REVIEW ARTICLE

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Major Themes for 2010 in Cardiothoracic and Vascular Anesthesia

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ABSTRACT

Significant variability in transfusion practice persists despite guidelines. Although the lysine analogues are effective antifibrinolytics, safety concerns exist with high doses tranexamic acid. Despite recombinant activated factor VII promising results in massive bleeding after cardiac surgery, it significantly increases arterial thromboembolic risk. Aortic valve repair may evolve to standard of care. Transcatheter aortic valve implantation is an established therapy for aortic stenosis. The cardiovascular anesthesiologist features prominently in the new guidelines for thoracic aortic disease. Although intense angiotensin blockade improves outcomes in heart failure, it might aggravate the maintenance of perioperative systemic vascular tone. Ultrafiltration is an alternative to diuresis for volume overload in heart failure. Management of heart failure titrated to brain natriuretic peptide activity reduces mortality. A major surgical advance has been the significant outcome improvement achieved with continuous-flow left ventricular assist devices. Advanced liver disease is a significant predictor for perioperative bleeding, transfusion and mortality after ventricular assist device insertion. Acquired von Willebrand syndrome is not only common in patients with these devices but often aggravating bleeding and transfusion in this setting. Metabolic myocardial modulation with perhexilene significantly enhances effort tolerance in hypertrophic cardiomyopathy. A landmark report has highlighted future priorities in this disease. Pediatric cardiac surgical trials have revealed the importance of perioperative cerebral oxygen saturation monitoring and the Sano shunt. Advances in pediatric-specific ventricular assist devices will likely revolutionize pediatric heart failure. Recent reports have highlighted the priorities for future perioperative trials and for training models in pediatric cardiac anesthesia.

Keywords: *aortic valve, aortic valve repair, transcatheter aortic valve implantation, thoracic aorta, guidelines, endovascular aortic repair, aortic dissection, aortic aneurysm, heart failure, ventricular-assist device, angiotensin; ultrafiltration, natriuretic peptide, model for end-stage liver disease, von Willebrand syndrome, hypertrophic cardiomyopathy, perhexilene, metabolic modulator, cerebral oxygen saturation, near-infrared spectroscopy, Norwood procedure, Sano shunt, Blalock-Taussig shunt, congenital heart disease, perioperative management.*

INTRODUCTION

This article is the second in an annual series for HSR proceedings in Intensive Care and Cardiovascular Anesthesia (1) and we thank the editorial board for this ongoing opportunity to discuss the major themes of the past year in the specialty of cardiovascular anesthesia.

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The 2010 highlights in cardiothoracic and vascular anesthesia commence with the ongoing progress in bleeding and transfusion after cardiac surgery.

ADVANCES IN TRANSFUSION

Variability in Transfusion Practice

Although there are guidelines for transfusion in cardiac surgery, considerable variability has persisted in clinical practice (2-4). A large observational study (N = 102 470 in 798 US medical centers during 2008) documented significant variation in perioperative transfusion for patients undergoing coronary artery bypass grafting (CABG) with cardiopulmonary bypass (CPB) (3). Multivariate predictors of hospital transfusion rates included geographic location (P = 0.007), academic status (P = 0.03) and hospital volume (P < 0.001) (3). This variability also exists in pediatric transfusion practice (5) and in anticoagulation management for CPB (6). Given this significant practice variation, the opportunity exists to determine whether clinical outcomes after cardiac surgery correlate with these hospital differences in perioperative practice of cardiac surgery.

A recent randomized controlled trial has already demonstrated that restrictive perioperative transfusion does not result in inferior clinical outcomes after cardiac surgery (7). Transfusion burden may in the future be interpreted as a quality indicator in cardiac surgery that must balance risks and benefits to achieve cost-effective optimal clinical outcomes (8). Perioperative transfusion algorithms can assist in preserving blood bank resources with no compromise of patient safety (9).

Advances in Hemostasis

The lysine analogues, tranexamic acid and aminocaproic acid, significantly reduce allogeneic blood transfusion after cardiac surgery, including off-pump CABG (10, 11). High doses tranexamic acid therapy, however, could be associated with perioperative complications, including mortality, seizures and stroke (12-16). Recent comparisons between the 2 lysine analogues both in pediatric and cardiac surgery have documented equivalent hemostatic efficacy with aminocaproic acid being cheaper and free from neurological complications (17, 18).

On top of his established use in cardiac surgery, tranexamic acid has a role in the management of massive hemorrhage and transfusion (19) and a recent large randomized trial with significant hemorrhage (N = 20 211: 274 hospitals in 40 countries) demonstrated that tranexamic acid significantly reduced all-cause mortality in trauma patients (relative risk 0.91; 95 % confidence interval 0.85 - 0.97; P = 0.0035) (20).

The safety and efficacy of tranexamic acid in acute trauma was also confirmed in recent meta-analysis (21). Future antifibrinolytic trials in cardiac surgical patients should be adequately powered to compare the lysine analogues for efficacy and safety related to meaningful clinical end-points (22).

Although rescue therapy with recombinant activated factor VII can be life-saving in massive bleeding after cardiac surgery, its safety has been questioned (19). A recent meta-analysis (N = 4468 from 35 randomized trials) demonstrated that this therapy significantly increased the rate of arterial but not venous thromboembolic events (23). This arterial thrombotic risk was particularly higher in patients older than 65 years of age (9.0 % versus 3.8 %; P = 0.003) (23). Given its cost and arterial thrombotic risk, it is likely that this hemostatic intervention will continue to be reserved for life-saving therapy of massive coagulopathy after cardiac surgery.

PROGRESS IN THE AORTIC VALVE

Aortic Valve Repair

Aortic valve repair for aortic regurgitation has matured with the development of a systematic classification of aortic regurgitation based on leaflet mobility within the functional aortic annulus (24, 25). The functional aortic annulus consists of the aortoventricualr junction, the aortic valve, the sinuses of Valsalva and the sinotubular junction (24, 25). A recent review has explored this classification and outcomes of these procedures in detail (24). Furthermore, these principles for aortic valve repair have demonstrated clinical efficacy for bicuspid aortic valves and the neoaortic root after the Ross procedure (25, 26). Since comprehensive intraoperative transesophageal echocardiography (TEE) has a central role in decision-making for these procedures, the intraoperative echocardiographer remains an indispensable clinical team member (24-27). It is likely that aortic valve repair will evolve into a standard of care in the near future, as has already happened for mitral valve repair.

Transcatheter Aortic Valve Implantation (TAVI)

The anesthetic management for TAVI has recently been thoroughly reviewed (28, 29). Recent case series have highlighted the utility of conscious sedation as an anesthetic option in TAVI (30, 31).

The reliability of TEE over computed tomography for crucial aortic annular measurements was also confirmed recently (N = 187) (32). In this clinical series, TEE data altered the TAVI procedure in 15.5 % of patients with no increase in clinical complications (32). It is clear that the frequent central role of TEE in TAVI anchors the echocardiographer as an essential TAVI team member, in a fashion analogous to aortic valve repair.

Risk assessment in TAVI remains a challenge since current scoring systems tend to overestimate procedural risk (33, 34). A landmark randomized controlled trial recently showed that TAVI is significantly superior to medical management of severe aortic stenosis in patients judged to be at excessive risk for conventional aortic valve replacement(N = 358: 21 participating centers) (35). In this trial, TAVI significantly reduced all-cause 1-year mortality [30.7 % versus 50.7 %; hazard ratio 0.55; 95 % confidence interval 0.40-0.74; $P < 0.001$] but with the perioperative risks of stroke [5.0 % versus 1.0 %; $P = 0.06$] and vascular compromise [16.2 % versus 1.1 %; $P < 0.001$] (35). Although clinical stroke is unusual in TAVI (1-3 %), recent studies have documented rates of cerebral embolism of 70 -80 % (35-37). Future trials should focus on interventions for stroke reduction after TAVI, including cerebral embolic protection. Furthermore, techniques for reduction of embolic load may also improve renal dysfunction after TAVI.

Although TAVI already has an established clinical niche, the durability of the valve has yet to be conclusively demonstrated beyond the short-term. In a recent TAVI series (N = 70: 2005-2006), the bioprosthetic valve demonstrated adequate durability in the medium term with preserved hemodynamics and absence of structural deterioration (38). Clearly, further studies are required to elucidate the long-term integrity and hemodynamic of TAVI prostheses, particularly as new devices are approved for commercial application. To this end, a valve consortium has recently published guidelines for standardized endpoints in TAVI trials (39).

Advances in Diseases of the Thoracic Aorta

Multidisciplinary guidelines for thoracic aortic diseases were published in 2010 (40).

Although a detailed discussion of this publication is beyond the scope of this annual review, it is essential to highlight the areas that concern perioperative cardiovascular practice. The 4th section discusses imaging techniques, including TEE.

This section emphasizes the significant role of TEE in the perioperative diagnosis and management of thoracic aortic disease. The 5th section reviews genetic syndromes associated with aortic aneurysm and dissection. This section is relevant because surgical decision-making in these aortopathies depends on echocardiographic features such as aortic diameter and the presence of dissection.

The 6th section highlights the ealier surgical intervention required for ascending aortic dilation in the setting of a bicuspid valve to aviod rupture or dissection. Therefore, it is essential to measure the ascending aorta diameter in patients with bicuspid aortic valves presenting for surgical aortic intervention. The eighth section is dedicated to acute aortic syndromes including aortic dissection. The Penn classification of type A dissection integrates type of clinical presentation with dissection extent to stratify perioperative outcome and facilitate decision-making about the type of surgical repair (41). As an example, a type A dissection involves the descending thoracic aorta (Debakey type I) could be managed with endovascular stenting at the time of aortic arch repair for obliteration of the false lumen in the descending thoracic aorta and significant freedom from subsequent thoracoabdominal aneurysm (42).

The 9th section reviews the management of aortic aneurysm. Hybrid repair of aortic arch aneurysms has emerged as low risk aortic repair in high-risk patients (43). Type I repairs have adequate proximal and distal landing zones: after off-pump anastomosis of the brachiocephalic vessels to the ascending aorta, an endovascular stent is deployed for complete arch repair. Type II repairs have adequate distal landing zone but insufficient ascending aorta to serve as a proximal stent landing zone: after ascending aortic replacement with aortic arch debranching, an endovascular stent is deployed for complete arch repair with the ascending aortic graft serving as the proximal landing zone. Type III repairs have inadequate proximal and distal landing zones: after total arch replacement with a distal elephant trunk, the descending thoracic aortic repair is completed by endovascular stenting with the elephant trunk serving as the proximal landing zone (43).

The 10th section covers the rare but important possibility of thoracic aortic diseases in the parturient. The 14th section reviews the perioperative care of patients with thoracic aortic diseases and therefore is recommended reading.

The American Heart Association recently published a position paper on the integrated management of descending thoracic aortic diseases that complements the recent guidelines from the Society of Thoracic Surgeons (44, 45). These guidelines together summarize the paradigm shift in the management of descending thoracic aorta pathologies due to endovascular therapies (44, 45).

In Stanford type B aortic dissection, the interventional management of patients presenting with refractory pain and hypertension has varied (46). A recent analysis (N = 365: 1996-2004) demonstrated that these presentations significantly correlated with short-term mortality [odds ratio 3.31; 95 % confidence interval 1.04-10.45; P = 0.041] (46).

These data provide a compelling indication for endovascular intervention of these type B dissection presentations (46). Although endovascular intervention is indicated in complicated presentations, randomized trials to date have not demonstrated a survival

advantage for uncomplicated presentations in acute type B dissection (47).

Advances in Heart Failure

The cardiology subspecialty of heart failure has matured as evidenced by the recent guidelines for clinical competency in this subspecialty (48). The medical management of heart failure continues to evolve. A recent randomized controlled trial (N = 3846: 255 sites from 30 countries) revealed that high-dose angiotensin blockade significantly improved survival and freedom from hospital admission for heart failure [hazard ratio 0.90; 95 % confidence interval 0.82-0.99; P = 0.027] (49). It remains important to discontinue angiotensin blockade prior to cardiac surgery to avoid adverse outcomes (50). If this is not possible, an alternative intervention is low-dose perioperative vasopressin therapy for maintenance of systemic vascular tone (51).

Mechanical removal of excess body fluid with ultrafiltration is an alternative to aggressive diuretic therapy for acute heart failure associated with volume overload (52). Contemporary data from a small trial (N = 200) demonstrated that ultrafiltration not only enhanced net fluid removal but also significantly rehospitalization for heart failure (53). In cirrhotic patients undergoing cardiac valve surgery, ultrafiltration significantly decreased bleeding, postoperative mechanical ventilation and hospital stay (P≤0.001) (54). Although ultrafiltration is beneficial in heart failure, further trials are required to develop its indications in the spectrum of conditions associated with heart failure (55).

Since B-type natriuretic peptide correlates with the severity of heart failure, it will likely be integrated into the management of heart failure. Medical management of advanced heart failure guided by this biomarker significantly enhanced short-term (P = 0.03) and mid-term (P≤0.04) survival (56). A recent meta-analysis has also revealed the perioperative predictive power of this biomarker in noncardiac surgery (57-59). Future trials should evaluate whether integration of this biomarker into risk stratification reduces perioperative mortality.

Although left ventricular assist devices (LVADs) are established as mechanical therapy for heart failure, the search for the optimal device continues. A recent multicenter trial (N = 200) revealed that continuous-flow LVADs are superior to pulsatile-flow devices in the long-term due to significant gains in freedom from device failure and stroke [46 % vs 11 %; hazard ratio 0.38; 95 % confidence interval 0.27-0.54; P < 0.001] (60). Furthermore, patient survival at 2 years was also significantly improved [58 % vs 24 %; P = 0.008] (60).

This advance in LVAD technology represent s a paradigm shift in mechanical therapy for heart failure that will likely disseminate this intervention to an even greater extent.

Since liver dysfunction affects bleeding risk and perioperative outcome, it is reasonable to expect that the model for end-stage liver disease (MELD) score would corerelate with these parameters in LVAD recipients. A recent clinical trial (N = 535) has demonstrated that for each 5 MELD units, the risk of perioperative mortality increased significantly (odds ratio 1.5; 95 % confidence interval 1.1.-2.0) and perioperative blood product exposure increased by 15.1 ± 3.8 units. Based on the results of this large study, it is clear that advanced liver disease is a significant risk factor for perioperative mortality, bleeding and transfusion burden.

A second determinant of bleeding and transfusion in LVAD recipients is acquired von Willebrand syndrome (61). Recent clinical investigations have demonstrated that the incidence of this syndrome is al-

most 100 % in VAD recipients (62, 63). While further research is required in this area, this coagulopathy can be managed with desmopressin and von Willebrand factor concentrates (64).
Furthermore, the incidence of this acquired coagulopathy will likely reduce the levels of anticoagulation in VAD patients, especially those bleeding complications (65).

Progress in Hypertrophic Cardiomyopathy

Hypertrophic cardiomyopathy (HCM) has an estimated prevalence of 0.2 % (66). The are multiple patterns of hypertrophy including asymmetrical septal hypertrophy with or without an outflow tract gradient (67). Besides medical management, interventional management options for HCM include a pacemaker, alcohol septal ablation, septal myectomy and mitral valve repair (66-68).
Based on myocardial magnetic resonance imaging, it has been established that the energy metabolism of the heart is disordered in HCM. The consequent energy deficiency may feature prominently in the pathophysiology of HCM (69, 70). Recent data has suggested that perhexilene, a myocardial metabolic modulator, may significantly improve myocardial energetics and enhance effort tolerance ($P < 0.001$) in HCM (71). This type of approach may usher in a paradigm shift in the medical management of HCM. Future trials will likely yield a broader understanding of this heterogeneous disease.
A recent report from the National Institute of Health highlighted future as clinical, translational, and basic research possibilities in this important and common disease (72). The report recommended further definition of genetic etiologies of HCM, further prospective study of the natural history of HCM, and encouragement of randomized trials for evaluation of novel therapies. It is likely that HCM will generate considerable research interest.

Progress in Pediatric Cardiac Anesthesia

Cerebral oxygen saturation by near-infrared spectroscopy (NIRS) has become widespread during cardiopulmonary bypass (73, 74). A recent landmark trial ($N = 104$: 86 % one year follow-up) demonstrated that persistent intraoperative cerebral desaturation below 45 % during infant heart surgery strongly predicted ($P = 0.04$) the occurrence of psychomotor delay associated with abnormal brain imaging (75).
This observation suggests that frequent monitoring of cerebral oxygen saturation in congenital heart surgery may lead to improved outcomes. Although further trials are indicated, it is likely that standardized monitoring for the brain during cardiopulmonary bypass will evolve in the near future. This is an important research opportunity.
The surgical approach to hypoplastic left heart syndrome has 3 stages (76). Stage I repair, known as the Norwood procedure, involves connection of the right ventricle to a neoaorta fashioned from the pulmonary artery. Pulmonary blood flow is established either by a modified Blalock-Taussig (MBT) shunt (connection by vascular graft from the pulmonary artery to the subclavian or innominate artery) or a Sano shunt (connection by vascular graft from the right ventricle to the pulmonary artery) (76). Stage II repair is characterized by shunt removal and anastomosis between the superior vena cava and the pulmonary artery to establish pulmonary blood flow. Stage III repair, known as the Fontan procedure, involves connection of the inferior vena cava to the pulmonary artery for complete separation of the pulmonary and systemic circulations (76).
The outcome effects of shunt type (MBT

versus Sano) were recently evaluated in a landmark randomized trial (77). This multicenter trial (N = 549: 275 MBT shunt and 274 Sano shunt: 15 North American centers) revealed that the transplantation-free survival was significantly higher in the Sano shunt cohort (74 % vs 64 %; P = 0.01). The Sano shunt, however, was associated with significantly more interventions (P = 0.003) and complications (P = 0.002). There was no significant outcome difference in transplantation-free survival between shunt types in the intermediate term. Further careful cohort follow-up is indicated to evaluate for outcome differences in the long-term.

This trial was conducted by the Pediatric Heart Network, established as a collaborative platform for the conduct of large trials in congenital heart surgery (78). There is also an adult cardiothoracic surgical network as a clinical platform for important trials in the operating room (full details of trials available at www.clincialtrials.gov) (78, 79).

A recent review of the USA pediatric VAD experience demonstrated that in 2006 187 children received a VAD (mean age 13 ± 7 years) (80). The in-hospital mortality rate was 30 % with a median length of stay = 29 days. The bridge to heart transplantation rate was 26 %. Independent predictors for mortality in this series included acute renal failure and the use of extracorporeal membrane oxygenation. Heart transplantation and therapy at a high-volume large teaching hospital were associated with a significant survival advantage (80). This profile of recent USA pediatric VAD experience will likely evolve as new VADs enter pediatric practice.

The working group of the Pediatric Heart Network have recently published a report on the perioperative management of congenital heart disease (81). The first challenge described was the deleterious outcome effects of cardiopulmonary bypass. In this first domain, the research group emphasized the imperative for randomized trials in neuroprotection (81-83). As an example, a randomized trial is required to assess whether deep hypothermic circulatory arrest or regional cerebral perfusion optimizes brain protection after pediatric aortic arch reconstruction. The remaining 3 domains discussed were the role of genetics, advances in devices and technologies, as well as variations in perioperative practice and quality.

Considerable progress has taken place in pediatric cardiac anesthesia. A working group of the Congenital Cardiac Anesthesia Society has recently published a proposal for fellowship training (84). The future for pediatric cardiac anesthesia appears full of promise.

CONCLUSIONS

The 2010 highlights in cardiothoracic and vascular anesthesia commence with the ongoing progress in bleeding and transfusion after cardiac surgery. Significant variations in transfusion practice persist despite the current guidelines. Although the lysine analogues, tranexamic acid and aminocaproic acid, are effective antifibrinolytics, recent data has raised safety concerns with high doses tranexamic acid.

Despite its off-label use in severe coagulopathy after cardiac surgery, recombinant activated factor VII significantly increases the risk of arterial thromboembolism, especially in the elderly.

Aortic valve repair has matured and is set to develop towards a standard of care. Transcatheter aortic valve implantation has become an established intervention for the management of high-risk aortic stenosis.

The endovascular revolution contributed significantly to the development and recent

publication of comprehensive multidisciplinary guidelines for diseases of the thoracic aorta. The roles of the cardiovascular anesthesiologist and perioperative echocardiographer feature prominently in these landmark guidelines. The role of endovascular intervention will likely contribute significantly to the evolving classifications and management options of thoracic aortic diseases.

Advances in heart failure have been both medical and surgical. Although intense angiotensin blockade improves outcomes in heart failure, it might further complicate the maintenance of systemic vascular tone in the perioperative period. Ultrafiltration is a promising alternative to pharmacologic diuresis for the management of volume overload in heart failure. It is also apparent that medical management of heart failure titrated to brain natriuretic peptide activity reduces mortality.

A major surgical advance in heart failure has been the significant outcome improvement achieved with continuous-flow left ventricular assist devices. Furthermore, advanced liver disease as reflected by the model for end-stage liver disease score is a significant predictor for perioperative bleeding, transfusion and mortality after ventricular assist device insertion. Acquired von Willebrand syndrome is not only common in patients with these devices but is frequently an aggravating factor in bleeding requiring transfusion in this setting.

The integrated management of hypertrophic cardiomyopathy has continued to evolve. Metabolic myocardial modulation with perhexilene improves myocardial diastolic energetics to achieve significant symptomatic improvement in hypertrophic cardiomyopathy. A landmark report was also recently published that outlines the major areas for future research and clinical innovation in this disease.

The perioperative management of congenital cardiac disease has progressed significantly. Landmark trials have documented the outcome importance of perioperative cerebral oxygen saturation monitoring and the outcome advantages of the Sano shunt in the Norwood procedure.

Furthermore, the advances in pediatric-specific ventricular assist devices will likely revolutionize the mechanical management of pediatric heart failure. Recently reports have highlighted the priorities for future perioperative trials and for training models in pediatric cardiac anesthesia.

The coming year most likely will be focused more and more on clinically relevant outcomes as suggested by the recently published international consensus conference on the reduction in mortality in cardiac anesthesia and intensive care (85, 86).

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