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Special Article

What's New in Cardiopulmonary Bypass

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This is a narrative review of recent articles (mainly published in 2017 and 2018) related to the conduct of cardiopulmonary bypass (CPB) that should be of interest to the cardiac anesthesiologist. Some of the topics covered include recent guidelines on temperature management, anticoagulation, perfusion practice, use of transesophageal echocardiography during CPB, optimal mean arterial pressure, vasoplegia, bleeding, perioperative anemia, post-cardiac surgery transfusion, acute kidney injury, delirium and cognitive decline, CPB during pregnancy, lung management, radial-to-femoral artery pressure gradients during CPB, prophylactic perioperative intra-aortic balloon pump, del Nido cardioplegia, antibiotic prophylaxis, and use of levosimendan in cardiac surgery. The review concludes with a perspective on the effect of these development on the practice of cardiac anesthesia.

Key Words: cardiopulmonary bypass; activated coagulation time; tranexamic acid; transesophageal echocardiography; vasoplegia; kidney injury; delirium; cognitive decline

CARDIAC SURGERY USING cardiopulmonary bypass (CPB) was first accomplished by John Gibbon Jr more than 65 years ago on May 6, 1953, but was first used routinely by John Kirklin and CW Lillehei in the spring of 1955 and became used by many groups during the next year, including by my mentor, K Alvin Merendino at the University of Washington, who initiated the first series of successful cardiac surgery using CPB on the West Coast of the United States.[1]

Many advances in the conduct of CPB and cardiac anesthesia have occurred since then. Some of these include hemodilution; membrane oxygenators; centrifugal pumps; biocompatible and miniaturized circuits; microfiltration; objective heparin monitoring; tepid cooling; alpha-stat pH management; and the use of transesophageal echocardiography (TEE), pulmonary artery catheters, and cerebral oximetry.[2] However, very little of how CPB is practiced, even today, is supported by a high level of evidence (eg, randomized controlled trials [RCTs]).[3,4]

The objective of this article is to provide a subjective (the author's opinion) review of recent publications and developments related to the conduct of CPB, mainly as it relates to adult cardiac surgery. This is an update of a refresher course lecture that I presented at the 40th Annual Meeting of the Society of Cardiovascular Anesthesiologists (SCA) in Phoenix, AZ, on April 28, 2018. It also represents an update of material in 2 recent textbooks related to CPB that were edited by Gravlee et al.[5,6]

Nonsurgical Strategies to Reduce Mortality in Patients Undergoing Cardiac Surgery

Based on a multinational consensus conference that reviewed the published literature, Landoni et al. identified 10 interventions that they concluded may reduce mortality after cardiac surgery and 1 intervention (aprotinin) that may increase mortality.[7] The interventions that they concluded may reduce mortality included prophylactic intra-aortic balloon pump (IABP), levosimendan, leuko-depleted red blood cell (RBC) transfusion, tranexamic acid (TXA), and use of volatile agents. Some of these interventions will be reviewed subsequently.

Temperature Management During CPB

In the past, CPB mostly was conducted using moderate systemic hypothermia (~28°C-32°C) in order to deal with the limited capacity of early oxygenators, and presumably

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1053-0770/

improved systemic and myocardial tolerance to potential ischemia. More recently the trend has been to use normothermia or "tepid"/"drift" mild hypothermia (~34°C-36° C). There remains some controversy about in which location temperature should be monitored, how arterial pH and partial pressure of carbon dioxide should be managed during hypothermia, and acceptable cooling and warming gradients. These issues have been addressed by recent Society of Thoracic Surgeons (STS)/SCA/American Society of Extracorporeal Technology (AmSECT) guidelines on temperature management during CPB.[8] These are summarized in Table 1.

Use of TEE During CPB

TEE has become an essential part of the conduct of cardiac surgery to diagnose and quantify lesions and assess results of surgical interventions. Not widely appreciated is the important role TEE plays in the conduct of CPB. For this reason, I advocate its use in all cases of CPB (in the absence of any contraindications). However, this is not based on a high level of evidence. A list of possible roles of TEE in the conduct of CPB are provided in Table 2.

Furthermore TEE is not free of risk, and this must be taken into consideration. In a retrospective analysis of 7,954 cardiac surgical patients who underwent intraoperative TEE, Purza et al. found that 1.4% of patients had possible complications, although no deaths were attributed to these complications.[9] The most common complications included gastric or esophageal inflammation; ulcers; bleeding (0.9%), including Mallory-Weiss syndrome (0.05%); dysphagia/odynophagia (0.3%); and vocal cord palsy (0.1%). Multivariate analysis showed an increased risk of complications associated with age, body mass index (BMI), previous stroke, procedures other than isolated coronary artery bypass grafting (CABG), and CPB time.

Dysphagia after cardiac surgeries was reviewed earlier by Hogue et al.[10] The incidence of dysphagia was 4%, and it was associated with aspiration in 90%. Patients with dysphagia had increased incidence of pneumonia, tracheostomy, and intensive care unit (ICU) and hospital length of stay (LOS). Risk factors for dysphagia included age, length of intubation, and use of TEE (incidence of dysphagia was twice as high in these patients). Others have reported an incidence of dysphagia after cardiac surgery involving the use of TEE of 0.3%, 7.9%, and 39.8%.[9,11,12] Rousou et al. found this incidence to be twice as high (7.9% *v* 1.8%) in those who had TEE versus those who did not.[11]

In an RCT of patients who underwent cardiac surgery, the TEE probe was left in place throughout surgery in half of the patients (group I), whereas in the other group (group II) the TEE probe was removed after initial examination, then reinserted for restudy before weaning from CPB, and then immediately removed.[12] The TEE probe was in the esophagus for about 201 minutes (interquartile range [IQR] 190-240) in group I and 70 minutes (IQR 50-95) in group II. The incidence of dysphagia was nearly twice as high in the long duration group (group I) (51% *v* 29%).

In a provocative essay, Ivascu and Meltzer addressed the common practice in academic medical centers for 1 or more trainees to conduct a TEE examination primarily for teaching purposes.[13] Because this practice may be associated with possible increased risk, these authors advocated for informing patients that multiple TEE examinations for teaching purposes may be performed.

STS/SCA/AmSECT Clinical Practice Guidelines for Anticoagulation During CPB

Guidelines for anticoagulation during CPB developed by the STS, SCA, and AmSECT recently were published.[14] I believe these should be reviewed in detail by all cardiothoracic anesthesiologists. The document provides 17 guidelines. However, like many other clinical practice guidelines, the level of evidence supporting them generally was not strong; none was supported by level A evidence, and most (11) were supported by only level C evidence. Some of the more important recommendations are summarized in Table 3. In addition to the guidelines themselves, the information provided in the discussion in these guidelines is most educational.

Activated Coagulation Time Target for CPB

The optimal target for activated coagulation time (ACT) remains unclarified, and there is no consensus, partly owing to a lack of high-level evidence, resulting in great variability of

Table 1
Temperature Management During CPB (STS, SCA, AmSECT Guidelines)

1. Oxygenator arterial outlet temperature is the recommended surrogate for cerebral temperature (class I recommendation, level C evidence)
2. Oxygenator arterial outlet temperature is assumed to underestimate cerebral temperature (class I, level C)
3. Nasopharyngeal or pulmonary arterial temperatures are reasonable estimates of core temperature after weaning from CPB (class IIa, level C)
4. Arterial outlet temperature should be no higher than 37°C during CPB to prevent cerebral hyperthermia (class I, level C)
5. Peak cooling temperature gradient between the oxygenator arterial outlet and venous inlet should not exceed 10°C to prevent the generation of gaseous emboli (class I, level C)
6. Peak warming temperature gradient between the oxygenator arterial outlet and venous inlet should not exceed 10°C to prevent outgassing (class I, level C)
7. During warming, when oxygenator arterial outlet temperature ≥30°C, the warming gradient between the oxygenator arterial outlet and venous inlet should be ≤4°C and/or warming rate ≤0.5°C/min (class IIa, level B)

Abbreviations: AmSECT, American Society of Extracorporeal Technology; CPB, cardiopulmonary bypass; SCA, Society of Cardiovascular Anesthesiologists; STS, Society of Thoracic Surgeons.
Modified from Engelman et al.[8]

Table 2
Role of TEE in the Conduct of CPB

A. Pre-bypass
1. Detect anatomic abnormalities that could affect conduct of CPB
   a. Access aorta for atherosclerosis (TEE and epi-aortic)
   (I and others recommend obtaining epiaortic examinations in all patients >50 years old or at least if they show evidence of significant atherosclerosis in ascending, transverse, or proximal descending aorta, if surgeon agrees and will act on this information)
   b. Aortic regurgitation
   c. ASD/PFO (2-dimensional imaging, color flow imaging, saline ± Valsalva maneuver)
   d. Large coronary sinus (if >11 mm may be a clue to presence of a persistent left superior vena cava)
   e. PDA
   f. Large Eustachian valve, prominent Chiari network, or right-sided cor triatriatum
2. Detect intracardiac devices (eg, electrodes) or masses (thrombi, vegetations, tumors) that could affect cannulation

B. In preparation for using CPB
1. Ensure proper placement of the following:
   a. Venous cannulas, especially those placed via peripheral sites (eg, from femoral vein into right atrium); first confirm that guidewire is in the R atrium and then the proper location of the tip of the cannula in the atrium
   b. Retrograde cardioplegia cannula in coronary sinus
   c. LV vent
   d. Left atrial cannula (eg, for left-sided heart bypass)
   e. Femoral artery inflow cannula (confirm that guidewire is intraluminal in descending aorta)
   f. IABP

C. During CPB
1. Adequate decompression of the left ventricle (more reliable than pulmonary artery pressure and surgeon's assessment)
2. Differential diagnosis of low arterial pressure on CPB (eg, rule out arterial dissection, which is particularly critical when using femoral artery inflow)
3. Assess possible malperfusion of cerebral vessels
4. Some have assessed flow in alimentary and renal arteries
5. Positioning of IABP

D. Toward the end of CPB
1. Assess presence of residual air and adequacy of de-airing
2. Assess ventricular and valvular function
3. Assess for pleural blood or fluid

E. Early post-CPB
1. Residual air
2. Filling of left and right sides of the heart
3. Contractility of left and right sides of the heart
4. Assess results of surgical repair/procedure
5. Rule out aortic injury or evidence of dissection

F. During sternal closure
1. Check for evidence of tamponade or occlusions of CABG grafts

G. Before end of case
1. Rule out evidence of aortic dissection/tear
2. Final assessment of filling, ventricular, and valvular function

Abbreviations: ASD, atrial septal defect; CABG, coronary artery bypass grafting; CPB, cardiopulmonary bypass; IABP, intra-aortic balloon pump; LV, left ventricular; PDA, patent ductus arteriosus; PFO, patent foramen ovale; TEE, transesophageal echocardiography.

Table 3
STS/SCA/AmSECT Clinical Practice Guidelines for Anticoagulation During CPB

Heparin dosing
(UFH is considered the gold standard for AC)
1. A functional whole blood test of anticoagulation, in the form of a clotting time, should be measured and should demonstrate adequate anticoagulation before initiating and at regular intervals during CPB (class I, LOE C)
2. Bolus administration of UFH based on weight is reasonable for achieving adequate anticoagulation (IIa, C) (but no dose recommended nor comment on dosing in obese patients)
3. It is reasonable to use ACT tests that produce "maximally activated" clotting times (IIa, B)
4. It is reasonable to maintain ACT greater than 480 seconds during CPB; for instruments using maximal activation of whole blood or microcuvette technology, values greater than 400 seconds are frequently considered therapeutic (IIa, C)
5. Use of a heparin dose−response formula may be informative (IIb, B)
6. Use of heparin concentration monitoring in addition to ACT might be considered for the maintenance of CPB (IIb, B)
7. During CPB, routine administration of UFH at fixed intervals, with ACT monitoring, might be considered and offers a safe alternative (IIb, C)

Abbreviations: AC, anticoagulation; ACT, activated coagulation time; AmSECT, American Society of Extracorporeal Technology; CPB, cardiopulmonary bypass; LOE, level of evidence; SCA, Society of Cardiovasular Anesthesiologists; STS, Society of Thoracic Surgeons; UFH, unfractionated heparin.
Modified from Shore-Lesserson et al.[14]

practice. A recent multinational survey reported the ACT target for instituting CPB as <400 seconds in ~5% of Europeans and ~10% of North Americans, 400 to 450 seconds in ~50% of Europeans and ~40% of North Americans, 451 to 500 seconds in ~30% of both groups, and >500 seconds in ~10% of both groups.[15] In an earlier survey, Lobato et al. reported that the most frequent target (46%) in Canada was 400 seconds, whereas in the United States it was 480 seconds (48%).[16] The ACT value is influenced by the device and activators used.[14] The acceptable level likely is influenced by the extracorporeal circuit used (eg, reservoirs, surface coating [especially heparin], use of cardiotomy suction) and perhaps the type of cardiac surgery.[14]

The use of ACT started with 2 landmark articles published in 1975 by Bull et al., in which ACT was introduced to monitor heparin administration and its reversal with protamine.[17,18] In their discussion in their first article, the authors stated, "It has been our experience that with an ACT in excess of 300 seconds, blood in the extracorporeal circuit never tends to form even small clots after conclusion of bypass whereas below 300 seconds clotting sometimes does occur."[17] However, sometimes overlooked, they go on to state, "Heparin merely delays the length of time before coagulation. However even at these levels (ACT above 300 seconds) it does not render the blood non-coagulable if abnormal surface activating coagulation is sufficiently large and effective." In their accompanying second article, they described the use of the ("Bull") dose response curve to guide the dosing of heparin.[18] Without explanation, they chose an ACT target of 8 minutes (ie, 480 s) for heparin dosing, and in the accompanying graphs indicated a "safe zone" of 300 to 600 seconds (Fig 1, A and B), and I suspect that this is where the common target of 480 seconds originated.

On the other hand, the recent European guidelines recommend that heparin level–guided heparin management should be considered over ACT-guided heparin management to reduce bleeding and that heparin level–guided protamine dosing may be considered over ACT-guided dossing to reduce bleeding and transfusion.[19]

AmSECT Standards and Guidelines for Perfusion Practice

The standards and guidelines for perfusion practice by the AmSECT first were published in 2013 were revised in May 2017, and recently were approved by the STS (http://www.amsect.org/p/cm/ld/fid=1617; accessed Nov 4, 2018).[20] Their recommendations were classified as either standards, which are mandatory, or guidelines, which are only recommended. I recommend that these should be reviewed by all cardiac surgery teams (anesthesiologists, surgeons, and perfusionists) to ensure that they are adhering to the standards and to consider following the guidelines (summarized in Table 4). Of note is the new standard (standard 12.1) that states that the cardiotomy suction shall be discontinued at the onset of protamine administration to avoid clotting within the CPB circuit. Also included in this document are some useful appendices.

Optimal Mean Arterial Pressure During CPB and Cerebral Autoregulation

The acceptable or optimal mean arterial pressure (MAP) during CPB has been debated since the dawn of CPB. This

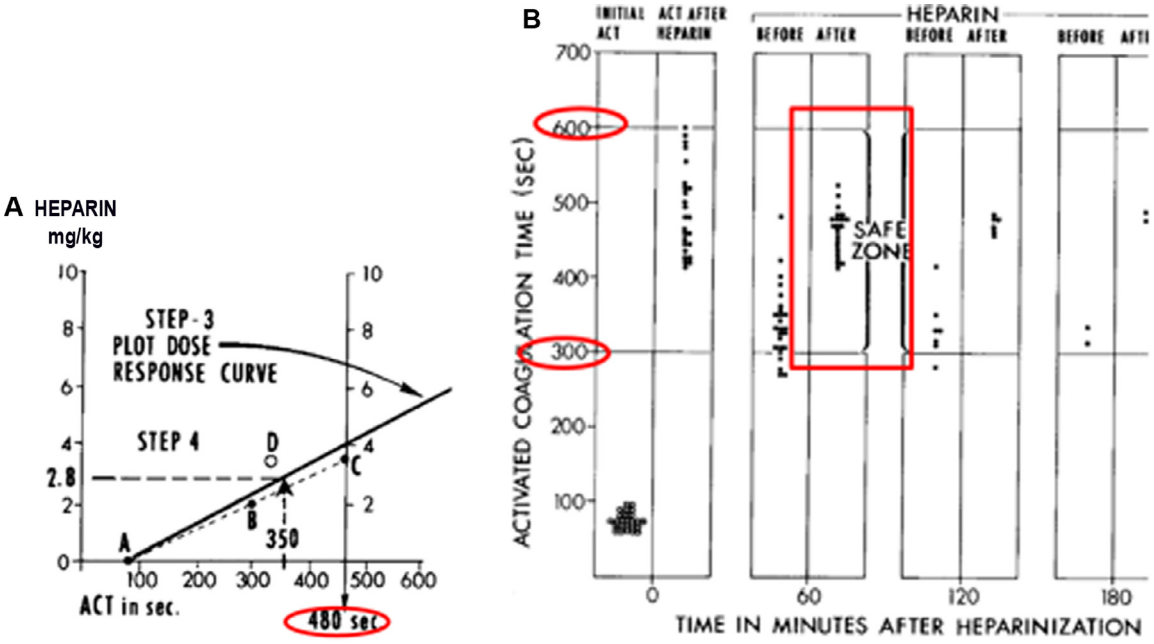


Fig 1. A, Bull curve (ACT *v* heparin dose). Note the activated coagulation time target (*circled in red*) for heparin dosing of 480 seconds. B, Distribution of activated coagulation times after administration of heparin. Note the "safe zone" for the initial activated coagulation time identified by Bull et al. (inside the *red box* [placed by the author of this review]) as being between 300 and 600 seconds (*encircled in red* by the author of this review). ACT, activated coagulation time.

From Bull et al.[17]; used with permission.

Table 4
AmSECT Standards and Guidelines for Perfusion Practice

Standard 1: Development of institutionally based protocols
- Standard 1.1: As a mechanism for applying each standard to clinical practice, an institution or service provider shall develop and implement an operating procedure (protocol) for each of the standards.
- Standard 1.2: The protocol shall be approved by the chairman of cardiac surgery or his/her designee, director of perfusion or equivalent, and other relevant clinical governance committees if available and reviewed and revised annually or more frequently when deemed necessary.
- Standard 3.1: A patient-specific management plan for the CPB procedure shall be prepared and communicated to the surgical team either during the preoperative briefing or before beginning the procedure.

Standard 5: Checklist
- Standard 5.1: The perfusionist shall use a checklist for each CPB procedure.
- *Guideline 5.1:* The perfusionist should use checklists in a read-verify manner where critical steps that should have been performed are confirmed; completion of the checklist should be performed by 2 people, 1 person being the primary perfusionist responsible for operation of the heart lung machine during the intraoperative period.
- *Guideline 5.2:* The perfusionist should use a checklist throughout the entire perioperative period (eg, set-up, pre-bypass, initial onset of bypass, before cessation of bypass, post-bypass, and/or any return to bypass).

Standard 6: Safety devices*
- Standard 6.1: Pressure monitoring of the arterial line, cardioplegia delivery systems, and venous reservoir (when augmented venous drainage is used) shall be used during CPB procedures.
- Standard 6.2: A bubble detector shall be used during CPB procedures.
- Standard 6.3: A level sensor shall be used during CPB procedures utilizing a (hard-shell) reservoir.
- Standard 6.4: Temperature monitoring of the arterial outflow from the oxygenator shall be used during CPB procedures.
- Standard 6.5: An arterial-line filter shall be used during CPB procedures.
- Standard 6.6: A one-way valve in the vent line shall be used during CPB procedures.
- Standard 6.7: A method for retrograde flow avoidance when using a centrifugal pump shall be used during CPB procedures.
- Standard 6.8: An anesthetic gas scavenge line shall be used whenever inhalation agents are introduced into the circuit during CPB procedures.
- Standard 6.9: Hand cranks shall be readily available during CPB procedures.
- Standard 6.10: A back-up gas supply shall be available.
- Standard 6.11: A back-up battery supply for the CPB machine shall be available.
- *Guideline 6.1:* A ventilating gas oxygen analyzer should be used during CPB procedures.
- *Guideline 6.2:* A level sensor should be used during CPB procedures utilizing a soft shell reservoir.

Standard 7: Monitoring
- Standard 7.1: Patient arterial blood pressure shall be monitored continually during CPB.
- Standard 7.2: Arterial line pressure shall be monitored continually during CPB.
- Standard 7.3: Arterial blood flow shall be monitored continually during CPB.
- Standard 7.4: Cardioplegia dose, delivery method, line pressure (antegrade), coronary sinus pressure (retrograde), and ischemic intervals shall be monitored continually during CPB.
- Standard 7.5: Patient and device temperatures shall be monitored continually during CPB (patient [eg, nasopharyngeal, rectal, bladder, esophageal]; heart lung machine [arterial, venous and cardioplegia]; heater-cooler [water temperature]).
- Standard 7.6: Blood gas analyses shall be monitored continually or at regular intervals during CPB (Appendix D).
- Standard 7.7: Hematocrit (or hemoglobin) shall be monitored continually during CPB.
- Standard 7.8: Oxygen fraction and gas flow rates shall be monitored continually during CPB (Appendix D).
- Standard 7.9: The percentage of venous line occlusion of the venous occluder shall be monitored continually.
- Standard 7.10: Venous oxygen saturation shall be monitored continually during CPB.

Standard 8: Anticoagulation
- Standard 8.1: The perfusionist, in collaboration with the physician-in-charge, shall define the intended treatment algorithm for anticoagulation management (heparin) and an alternative algorithm for when heparin is not suitable, including acceptable ranges for ACT.
- *Guideline 8.1:* The surgical care team should determine the target ACT time by considering relevant factors, including variability in the measurement of ACT attributed to the device's performance characteristics.
- *Guideline 8.2:* Patient-specific initial heparin dose should be determined by one of the following methods: weight, dose response curve (automated or manual), blood volume, body surface area.
- *Guideline 8.3:* Anticoagulation monitoring should include the testing of ACT; additional monitoring tests may include heparin level measurement (eg, heparin/protamine titration or unfractionated heparin level), partial thromboplastin time, thromboelastograph, thrombin time, anti-Xa.

Standard 9: Gas exchange
- Standard 9.1: Gas exchange shall be maintained during CPB according to protocol.
- *Guideline 9.1:* Point-of-care testing should be considered to provide accurate and timely information for blood gas analysis.
- *Guideline 9.2:* The following oxygen delivery and consumption calculations should be used to evaluate and optimize gas exchange:
  Oxygen delivery: $DO_2 = 10 \times CI \times CaO_2$
  Oxygen consumption: $VO_2 = 10 \times CI \times (CaO_2 - CvO_2)$

Standard 10: Blood flow
- Standard 10.1: Target blood flow rates shall be determined before CPB according to protocol.
- Standard 10.2: The perfusionist shall work closely with the surgical care team to maintain targeted blood flow rate during CPB.

Standard 11: Blood pressure
- Standard 11.1: The perfusionist, in collaboration with the physician-in-charge, shall define and communicate the intended treatment algorithm for blood pressure management before CPB, including acceptable ranges for blood pressure.

(*continued*)

Standard 12. Protamine and cardiotomy suction
Standard 12.1: Cardiotomy suction shall be discontinued at the onset of protamine administration to avoid clotting within the CPB circuit.
Standard 13: Blood management
Standard 13.1: The perfusionist shall participate in efforts to minimize hemodilution and avoid unnecessary blood transfusions.
Standard 13.2: The perfusionist shall minimize the CPB circuit size to reduce prime volume.
Standard 13.3: The perfusionist shall calculate and communicate to the surgical team before initiating CPB a patient's predicted post-dilutional hemoglobin or hematocrit.
Standard 15: Staffing and on-call
Guideline 15.1: The "n+1" staffing model should be used at all times, where "n" equals the number of operating/procedure rooms in use at any given time at a single site.
Guideline 15.2: An on-call perfusionist should be present and clinically ready for unscheduled and emergency procedures within 60 minutes of being called.
Standard 16: Duty hours
Standard 16.1: In order for the perfusionist to ensure proper provision of care, he/she shall receive an adequate rest period between scheduled work hours.
Guideline 16.1: The perfusionist should receive a minimum of 8 hours of rest for every 16-hour consecutive work period.
Appendices
Appendix A: (Desired) Patient information
Appendix B: Information sufficient to accurately describe the procedure, personnel, and equipment
Appendix C: Patient physiological and perfusionist practice parameters documented at a frequency determined by institutional protocol
Appendix D: Blood gas, electrolyte, and anticoagulation monitoring results
Appendix E: Regulatory documents, revision 2016
Appendix F: Perfusion checklist

Abbreviations: ACT, activated coagulation time; AmSECT, American Society of Extracorporeal Technology; CaO_2, arterial oxygen content; CPB, cardiopulmonary bypass; CvO_2, venous oxygen content; CI, cardiac index; DO_2, oxygen delivery; VO_2, oxygen consumption.
* The author recommends that all anesthesiology groups use these.
Modified from guidelines published online at http://www.amsect.org/p/cm/ld/fid=1617; accessed Nov 4, 2018.

target was chosen empirically on the basis of physiologic principles, expert opinion, observational studies, and local practice. It often has been selected on the basis of patient age; usual preoperative blood pressure; coexisting disease (eg, renal, diabetes); and evidence of vascular disease.[3]

The review article on cerebral blood flow (CBF) and metabolism during CPB published by Schell et al. more than 25 years ago still is relevant.[21] The scientific approach to the management of MAP during CPB was largely introduced by the landmark study by Govier et al. in 1984. They found, based on measurements of CBF during hypothermic CPB, no significant effect of variations of MAP between ~35 mmHg and ~85 mmHg (Fig 2)![22] However, in 1995 Gold et al. in an RCT of patients undergoing CPB that compared a high (80-100 mmHg, actual average achieved ~70) versus a low (50-60 mmHg, actual average achieved ~52) target during CPB found that the incidence of the combined 6-month outcome of mortality and major cardiac or neurologic morbidity was lower in those managed with the higher MAP (4.8% *v* 12.9%).[23] However, the incidence of specific adverse outcomes was not different in the 2 groups. In a more recent RCT, Siepe et al. compared the incidence of early (48 h) postoperative delirium (POD) and postoperative cognitive dysfunction (POCD) in patients undergoing elective on-pump CABG managed with higher MAP (80-90 mmHg, actual average 84 ± 11 mmHg) versus lower MAP (60-70 mmHg, actual average 65 ± 8 mmHg) during CPB.[24] The incidence of postoperative delirium was much lower (0% *v* 13%) and the drop in Mini-Mental State Examination scores were less (1.1 *v* 3.9) in those managed with the higher pressure. Interestingly the cerebral oxygen saturations measured using near-infrared spectroscopy (NIRS) (ie, cerebral oximetry) were nearly identical in the 2 groups. Studies such as these have led to the popular adoption of the use of higher perfusion pressures during CPB.

However, this debate was reenergized by a recent provocative study by Vedel et al.[25] In their single-center RCT of adult patients who underwent cardiac surgery during normothermic CPB, the authors compared patients managed with low MAP (40-50 mmHg, mean ~45 ± 7) versus high MAP (70-80, mean ~67 ± 5). The latter was achieved by administering phenylephrine or norepinephrine. New evidence of cerebral injury on diffusion-weighted magnetic resonance imaging was observed in ~54% of all patients and was not different in the 2 groups The volume of these new lesions also was similar, and the incidence of clinical evidence of strokes and new early and late postoperative cognitive decline also were not different in the 2 groups. The authors concluded that vasopressor-facilitated high-targeted MAP did not appear to be beneficial. This conclusion was discussed in an informative and insightful accompanying editorial by Cheung and Messé.[26]

On the other hand, opposite findings were reported in a recently published study by Sun et al.[27] They reported on a retrospective analysis of prospectively collected continuous arterial blood pressure during cardiac surgery using CPB in 7,457 patients. They found that the time MAP was 55 to 64 mmHg and less than 55 mmHg (compared with 65-74 mmHg) during CPB was associated with an increased risk of stroke (2.1% and 3.8% *v* 1.6%, respectively) and that each progressively longer 10 minutes that MAP was <55 mmHg was an independent predictor of stroke. Other independent predictors of stroke risk included older age, history of hypertension, combined CABG/valve surgery, emergency surgical status, prolonged CPB duration, and postoperative new-onset atrial fibrillation. This study had a number of limitations, which were mentioned by the authors and thus caution is required in interpreting these results.

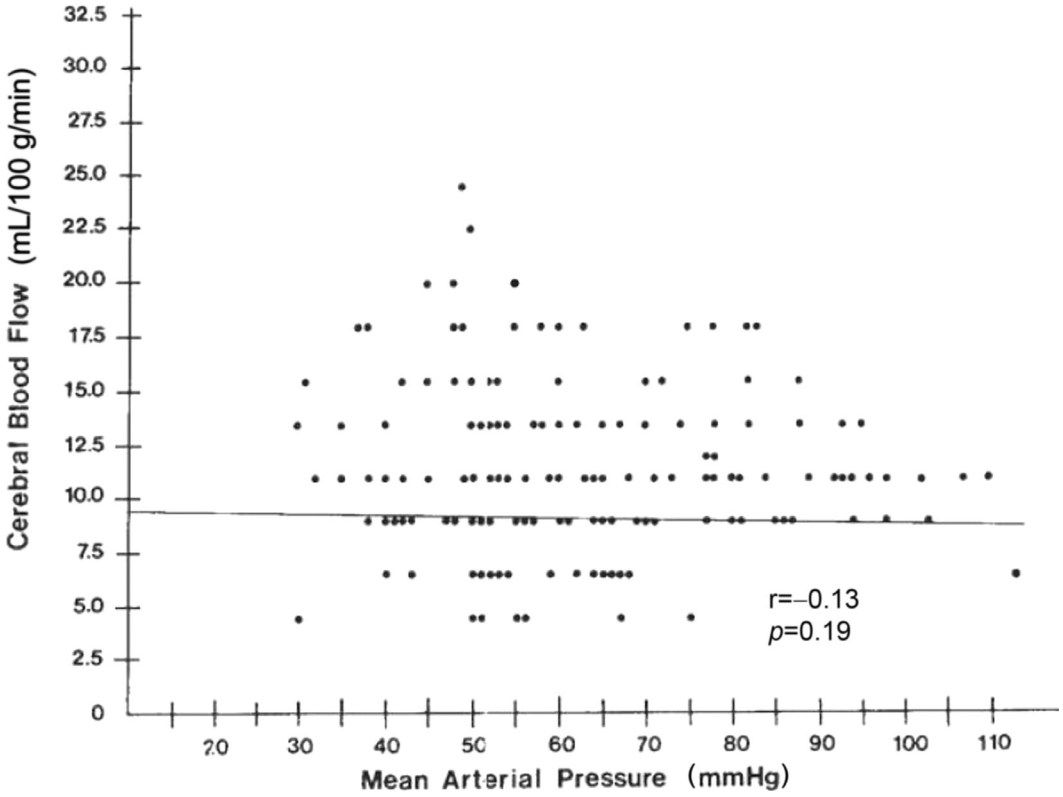


Fig 2. Cerebral blood flow versus mean arterial pressure during moderate hypothermic cardiopulmonary bypass. Note no significant change in cerebral blood flow with mean arterial pressure varying from about 35 to 85 mmHg.
From Govier et al.[22]; used with permission.

It is difficult to reconcile the results of these 2 studies, 1 much larger in size but retrospective and observational[27] and the other smaller but prospective and randomized.[25] Differences in anesthetic technique and the conduct and management of CPB, which were not fully defined, and criteria for diagnosing stroke may explain some of these discrepant observations.

Rather than base the MAP target on an arbitrary level or on patient characteristics, it has been suggested that a more rational target would be the individual patient's cerebral autoregulatory range. Over the past several years, the group at Johns Hopkins University has attempted to identify the cerebral autoregulatory range of MAP in patients during CPB. In 2012, it reported using transcranial Doppler (TCD) monitoring of the middle cerebral arteries and NIRS monitoring to identify the lower limit of cerebral autoregulation in patients undergoing CPB.[28] They found the average lower limit of autoregulation was 66 mmHg (95% prediction interval, 43-90 mmHg) (Fig 3) and notably that there was no relationship between preoperative MAP or a history of diabetes, hypertension, and prior cerebrovascular accident and this lower limit of autoregulation. This study demonstrated that real-time monitoring of autoregulation with cerebral oximetry index is possible and may provide a more rational means for individualizing MAP during CPB.

This group recently reported on a retrospective study of 614 patients who underwent cardiac surgery at 3 hospitals using TCD to identify the range of cerebral autoregulation.[29] Monitoring was able to be used to identify the optimal MAP during CPB in 71% to 83% of patients. They found that optimal MAP during CPB was 78 ± 11 mmHg (Fig 4) and, as before, that optimal MAP was not influenced by age or history of hypertension or diabetes. Importantly, although the average optimal MAP during CPB was 78 ± 11 mmHg, the lower limit of autoregulation in 17% of patients was above this range, which, if chosen, could lead to possible cerebral hypoperfusion, whereas in 29% of patients, the upper limit of autoregulation was below this range, which, if chosen, could lead to possible

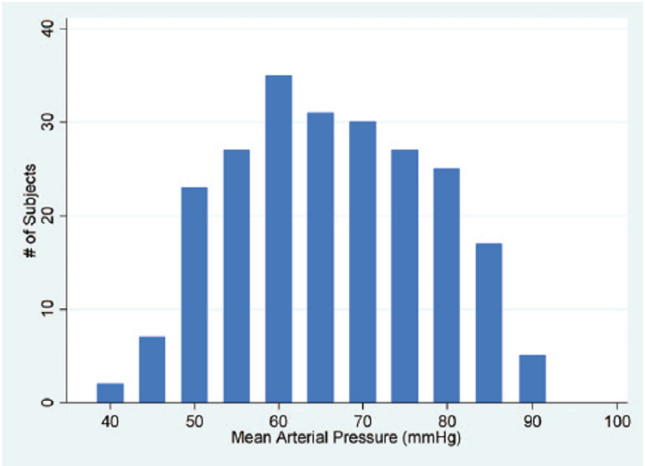


Fig 3. Lower limit of cerebral autoregulation during clinical cardiopulmonary bypass. Note that even though the average lower limit of cerebral autoregulation was about 65 mmHg, it ranged from 40 to 90 mmHg.
From Joshi et al.[28]; used with permission.

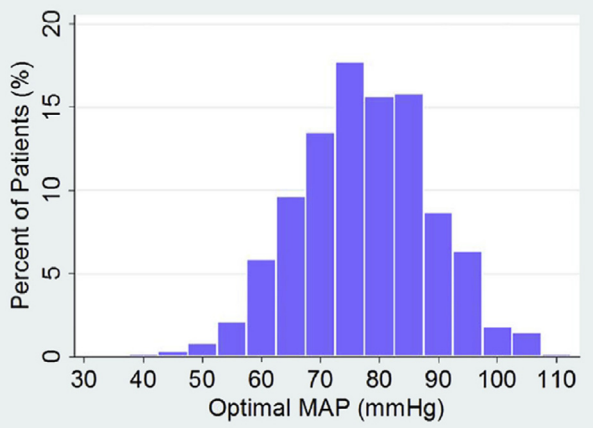


Fig 4. Optimal arterial pressure during clinical cardiopulmonary bypass. Note that even though the mean optimal mean arterial pressure defined by cerebral autoregulation monitoring during cardiopulmonary bypass was 78 mmHg, it ranged from 45 to 105 mmHg. MAP, mean arterial pressure.

From Hori et al.[29]; used with permission.

cerebral hyperperfusion. This group also found that perfusion at a MAP below the lower limit of autoregulation could lead to increased morbidity (eg, strokes) and mortality,[30] whereas MAP above the upper limit of autoregulation may be associated with an increased incidence of POD.[31,32] Thus, one cannot rely on simply using the average optimal MAP for this population on all patients.

In summary, the optimal MAP during CPB remains unclear. A reasonable hypothesis is that this should be best guided by maintaining the MAP within the autoregulatory range of CBF. However, studies have shown that this may vary considerably in individual patients from traditionally accepted values and is not predictable. Although prior studies by the Hopkins group have suggested an association between a MAP below or above the limit of autoregulation during CPB and harm and although it is reasonable to suspect that maintaining patient MAP within the patient's autoregulatory range would improve outcome, no prospective studies reported to date have documented such a benefit. Such studies are ongoing and will be required before this technique should be advocated for routine clinical care. Although the Hopkins group has used analysis of NIRS instead of the more-difficult-to-obtain TCD to identify the autoregulatory range clinically,[28,33] the type of monitoring devices used by these authors generally are not available.

Vasoplegia During or After CPB

Vasoplegia is relatively common after cardiac surgery and often is associated with adverse outcomes, including prolonged ICU and hospital LOS, renal failure, and mortality. Mortality as high as 35% has been reported if vasoplegia persists for >48 hours. Several review articles on this subject were published recently.[34-41] However, much of the literature relates to vasoplegia associated with sepsis, which may not apply to that associated with cardiac surgery.

A commonly used definition of vasoplegic syndrome is hypotension with evidence of end-organ hypoperfusion in the presence of normal or elevated cardiac output, after excluding other causes (eg, artefactual pressure or cardiac output measurement, sepsis/infection, anaphylaxis, adrenal insufficiency). Vasoplegia associated with cardiac surgery occurs in about 20%[40] (range 3%-50%)[37] of cases and is characterized as "severe" in between 7%[39] and 25% of patients.[34]

Various risk factors have been identified, including preoperative administration of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers, poor preoperative left ventricular (LV) function, preexisting renal failure, older age, male sex, presence of or planned insertion of an LV assist device, valve surgery, surgery for endocarditis, heart transplantation, blood transfusion, and long-duration CPB.[40] Some data suggest a lower incidence with off-pump versus on-pump CABG.[42,43]

Multiple hypotheses have been proposed regarding its pathophysiology, but most focus on the role of the inflammatory response and release of various mediators such as oxygen-free radicals, prostenoids, and cytokines and an increase in nitric oxide (through activation of nitric oxide synthetase), hydrogen sulfide, and non-endothelin potassium hyperpolarization. Vasopressin deficiency and reduction of vasopressin receptors or their responsiveness also are suggested.

Initial therapy is directed at ensuring adequate LV function, intravascular volume status, and administration of various catecholamines. Most advocate for early addition of vasopressin. A recent RCT (the VANCS trial) compared the outcome of patients with vasoplegic shock post-cardiac surgery treated with infusions of either vasopressin or norepinephrine.[44] The primary composite outcome of mortality or severe complications at 30 days was lower in those treated with vasopressin (32% *v* 49%), as was the incidence of acute renal failure and atrial fibrillation. Dünser et al. recently reported on their meta-analysis comparing the effect of use of vasopressin in addition to other vasopressors in cardiac surgery, which included the aforementioned study.[45] They also observed a decrease in postoperative complications with the use of vasopressin but no decrease in mortality.

When these initial measures fail, methylene blue is widely used and may be effective, although the evidence of its efficacy is somewhat controversial, as is the optimal dose and proper timing (ie, early *v* rescue therapy).[46-48] This agent inhibits nitric oxide synthetase and competes with the effect of soluble guanylyl cyclase, which mediates smooth muscle relaxation. However, methylene blue is a coronary and splanchnic vasoconstrictor, may cause hemolytic anemia, and interferes with hemoglobin oximetry. A major concern is the risk of it causing serotonin syndrome in patients receiving various antidepressants (eg, selective serotonin reuptake inhibitor, norepinephrine reuptake inhibitor, tricyclic antidepressant, monoamine oxidase inhibitor) and narcotics, including meperidine and fentanyl. At least 13 case reports of serotonin syndrome attributed to the use of methylene blue for vasoplegia associated with cardiac surgery have been reported.[49-51] A significant percent of patients presenting for cardiac surgery are receiving antidepressants, thus this probably should be considered before electing to use methylene blue.

Often, corticosteroids are used for their anti-inflammatory effects, but benefit is unclear.[35,37] Other recently recommended

drugs being considered or used include hydroxocobalamin (vitamin B_{12}), vitamin C (ascorbic acid), and angiotensin II.

Hydroxocobalamin (vitamin B_{12}) is a nitric oxide scavenger, binds hydrogen sulfide, and commonly is used in the treatment of cyanide poisoning. Several case reports have reported effectiveness in treating vasoplegic syndrome associated with liver transplantation[52,53] and CPB,[54-56] and recently Shah et al. reported their experience with the administration of 5 g over 15 minutes in 33 cases of cardiac surgery–associated vasoplegia.[57] Twenty-four percent had a good and prolonged response, 27% had a poor response, and the remaining had only a modest (27%) or a temporary brisk response (21%). No adverse effects other than chromaturia (red urine)[58] were noted in the small series by Shah et al.[57] Further investigation of this promising agent is needed.

Ascorbic acid (vitamin C) is an essential cofactor in endogenous biosynthesis of catecholamines. Stores of norepinephrine are depleted in ascorbate-deficient animal models, and critically ill and cardiac surgery patients after CPB have been found to be ascorbate deficient or to have low ascorbic acid concentrations.[59] Administration of intravenous vitamin C has been advocated by some for the treatment of vasoplegia associated with sepsis on theoretic grounds but with little supportive evidence.[60,61] Wieruszewski et al. reported the results of administering 1,500 mg of ascorbic every 6 hours to 3 patients with persistent vasoplegia 2 to 3 days post-cardiac surgery; 2 improved within hours.[59]

Intravenous angiotensin II (Giapreza; La Jolla Pharmaceuticals, San Diego) recently received Food and Drug Administration approval for treatment of vasoplegia associated with septic shock based on the results of a single RCT (Athos) that found a higher rate of improved arterial pressure at 3 hours (70% *v* 23%) but no statistically significant decrease in death at 28 days.[62] The use of this drug has been the subject of a number of reviews.[63-69] Concerns have been expressed regarding safety issues and expense. Furthermore, as far as this reviewer can find, there have been no reports of its use for vasoplegic syndrome associated with cardiac surgery.

Bleeding, Perioperative Anemia, and Transfusion After Cardiac Surgery

These topics remain of considerable concern to cardiac anesthesiologists and the subject of a number of recent publications. The recently published 2017 European Association for Cardio-thoracic Surgery/European Association of Cardiothoracic Anaesthesiologists guidelines on patient blood management for adult cardiac surgery deserve study by anesthesiologists.[19]

Antifibrinolytics and TXA

The STS/SCA blood conservation guidelines strongly support and recommend the use of antifibrinolytics (TXA or epsilon aminocaproic acid [EACA]) in cardiac surgery (class IA)[70] as do the European guidelines (class IA).[19] The use of antifibrinolytics recently was reviewed by several authors.[71-73]

TXA

Since the removal of aprotinin in 2007 (although partially re-approved for marketing in Canada and Europe in 2011), TXA currently is the most commonly used antifibrinolytic. Dosing of TXA often is classified as "low" (eg, 10 mg/kg load plus 1 mg/kg/h, or ~14 mg/kg total)[74] or "high" (eg, 50-100 mg/kg bolus load, 30 mg/kg load plus 16/kg/h infusion plus 2 mg/kg in prime, or ~96 mg/kg total).[75-77] TXA appears to follow first-order kinetics (two-compartment model) with total body clearance approximating the glomerular filtration rate.[73,75,78] However, the desired and optimal dose remain controversial[71,73] as do the incidence and significance of seizures associated with the use of TXA. The Toronto group found that a plasma concentration of TXA of 100 mg/L provided near 100% inhibition and maximal antifibrinolysis.[78]

A review of the use of antifibrinolytics by academic cardiac anesthetists during cardiac surgery in Canada found that 86.3% administered TXA to all patients and 13.7% administered it to some.[79] There was significant heterogeneity in practice between individuals. Most (68.4%) administered an infusion after a bolus. The mean dose given to a "standard" patient (80 kg in the 3 h from the start of a case to coming off bypass) was 49 ± 24 mg/kg, with a range of 10 to 100 mg/kg. The authors concluded practice was not evidence based, but I suggest that the literature is confusing.

The largest and most recent RCT evaluating the use of TXA was the multicenter, international ATACAS study reported by Myles et al.[77] They included 4,631 patients deemed at increased risk of perioperative complications undergoing isolated CABG or CABG plus valve or other. Half received placebo and half TXA, given as a bolus post-induction with no follow-up infusion. The first 750 TXA patients received 100 mg/kg, and the last 1,553 patients received 50 mg/kg. The incidence of the primary outcome (death or thromboembolic complications) was not different between the TXA and placebo groups. This also was true of individual complications, including death, myocardial infarction, stroke, pulmonary embolism, and bowel infarct. On the other hand, the use of TXA was associated with a decreased incidence of transfusion of RBCs (33% *v* 47%) and other blood products (38% *v* 55%) and a reduction of redo surgery for major hemorrhage or tamponade (1.4% *v* 2.8%, relative risk [RR] 0.46, number needed to treat 71). However, the incidence of seizures was significantly higher in patients who received TXA (0.7% *v* 0.1%, RR 7.6; $p = 0.002$; number needed to harm 177). The increased incidence of seizures was significant only in patients receiving TXA who underwent open chamber procedures but not in patients who underwent isolated CABG. The occurrence of seizures in this study is discussed further in a following section.

Dosing of TXA Versus Effectiveness on Bleeding

The effect of TXA dosing on its effectiveness remains unclear owing to the few comparative studies and lack of large high-quality studies.[71] In one of the earliest RCTs comparing various TXA dosing regimens, Horrow et al. reported that a loading dose of 10 mg/kg followed by an infusion of 1 mg/kg/h

(now referred to as the "Horrow low dose" regimen) or more was associated with a decrease in bleeding but no significant decrease in administration of blood products.[74] Furthermore, they detected no advantage to the use of the highest dose studied (40 mg/kg loading followed by 4 mg/kg/h infusion) on blood loss or transfusion.

Santos et al. compared the effectiveness of the Horrow dosing versus placebo in an RCT of 65 patients undergoing CABG.[80] They observed a decrease in 12-hour blood loss (300 *v* 450 mL) in those who received TXA but no difference in percent of patients who received RBCs, fresh frozen plasma (FFP), or platelet transfusion or underwent redo surgery for bleeding versus those who received placebo. In a pseudorandomized trial of patients undergoing various types of cardiac surgery, Waldo et al. compared the outcome of patients who received a "low" (~15 mg/kg), "medium" (~58 mg/kg), or "high" (~72 mg/kg) dose of TXA (none received no TXA).[81] The 3 doses were associated with equal blood loss, reexploration for bleeding rates, and mortality. In an RCT of patients who underwent cardiac surgery, Karski et al. compared the outcome with bolus dosing of 50, 100, and 150 mg/kg TXA.[82] Although blood loss was somewhat less (~20%, or about 45 mL less at 6 h) with the 2 higher doses compared with the 50 mg/kg dose, the RBC transfusion rate and units administered were the same in all 3 groups, and no patients in any of the groups received FFP, platelets, or cryoprecipitate nor required redo surgery for bleeding. The widely quoted study by Sigaut et al. found no difference in the incidence of total blood product use over 7 days (their primary outcome) in an RCT of patients who received either high dose (30 mg/kg bolus + 16 mg/kg/h infusion) or low dose (10 mg/kg bolus + 1 mg/kg/h) of TXA.[83] However, those who received the high dose received significantly less FFP, platelets, and blood product and had less blood loss postoperatively and less redo surgery for bleeding (2.5% *v* 6%). In an RCT of patients who underwent on-pump CABG, Casati et al. compared the administration of TXA (a bolus followed by an infusion for a total dose of ~48 mg/kg) versus placebo.[84] They found a decrease in blood loss (550 *v* 750 mL), incidence of excessive bleeding (39% *v* 68%), and total units of RBCs administered but no statistically significant decrease in reexploration for bleeding (4% *v* 12%) or transfusion of FFP (4% *v* 16%) and platelets (4% *v* 8%) in those who received TXA.

The strongest evidence of the benefit of TXA is from the aforementioned RCT by Myles et al.,[77] who found that the administration of a single initial bolus of 50 or 100 mg/kg of TXA was associated with a decreased incidence of transfusion of RBCs (33% *v* 47%) and other blood products (38% *v* 55%) and a reduction of redo surgery for major hemorrhage or tamponade (1.4% *v* 2.8%, number needed to treat 71). In a post hoc analysis no difference between the median blood loss (EBL), transfusion rates, units transfused, or reexploration for bleeding or tamponade was identified between the 2 doses (50 mg/kg *v* 100 mg/kg) of TXA.

These data suggest to the author of this review, that for the best effect on bleeding, and in particular to reduce the need for transfusion and redo surgery for bleeding and tamponade, a higher-dose regimen (eg, ~>50 mg/kg, either as a single initial bolus or as the total dose throughout CPB) may be better.

TXA and the Risk of Seizures

A major concern with the use of TXA is the risk of seizures. Seizures are a well-known complication after cardiac surgery.[85] A retrospective study of patients who underwent cardiac surgery (all of whom received prophylactic EACA but none received TXA) demonstrated an incidence of seizures of 1%.[86] It was lowest in isolated CABG (0.1%), intermediate in isolated valve and combined CABG plus valve (1% and 3%, respectively), and highest with aorta surgery (5%). Fifty-three percent had evidence of ischemic strokes (64% embolic, 33% watershed). Mortality was 5-fold higher in those with seizures (29% *v* 6%).

For a number of years, an increased risk of seizures was noted with the use of TXA in cardiac surgery.[85,87-94] A retrospective analysis of patients who underwent cardiac surgery with CPB demonstrated a seizure incidence of 0.9%.[95] Seizures occurred in 0.1% after closed chamber and 1.5% after open chamber surgery. Patients who experienced seizures had a 2.5-fold increase in mortality and a 2-fold longer LOS. However, only 16% had evidence of acute organic brain injury on neuroimaging. The incidence of seizures was 0.9% in those who received TXA and 0.2% in those who received aprotinin. Independent predictors of seizures included age, female sex, redo surgery, ascending aortic disease, deep hypothermic circulatory arrest, cross-clamp time, and TXA. Notably, the incidence of seizures in patients who underwent closed chamber surgery was not increased in those who received TXA. Another observational study demonstrated an incidence of seizures of 0.9%.[96] None was observed in patients who did not receive an antifibrinolytic, 0.2% in those who received aprotinin, and 0.9% in those who received TXA. The incidence of seizures was higher in open chamber surgery than in CABG (1.2% *v* 0.2%). An ischemic cause was identified with neuroimaging in only about 18%. As noted earlier, in the ATACAS RCT the incidence of seizures was significantly higher in patients who received TXA versus placebo (0.7% *v* 0.1%).[77] However, the increased incidence of seizures in patients who received TXA was significant only in patients who underwent open chamber procedures (2.0% *v* 0.0%) but not in patients who underwent isolated CABG. In a small prospective study of patients at high risk of postoperative bleeding who also had evidence of preoperative chronic renal dysfunction (CRD) and were given high dose TXA (50 mg/kg as a bolus), Jerath et al. observed an incidence of seizures of 18% in patients with Kidney Disease Outcomes Quality Initiative stage 2 to 5 CRD and 50% in those with class 5 CRD.[78] A meta-analysis of 10 studies found an incidence of seizures of 2.7% when TXA was used during cardiac surgery.[97] In the studies that compared the incidence of seizures in those who did not receive TXA (0.5%) with those who received TXA, the odds ratio for seizures when TXA was given was 5.4. Another meta-analysis of 16 studies (5 RCTs and 11 observational studies) found a marked increased risk of seizures with the use of TXA compared with placebo or another antifibrinolytic (odds ratio 4.1).[98]

Several studies have reported an association of seizures with higher doses of TXA. Sharma et al. found that the incidence of

seizures in those who received TXA was mainly observed in those who received more than 80 mg/kg.[95] The mean dose in those with seizures was 100 mg/kg. The incidence of seizures in the TXA patients who received only 50 mg/kg as a loading bolus was 0.3%, whereas the incidence was 2.6% in those who received a loading dosing followed by an infusion. Jerath et al. observed that the total dose of TXA was higher in those who experience seizures than in those who do not (115 mg/kg *v* 85 mg/kg),[78] and Couture et al. observed that the incidence of seizures was twice as high (1.55% *v* 0.70%) in those who received their higher total dose of TXA (58 mg/kg) versus their lower dose (average 34 mg/kg).[96] A meta-analysis found that the incidence of seizures increased with increasing dosage (1.4% with low dose [24-50 mg/kg], 2.4% with medium dose [59 mg/kg], and 3.5% with high dose [80-109 mg/kg]).[97] On the other hand, Sigaut et al. observed no difference in incidence of seizures with high dose (30 mg/kg bolus + 16 mg/kg/h infusion) versus low dose (10 mg/kg bolus + 1 mg/kg/h) (1.4% *v* 0.7%; p = 0.7),[83] and Myles et al. also observed no difference in the incidence of seizures in patients who received a high (100 mg/kg) or low (50 mg/kg) bolus of TXA.[77]

Based on the assumption that higher doses of TXA are associated with greater risk of seizures and pharmacokinetic studies of patients who had Kidney Disease Outcomes Quality Initiative stage 2 to 5 CRD using the BART TXA dosing protocol, Jerath et al. suggested a modification of the BART TXA dosing protocol (loading 30 mg/kg, infusion 16 mg/kg/h, plus 2 mg/kg in pump prime) in patients with CRD in order to achieve but not exceed a target concentration of 100 mg/L.[78] They recommended reducing the loading dose in patients with stage 3 to 5 CRD to 25 to 30 mg/kg and reducing the infusion to 11 to 16 mg/kg/h in those with stage 2 CRD, 5 to 10 mg/kg/h in those with stage 3 CRD, and 3 to 5 mg/kg/h in those with stage 4 or 5 CRD. However, the clinical results from following these guidelines in terms of hemostasis or seizures have not been reported.

The mechanism by which TXA is associated with increased risk of seizures is not known with certainty but may be related to the inhibitory effect of TXA on hippocampal gamma-aminobutyric acid type A (GABA/A) and on the glycine receptor,[99] which are antiepileptics (ie, disinhibition). In a study of 4 patients who underwent repair of thoracoabdominal aneurysm involving CPB, Lecker et al. found that peak TXA concentration in the cerebrospinal fluid occurred after termination of drug infusion and in 1 patient coincided with the onset of seizures.[99]

The significance of these seizures associated with TXA is unclear.[71] An analysis of a Japanese national database of pediatric patients who underwent cardiac surgery found a marked increase in the incidence of seizures (1.6% *v* 0.2%) in those who received TXA but no difference in clinical outcomes, including mortality (2.3% *v* 2.1%) and LOS (19 *v* 20 d).[100] On the other hand, Myles et al. observed that patients who experienced seizures had an increased incidence of strokes (RR 21.9) and death (RR 9.5).[77] These authors opined that the results of their trial suggest a possible underlying thromboembolic cause of the seizures.

In summary, seizures occur after cardiac surgery, even in the absence of TXA. However, they occur more often after the use of TXA versus aprotinin. There are inadequate data regarding the risk of seizures with the use of EACA (Amicar). Incidence of seizures associated with the use of TXA is likely dose related (especially in doses >50-80 mg/kg), but data are conflicting. The incidence of seizures is strongly associated with open ventricle surgery. When seizures occur after cardiac surgery, they are highly associated with stroke and mortality. However, it is not clear that the seizures are caused by the TXA and are the cause of increased stoke and mortality or whether TXA may simply render patients with central nervous system injury more vulnerable to seizures (ie, seizures are simply a surrogate of evidence of central nervous system injury and risk of stroke or mortality).

TXA in Patients With Endovascular Stents

Some authors have expressed concerns and have recommended against using TXA in patients with endovascular stents.[101,102] In personal communications with authors of recent studies involving the use of TXA during cardiac surgery, especially in patients undergoing CABG, many of whom may have coronary stents, these authors have not detected any evidence of problems associated with the administration of TXA in patients with coronary stents (personal communications with DA Fergusson, D Mazer, PS Myles, J Spence, February 2018.) However, because of this theoretic concern, I administer 5,000 U of heparin before administering TXA to patients with significant coronary artery disease or those with coronary or other endovascular stents.

Aprotinin

Aprotinin was taken off the market in the United States and elsewhere in November 2007 based on safety concerns highlighted by the BART study, although it has been reintroduced in Canada and Europe but without any apparent additional studies documenting its safety. Benedetto et al. have raised concerns again about its safety.[103] They reported a retrospective analysis of 536 propensity matched patients who received aprotinin versus no fibrinolytic during an unrelated RCT comparing bilateral versus single internal mammary artery grafting for CABG (the Arterial Revascularization Trial). Aprotinin was used in about 27% of the patients enrolled in the study. Use of aprotinin compared with no aprotinin was associated with increased hospital mortality (1.7% *v* 0.2%), increased 5-year mortality (10.6% *v* 7.3%), and increased acute kidney injury (AKI) (19.0% *v* 14.2%). Thus, these authors recommend caution in the use of aprotinin until strong evidence of its safety becomes available.

Conclusions and Recommendations Regarding the Use of Antifibrinolytics and TXA in Cardiac Surgery

Based upon the publications just reviewed above, this author has reached the following conclusions and makes the following recommendations:

1. Use of aprotinin it not recommended at the present time owing to unresolved safety issues.
2. Even though likely effective at reducing blood loss, there is limited high-level evidence of the effectiveness of EACA

(Amicar) in reducing blood product administration and the need for redo surgery for bleeding or tamponade and of its safety profile. Thus, the use of EACA cannot be strongly recommended at this time.

3. TXA appears to be the agent of choice if one choses to administer an antifibrinolytic.

When TXA is used, the following are recommended.

4. The benefit/risk ratio in patients at low risk of bleeding (eg, primary CABG) suggests using a low dose (eg, 10 mg/kg loading followed by 1 mg/kg/h infusion) or none.
5. The best evidence of significant reduction in bleeding (administration of blood products, reexploration for bleeding complications) is from studies that used a relatively high dose of TXA (eg, 50 mg/kg total dose); therefore, this higher dose is recommended in patients undergoing cardiac surgery at higher risk of bleeding (eg, redo surgery, multivalve, aortic surgery, endocarditis surgery, combined procedures).
6. It should be noted that the use of the higher dosage of TXA may be associated with increased seizures (which are of unclear significance). Patients at increased risk of seizures include those undergoing open ventricle surgery or requiring a long duration of CPB and patients with reduced renal function.
7. In the aforementioned patients, consider lowering the infusion rate and stopping the infusion earlier. See the previously mentioned recommendations of Jerath et al. regarding TXA dosing of patients with CRD.[78]

Similar precautions have been recommended by Gerstein.[104]

Anemia and Transfusion

Perioperative anemia and the need for transfusion continue to be major concerns and problems related to CPB. Anemia during CPB (eg, hematocrit [Hct] <20-25) is associated with increased risk of death, stroke, and renal failure, but transfusion of RBCs is associated with increased morbidity and mortality. In a retrospective, observational study of patients who underwent isolated CABG surgery in 19 centers participating in the Virginia Cardiac Services Quality Initiative, LaPar et al. reconfirmed that preoperative anemia was strongly associated with likelihood of transfusion, renal failure, and mortality.[105] Thirty-one percent of the patients received packed red blood cells (PRBCs) (median 2 U). However, after risk adjustment, PRBC transfusion was more strongly related to mortality, renal failure, and stroke than was preoperative anemia. Models that included PRBC transfusion had superior predictive power compared with preoperative Hct alone for all outcomes. The authors suggested that perioperative Hct should be included in the STS risk calculations and efforts directed at reducing preoperative anemia to reduce administration of PRBCs.

Liberal or Restrictive Transfusion After Cardiac Surgery

In a multicenter study of patients who underwent nonemergency cardiac surgery with a postoperative hemoglobin level of less than 9 g/dL, Murphy et al. compared the outcome of patients randomly assigned to restrictive transfusion threshold (hemoglobin level <7.5 g/dL) or a liberal transfusion threshold (hemoglobin level <9 g/dL).[106] Transfusion rates were 53.4% versus 92.2% in the restrictive versus liberal groups. The primary outcome (serious infection or permanent stroke, myocardial infarction, infarction of the gut, or AKI) occurred in a similar percent in the 2 groups (~34%), which was true of other serious postoperative complications, but more deaths were observed in the restrictive than in the liberal threshold group (4.2% *v* 2.6%). These authors concluded that a restrictive transfusion threshold after cardiac surgery was not superior to a liberal threshold. Koch et al. reported the results of a 2-center RCT comparing a lower (24%) or higher (28%) Hct trigger for transfusion in adults undergoing cardiac surgery.[107] The lower trigger group received fewer RBC transfusions than did the higher trigger group (54% *v* 75%). There was no detected treatment effect on the composite outcome (postoperative morbidities and mortality). Mazer et al. reported the results of a multicenter noninferiority RCT (TRICS III) in adults who underwent cardiac surgery who had a EuroSCORE I of 6 or more, comparing a restrictive red-cell transfusion threshold (transfuse if hemoglobin level was <7.5 g/dL) with a liberal red-cell transfusion threshold (transfuse if hemoglobin level was <9.5 g/dL in the operating room or ICU or was <8.5 g/dL thereafter).[108] RBCs were administered to fewer patients in the restrictive threshold group (52% *v* 73%). The primary composite outcome (death from any cause, myocardial infarction, stroke, or new-onset renal failure with dialysis) occurred in 11.4% of the patients in the restrictive threshold group compared with 12.5% of those in the liberal threshold group, which indicated that noninferiority and mortality were not different in the 2 groups. Subgroup analysis only revealed a difference in primary outcome based on age. In patients ≥75 years old the restrictive strategy was associated with a lower incidence of the (adverse) primary outcome (10.2% *v* 14.1%), but this was not observed in those <75 years old. At 6-month follow-up, similar results in regard to overall noninferiority in all patients but better outcome in patients ≥75 years old with restrictive management were observed.[109] This trial had a number of limitations. These included that it was unblinded and that the difference in hemoglobin concentrations between the 2 groups was less than the differences in the triggers. In addition, the study did not answer the question of the safety of using an even lower threshold nor did it address the effect on patients with acute coronary disease. We look forward to the results of the ongoing Myocardial Ischemia and Transfusion (MINT) trial (NCT02981407; https://clinicaltrials.gov/ct2/show/NCT02981407), which may give an answer to this latter question. The interesting observation regarding patients ≥75 years old does not prove that a restrictive strategy is more beneficial in older patients, but it does suggest that it is at least as safe in older patients. In summary, these 3 studies appear to indicate that restrictive transfusion strategies are associated with less transfusion of RBCs but liberal strategies are not associated with worse mortality or major morbidity.

Effect of a Single Unit Transfusion on CABG Outcomes

Using propensity score matching of data from the Maryland Cardiac Surgery Quality Initiative for patients who underwent isolated CABG, Crawford et al. compared outcomes of patients who received only 1 U of RBCs versus those received no RBCs.[110] Patients who received no RBCs experienced a lower 30-day mortality (0.9% *v* 2.2%) and reduced prolonged LOS (>14 d) (3.7% *v* 4.0%) but no difference in incidence of prolonged ventilation, renal failure, or surgical site infections. Thus, exposure to a single unit of RBCs may adversely affect CABG outcome.

Effect of Prolonged Storage of RBC

Older observational studies[111] suggested impaired outcome after cardiac surgery with administration of older versus fresher RBCs. However, recent systematic reviews and meta-analyses[112,113] have challenged this concept, and recent RCTs in cardiac surgery (RECESS trial),[114] in general hospital populations (INFORM trial),[115] and in critically ill patients (ABLE study)[116] have demonstrated no difference in outcome associated with the use of fresher (<10 d) *vs* older (>20 d) RBCs. These studies do not resolve the question of whether use of even fresher RBCs (eg, ≤5 d of storage) might be associated with superior outcomes or whether use of much older RBCs (ie, 35-43 d of storage) might have adverse effects. Furthermore, the average amounts of RBCs transfused in these studies were relatively small (~2 U). Whether the same outcomes would be observed with transfusion of larger amounts of older RBCs is unknown. To assess the concern about older blood, Ng et al. analyzed data from 16 observational studies on the effect of the age of transfused RBCs on in-hospital mortality.[117] Overall there was no association between mean RBC age and in-hospital mortality or between maximum transfused RBC age and mortality. However, "extremes analysis" found an increased mortality in those who received RBCs stored at ≥30 days versus those who received RBCs stored at ≤5 to 10 days. On the other hand, Cartotto et al. did not find an association with transfusion of "very old" RBCs (≥35 d storage) and mortality.[118] However, mean storage age and proportion of very old RBC units were associated with an increased duration of ventilation.

To summarize, the administration of a few units of RBCs after up to about 3 weeks of storage does not appear to have adverse consequences. The possible negative effects of administration of larger amounts and of much older stored blood remain to be determined.

Effect of Mean Corpuscular Volume on Outcome of Anemic Patients Undergoing Cardiac Surgery

A provocative observational, single-center study evaluated the effect of mean corpuscular volume (MCV) on outcome in anemic patients who underwent elective cardiac surgery.[119] Of more than 10,000 patients, 26% were anemic. Anemic patients received more red cell transfusion than did non-anemic patients (67% *v* 26%) and compared with non-anemic patients they experienced more complications and higher mortality. However, this effect on outcome varied depending on MCV measurements. Eighty-seven percent (87%) of the anemic patients were normocytic, 8.1% microcytic, and 4.8% macrocytic. Adverse outcome was most marked in macrocytic patients and least in microcytic patients. Those with macrocytic anemia were older, included fewer women, and had a lower BMI, whereas those with microcytic anemia were younger, included more females, and had a higher BMI. The effect of MCV apparently had not been reported previously and will require verification. The explanation for the possible negative effect of macrocytic anemia has not been explained.

Use of Prothrombin Complex Concentrates, Activated Prothrombin Complex Concentrates, Recombinant Activated Factor VII, and Fibrinogen Concentrates to Reduce Postoperative Bleeding

Two recent pro-con debates addressed the use of 3-factor prothrombin complex concentrates (PCCs); 4-factor PCCs; activated PCC (ie, factor eight inhibitor bypass activity); recombinant activated factor VII (rFVIIa); and fibrinogen concentrates.[120-123] These debates provide informative updates regarding benefits and risks. Even though small and largely uncontrolled studies have shown potential benefit from administration of these products to manage post-CPB bleeding, the proper basis for selection of which therapy to use, proper dosing, potential risks of thrombotic complications, and cost-benefit analyses are yet to be resolved. The need for adequate fibrinogen levels and platelet numbers and function is emphasized as is the continued role for conventional blood and coagulation products. The European guidelines recommend considering the administration of PCCs or FFP for bleeding when coagulation deficiency is present.[19]

Fibrinogen is a key component of clotting; its level is among the first to decrease to critical levels during major bleeding, and observational studies have suggested an association between low fibrinogen levels and bleeding post-CPB.[124] Thus, some guidelines have recommended administration of fibrinogen in this circumstance, although the level of fibrinogen at which it should be treated is unclear. Fibrinogen commonly is replaced with cryoprecipitate, but pathogen-reduced fibrinogen concentrate is available and has been advocated for use in cardiac surgery. To assess the benefits and risks of administering fibrinogen concentrates to patients undergoing CPB, Li et al. reported on a meta-analysis of 8 RCTs involving patients at mixed or high risk of postoperative bleeding who underwent cardiac surgery involving CPB.[124] They found that administration of fibrinogen concentrate was associated with a decreased incidence of RBC transfusion but no significant decrease in number of patients receiving FFP or platelets or overall exposure to allogeneic blood products, nor did they find a significant decrease in mortality, although subgroup analysis suggested that a dose of 4 g or greater and using ROTEM/FIB-TEM–guided therapy might be beneficial. No differences were found in the incidence of stroke, myocardial

infarction, renal failure, or venous thromboembolism. The authors concluded that the evidence is insufficient to refute or support the routine perioperative administration of fibrinogen concentrate to these patients but noted the limitations of existing evidence. The accompanying editorial by Henderson et al. was more optimistic.[125] The European guidelines recommend against prophylactic administration of fibrinogen but that its administration may be considered for bleeding if the fibrinogen level is <1.5 g/L.[19]

The 2011 STS/SCA blood conservation guidelines gave a class IIb recommendation for the consideration of the use of rFVIIa for the management of intractable nonsurgical bleeding that is unresponsive to routine hemostatic therapy after cardiac procedures using CPB,[70] as do the European guidelines.[19] The STS/SCA guidelines cited an RCT on the use of rFVIIa in patients with bleeding after cardiac surgery that reported a significant decrease in redo surgery and allogeneic blood products but a higher incidence of critical serious adverse events, including stroke, with rFVIIa treatment. The STS/SCA guidelines concluded that there is little doubt that rFVIIa is associated with reduction in bleeding and transfusion in some patients. However, which patients are appropriate candidates for rFVIIa is unclear and neither the appropriate dose nor the thrombotic risks of this agent is totally clear. A Canadian registry found that rFVIIa was used in about 250 cardiac surgery patients each year between 2007 and 2010.[126] I have found no data on its current rate of use in Canada or elsewhere in the world, but I believe it continues to be commonly administered in bleeding patients post-CBB. However, little recent literature has clarified the uncertainties highlighted in the aforementioned STS/SCA guidelines.[127] A retrospective, single-center, matched cohort study that compared patients who received rFVIIa with patients who did not found that those who received rFVIIa had no increased incidence of stroke, renal failure, or mortality but a higher incidence of re-bleeding requiring redo surgery and administration of all blood products.[128] A study of propensity matched adult patients who underwent complex cardiac surgery who either received or did not receive rFVIIa found that those who received rFVIIa had a higher mortality and renal morbidity but no statistically significant increase in neurologic or thromboembolic complications.[129] A similar study of pediatric patients compared propensity matched children who did or did not receive rFVIIa.[130] Those who received rFVIIa had a higher incidence of thrombotic complications and prolonged ICU and hospital LOS but no difference in reexploration rate or 30-day mortality. A single-center observational study of patients with significant bleeding after coronary artery surgery compared those who received rFVIIa with those who did not and found that those who received rFVIIa had a higher incidence of thromboembolic adverse events and that receiving rFVIIa was the only independent predictor of thromboembolic adverse events.[131] Although its use was associated with a more rapid decrease in chest tube output and reduced blood product administration in the first 24 hours, its use was not found to be an independent predictor of reexploration for bleeding. A retrospective, single-center, observational study compared the outcome in patients who received moderate-dose (40-50 μg/kg) versus high-dose rFVIIa (90-120 μg/kg) for severe postoperative cardiac surgical bleeding.[132] There was no significant difference between the 2 doses in reduction of chest tube bleeding, transfusion requirements, or need for reexploration nor was there any difference in all-cause mortality or thromboembolism. Hoffmann et al. compared the effectiveness of even lower doses of rFVIIa (≤20 μg/kg) in patients with refractory bleeding post-cardiac surgery who failed aggressive evaluation and other hemostatic therapy.[133] Administration of low-dose rFVIIa led to complete hemostasis in 89% of these patients but was not associated with increased 30-day mortality or increased thromboembolic and other complications. Finally, in a single-center retrospective study, Harper et al. compared patients who received rescue therapy in 53 matched pairs of patients who received either rFVIIa or 3-factor PCC.[134] Those who received the 3-factor PCC had less chest tube drainage, were less likely to receive FFP and platelets, and had a lower incidence of postoperative dialysis. They observed no difference in postoperative stroke, deep venous thrombosis, pulmonary embolism, myocardial infarction, or 30-day mortality. Prophylactic administration of rFVIIa is not recommended by the European guidelines (class III).[19]

Thus, many different agents have been shown to reduce bleeding post-CPB, but as to be expected, they are all associated with some increased risk of thrombotic complications. When to use, which one to use, and at what dosage remain a clinical challenge.

Acute Kidney Injury

Renal dysfunction, or AKI, which ranges from a rise in creatinine and release of renal tubular proteins to severe renal failure requiring renal replacement therapy, remains a persistent and prevalent problem after cardiac surgery involving CPB, so-called "cardiac surgery–associated AKI." A systematic review of 32 studies of patients who underwent cardiac surgery reported an incidence of AKI of 22% (IQR 14%-34%) and of renal replacement therapy of 3.1% (IQR 2%-5%).[135] The general topic of perioperative AKI recently was reviewed by Zarbock et al.,[136] whereas O'Neal et al. reviewed cardiac surgery–associated AKI,[137] and Hoste et al. its epidemiology.[138]

Vandenberghe et al. reviewed the diagnosis of cardiac surgery–associated AKI.[139] They noted that even though it typically is diagnosed based on a rise in creatinine and reduced urine output (Kidney Disease Improving Global Outcomes [KDIGO] criteria), creatinine is slow to rise (hours to 2 d), and thus the use of various biomarkers to permit earlier recognition and therapeutic interventions are coming into practice. Prominent biomarkers include neutrophil gelatinase–associated lipocalin, tissue inhibitor of metalloproteinases 2 (TIMP-2), and insulin-like growth factor–binding protein 7 (IGFBP7). Meersch et al. observed that a urinary TIMP-2 × IGFBP7 ≥0.3 ng/mL 4 hours post-CPB was predictive of cardiac surgery–associated AKI,[140] and McIlroy et al. found that the combination of elevated urinary biomarkers (cysteine-c, kidney injury molecule-1,

chemokine ligand 2, or interleukein-18) and a rise in serum creatinine ≥0 at 3 hours was superior in predicting hospital mortality or renal replacement therapy.[141]

AKI is associated with increased morbidity and short- and long-term mortality. Even mild elevations of serum creatinine are associated with increased morbidity and mortality, whereas renal replacement therapy is associated with a mortality of as high as 60%. Features of cardiac surgery and CPB believed to contribute to AKI include the inflammatory response; ischemia/reperfusion; embolization (microparticles, air, and atheroma); hypotension; low cardiac output; elevated inferior vena cava pressure; damage–associated molecules (eg, high mobility group proteins, hemoglobin, myoglobin, and uric acid); transfusion of blood products; and administration of nephrotoxic drugs. CPB per se commonly is considered as one of the contributors to cardiac surgery–associated AKI. Based on a review of RCTs comparing off-pump versus conventional CABG, a consensus conference concluded that off-pump CABG is associated with a decreased incidence of renal dysfunction or failure at 30 days but no decrease in need for renal replacement therapy.[142]

A single-center observational study of patients who underwent cardiac surgery demonstrated hospital mortality of 1.4% in patients without preexisting renal failure, whereas hospital mortality was 10.9% in patients with preexisting renal failure.[143] In patients without preexisting renal failure, 1.4% developed nonhemodialysis acute renal failure and 1.3% dialysis acute renal failure, with respective mortalities of 22% and 65%. Diabetes mellitus, prior cardiac surgery, lower LV ejection fraction, lower baseline glomerular filtration rate, intraoperative blood product transfusion, and IABP use were risk factors for dialysis acute renal failure. Eighty-four percent of those who survived acute renal failure regained baseline renal function, whereas 11% were dialysis dependent at last follow-up.

Although previous studies have shown no association between intraoperative urine output and postoperative AKI, 2 recent single-center observational studies in noncardiac surgery found an increased incidence of AKI in patients with intraoperative oliguria.[144,145] I am unaware of similar studies reported recently in patients undergoing cardiac surgery.

Evans et al. recently reviewed renal hemodynamics during and after cardiac surgery with CPB.[146] They suggested that there is strong evidence for renal medullary ischemia and hypoxia during CPB and that monitoring for this and manipulating the conduct of CPB to minimize this effect could reduce the incidence of AKI. Evidence of such renal hypoxemia during clinical CPB was demonstrated in a recent prospective, observational study of adult patients who underwent cardiac surgery using CPB and that measured renal perfusion, hemodynamics, filtration, and oxygenation.[147] With the onset of CPB, an increase in renal vasoconstriction (~20%), decrease in percent of systemic flow to the kidney (~28%) and renal oxygen delivery (~20%), and an increase in renal oxygen extraction (~40%) were observed. After CPB, renal oxygenation was further impaired, attributed to hemodilution and an increase in renal oxygen consumption; this was associated with a 7-fold increase in the urinary N-acetyl-beta-D-glucosaminidase/creatinine ratio, a sign of tubular injury. All these changes suggested to the authors impaired renal oxygenation (ischemia) during conventional CPB. The renal resistive index also may be elevated in patients with AKI, which may reflect an increase in intracapsular pressure (ie, injury-related "renal compartment syndrome"). The renal resistive index can be measured using TEE and has been found to be elevated early post-CPB in some patients and to be an early predictor of AKI.[148-150]

Newland et al. assessed the effect of the duration of time that the inflow arterial temperature was greater than 36°C, >36.5°C, or >37°C during rewarming on the incidence of AKI in patients undergoing cardiac surgery using CPB.[151] The duration of rewarming >36°C or >36.5°C was not found to have a univariate association with AKI, but in propensity matched patients, every 10-minute increase in duration of rewarming greater than 37°C was associated with a 51% increase of AKI. A single-center observational study also assessed the effect of the duration of time during which oxygen delivery was more than or less than 270 mL/min/m^2 during CPB on the incidence of AKI.[152] The incidence of AKI was 14.3%; it was stable and low in patients with a positive area under the curve for oxygen delivery greater than 270 mL/min/m^2 but progressively increased with the greater negative area under the curve.

Based these and other data, Ranucci et al. recently reported a prospective multicenter RCT in patients undergoing cardiac surgery with CPB that compared **the incidence of AKI in** those who had oxygen delivery maintained at ≥280 ml/kg/m^2 (by increasing pump flow or Hct if necessary), what the investigators referred to as 'goal-directed perfusion' (GDP) **with those who received conventional perfusion**.[153] The incidence of AKI Network stage 1 was reduced significantly in those receiving GDP but not the incidence of AKI stage 2 or 3. In a pilot, single-center observational study, Magruder et al. compared patients managed with another GDP strategy during cardiac surgery in 88 patients propensity matched with historical control patients.[154] Their GDP included minimizing the CPB circuit volume, avoiding mannitol in prime, avoiding hypovolemia, maintaining oxygen delivery >300 mL/min/m^2, monitoring NIRS to maintain at baseline, using hemoconcentrator and zero balance ultrafiltration, using heparin infusion on CPB, minimizing the use of phenylephrine and instead increasing CPB flow if possible, rewarming no faster than 1°C/5 minutes, and keeping the temperature difference between arterial and venous blood during rewarming <3°C. Patients managed with this GDP received less phenylephrine during CPB, had a higher nadir oxygen delivery, and had a less percent increase in creatinine and a lower incidence of AKI.

It has been suggested that the administration of statins may reduce the risk of cardiac surgery–associated AKI. This was assessed in a recent meta-analysis of 8 RCTs.[155] Overall, perioperative statin therapy was not associated with a decreased incidence of. However, subgroup analysis of studies with a clear definition of AKI, studies with a sample size >500, and studies of higher quality (**Jadad** score >3) demonstrated that perioperative statin therapy increased the risk of AKI. Additional analysis suggested that the use of rosuvastatin was associated with a higher risk than use of atorvastatin and that postoperative continuation seemed to confer higher risk.

Table 5
Results of Some Studies Published in 2017 Regarding Interventions That May Influence the Incidence of Cardiac Surgery–Associated AKI

May reduce AKI after CPB
High density lipoproteins may improve AKI rates
Prophylactic furosemide infusions during and after CPB improve AKI rates
Dexmedetomidine during CPB improves AKI rates
Peritoneal dialysis in children
Optimization of KDIGO "bundle" (reduce hyperglycemia, optimize hemodynamics, avoid nephrotoxic drugs)
Atrial natriuretic peptide
Remote ischemic preconditioning during CPB
Worsen AKI rates after CPB
Hydroxyethyl starch prime may worsen
Transfusion of red blood cells increases risk of AKI
Did not affect AKI after CPB
Ascorbic acid
Levosimendan
Bicarbonate
Remote ischemic preconditioning
Atrial natriuretic peptide
Preoperative b-blocker
Allogeneic mesenchymal stem cells
Statin therapy
Spironolactone after CPB
Proposed but not tested
Small interfering RNA
Hyperoxygenation during CPB

Abbreviations: AKI, acute kidney injury; CPB, cardiopulmonary bypass; KDIGO, Kidney Disease Improving Global Outcomes; RNA, Ribonucleic Acid.
Modified from Ferraris.[165]

The effect of levosimendan on the incidence of AKI continues to be debated. Several recent studies,[156-158] but not all,[159] have reported a trend for less evidence of renal injury with the use of levosimendan during cardiac surgery, but these were not statistically significant. A meta-analysis of 18 levosimendan trials found that in all studies the incidence of AKI was lower in patients who received levosimendan, as was the incidence of renal replacement therapy.[160] However, on analysis of the 4 studies with a low risk of bias, these benefits were not demonstrated.

A meta-analysis of 10 RCTs comparing patients who underwent cardiac surgery and received or did not receive dexmedetomidine found that dexmedetomidine reduced the incidence of postoperative AKI without a difference in postoperative mortality.[161] A subsequently published single-center RCT reported a decrease in postoperative levels of blood urea nitrogen, creatinine, and serum neutrophil gelatinase–associated lipocalin levels at some time points in patients who received dexmedetomidine versus those who did not.[162]

Meersch et al. reviewed the prevention of AKI[163] and recently reported encouraging results of a single-center pilot study on the effect of implementing the KDIGO bundle approach post-cardiac surgery to patients predicted to be high risk of AKI identified using urinary biomarkers ([TIMP-2] × [IGFBP7]) at 4 hours post-CPB.[164] Thirty-one percent of the postoperative patients were found to have a urinary TIMP-2 × IGFBP7 ≥0.3 ng/mL, which in their previous study was found to be predictive of AKI.[140] These patients were randomly assigned to receive conventional postoperative care or the KDIGO cardiothoracic surgery bundle consisting of avoidance of nephrotoxic agents, discontinuation of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers for the first 48 hours after surgery, close monitoring of serum creatinine and urine output, avoidance of hyperglycemia for the first 72 hours, consideration of alternatives to radiocontrast agents, close hemodynamic monitoring, and optimizing the volume status. Patients who received the KDIGO bundle had a lower incidence of AKI and of moderate or severe AKI.

In an editorial of the previously summarized study by Ranucci et al. on GDP,[153] Ferraris reviewed the various methods introduced to reduce the incidence of AKI post-CPB.[165] A list of the results of studies published in 2017 that Ferraris found are included in Table 5.

Postoperative delirium (POD) and Postoperative cognitive dysfunction (POCD) After CPB

"Although postoperative delirium and postoperative cognitive dysfunction are distinct disorders ... similarities in their likely mechanisms, risk factors, and long-term sequelae suggest they may be part of an underlying neurobiologic continuum."[166] The 2018 recommendations for the nomenclature of cognitive change associated with anesthesia and surgery recommend that preexisting cognitive impairment, POD; and early (first 30 d), intermediate (30 d-12 mo), and late (beyond 12 mo) POCD be included under the overarching term of "perioperative neurocognitive disorders."[167] They recommend the severity to be indicated as "mild" or "major" based on the *Diagnostic and Statistical Manual for Mental Disorders, 5th edition* criteria. Abnormalities detected in the first 30 days are termed "delayed neurocognitive disorders" ("NCD"), those present between 30 days and 12 months are termed "postoperative NCD" ("POCD"), and those present beyond 12 months are termed "NCD." Thus, in the recent informative review article by Berger et al. on neurocognitive function after cardiac surgery, which, in my opinion, should be read by all cardiac anesthesiologists, they refer to both delirium and POCD as types of "neurocognitive dysfunction."[166] The general topic of perioperative neurocognitive disorder recently was addressed by an international workshop.[168]

POD

POD is prevalent and is associated with increased morbidity, hospital LOS, costs, and perhaps acute and long-term mortality.[169] It is particularly common after cardiac surgery, and its incidence, risk factors, possible pathophysiology/etiology, and consequences were reviewed recently in a special section of the August 2017 issue of the *British Journal of Anaesthesia* and in a number of other articles.[166,170-173]

The reported incidence of POD after cardiac surgery has varied from about 7.6% to 12%,[174-177] 26%,[178] and ~55%,[179-182] likely related to the type of surveillance and diagnostic criteria used and perhaps patient population and management. Older age is strongly associated with the incidence of POD. Leenders

et al. found an incidence of 0% in patients <50 years old, ~8% in patients 50 to 69 years old, 14.5% in patients 70 to 79 years old, and 54% in patients >80 years old.[176] In a retrospective analysis of prospectively collected data, Kotfis et al. found an incidence of 21.4% in patients ≥65 years old and 31.5% in patients ≥80 years old.[181]

A review of 196 articles listing possible risk factors identified at least 123 possible risk factors, 25 of which were considered modifiable.[170] The following 8 risk factors were mentioned in more than 10 studies: older age, cardiac status, personality traits, cerebrovascular or peripheral vascular disease, metabolic syndrome, preoperative cognitive impairment, type of surgery, and duration of surgery. Gosselt et al. reviewed high-quality studies that identified risk factors for POD after on-pump cardiac surgery.[183] They concluded strong evidence supported the association of POD with increasing age, previous psychiatric conditions, cerebrovascular disease, preexisting cognitive impairment, type of surgery, and perioperative blood product administration, but not CPB duration or sex. An RCT demonstrated a decreased incidence of POD in those managed with a higher MAP (80-90 mmHg) versus a lower level (60-70 mmHg) during on-pump CABG.[24] On the other hand, Hori et al. found a possible association of POD with a MAP above the upper limit of autoregulation.[31,32] A 2-center observational study of patients who underwent cardiac surgery found an incidence of POD of 11.5.%.[177] Independent risk factors identified on multivariate logistic regression analysis included age >70 years, higher EuroSCORE points, longer aortic occlusion time, and profuse chest tube drainage.

CPB (*v* off-pump CABG),[184,185] long duration of CPB,[186] low arterial pressure, low hemoglobin, and transfusion of RBC and platelets also have been suggested as risk factors.[178,180] A retrospective study comparing the incidence of POD after off-pump versus on-pump CABG found that the incidence of POD was higher in the on-pump cohort (23.8% *v* 19.0%).[185] Furthermore, they found that the incidence of POD increased with duration of CPB. A prospective, observational study found that duration of mixed venous oxygen <75%, increased fluid balance, and older age were independent predictors of POD.[180] A retrospective analysis of prospectively collected data on patients who underwent on-pump CABG with monitoring of oxygen delivery during CPB found that 12% developed POD.[176] Patients who developed POD had a lower nadir oxygen delivery. On univariate analysis, all parameters of reduced oxygen delivery were associated with POD, but on multivariate analysis, none was associated with POD. However, cross-clamp time, older age, kidney dysfunction, and previous cognitive impairment were associated with POD.

Most studies have reported that the occurrence of POD is associated with increased morbidity and LOS, and some have found it to be associated with increased hospital mortality.[181] The long-term consequences of POD are unclear. Crocker et al. reported a systematic review of the long-term effects of POD after cardiac surgeries.[174] They concluded that POD was strongly associated with a greater likelihood of readmission to the hospital, decreased cognition, functional decline, lower health-related quality of life, and death. In a systematic review and meta-analysis of 34 studies of patients who underwent noncardiac surgery, Hamilton et al. found that POD was associated with a 4-fold increase in the odds of death up to beyond 6 months (21.8% *v* 8.7%).[169] However, they noted that few studies controlled for confounders and in studies that did control for confounders, there was no statistically significant association between POD and mortality.

Of particular relevance to this discussion of postoperative neurocognitive dysfunction is the possible relationship between POD and subsequent POCD/dementia. In an analysis of patients who underwent a neuropsychological test battery before and 1 month and 1 year after elective cardiac surgery with CPB, Sauër compared the incidence of POCD in patients who did or did not develop POD.[175] Post-discharge mortality at 1 year was not different in the 2 groups. Cognitive performance decreased in both groups at 1 month but was greater in those with POD. Cognitive performance improved at 1 year in both groups, but less in those with POD. POD was not associated with overall cognitive decline but was found to be associated with decline in some domains (motor skills and executive function). Predisposition for POD was observed in patients with worse baseline performance in attention-requiring tasks. In a prospective, observational study of patients who underwent cardiac surgery with CPB, Brown et al. also compared results of neuropsychological testing in patients who did or did not experience POD.[179] POD occurred in 53.5%. Composite cognitive score at 1 month declined greater in those with POD. However, at 1 year there was no difference in change in the overall cognitive score between the 2 groups, but there was a greater decline in processing speed in the POD group (Fig. 5 and 6). In a prospective longitudinal cohort study, Lingehall et al. reported the incidence of postoperative dementia in patients ≥70 years old (mean 76.5 y) followed-up for up to 5 years after cardiac surgery involving CPB.[182] None had dementia preoperatively, but 8% had mild cognitive impairment (MCI) preoperatively. Fifty-six percent of all patients developed POD, and 26% developed postoperative dementia by 5 years. Dementia developed in 41% of those who experienced POD and in only 8% of those who did not. Dementia developed in 89% of those with preexisting MCI and in 21% without evidence of preoperative MCI. Multivariable logistic regression found that older age, POD, and MCI were associated with dementia occurrence.

POCD

Evered et al. recently reviewed POCD after noncardiac surgery,[186] whereas Berger et al. reviewed neurocognitive dysfunction after cardiac surgery,[166] and Bhamidipati et al. reviewed cognitive outcomes after CABG.[187] The incidence of POCD depends on the measurement method used and time of the examination. It has been reported to be as high as 33% to 83% at 1 week or at time of discharge,[188] 25% to 40% at 1 month, 20% to 30% at 3 months, 25% at 6 months, and 26%[183] to 40% at 5 years. Berger et al. thoroughly reviewed the possible pathophysiologic mechanisms for neurocognitive dysfunction after cardiac surgery and possible methods of

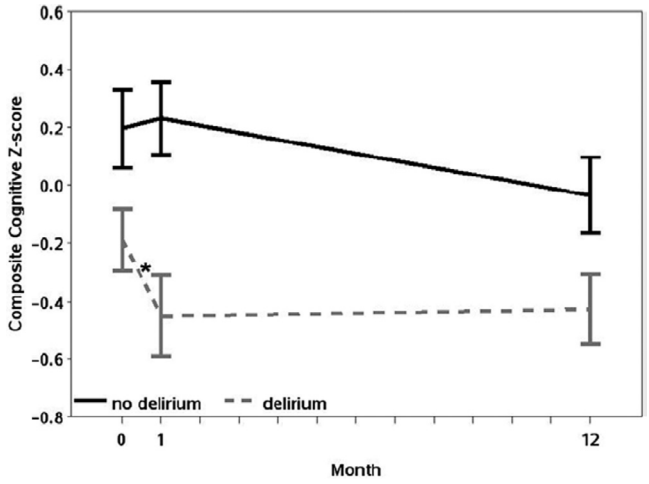


Fig 5. Effect of postoperative delirium on postoperative cognitive decline. Note that patients with postoperative delirium had lower baseline cognitive scores compared with those who did not have postoperative delirium and in distinction to the latter group, their scores declined at 1 month and remained about the same at 12 months.

From Brown et al.[179]; used with permission.

ameliorating it (Fig 7 and Table 6).[166] They concluded that POCD is likely multifactorial and that bundled management protocols likely will be required to improve clinical outcomes. Key contributors to POCD identified by Berger et al. included inflammation, embolization, endothelial dysfunction, cerebrovascular disease, and perhaps preexisting abnormal neuronal/synaptic function (eg, latent Alzheimer's syndrome). They suggested that off-pump CABG does not significantly reduce neurocognitive dysfunction, especially at 1 year, but that conduct of CPB may. The latter may include management of arterial pressure, Hct, glucose, and temperature, and they suggested that both high and low values may be detrimental. They opined that optimal MAP likely needs to be individualized based on the individual patient's autoregulatory range. The possible role of depth and choice of anesthesia also was discussed. On the basis of preliminary data, they suggested that excessively deep anesthesia (eg, low bispectral index values) may be associated with worse POD and POCD. As mentioned earlier, Lingehall et al. identified older age, preoperative MCI, and POD as independent risk factors for developing dementia post-CPB.[182]

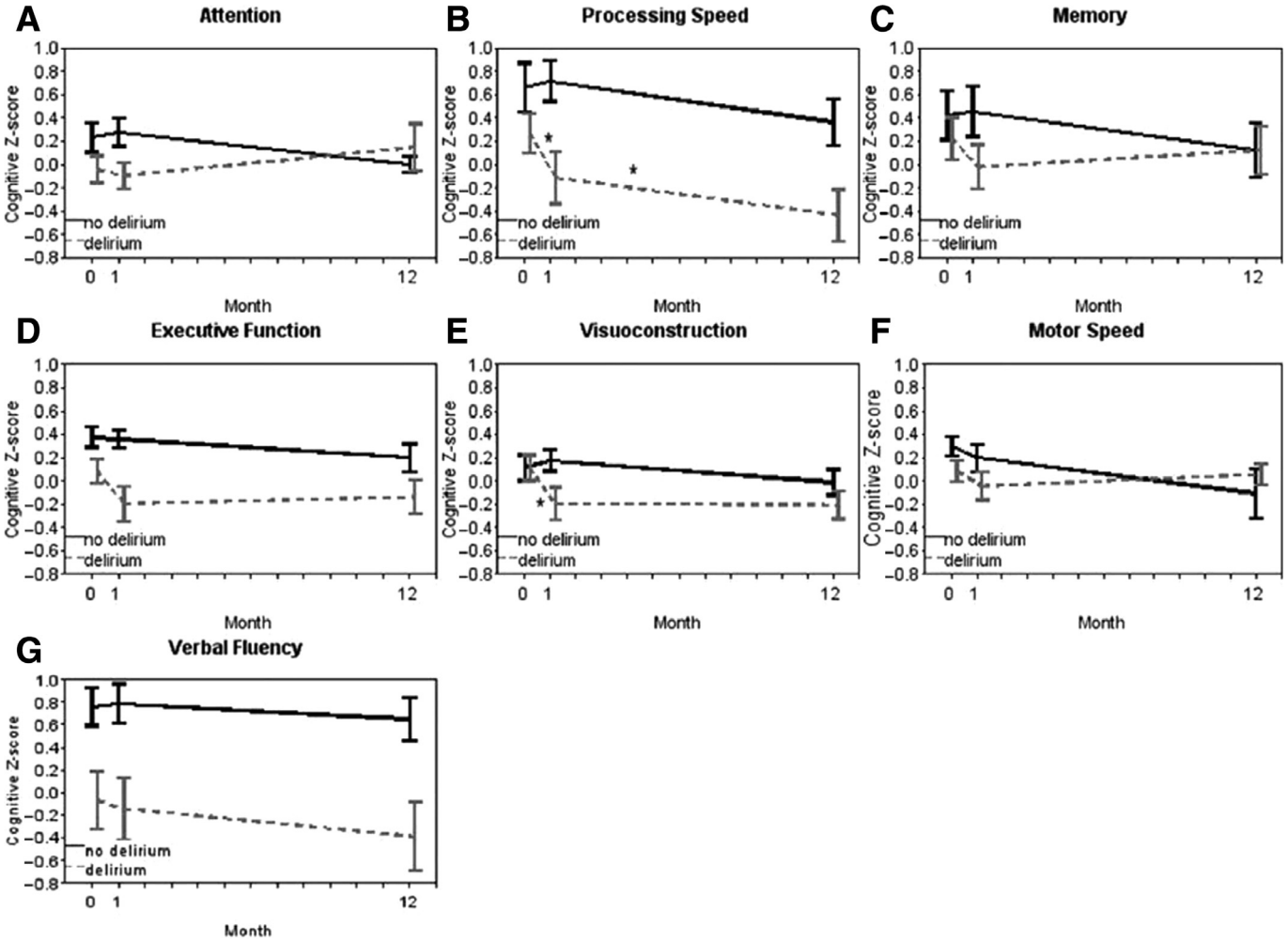


Fig 6. Effect of postoperative delirium on postoperative cognitive decline.

From Brown et al.[179]; used with permission.

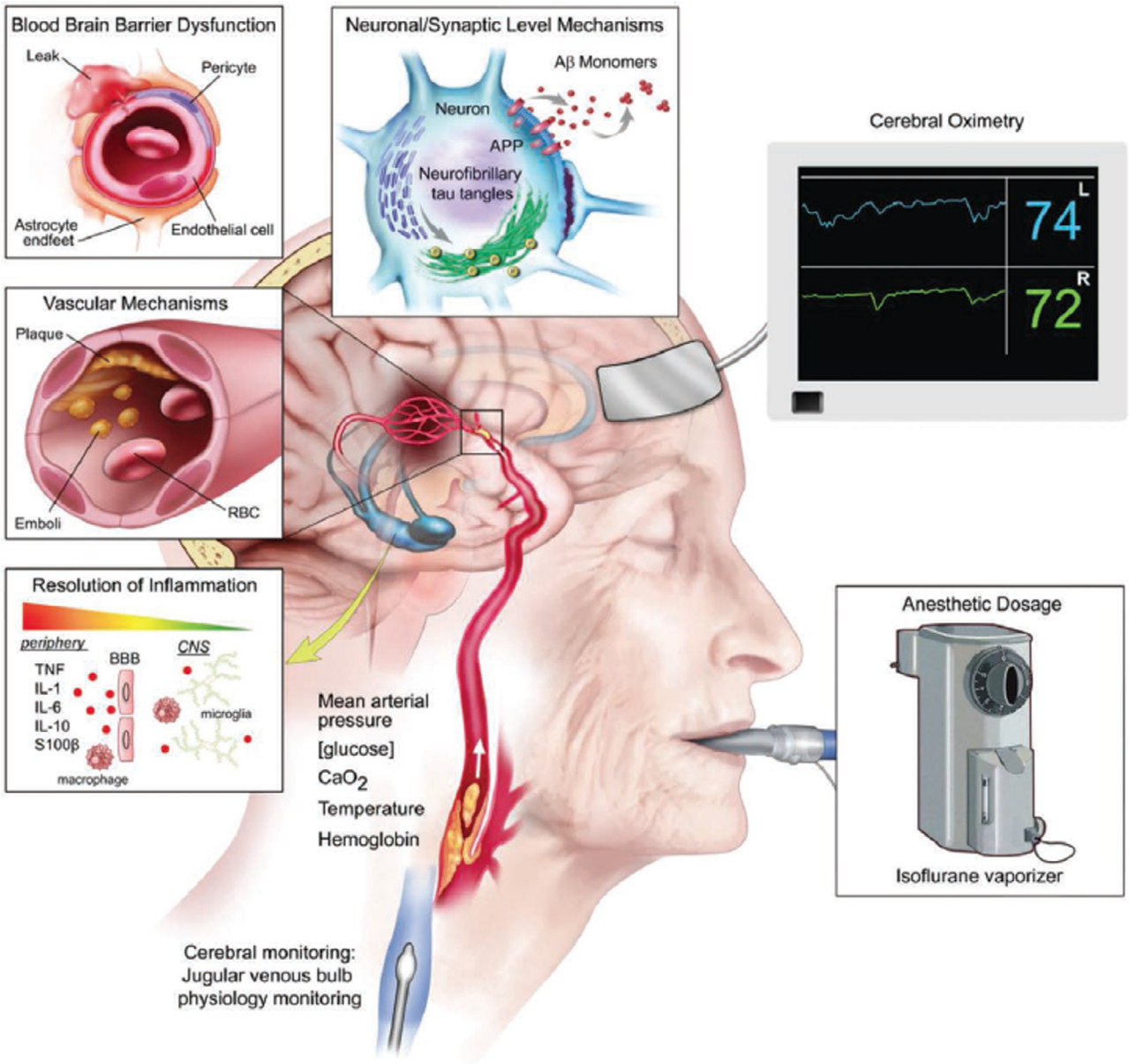


Fig 7. Pathophysiologic mechanisms that may play a role in postoperative cognitive dysfunction and/or delirium. BBB, blood brain barrier; CaO_2, arterial oxygen content; CNS, central nervous system; IL, interleukin; RBC, red blood cells.

From Berger et al.[166]; used with permission.

Thromboembolism from the ascending aorta associated with surgical manipulation and cannulation is believed to be an important contributor to stroke after cardiac surgery and use of embolic protections devices have been advocated by some. However, a recent multicenter RCT found that use of 2 such devices (the suction-based extraction aortic cannula CardioGard (CardioGard Medical, Or-Yehuda, Israel) and the intra-aortic filtration cannula [Embol-X; Edwards Lifesciences, Irvine, CA]) was not associated with a reduced incidence of evidence of diffusion-weighted magnetic resonance imaging cerebral infarcts, clinical strokes, POD, or mortality but was associated with an increased incidence of AKI.[189]

The role of type of anesthesia is unclear. A systematic review and meta-analysis of RCTs found that patients who received volatile agents had lower S100B levels and better mini-mental state scores than those who received total intravenous anesthesia.[190] The implications of these results need to be evaluated with large RCTs using neuropsychological testing late postoperatively.

Inflammation is considered to be an important contributor to POCD, and hence possible benefits of administration of dexamethasone have been explored. However, an earlier multicenter RCT of patients who underwent cardiac surgery with CPB found that at 1 month patients who received dexamethasone had a higher incidence of POCD and a higher incidence of POCD at 12 months.[191] On the other hand, a more recent single-center RCT reported that a single dose of preoperative dexamethasone was associated with a decreased incidence of POCD and systemic inflammatory response syndrome at 6 days.[192] Adding to this quandary, an observational study of patients ≥60 years old who underwent cardiac surgery with CPB demonstrated no

Table 6
Factors That May Contributed to Postoperative Delirium and/or Postoperative Cognitive Dysfunction After Cardiac Surgery

Preoperative/Postoperative
Modifiable
1. Preoperative blood pressure control
2. Preoperative glycemic control
3. Sleep disruption/sleep apnea
4. Alcohol abuse
5. Postoperative sedation, analgesia, and delirium management
Partly modifiable
1. Patient frailty
2. Preoperative cognitive function
3. Preoperative neurocognitive reserve
4. Depression
Nonmodifiable
1. Patient chronologic age
Intraoperative
Modifiable
1. Use of cardiopulmonary bypass
2. Temperature management
3. Surgery duration
4. Arterial pressure management
5. Glycemic control
6. Hemodilution
Partly modifiable
1. Surgical approach (ie, median sternotomy *v* lateral thoracotomy, on-pump *v* off-pump CABG
2. Anesthetic dosage and electroencephalography responses
Nonmodifiable
1. Direct myocardial injury

Abbreviation: CABG, coronary artery bypass grafting.
Modified from Berger et al.[166]

difference in incidence of POCD at 6 days in those with an a priori defined low or high inflammatory response.[193]

The debate on arterial pressure management during CPB was discussed earlier but is relevant to this discussion of POCD. A previously mentioned RCT found less decline in mini-mental status scores in patients managed with a higher (80-90 mmHg, average 84 ± 11 mmHg) versus lower (60-70 mmHg, average 65 ± 8 mmHg) MAP during CPB for CABG.[24] However, Berger et al. suggested that keeping MAP within the autoregulatory range determined in each individual patient might be optimal.[166]

A small, single-center, observational study of patients who underwent on-pump CABG found no association between short-term episodes of decreased regional cerebral oxygen saturation (NIRS) (which occurred in 34%) and POCD at 10 days (which occurred in 37%).[194] However, in apparently this same group of patients, they found that the duration of the single longest period of cerebral autoregulation impairment was associated with occurrence of POCD (critical duration 5 min).[188]

A prospective, single-center observational study of patients who underwent elective cardiac surgery found that the 6-minute walk distance was an independent predictor of the incidence of POCD measured at 14 days using the Mini-Mental State Examination score.[195]

In a provocative preliminary study, Smith et al. measured regional cerebral perfusion with magnetic resonance perfusion imaging and cognitive function in patients who underwent on-pump cardiac surgery.[196] Baseline cerebral perfusion was lower in these patients compared with matched control patients with cardiac disease, but at 6 weeks cerebral perfusion had increased and matched that in the control group; perfusion was similar in both groups at 1 year. Increases in perfusion in the cardiac surgery patients were associated with improved psychomotor speed but not in verbal or visual memory or executive function. These data support the hypothesis that cardiac surgery requiring CPB could have beneficial effects on cerebral perfusion and cognitive function in some patients despite the potential adverse effects that have been reviewed.

The Fifth International Perioperative Neurotoxicity Working Group recently provided recommendations for optimizing postoperative "brain health," including the following[168]:

1. All patients older than 65 should be informed of the risks of perioperative neurocognitive disorder, including confusion, inattention, and memory problems after undergoing surgery.
2. Baseline cognition should be objectively evaluated with a brief screening tool during preoperative evaluation in all patients older than 65 and in any patient with risk factors for preexisting cognitive impairment.
3. Avoid centrally acting anticholinergics, benzodiazepines, and meperidine.
4. Avoid relative hypotension.
5. Maintain normothermia.
6. Monitor age-adjusted end-tidal minimal alveolar concentration.
7. Use electroencephalography-based intraoperative brain monitoring to titrate anesthetic management in older adults.
8. Strive to optimize cerebral perfusion.

CPB During Pregnancy

Earlier meta-analyses have suggested that the outcome of surgery involving CPB during pregnancy in the modern era is quite good. Thus, Jha et al. conducted a meta-analysis of 10 studies that included at least 4 cases, published since 1990 (154 women), on the outcome associated with CPB during pregnancy.[197] Most surgeries were performed during the 2nd trimester; mitral stenosis was the most common indication (29%), followed by prosthetic valve dysfunction (26%) and aortic stenosis (13%). Eighty-nine percent of procedures were urgent or emergency. Maternal mortality was 11.2% (95% confidence interval [7-19]), and pregnancy loss was 33% (95% confidence interval 25-41). Maternal complications occurred in 8.8% and neonatal complications 10.8%. Preterm labor occurred in 28% and cesarean delivery in 33%. According to Jha et al, these outcomes are worse that those reported in earlier literature. Possible explanations are discussed in an accompanying commentary by Oliver.[198] Clearly, additional research is required to reduce this apparently high incidence of maternal mortality and fetal loss associated with CPB.

Lung Management During CPB

Pulmonary complications and acute lung injury are common after cardiac surgery. During CPB the lungs are deprived of pulmonary blood flow, and bronchial arterial flow also has been shown to decline. Thus the lungs become somewhat ischemic. Typically, ventilation is interrupted, and the lungs are exposed to atmospheric pressure during CPB based on the assumption that ventilation is not required and to facilitate surgical exposure. The possible benefits of applying continuous positive airway pressure (CPAP) or intermitted ventilation during CPB (and if so, at what pressures, tidal volumes, rates, and inspired oxygen concentration) has been debated with conflicting experimental and clinical data.[199,200] In an attempt to shed light on this controversy, 2 meta-analyses of RCTs recently were reported.[201,202] Chi et al. reported on an RCT of 17 trials (1,169 patients) comparing ventilation versus apnea during CPB.[201] Ventilation was associated with a significantly higher partial pressure of arterial oxygen/fraction of inspired oxygen ratio (~25 mmHg) and lower $AaDO_2$ (~50 mmHg) immediately post-CPB, but no difference in incidence of postoperative pulmonary complication or hospital LOS was observed. The authors evaluated the quality of the studies to be very low. Wang et al. reported on a meta-analysis of 15 RCTs in 749 patients who underwent CPB, comparing the effect of either CPAP or ventilation versus apnea.[202] CPAP versus apnea was associated with a small improvement in hypoxemia score (partial pressure of arterial oxygen/fraction of inspired oxygen ratio) within 4 hours after CPB (31 mmHg). Ventilation versus apnea was not associated with improved hypoxemia scores nor diffusion capacity. Neither CPAP nor ventilation was associated with fewer pulmonary complications, shorter mechanical ventilation, or hospital stay. Thus, current data suggest that CPAP or ventilation versus apnea during CPB temporarily may improve oxygenation, but there is little evidence that it has important clinical significance. We look forward to the results of the large multicenter RCT CPBVENT 2014 that will compare outcomes using CPAP, ventilation, or apnea during CPB.[203]

Central Arterial-to-Radial Pressure Gradients During CPB

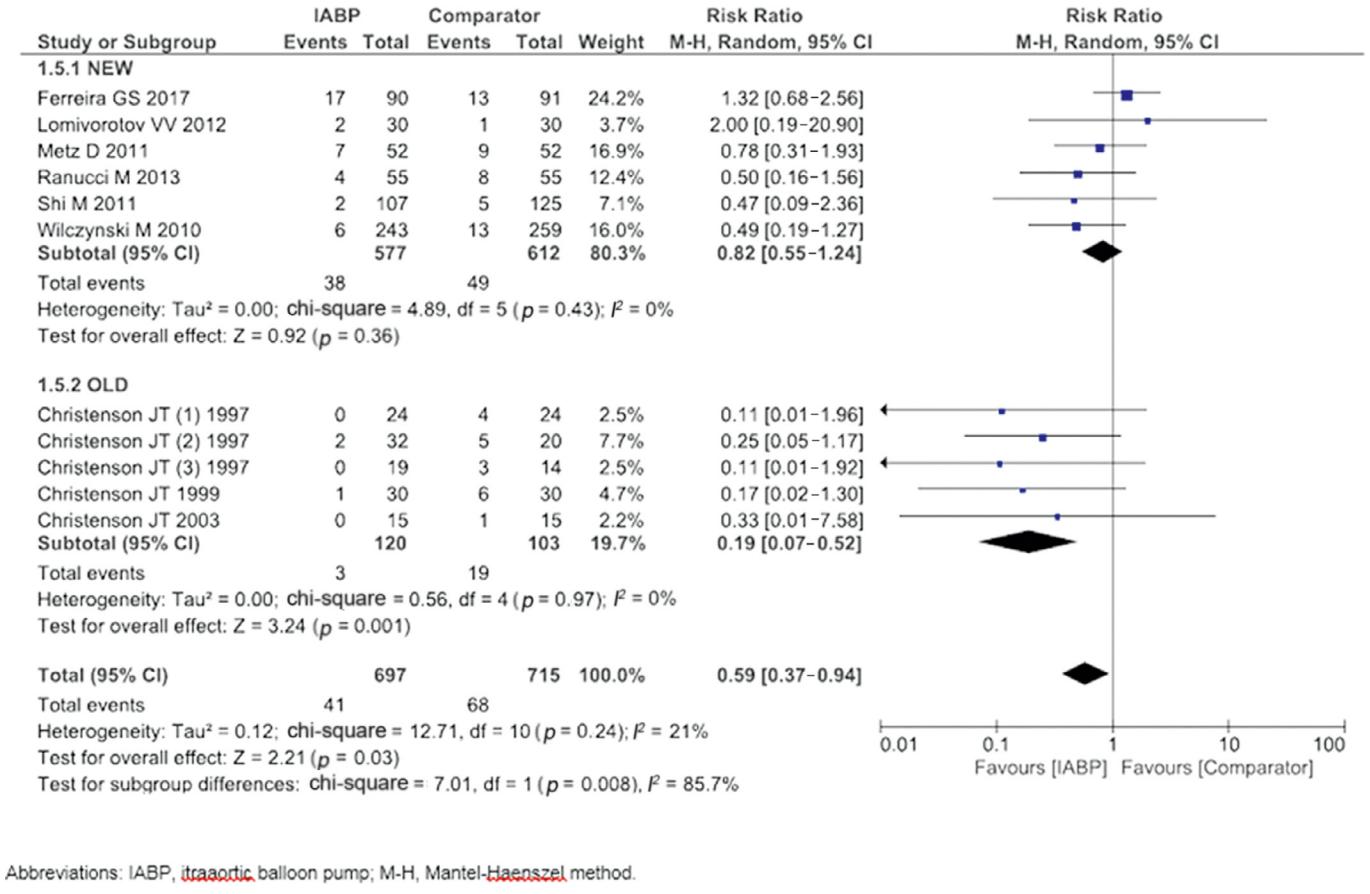
The relative frequent appearance of gradients between the central and radial artery pressures has been recognized for more than 30 years. The major significance to the practice of cardiac anesthesia is that if the radial artery pressure is clinically significantly (but falsely) low, it can lead to mismanagement of the patient. It also raises the question of which is the best site to monitor arterial pressure in patients undergoing CPB. The definition of a significant pressure gradient, its incidence, pathophysiology, and risk factors continue to be debated. Adding to their earlier smaller prospective, observational study,[204] the group at the Montreal Heart Institute where they nearly routinely (~80%) insert both radial and femoral artery lines in patients undergoing CPB reported on a retrospective, observational study in 435 patients.[205] The incidence of a "significant" pressure gradient (defined by them as a systolic gradient ≥25 mmHg or MAP gradient ≥10 mmHg) was 34%. Independent variables associated with the occurrence of a gradient included lower BMI, longer aortic cross-clamp time, reduced fluid balance, and preoperative hypertension. In their smaller prospective study, independent predictors also included a higher Parsonnet risk score and shorter patient height.[204] The cause of this gradient and the questions of whether one should rely on radial artery lines for cardiac surgery patients (and if not for all patients, in which patients) and which site (eg, brachial, axillary, femoral) should be used remain to be resolved.

Use of Prophylactic Perioperative IABP

The benefits of prophylactic IABP during cardiac surgery in high-risk patients remain controversial. A single-center RCT in high-risk patients (41% with LV ejection fraction ≤40%, 36% with EuroSCORE ≥6, and 23% meeting both criteria 23%) who underwent cardiac surgery found no difference in the incidence of the primary composite outcomes (30-d mortality or major postoperative complications) or in any of the components, including mortality, with or without prophylactic IABP.[206] In the same article, the authors also reported on a systematic review and meta-analysis of 11 single-center RCTs. They found a lower mortality in the IABP groups (RR 0.59) but observed significant evidence of publication bias, and their meta-regression showed mortality benefit only in studies performed before 2010 (Fig. 8 and 9). A recent propensity matched cohort of patients with left main coronary artery disease who underwent isolated CABG with or without prophylactic use of IABP also observed no difference in 30-day mortality or any other adverse outcomes.[207]

del Nido Cardioplegia

del Nido cardioplegia solution has been used extensively in congenital heart surgery for more than 20 years and more recently for adults. It is a blood:crystalloid (Plasmalyte A) (1:4) solution containing potassium (~26 mEq/L), lidocaine (~130 mg/L), magnesium (~2 g/L), sodium bicarbonate (~13 mEq/L), and mannitol (~3.3 g /L) administered as a single dose and usually not repeated for 60 to 90 minutes. Ad et al. reported on their results in an RCT of its use in first-time adult cardiac surgery.[208] The del Nido group showed higher return to spontaneous rhythm (97.7% *v* 81.6%) and an insignificant lower requirement for inotropic support (65.1% *v* 84.2%) and a lower increase in troponin levels. There was no difference in CPB or cross-clamp time or incidence in STS-defined morbidity, which was low in both groups. In the accompanying editorial, Lazar asked the question "What, then, is the current role of DN cardioplegia in adult cardiac surgery?"[209] He concluded that on the basis of this and other limited, retrospective, small series of stable, healthy patients undergoing less complex procedures, del Nido cardioplegia may result in myocardial protection that is equivalent but not superior to current multidose blood cardioplegia techniques. However, Lazar hypothesized that it might be shown to be beneficial in other patient groups



Abbreviations: IABP, itraaortic balloon pump; M-H, Mantel-Haenszel method.

Fig 8. Effect of prophylactic intra-aortic balloon pump on mortality. Forest plot of meta-analysis, new versus old reports. Note the significant mortality benefit associated with use of prophylactic intra-aortic balloon pump in "older" articles (published before 2004) but not in "new" articles (published between 2010 and 2017). CI, confidence interval; IABP, intra-aortic balloon pump.

From Rocha Ferreira et al.[206]; used with permission.

such as those with significant multivessel coronary artery disease with LV hypertrophy, in whom cardioplegic delivery may be an issue; patients with a reduced ejection fraction; patients who require a longer period of cross-clamping for more complicated procedures; and patients with pulmonary hypertension and reduced right ventricular function. Lazar also suggested that another issue that must be resolved is that when the cross-clamp time exceeds 60 minutes, when should the next dose of del Nido cardioplegia be given and how much? To answer these questions, it will be necessary to proceed with lines of investigation that initially led to the development of cardioplegia in cardiac surgery.[209]

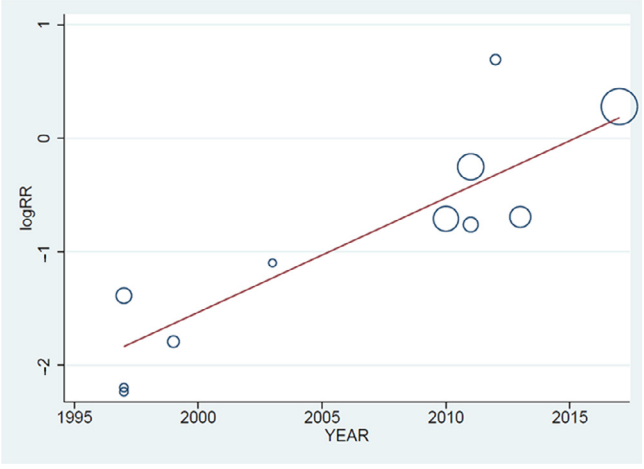


Fig 9. Effect of prophylactic intra-aortic balloon pump on mortality. Meta-regression analysis of effect of time of publication of study. Note progressively less mortality benefit found with use of prophylactic intra-aortic balloon pump from time of publication of studies starting in 1997 until 2016. logRR, log relative risk of mortality.

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Dosing Antibiotic Prophylaxis During CPB

Evidence from the limited pharmacokinetic studies suggests that subtherapeutic concentrations may occur when conventional dosing regimens of antibiotics are used. In their provocative review, Paruk et al. provided evidence suggesting that prophylactic dosing regimens may need to be re-assessed to ensure sufficient drug exposures that will minimize the risk of surgical site infections.[210] There is concern that when CPB is initiated, the plasma antibiotic concentration may fall below the minimum inhibitory concentration required for the relevant pathogens. It is customary for many to add an extra dose of prophylactic antibiotic within the CPB circuit or to re-dose after completion of CPB in anticipation of anticipated decreases in antibiotic

concentration during the procedure. Use of continuous or extended infusion also could be an effective means of maximizing antibiotic exposure. The benefits of continuous infusions of antibiotics at reducing surgical site infections in cardiac surgery were reported in recent observational studies from a single center,[211,212] but as Paruk et al. indicate, much additional research is needed to clarify optimal dosing regimens in cardiac surgery.[210]

Levosimendan

A consensus conference in 2015 recommended the use of levosimendan in low ejection fraction patients undergoing CABG to reduce mortality.[7] This may need to be reconsidered on the basis of recent studies. One multicenter, placebo-controlled RCT (LEVO-CTS) of the prophylactic perioperative infusion of levosimendan in patients with an LV ejection fraction ≤35% demonstrated no difference in the incidence of the primary endpoint (composite of 30-d mortality, renal replacement therapy, perioperative myocardial infarction, or mechanical cardiac assistance through d 5); in the composite outcome of 30-day mortality or use of mechanical cardiac assistance through day 5; or in 30-day mortality in the levosimendan versus placebo groups.[157] Another multicenter, placebo-controlled trial (CHEETAH) of patients who required perioperative hemodynamic support after cardiac surgery was stopped for futility after finding no differences in 30-day mortality nor in duration of mechanical ventilation or ICU or hospital LOS.[158] Yet another multicenter RCT (LICORN trial) that compared the outcome in patients with an LV ejection fraction ≤40 who underwent isolated or combined CABG who received either a 24-hour infusion of levosimendan or placebo demonstrated no difference in the incidence of the composite outcome (prolonged catecholamine infusion, use of LV mechanical assist device, or renal replacement therapy) or 28-day mortality.[159]

Because these 3 studies were published in 2017, 2 meta-analyses of RCTs on the use of levosimendan in cardiac surgery including these 3 recent studies[157-159] have been published.[160,213] Zhou et al. included 30 RCTs in their meta-analysis.[213] In their analysis of 20 studies that evaluated perioperative mortality, the use of levosimendan was associated with a decrease in perioperative mortality (5.8% *v* 8.5%). However, a subset analysis of the 8 trials published after 2015 found no statistically significant decrease in mortality, and a meta-regression indicated that the publication year influenced the association between levosimendan and mortality (Fig 10). Putzu et al. included 40 RCTs in their meta-analysis and sequential analysis.[160] Again, overall use of levosimendan was associated with a lower postoperative mortality, AKI, and renal replacement therapy. However, a pooled analysis of the 5 low-risk-of-bias studies found no statistically significant decrease in mortality, AKI, and renal replacement therapy but a possible increase in supraventricular tachycardia in those who received levosimendan.

Thus, recently reported studies and those with a low risk of bias do not support the advantages of using levosimendan. A recent panel of experts concluded that levosimendan is safe and effective, but the effect is not large and cannot be recommended for routine use in all cardiac surgery settings.[214] The reader also is referred to the previous discussion of the possible favorable effect of levosimendan on cardiac surgery–related AKI.

Early CPB After Stroke From Infective Endocarditis

Infective endocarditis (IE) is becoming an epidemic, and cardiac surgeons and anesthesiologists are frequently faced with the dilemma of when to perform surgery on such patients who have experienced a recent stroke, which may occur in up to 40% of cases of IE.[215] Surgery for IE is associated with higher risk of neurologic complications than valve surgery in non-IE patients, including hemorrhagic transformation of ischemic strokes and new ischemic or hemorrhagic lesions.[215] Older studies suggest that the risk of surgery is lower when the procedure is delayed by 2 to 4 weeks.[215] More recent studies suggest that the risk of early surgery is lower than previously believed and that early surgery is reasonable in patients with compelling indications for surgery, including hemodynamic instability, uncontrolled infection, or high risk for recurrent embolization with low risk for hemorrhagic transformation.[215] In their review of this dilemma, Hodges et al. concluded that the decision about surgical timing should be made by a multidisciplinary team, taking into account the patient's hemodynamic status, risk of new or recurrent embolization, and risk of neurologic deterioration with valve surgery but that there are still insufficient data on the timing of surgery for IE complicated by ischemic stroke and that only careful neurologic evaluation and brain imaging of all patients with IE preoperatively will eventually improve the precision of prognostication and decision-making.[215]

To address this issue, Ghoreishi et al. reported on a single-center retrospective review of consecutive patients who underwent early surgery (median time from admission to surgery was 5 d) for active mitral valve IE from 2003 to 2015.[216] Patients were categorized into the following 2 groups: the 174 with no preoperative acute stroke (clinical, radiographic, or both) and the 69 with stroke. Among patients who presented with stroke, 33% were asymptomatic and had only positive imaging findings. The rate of postoperative stroke was not different between the 2 groups (4% in each). Only 1 patient developed a hemorrhagic conversion. Surgical mortality was identical in both groups (7%). The authors concluded that mitral valve surgery for IE and acute stroke can be performed early with a low risk of postoperative neurologic complications and that when indicated surgical intervention should not be delayed.

Use of Third-Generation Hydroxyethyl Starches During Cardiac Surgery

For years controversy has continued regarding the relative benefits and risks of using colloids versus crystalloids for volume resuscitation. This is a particularly important issue in CPB for which hemodilution is inevitable and intravascular

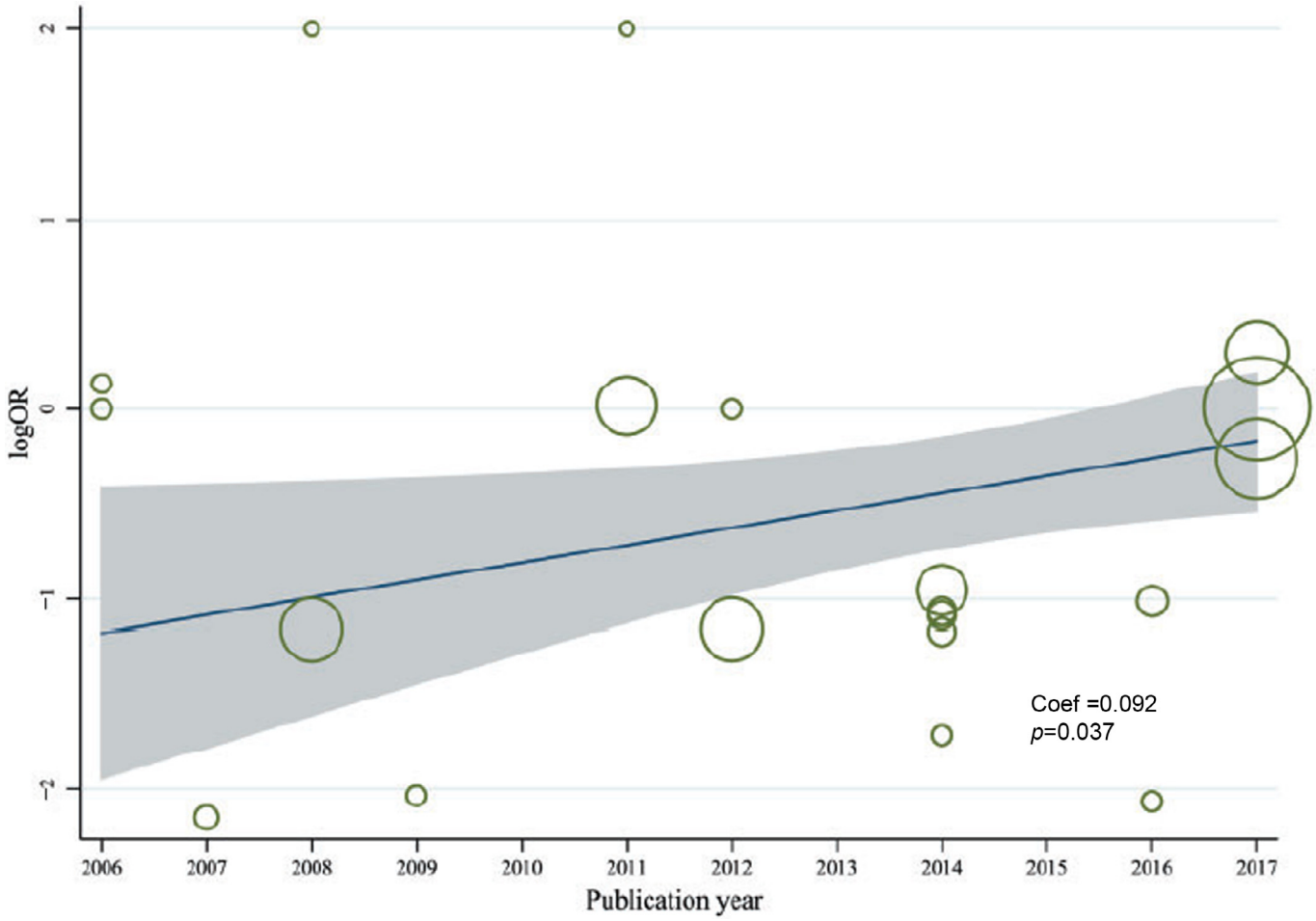

Fig 10. Less reduction in mortality with levosimendan in more recently published studies of levosimendan as demonstrated in meta-regression analysis. logRR, log relative risk of mortality.

From Zhou et al.[213]; used with permission.

volume support is critical. If one choses to use colloids, another issue is which one to use. Several decades ago the use of hydroxyethyl starches (HES) (eg, HES 130/0.4) became popular; however, concern about their use has been raised because of risk of impaired coagulation, kidney injury, and even excess mortality. This led the Food and Drug Administration to issue a warning in 2013 against their use in high-risk patients including patients undergoing open heart surgery in association with CPB. Newer solutions of HES with lower molecular weight and substitution number (eg, HES 130/0.4) have been introduced to reduce these adverse effects. Whether even this newer formulation of HES should be used recently was debated by McConnell et al. (pro)[217] and Sacchet-Cardozo et al. (con).[218] These authors presented arguments and data supporting and refuting the safety of HES 130/0.4. Several other recent studies were not mentioned by these authors. Use of HES 130/0.4 was found to increase bleeding in 1 study[219] and not to increase in bleeding other 2 studies.[220,221] On the other hand, use of HES 130/0.4 was found to increase evidence of AKI in 5 studies[221-225] and not to increase AKI in 3 studies.[219,220,226] Thus its safety when used in cardiac surgery remains unclear. Notably, the recent European guidelines on blood management for adult cardiac surgery recommend against using "modern" low molecular weight starches in priming and nonpriming solutions (class III recommendation, class C evidence).[19]

Acute Intracardiac Thrombosis and Pulmonary Thromboembolism After CPB

Acute intracardiac thrombosis and pulmonary thromboembolism after CPB are rare but life-threatening events, with pathological mechanisms not well-defined. Williams et al. recently provided a systematic review of 48 such cases reported in the literature.[227] Mortality was very high (85%). Common features included prolonged CPB, depressed myocardial function, major vascular injury, and hemostatic intervention. Potential risk factors are thoroughly discussed in their article and summarized in an accompanying figure (Fig 11).

Mycobacterium Chimaera Infection Subsequent to Heater-Cooler Units Used in Cardiac Surgery

An outbreak of *Mycobacterium chimaera* infection was first reported in Europe in 2013 and was attributed to contamination of heater-cooler units.[228-230] By 2017, 70 cases had been

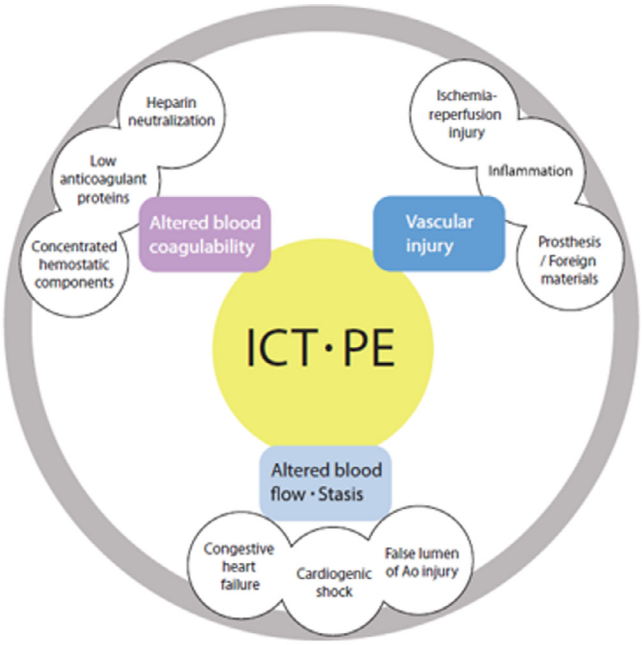

Fig 11. Risk factors for intracardiac thrombosis/pulmonary embolism during cardiac surgery. Ao, aortic; ICT, intracardiac thrombosis; PE, pulmonary embolism.

From Williams et al.[227]; used with permission.

reported, and recently Scriven et al. reported on 30 cases discovered in the United Kingdom.[231] The mortality is high (~50%), partly attributed to nonspecific presentation, variable latency, and thus delayed diagnosis and insufficient drug therapy. The source has been traced to bioaerosols emitted from contaminated heater-cooler unit water systems. Methods of preventing contamination, decontamination, recognition, and treatment of this infection are addressed in the previously cited articles.

Conclusion

Much progress has been made in the conduct of CPB since it was first introduced more than 65 years ago, and as just reviewed here, substantial contributions have been added in the past couple of years that guide management, although many questions remain to be resolved. That being said, have these advances made us better than our predecessors? In 1965 cardiac surgeon Dwight McGoon and cardiac anesthesiologist Emerson Moffitt at the Mayo Clinic reported on performing 100 consecutive aortic valve replacements between 1963 and 1964 without a death![232] This was accomplished before the use of many of the factors that we consider essential to successful contemporary cardiac surgery and CPB, including preoperative coronary angiography, monitoring with pulmonary artery catheters, TEE, pulse oximetry and capnography, narcotic anesthesia, use of cold potassium cardioplegia and conduct of CPB with membrane oxygenators, centrifugal pumps, coated and low prime circuits, minimal use of RBCs, minimal re-administration of cardiotomy suction, use of cell savers, and ACT monitoring.

More than 50 years ago, in December 1967, cardiac surgeon Christiaan Barnard and cardiac anesthesiologist Joseph Ozinski and their team accomplished the first "successful" human-to-human heart transplantation in Cape Town, South Africa.[233-235] The recipient (Louis Washansky) had severe pulmonary hypertension (pulmonary vascular resistance 11.5 Wood U) perioperatively. The donor likely was brain dead, although no accepted criteria for the determination of brain death were in place at that time. However, the donor heart was not removed until after asystole occurred 10 minutes after discontinuing ventilation (ie, it was a donation after cardiac death, or "DCD," heart)! Monitoring during the transplantation procedure was limited to a blood pressure cuff, 1 lead electrocardiography, a water manometer on an inferior vena cava line, a urinary catheter, and rectal and esophageal temperature. No arterial blood gases, pulse oximeter, capnography, arterial line, pulmonary artery catheter, or TEE were used. The patient was induced with pentothal and succinylcholine and was maintained with nitrous oxide and halothane with no additional muscle relaxant; narcotics were limited to 25 mg meperidine that were given at the end of the case. No synthetic narcotics, etomidate, antifibrinolytics or aprotinin, milrinone, nitric oxide, or intravenous pulmonary vasodilators were available. A bubble oxygenator and roller pump were used without an arterial line filter; the extracorporeal circuit was primed with 6 U of blood and 1,800 mL of crystalloid. CPB lasted 223 minutes. The patient was weaned off CPB with infusions of only isoproterenol and lidocaine. He was extubated the morning after and did well for 11 days but then developed progressive pulmonary insufficiency, which was attributed to rejection of the donor heart and was treated with more immune suppression. However, his condition continued to deteriorate, and he died on the 18th day. Autopsy revealed severe *Klebsiella* and fungal pneumonia, with only mild evidence of rejection of the heart.

Thus have these advances I have just reviewed made us better than our predecessors? Probably. However, these remarkably good results suggest that we should be humble and that the key to success likely is not merely technical advances but the practice by talented, experienced, rational clinicians using the best available evidence at any given time.

Conflict of Interest: The author has no conflict of interest.

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