %; $p = 0.009$).

Since then, the above-mentioned observations have not been confirmed in further well-designed studies performed in both medical and surgical intensive care settings. A meta-analysis published in JAMA in 2008, covering 29 randomised studies, revealed that short-term mortality did not differ between tight and usual glucose control in medical and surgical intensive care patients and also after stratification by glucose target or intensive care unit (ICU) setting [10]. Another meta-analysis of 21 trials including ICU and non-ICU hospitalised subjects found no benefit associated with IIT on short-term or medium-term mortality [11]. Finally, investigating perioperative outcomes in patients with diabetes, Sathya et al. in their meta-analysis revealed that moderate glycaemic control (150–200 mg/dL) compared to a liberal target (>200 mg/dL) was associated with reduced postoperative mortality (OR 0.48; 95 % CI 0.24–0.76, $p = 0.004$) and stroke (OR 0.61, 95 % CI 0.38–0.98, $p = 0.04$) and with no differences in atrial fibrillation (OR 0.54; 95 % CI 0.17–1.76, $p = 0.31$) or wound infection (OR 0.25; 95 % CI 0.01–5.20, $p = 0.04$) [12]. In addition, no significant differences in postoperative outcomes between moderate versus strict (i.e. 100–150 mg/dL) perioperative glycaemic target were found [12].

The successive multicentre NICE-SUGAR study, the largest included into above-mentioned analyses (including 2,232 surgical subjects), showed even an increase in mortality in subjects with a target glucose level of 80–108 mg/dL when compared with those with blood glucose <180 mg/dL (RR = 1.14, 95 % CI 1.02–1.28; $p = 0.02$) [13]. A post hoc analysis corroborated the results showing that moderate (blood glucose of 41–70 mg/dL) and severe hypoglycaemia (≤40 mg/dL) were associated with an increased risk of death (adjusted HR 1.41; 95 % CI 1.21–1.62, $p < 0.001$ and 2.10; 95 % CI 1.59–2.77, $p < 0.001$, respectively) [14]. In addition, two randomised trials were stopped prematurely for safety reasons due to high incidence of severe hypoglycaemia and serious adverse events. In the GLUCONTROL trial covering surgical and medical ICU patient, an increased incidence of hypoglycaemia was associated with increase in mortality (hypoglycaemia rate of 8.7 % and mortality of 17.2 % in the strict glucose control compared with 2.7 % and 15.3 %, respectively, when more liberal control was applied; $p < 0.001$) [15].

Additional evidence is given for critically ill neurosurgical and neurological patients, in whom a meta-analysis of nine studies also found no association between tight glycaemic control and mortality [16], but there was an eightfold higher risk of hypoglycaemia in IIT group.

In cardiac surgery setting, in a meta-analysis of seven randomised trials, Haga et al. [17] revealed that compared to liberal approach, keeping the blood glucose lower than 180 mg/dL reduced early mortality (OR = 0.52, 95 % CI 0.3–0.91; $p < 0.02$). A bit contradictory findings were published more recently by Hua et al. in 2012 [18] who found no association between more intensive insulin regimen (than those in a study by Haga) and the outcome. Moderate glycaemic control (127–179 mg/dL) was also superior to tight (≤126 mg/dL) or liberal (≥180 mg/dL) glycaemic control in a study of 4,658 cardiac surgery patients with perioperative hyperglycaemia [19], with a short-term mortality rate of 2 %, 2.9 % and 3.4 % ($p = 0.02$), respectively, for moderate, tight and liberal management. In 2015, Umpierrez et al. revealed no significant differences in the composite of complications between cardiac surgery patients randomised into an intensive (blood glucose of 100–140 mg/dL) or conservative (i.e. 140–180 mg/dL) treatment (42 vs. 52 %, $p = 0.08$). There were also no differences in complications among patients with diabetes treated with intensive or conservative regimens (49 vs. 48 %, $p = 0.87$), but a significant lower rate of complications in patients without diabetes treated with intensive treatment regimen (34 vs. 55 %, $p = 0.008$) [20].

More to the point, in nearly all large-cohort interventional trials (including NICE-SUGAR and two Van der Berghe trials), the impact of IIT on mortality was lower among diabetics than among nondiabetic individuals [21]. The association between increasing median or mean blood glucose and mortality was found to be much stronger among nondiabetics than diabetic ICU patients [21].

12.3 Pharmacologic Properties

Human insulin is polypeptide secreted by beta cells of pancreatic Langerhans islets containing two chains, a 21-aa A chain A and a 30-aa B chain, linked by two disulphide bonds [22]. Its secretion is triggered by the closure of ATP-dependent potassium channels caused by the increase of glucose level in blood. The translation of insulin initially results in synthesis of pre-proinsulin, which is then cleaved into proinsulin in endoplasmic reticulum and subsequently lysed into insulin by removing the somatomedin-like C-peptide in the Golgi network [23]. In response to secretion stimuli, both insulin and C-peptide are released, and thus, the concentration of the latter particle is the indicator of internal source of circulating insulin.

Insulin acts by binding to the extracellular portion of the alpha subunit of the cell-membrane insulin receptor, which activates the intracellular kinase domain [24]. This part of insulin receptor triggers further signal transduction via kinase pathway, which eventually leads to increased peripheral glucose uptake associated with activation of GLUT-4 glucose transporter, predominantly in fat tissue and muscles, promotion of glycolysis and hepatic glycogenesis (glycogen synthesis) and simultaneous inhibition of gluconeogenesis, glycogenolysis, lipolysis and proteolysis. This causes a rapid reduction in serum glucose concentration.

12.4 Therapeutic Use

In the operating room setting, glucose level should be controlled by means of a continuous intravenous infusion of regular human insulin or, in selected cases, of fast-acting insulin analogues. However, this rule does not apply to ambulatory minor surgical procedures performed on noncritically ill subjects, in whom target glucose level can be attained by means of repeated subcutaneous injections, preferably using rapid-acting insulin analogues [25, 26]. Because of the stacking risk of subcutaneous injections of insulin, additional doses should not be administered until the time to peak effect has passed [27].

The target for preoperative glycaemic control is fasting glucose level of 100–120 and 140–160 mg/dL 2 h after food intake. In patients with post-prandial glycaemia >200 mg/dL and HbA1c >9.0 %, surgery should be postponed to allow proper glycaemic control, except for urgent and emergent instances.

12.4.1 Insulin Solutions

Most of insulin formulations have 100 units of insulin per mL; however, 40 and 500 units/mL solutions can also be found. For intravenous (IV) use, recombinant human insulin (or fast-acting analogues) should be used at concentrations ranging from 0.05 to 1.0 IU/mL in infusion systems with 0.9 % sodium chloride.

12.4.2 Pharmacokinetics

Intravenous insulin has an average elimination half-life of less than 10 min, while action half-life is approximately 40 min. Liver and kidneys deactivate insulin (see Table 12.1).

12.4.3 Perioperative Therapy, Route of Administration and Dosing

In the direct preoperative period, patients with diabetes type 1 should follow their usual regimen, while patients with type 2 diabetes should be bridged to intensive insulin therapy (with the exception of patients successfully treated with diet together with metformin and on condition of minor procedures, such as tooth extraction, abscess incision, small amputation, cataract surgery). Oral hypoglycaemic agents (OHA) should be withdrawn 48 h before the surgery. Total daily intake (TDI) of insulin should be equal to 0.3–0.7 IU/kg. Long-acting insulin is expected to cover 40–50 % of daily dose (NPH injected twice daily at 8:00 a.m. and 10:00 p.m. or a single injection of long-acting analogue before sleep). Pre-prandial rapid-acting insulin is recommended to be given 3 times daily before meals according to proportions of 50–20–30 and should represent approximately 50–60 % of TDI [25].

Table 12.1 Pharmacokinetics of various insulin formulations

Route of administration	Insulin	Onset of action	Peak of action	Effective duration of action
Subcutaneous	Regular human insulin	30–60 min	2–3 h	4–6 h
”	Rapid-acting analogues (aspart, lispro, glulisine)	15 min	30–90 min	3–4 h
”	Isophane insulin (NPH)	1–4 h	6–10 h	10–16 h
”	Detemir	1–4 h	Slight peak after 6–14 h	12–20 h
”	Glargine	1–4 h	No peak activity	24 h
”	Degludec	30–90 min	No peak activity	40 h
Inhaled	Short-acting inhaled insulin	15 min	30–90 min	4–6 h
Intravenous	Regular human insulin or rapid-acting analogues	<10 min	Elimination half-life of 40 min (columns 4–5)	

The American Association of Clinical Endocrinologists and the American Diabetes Association 2009 consensus recommends that in the intensive care setting, target glucose level should be ≤180 mg/dL (10 mmol/L) and that glycaemia should be maintained in the range between 140 and 180 mg/dL (7.8–10 mmol/l). For surgical patients, a pre-prandial glucose concentration <140 mg/dL (7.8 mmol/L) and a random glucose concentration <180 mg/dL (10 mmol/L) are recommended [25]. The Society for Ambulatory Anesthesia Consensus Statement advocates to maintain intraoperative blood glucose levels between 100 and 180 mg/dL (5.5–10 mmol/L) [28]. The American College of Physicians 2014 updated guidelines for the management of inpatient hyperglycaemia recommend a target blood glucose level of 140–200 mg/dL (7.8–11.1 mmol/l) when insulin therapy is used in medical or surgical intensive care unit patients. Clinicians should avoid targets less than 140 mg/dL (<7.8 mmol/L) because harming risk increases with lower blood glucose targets. Moreover, they strongly recommend not using intensive insulin therapy to normalise blood glucose in patients with or without diabetes [29]. The Society of Thoracic Surgeons 2009 guidelines regarding blood glucose management in cardiac surgery recommend maintenance of blood glucose lower than 180 mg/dL (10 mmol/L) [30]. In patients who spend ≥3 days in ICU, require an intra-aortic balloon pump/inotropic/left ventricular assist device support, receive antiarrhythmic drugs or are on dialysis/continuous veno-venous hemofiltration, a blood glucose level of ≤150 mg/dL (8.3 mmol/L) is recommended [30].

Wilson et al. [31] reviewed and described 12 different insulin infusion protocols and found significant variations in initiation and titration of insulin, use of bolus dosing and calculations used for insulin dose adjustment. In clinical setting, however, two major well-recognised intraoperative algorithms of blood glucose control exist. The first algorithm is based on intravenous pump infusion of 50 IU of insulin dissolved in

Table 12.2 Rate of insulin and glucose infusion depending on the blood glucose level

Glycaemia [mg/dL]	10 % glucose infusion [mL/h]	Insulin delivery (IU/h)
<100	100	Stop infusion for 15–30 min
100–140	100	3–4
140–180	80	3–4
180–250	80	4–6
250–300	Stop the infusion until glycaemia decreases below 180 mg/dL	4–6

50 mL 0.9 % saline and a separate infusion of 10 % glucose. In this protocol, 1 g of exogenous glucose is used every 0.3 IU of insulin. The rate of both simultaneous infusions is adjusted according to actual blood glucose level (Table 12.2). The second scheme is based on a single infusion drip with 500 mL of 5–10 % glucose containing approximately 8–16 IU of insulin and 10–20 mEq of potassium chloride administered at the rate of 80 mL/h. The amount of insulin in the solution should be higher (>20 IU) in case of obesity, cardiothoracic surgery, concomitant infection, hypothermia or initial glucose concentration >180 mg/dL. Conversely, the contents of insulin should be less than 12 IU in patients with low body mass index and previously treated with OHA. The amount of insulin in the solution should be increased by 2 IU for every 30 mg/dL increase of blood glucose above the threshold of 180 mg/dL and decreased by 4 IU if the blood glucose level falls to 100 mg/dL.

During intravenous administration of insulin, blood glucose level should be measured every 1 h using bedside or nearby stat laboratory monitoring. Of note, point-of-care testing can be disputed in the situation of hypoglycaemia, when it tends to overestimate blood glucose level [32]. Accordingly, higher alert value for hypoglycaemia (e.g. <70 mg/dL) should be implemented to trigger early glucose supplementation so as to allow time for prevention of symptomatic hypoglycaemia, which usually occurs at blood glucose levels of 45–55 mg/dL [33].

12.4.4 Side Effects and Toxicity

Insulin promotes intracellular potassium shift, possibly leading to hypokalaemia. Since perioperative IV insulin administration has a rapid onset of action, glucose and potassium levels must be strictly monitored.

Excessive doses of insulin can cause symptomatic hypoglycaemia (blood glucose level <45–55 mg/dL) manifested by sweating, tachycardia, mydriasis, pallor, weakness, nausea, confusion, aggressive behaviour, seizures, loss of consciousness, convulsions, brain damage and demise. Yet, this symptomatology is absent in patients under general anaesthesia, barring tachycardia and excessive sweating. This supports the need for hourly glucose monitoring.

Other side effects of insulin therapy include allergic reactions, lipodystrophy and weight gain.

12.5 Summary Table

Clinical summary					
Drugs	Indications	Cautions	Side effects	Dosage	Notes
Insulin in intravenous infusion (regular human insulin or short-acting analogue)	Perioperative management of hyperglycaemia in patients with diabetes type 1/2 and excessive intraoperative hyperglycaemia in patients without previous history of diabetes	Severe risk of hypoglycaemia and hypokalaemia	Hypoglycaemia	Initial insulin infusion of 0.5–1 IU/h, then 0.3 IU/h increments or decrements depending on blood glucose level	Target intraoperative blood glucose level is 140–180 mg/dL
		Glucose level should be checked directly before surgery and every 1 h during and after the procedure	Hypokalaemia		Minor ambulatory procedures in diabetes type 2 can be performed without IV insulin
		[K+] should be verified before and after the procedure	Allergic reactions		In patients with a well-controlled diabetes type 2 treated with diet or oral agents, IV insulin is not obligatory
			Weight gain		
			Lipodystrophy		

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Aprotinin: Pharmacological Benefits and Safety

13

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13.1 General Principles

In cardiac surgery, perioperative blood transfusion carries considerable risk of complications and increases resource utilization. Antifibrinolytics, particularly aprotinin, have been used effectively to reduce bleeding and transfusion needs. In 2008, the manufacturer withdrew aprotinin from the market due to the discontinued "Blood conservation using Antifibrinolytics in a Randomized Trial" (BART) study, which showed an increased mortality associated with the usage of aprotinin [1]. The consensus conference held on June 8, 2011 in Milan identified aprotinin as a drug, which increases 30-day mortality after cardiac surgery [2, 3]. Recently, the database of the BART study was reanalyzed, and the European Medicines Agency and Health for Canada recommended lifting the suspension of aprotinin-containing medications [4, 5]. The purpose of this chapter is to describe the pharmacokinetic and pharmacodynamic properties of aprotinin and to discuss the literature evidences related to mortality.

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13.2 Pharmacologic Properties

Aprotinin, which is a proteinase inhibitor extracted from bovine lungs, forms a stable complex with the protease inhibitor and blocks the active sites of enzymes. The binding is reversible. Through this universal protease inhibition [e.g., kallikrein, plasmin], aprotinin attenuates the magnitude of the systemic inflammatory reaction and decreases fibrinolysis and thrombin generation associated with cardiopulmonary bypass [6].

After intravenous injection, rapid distribution occurs in the extracellular space. Its plasma half-life is 0.3–0.7 h; terminal elimination phase is 5–10 h. Aprotinin binds to plasma proteins (approx. 80 %) and is accumulated in the kidneys. Human investigations measured higher postoperative creatinine levels after cardiac surgery, particularly if a high dose of aprotinin was administered [7]. The nephrotoxic effect of aprotinin was partly explained by the inhibition of tubular protease secretion, renin synthesis, and bradykinin release [8]. Aprotinin does not pass the blood-brain barrier and is metabolized into shorter amino acids by the renal lysosomal activity.

13.3 Therapeutic Use

A loading dose of 10,000 KIU (kallikrein inhibitor unit) aprotinin should be administered through a central intravenous line after induction and before sternotomy. One to two million KIU aprotinin should be added to the priming solution of the cardiopulmonary bypass system. Adequate admixture and dilution are required to avoid the physical incompatibility of heparin and aprotinin. Continuous infusion of 250,000–500,000 KIU aprotinin per hour is advised until the end of the operation. According to the latest aprotinin label, no dose adjustment is required in geriatric patients or in patients with renal dysfunction. The safety and efficacy have not been established in pediatric patients [9].

Hypersensitivity to aprotinin contraindicates its use. Positive aprotinin-specific IgG test carries an increased risk for allergic reaction. Patients who received aprotinin before the recent exposure have greater risk for anaphylactic reaction, particularly in patients with reexposure within 12 months. Besides anaphylactic or anaphylactoid reactions, renal effects of aprotinin should be emphasized as observational studies suggested an increase of creatinine level (>0.5 mg/dL above baseline) after aprotinin administration [10]. In the majority of cases, renal dysfunction was not severe and it was reversible. Extreme precaution is required in patients with preexisting renal dysfunction, those with renal risk factors, and those with operation involving the thoracic aorta with cardiopulmonary bypass and deep hypothermic cardiac arrest. During extracorporeal circulation, anticoagulation should be measured by fixed heparin dosage or by measurement of the heparin levels. Celite-based ACT (activated clotting time) tubes should be used.

13.4 Main Evidences

In 2006, two propensity score-adjusted analyses reported the adverse effect of aprotinin on renal function and higher incidence of renal replacement therapy [11, 12]. Because of these safety concerns, the Canadian Institutes of Health Research and the Ontario Ministry of Health sponsored the BART study, which randomly enrolled high-risk cardiac surgery patients receiving aprotinin, aminocaproic acid, or tranexamic acid [1]. The study outcomes included bleeding, reoperations, in-hospital death, 30-day mortality, and serious adverse clinical events, such as myocardial infarction, stroke, renal failure, respiratory failure, and cardiogenic shock. The study was terminated early because of a trend showing a higher mortality in the aprotinin group; this was found when comparing aprotinin to aminocaproic acid, the relative risk of death at 30 days from any cause being 2.82 (95% CI, 1.37–5.83) among patients with massive bleeding and 1.20 (95% CI, 0.69–2.08) among those who did not have this outcome ($P = 0.04$, Breslow-Day test for homogeneity). The BART study was found to have several methodological limitations including heterogeneous patient selection (reoperations, aortic root, and congenital heart surgery), lack of proper stratification of treatment allocation by procedure, cardiac risk profile and center, and unspecified details of the statistical method applied [13]. In 2012, the data was reanalyzed, and the European Medicines Agency's Committee for Medicinal Products for Human Use (CHMP) concluded that "benefits of aprotinin in preventing blood loss outweigh its risks in patients undergoing bypass with high risk of major blood loss" [4].

In the past 4 years, several meta-analyses were published [13–15]. The review of the Cochrane Database included 252 randomized controlled trials (RCTs) [15] and found no difference in mortality when comparing aprotinin to placebo control. Similarly, there was no difference in mortality when comparing aprotinin either to tranexamic acid or to epsilon-aminocaproic acid. Risk of death was higher if the results of the BART study were included. In this case, patients treated with aprotinin had a higher risk of death compared to lysine analogue antifibrinolytics (RR, 1.22; 95% C.I., 1.08–1.39).

On the other hand, epidemiological and large observational studies consequently reported a significant increase in mortality associated with aprotinin [15]. These epidemiological and observational studies had relatively large sample sizes, and they included high-risk patients. The meta-analysis by Hutton et al. tried to analyze both randomized controlled trials and observational studies [15]. Inclusion of observational studies in the analysis showed an increased risk of mortality compared to either tranexamic acid or aminocaproic acid but not to placebo control (Tables 13.1 and 13.2). No difference was found among the same meta-analysis of RCTs in the occurrence of renal dysfunction, but the inclusion of observational studies found that aprotinin treatment was associated with higher risk when compared either with placebo or with other antifibrinolytics.

Meta-analyses and the majority of the studies found that aprotinin is more effective in reducing bleeding compared to placebo or to other fibrinolytics [13–15].

Table 13.1 Meta-analyses of aprotinin-related studies – mortality

Meta-analysis	Year of publication	No. of patients	No. of studies	OR (CI 95 %)	OR (CI 95 %)	OR (CI 95 %)
–	–	–	–	Aprotinin vs. tranexamic acid	Aprotinin vs. aminocaproic acid	Aprotinin vs. placebo
Howell [13][a,b,c]	2013	15,528	88	0.73 (0.45–1.12)	0.88 (0.50–2.13)	1.11 (0.75–1.53)
Hutton [15][a,c]	2012	14,773	82	0.64 (0.41–0.99)	0.79 (0.47–1.55)	0.99 (0.72–1.36)
Hutton [15][a,b,c]	2012	41,350	93	0.71 (0.50–0.98)	0.60 (0.43–0.87)	0.91 (0.71–1.16)
Henry [14][a,d]	2011	17,136	85	1.35 (0.94–1.93)	1.51 (0.99–2.30)	0.81 (0.63–1.06)

OR odds ratio, *CI* confidence interval
[a]BART study included in meta-analysis
[b]Observational studies included in meta-analysis
[c]OR <1 favors second listed treatment
[d]OR >1 favors second listed treatment. Significant values in bold

Table 13.2 Meta-analyses of aprotinin-related studies – mortality with patient numbers

Meta-analysis	No. of patients	No. of studies	No. of patients/deaths (%) (column 4–7)				RR 95 % CI
–	–	–	*Aprotinin*	*TXA*	*EACA*	*Control*	–
Howell [13][a,b,c]	*15,528*	*88*	6284/177 (2.81 %)	3048/62 (2.03 %)	1309/44 (3.36 %)	4887/110 (2.25 %)	NS
Henry [14][d] (Cochrane):	–	–	–	–	–	–	–
A vs. control	*8876*	*63*	4889/116 (2.37 %)	–	–	3987/104 (2.6 %)	0.81 (0.63–1.06)
TXA vs. control	*2917*	*30*	–	1478/15 (1.01 %)	–	1439/28 (1.94 %)	0.60 (0.33–1.10)
EACA vs. control	*922*	*8*	–	–	504/10 (1.98 %)	484/8 (1.65 %)	1.07 (0.44–2.57)
A vs. TXA[a]	*4130*	*17*	2060/67 (3.25 %)	2070/51 (2.46 %)	–	–	1.35 (0.94–1.93)
A vs. EACA[a]	*1891*	*5*	949/52 (5.47 %)	–	942/34 (3.6 %)	–	1.51 (0.99–2.30)
TXA vs. EACA[a]	*1958*	*5*	–	980/33 (3.36 %)	978/37 (3.78 %)	–	0.93 (0.59–1.47)
A vs. TXA and EACA[a]	*5127*	*19*	2115/71 (3.35 %)	3012/85 (2.82 %)	–	–	1.39 (1.02–1.89)

Only trials reporting mortality are included
A aprotinin, *TXA* tranexamic acid, *EACA* epsilon-aminocaproic acid, *RR* risk ratio, *CI* confidence interval, *NS* non-significant
[a]BART study included in meta-analysis
[b]Observational studies included in meta-analysis
[c]OR <1 favors second listed treatment
[d]OR >1 favors second listed treatment

Moreover, the role of two confounding variables cannot be ruled out: duration of cardiopulmonary bypass and blood transfusion (institutional policy, type of blood products, etc.). These factors have been found to be independently associated with mortality after cardiac surgery. Therefore, they serve as significant contributors to inter-study heterogeneity and comparative differences.

In the last 3 years, a critical paper from the BART investigators was published which debated and reflected on the conclusions and concerns raised by Health Canada [16]. Another case-controlled, single-center study showed that after the withdrawal of aprotinin, the adjusted risk for mortality increased in the high-risk cardiac surgical population [17]. In January 2012, all worldwide rights excluding the USA for aprotinin was acquired by Nordic Group. In the last 5 years, the number of papers about aprotinin is decreasing, and the expectations (design, conduction, control, and report) of clinical trials have been strengthened, letting us up for a strong evidence-based final conclusion on the matter in the near future.

Conclusion

In conclusion, aprotinin reduces bleeding, the amount of blood transfusion required, and the need for re-exploration for bleeding. Meta-analyses of randomized controlled trials suggest that aprotinin is not associated with increased risk for mortality compared with placebo, tranexamic acid, or epsilon-aminocaproic acid. However, the inclusion of observational studies to the meta-analysis still raises concerns regarding the safety of aprotinin.

Summary Table

Clinical summary				
Drug	Indications	Cautions	Side effects	Dose
Aprotinin 100 ml vial, 10,000 KIU/ml = 1.4 mg/ml	Treatment of patients at high risk of major blood loss during and following open heart surgery with extracorporeal circulation	Aprotinin is incompatible with heparin or any other solution. Fixed heparin dosage or heparin titration is recommended; celite-based ACT should be used	Anaphylactic or anaphylactoid reactions	Initial (test) dose, 1 ml
			Careful consideration in patients with renal dysfunction	Loading dose, 200 ml
			Pump prime dose, 200 ml	Constant infusion dose, 50 ml/h

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Liberal Transfusion Strategy in the Perioperative Period

14

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14.1 General Principles

A proper oxygen and nutrients' supply is physiologically essential. Similarly, a prompt removal of carbon dioxide and catabolites is as much important. For these reasons, it is fundamental to assure an efficient blood perfusion to all tissues at any time. This is possible thanks to three strictly associated components: (1) *the heart*, (2) *the vascular system* (*arterial and venous*), and (3) *the blood*. The impairment of even only one of them may seriously compromise tissues' perfusion and thus cause one or more organ failure.

Oxygen delivery (DO_2) is the amount of oxygen delivered, through the blood, from the lungs to all tissues each minute. It depends on the cardiac output (CO) and the arterial content of oxygen (CaO_2):

$$DO_2 = CO \times CaO_2$$

CaO_2 is the sum of oxygen bound to hemoglobin and oxygen dissolved into the plasma and is calculated as follows:

$$CaO_2 = \left(1.34 \times Hb \times SaO_2\right) + \left(0.003 \times PaO_2\right)$$

where *1.34* is the amount of oxygen bound by each gram of hemoglobin (mL/g), *Hb* is the concentration (g/L) of hemoglobin in the blood, *SaO2* is the percentage of

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arterial oxygen saturation of the hemoglobin, *0.003* is the solubility coefficient of oxygen into the blood (mL/L/mmHg) at body temperature (37 °C), and *PaO2* is the arterial partial pressure of oxygen (mmHg). The most important factor determining the overall CaO_2 is the Hb concentration, rather than PaO_2 (considering a normal PaO_2 of 95 mmHg, $0.003 \times 95 = 0.28$ mL/L). This may explain why it is so important to assure adequate hemoglobin levels.

In the perioperative periods, suboptimal hemoglobin concentrations before surgery are quite frequent (e.g., due to chronic diseases; acute, subacute, or chronic bleeding; renal failure; cancer; etc.). Furthermore, expected or unexpected bleeding during surgery may cause severe anemia or even worsen the anemic preexisting status. For this reason blood transfusion is quite important in this setting.

Hemoglobin levels have always been the most important parameter to guide transfusions, usually fixing at 8 g/dL the threshold for transfusion [1, 2]. However, in recent years concerns are rising about "when to transfuse." In particular, more liberal transfusion strategies with higher hemoglobin level as a limit to decide when to transfuse are emerging.

In this chapter, we will discuss the scientific evidences available at the moment about a more restrictive versus liberal transfusion strategy in the perioperative period.

14.2 Main Evidence

A 2012 Cochrane review analyzed 19 randomized controlled trials (RCTs), enrolling 6,264 patients overall, that compared restrictive versus liberal transfusion strategies in different clinical settings (surgery, acute blood losses, and/or trauma and critical care units) [3]. Results showed a reduction of the transfusion rates in the restrictive group compared to liberal group (risk ratio (RR) 0.61, 95 % confidence interval (CI) 0.52–0.72; $p < 0.00001$; $I^2 = 93\,\%$). Such results were not confirmed in the vascular surgery sub-analysis (RR 0.91, 95 % CI 0.77–1.08; $p < 0.3$). Heterogeneity among trials for this outcome was statistically significant (Chi2 = 238.95, df = 16, $p < 0.00001$, $I^2 = 93\,\%$). Furthermore, hospital mortality was 23 % lower in the restrictive group (RR 0.77, 95 % CI 0.62–0.95; $p < 0.018$; $I^2 = 0\,\%$). Thirty-day mortality, hospital length of stay, and complications (cardiac events, myocardial infarction, pulmonary edema, cerebrovascular accidents/stroke, pneumonia, and infection) were not different in the two groups.

In 2015, an update of the Cochrane review and meta-analysis [4] of both single-center and multicenter RCTs (overall 9,813 patients of both surgical and medical settings) confirmed the reduction of the transfusion need with the restrictive strategy versus the liberal one (RR 0.54, 95 % CI 0.47–0.63; $p < 0.001$; $I^2 = 95\,\%$). Even in this case, no difference in terms of mortality, myocardial infarction, overall morbidity, and adverse events (cardiac complications, renal failure, thromboembolic stroke, transient ischemic attack, or hemorrhage) was observed between groups. Only a possible association between the restrictive strategy and a reduced rate of infections was noted (RR 0.73, 95 % CI 0.55–0.98; $p = 0.03$; $I^2 = 53\,\%$).

Recently, three RCTs performed in perioperative period demonstrated benefits from a liberal transfusion strategy [5–7]. Two of them were not included in the 2015 update of the Cochrane review.

De Almeida and colleagues [5] studied 198 patients undergoing major abdominal surgery for cancer and who required postoperative ICU stay for at least 24 h. Patients were randomly assigned to either the restrictive or the liberal transfusion strategy group. Patients received erythrocyte units each time the hemoglobin level decreased below 7 g/dL (restrictive group) or 9 g/dL (liberal group) during their ICU stay. The authors observed, in the liberal strategy group, a lower 30-day (8[8.2%] vs. 23[22.8%]; $p=0.005$) and 60-day (11[11.3%] vs. 24[23.8%]; $p=0.022$) mortality rate compared to the restrictive strategy group. Furthermore, a lower incidence of overall major cardiovascular events in the liberal group (5[5.2%] vs. 14[13.9%]; $p=0.038$) and a higher incidence of intra-abdominal infections in the restrictive group (15[14.9%] vs. 5[5.2%]; $p=0.024$) were observed.

The Transfusion Indication Threshold Reduction (TITRe2) trial (17 cardiac surgery centers in the United Kingdom) randomized 2003 patients undergoing non-emergency cardiac surgery to the restrictive-threshold group (hemoglobin level of 7.5 g/dL) or to the liberal-threshold group (hemoglobin level of 9 mg/dL). Results of this trial showed a higher mortality rate within 3 months in the restrictive group than in the liberal one (4.2% vs. 2.6%; hazard ratio 1.64; 95% CI 1.00–2.67; $p=0.045$). No differences were found between the two groups with regard to the other outcomes (infections, ischemic events, ICU, high-dependency unit, and hospital length of stay) [6].

The Transfusion Requirements in Frail Elderly (TRIFE) trial, conducted by Gregersen and colleagues, is a single-center trial that enrolled 284 patients, aged ≥65 years, undergoing surgery for unilateral hip fracture, coming from nursing homes or from sheltered housing facilities. Patients in the restrictive strategy group received transfusions if their postoperative hemoglobin levels were lower than 9.7 g/dL, while patients in the liberal strategy group received transfusions if postoperative hemoglobin levels were lower than 11.3 g/dL. The authors found no difference for the primary outcome (recovery from physical disabilities at 10, 30, and 90 days after surgery) between the two groups. Concerning the secondary outcome (30-day and 90-day mortality), no difference was found between groups analyzing the data by the intention-to-treat, while a higher 30-day mortality was observed in the restrictive group using the per-protocol analysis (HR 2.4; 95% CI 1.1–5.2; $p=0.03$). Subgroup analysis showed a higher 90-day mortality in the nursing home patients of the restrictive group with both the intention-to-treat (HR 2.0; 95% CI 1.1–3.6; $p=0.01$) and the per-protocol (HR 1.9; 95% CI 1.0–3.4; $p=0.04$) methods [7].

These three RCTs raised the possibility that a more restrictive transfusion strategy may be associated with a higher mortality. For this reason and since the above-mentioned Cochrane reviews considered RCTs conducted in different contexts (e.g., surgery, ICUs, etc.) without distinguishing among them and considered both adults and children, Fominskiy et al. performed a new meta-analysis of RCTs [8]. The authors considered RCTs that enrolled only adults (age ≥18 years). Furthermore, they analyzed separately studies performed in perioperative settings (17 studies of

which 9 in orthopedic surgery, 5 in cardiac surgery, 1 in vascular surgery, 1 in cancer surgery, and 1 in obstetrics) and studies performed in critically ill contexts (10 studies) for a total of 11,021 patients. Fourteen trials were multicenter; 18 trials included more than 100 patients and 2 studies more than 1,000 patients. Results of this meta-analysis showed that, in perioperative setting, mortality for all causes is reduced with the liberal transfusion strategy groups compared with the restrictive transfusion strategy groups (Odds Ratio 0.81, 95% CI 0.66–1.00; $p=0.05$; $I^2=25\%$). In the critically ill setting, there was no difference in all-cause mortality between liberal and restrictive groups (RR 1.10, 95% CI 0.99–1.23; $p=0.07$; $I^2=34\%$). No differences were also found in all-cause mortality between liberal and restrictive strategies when considering together the perioperative and the critically ill settings (Odds Ratio 0.96, 95% CI 0.78–1.18; $p=0.68$). This is a further step forward in understanding the importance of tailoring the best transfusion strategy on each clinical setting.

Finally, another meta-analysis investigated separately six RCTs that assessed the effect of liberal RBC transfusion strategy versus restrictive RBC transfusion strategy in patients undergoing cardiac surgery, 19 RCTs that assessed the same effect in patients undergoing noncardiac surgery, and 39 observational studies that assessed the effect of RBC transfusion versus no transfusion on outcomes in patients undergoing cardiac surgery [9]. Results of the RCT analysis showed no differences between liberal and restrictive strategies on mortality for both cardiac and noncardiac surgery. Conversely, the analysis of the observational studies showed that transfusion is associated with an increased mortality compared with no transfusion (OR 2.72, 95% CI 2.11–3.49; $p<0.0001$; $I^2=93\%$). These contrasting results may be ascribed to the different nature of randomized controlled trials and observational studies. The high interstudies heterogeneity ($I^2=93\%$) of the latter confirms the weakness of observational studies.

14.3 Therapeutic Use

Deciding univocally when to transfuse a patient is still a challenge and a matter of debate. To use a single parameter, such as blood hemoglobin level, to guide the administration of RBC in patients with anemia is not always the right way to go. A lot of factors such as age, gender, disease's features and its development and worsening speed, the presence of comorbidities, functional organ reserve, etc., influence the compensatory reactions of the organism to anemia.

Etiology and pathophysiology of anemia are not the same in surgical and critically ill patients. Acute blood loss and hemodilution are the main causes of anemia in the perioperative period. Moreover, in the perioperative period, O_2 and nutrient demand is higher and thus anemia less well tolerated. Conversely,

etiology of anemia in critically ill patients is quite always multifactorial including advanced chronic diseases, phlebotomy and hemorrhagic losses, substrate deficiency for RBC production, inappropriate erythropoietin production/release from the kidneys, poor erythroid response to preexisting anemia, reduced RBC survival, increased RBC destruction, and hemodilution [10]. Furthermore, the organism compensatory mechanisms to anemia are different in surgical and in critically ill patients. In fact a rapid anemia development requires a more rapid response to overcome the acute DO_2 reduction, while a more progressive anemia onset let the organism to adopt a series of molecular, cellular, and tissue modifications that make anemia tolerable [11]. For these reasons, it is important to consider and distinguish the different context in which RBC transfusions are required.

Nowadays there is increasing evidence that liberal RBC transfusion strategy can reduce mortality in the perioperative period, probably because an earlier restoration of blood lost, especially during surgery, limits tissue suffering. This is quite important in people whose needs are higher than usual like the ones undergoing surgical interventions whose metabolism is augmented [12], and therefore an optimal tissue perfusion and O_2 delivery should be assured at the best level.

Anyway, RBC transfusions are not free of risks. Despite large progress in methods and quality of blood components preparation, potential complications, such as transfusion-related immunomodulation, acute lung injury, microcirculatory dysfunction, and infection transmission, still remain [13]. Nevertheless, the use of RBC can be considered safe in appropriate patients and with appropriate amount [8, 9, 14].

Conclusion

In the perioperative setting, blood transfusion is an essential tool to face ongoing anemia, most often due to blood losses, and thus to assure a satisfying tissue delivery of oxygen and nutrients. Today there is a growing interest of the scientific community towards a more liberal transfusion strategy in this kind of patients. In fact, it has been one of the topics discussed in the international consensus conference on nonsurgical interventions that might influence perioperative mortality [15, 16]. However, further large RCTs are needed to better establish the most appropriate blood management strategies in other clinical settings (e.g., trauma, brain injury, etc.) and in different subgroups of patients (e.g., patients with or without preexisting anemia of any etiology, undergoing urgent or nonurgent surgery, with and without renal failure, hematologic malignancies, etc). Finally, another direction of research could be the investigation of other physiological triggers to guide blood transfusion that may allow a more selective and individualized RBC use.

Summary Table

Clinical summary					
Drugs	Indications	Cautions	Side effects	Dosage	Notes
Liberal versus restrictive transfusion strategy	Patients undergoing any kind of surgery	Blood transfusion should be individualized taking into account patient's comorbidities, preexisting chronic anemia, etc.	Transfusion-related immunomodulation, acute lung injury, microcirculatory dysfunction, infection transmission	Depending on hemoglobin level, hemodynamic response, signs of tissue's suffering, preexisting anemia, or cardiac disease	Further studies are needed so that more accurate indications can be given

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Reducing Mortality in the Perioperative Period: Remote Ischemic Preconditioning

15

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15.1 Introduction

Despite the upsurge of publications on ischemic preconditioning in recent years, the concept of preconditioning an organ with ischemia is not new. In 1986, Murry et al. demonstrated short periods of regional ischemia and reperfusion resulting in protection against necrosis to a later longer period of ischemia in the canine myocardium [1]. In reperfusion injury following a brief period of ischemia, tissues begin to adapt to anaerobic metabolism. Restoration of blood flow can lead to an oxygen supply that exceeds tissue requirements, the activation of macrophages, and the generation of reactive oxygen species [2]. This can ultimately result in endothelial injury and further release of pro-inflammatory cytokines [3]. Ischemic preconditioning occurs when a tissue undergoes brief periods of ischemia to later protect against longer ischemic events and reperfusion injury.

The protection conferred by brief episodes of ischemia and reperfusion to a later more sustained episode of ischemia occurs in organs other than the heart, such as the kidneys and the brain. In 1985, Zager et al. reported that rats exposed to 15 min of bilateral renal artery occlusion had improved renal function when compared to a control group of rats after exposure to a second ischemic insult 30 min later [4]. In mice Joo et al. performed right nephrectomies and ischemic preconditioning by 5-min episodes of left-sided renal ischemia followed by reperfusion [5]. When the mice were later subjected to a more prolonged ischemic event, serum creatinine levels in the mice that underwent ischemic preconditioning were significantly lower when compared to a control group of mice who had just received unilateral nephrectomy [5]. Kitagawa and colleagues introduced the concept of "ischemic tolerance" in the brain

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when they introduced cerebral ischemia in gerbils by occluding both common carotid arteries [6]. Two-minute ischemic treatments performed daily for 2 days leading up to a 5-min cerebral ischemic period provided protection against neuronal death [6].

Remote ischemic preconditioning (RIPC) was first described in the literature in 1993 with an experiment in dogs where occlusion of the circumflex artery protected the myocardium supplied by the left anterior descending artery (LAD) [7]. When infarct sizes of the LAD were evaluated after 1 h of sustained LAD occlusion by triphenyltetrazolium staining, the infarct size of the preconditioned group was significantly less than the control group [7]. Since that time, numerous studies have been published on the clinical use of RIPC whereby a brief ischemic insult is provided to one area of the body to induce protection to a longer ischemic insult at a remote site. This chapter will review the most commonly discussed mechanisms for RIPC as well as the more recent clinical studies done using RIPC as they pertain to reducing morbidity and mortality in the perioperative period [8, 9].

15.2 Proposed Mechanisms of Remote Ischemic Preconditioning

15.2.1 Humoral Mechanism

The process by which RIPC occurs is complex and not fully understood. There have been numerous proposed mechanisms in the literature. The hypothesis that the RIPC event is triggered by a humoral mediator has been investigated. Dickson et al. provides evidence of the involvement of humoral mediators for eliciting RIPC by showing that a rabbit could be preconditioned by transfer of coronary effluent [10]. Effluent was collected during normal perfusion from donor hearts and during ischemia-reperfusion from donor preconditioned hearts. The effluent was then transferred to acceptor control and acceptor preconditioned hearts. All hearts were subject to 40 min of ischemia [10]. The resulting mean infarct size was smaller in the donor and acceptor preconditioned hearts [10]. There was an increase in adenosine and norepinephrine in the effluent from the preconditioned animals [10]. These results support the release of a hormonal trigger signal that is given off from the preconditioned myocardium and that when delivered to an acceptor heart evokes a cardioprotective effect. Some of the common mediators that have been studied include adenosine, catecholamine, bradykinin, and opioids [11–14].

In a recent review, Zarbock and Kellum discuss that kidney protection with RIPC occurs through the release of damage-associated molecular patterns (DAMPs) [15]. Increased levels of high-mobility group box 1 (HMGB-1), a prototypical DAMP, after RIPC were associated with a lower risk of AKI in an investigation discussed in more detail later in this chapter (OR 0.75, CI 0.35–0.94, $p = 0.03$) [16]. It is possible that DAMPs released from an initial location of ischemia-reperfusion travel to a target organ. In this case DAMPs may be filtered by the kidney and, through pattern-recognition receptors in the proximal tubular epithelia, signal renal protective mechanisms [15].

15.2.2 Neural Pathway

The potential for a neural pathway of communication to a target organ has been shown. Pretreatment with hexamethonium, a ganglion blocker, negated remote cardioprotection in rats receiving 15 min of mesenteric artery occlusion [17]. In humans endothelial injury caused by arm ischemia and reperfusion was measured with a reduction in flow-mediated dilation. The protective effect of RIPC prior to injury was reduced with the infusion of trimetaphan, another ganglion blocker [18]. In rabbits, vagal nerve ligation and atropine administration negated RIPC-induced reduction in myocardial infarct size [19].

15.2.3 The Final Common Event

The final common event in the protection induced by RIPC most commonly cited in the literature involves intracellular kinases acting on the mitochondria causing a closure of the mitochondrial transition pore, preventing the influx of ions [20]. Three main pathways acting on the mitochondrion have been proposed: (i) the reperfusion injury salvage pathway [21], (ii) the cyclic guanosine monophosphate/CGMP-dependent protein kinase pathway [22], and (iii) the survivor activating factor enhancement pathway [23]. The potassium-dependent adenosine triphosphate (ATP) channel blocker glibenclamide was shown to block the benefit of RIPC indicating that the protection may depend on potassium-dependent ATP channel activation [24]. Thus, it is proposed that in RIPC the potassium-dependent ATP channel is activated, leading to closure of the mitochondrial transition pore, reducing mitochondrial permeability in a target organ, and slowing the rate of ATP depletion [25].

15.3 Clinical Studies on Remote Ischemic Preconditioning

The majority of clinical studies describe the application of a blood pressure to the arm or leg to induce RIPC. Generally the cuff is inflated to 200 mmHg or 50 mmHg greater than the systolic atrial pressure and then deflated. This procedure is then repeated three to five times. The majority of clinical studies using RIPC have been done on the cardiothoracic patient population prior to cardiopulmonary bypass. Most studies report the effect of cardiac biomarkers in patients who receive RIPC when compared to a control group of patients [26–39]. For example, one of the initial studies to demonstrate the effect of RIPC on troponin T levels randomized 57 adult patients prior to coronary bypass grafting to receive RIPC through the use of timed arm blood pressure cuff inflations or to a control group [27]. When troponin T was measured prior to surgery and at time points after surgery, RIPC decreased the total area under the curve of troponin T by 43 % when compared to controls [27]. In 37 children undergoing congenital heart defect repair, Cheung et al. reported lower troponin I levels, airway resistance, and postoperative need for ionotropic

medications for patients who received preoperative RIPC when compared to children who did not receive RIPC [26]. Regarding cardiac outcomes in both children and adults in the perioperative period, there have been discrepant findings with some studies showing a benefit to RIPC [26–29, 33] and other showing no benefit [31, 34, 36–39].

Additionally, the effect of RIPC on kidney outcomes has been studied in both the adult and pediatric cardiac and vascular surgery populations. The association of surgical procedures and AKI has been consistently shown [40–42]. When 82 adult patients were randomized to receive abdominal aortic aneurysm repair with either RIPC by intermittent cross clamping of the common iliac artery for 10 min followed by 10 min of reperfusion or no RIPC prior to surgery, RIPC was found to reduce the incidence of myocardial injury by 27 % and renal impairment by 23 % [43]. When AKI was defined as a rise in serum creatinine ≥0.3 mg/dL or ≥50 % within 48 h after cardiac surgery where cardiopulmonary bypass was expected, a 27 % absolute risk reduction in AKI was found when comparing a randomized group of patients who received RIPC to those who received no intervention prior to surgery [44]. However, there have been investigations that have not reported a protective effect of RIPC for AKI [45–48].

Given the differences in study results, it may be that different patient characteristics make an individual more or less likely to respond to RIPC. For example, it may be those patients at a greater risk for AKI that will be more likely show a beneficial effect of the intervention. In a recent study, 240 adult patients at very high risk for AKI (Cleveland Clinic Foundation scores ≥6 [49]) undergoing cardiac surgery were randomized to RIPC with upper arm blood pressure cuff inflation compared to a control group [16]. There was a 15 % absolute risk reduction (95 % CI 2.56–27.44 %, $p = 0.02$) for those who received RIPC when compared to those who did not [16]. A unique feature of this study was the use of urinary biomarkers of AKI, tissue inhibitor of metalloproteinase-2 (TIMP-2), and insulin-like growth factor-binding protein 7 (IGFBP7), which increased in the majority of patients who are receiving RIPC [16]. Furthermore, in those who experienced an increase in TIMP-2 and IGFBP7 after RIPC and prior to cardiopulmonary bypass, the incidence of AKI was reduced when compared to those who did not [16]. Also, higher levels of HMGB-1 after RIPC, discussed earlier in this chapter, were associated with a reduction in AKI [16].

The use of RIPC for neurologic as well was pulmonary protection prior to surgical procedures has been explored. Patients undergoing elective carotid endarterectomy (CEA) were randomized to receive either RIPC with 10 min of lower limb ischemia followed by reperfusion or no RIPC prior to CEA [50]. There were less saccadic latency deteriorations in the patients who received RIPC; however, this did not reach statistical significance (32 % versus 53 %, $p = 0.11$) [50]. Patients undergoing elective thoracic pulmonary resection ($N = 216$) were randomized to either RIPC or a sham procedure [51]. Compared to the control group, the patients who received RIPC had a significantly increased PaO_2/FiO_2 at 30 and 60 min after one-lung ventilation, 30 min after lung reexpansion, and 6 h after surgery [51].

15.4 The Future of Remote Ischemic Preconditioning for Improving Surgical Outcomes

Over 15 clinical trials were published in 2015 on the clinical use of RIPC. The ease of administration of the RIPC procedure and lack of adverse events reported in clinical trials are likely contributing factors to the continued interest in this intervention. However, RIPC is not used in routine perioperative care. The differences between study results as discussed above make it difficult to identify the patients that may benefit from the intervention. The use of biomarkers to predict RIPC response shows great promise for this purpose.

There is a need to standardize the RIPC procedure. The timing of placement of the blood pressure cuff, location of the blood pressure cuff, and duration of cuff inflation/deflation varies between studies. Also, future studies controlling for medication administration around the time of the RIPC procedure are important. Medication exposure has been discussed as a potential reason for a lack of RIPC benefit in two recently published large multicenter trials. Mehbohm et al. randomly assigned 1,403 patients undergoing cardiopulmonary bypass from 14 centers to four 5-min cycles of RIPC or sham-RIPC [38]. No differences were seen in mortality, stroke, or stage 2–3 AKI [38]. Hausenloy and colleagues using 30 centers randomized 1,612 patients undergoing cardiopulmonary bypass to RIPC or sham-RIPC as well and also found no difference in their combined primary endpoint of nonfatal myocardial infarction, death from cardiovascular causes, coronary revascularization, or stroke when evaluated 12 months after randomization [39]. Propofol was used in the perioperative period in the majority of patients in both studies [38, 39]. Propofol as well as certain inhaled anesthetics have been thought to affect the RIPC response [52–54].

Conclusion

Given that surgical procedures are often associated with a predicted ischemic insult to an organ, there is great potential benefit for the use of RIPC in the perioperative period. Future studies comparing differing blood pressure cuff positions and RIPC timing may help to standardize a preconditioning protocol. Investigations stratifying patients by risk factors and comorbid conditions are warranted. Additionally, studies exploring the use of biomarkers as a method to predict which surgical patients may ultimately benefit from the routine clinical use of RIPC are needed.

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Statins and Perioperative Mortality

16

Hynek Riha and Tomas Drabek

16.1 General Principles

Cardiovascular disease is the leading cause of death in the Western world. One of the major underlying pathologies of cardiovascular disease is atherosclerosis. Atherogenesis is a multifactorial process; hypercholesterolemia represents a major risk factor for atherosclerotic changes. Hypolipidemic drugs including statins have paramount importance in managing patients with chronic cardiovascular disease.

Statins reduce the risk of myocardial infarction (MI), stroke, and death due to the reduction of plasma cholesterol levels. Other pharmacodynamic effects exerted by statins, commonly recognized as "pleiotropic," include improving endothelial function, attenuating vascular and myocardial remodeling, reducing inflammation in vascular wall, inhibiting platelets, and stabilizing atherosclerotic plaques, thus preventing their rupture [1]. These underpinning mechanisms form the basis for the use of statins aimed at reducing morbidity and mortality associated with surgery.

The majority of studies published hitherto clearly favored the use of statins during perioperative period. However, recent data lessen this enthusiasm, revealing that statins may worsen renal function in cardiac surgical patients. For these reasons, the recent Consensus Conference Update on the reduction of perioperative mortality did not include statins among the drugs with proven survival benefit [2, 3]. Taking into consideration the frequent use of statins among patients scheduled for major surgical

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procedures, extensive discussion of current and coming data can be expected. This chapter is built on currently (June 2016) available evidence including international guidelines.

16.2 Main Evidences

Many clinical studies demonstrated that perioperative therapy with statins reduces not only morbidity but also mortality associated with the surgery.

One of the first prospective randomized controlled trials (RCTs) in cardiac surgery showed that simvastatin (20 mg/day for 4 weeks) administered before coronary artery bypass grafting (CABG) in patients with hypercholesterolemia decreased not only LDL (low-density lipoproteins)-cholesterol and total serum cholesterol levels before the surgery, but significantly lowered the occurrence of thrombocytosis, renal failure, and MI in postoperative period [4].

A double-blind RCT with fluvastatin started before vascular surgery and continued for at least 30 days afterward showed a reduced occurrence of myocardial ischemia (10.8 vs. 19.0 %) and composite of death from cardiovascular causes and nonfatal MI (4.8 vs. 10.1 %) [5].

A retrospective analysis of data from 16,192 patients (≥40 years) undergoing CABG explored the association of various preoperative cardiovascular medications with perioperative outcomes [6]. Statins were the most prevalent drug used (85.1 %), even more than beta-blockers (72.8 %). Preoperative statin administration was associated with reduced postoperative mortality (0.4 vs. 0.8 %, odds ratio adjusted to various confounders 0.26–0.35). Analysis of different statins and their doses revealed interesting fact that only simvastatin 40 mg was protective. This could be ascribed to smaller number of other statins.

Another meta-analysis (16 RCTs, 2,275 patients) examined the influence of perioperative statin therapy on postoperative outcomes in patients without long-term statin therapy [7]. This approach significantly reduced mortality (1.8 vs. 3.4 %) and the incidence of MI (4.1 vs. 8.9 %). The incidence of stroke was not significantly reduced (1.0 vs. 1.7 %). Moreover, statin therapy significantly reduced the incidence of postoperative atrial fibrillation (AF) (12.1 vs. 23.4 %) and in-hospital length of stay (LOS). Most of included RCTs were from CABG patients, two studies were from vascular surgery, and only one from non-cardiovascular surgery. Subgroup analysis of noncardiac surgical patients revealed significant reduction in mortality and MI, but not in stroke, AF, or hospital LOS. Subanalysis exploring duration of statin therapy showed significant reduction in mortality and the incidence of MI only when statin administration was started more than 1 week before surgery.

16.3 Pharmacological Properties

Statins are competitive inhibitors of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, which is the rate-limiting step in the biosynthesis of cholesterol. Inhibition of this enzyme reduces plasma levels of total and LDL-cholesterol

by 17–35 % and 24–49 %, respectively [8]. Moreover, plasma level of triglycerides also reduces and plasma level of HDL (high-density lipoproteins)-cholesterol increases.

Statins differ in their pharmacokinetic and pharmacodynamic properties. Lipophilic statins (active at hepatic and extrahepatic sites) include atorvastatin, fluvastatin, lovastatin, simvastatin, and cerivastatin. Hydrophilic statins (active mainly in the liver) are represented by rosuvastatin and pravastatin [9]. Regarding potency for reducing LDL-cholesterol levels, statins can be classified as highly potent (atorvastatin and rosuvastatin) and low potent (simvastatin, fluvastatin, lovastatin, and pravastatin) [10]. The major enzymatic pathway in statin pharmacokinetics includes cytochrome (CYP) P450 enzymes family in the liver, except rosuvastatin and pravastatin. Coadministration of drugs with a higher affinity for CYP3A4 isoenzyme increases plasma levels and bioavailability of statins with associated risk of side effects. Simvastatin, lovastatin, and atorvastatin have the strongest potential for pharmacological interactions [9]. Statins are administered orally; intravenous formulation is not available. Statins with long half-life (atorvastatin) or extended-release formulations (lovastatin) can be preferred before the surgery if a prolonged break in postoperative oral intake is expected [11]. After initiation of statin therapy, full hypolipidemic potential is achieved after 4–6 weeks, with 75 % of effect seen after 2 weeks [12]. Other beneficial effects (e.g., improved endothelial function) could be seen within days.

Statins can induce class-related adverse reactions. Muscle-related side effects (1.5–5 % of patients) range from myalgia, myopathy, and myositis to myonecrosis with increases of creatinine kinase or even clinically significant rhabdomyolysis with acute renal failure [13]. An isolated increase in liver enzymes is usually benign. Adverse reactions are more frequent with higher doses, advanced age, small body surface area, and chronic conditions as renal failure, liver dysfunction, and alcoholism.

16.4 Therapeutic Use

16.4.1 Cardiac Surgery

In cardiac surgery, the ACC/AHA guidelines (2011) recommend statin therapy for all hyperlipidemic patients undergoing CABG surgery. In patients presenting for urgent/emergent CABG, statins should be initiated immediately. Discontinuation of statin therapy is not recommended [14].

16.4.1.1 CABG

Pooled analysis of data from 13 studies (19,542 patients) demonstrated a statistically significant 45 % reduction in postoperative all-cause mortality with preoperative statin therapy relative to control [15].

In a large retrospective evaluation of multiple cardiovascular drugs used in cardiac patients, statins appear consistently protective against perioperative mortality (statins 0.4 % vs. non-statins 0.8 %) from CABG surgery in multiple models.

Simvastatin 40 mg was the only statin in a given dose from those tested that showed protective effects [6]. The salutary effects on mortality are consistent with prior meta-analyses [16, 17].

In contrast, a contemporary Cochrane review of six studies in CABG patients concluded that preoperative statin therapy reduced the odds of postoperative AF and shortened the ICU and hospital LOS but had no influence on perioperative mortality, stroke, MI or renal failure [18]. Another meta-analysis (12 RCTs, 1,116 patients) confirmed beneficial effects on decreased incidence of AF and hospital LOS, with more robust effects after CABG vs. heart valve surgery [19]. Lower rates of AF and perioperative MI after cardiac surgery were also reported with only short-term pretreatment with statins (<3 weeks). In-hospital mortality and stroke rate were also lower with statin therapy although non-significantly [20].

16.4.1.2 Valvular Surgery

In high-risk non-emergent isolated heart valve surgery, preoperative statin therapy had beneficial effect on postoperative mortality [21]. These results were upheld in a recent meta-analysis of ten observational studies (22,518 patients). A significant reduction by statin therapy also was observed for AF, but not for postoperative stroke, MI, or renal failure [22].

16.4.1.3 Heart Transplantation

In a small longitudinal study, heart transplant recipients were treated with pravastatin or control from the time of surgery. Importantly, the majority of control patients were switched to pravastatin during the ten-year follow-up. In an intention-to-treat analysis, pravastatin group compared with control had increased survival and appeared to have reduced development of cardiac allograft vasculopathy [23].

16.4.1.4 Kidney Injury After Cardiac Surgery

Analysis of previously available data did not suggest that preoperative statin use is associated with decreased incidence of acute kidney injury (AKI) in adults after CABG [24, 25]. Patients undergoing CABG might benefit from preoperative statin treatment due to the reduction in the need for postoperative renal replacement therapy and mortality. The effects of reno-protective efficacy of preoperative statin therapy in patients undergoing isolated heart valve surgery remain uncertain [25].

Two recent major RCTs investigating the effects of statins in cardiac surgical patients revealed negative effect of statins on postoperative renal function. In Statin AKI Cardiac Surgery RCT [26], short-term high-dose atorvastatin was started before cardiac surgery. Overall, AKI occurred in 20.8 % of patients in the atorvastatin group compared to 19.5 % in the placebo group; among patients without chronic statin administration, AKI occurred in 21.6 % of patients treated by atorvastatin vs. 13.4 % in the placebo group. None of these differences reached statistical significance and the study was stopped prematurely for futility. The STICS (Statin Therapy in Cardiac Surgery) RCT [27] randomized 1,922 cardiac surgical patients

to 20 mg of rosuvastatin daily or placebo. Statin therapy was initiated shortly before the surgery, with maximum duration of up to 8 days. Primary outcomes, i.e., the rate of postoperative AF within 5 days after the surgery and extent of myocardial injury, did not significantly differ between the groups. However, statin administration was associated with a significant absolute 5 % increase in the occurrence of postoperative AKI at 48 h. The effects at delayed timepoints or the need for renal replacement therapies were not reported.

16.4.2 Vascular Surgery

Patients with peripheral artery disease represent a unique target population in which statin therapy could be beneficial. Indeed, in a nonoperative management of patients with lower limb atherosclerotic arterial disease, statin therapy seems to be effective in reducing all-cause mortality and the incidence of cerebrovascular events [28].

Several studies investigated the effects of statins in patients undergoing vascular surgery. Perioperative fluvastatin therapy was associated with an improvement in postoperative cardiac outcome [5]. Recently published meta-analysis compared short-term statin therapy, either commenced de novo or with existing users randomly assigned to different dosages, in adult participants undergoing elective and emergency noncardiac arterial surgery, including both open and endovascular procedures. Evidence was insufficient to allow to conclude whether statin therapy resulted in either a reduction or an increase in any of the outcomes recorded. Pooled results from three studies (178 participants) showed mortality of 6.7 % in the statin group vs. 13.7 % in the control group [29].

In a retrospective analysis of patients undergoing carotid endarterectomy, statins significantly decreased death rates in diabetic patients and tended to decrease both death and stroke rates in patients with diabetes and with hypercholesterolemia but had no effect on post-procedural restenosis [30].

16.4.3 Noncardiac Surgery

Regarding noncardiac surgery, the ACC/AHA guidelines on perioperative cardiovascular evaluation and management (2014) recommend continuing statins in patients who are currently under this treatment. Perioperative initiation of statin therapy is reasonable in patients undergoing vascular surgery and may be considered in patients with a clinical risk factor undergoing high-risk procedures [31]. Similar guidelines developed by European scientific societies ESC and ESA (2014) state that perioperative continuation of statins is recommended, favoring statins with a long half-life or extended-release formulation. Preoperative initiation of statins should be considered in patients undergoing vascular surgery, ideally at least 2 weeks before the surgery [11].

In a large randomized prospective multicentric study in noncardiac surgery, preoperative statin treatment was independently associated with a lower risk of composite cardiovascular outcomes (all-cause mortality, myocardial injury, or stroke) at 30 days after the surgery. Statins were also associated with a significantly lower risk of all-cause mortality (relative risk 0.58), cardiovascular mortality (relative risk 0.42), and myocardial injury (relative risk 0.86). However, there were no statistically significant differences in the risk of MI or stroke [32]. Meta-analysis of studies exploring the effects of statins on AKI after major surgery showed that preoperative statin therapy was associated with a significant risk reduction for postoperative AKI and need for renal replacement therapy. These benefits were, however, not observed when restricting the analysis only to available RCTs [31].

In kidney transplant recipients, statins may reduce cardiovascular events. Statins had uncertain effects on overall mortality, stroke, kidney function, and toxicity outcomes [33].

Conclusion

Statins are effective hypolipidemic agents with other important "pleiotropic" effects. They have well-established role in primary and secondary prevention of cardiovascular disease.

In cardiac surgery, preoperative statin therapy reduces the odds of postoperative AF and reduces ICU and in-hospital LOS. The effects on MI and stroke are generally positive, with some reports showing benefits on individual outcome parameters but none showing harm. Results from patients undergoing CABG are more robust than after other cardiac surgical procedures such as valvular or aortic surgery. However, recent studies revealed an increased occurrence of AKI associated with statins in cardiac surgical patients. Furthermore, ongoing studies including robust meta-analyses will shed the light on the issue of statin-associated changes in perioperative mortality.

Statins decreased mortality in nonsurgically managed patients with peripheral vascular disease. The effects in patients with vascular surgery were not consistent, but some studies suggested improved outcomes including mortality in patients with specific comorbidities. In patients undergoing major noncardiac surgery, statins may decrease mortality.

Taking into account currently available evidence, continued statin administration in the patients receiving statins preoperatively is recommended. Commencement of statin therapy before cardiac, vascular, and major noncardiac surgery should be considered with caution as recent studies have pointed out the risks associated with statins.

Summary Table

Clinical summary				
Indications	Cautions	Side effects	Dose	Notes
Hypercholesterolemia Primary and secondary prevention of cardiovascular disease		Muscle-related (myalgia, myopathy, myonecrosis, rhabdomyolysis) in 1.5–5 % of the patients Isolated increase in liver enzymes (usually benign)	Depending on particular statin: 10–80 mg once daily	Statin therapy should be continued in perioperative period
Reducing perioperative risk in cardiac, vascular, and major noncardiac surgery	Possible increased occurrence of postoperative AKI and ambiguous effect on mortality			Existing statin therapy should be continued; commencement of new statin therapy treatment before the surgery (1–3 weeks) could be considered with appropriate caution

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Tranexamic Acid to Reduce Perioperative Mortality

17

Giovanni Borghi, Roberta Maj, and Laura Ruggeri

17.1 General Principles

Intraoperative and postoperative bleeding is one of the most important complications of many kinds of major surgery (mainly cardiac and orthopedic surgery, but also liver, vascular, thoracic, gynecological, and urologic surgery and neurosurgery). Red blood cell transfusion is fundamental to manage anemia and is one of the few treatments that adequately restores tissue oxygenation when oxygen demand exceeds supply.

Perioperative bleeding is one of the most common causes of allogeneic blood transfusions worldwide [1]. Blood transfusion, however, is also associated with increased mortality after major surgery. An observational study by Karkouti et al. in patients undergoing cardiac surgery with cardiopulmonary bypass found that major blood loss (defined as transfusion of five or more units of red blood cells within 1 day of surgery) is independently associated with mortality [2]. After controlling for important confounders, including disease severity, intraoperative course, and perioperative complications, major blood loss was associated with an 8.1-fold (95 % confidence interval, 3.9–17.0) increase in the odds of death. There is also evidence that blood loss that requires transfusion of blood products is harmful and that the amount of blood loss is directly related to the degree of harm [3].

Blood transfusions have rare but potentially serious adverse effects. Immune-mediated effects include hemolytic reactions (acute and delayed), acute lung injury, and immunomodulation. Other effects include coagulopathic complications from massive transfusion, mistransfusion, and nonimmune hemolysis [4].

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Transfusion-associated infections are still a concern for allogeneic transfusions. Worldwide, most people do not have access to safe blood: the most important transfusion-related risks are HIV, hepatitis B virus, and hepatitis C virus, due to their high prevalence. Additionally, blood is a scarce resource, and there are substantial economic costs associated with allogeneic transfusions.

The antifibrinolytic drug tranexamic acid is one of the pharmacological agents most commonly used to reduce perioperative blood loss and the need of blood product transfusions.

The first Consensus Conference about randomized evidence for reduction of perioperative mortality by Landoni et al. classified the use of tranexamic acid as a major exclusion, because available evidence on mortality mainly regarded adult trauma patients [5]. Since that Consensus Conference, two meta-analyses have been published, showing a statistically significant improvement in survival in surgical patients due to tranexamic acid [6, 7]. For this reason, tranexamic acid was included in the update of the Consensus Conference among the topics which reduce perioperative mortality [8].

17.2 Main Evidences

Tranexamic acid is associated with a reduction of mortality in surgical patients in one meta-analysis by Ker et al. [6]. The work focused on the effect of tranexamic acid on blood transfusion, thromboembolic events, and mortality in patients undergoing any kind of surgery. The authors found that fewer deaths occurred in the tranexamic acid group (RR 0.61, 95 % CI, 0.38–0.98; $p = 0.04$), although there was uncertainty about this effect, since statistical significance was lost when restricting the analysis to the trials with adequate concealment (0.67, 0.33–1.34; $P = 0.25$). They also confirmed that the use of tranexamic acid is associated with a reduction of the probability of receiving a blood transfusion by 38 % (pooled risk ratio 0.62, 95 % confidence interval 0.58–0.65; $P < 0.001$), with no evidence that the relative effect of tranexamic acid on blood transfusion varies by type of surgery. Interestingly, with a cumulative meta-analysis, they demonstrated that this effect of tranexamic acid on blood transfusion is well established since 2001. No statistically significant difference was found in the incidence of myocardial infarction, stroke, deep vein thrombosis, and pulmonary embolism in patients treated with tranexamic acid.

A network meta-analysis by Hutton et al. focused on the use of antifibrinolytics in patients undergoing cardiac surgery [7]. Restricting the analysis to randomized studies, this meta-analysis showed that tranexamic acid has a survival advantage when compared with aprotinin (odds ratio 0.64, 95 % credible interval 0.41–0.99) and suggested a survival advantage also when it is compared with no treatment, even though there isn't a statistically significant difference (odds ratio 0.64, 95 % credible interval 0.41–1.02). Tranexamic acid is estimated to have a 73.4 % probability of being the lowest risk of treatment, followed by epsilon-aminocaproic acid (24.0 %), aprotinin (0.9 %), and no treatment (1.7 %).

In conclusion, two meta-analyses showed that tranexamic acid might be associated with an improvement of survival in the perioperative period, but further randomized evidences are needed. On the contrary, its effect on the need of blood transfusion is well established in this setting.

The ongoing ATACAS study is a multicenter large randomized trial aiming to assess whether tranexamic acid can reduce the incidence of mortality or major morbidity in patients undergoing elective coronary artery surgery and at increased risk of complications [9]. Hopefully, data from this trial will permit to draw more precise conclusion about the effect of tranexamic acid on mortality in the perioperative period.

The most relevant evidence about an effect of tranexamic acid on survival does not regard its use in the perioperative setting but its use in adult trauma patients. CRASH 2 is a large randomized controlled trial that enrolled more than 20,000 trauma patients with, or at risk for, significant bleeding. In this study, early treatment with tranexamic acid significantly reduced all-cause mortality (14.5 % in the tranexamic acid group versus 16.0 % in the placebo group; relative risk 0.91, 95 % CI 0.85–0.97; $p = 0.0035$) [10].

There is no clear evidence of an effect of tranexamic acid on mortality in traumatic brain injury and postpartum hemorrhage [11, 12].

17.3 Pharmacologic Properties

Tranexamic acid is a synthetic derivative of the amino acid lysine that exerts an antifibrinolytic effect reversibly blocking the lysine binding sites on plasminogen molecules. Lysine residues on fibrin mediate the binding of plasminogen to fibrin. The inhibition of the interaction of plasminogen with lysine residues on the surface of fibrin inhibits the dissolution of fibrin clots [13].

Tranexamic acid almost completely blocks the binding of plasminogen or the heavy chain of plasmin to fibrin. Although plasminogen may still be converted to plasmin in the presence of a plasminogen activator, such as tissue plasminogen activator, it can no longer interact with and digest fibrin after binding to tranexamic acid.

The mechanism of reduction of mortality in surgical patients by tranexamic acid is unclear. Probably this effect is partly due to the reduction of the noninfectious adverse effects of blood transfusions. Another possible mechanism is that tranexamic acid exerts an anti-inflammatory effect in these patients. In a randomized, double-blind, placebo-controlled trial in patients undergoing cardiac surgery with cardiopulmonary bypass, tranexamic acid significantly reduced, compared with placebo, the proportion of patients with an inflammatory response (17 % vs 42 %, $p < 0.05$) and significantly reduced the incidence of vasoplegic shock (0 vs 27 %, $p < 0.01$) [14].

17.4 Therapeutic Use

Tranexamic acid is administered as prophylaxis for surgery that confers a high risk of bleeding or can be used as an intervention for massive refractory bleeding.

The plasma concentration of tranexamic acid effective to obtain inhibition of fibrinolysis is ≥10 mg/L [13]. When administered intravenously, a single 1 g dose of tranexamic acid produces a plasma concentration ≥10 mg/L for about 6 h.

Tranexamic acid is excreted in urine as unchanged drug. The elimination half-life of a single dose of tranexamic acid is 2–3 h (about 30 % is recovered unchanged in urine within 1 h and about 90 % by 24 h). Dosage of tranexamic acid should be adjusted in patients with renal impairment, since its urine excretion is reduced when plasma creatinine levels are increased, while no adjustment is needed in patients with hepatic impairment.

There is a wide range of dosage regimens of tranexamic acid that have been described in clinical trials. There is no agreement about the ideal dosage regimen. Usually tranexamic acid is administered intravenously with a slow loading dose before surgery over 20–30 min followed by a continuous infusion during surgery. In most of the trials, mainly performed in the setting of cardiac surgery, the loading dose is 1–2 g or 10–30 mg/kg and the constant infusion is 0.4–1 g/h or 1–16 mg/kg/h [13, 15].

Allergy and hypersensitivity to the drug and ongoing acute venous or arterial thrombosis are contraindications to tranexamic acid use. Tranexamic acid should be administered carefully and balancing possible advantages and disadvantages in patients with a history of thromboembolic disease or hereditary thrombophilia and in the concomitant use of hormonal oral contraceptives and other prothrombotic medications, including coagulation factor concentrates.

The most frequent adverse events associated with the use of tranexamic acid are mild and include headache, nausea, vomiting, diarrhea, dyspepsia, dizziness, back pain, and numbness.

Nowadays, tranexamic acid is the only drug that showed to improve the hemostatic function without being associated with increased risk of thrombotic adverse events, also in long-term follow-up [13, 15–17]. Many randomized controlled trials and meta-analyses have shown that perioperative use of tranexamic acid is not associated with an increased incidence of myocardial infarction, myocardial ischemia, stroke, deep vein thrombosis, pulmonary embolism, or other thromboembolic complications.

In cardiac surgery, high doses of tranexamic acid are associated with an increased risk of postoperative generalized seizures, and patients with seizures have a higher mortality rate.

Conclusion

Perioperative administration of tranexamic acid is associated with a reduction of mortality in surgical patients in two meta-analyses, but the evidence about this effect is still weak. On the contrary, it is well demonstrated that this drug reduces perioperative blood loss and the need of blood product transfusions in patients undergoing many different kinds of surgeries. This effect is not associated with an increased risk of thromboembolic events.

Further evidences to confirm the effect of tranexamic acid on mortality are needed from large randomized controlled trials, possibly involving different

kinds of surgeries. The results from the ATACAS Trial may help to draw stronger conclusion about safety and the effect on mortality of tranexamic acid in the perioperative period [9].

17.5 Summary Table

Clinical summary				
Drug/ technique	Indications	Cautions	Side effects	Dose
Tranexamic acid	Prophylaxis for surgery that confers a high risk of bleeding or intervention for massive refractory intraoperative/ postoperative bleeding	Absolute contraindications: allergy/ hypersensitivity to the drug, ongoing acute venous or arterial thrombosis. Relative contraindications: patients with a history of thromboembolic disease or hereditary thrombophilia, concomitant use of hormonal oral contraceptives and other prothrombotic medications (including coagulation factor concentrates)	Headache, nausea, vomiting, diarrhea, dyspepsia, dizziness, back pain, numbness. In cardiac surgery, high doses of tranexamic acid are associated with an increased risk of postoperative generalized seizures (and patients with seizures have a higher mortality rate)	Intravenous administration Slow loading dose before surgery over 20–30 min: 1–2 g or 10–30 mg/kg Continuous infusion during surgery: 0.4–1 g/h or 1–16 mg/kg/h

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Reducing Mortality in the Perioperative Period: A Continuous Update

18

Marta Mucchetti and Giovanni Landoni

18.1 Introduction

According to the EUSOS study, perioperative mortality for noncardiac surgery is 1–4 % [1], considering that up to 230 million surgical procedures are performed each year in the world [2], even a small reduction would have a tremendous impact on public health.

The first Consensus Conference on mortality reduction in the perioperative period was published in 2012 [3]. Three years later an official update was held. Thirteen interventions showing a significant impact on mortality were selected and are the object of this book [4]. Three topics included in the first Consensus Conference were excluded (clonidine, perioperative supplemental oxygen, and chlorhexidine oral rinse), and two new interventions were added (tranexamic acid and remote ischemic preconditioning).

This chapter briefly reports the papers published after the second Consensus Conference was held, which showed a statistical significant effect on perioperative mortality (Table 18.1).

18.2 Methods

A sensitive PubMed search was performed to systematically identify all papers dealing with interventions influencing perioperative mortality, published since the Consensus Conference Update. The same three search strategies were used (Table 18.1); time limits were set from the 7th of March 2015 and the 30th of January 2016. Further topics were identified by cross-checking of references.

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Box 18.1 The full three search strategies used to identify all RCT and the meta-analysis of RCT reporting a significant effect on perioperative mortality

Systematic[sb] AND (surgery[tiab] OR surgic*[tiab] OR operation*[tiab]) AND ((myocardial AND infarction) OR (death* OR survival OR mortality OR prognosis)) AND (prevent* OR reducti* OR reduci*)
(Surgery[tiab] OR surgic*[tiab] OR operation*[tiab]) AND ((death* OR survival OR mortality)) AND (prevent* OR reducti* OR reduci*) AND (significat* OR significan*) AND (randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized controlled trials[mh] OR random allocation[mh] OR double-blind method[mh] OR single-blind method[mh] OR clinical trial[pt] OR clinical trials[mh] OR (clinical trial[tw] OR ((singl*[tw] OR doubl*[tw] OR trebl*[tw] OR tripl*[tw]) AND (mask*[tw] OR blind[tw])) OR (latin square[tw]) OR placebos[mh] OR placebo*[tw] OR random*[tw] OR research design[mh:noexp] OR comparative study[tw] OR follow-up studies[mh] OR prospective studies[mh] OR cross-over studies[mh] OR control*[tw] OR prospectiv*[tw] OR volunteer*[tw]) NOT (animal[mh] NOT human[mh]) NOT (comment[pt] OR editorial[pt] OR meta-analysis[pt] OR practice-guideline[pt] OR review[pt]))
(Dead[tiab] or death[tiab] or die[tiab] or died[tiab] or mortality[tiab] or fatalit*[tiab] or exitus[tiab] or surviv*[tiab]) and (“anesthesia”[tiab] OR “cardiac arrest”[tiab] or “critical care”[tiab] or sepsis[tiab] or “critical illness”[tiab] or “critically ill” [tiab] or “ARDS”[TIAB] or “acute respiratory distress syndrome”[tiab] OR “ecmo”[tiab] OR “intensive care”[tiab] or emergen*[tiab]) AND (“randomized controlled trial”[tiab] OR “controlled clinical trial”[tiab] OR “randomized controlled trials”[tiab] OR blind*[tiab] OR “clinical trial”[tiab] OR “clinical trials”[tiab] OR placebo*[tiab] OR random*[tiab]) NOT (animal[mh] NOT human[mh]) NOT (comment[pt] OR editorial[pt] OR meta-analysis[pt] OR practice-guideline[pt] OR review[pt] OR pediatrics[mh])

Selected papers fulfilled all the following criteria: (a) published in a peer-reviewed journal, (b) dealing with a nonsurgical intervention (drug/technique/strategy) in adult patients undergoing any surgery, and (c) reporting a statistically significant reduction or increase in mortality, (d) conduced as randomized trial (RCT) or meta-analysis of RCT.

18.3 Interventions That Have Shown an Effect on Perioperative Mortality

The three search strings described in Box 18.1 identified 362, 355, and 1,092 results, respectively. After a careful screening, nine studies [5–13], dealing with seven different interventions, were included in the present update. The summary of new evidences at the end of this chapter reports the main characteristics of the selected papers.

Three interventions not already selected by the Consensus Conference have been found to possibly improve survival: miniaturized extracorporeal circulation (MECC) [5], non-adrenergic vasopressors [6], and perioperative goal-directed hemodynamic therapy (GDHT) [7]. The other six papers dealt with four interventions already present in the Consensus Conference Update: volatile agents [8], perioperative intra-aortic balloon pump (IABP) [9, 10], levosimendan [11, 12], and remote ischemic preconditioning (RIPC) [13].

Eight out of nine studies were set in cardiac surgery [5, 6, 8–13]. Two papers focused on a mixed population (i.e., surgical and medical) [6, 13]. All the selected papers were meta-analyses of RCTs; one of them included also observational studies which were analyzed separately [10], and two were network meta-analyses [5, 8]. All selected papers dealt with intervention that showed a positive effect on survival.

18.4 Miniaturized Extracorporeal Circulation in Coronary Artery Bypass Grafting

Coronary artery bypass grafting is associated with a reduction of mortality in extensive coronary artery disease. The gold standard technique is the CABG with the use of cardiopulmonary bypass (CPB). Nevertheless conventional extracorporeal circulation (CECC) is believed to be a major determinant for postoperative morbidity. Consequently novel solutions have been developed to reduce its impact, such as off-pump CABG (OPCAB) and MECC. Miniaturized extracorporeal circulation reduces the air-blood contact using a shorter circuit and no venous reservoir: therefore, it lowers blood loss and need for transfusions and minimizes inflammatory response.

Kowalewski et al. [5] conducted a network meta-analysis comparing the effect of these three strategies on mortality and postoperative complications. They selected 134 RCTs, enrolling 22,778 patients. Data on mortality were extracted from 50 RCTs (17,638 patients). MECC and OPCAB were associated with a significant reduction of all-cause mortality (OR (95 % CI), 0.46 (0.22–0.91), and 0.75 (0.51–0.99)) when compared with CECC. These techniques offered a significantly higher protection against cerebral stroke, postoperative atrial fibrillation, and renal dysfunction, while no significant differences among three strategies were seen in regard to myocardial infarction. No significant difference between OPCAB and MECC was observed from direct comparison, but the hierarchy of numerical treatments emerging from the probability inference analyses was MECC >OPCAB >CECC.

Previous observational studies and meta-analyses reported increased long-term mortality with OPCAB. Selection bias seems to be the obvious explanation for the discrepancies between observational and randomized strata. Patients included in the OPCAB group were more likely to be at higher baseline risk.

The main limitations of this work are that the authors did not have access to individual patients' data and that the number of event observed was small.

18.5 Non-adrenergic Vasopressors in Vasodilatory Shock

Non-adrenergic vasopressors are a group of drugs that are used in hemodynamic shock in association with or instead of catecholamines. Their use reduces catecholamines side effects, such as increased myocardial oxygen consumption and arrhythmias. Moreover, they are essential in the treatment of late-phase shock, when standard treatment became ineffective.

Belletti et al. conducted an extensive meta-analysis, including twenty RCTS (1,608 patients), to investigate the effect on mortality of non-adrenergic vasopressor in vasodilatory shock [6]. The intervention agents were vasopressin, terlipressin, and methylene blue. The comparators were placebo, standard treatment, norepinephrine, and dopamine. Most of the selected studies were performed in the setting of sepsis (10/20) and in the setting of cardiac surgery (7/20). Overall pooled analysis showed that the use of non-adrenergic vasopressors was associated with a significant mortality reduction (RR (95 % CI): 0.88 (0.79–0.98), $p = 0.02$). Considering the study drugs independently, all agents were associated with a nonsignificant trend toward improved survival of the same direction and magnitude. When analyzing different settings, non-adrenergic vasopressors were found to reduce mortality both in sepsis (RR (95 % CI): 0.87 (0.77–0.98), $p = 0.02$) and cardiac surgery (RR (95 % CI): 0.16 (0.04–0.69), $p = 0.01$). The authors speculate that the survival benefit observed might be a consequence of their catecholamine-sparing effect, rather than a beneficial effect per se.

18.6 Perioperative Goal-Directed Hemodynamic Therapy in Noncardiac Surgery

Goal-directed hemodynamic therapy (GDHT) is the use of a hemodynamic optimization algorithm that aims to achieve normal or supranormal hemodynamic values, through fluids, vasopressors, and inotropes. This implies the use of more or less invasive hemodynamic monitoring. The objective is to prevent hypoperfusion and imbalance between oxygen delivery and consumption.

Ripollés-Melchor and colleagues [7] conducted a meta-analysis of RCTs to assess whether this approach reduces complications and mortality compared to conventional fluid therapy in noncardiac surgery patients. Studies where GDHT was limited to the intraoperative period were excluded. Twelve RCTs and 1,527 patients were included. Mortality was analyzed in all RCTs included and was significantly reduced by perioperative GDHT (RR (95 % CI): 0.63 (0.42–0.94), $p = 0.02$). In subgroup analyses, mortality was reduced only when a supranormal target was set (RR (95 % CI): 0.42 (0.23–0.76), $p = 0.004$) and when perioperative GDHT was performed (RR (95 % CI): 0.61 (0.39–0.96), $p = 0.03$). No significant difference in the complication rate was detected. In sensitivity analysis, authors found that if studies with lower methodological quality were excluded, there were no differences between GDHT and standard fluid therapy.

18.7 Volatile Agents in Cardiac Surgery

Volatile agents are among the few interventions that might reduce perioperative mortality [3, 4], probably through their ability to mimic the early phase of ischemic preconditioning.

Here we sum the results of the only meta-analysis published since the Consensus Conference Update, while details on this intervention are discussed in a dedicated chapter (Chap. 4).

Zangrillo et al. [8] performed a Bayesian network meta-analysis to assess whether the cardioprotective properties of volatile agents and of RIPC have survival effects in patients undergoing cardiac surgery. To be included, the studies had to compare TIVA to a combined plan including the administration of a volatile agent and/or to include the comparison between the use of RIPC and not. A total of 55 RCTs were selected, randomizing 6,921 patients, of whom 39 % (in 50 studies) received volatile agents, 37 % (in 41 studies) received TIVA, 13 % (in 7 studies) received RIPC+TIVA, and 11 % (in 15 studies) received RIPC+volatile agents. The most common pairwise comparison was volatile agents versus TIVA, present in 34 (62 %) of the selected studies. Through simple direct comparison, volatile agents significantly reduced mortality when compared to TIVA (OR (95 % CI): 0.56 (0.36–0.88), $p=0.01$). This advantage was maintained when the Bayesian hierarchical model was used (OR (95 % CI): 0.50 (0.28–0.91)). As discussed later on this chapter, the Bayesian network meta-analysis assessed an additive positive effect of volatile agents and RIPC when compared to TIVA with or without RIPC.

18.8 Preoperative Intra-aortic Balloon Pump in Cardiac Surgery

Cardiac surgery may lead to a variable degree of myocardial stunning and depressed contractility, which can cause postoperative low cardiac output syndrome (LCOS). Intra-aortic balloon pump (IABP), which enhances myocardial perfusion and lowers left ventricle work, has been used to prevent this phenomenon in hemodynamic stable patients at high risk of perioperative complications.

The impact of preoperative IABP on mortality has already been stated in the Consensus Conferences by Landoni et al. [3, 4], and details about this intervention have already been described in Chap. 10. This paragraph deals with the two significant meta-analyses published since the Consensus Conference update.

Pilarczyk et al. [9] analyzed nine RCTs that compared aortic counterpulsation started preoperatively with no intervention in 1,171 adult patients undergoing cardiac surgery. The use of preoperative IABP seemed to reduce hospital mortality (OR (95 % CI): 0.38 (0.23–0.68), $p<0.001$); this effect was maintained when comparing only on-pump CABG studies (OR (95 % CI): 0.27 (0.13–0.55), $p<0.001$). In addition, a significant reduction in LCOS and length of ICU stay was noted. Complications were reported in seven out of nine studies, with overall incidence being 5.6 %. Most frequent complications were limb ischemia and hematoma.

Poirier's meta-analysis [10] included both RCTs and observational studies, which were analyzed separately. A total of 11 RCTs and 22 observational studies were included. In this meta-analysis, the interventional group received preoperative IABP, while control group did not. The analysis of RCT confirmed a reduction in in-hospital mortality (OR (95 % CI): 0.2 (0.09–0.44), $p<0.001$), 30-day mortality (OR (95 % CI): 0.43 (0.25–0.76), $p=0.003$), length of ICU stay (−1.47 day, 95 % CI: – 1.82–1.12, $p<0.001$), and length of hospital stay (−3.25, 95 % CI: −5.18–1.33, $p<0.001$). However, such benefit could not be confirmed in data obtained from observational studies, despite inclusion of much larger number of patients

with higher baseline risk profiles. Furthermore, severe IABP-related complications were reported in 3 % of patients.

The RCTs included in both meta-analyses overlapped and showed important limitations. First, five RCTs have been performed by the same group, second some RCTs were funded by the industry, third sample size was small, and fourth the rate of IABP crossover varied widely.

18.9 Levosimendan in Cardiac Surgery

Levosimendan is a calcium sensitizer with inotropic and vasodilatory effects that has been found to improve cardiac output in patients with low-output heart failure without increasing cardiac work. The Consensus Conference identified this drug as potentially lifesaving in the perioperative period [3, 4], and details about available evidences and use are described in this book in a dedicated chapter (Chap. 7).

Since the Consensus Conference update, two novel meta-analyses have been published, showing a significant effect on mortality.

Qiao and colleagues [11] assessed the effect of levosimendan on mortality of high-risk (i.e., patients who developed multiple organ dysfunction syndrome) cardiac surgical patients. Ten RCTs (440 patients) were included in the final analysis. In four trials, control group received placebo, while in six control group received an alternative inotropic agent, either dobutamine or milrinone. The use of levosimendan was associated with a significant reduction in perioperative mortality (OR (95 % CI): 0.35 (0.18–0.71), $p=0.003$), atrial fibrillation (OR (95 % CI): 0.48 (0.29–0.78), $p=0.003$), myocardial infarction (OR (95 % CI): 0.26 (0.07–0.97), $p=0.04$), and acute renal failure (OR (95 % CI): 0.26 (0.12–0.60), $p=0.002$). The subgroup analyses showed that the survival benefit of levosimendan was maintained when compared to each inotropic agent; unfortunately the effect compared with placebo was not reported.

Zhou and collaborators [12] focused their attention on the beneficial effects of levosimendan on renal function after cardiac surgery. They selected 13 RCTs concerning 1,254 adult cardiac surgery patients. Postoperative incidence of acute kidney injury was significantly reduced by levosimendan (OR (95 % CI): 0.51 (0.34–0.76), $p=0.001$). Accordingly a lower rate of renal replacement therapy was observed in the intervention group (OR (95 % CI): 0.43 (0.25–0.76), $p=0.002$). Again, a survival benefit for patients treated with levosimendan was documented (OR (95 % CI): 0.41 (0.27–0.62), $p=0.001$).

The sample size of the RCTs included in these meta-analyses was small. Moreover, data on long-term mortality were still inconclusive.

18.10 Remote Ischemic Preconditioning in Cardiac Surgery

Ischemic preconditioning is a response at cellular level to brief sublethal episodes of ischemia leading to a major protection against subsequent lethal ischemia. Remote ischemic preconditioning consists in the stimulation of short episodes of

ischemia and reperfusion in a tissue different from the heart, inducing myocardial protection from ischemia. This conservative and cost-effective technique has been selected by the Consensus Conference update [4], and it is described in detail in Chap. 15.

Since then, two meta-analyses dealing with RIPC have been published.

Le Page and colleagues [13] conducted an extensive research on the effects of RIPC in mixed population, including both cardiac surgery and interventional cardiology patients. The primary end point was myocardial injury, while all-cause mortality was a secondary end point. Forty-four RCTs, involving 5,317 patients, were selected. Among them 22 RCTS were conducted in cardiac surgery (3,093 patients). The authors demonstrated a significant reduction of the myocardial injury markers (troponin area under the curve, OR (95 % CI): −0.27 (−0.36 to –0.18), $p<0.001$), and significance was maintained in the subgroup analysis involving only adult cardiac surgery patients. All-cause mortality occurring over a year after the initial event was significantly reduced by RIPC in three studies (OR (95 % CI): 0.27 (0.13, 0.58), $p=0.0008$). Nonsignificant reduction was observed in short-term all-cause mortality (30 days and less than a year) (OR (95 % CI): 0.79 (0.49, 1.27), $p=0.33$).

In the Bayesian network meta-analysis by Zangrillo et al. already mentioned above [8], the effect on mortality of RIPC in association with either volatile agents or TIVA was studied through simple direct comparison and Bayesian hierarchical model. Direct comparison did not show any significant difference in mortality associated with RIPC, regardless of the anesthetic regimen. Instead, the Bayesian analysis showed a survival benefit associated with the combination of RIPC and volatile agents when compared to both TIVA (OR (95 % CI): 0.15 (0.04–0.55)) and TIVA+RIPC (OR (95 % CI): 0.19 (0.04–0.94)). According to the authors, the probability that the association of volatile agents and RIPC is the best conduct in cardiac surgery is 0.96.

The authors identified several limitations to their work. First, included RCTs were small, single center, and not double blind. Second, in some studies, confounding factors were not disclosed, e.g., the use of sulfonylurea, theophylline, and allopurinol, which can interfere with the preconditioning mechanism, and the total amount of intraoperative opioids that can influence volatile cardioprotective effects.

Conclusion

Evidence-based medicine is constantly evolving. In 11 months, nine papers, dealing with seven interventions, with a significant effect on perioperative mortality were published. Three new interventions have been found to possibly improve survival, MECC, non-adrenergic vasopressors, and GDHT. The other six papers dealt with four interventions already selected in the Consensus Conference Update: volatile agents, perioperative IABP, levosimendan, and RIPC. Goal-directed hemodynamic therapy was the only intervention set in noncardiac surgery. All the selected papers were meta-analyses of RCTs. All selected papers dealt with intervention that showed a positive effect on survival.

18.11 Summary of the New Evidences

New topic	Intervention	Author	Control	Setting	*N* of RCT	*N* of patients	Size effect	Notes
Yes	Miniaturized extracorporeal circulation	Kowalewski M	Conventional extracorporeal circulation	CABG	134	22,778	OR 0.46 (95 % CI 0.22–0.91)	Network meta- analysis, comparing also off-pump CABG
	Vasopressin, terlipressin or methylene blue	Belletti A	Placebo or norepinephrine or dopamine or standard treatment	Vasodilatatory shock (cardiac surgery/ critically ill (sepsis))	20	1,608	RR 0.88 (95 % CI 0.79–0.98)	Multiple comparators Mixed population
	Perioperative goal-directed hemodynamic therapy	Ripollés-Melchor J	Conventional fluid therapy	Noncardiac surgery	10	1,527	RR 0.63 (95 % CI 0.42–0.94)	

No	Volatile agents	Zangrillo A	TIVA	CCH	55	6,921	OR 0.56 (95% CI 0.36–0.88)	Network meta-analysis (volatile, TIVA ± RIPC). Significant effect in direct comparison for volatile vs TIVA (36 studies, 3,680 patients)
	Preoperative IABP	Poirier Y	No intervention	CCH	11	1,293	OR 0.20 (95% CI 0.09–0.44)	Observational studies were included, but were analyzed separately
		Pilarczyk K	No intervention	CCH	9	1,171	OR 0.38 (95% CI 0.23–0.63)	
	Levosimendan	Zhou C	Placebo or dobutamine or milrinone	CCH	13	1,254	OR 0.43 (95% CI 0.25–0.76)	Multiple comparators
		Qiao L	Placebo or dobutamine or milrinone	CABG(high-risk surgical patients)	10	440	OR 0.35 (95% CI 0.18–0.71)	Multiple comparators
	Remote ischemic preconditioning	Le Page S	No intervention	CCH and interventional cardiology	44	5,317	OR 0.27 (95% CI 0.13–0.58)	Mixed population. Long -term mortality was reported only in three RCTs (383 patients)

95% CI 95% confidence interval, *CABG* coronary artery bypass graft, *CCH* cardiac surgery, *IABP* intra-aortic balloon pump, *N* number, *OR* odd ratio, *RCT* randomized controlled trial, *RIPC* remote ischemic preconditioning, *RR* relative risk, *TIVA* total intravenous anesthesia

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Randomized Evidence of Mortality Reduction Not Confirmed in Most Recent Works: A Methodological Problem

19

Laura Ruggeri and Martina Baiardo Redaelli

19.1 General Principles

In 2011, a first manuscript published by our group suggested a new strategy to analyze medical evidence [1]. Under the name of "democracy-based medicine," a plenty of papers and books were published thereafter [1–9]. They focused on:

- Randomized evidence with significant effect on mortality
- Web-global polling, during which thousands of physicians from different countries were asked to vote the findings about each topic and to reveal their clinical habits related to the mentioned topic.

About the perioperative period, in 2011 all the literature was collected and analyzed, to select those drugs, techniques, or strategies that could affect survival. This rigorous work brought to the selection of 14 topics (12 reducing mortality and 2 reducing survival) and involved many clinicians all over the world who collaborated with our group answering some brief question about the findings (see Chap. 2).

In 2015 the same procedure was replicated, and an updated selection of interventions was surveyed among 500 clinicians via web.

Not surprisingly, this new updated selection did not include all the topics present in the first edition. In details, chlorhexidine oral rinse, α_2-adrenergic agonists, and perioperative supplemental oxygen were not confirmed in the updated process to possibly reduce perioperative mortality because the most recent evidence challenged the previous results. On the other hand, two new interventions possibly reducing perioperative mortality were included: tranexamic acid and remote ischemic preconditioning.

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19.2 Published Evidence

The following paragraphs briefly describe each excluded topic together with their related update evidence.

19.2.1 Chlorhexidine Oral Rinse

One of the most frequent life-threatening nosocomial infection in patients undergoing cardiac surgery is VAP (ventilator-associated pneumonia), which is associated with 15–45 % [10, 11] (or even higher) [12] rate of mortality. Since oropharyngeal secretions contaminated with nosocomial organisms are the major route for lower respiratory tract invasion [13–15], the use of an antiseptic drug for oral decontamination seemed to be a promising intervention to reduce the incidence of VAP. Chlorhexidine's antimicrobial activity, together with its capability of binding to mucosal proteins, makes its use as oral rinses interesting.

The only randomized evidence reporting a mortality reduction from oral rinse with chlorhexidine was that by DeRiso et al. in cardiac surgical patients admitted to ICU [13]. In this RCT comparing patients receiving chlorhexidine gluconate 0.12 % oral rinse with placebo, the group randomized to receive treatment showed a mortality rate significantly lower than the ones receiving placebo (mortality rate of 1.16 % in the chlorhexidine group, 5.56 % in the placebo group, $p < 0.05$). Although this RCT suggested that 0.12 % chlorhexidine gluconate might reduce perioperative mortality in patients undergoing cardiac surgery, other studies investigating the role of chlorhexidine oral rinse failed to demonstrate a significant mortality reduction.

Klompas et al. conducted a systematic review and meta-analysis which concluded that even if chlorhexidine oral care reduces the incidence of hospital-acquired pneumonia in cardiac surgery patients, in noncardiac surgery settings, it does not decrease the incidence of VAP [16]. Authors concluded that the role of chlorhexidine oral care should be reevaluated.

Furthermore a recent network meta-analysis by Price et al. demonstrated that both oropharyngeal and digestive selective decontamination were superior to chlorhexidine for mortality prevention in intensive care units [17]. This study also highlighted a possible detrimental effect on survival related to topical oropharyngeal chlorhexidine, since its use was associated with an increase in mortality (odds ratio 1.25, 1.05–1.50). An important limitation about this evidence, contrasting with previous findings, is that in the studies considering the effect of chlorhexidine on mortality, mortality was not the primary outcome.

During the Consensus Conference update held in 2015, only 64.1 % of participants agreed about the survival benefit of chlorhexidine oral rinse, and this topic was therefore excluded.

19.2.2 Perioperative Supplemental Oxygen

Oxygen is a drug routinely administered during the perioperative period. Supplemental oxygen is a possible strategy to maintain an adequate DO_2, together with respiratory support, hemodynamic optimization, blood administration, temperature management, and adequate analgesia [18]. Moreover, oxygen tension exerts a key role in reducing surgical site infections [19]: hyperoxia increases the oxidative killing of bacteria by neutrophils [20–22], it helps wound healing enhancing tissues' reparative processes, and it also activates the immune response due to the interaction with tumor necrosis factor α [22–24]. On the other hand, the prolonged exposure to high oxygen can cause some undesired effects, such as lung atelectasis, increased alveolar-capillary gradient, inflammation of the upper airways (especially in patients with chronic obstructive pulmonary disease), and an increase in systemic and coronary vascular resistances, probably attributable to ROS production, oxidative stress, and DNA damage [23–26].

The first Consensus Conference included perioperative supplemental oxygen among the drugs presenting a survival benefit. This conclusion was based on the meta-analysis performed by Brar et al., which didn't attribute the result of mortality reduction to a statistically significant reduction in surgical site infection [27].

However, the recent RCT by Hayes et al., identified during the Consensus Conference Update, found a higher mortality in the group treated with a DO_2, maintained above the target level. The authors suggested that the DO_2 increase seemed anyway associated with a reduction in the oxygen-extraction ratio. Moreover, a more recent, large mRCT conducted in patients undergoing elective or emergency laparotomic surgery, and randomized to receive either 0.8 or 0.3 inspiratory oxygen fraction during the perioperative period, demonstrated an increased long-term mortality in the group randomized to receive 0.8 oxygen fraction [28]. Thus, since evidences on perioperative supplemental oxygen administration are contrasting, a clear mechanism of action is lacking, and the web vote by the Consensus Conference participants met low agreement (30.5 %), this topic was no more included in the Consensus Conference Update.

19.2.3 Alpha-2 Adrenergic Agonists

Clonidine is a commonly used α2-adrenergic agonist antihypertensive drug that may prevent myocardial infarction in patients at risk for cardiovascular complications, thanks to its analgesic, anxiolytic, anti-inflammatory, and anti-shivering effects [29–32]. Clonidine can also blunt surgical stress response, by the reduction of the central sympathetic outflow and the inhibition of the pre-junctional nerve catecholamine release [33, 34]. This pathophysiological basis was supported in the clinical practice by the results of small RCTs [29, 35, 36], meta-analysis of RCTs

[37, 38], and a large quantitative systematic review [39], suggesting that in noncardiac surgery, the perioperative administration of low-dose clonidine may reduce mortality due to the prevention of myocardial ischemia. In the first Consensus Conference by Landoni et al., the authors suggested caution in the application of this strategy to general population, in view of reported episodes of hemodynamic instability attributable to clonidine administration. Furthermore, the only RCT finding a reduction in perioperative mortality with the use of clonidine was the work by Wallace et al. [40], which was considered too small and underpowered to make firm conclusions [41].

The POISE-2 investigators conducted a more recent mRCT [42], involving 10,010 patients in 135 centers in 23 countries, randomly comparing the administration of low-dose clonidine with placebo in patients undergoing noncardiac surgery. This study confirmed the safety concerns about hemodynamic instability, since significantly more patients in the clonidine group had clinically important hypotension. Furthermore, in the clonidine group, an increased rate of nonfatal cardiac arrest was noted. The POISE-2 trial also did not confirm the findings of improved outcome in terms of lower mortality and less myocardial infarction [34].

19.3 Discussion

The evolution of scientific evidence is a well-known process, involving new findings which are discussed many times, sometimes confirmed and sometimes erased. Many reasons can be advocated to explain this phenomenon and certainly medical evidences have their own peculiarity.

Many factors contribute to the solidity of a research: the methodology (randomized controlled trials versus other retrospective studies), how the randomization process is performed, the sample size, the number of centers involved, the presence and the quality of blinding, the quality of statistical analysis, the so-called plausibility, the source of funding and eventual conflicts of interests, and many others.

As a matter of fact, the findings coming from low-quality trials are capable of being replaced by new stronger evidence and this is what happened to the three topics described hereby.

In critical care medicine, high-quality research method is observed in very few papers, as described in a recent work [4], although in recent years more evidence is coming from large, well-conduced RCTs. Hopefully, this trend toward the good research will transpose its effects in the clinical practice allowing a better care of patients.

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