

Major themes for 2011 in cardiovascular anesthesia and intensive care

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ABSTRACT

The past year has witnessed major advances in cardiovascular anesthesia and intensive care. Perioperative interventions such as anesthetic design, inotrope choice, glycemic therapy, blood management, and noninvasive ventilation have significant potential to enhance perioperative outcomes even further.

The major theme for 2011 is the international consensus conference that focused on ancillary interventions likely to reduce mortality in cardiac anesthesia and intensive care. This landmark conference prioritized volatile anesthetics, levosimendan, and insulin therapy for their promising life-saving perioperative potential. Although extensive evidence has demonstrated the cardioprotective effects of volatile anesthetics, levosimendan as well as glucose, insulin and potassium therapy, the clinical relevance of these beneficial effects remains to be fully elucidated. Furthermore, controversy still persists about how tight perioperative glucose control should be in adult cardiac surgery because of the risk of hypoglycemia.

A second major theme in 2011 has been perioperative hemostasis with the release of multispecialty guidelines. Furthermore, hemostatic agents such as recombinant factor VIIa and tranexamic acid have been studied intensively, even in the setting of major non-cardiac surgery. This review then highlights the remaining two major themes for 2011, namely the expanding role of noninvasive ventilation in our specialty and the formation of the Roland Hetzer International Cardiothoracic and Vascular Surgery Society.

In conclusion, it is time for large adequately powered multicenter trials to test whether prioritized perioperative interventions truly reduce mortality and morbidity in cardiac surgical patients. This essential paradigm shift represents a major clinical opportunity for the global cardiovascular anesthesia and critical care community.

Keywords: cardiac anesthesia, cardiac surgery, intensive care, mortality, review.

INTRODUCTION

This article is the third in an annual series for the journal (1, 2). We thank the editorial board for this opportunity to review the major themes for 2011 in cardiovascular anesthesia and intensive care.

The major theme for 2011 is the first international consensus conference that was convened in Milan to define ancillary interventions likely to reduce mortality in cardiac anesthesia and intensive care. Three interventions prioritized at this conference receive special focus as major themes for 2011, given their promising life-saving potential in the perioperative care of cardiac surgical patients: volatile anesthetics levosimendan, and insulin therapy.

This review then highlights the major focus

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on hemostasis seen throughout 2011 in the form of guidelines, consensus papers, meta-analyses and clinical trials.

In conclusion, the expanding role of noninvasive ventilation in our specialty and the formation of the Roland Hetzer Society are discussed.

Can Anesthetic Interventions Improve Survival after Cardiac Surgery?

Despite extensive evidence, there is currently minimal consensus about the menu of non-surgical interventions that can significantly reduce perioperative mortality in cardiac surgery. In an effort to address this quality gap, a recent international consensus conference was held (3). The conference was initiated as an internet-based discussion of major topics that were formulated after an extensive literature review. This dialogue involved cardiac anesthesiologists, cardiac surgeons, and cardiologists from 65 countries and was concluded with a 2010 meeting in Milan at the Vita-Salute University.

A shortlist of topics was selected, based on the quality of supporting evidence and their clinical applicability. Based on this global consensus, eight interventions were prioritized for reduction of perioperative mortality in cardiac surgical patients. Six of these interventions concerned drug therapy: chronic beta-adrenergic blockade; statin exposure; anesthetic technique utilizing volatile agents; inotropic support with levosimendan; glucose control with insulin; and, early aspirin therapy. The remaining two interventions concerned preoperative planning, namely referral to a high-volume center and utilization of intra-aortic balloon counterpulsation (3).

This international consensus conference has identified eight life-saving interventions in cardiac surgical patients that merit urgent study. These interventions represent major research opportunities for the global cardiovascular anesthesia community.

Do Volatile Anesthetic Agents Reduce Mortality after Cardiac Surgery?

A recent meta-analysis (cumulative N=1922: 22 randomized cardiac surgical trials) demonstrated that a volatile anesthetic technique significantly reduced the risks of perioperative myocardial infarction (odds ratio 0.51; 95% confidence interval 0.32-0.84; P=0.008) and mortality (odds ratio 0.31; 95% confidence interval 0.12-0.80; P=0.02) (4). Based on this promising analysis, volatile anesthesia was shortlisted in the international consensus conference as a perioperative intervention with life-saving potential in cardiac surgery.

The promising outcome effects of volatile anesthetic exposure in patients undergoing coronary artery bypass grafting (CABG) have also been highlighted by at least 2 further meta-analyses (5, 6). In the Canadian meta-analysis (cumulative N=2841: 32 randomized CABG trials), sevoflurane and desflurane significantly reduced perioperative myocardial ischemia as reflected by cardiac troponin release (P<0.00001) (5). In the Chinese meta-analysis (cumulative N=1392: 13 randomized CABG trials), sevoflurane exposure significantly decreased the incidence of myocardial ischemia (odds ratio 0.37; 95% confidence interval 0.16-0.83; P=0.02) as well as length of stay in the intensive care unit (weighted mean difference -10.99; 95% confidence interval -12.97 to -9.01; P<0.00001) and the hospital (weighted mean difference -0.78; 95% confidence interval -1.00 to -0.56; P<0.00001) (6). This series of meta-analyses suggests the need for further randomized trials to explore the promising outcome effects of volatile anesthetics in diverse cardiac surgical settings beyond CABG.

In an effort to address this evidence gap, a recent trial (N=100) randomized patients with coronary disease undergoing mitral surgery to an anesthetic technique with sevoflurane or propofol (7). The main find-

ing from this study was that anesthetic technique did not significantly affect peak postoperative release of troponin ($P = 0.4$) (7). The lack of clinical benefit from the promising cardioprotective properties of volatile agents in high-risk patients undergoing cardiac surgery shows the ongoing controversy on the optimal general anesthetic technique for cardiac surgery (8-10).

Furthermore, in noncardiac surgery, the recent first randomized trial ($N = 88$) to evaluate the cardioprotective outcome effects of volatile anesthesia failed to demonstrate any significant difference in postoperative peak troponin release ($P = 0.4$) (11).

Although the recent American College of Cardiology/American Heart Association Guidelines supported the choice of volatile anesthesia in patients at risk for myocardial ischemia in noncardiac surgery, further randomized trials are required to explore whether there is outcome benefit from this anesthetic technique in noncardiac surgery (12). In summary, the current evidence base is insufficient to delineate clearly the clinical relevance of the cardioprotective effects of volatile anesthetics.

Is Levosimendan a Life-Saving Drug in Cardiac Surgical Patients?

Recent meta-analysis have focused on outcome benefits of levosimendan in cardiac surgical patients (13, 14). Levosimendan significantly reduces troponin release after cardiac surgery (weighted mean difference 2.5 ng/dL; 95% confidence interval -3.86 to -1.14; $P = 0.0003$; cumulative $N = 139$ from 5 randomized trials) and postoperative mortality (odds ratio 0.35; 95% confidence interval 0.18-0.71; $P = 0.003$; cumulative $N = 440$ from 10 randomized trials) (13, 14).

A further meta-analysis focused exclusively on patients undergoing coronary revascularization, whether by percutaneous intervention or by CABG (cumula-

tive $N = 729$ from 17 studies) (15). This analysis demonstrated that levosimendan significantly reduced mortality (odds ratio 0.40; 95% confidence interval 0.21-0.76; $P = 0.005$), atrial fibrillation (odds ratio 0.54; 95% confidence interval 0.36-0.82; $P = 0.004$), and length of stay in the intensive care unit (mean difference = -26.18 hours; 95% confidence interval 46.20-6.16; $P = 0.01$) (15). The limitations of this meta-analysis included significant heterogeneity across the included studies, leading the investigators to suggest that further clinical trials are indicated to test the outcome effects of levosimendan in cardiac surgical patients (15, 16).

The promising cardioprotective outcome effects of levosimendan recently prompted a pilot clinical study comparing levosimendan to intra-aortic balloon counterpulsation in high-risk cardiac surgery patients undergoing CABG ($N = 22$) (17). Levosimendan was infused for 24 hours preoperatively in the intervention group while the control group received preoperative intra-aortic balloon counterpulsation. The main finding in this study was that the length of stay in the intensive care unit was reduced significantly by levosimendan therapy (median difference -2.5 days; $P = 0.01$). Based on these findings, the investigators have suggested that a large randomized trial is indicated to confirm these positive outcome effects (17).

The survival advantage from levosimendan exposure also appeared to extend to critical care. A recent meta-analysis (cumulative $N = 3350$ from 27 randomized trials) demonstrated that in critical ill adults levosimendan significantly reduced mortality (odds ratio 0.74; 95% confidence interval 0.62-0.89; $P = 0.001$) (18). Further meta-analysis (cumulative $N = 5480$ from 45 randomized trials) showed that in diverse adult cardiac surgical and cardiology settings, levosimendan significantly reduced

mortality (risk ratio 0.80; 95 % confidence interval 0.72-0.89; $P < 0.001$) and length of intensive care unit stay (weighted mean difference -1.31; 95 % confidence interval -1.95 to -0.31; $P = 0.007$) (19).

Levosimendan is a unique inodilator due to its calcium sensitizing properties in the myocardium and an associated array of pleiotropic effects (19). The evidence and consensus thus far suggest that levosimendan has life-saving effects in cardiovascular anesthesia and intensive care. This clinical momentum continues to inspire randomized trials and ongoing controversy (20, 21). A large recent randomized adult cardiac surgical trial ($N = 200$) confirmed that levosimendan reduced the risk of heart failure (risk ratio 0.26; 95 % confidence interval 0.16-0.43; $P < 0.001$) but demonstrated neither mortality nor morbidity benefits (20). It is likely that this study was underpowered to assess adequately for these outcome effects. Perhaps the time has come for a very large randomized multicenter trial to evaluate definitively whether levosimendan is a lifesaver after cardiac surgery. As in the case of volatile anesthetics, this is a major clinical research opportunity for the global cardiovascular anesthesia community.

Is Insulin Therapy a Lifesaving Intervention in Cardiac Surgical Patients?

Based on recent international consensus, perioperative insulin therapy in cardiac surgery was highly ranked as a possible lifesaving ancillary technique in cardiac anesthesia and intensive care (3). This recommendation was largely based on a single landmark randomized trial by van den Bergh and colleagues (22). Dr. van den Bergh has recently discussed this issue in an expert opinion article published in HSR Proceedings in Intensive Care and Cardiovascular Anesthesia (23). In this excellent article, the author highlights that the implementation of this perioperative strat-

egy is part of a package that entails multiple aspects including provider education and protocol development (23, 24). This translational process of a perioperative goal is a paradigm shift that is often required to overcome barriers to safe and effective implementation (23, 24). Controversy still persists about how tight glucose control should be in the perioperative period for adult cardiac surgical patients (25).

The benefits of insulin administration in cardiac surgery appear to extend beyond the avoidance of hyperglycemia (26). Tight monitoring and consecutive management of glucose, insulin and potassium (GIK) therapy in cardiac surgery appears cardioprotective (27). A recent large single-center randomized trial ($N = 217$ with a 4 year enrollment period) demonstrated that in patients undergoing aortic valve replacement, GIK therapy significantly reduced the risk of postoperative low cardiac output (odds ratio 0.22; 95 % confidence interval 0.15-0.60; $P = 0.0007$) and postoperative inotrope utilization (odds ratio 0.30; 95 % confidence interval 0.15-0.60; $P = 0.0007$) (28). These findings suggest that GIK therapy is perhaps much more than a refined energy source for the myocardium (29).

A recent meta-analysis (cumulative $N = 2113$ from 33 randomized trials) has also demonstrated that GIK therapy in cardiac surgery significantly reduced perioperative inotropic support (relative risk 0.66; 95 % confidence interval 0.45-0.96), the risk of low cardiac index (weighted mean difference 0.43; 95 % confidence interval 0.31-0.55), myocardial infarction (relative risk 0.63; 95 % confidence interval 0.42-0.95), and length of stay in the intensive care unit (weighted mean difference -7.96; 95 % confidence interval -13.36 to -2.55) (30). Further analysis in diabetic patients confirmed that they had benefit from GIK therapy with glycemic control in place (30). The investigators concluded that GIK ther-

apy was significantly cardioprotective in cardiac surgery.

The intriguing question is whether cardioprotective properties of GIK therapy may reduce mortality in cardiac surgery. Further adequately powered multicenter randomized trials are indicated to revise this hypothesis.

What are the Hemostasis Highlights in Cardiac Anesthesia and Intensive Care?

There has been considerable focus on blood management for cardiac surgery in 2011 with the publication of society guidelines and consensus statements (31, 32). The 2011 guideline update from the Society of Thoracic Surgeons and the Society of Cardiovascular Anesthesiologists included eight areas of major revision with respect to the 2007 guideline: management of preoperative dual antiplatelet therapy; drugs for blood volume expansion or hemostasis; utilization of diverse blood derivatives; blood salvage management; focus on minimally invasive procedures; blood conservation in extracorporeal circulation; topical hemostatic agents; and, team dynamics in blood management (31).

A detailed discussion of this important clinical document is beyond the scope of this article. It is likely that these recommendations will only gradually be integrated into clinical practice, taking into account the evidence base and the practice trend since the 2007 guideline (33, 34).

Recombinant activated factor VII (rFVIIa) has received considerable attention recently. Firstly, it may trigger intraoperative anaphylaxis which responds to aggressive conventional management (35). Secondly, a recent meta-analysis (cumulative N = 470 from 6 cardiac surgery trials) demonstrated that rFVIIa increased the risk of stroke (odds ratio 3.69; 95 % confidence interval 1.1-12.38; P = 0.03) and did not significant-

ly reduce the risk of surgical re-exploration (odds ratio 0.27; 95 % confidence interval 0.04-1.90; P = 0.19) (36). The investigators concluded that in light of this stroke risk, rFVIIa therapy should be reserved for refractory life-threatening bleeding in cardiac surgery (36).

Recent studies suggest that the therapeutic dose of rFVIIa therapy can be titrated to clinical effect in the setting of refractory bleeding. In pediatric cardiac surgery, the therapeutic dose for hemostasis appears to be age-dependent, with neonates requiring 131.7 ± 69.8 mcg/kg, infants 104.6 ± 36.0 mcg/kg and children aged 1 to 18 years 44.6 ± 15.3 mcg/kg (37). In this single-center retrospective series (N = 90), there was no evidence of thrombosis up to 24 hours after rFVIIa administration, despite the higher doses required in neonates and infants (37). In adult complex aortic surgery, low doses of rFVIIa (23.0 ± 12 mcg/kg) significantly reduced bleeding; blood component transfusion, duration of mechanical ventilation and risk of surgical re-exploration (38). There was no increase in thrombotic complications noted in this propensity-matched single center analysis (N = 56: 1999-2010) (38).

Furthermore, rFVIIa therapy can also be advantageous in the intensive care unit after complex cardiovascular surgery associated with refractory bleeding (39). A single-center clinical study demonstrated that rFVIIa therapy resulted in prevention of reoperation in 75 % of cases. As compared with surgical re-exploration, administration of rFVIIa had equivalent efficacy, safety and economic outcomes. The investigators concluded that this pilot data suggested that rFVIIa therapy may be a reasonable clinical alternative to surgical re-exploration for refractory bleeding after complex cardiovascular surgery. Further trials are essential to define the role of rFVIIa in this clinical scenario.

Although tranexamic acid is an established

antifibrinolytic agent in cardiac anesthesia and intensive care, its hemostatic role has only relatively recently received considerable attention in noncardiac surgery. An example is a recent randomized trial (N = 200 at a single university hospital) in adults undergoing radical retropubic prostatectomy that demonstrated a significant reduction in the transfusion risk associated with tranexamic acid exposure (relative risk 0.62; 95 % confidence interval 0.45-0.85; $P = 0.004$) (40). Based on the proceedings of a recent transfusion consensus conference, tranexamic acid therapy has also become a recommended early medical intervention in the response to massive bleeding in trauma (41). Recent meta-analysis suggests that this antifibrinolytic drug also has hemostatic efficacy in total knee replacement, significantly reducing the risk of blood transfusion (relative risk 2.56; 95 % confidence interval 2.1-3.1; $P < 0.001$) (42). The hemostatic efficacy of tranexamic acid can also significantly enhance the quality of the surgical field during endoscopic sinus surgery (43). While the hemostatic benefit of tranexamic acid gains raising interest as a perioperative intervention throughout noncardiac surgery procedures, it remains important for clinical investigators to balance its risks and benefits, while consequently monitoring the considerable trial's experience in cardiac surgery for applicable solutions. As an example, high-dose tranexamic acid has recently been identified in multiple studies as a risk factor for seizures after cardiac surgery, particularly in the setting of renal dysfunction (44-48). Furthermore, high-dose therapy does not always appear to offer greater hemostatic benefit (46).

Noninvasive Ventilation in Cardiac Anesthesia and Intensive Care

The application of noninvasive ventilation (NIV) in various forms has received considerable recent attention in the practice

of cardiovascular anesthesia and intensive care (49). The role of NIV has recently been described in the conduct of transcatheter aortic valve implantation (50-52). A recent single academic center series (N = 126: 2006-2010) demonstrated that in patients undergoing transfemoral aortic valve implantation, the application of regional anesthesia and sedation, as compared to general anesthesia, was associated with significant reductions in procedure duration, intraprocedural volume expansion, intraprocedural catecholamine requirement, postprocedural peak serum creatinine, and hospital stay ($P < 0.005$ overall) (52). Although this was a single center retrospective study, it does provide suggestive data that in selected patients undergoing transfemoral aortic valve implantation, the avoidance of general anesthesia and endotracheal intubation offers significant clinical advantages.

The clinical utility of NIV after cardiac surgery was recently evaluated in a single university medical center series (53). The incidence of NIV in the intensive care unit was 5.1 %, typically applied about 40 hours after tracheal extubation (range 18-96 hours). Lobar atelectasis was the most frequent indication for NIV in this setting. The failure rate of NIV in this series was 52.4 %, with a time interval < 24 hours from tracheal extubation to NIV significantly predicting the risk of repeat tracheal intubation (odds ratio 4.6; 95 % confidence interval 1.2-17.9) (53). Although NIV is an effective respiratory intervention for rescue from repeated endotracheal intubation after cardiac surgery, patients who fail NIV in this setting still suffer from a significantly higher mortality risk (53, 54). This mortality risk is most likely secondarily related to the severity of the underlying cardiopulmonary disease.

The clinical utility of NIV after lung surgery was recently evaluated in a single academic center series (55). The incidence of NIV was 20.3 % with a 29.6 % failure rate. Sig-

nificant predictors for NIV failure included increased respiratory rate (odds ratio 4.17; 95% confidence interval 1.63-10.67), increased sequential organ failure assessment score (odds ratio 3.05; 95% confidence interval 1.12-8.34), number of performed fiberoptic bronchoscopies (odds ratio 1.60; 95% confidence interval 1.01-2.54), and hours spent on NIV (odds ratio 1.06; 95% confidence interval 1.01-1.11) (55). Pneumonia was the leading cause of NIV failure and resulted in a significant mortality risk ($P < 0.0001$), again highlighting the underlying disease rather than NIV failure as the etiology of this additional mortality (55). The application of NIV in lung transplantation remains an important perioperative intervention to decrease the risk of nosocomial pneumonia in patients who are immunosuppressed (56). Despite demonstrated benefit of NIV in cardiovascular anesthesia and intensive care, further trials are required to fully delineate the net outcome advantages in the perioperative period (57).

Roland Hetzer International Cardiothoracic and Vascular Surgery Society

The Roland Hetzer International Cardiovascular and Vascular Surgery Society (RHICS) was founded on May 20th 2011 by cardiothoracic and vascular surgeons from all over the world to honor the achievements of this remarkable German surgeon, educator, leader and innovator (58). The four main objectives of the RHICS are as it follows:

- 1) provide a forum for expert discussion about the practice of cardiothoracic and vascular surgery;
- 2) promote individualized patient-based treatment approaches in cardiothoracic and vascular practice;
- 3) promote continuing medical education through regular meetings;
- 4) foster international collaboration in the Pursuit of Excellence in Cardiothoracic and Vascular Surgery (58).

The first expert forum of the RHICS was held on October 1st 2011 in Lisbon, Portugal (59). This first meeting had two main sessions, namely 'current status of coronary revascularization' and 'current status of allied health professionals: issues and concerns'. The expert opinions expressed in this first meeting of the RHICS are published in the final 2011 issue of this journal. The second expert forum of the RHICS is planned for February 12, 2012 in Freiburg, Germany (59). This international society with its clear objectives and regular symposia has great promise to further clinical excellence in the practice of cardiovascular anesthesia and intensive care.

CONCLUSION

The past year has witnessed major advances in the practice of cardiovascular anesthesia and intensive care. Perioperative interventions such as anesthetic design, choice of inotrope, glycemic therapy, blood management, and noninvasive ventilation have significant potential to enhance perioperative outcomes for our patients. The time has now arrived for large adequately powered multicenter trials to test whether prioritized perioperative interventions truly reduce mortality and morbidity in cardiac surgical patients. This essential paradigm shift represents a major clinical opportunity for the global cardiovascular anesthesia and critical care community.

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