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Guest Editors

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Genetics and Outcome After Cardiac Surgery

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Well before the completion of the enormous task to characterize the human genome (1), it was long thought that one’s genetic makeup had the ability to influence patterns of both health and disease. Although each of us contains roughly the identical 30,000 or so genes that were identified in the human genome project (surprisingly fewer genes than was initially predicted and also making us different from lesser species by only a few thousand genes), it is the subtle differences within these 30,000 genes that can dramatically influence both the susceptibility and response to various disease states. No better an example of these subtle differences and the ability of one to respond to injury is in the setting of cardiac surgery where already several genetic influences have been demonstrated to effect changes in both intermediate endpoints (such as measured cytokines of the inflammatory response) (2,3) as well as functional outcome [such as bleeding (4) and stroke (5)].

There are several types of studies that have been reported in cardiac settings that have added to our understanding of how genetics can influence outcome. The earliest were association studies focusing on the relationship between single gene variants or single nucleotide polymorphisms (SNPs) where individual nucleotides differ within specific genes (thus producing various alleles) (6). These studies were followed with more sophisticated ones (7,8) that focused on how particular SNPs influenced potentially important intermediate endpoints (such as the inflammatory response to bypass or physiologic parameters during bypass) (3,9–11).

The more recent and arguably more sophisticated types of studies, many of which are currently underway, focus on better linking the genetic influences of multiple genes to outcomes. Not only do these multi-gene studies look at how several genes can influence outcome, but they also examine critical gene-gene interactions. These more complex studies provide further information on gene associations and provide plausible biologic mechanisms explaining their associations to disease.

Of the earliest studies, Tardiff et al. in 1997 published preliminary results linking the APOE4 allele to adverse cognitive outcome after cardiac surgery (6). Although this study had several weaknesses (such as its relatively small size, n = 65), it heralded a new phase of investigation in cardiac surgery and spawned a series of further investigations trying both to corroborate this relationship and to understand the mechanisms surrounding this link. The presence of the APOE4 allele was the same specific allele to adverse cerebral outcome relationship that was found in studies linking both sporadic as well as late onset Alzheimer’s disease with the APOE4 allele (12). A similar association of APOE4 worsened outcome has since been demonstrated after stroke, subarachnoid hemorrhage, closed-head injury, and several other cerebral injury syndromes (13–15). In short, it seemed plausible that this allele (present in approximately 25% of patients) that had already been associated with worse outcome in many other cerebral settings would also be associated with worse outcome after cardiac surgery.

To further elaborate on this APOE adverse cerebral outcome relationship, we undertook a number of investigations to better understand the potential mechanism by which the APOE4 allele affects the brain during cardiac surgery. In a study by Ti et al. APOE4 was found to have no effect on cerebral blood flow (CBF) during CPB negating any adverse effects on CBF during CPB as a potential influence on outcome. (16) A possible link between APOE4 and outcome was found by Mackensen et al. showing a relationship between worse atheroma burden and APOE4 in cardiac surgery patients (17). However, the paradox between APOE4 and atheroma was the fact that an association between worse atheroma and cognitive dysfunction has been difficult to demonstrate (18). Similarly, we examined whether APOE would have an influence on the inflammatory response to bypass thus trying to identify an APOE-specific effect on inflammation as a potential moderator of cerebral outcome after cardiac surgery. Indeed, we demonstrated that APOE4 was linked to an enhanced inflammatory response marked by APOE4 patients having lower levels of the anti-inflammatory cytokine IL-10 in effect representing a more pre-inflammatory state (3). These results were similar to the work performed by Grunenfelder et al. that also documented an APOE4-dependent effect on inflammation (2,19).

However, in the intervening time since this early APOE4 study was published, it has become increasingly likely that the relationship between adverse cognitive outcome and cardiac surgery and any genetic link is likely far more complex than a single isolated gene. Corroborating the APOE4 hypothesis (more than 10 years in the making) has been very difficult. Steed et al. (20) found no such relationship leading most investigators to question the significance of the impact of this one gene, or any one gene, on cognitive outcome. Gaynor et al. for example, was not only unable to demonstrate a similar APOE4 effect in pediatric cardiac surgery patients, but in fact demonstrated that it was the presence of APOE2 and not APOE4 that was associated with worse outcome (21). In summary, it seems unlikely that APOE, at least by itself alone, plays a significant role in cardiac surgery related cerebral injury.

Second generation studies have gone further and have described not only the genomic influences, but also the corresponding protein changes associated with various SNPs. Polymorphisms to several genes have been examined, including interleukin-6 (IL6), C-reactive protein (CRP) and, tumor necrosis factor α (TNFα), as to whether they influence the inflammatory response to bypass. What makes these particular studies stand out from the preceding studies was the fact that not only did they link a genetic polymorphism with an enhanced inflammatory response, but further linked that enhanced inflammatory response with increases in adverse outcome after cardiac surgery (22). The field of cardiac transplantation has also added to our understanding of genetics and outcome (23–27). With an increasing number of studies finding single effects on either intermediate endpoints (various proteins) or outcome, it is apparent that perhaps multiple genes could be working in concert to impact outcome.
With the advent of more economic and rapid technologies that now allow hundreds of genes to be queried for variants simultaneously, it is now evident that looking at single genes in isolation of others, although convenient (and previously "cutting edge"), likely represents a naïve ideal of how genes can impact outcome. Another point that has become very apparent in genetic studies is the large numbers of patients who will need to be genotyped before valid associations and mechanisms can be discovered. One of the largest hurdles in carrying out these studies is the need for enormous bioinformatic resources to handle the large amounts of data and constantly changing statistical methodology.

Most recently we initiated a large genomics initiative involving many thousands of patients examining more than 200 genes, and already several fascinating relationships between genetic constituents and outcome have been discovered. Although most of these represent associations, they represent the next step in understanding genetics and disease because they consider the importance of multiple single genes and gene-to-gene interactions. In addition, they represent attempts to describe distinct plausible biologic mechanisms.

Stafford-Smith et al. have established an association of a certain interaction between various SNPs and adverse renal outcome after cardiac surgery (28). In this study of 1671 patients undergoing CABG surgery, 12 SNPs on 7 different genes suspected (based on a priori hypothesis developed after surveying the literature for renally relevant genes) were studied. Several interesting findings were described. Firstly, a significant race effect was discovered with widely different gene relationships to outcome in Caucasians compared to African Americans highlighting the need to take into account issues related population structure in genetic analyses. In the Caucasians it was the presence of the minor alleles of angiotensinogen (AGT) and interleukin 6 (IL-6) that were associated with significant renal dysfunction. In the African American population, it was endothelial nitric oxide synthetase (eNOS) and angiotensin covering enzyme (ACE). Another important discovery was the way in which these genes significantly enhanced the ability of various clinically-based models to predict those patients suffering renal dysfunction.

In an unrelated study ($n=877$) from our group published by Welsby et al(4) the possible polymorphisms associated with bleeding after cardiac surgery were investigated. In an elegant mechanistic fashion, he described, after studying 19 SNPs present on 13 genes, that 7 different SNPS related to thrombosis and hemostasis had an effect on the chest tube output 12 hours after surgery. Interestingly, some SNPs identified increased bleeding while others decreased bleeding risk. The ACE insertion/deletion SNP, for example increases ACE levels possibly enhancing vasoconstriction that mechanistically may have decreased bleeding (by altering tissue blood flow.) Alternatively, variants of the platelet glycoprotein IIaIa protein lead to enhanced activation of platelets during bypass thereby reducing their effectiveness at reducing bleeding after bypass. This is similar to the work done by Donohue et al. and adds to the work by Faraday et al. although with an additional degree of sophistication inherent in studying multiple genes as opposed to just single genes (29,30).

One of the most striking findings from our genetics initiative was related to neurologic outcome (specifically, stroke). In a study of 2140 patients examining 26 different SNPs, we identified an association between genes related to the inflammatory response (CRP and IL6) and an increased risk of stroke. The presence of the minor alleles of CRP, IL-6 had a three-fold increase in the risk of stroke after cardiac surgery (5). Interestingly, there was no single (or combination) of prothrombotic genes associated with stroke suggesting that inflammatory mechanisms supersede thrombotic in post-op patients at risk of a stroke.

Even more recently we have revisited the issue genetics and of cognitive dysfunction after cardiac surgery (31). This time we examined more than 30 genes, establishing not only a relationship between gene combinations and adverse outcome but also biologically plausible mechanisms based on work related to platelet activation after cardiac surgery. This work is still ongoing but has yielded exciting results implicating the inflammatory response to bypass as a mechanism of worsened cognitive outcome.

Although great strides have been made in our understanding of how the genome can impact outcome after cardiovascular surgery, the genome represents only one layer of a many layered set of independent processes within the cell. These multilayer constituents include the genome (DNA), the transcriptome (messenger RNA), the proteome (which represents a collection of all of the proteins within the DNA), the physiome (which are the regulatory networks and signaling pathways with the cell), the metabolome (which is the whole set of metabolic entities and small pathways in cells, tissues, organs, and organisms), as well as what can broadly be considered the phenome (which is the quantitative description of the integrative functions of the living organism and how it interacts with this environment). It is only with this integrative systems approach that we will ultimately be able to quantitate and mechanistically describe the important and unifying signaling networks in cardiovascular medicine all of which will ultimately be focused upon impacting positively in both preventative as well as therapeutic approaches to the patient undergoing cardiac surgery (32). What we have accomplished thus far is only the tip of the iceberg and what lies below the surface is considerably vaster and exponentially less understood.

One of the ironies of understanding the influence of genetics on outcome after cardiac surgery is the fact that technology is moving faster than one can plausibly move forward with clinical trials. This requires not only a great deal of foresight in designing clinical trials (making them adaptable to newer techniques), but also emphasizes the need to develop expansive research consortia where large numbers of patients can be genotyped for many hundreds of genes. It is only in the large trials examining multiple relationships that meaningful associations and mechanisms will ever be elucidated. One thing is clearly emerging from these complex studies—they require an equally complex but none the less cohesive collaborative group with representatives with expertise in understanding the relevant clinical outcomes, access to large numbers of study subjects, clinical study design and conduct, genetics, bioinformatics, and statistics. Obviously no one person (nor likely research group) possesses all these components further emphasizing the need to form collaborative research consortia, either within or between institutions.

REFERENCES


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Development of a Novel Perfusion Technique to Allow Targeted Delivery of Gene Therapy–The V-Focus System

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BACKGROUND

Current techniques for delivery of gene therapy, deliver the vector to the target organ and also to the systemic circulation. Targeted gene therapy aims at delivering the vector to specific and restricted cell populations, thus sparing all other cells of the


unwanted effects of the gene product. Our aim was to develop an extracorporeal delivery system that would deliver a vector to our target organ, the heart, with little or no systemic leakage. Recirculation of the vector would allow even distribution of the vector through the target organ.

METHODS

A low volume extracorporeal circuit was designed using commercially available components. Using an ovine pacing induced heart failure model, the animals were placed on percutaneous extracorporeal cardiac support via a 9 Fr cannula in the Left coronary artery (LCA) and a novel 9Fr cannula in the Coronary Sinus (CS). After establishing cardiac support and stabilizing the subject. The vector was introduced into the circuit and recirculated for 10 minutes. At the end of this period to prevent the vector entering the systemic circulation, the circuit was emptied into a collection bag.

RESULTS

We delivered adenovirus (3.5x10^{12} vp) encoding a pseudophosphorylated mutant PLN (AdS16EPLN, n = 9) or AdLacZ (n = 6, 4.7x10^{12} vp) to sheep with pacing induced HF. Despite 2 weeks further pacing, treatment with adenovS16E PLN significantly improved contractile function despite ongoing pacing stress and prevented ventricular remodeling in contrast to AdLacZ animals.

<table>
<thead>
<tr>
<th>Parameter (% change vs baseline)</th>
<th>AdS16EPLN</th>
<th>AdLacZ</th>
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</thead>
<tbody>
<tr>
<td>LV End Diastolic Area</td>
<td>−14**</td>
<td>13**</td>
</tr>
<tr>
<td>LV Ejection Fraction</td>
<td>−87***</td>
<td>−23*</td>
</tr>
<tr>
<td>LV End Diastolic Pressure</td>
<td>−24*</td>
<td>5</td>
</tr>
<tr>
<td>dP/dt</td>
<td>+31*</td>
<td>−5</td>
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*p < 0.05, **p < 0.01, ***p < 0.001

CONCLUSIONS

Together the deployment of targeted delivery strategies and targeted molecular therapy has major potential for the treatment of heart failure. The V-Focus system is capable of delivering a vector to a target organ with little systemic leakage.

Thrombin Inhibitors and Cardiopulmonary Bypass

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INTRODUCTION

Unfractionated heparin (UFH) has almost always been the drug chosen for controlled anticoagulation in cardiac surgery (1). Coronary artery bypass grafting (CABG) was first undertaken in 1953 (2). Off-pump coronary artery bypass surgery (OPCAB) has not been established as definitively superior to CABG using cardiopulmonary bypass (CPB). Important complications with either technique include death, perioperative myocardial infarction, bleeding, stroke, defects in postoperative neurocognitive function, and renal failure and are still relatively frequent compared with other common operations (3).

There are many factors in the causation of these problems (4–6). The management of anticoagulation may affect the complex interplay between the endothelium, drugs, the coagulation cascade and the inflammatory response which characterizes all cardiac surgery (7).

LIMITATIONS OF HEPARIN AND PROTAMINE

Unfractionated heparin is an animal extract of variable composition and activity. It has been associated with platelet activation and dysfunction and with the inflammatory response to surgery and cardiopulmonary bypass (8).

Unfractionated heparin binds to and augments antithrombin III (antithrombin) and heparin cofactor II. Antithrombin inhibits factors IIa (thrombin) and Xa (and to a lesser extent IXa, XIa, and XIIa). Heparin cofactor II also inhibits thrombin. The ratio of anti-IIa activity produced by UFH to the anti-Xa activity is 1. Unfractionated heparin is only effective against thrombin in the fluid phase. Platelet bound factor Xa is also protected from inhibition by the heparin/antithrombin complex (9). In addition, heparin is neutralized by platelet factor 4 (PF4) and high-molecular-weight multimers of van Williebrand factor released from active platelets.

Resistance to heparin may develop, typically by depletion of the antithrombin needed for its activity. Congenital antithrombin deficiency is rare. Acquired antithrombin deficiency may be associated with certain chemotherapeutic regimens, nephrotic syndrome, liver failure, pre-eclampsia, shock, disseminated intravascular coagulation and chronic or excessive

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heparin administration. It is usually relatively easily managed by the administration of plasma (or, if available antithrombin concentrate) (10).

Heparin releases PF4 from endothelial cells, and forms complexes with it which bind to the surface of platelets and activate them. Antibodies may form and interact with these complexes. Anaphylactic reactions to heparin are uncommon, but antibodies to the heparin/PF4 complex are seen more often, and may be prothrombotic, predict myocardial infarction (MI) during acute coronary syndromes (11–13) and be a risk factor for 30 day mortality following cardiac interventions (14,15). These antibodies lead to heparin induced thrombocytopenia (HIT) (16) with thrombosis in 1%–3% of these cases (7,17). The use of heparin is contraindicated in HIT.

Protamine is also an animal extract, and is prone to anaphylactoid and anaphylactic reactions. It has a short half-life (4.5 minutes) (18) which predisposes to un-opposed heparin effects post-operatively. It stimulates the systemic inflammatory response when complexed with heparin (19,20). These two drugs in combination probably contribute to excessive bleeding after cardiac surgery in some patients. Heparin is difficult to use for CPB without protamine.

Options for anticoagulation in cardiac surgery when heparin or protamine is contraindicated include:

- Low molecular weight heparins (LMWHs: e.g., nadroparin, enoxaparin, and dalteparin) (16,21–24);
- Danaparoid (a mixture of the heparinoids heparan, dermatan, and chondroitin sulfate) (25);
- Ancrod (a serine protease isolated from the Malayan pit viper) (26);
- Argatroban, an arginine derivative, acts as a competitive thrombin inhibitor. Argatroban is an arginine derivative, acts as a competitive thrombin inhibitor at only the active (or catalytic) site of thrombin. They do not require antithrombin, platelet factor II, or any other cofactor for their effect.
- Hirudin (lepirudin, Refludan®) is a 65 amino-acid polypeptide originally isolated from leech saliva. Its amino-terminal domain interacts with the active site of thrombin and its acidic carboxyterminal domain binds to exosite 1 of thrombin (9) forming an irreversible 1:1 complex. Recombinant hirudin lacks a sulphated tyrosine residue at position 63, and is therefore called desulfatohirudin or desirudin (Revasc®). Desirudin’s affinity for thrombin is lower. Desirudin is eliminated by the kidney; it has a plasma half-life of about 60 minutes which is prolonged in renal insufficiency (9). Dialysis requires a polymethyl-methyl acrylate (PMMA) membrane. Desirudin is a protein and therefore potentially antigenic, but there have been no reports of antibody formation associated with its use in CPB. However there have been reports of fatal anaphylaxis following re-exposure to lepirudin. It is possible that some of these reactions are attributable to traces of yeast proteins in preparations of the drug (33). Desirudin is active against fibrin-bound a.

- Iloprost (a stable prostacyclin analogue with a half-life of 15–30 minutes) (27): Platelet glycoprotein (GP) IIb/IIIa antagonists (e.g., tirofiban) (30–31);
- Delay of surgery (32);
- Direct thrombin inhibitors (e.g., the uivalent argatroban, efegatran and inogatran, and the bivalent hirudin and bivalirudin).

**DIRECT THROMBIN INHIBITORS**

The direct thrombin inhibitors bind directly and specifically to thrombin. They do not require antithrombin, platelet factor II, or any other cofactor for their effect.

Hirudin (lepirudin, Refludan®) is a 65 amino-acid polypeptide originally isolated from leech saliva. Its amino-terminal domain interacts with the active site of thrombin and its acidic carboxyterminal domain binds to exosite 1 of thrombin (9) forming an irreversible 1:1 complex. Recombinant hirudin lacks a sulphated tyrosine residue at position 63, and is therefore called desulfatohirudin or desirudin (Revasc®). Desirudin’s affinity for thrombin is lower. Desirudin is eliminated by the kidney; it has a plasma half-life of about 60 minutes which is prolonged in renal insufficiency (9). Dialysis requires a polymethyl-methyl acrylate (PMMA) membrane. Desirudin is a protein and therefore potentially antigenic, but there have been no reports of antibody formation associated with its use in CPB. However there have been reports of fatal anaphylaxis following re-exposure to lepirudin. It is possible that some of these reactions are attributable to traces of yeast proteins in preparations of the drug (33). Desirudin is active against fibrin-bound a.

Argatroban, an arginine derivative, acts as a competitive thrombin inhibitor at only the active (or catalytic) site of thrombin. Its half life is 45 minutes and is prolonged with hepatic dysfunction, but not renal failure. Its has been used during CPB in two patients with HIT, both of whom bled excessively and died shortly following their operations (21), two patients with chronic renal failure (39,40) and one patient with severe liver dysfunction (41).

Bivalirudin (Angiomax®, previously known as Hirulog®) is a synthetic 20 amino-acid peptide in which the functional carboxy and amino terminals of hirudin have been retained. It is unlikely to be immunogenic. Bivalirudin binds bivalently with thrombin. There is no reversal agent. The Arg-Pro bond at the amino-terminus of hirudin has been retained. It is therefore potentially antigenic, but there have been no reports of antibody formation associated with its use in CPB. However there have been reports of fatal anaphylaxis following re-exposure to lepirudin. It is possible that some of these reactions are attributable to traces of yeast proteins in preparations of the drug (33). Desirudin is active against fibrin-bound a.

There is considerable experience with the use of bivalirudin in acute coronary syndromes. During coronary angioplasty for unstable angina the recommended initial intravenous bolus is 1 mg/kg, followed by an infusion of 2.5 mg/kg/h.

**MONITORING OF ANTICOAGULATION WITH THROMBIN INHIBITORS**

The aim in anticoagulation is to ensure an adequate effect without excessive blood concentrations of drug. With most drugs the relationship between concentration and effect varies substantially, so direct information about the status of the coagulation system (i.e., the effect of the drug) is needed. Unfortunately, many of the tests used to assess coagulation are non-specific, so it is helpful also to know the drug concentration.

The PT, APPT, thrombin time, and ACT are all prolonged by direct thrombin inhibitors. The APPT has been used to monitor anticoagulation with direct thrombin inhibitors, including bivalirudin (44–46). Prolongation of the APTT correlates well with increasing plasma levels of bivalirudin in doses between 0.05 mg/kg and 0.6mg/kg (43), but less well with plasma levels of lepirudin (47). The APPT is not useful at the doses of direct thrombin inhibitor needed for cardiac surgery (48).

There is a poor correlation between the ACT and the concentration of desirudin (49), and disproportionate prolongation.
occurs with concentrations ≥2 μg/ml. This is partly attributable to hemodilution of coagulation factors and platelets and can be overcome the addition of normal plasma to the ACT samples (48). Similar comments apply to UFH on CPB (49,50). The ecarin clotting time (ECT) is a more specific test of thrombin inhibition and has been used to monitor anticoagulation with desirudin on CPB (35) and during OPCAB (51) and bivalirudin on CPB (37,52). Ecarin is a snake venom enzyme. It converts prothrombin to meizothrombin thereby stimulating the blood to form clot. Meizothrombin is rapidly neutralized by direct thrombin inhibitors (including lepirudin and bivalirudin) (52) resulting in a dose-dependent prolongation of the time for clot to form. Although the test is specific for antithrombin agents, heparin cofactor II-mediated thrombin inhibitors are capable of prolonging the ECT (53). The ECT provides a more accurate assessment of bivalirudin-mediated anticoagulation than the ACT up to blood concentrations of about 12 μg/ml, but the place of this test is probably not yet fully established (21). The thromboelastograph has been used to monitor desirudin on CPB (54).

There is a dose-proportional relationship between blood concentration of bivalirudin and the ACT (55,56). The threshold for prevention of ischemic events in percutaneous coronary intervention (PCI) seems to be a blood concentration of 6.5 μg/ml (56). A bolus of 0.75 mg/kg followed by an infusion of 1.75 mg/kg/h usually results in a plasma concentration of 7–10 μg/ml and an ACT between 300 and 350 seconds. An ACT in this range has been reported as appropriate for OPCAB (57).

Experience with bivalirudin on CPB is still limited and the relationship between dose, effect, other influences on the coagulation system and the ACT in this setting is not entirely clear. It is essential to avoid stasis in the blood in the bypass circuit. Bivalirudin (with its shorter half life) is probably easier to manage during CPB than lepirudin.

COULD DIRECT THROMBIN INHIBITORS INFLUENCE GRAFT PATENCY?

In the first few months after surgery, flow through conduits is influenced by technical and surgical considerations, the caliber of the native artery, and neointimal hyperplasia and thrombus formation. Drugs may influence graft patency and perioperative myocardial infarction via the last two factors.

Advantages have been shown for direct thrombin inhibitors over heparin (typically without protamine reversal) in patients with acute coronary syndromes or undergoing PCI (44,58–60). These include a lower risk of the combined outcome, death or myocardial infarction (primarily due to an effect on myocardial infarction). The benefit is not seen with the univalent agents. Major bleeding is typically reduced with bivalirudin, but not with desirudin. In HERO-2 (4), there was an increase in moderate bleeding with bivalirudin. A key point about these studies in acute coronary syndromes is that the heparin was not reversed. Also the levels of anticoagulation were lower than those needed for CPB.

DIRECT THROMBIN INHIBITORS IN OFF-PUMP CORONARY ARTERY SURGERY

The degree of anticoagulation typically used in OPCAB surgery is less than with CPB, and postoperative bleeding is less often a problem (61,62). Because OPCAB surgery may produce a postoperative procoagulant state, heparin is sometimes only partially reversed after these operations (57,58,63,64).

In the first randomized comparison of an alternative to heparin in cardiac surgery it was confirmed that anticoagulation for OPCAB with bivalirudin could be provided without a clinically important increase in perioperative blood loss in comparison to heparin with protamine reversal (1). There was also a significant advantage for bivalirudin in the secondary outcome variable of graft flow at 3 months.

The findings of the OPCAB study should not be extrapolated to the management of patients undergoing CPB. However experience is increasing in the use of bivalirudin in cardiac surgery, both on pump and off (37,65,66).

The following studies are currently in progress: two studies comparing bivalirudin to heparin with protamine reversal in patients undergoing OPCAB (“EVOLUTION-off”); and CABG surgery on CPB (“EVOLUTION-on”); two studies of bivalirudin in patients with HIT and HITT undergoing OPCAB (CHOOSE-off) and CABG surgery on CPB (“CHOOSE-on”).

CONCLUSION

Experience with bivalirudin in the management of CPB is increasing and it is clear that it is possible to use the drug in patients who have a contraindication to heparin or protamine. Bivalirudin may provide an advantage over heparin with protamine reversal in respect to flow through grafted arteries. It is disappointing that no studies are currently underway in which this important outcome is the primary endpoint.

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Urban Myths and the ACT: What is Not True and What Really Matters When it Comes to Monitoring Anticoagulation

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INTRODUCTION

The activated clotting time (ACT) was developed in 1966 by Hattersley (1). However, it was Bull et al. that first suggested that Hattersley’s test should be applied to coagulation monitoring of the systemically heparinized CPB patient (2). In their cornerstone manuscript it was noted that visible clot formation rarely occurred below ACT times of 300 seconds. Consequently, a safety margin was added to this minimum time and the recommendation was made that regular monitoring and maintenance of ACT values of >480 seconds was appropriate for CPB. This recommendation quickly became the gold standard. Since that time nearly a dozen automated machines and tests have been developed to provide ACT results and ACT monitoring has become standard of care for the CPB patient. Despite the widespread acceptance of the ACT test, there is no shortage of references which mischaracterize the ACT test thereby promulgating a degree of misinformation which permeates our profession. Therefore, the purpose of this presentation is to dispel some of the most common myths associated with ACT test results. Original data from our laboratory will be used to compliment an extensive literature review on this topic.

MYTH: AN ACT IS AN ACT IS AN ACT . . .

All too commonly the results of ACT tests have been generically referred to in scientific literature and conversation as if there were no more difference between the results of different ACT tests than there is between the flow rates of different roller pumps. In an effort to provide evidence of the similarity or disparity between results of different ACT tests we initiated a project to identify the comparability and reproducibility of all the major ACT tests available in the USA (3,4).

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METHODS
With IRB approval, blood samples from 17 CPB patients were collected at six time points during surgery. All tests were performed in duplicate on 8 different ACT devices (ACTalyke, Gem, HMS, Hemochron 801, Response, Jr. Signature, Rapidpoint, and Sonoclot). Duplicate samples from each machine were compared to determine reproducibility. The average of the duplicate samples was used for comparison between machines.

RESULTS
Reproducibility for all devices produced a range from 3.7 ± 5.3–20.6 ± 27.3 seconds for unheparinized samples with the HMS and the Rapidpoint being the most and least reproducible respectively. For heparinized samples, the range was 16.0 ± 16.8–69.7 ± 81.2 seconds with the Rapidpoint and the Sonoclot being the most and least reproducible respectively. The Rapidpoint was the most consistently reproducible at all time points. Comparison between machines of unheparinized samples demonstrated a range of ACT values from 107.1 ± 34.4–136.4 ± 14.2 seconds with the Rapidpoint and the Response having the lowest and highest values respectively. Heparinized samples had a range from 451.1 ± 117.5–633.5 ± 158.3 seconds with the Rapidpoint and Hemochron 801 having the lowest and highest values respectively. The difference between the highest and lowest unheparinized results were 29 seconds (27%) and for heparinized results, 182 seconds (40%).

CONCLUSION
Overall, heparinized samples had the poorest reproducibility. The HMS was the most reproducible and the Sonoclot was the least reproducible. For unheparinized samples, the Rapidpoint and Sonoclot were significantly shorter than all other machines. For heparinized samples, the ACTalyke, Rapidpoint, and Sonoclot were significantly shorter while the Hemochron 801 and Response were significantly longer than most other machines.

MYTH: APROTININ PROLONGS THE CELITE ACT TEST THROUGH AN IN VITRO MECHANISM
In the mid 1980s, reports of aprotinin’s ability to decrease hemorrhage after cardiopulmonary bypass introduced the drug to the realm of cardiac surgery. Unfortunately, its introduction into this arena was followed by the publication of multiple studies and case reports that blamed aprotinin for poor outcomes in the form of early graft closure. Almost 20 years have passed since the initial manuscript describing the use of aprotinin during cardiopulmonary bypass, and with time there has been a significant increase in scientific knowledge and clinical experience. For a comprehensive review of the literature with regard to aprotinin’s anticoagulant properties the reader is referred to the Swartz et al. article (5). Unfortunately, many clinicians still believe that aprotinin is procoagulant and that celite ACT tests are unreliable in the presence of aprotinin. Therefore, we set out to identify the exact influence that aprotinin does have on all the major ACT tests (6).

METHODS
With IRB approval, blood samples were collected from patients undergoing CPB before and after full heparinization (300 u/kg). Each blood sample was divided into two aliquots and aprotinin was added to one sample to yield a final calculated concentration of 300 KIU/ml. Both aliquots were used simultaneously to perform the 12 ACT tests. A paired student T-test was performed on the data.

RESULTS
Overall, test results from 9 of 12 devices were significantly increased by aprotinin. Of these, 4 were increased only when the sample was heparinized, 3 were elevated by both heparinized and unheparinized blood, and 2 were elevated only when the sample was unheparinized.

CONCLUSION
Each affected test responded uniquely to aprotinin producing ACT test results ranging from 12–51% above nonaprotinized values. Several tests that were affected by aprotinin using heparinized blood samples were unaffected using unheparinized blood samples.
As we have reported, aprotinin administration does influence the results of various ACT tests, and consequently different methods of anticoagulation have been developed. It has been suggested that the mechanism behind the elevation of ACT test results by aprotinin is a result of aprotinin’s anticoagulatory activity. Researchers have demonstrated that, in fact, the celite ACT is not “artificially” prolonged in the presence of heparin and aprotinin, rather the kaolin ACT is “artificially” shortened due to binding of the aprotinin by the activator (7).

MYTH: ACTS ARE USED TO MONITOR HEPARIN
While the primary function of the pressure transducer on your arterial line may be to detect aortic dissection, we would all agree that there are many other causes for an elevated line pressure. The results of your ACT are very similar; the primary cause of elevated ACT during CPB is heparin concentration, however, because it is a nonspecific measurement of whole blood coagulation, anything that affects coagulation will ultimately affect the ACT. Unfortunately this detail is largely overlooked by many authors and clinicians and consequently there is a widespread acceptance that ACTs are used to monitor heparin during CPB. Curiously, most perfusionists will agree that the ACT is effected by other variables such as hemodilution, hypothermia and (as discussed above) aprotinin (8, 9). Paradoxically, these two concepts manifest themselves into the belief that ACT test results are mistaken in the face of these non-heparin variables. Therefore we determined to identify the relationship between ACT results and heparin concentrations during CPB (4).
METHODS

With IRB approval, blood samples from 17 CPB patients were collected at six time points during surgery. Test results were performed in duplicate on 8 different ACT devices (ACTalyke, Gem, HMS, Hemochron 801, Response, Jr. Signature, Rapidpoint, and Sonoclot) and compared to results of anti Xa activity (STA Rotochrom Heparin assay). The average of the duplicate samples was used for comparison to the anti Xa results.

RESULTS

Correlation of results to anti Xa activity (1.1 – 5.75 IU/ml) for each device produced a range of r = .071 to .502. Conclusion: No device correlated with the laboratory anti Xa data.

CONCLUSION

In summary, the ACT test is a whole blood coagulation test which is useful for monitoring anticoagulation during CPB. It is affected by anything that affects coagulation, especially heparin, but also non heparin variables such as hemodilution, hypothermia, aprotinin and others. There are many automated devices available to the clinician for ACT monitoring. Each machine responds to anticoagulant variables uniquely and therefore it should not be assumed that the results from different machines are interchangeable. Each institution should develop clinical parameters based on the device they are using and their clinical environment.

REFERENCES


From Trash To Leucocytes: What Are We Filtering and Why?

Simon J. Mitchell, MB, ChB, DipDHM, PhD
Department of Anaesthesia, Auckland City Hospital, Auckland, New Zealand

INTRODUCTION

A filter processes non-homogeneous matter to allow the free passage of some elements, whilst preventing downstream passage of specific others. In the context of cardiac surgery, blood is the most commonly filtered “matter.” Filters can be classified as either “screen filters” or “depth filters” (1). Screen filters are typically comprised of material “woven” into a “screen” with a carefully calibrated pore size. Consistency of pore size is a characteristic of screen filters, and they are frequently named by this parameter, for example, a “40 micron filter.” Clearly, they are designed to remove matter larger than the screen pores. Depth filters are typically comprised of material that is not precisely woven and through which the filtered matter must pass, typically over a longer distance and greater time when compared to screen filters. In these devices, the removal of matter occurs by several possible means that are discussed later.

Potential filtration sites in cardiopulmonary bypass (CPB) are itemized in Table 1 along with examples of the targets for removal. The majority of relevant research has been focused on filtration of arterial blood, and arterial line filtration will occupy most of this review.

Table 1. Filtration sites and targets in cardiopulmonary bypass

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<td>Aggregates, bubbles, bone, other tissue, surgical material, lipid, leucocytes</td>
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<tr>
<td>6. Allogenic blood</td>
<td>Leucocytes, aggregates</td>
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<td>7. Autologous blood</td>
<td>Leucocytes, aggregates, bubbles</td>
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From Trash To Leucocytes: What Are We Filtering and Why?
ARTERIAL LINE FILTRATION
The use of arterial line filters gathered momentum in the 1960s, driven by concerns over the introduction of bubbles into arterial blood by bubble oxygenation. The earliest filters were Dacron wool depth types (2). A stainless steel screen filter developed around the same time was not used clinically because it caused haemolysis (3). Nevertheless, polyester mesh screen filters did achieve wide acceptance in the 1970s (4), and by the early 1980s 99% of arterial line filters used were of the screen type (5). Around the millennium, arterial line filters were used in more than 99% of cases in the USA (6), but interestingly, only 57% of cases in the UK (7).

The most recent comprehensive review of the use of arterial line filters in cardiac surgery was published by Whitaker et al. in 2001 (4). They defined 6 separate outcome goals that have driven the recent use of arterial filters as follows: reduction of microemboli; improvement of cerebral outcome; reduction of the inflammatory response to CPB; improvement of cardiac outcomes; improvement of pulmonary outcomes; and improvement in hospitalisation-related indices such as length of stay. These same outcome goals are adopted for this review.

REDUCTION IN MICROEMBOLI BY ARTERIAL LINE FILTRATION
Not surprisingly, there is irrefutable evidence that filters reduce microemboli both downstream in the CPB arterial line (8,9) and when measured at cerebral arterial sites in patients (10). In the study by Loop et al. (8) a dacron wool depth filter was most efficient (99% emboli removed) and a 40 micron screen filter the least efficient (72% emboli removed). Nevertheless, one of the depth filters became obstructed, and concerns about such events have seen screen filters with pore sizes around 40 micron become the most widely used. It is notable that the study by Mitchell et al. (9) was one of the few in which the emboli had been positively identified as bubbles, and it showed that a significant proportion of bubbles can be stopped by a 40 micron screen filter.

It is appropriate at this point to reflect on the potential value of reducing the number of emboli to which patients are exposed during CPB. The vast majority of studies investigating the potential for harm by arterial emboli in CPB have correlated peri-operative emboli exposure against post-operative neuropsychological (NP) outcomes, and there are now a number of studies that, independent of any manipulation of filtration, have demonstrated that NP outcomes are worse if emboli exposure is greater (11–17). This raises an obvious question: if emboli cause NP impairment, and arterial line filters reduce emboli, will arterial line filtration therefore reduce NP impairment?

IMPROVEMENT OF CEREBRAL OUTCOMES BY ARTERIAL LINE FILTRATION
Two early studies that used retrospective controls suggested improved NP outcomes in filtered patients, but are difficult to interpret because of their methodology (18,19). The study published by Pugsley et al. (20) is the most widely quoted and provides the most convincing evidence that filtration improves NP outcomes. The “filtered patients” (40 micron screen filters) were exposed to less emboli and exhibited less NP deficits than the non-filtered controls. In addition, there was a step-wise correlation between emboli exposure (measured by middle cerebral artery Doppler) and the incidence of NP deficits when patients were assessed 8 weeks after surgery. It must be emphasized that this study was performed using pH stat acid—base control and CPB circuits with bubble oxygenators. Most recently Whitaker et al. (21) demonstrated less emboli exposure and a strong trend toward less NP decrement in patients who had a leukocyte depleting arterial line filter compared to patients who had a standard 40 micron filter, but it is difficult to interpret the meaning of this finding given that emboli reduction and anti-inflammatory effects are both potential contributors.

It is notable that none of these studies have investigated an advantage for standard arterial line filtration vs. no filtration under the CPB conditions most prevalent in modern cardiac surgery theatres, viz: membrane oxygenation and alpha-stat acid-base management. Indeed, the only relevant study in this regard was that by Taggart et al. (22), which showed a smaller post-operative rise in serum s100β levels in patients whose arterial line included a 43 micron heparin coated filter. However, the s100β protein has become a controversial marker for brain injury in cardiac surgery, and the significance of this result is unclear. It is possible that this lack of data demonstrating a need for filters in modern CPB circuits may account for the lower uptake of filtration in the UK (4).

REDUCTION OF INFLAMMATION BY ARTERIAL LINE FILTRATION
There has been intense interest in the inflammatory response to CPB over the last decade. Cellular and biochemical mediators of inflammation are activated in CPB by a variety of means which are summarized by deVrooge et al. (23). This occurs to some extent in all patients undergoing CPB, but with a combination of homeostatic correction and skillful clinical management, there may be no consequences of any significance in most patients. On the other hand, some patients may develop exaggerated manifestations of inflammation known as the “systemic inflammatory response syndrome” (SIRS). This is characterized by widespread microcirculatory failure with associated morbidity.

Strategies for preventing SIRS can be classified as either biomaterial dependent or independent (24). “Biomaterial dependence” refers to the manipulation of CPB circuit blood-contact surface modification to minimize activation of inflammatory cascades, and is beyond the scope of this review on filtration (though some filters may incorporate biocompatible surfaces). Filtration strategies fall into the category of “biomaterial independent” interventions, and almost without exception, the literature describing a reduction in the inflammatory response to CPB by filtration has focused on leukocyte filtration. It is therefore relevant to briefly discuss the role of leukocytes in CPB-related inflammation.

During CPB leukocytes may be activated either primarily by contact with foreign surfaces or by trauma. They may also be activated secondarily by inflammatory proteins such as complement, or cytokines released by damaged tissue. Another important component of the CPB inflammatory response, and one of particular significance to leukocytes is the activation of
endothelium. This can occur in a variety of ways which include ischemia-reperfusion, and damage to endothelial surfaces by emboli. Anaerobic metabolism in the endothelial cell during ischemia results in production of hypoxanthine and the conversion of the enzyme xanthine dehydrogenase to xanthine oxidase. When oxygen supply is restored, xanthine oxidase converts hypoxanthine to xanthine, with superoxide and hydroxyl radicals produced as by-products. These highly reactive molecules may cause lipid peroxidation of the cell membrane, and cause expression of leukocyte binding molecules on the cell surface. Leukocytes that are pre-activated by other means as mentioned above marginate very readily on damaged endothelium, and are themselves capable of liberating large quantities of extracellular oxygen radicals which may further damage the endothelium. These processes are well summarized by Zamboni (25). This process of ischemia-reperfusion damage is particularly relevant to organs that undergo a period of relative ischemia during CPB, such as the heart and lungs.

Given the above, it is not surprising that removal of leukocytes from the CPB arterial blood has been proposed as a potential means of reducing inflammation, and protecting the heart and lungs during CPB. Leukocyte reduction (LR) filters for the arterial line were first developed by Pall in the late 1980s. The "archetypal" Pall LR filter is the "Leukoguard 6" (LG-6) device. This consists of a conventional 40 micron woven polyester screen, followed downstream by a non-woven polyester depth filter. Leukocytes are too small to be trapped by the screen filter, but may become trapped in the non-woven segment of the filter by processes such as blocking (where closely aligned fibers create a small "pore"), bridging (where two or more cells become obstructed together in a space that would normally allow passage of either alone), or by adhesion of activated cells to the fibers (1). The process of adhesion seems particularly important and it is not surprising that these devices appear selectively capable of removing pre-activated (and therefore readily adherent) leukocytes (26).

There are different strategies for employing LR filters during CPB (27). In respect of the arterial line, some use the filter throughout the period of CPB, while others bypass it until the period of organ reperfusion, which is usually defined as beginning at aortic declamping. Leukocyte reducing filters have also been used in the venous line, cardioplegia line, and in filtration of residual CPB perfusate prior to return to the patient. These strategies will be mentioned briefly later.

In keeping with the sub-title of this section (“Inflammation”) we next consider those controlled studies that have compared inflammatory indices in humans undergoing CPB with or without an arterial LR filter. These inflammatory indices take the form of either leukocyte counts or measurement of inflammatory markers or both, and the results can only be described as widely variable. Although this review has probably not cited all the relevant studies, there was no selection of those studies that are presented, and the outcome variability demonstrated here is almost certainly representative of the literature.

A number of studies have demonstrated that LR filters deployed in the arterial line throughout CPB do reduce leukocyte counts (28) and/or markers of inflammation post CPB (29–33). There is also one study that demonstrated mixed results when the period of filtration was limited to reperfusion (34) (positive for counts, but negative for markers). In contrast, there are as many studies that have failed to demonstrate any effect on inflammatory cell counts (21,35–39) or inflammatory markers (35–41) by arterial LR filtration throughout CPB.

There were no obvious reasons for this variation, though a more fastidious review of the relevant studies might uncover relevant issues, and is due. Variables that have been mentioned as potential confounders, and which would ideally be accounted for in such a review include: duration of use, pressure conditions, flow conditions, selection of markers, measurement of activated vs. non-activated leukocytes, and the use of other anti-inflammatory strategies such as aprotinin, steroids and biocompatible circuits in the respective studies.

IMPROVEMENT OF CARDIAC OUTCOMES BY ARTERIAL LINE FILTRATION

The few studies that have considered cardiac outcomes in the context of arterial line filtration have investigated the effect of LR filters in comparison to simple screen filters. In fact, the cardioplegia circuit is a more common filtration target where the aim is improving cardiac outcomes by LR filtration, and this will be considered shortly.

The use of an arterial line LR filter throughout CPB vs. similar use of a standard 40 micron screen filter was associated with a reduction in enzyme markers of myocardial injury in two studies (42,43). The study by Hachida et al. (43) also demonstrated a reduced requirement for post-operative inotropic support in the LR filter group. The same findings were reported by Matheis et al. (33) in a study where both groups underwent CPB with a standard 40 micron arterial line filter except for a period of 15 minutes after aortic declamping when one group had LR filtration while the controls continued with 40 micron filtration, but via a new filter. It should be noted that these were all small studies (less than 40 patients) and the reduced requirements for inotropic support were small differences in the proportions of patients requiring or not requiring support.

IMPROVEMENT OF PULMONARY OUTCOMES BY ARTERIAL LINE FILTRATION

As with the investigation of cardiac outcomes, virtually all studies that have investigated improvement in pulmonary outcomes by filtration have compared LR filters to simple screen filters. Once again, there is a dichotomy of opinion on the optimal period over which to remove leukocytes; some studies applied LR filtration throughout CPB whilst others restricted it to the period of reperfusion. Pulmonary function indices shown to be improved by LR filtration of the arterial line either throughout CPB or during reperfusion are: indices of oxygenation (such as PaO2, A-a gradient, PaO2/FIO2 ratio) (throughout 28, 43–45; reperfusion only 46); reduced duration of post-operative ventilation (throughout 28,44, reperfusion only 46,47); improved pulmonary microvascular pressures (reperfusion only 47); and reduced extravascular lung water (throughout 44).

Some studies have reported no pulmonary benefit from LR filtration of the arterial line (35,39,41), but these were all small studies, and hopelessly underpowered to show anything other than large differences between the groups.

IMPROVEMENT IN HOSPITALIZATION INDICES BY ARTERIAL LINE FILTRATION.

Once again, those studies that have recorded hospitalization indices in controlled trials have investigated the impact of LR in comparison to “standard” arterial line filtration. It has been shown that the use of a LR filter in the arterial line is associated
with reduced hospital stay in the order of 1–2 days (28,46–48). Not surprisingly this is associated with reduced per patient cost (reduction of $2000–$9000 per patient) (47,48). A reduced requirement for transfusion and fluid administration has also been noted (33,36).

NON ARTERIAL FILTRATION STRATEGIES

Filtration in the Cardioplegia Circuit

It is not surprising, given the earlier discussion of ischemia-reperfusion injuries, that there may be potential for enhancing the myocardial protection afforded by blood cardioplegia if leukocytes are removed from the perfusate. Moreover, given the comparatively low volumes and flows involved (in comparison to arterial line parameters), leukocytes may be removed more efficiently. Indeed, using the Pall BC1B cardioplegia LR filter, Heggie et al. (49) demonstrated that more than 90% of leukocytes were removed. However, others have shown that these filters may begin to fail after a threshold filtered volume in the vicinity of 1000–1300 ml (50).

The overwhelming majority of human studies that have addressed this issue suggest that plasma markers of myocardial injury are reduced post-operatively when a LR cardioplegia filter is used (50–56). Indeed, only one study was found in which no such reduction was demonstrated (57). It is notable that the study by Sawa et al. (53) included the collection of left ventricular biopsies which demonstrated reduced leukocyte adherence in capillaries in LR cardioplegia patients.

Perhaps not surprisingly, this apparent benefit has been reflected in improved post-operative myocardial performance indicators such as cardiac index, ejection fraction, and inotrope requirements (50,51,53,55,56). A more detailed review of this issue (58) suggests that the greatest benefits for LR filtration of cardioplegia are to be gained in the sickest hearts or most complicated surgical procedures where, for example, the cross clamp times are prolonged. Another recent review also suggested that there may be merit in withholding filtration until administration of the terminal dose of cardioplegia (the “hotshot”) (59).

Filtration of Pericardial Suction (PCS) Blood

Blood suctioned from the surgical field has “traditionally” been returned to the CPB circuit via a “cardiotomy reservoir.” It is well recognized that pericardial suction (PCS) blood is “dirty”, with potential contaminants including fat, bone, other tissue fragments, surgical debris such as bone wax, activated leukocytes and platelets, and others. A groundswell of concern has built in the literature over the potential for cerebral injury arising from the reinfusion of this blood. This reached a crescendo with the identification of so-called “small capillary and arteriolar dilatations” (SCADs) in the brain after CPB, and the further characterization of these as lipid from the pericardial suction (60,61). Lipid contamination was also identified as the cause for disadvantageous changes in the rheology of the PCS blood plasma fraction (62). As compelling as these findings seem, there is a paucity of data definitively linking them to functional brain injury. The only study which randomized patients to receive non-processed or processed PCS blood (from which most contaminants are removed) showed no difference in post-operative memory (63). Nevertheless, the appropriate handling of PCS blood remains an issue of high interest to those in the field.

It is well established that neither integral integrated cardiotomy reservoir filters nor arterial line filters are efficient in the removal of lipid emboli from PCS blood. One approach to avoiding any adverse effects of infusing these emboli is to avoid the reinfusion of PCS blood altogether. Another is to process scavenged blood through a cell saver. This has been shown to reduce the amount of lipid returned to the patient in human CPB (64) and to reduce the density of cerebral SCADs by more than 50% in vivo (65), but any neuroprotective benefit remains to be demonstrated (see above). There has also been advocacy for the use of accessory PCS blood filters, and one study suggested that these were more efficient at removing lipid than cell saver processing (66). Others, however, suggest that the efficiency of these filters is temperature dependent and that they might be prone to obstruction, somewhat paradoxically, when operated at the temperatures at which they are most efficient (67).

ISSUES THAT ARISE AND RESEARCH DIRECTIONS

1. It is almost 5 years since the literature on filtration in CPB was formally reviewed by Whitaker et al. (4) and they restricted their review to arterial line filtration. Similarly it is 4 years since the review of leukofiltration in cardiac surgery by Ortolano et al. (59). A large number of relevant papers have subsequently been published, especially in relation to clinical application of LR filtration. This is an area that is ready for review again. A fastidious systematic review might be rewarded by some interesting correlations. It is possible that there are now sufficient studies in the area of cardiac or pulmonary outcomes to justify a Cochrane type meta-analysis.

2. It is remarkable that there is still no study that addresses functional neurological outcomes in filtered vs. non-filtered CPB where a membrane oxygenator and alpha-stat acid base management are used. This is especially so given the regional disparity in uptake (implying differing opinions on the necessity for such filtration). The latter point would justify a randomized trial from an ethics standpoint.

3. The study by Whitaker et al. (21) raises the question as to whether or not LR filters are better filters of all material, as opposed to just leukocytes, than conventional arterial line filters. This reviewer has found no relevant formal evaluation (other than the Whitaker paper itself), and such an evaluation would be a very simple and cheap experiment to perform in vitro.

4. Given the magnitude of interest and concern surrounding the reinfusion of PCS blood, it is surprising that there is no comprehensive study of functional outcomes in processed vs. unprocessed perfusate. Such a trial may be justifiable given the recent negative (but small) study by Svenmarker et al. (63).

5. As a closing observation, the recent uptake of closed extracorporeal circuits (or “mini-CPB”) must be acknowledged as an emerging trend (68). If this trend gains traction, it will generate a variety of questions with some relevance to the issue of filtration. Examples will include the appropriate way of dealing with PCS blood, the venous air handling capabilities of the circuit, and the implications of operating the circuit without an accessory arterial line filter.
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Ultrafiltration Techniques and CPB: What We Know and What We Think We Know

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INTRODUCTION

Today, the application of ultrafiltration with cardiopulmonary bypass (CPB) is commonplace. The myriad of ultrafiltration techniques can be characterized into two primary rationales: 1) volume management and 2) mediator-removal. These rationales have emerged successively during the development of ultrafiltration and influence the technical integration and use of the hemoconcentrator with the CPB circuit.

HISTORY

The Volume Management Rationale (1976–Present)

The initial use of ultrafiltration in conjunction with CPB was reported in 1976 as a way to concentrate the dilute extracorporeal circuit contents following bypass (1). Soon after, Darup et al. described the first use of ultrafiltration during CPB (2). The bypass circuit was found to be ideally suited for ultrafiltration as it offers easy access to the blood path and provides either a pump or a positive pressure site to drive blood through the hemoconcentrator. The application of ultrafiltration during CPB was initially reserved for the management of volume overload in patients with renal insufficiency and/or failure. However as the 1980s progressed this conventional ultrafiltration (CUF) technique became more widely adopted (3–7).

The ultimate fluid management/blood salvage ultrafiltration technique was first described by the Hospital for Sick Children in London (8). They reported on a modified ultrafiltration (MUF) technique which was used in the immediate post CPB period to concentrate the blood volume of their pediatric patients. By 1990, ultrafiltration was well accepted as an important adjunct to CPB that could fulfill a role in fluid balance control and blood conservation.

The Mediator-Removal Rationale (1990–Present)

While conventional and modified ultrafiltration techniques were experiencing an ever increasing clinical acceptance during the early 1990s some clinicians theorized that there was an additional benefit to ultrafiltration. Coraim et al. reported improved hemodynamics in patients following cardiac surgery when continuous arterio-venous hemofiltration (CAVH) was applied. They attributed this observation to the convective removal of myocardial depressant substances (9). Further work by researchers in a septic animal model suggests that left ventricular function improves with ultrafiltration and volume replacement (10). In 1992 a study by Grootendorst et al. demonstrated that when endotoxemic pigs underwent high volume ultrafiltration (6 L/h in an ~80 lbs pig), cardiac performance improved (11). This improvement did not occur when the blood passed through the hemoconcentrator with the ultrafiltrate line clamped. In a follow-up study, the same researchers collected and infused the ultrafiltrate from endotoxemic pigs into control animals and found that myocardial performance became depressed in the healthy pigs (12). The work of these researchers fuelled the emergence of the conceptual framework that ultrafiltration was doing more than simply removing free water and electrolytes, but, rather, it also removes potential deleterious substances from the blood thereby improving the patient’s status.

Given the myriad of ultrafiltration techniques that have been developed and the debate over the therapeutic effect of large volume ultrafiltration, the two-fold purpose of this presentation is to review and discuss various ultrafiltration techniques and to demonstrate the effectiveness of zero-balance ultrafiltration (ZBUF) at reducing the mortality in an acute animal model (13).

METHODS

Following committee approval, a control and treatment group consisting of Yorkshire pigs (30–40 kg) were anesthetized, ventilated, and then cannulated via the right femoral vein and artery and exposed to CPB for 60 minutes. Following CPB, a low-dose endotoxin (1 g/kg) was administered and the animals were monitored for 3.5 hours. The treatment group (n = 5) received high-volume Z-BUF (122 ± 41 ml/kg) and the control group (n = 5) did not. Hemodynamics, blood gases, and pulmonary functions were measured before, during, and after CPB.

RESULTS

During the experimental time course there were no differences in CO, MAP, Na+, K+, Ca++, and IL-8 concentrations between groups. However, in the control group, the PaO2 decreased (238 ± 60 mmHg vs. 78 ± 40 mmHg) and the pulmonary compliance decreased (32.2 ± 5.9 mmHg vs. 8.4 ± 4.2 mmHg) significantly compared to the treatment group. These same parameters were unchanged in the treatment group. Furthermore, histologic examination of lung biopsy showed significantly increased leukocyte infiltration and tissue density in the control group.

Disclaimer: This mini manuscript represents a vignette of the content materials and references originally prepared for a text book chapter authored by Searles and Darling for a book titled: On Bypass: Advanced Techniques in Cardiopulmonary Bypass; Editors: Oz, Mongero, and Beck. Publisher = Humana Press. Scheduled for publication in 2006.
CONCLUSION

This result suggests that Z-BUF improves the pulmonary function in this model of severe lung injury and may be an effective tool in attenuating the CPB derived inflammatory process.

SUMMARY

Unfortunately there have been very few prospective randomized studies comparing the clinical outcomes of patients treated with large volume ultrafiltration (14,15). Given the shortage of impressive clinical outcome data and the varying results of mediator removal studies, the application of ultrafiltration as a therapeutic technique is still a controversial topic. A few researchers have suggested that different membrane materials may have significantly different mediator removal potential (16–18). One important future direction for research in this area should include a comprehensive comparison of different membrane materials with regard to their clinical performance.

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Glucose and Outcome After Cardiac Surgery: What are the Issues?

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Hyperglycemia frequently occurs during the conduct of cardiopulmonary bypass (CPB) for cardiac surgery. In addition to the exogenous administration of glucose containing solutions [most notably with dextrose containing cardioplegia as well as variably in the pump prime] (1), the stress response to both surgery and CPB marked by significant increases in circulating catecholamines (epinephrine and norepinephrine) and cortisol (2) results in significant peripheral insulin resistance and marked increases in blood glucose concentrations (3–5). Hyperglycemia, defined arbitrarily as a serum glucose >200 mg/dL occurs in as many as 75% of patients during surgery with patients with pre-existing diabetes mellitus having an even higher incidence (6).

Attenuating this hyperglycemic response to cardiac surgery has proven difficult, with even high insulin doses more often than not failing to return glucose to normal levels during surgery. Part of this failure is reflective of the significant anti-insulin effects of elevated circulating catecholamines and cortisol (7), and partly it is related to the impaired ability of insulin to transport glucose intracellularly under the hypothermia that is frequently used during the normal conduct of cardiac surgery (3). Indeed, Chaney et al. found that not only was normoglycemia difficult to attain during cardiac surgery, but that with large insulin doses administered during surgery, a high incidence of hypoglycemia in the post-bypass period posed a significant risk (8). In addition, excessive insulin can also result in hypokalemia due to its enhancement of potassium transmembrane transport.
mechanisms. Although it would seem intuitive that the administration of additional insulin or insulin/glucose solutions to target normoglycemia would be safe and efficacious, the use of these protocols to achieve normoglycemia has not been adequately studied. More recently, some moderate successes have been demonstrated with the use of insulin/glucose infusions to better maintain appropriate serum glucose levels during surgery. Indeed, Carvalho et al. (9) described methodology to essentially lock in the glucose level at a predefined target. Although their study was relatively small (n = 47), it demonstrated clear efficacy compared to previous surgery trials (8) and warrants further large scale evaluation. Using a slightly different approach than previous studies, they described a hyperinsulimenia normoglycemic clamp technique that rather than using insulin administration as a “reaction” to hyperglycemia, purposely administered high doses of insulin so that exogenous glucose would have to be given to prevent hypoglycemia. In doing so, when patients were exposed to the usual periods of stress-induced hyperglycemia, the amount of glucose that was being infused was reduced resulting in optimal glucose control. Importantly, they supplemented potassium by continuous infusion and also monitored glucose levels every 5–10 minutes. Compared to conventionally treated patients, >95% of patients managed by their “clamp” technique achieved normoglycemia.

So with hyperglycemia being common and with most previously studied protocols for hyperglycemia being difficult, if not impossible, to achieve normoglycemia, a number of investigators have examined some of the adverse sequelae associated with hyperglycemia during cardiac surgery. There is emerging clinical and experimental evidence implicating hyperglycemia with various immunomodulatory effects, particularly in those patients with critical illness (10,11). In particular, hyperglycemia has been demonstrated to reduce white blood cell function, most notably macrophages and neutrophils (12). Furthermore, Rassias et al (13) demonstrated that insulin infusions can significantly improve neutrophil function (in diabetic patients) thus reversing some of the hyperglycemia-mediated immunosuppression.

Mediastinitis is a particularly ominous infection that can occur in the post-cardiac surgery period. Although the risk factors for this potentially devastating infection are multiple, hyperglycemia has recently been demonstrated to be associated with a higher incidence of mediastinitis, particularly in patients who are diabetic and/or obese (14,15). As a result, efforts have been targeted at lowering the incidence of hyperglycemia in hopes of decreasing significant mediastinal infection. Although there is some evidence that this may be effective, it has not been studied in sufficiently large populations to be confidently proven. Although perhaps not directly applicable to the issue of infection and cardiac surgery, van den Berghe et al. in a recent study of intensive insulin therapy in intensive care unit patients, demonstrated that not only did aggressive insulin treatment effectively achieve normoglycemia and reduce bloodstream infection by 45%, but it also reduced mortality (8.0% for conventional treatment vs. 4.6% for intensive insulin therapy; p < 0.04) (12).

In addition to its immunomodulatory effects, hyperglycemia, because of its osmotic effects, also has an impact on the kidney, acting as a potent osmotic diuretic. However, little work has focused on its potential impact on longer-term renal impairment that has been demonstrated in certain subsets of patients after cardiac surgery (16,17).

With respect to neurologic outcome, a great body of work has demonstrated a relationship between hyperglycemia and worse outcome after a number of different cerebral injuries. Experimentally, there is a wealth of data linking hyperglycemia with adverse cerebral outcome after stroke (18–21). Although this has also been demonstrated clinically for stroke in non-surgical settings (22–24), in cardiac surgery patients, the link between hyperglycemia and adverse neurologic outcome is far less clear (25).

The potential mechanisms for hyperglycemia’s association with adverse neurologic outcome are several-fold. Firstly, higher glucose levels lead to a higher degree of substrate availability for the production of lactate during anaerobic metabolism consequent with cerebral ischemia (26–28). The resulting intracellular acidosis then interferes with glycolysis, protein synthesis, hemeostasis, enzyme function, and other critical intracellular process (28–30). In addition, hyperglycemia has been shown to increase the release of excitotoxic amino acids (glutamate and aspartate) during cerebral ischemia (31). The release of these amino acids is a key mediator in the ischemic cascade; the presence of hyperglycemia augments this injurious response (32). Furthermore, there is potentially some evidence suggesting that the presence of hyperglycemia itself may enhance the inflammatory response (33). As it is already known that CPB stimulates a vigorous inflammatory response (34,35), and that inflammation may mediate adverse outcomes including cerebral, the additional hyperglycemia-mediated inflammation may cause further injury. Given that cerebral ischemia has the potential to occur during cardiac surgery, this may be one potential mechanism why adverse cerebral outcome would be expected to be linked with hyperglycemia during cardiac surgery. Thus far, however, most studies have been too small (and consequently underpowered) to demonstrate any meaningful associations between hyperglycemia and adverse cerebral outcome during cardiac surgery. This is particularly true for stroke. Until recently, this was similarly true for cognitive dysfunction where, although thought for a number of years to be related to hyperglycemia, studies had failed to demonstrate any association (25). Most recently, however, our research group reported the results of a study involving patients (n = 709) undergoing CABG with CPB where cognitive function was assessed both pre- and post-op (6 weeks). The incidence of cognitive deficit was compared between those who developed hyperglycemia vs. those who did not. The hyperglycemic patients had a cognitive deficit rate of 40% vs. 29% in the normoglycemic group (OR, 1.85, 95% CI 1.1–3.0; p = 0.0165). The presence of hyperglycemia increased the risk of cognitive dysfunction by as much as 85% (6).

The next logical steps in our understanding of hyperglycemia’s (and its therapy) link to outcome is to move forward with well designed, adequately powered interventional studies. Because of repeated failures in hyperglycemia therapy during cardiac surgery, there is little data focusing on whether treating or preventing hyperglycemia (with insulin/glucose infusions) can actually reduce some of this cognitive dysfunction and other neurologic injury. This remains a potentially fruitful avenue for future study.

REFERENCES

JECT. 2006;38:49–80


Glucose Monitoring on CPB

Michael McDonald, CCP; James McMillan, CCP
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Serum glucose levels rise during cardiopulmonary bypass (CPB). This appears to be regardless of temperature during CPB. The cause of this rise is multifactorial but there are two prime areas of cause;

1. increased transformation of glycogen to glucose as a response to stress
2. decreased insulin secretion secondary to surgery, anesthesia and hypothermia.

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It has been shown in many publications that hyperglycemia can cause increased cerebral injury when the brain is ischemic, increased propensity for wound infection, increased propensity for renal dysfunction post-operatively, and other complications. Many units don’t routinely monitor blood sugar levels (BSL) during CPB and many more only on known diabetic patients.

METHODS

We retrospectively analyzed 2095 consecutive CPB cases performed during 2003-4. We reviewed at gender, age, diabetic status, requirement for insulin, highest, lowest and mean BSL recorded at four time points (post-heparin pre-CPB, 5’ , 30’ and 60’ into CPB), and percentage of cases with a BSL > 8.0 mmol/l.

RESULTS

In over 8000 tests, no patient recorded a BSL < 3.0 mmol/l, i.e., hypoglycemia. The lowest BSL recorded was 3.9 mmol/l. Pre-CPB 19% of non-diabetic patients recorded a BSL > 8.0 mmol/l. Twenty-seven percent of diabetic patients had a BSL > 8.0 mmol/l at this point.

At CPB+5’ this fell to 17% and 24% respectively, most likely due to dilution with the pump prime. All age group’s BSL either fell or remained at pre-CPB levels except the <50 year-old group where the BSL almost doubled from 21% to 39% and 25%-40% respectively.

At CPB+30’ 45% of all non-diabetic patients recorded a BSL > 8.0 mmol/l (48% for diabetics). At CPB+60’ 72% of all non-diabetic patients recorded a BSL > 8.0 mmol/l, the percentages were higher for the diabetic patients (82%). This was despite insulin treatment in many of these patients.

Further, this rise in BSL was seen across all age groups and both genders. Interestingly the highest rise in BSL was seen in the under 50 years of age group at all time points and in both diabetics and non-diabetics.

CONCLUSION

This retrospective audit has demonstrated the difficulty in effective control of blood glucose and the need to monitor BSL carefully in all patients during CPB.

Review on the Usage of Mannitol During Cardiopulmonary Bypass

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INTRODUCTION

Mannitol is an inert, undissociated six-carbon polyhydric alcohol. It is an osmotic diuretic. Mannitol is used during cardiac surgery as it improves renal blood flow, minimizes extra vascular fluid shifts and reduces positive fluid balance.

METHODS

A retrospective analysis was performed on the usage of mannitol during cardiopulmonary bypass. Mannitol was not used as a constituent of the prime, however was administered during cardiopulmonary bypass, at the discretion of the perfusionist, to augment diuresis and to minimize fluid movement to the extra vascular space. Data was collected from sixty-five consecutive patients who underwent routine cardiopulmonary bypass procedures. The patients were divided into two groups. Group A did not receive any mannitol during the surgery; Group B received 0.25 g/kg body weight mannitol during surgery. The parameters analyzed were age, pre operative hemoglobin, weight, renal function, intra operative hemoglobin, bypass time, urine output, volume added during bypass and the fluid balance. Statistical analysis was performed with SPSS for windows V 13.

RESULTS

32 patients (group A) did not receive any mannitol. 33 patients (group B) received mannitol. The demographics show that the two groups were similar in all respects except for the bypass time (p < 0.05), which was significantly longer in group B (88.1 vs. 109.8 mins).

<table>
<thead>
<tr>
<th></th>
<th>Group A (no Mann)</th>
<th>Group B (Mann)</th>
<th>p Value</th>
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</thead>
<tbody>
<tr>
<td>Age</td>
<td>64.9 (±12.5)</td>
<td>69.4 (±12)</td>
<td>0.14</td>
</tr>
<tr>
<td>Hb (pre-op)</td>
<td>134 (±18.4)</td>
<td>137.8 (±17.4)</td>
<td>0.40</td>
</tr>
<tr>
<td>Weight</td>
<td>79.5 (±14.4)</td>
<td>78.6 (±14.6)</td>
<td>0.79</td>
</tr>
<tr>
<td>Urea</td>
<td>7.23 (±2.9)</td>
<td>9.2 (±12.1)</td>
<td>0.26</td>
</tr>
<tr>
<td>Creatinine</td>
<td>89.4 (±31.8)</td>
<td>91.8 (±28.8)</td>
<td>0.76</td>
</tr>
<tr>
<td>Fluid balance</td>
<td>3131.3 (±840.0)</td>
<td>3349.1 (±1064.4)</td>
<td>0.38</td>
</tr>
<tr>
<td>Bypass time</td>
<td>88.09 (±23.2)</td>
<td>109.8 (±41.9)</td>
<td>0.01</td>
</tr>
<tr>
<td>Urine output</td>
<td>725 (±467.3)</td>
<td>806.7 (±516)</td>
<td>0.51</td>
</tr>
<tr>
<td>Hb (bypass)</td>
<td>76.1 (±15.3)</td>
<td>77.7 (±12.1)</td>
<td>0.63</td>
</tr>
</tbody>
</table>

JECT. 2006:38:49-80
CONCLUSION

The results of the review showed no significant difference in fluid balance and urine output with the addition of mannitol. There was a trend for increased urine output in patients with prolonged bypass time. A prospective randomized control trial with larger patient group and addition of mannitol either in the prime or at a discrete time during bypass to reduce the variability between the groups is recommended.

What Blood Pressure is Appropriate for Cardiopulmonary Bypass and How To Get It

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Auckland City Hospital, Auckland, New Zealand

In 1995, Gold et al. published the results of a randomized clinical trial of elective coronary artery bypass grafting in 248 patients randomized to two groups (1). In one group, mean arterial pressure was maintained between 50 and 60 mmHg during cardiopulmonary bypass and in the other it was maintained between 80 and 100 mmHg. The incidence of combined cardiac and neurological complications was significantly lower in the high pressure group (4.8%) than in the low pressure group (12.9%; p = 0.026). Six months postoperatively, the mortality rates were 1.6% and 4%, stroke rates 2.4% and 7.2%, and cardiac complication rates 2.4% and 4.8%. Cognitive and functional status outcomes did not differ between the groups. This study precipitated a change in practice in our unit, more in response to casual discussion than in any formalised way. The use of vasoconstrictors to maintain higher mean arterial pressures has become the norm.

Gold’s study was criticised when published on a number of grounds, notably the unjustifiable technique of selectively pooling data to achieve statistical significance. Other criticisms included the lack of data on the prevalence of post bypass and postoperative hypotension or hypertension.

WHAT IS THE TRUTH OF THE MATTER?

The primary reason for worrying about blood pressure on CPB is the potential for injury to the brain. Adverse cerebral outcomes after cardiac surgery are associated with higher in-hospital mortality, longer hospitalisation, and a higher rate of discharge to other facilities for further care (2). Factors which have the potential to affect neurocognitive outcomes after cardiac surgery include:

1. hypoperfusion (3,4,5)
2. cerebral embolic load (6)
3. hypoglycaemia (6)
4. hypertension (7)
5. atheromatous disease (8)
6. therapeutic agents (9)
7. temperature (10)

Studies of pressure during CPB need to take each of these into account. This has not always been the case. Stockard established the concept of \( \text{tm}^{50} \) (the integral of perfusion pressure \( \leq 50 \) mmHg over time) (11). We have the opportunity to study this in our own patients.

Cerebral perfusion pressure is the difference between mean arterial pressure and central venous pressure. The argument around perfusion pressure and cerebral blood flow is complicated. Low flow may be associated with hypoperfusion. High flow may increase embolic load. Brown has demonstrated a relationship between embolic load and bypass time (12) which links to other work showing poorer neurological outcomes with increased bypass times. Schmidt has demonstrated that cardiopulmonary bypass is associated with a significantly higher rate of cerebral injury in patients who were hypertensive preoperatively (7). Technical matters are also important (13)—including the design of equipment used during CPB (14,15). Putting the patient head down at critical moments in the procedure may reduce embolisation to the brain (16). Reducing the haematocrit may improve flow but the lowest haematocrit during CPB is an independent risk factor for mortality (risk is increased if the haematocrit \( \leq 14\% \)) (17). Transient hypertension during cardiac surgery has been associated with stroke. High perfusion pressure may be associated with more damage to blood elements and thereby exacerbate the inflammatory response to CPB. It may also compromise the surgical field.

Table 1. Some factors which affect cerebral blood flow.

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<th>Item</th>
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<td>1</td>
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<td>6</td>
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<td>7</td>
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</table>
The notion that 50 mmHg is a safe lower limit for MAP on CPB appears to reflect the notion that this is the lower limit at which autoregulation of the cerebral circulation occurs. Within the limits of autoregulation, flow is driven by cerebral metabolic rate rather than perfusion pressure. Cerebral metabolic rate is influenced (amongst other things) by hypothermia. In reality, the range of cerebral autoregulation varies between individuals, and studies show enormous between-patient variability in blood flows at any given pressure. The concept of a lower range of 50 mmHg seems to have been predicated on one or two older studies which have been subject to serious methodological criticism.

Acid base management is integral to any discussion of perfusion on bypass. pH is defined as the negative logarithm of the Hydrogen ion concentration ([H+]), or pH = -log [H+]. Electrochemical neutrality is defined as the point where [H+] = [OH-]:

- Neutral pH (pN) is 7.00 at 25°C where [H+] = [OH-] = 1 × 10^-7 mole/L.
- For water, at 37°C pN is 6.80; at 17°C pN is 7.14.
- At 37°C intra-cellular pN is 6.80 and extra-cellular pN is 7.4 (the pN of blood).

During cooling of aqueous solutions, both [H+] and [OH-] decrease because the spontaneous dissociation of water decreases. Homeotherms maintain their temperature despite changes in their environment. Poikilotherms’ temperature changes with changes in the environmental temperature. Most poikilotherms tend to maintain intracellular pH near pN over a wide range of temperatures. As they cool, intra- and extra-cellular pH increases and so does pN (much as for water).

The constituent of proteins thought responsible for the remarkably constant intra-cellular balance between [H+] and [OH-] as temperature varies is histidine. The degree of dissociation of the imidazole group of histidine (approximately 0.55—called “α”) doesn’t change appreciably with temperature; instead, the pKa of the imidazole does vary. Humans appear to maintain α-stat physiology. This includes keeping the CO2 content of the blood constant with varying temperature, because a change in CO2 content would alter α.

Henry’s law states that the amount of gas in a solution is proportional to its partial pressure; as temperature drops, the partial pressure of CO2 decreases, but its solubility increases, so the total content of CO2 remains constant and so does α.

The object in α-stat management of CPB is to keep pH at 7.4 and pCO2 at 40 mmHg as measured at 37°C. If the same samples were corrected to the patient’s temperature, these results would indicate a respiratory alkalosis (pH high, pCO2 low). pH-stat involves aiming for the same targets after correction for temperature; this requires the addition of pCO2 and is a more acidic technique. Most enzyme reactions have pH optima that follow the predictions of α-stat theory. Therefore metabolic rate would be expected to reduce with pH-Stat, and this is thought to be the mechanism by which hibernating species conserve oxygen (they follow pH-stat acid base physiology). However, in a study by Murkin discussed below (18), cerebral metabolic rate did not vary between pH-stat and α-stat management, so the former approach produced more flow for a given metabolic rate (see below). Other studies have shown lower metabolic rates with pH-stat, but at the temperatures typically used for adult CPB, the weight of current evidence suggests that there is very little difference in metabolic rate between the two approaches.

The relationship between cerebral blood flow and perfusion pressure depends on whether α-stat or pH-stat management of acid base is used. Murkin et al. has demonstrated that cerebral blood flow autoregulation is better maintained in presence of α-stat management (18). For most given cerebral perfusion pressures, cerebral blood flow is higher with pH-stat management of CPB (which may be a good or a bad thing—see above). At some temperatures this relationship reverses. Bashein et al. showed that at moderate hypothermia, carbon dioxide management during cardiopulmonary bypass has no clinically significant effect on either neurobehavioural or cardiac outcome (19). In a study by Stephan and co-workers, new neurological deficits were more common in pH-stat patients. In a study by Patel and co-workers, the conclusion was “patients receiving alpha-stat management had less disruption of cerebral autoregulation during cardiopulmonary bypass, accompanied by a reduced incidence of postoperative cerebral dysfunction.” (20). This clinical advantage was consistent with findings in another study by Murkin (21).

How then should one control blood pressure on CPB? Dilators and constrictors seem to be more popular than alterations in flow rate, however we have a very poor understanding of the regional effects of these drugs. Given the forgoing discussion, it seems that the outcome of changing pressure by these manipulations is even less certain.

REFERENCES

Conducting Clinical Trials

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EVIDENCE BASED MEDICINE

Sackett has defined evidence based medicine (EBM) as “the conscientious, explicit and judicious use of current best evidence in making decisions about the care of individual patients. The practice of EBM means integrating individual clinical expertise with the best available external clinical evidence from systematic research.” (1). Sources of external clinical evidence include clinical research (of which randomized controlled trials are only a part), research from basic science, and research which synthesises expert opinion. A hierarchy has been proposed (Table 1) for use in evaluating this evidence.

Table 1. Hierarchies of evidence defined by Eccles et al. (2)

<table>
<thead>
<tr>
<th>Category of Evidence</th>
<th>Description</th>
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<tbody>
<tr>
<td>Ia:</td>
<td>evidence from meta-analysis of randomised controlled trials</td>
</tr>
<tr>
<td>Ib:</td>
<td>evidence from at least one randomised controlled trial</td>
</tr>
<tr>
<td>Iia:</td>
<td>evidence from at least one controlled study without randomisation</td>
</tr>
<tr>
<td>III:</td>
<td>evidence from non-experimental descriptive studies; such as comparative studies, correlation studies and case-control studies</td>
</tr>
<tr>
<td>IV:</td>
<td>evidence from expert committee reports or opinions and/or clinical experience of respected authorities</td>
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</table>

Since more weight is placed on the results of the randomized controlled trial (RCT) than on expert opinion, it follows that a basic understanding of clinical research is relevant to all clinicians who wish to practice EBM. Does it also follow that all clinicians should undertake research? Research is expensive in time, and often also in other resources. Our patients are our most precious resource. The world literature has been flooded with reports of studies varying from excellent to un-interpretable. Separating the meaningful from the meaningless and synthesizing these data into useful information has become a major challenge. In fact, a whole industry has arisen around systematic reviews of clinical studies (Box 1). Unfortunately, systematic reviews (with or without meta-analysis) can only be as good as the trials they review.

THE VARIABLE QUALITY OF PUBLISHED RESEARCH

A persistent problem with the interpretation of the results of research relates to the variable quality of the research. This may seem surprising, at least in respect of peer reviewed journals. However, the assumption that the process of editorial peer review ensures adequate quality in either the conduct or the reporting of research seems to be unfounded. In 1983, Bailar and Patterson identified that part of the problem of poor quality in published research was a lack of empirical research into the peer review and editorial processes at the heart of medical literature, and called for studies to be done on these processes (3). Editors at JAMA responded by convening a conference at which the results of such research could be presented. By 2002 nearly 200 papers per year dealt with this subject. However, in an editorial on the fourth such conference Rennie quoted the following comment made after the third conference and indicated that it still applied.

“...there are scarcely any bars to eventual publication. There seems to be no study too fragmented, no hypothesis too trivial, no literature citation too biased or too egotistical, no design too warped, no methodology too bungled, no presentation of...
results too inaccurate, too obscure, and too contradictory, no analysis too self-serving, no argument too circular, no conclusions too trifling or too unjustified, and no grammar and syntax too offensive for a paper to end up in print” (4).

Some of the deficiencies which have repeatedly been identified in clinical trials, even those reported in major journals are:

- Inadequate review of the literature in relation to the study
- inadequate formulation of hypotheses;
- inadequate blinding;
- incorrect statistical analyses;
- inadequate discussion of limitations;
- ghost or guest authorship;
- publication bias (positive results are more likely to be published than negative);
- fraud (e.g., data that have simply been fabricated).

It can be seen that the pressing need in research is not more volume, it is better quality. We should be focusing the use of our time and resource, particularly our patient resource, on high quality, important research. This requires expertise which can only be obtained by experience or through training. It follows that the primary responsibility for research should be assumed only by those with reasonable experience in this activity, but a contribution to research can be made and is needed from all clinicians.

**QUANTITATIVE AND QUALITATIVE RESEARCH**

It is often said that research is about finding the answer to an answerable question. This is true for clinical trials but it is not true of all research. Medicine is based on phenomenological or observational research. This is one example of qualitative research, the importance of which is being recognized increasingly in recent years (5). Qualitative research tends to be inductive and one of its roles is to develop hypotheses. Quantitative research is generally about testing these hypotheses. In addressing a particular question for research, the best method is the one best suited to answering the question, and this is not always an RCT. Runciman (6) [and others (7,8)] think EBM should include qualitative data (9).

This paper will concentrate on quantitative clinical trials and will focus on four aspects of these trials:

- the process of research;
- compliance with regulatory requirements for research;
- reporting research (i.e., writing the paper);
- inspirational aspects of research.

**THE PROCESS OF RESEARCH**

**Literature Review**

This is the first step. Research is about adding to the existing body of knowledge. It is a waste of time and resource, and unethical, to expose patients to the risks and inconvenience of research in relation to question that have already been answered.
The literature review needs to be systematic and comprehensive. It needs to summarise what is known on the subject, identify what is not known and justify the primary hypothesis of the study.

**Formulation of the Research Question**

The generation of an accurate, testable, primary hypothesis is possibly the most important step in the development of a research protocol. I recently spent two hours in a meeting, involving some of the most prestigious researchers in the country, in which the discussion was entirely focused on refining a primary hypothesis. Closely linked to the primary hypothesis is a defined primary outcome variable. Put simply, it is essential to define the question you intend to answer, and to define how you are going to answer it.

**Definition of Population**

Inferential statistics utilise samples to infer information about populations. The population might be all patients in New Zealand, all patients admitted to Auckland Hospital in 2005, or all patients between the ages of 70 and 71 who bank with the Auckland Savings Bank. The results of the study will only apply to that population. In general, a high degree of selectivity in defining the research population increases the chance of showing a difference between intervention and placebo but reduces the degree to which the results can be extrapolated to wider groups of patients. Recruitment is always difficult, so inclusion and exclusion criteria need to be considered carefully.

**Definition of Sampling Strategy**

To make valid inferences from a sample about a population, it is essential that the sample is taken in an appropriate way. There are various techniques of sampling, depending on the objective of the study, but usually a random selection of subjects from the population will be used. The method of making this selection needs to be clear and explicit.

**Allocation Between Groups**

Typically, the clinical trial will involve randomisation of patients to an intervention or a control situation. Randomisation needs to be rigorous and explicit. The methods by which randomisation is achieved need to be clearly spelled out.

**Patient Information Sheets**

These are important and tend to be inadequately developed. They should be written clearly in simple language. They should be explicit about possible risks. The protocol should explain who will get consent. Some authorities require the formal signed consent to be obtained by a doctor. A combination of provision of information by a nurse and final confirmation and form signing by a doctor works well.

**Sample Size Estimation**

This is a black art, but very important. Most researchers will need advice. Sample size estimation is more about understanding the implications of the sample size than about getting an absolute answer to the question of how many patients should be studied.

**A Protocol**

A fully developed protocol is essential for a successful research project (Table 2). Protocols tend to be well done with company sponsored research but are often neglected in smaller projects. The protocol should define every aspect of the study. It is a tool for the conduct of the study and for the subsequent write up of the results. There is an increasing trend towards registering protocols at the time the study begins. For the FDA and industry research this has becoming particularly important.

**Table 2.** Check list for evaluating the quality of a clinical trial, modified from Huwiler-Muntener et al. (10) following the items in the Consort Statement (11) (indicated by a +). This check list can be used as a template for writing a protocol or a paper.

<table>
<thead>
<tr>
<th>Section</th>
<th>Item</th>
<th>Consort</th>
</tr>
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<tbody>
<tr>
<td>Title</td>
<td>1. Does the title identify the study as a randomized controlled trial?</td>
<td>+</td>
</tr>
<tr>
<td>Abstract</td>
<td>2. Is the trial identified as prospective and blinded?</td>
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<td></td>
<td>3. Does the title give a balanced indication of the significant findings of the trial?</td>
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<td>4. Is the abstract presented in a structured format?</td>
<td>+</td>
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<td>5. Are the key methods described?</td>
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<td>6. Are as many data as possible included in the abstract?</td>
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<td></td>
<td>7. Is there a balanced conclusion indicating the significant findings of the trial?</td>
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<tr>
<td></td>
<td>8. Are all parts of the abstract strictly in concordance with the same parts of the main body of the paper? No new or different claims or material should appear in the abstract.</td>
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<tr>
<td>Introduction</td>
<td>9. Is there a brief summary of a systematic review of the relevant literature?</td>
<td>+</td>
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<td></td>
<td>10. Are deficiencies in current knowledge identified?</td>
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<td>11. Is the importance of the study explained?</td>
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<td></td>
<td>12. Are the objective stated?</td>
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<td></td>
<td>13. Is the hypothesized stated?</td>
<td>+</td>
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<tr>
<td>Methods</td>
<td>14. Is the study population described?</td>
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<td>15. Are start and end dates of data collection stated?</td>
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<td>16. Is Ethics Committee approval indicated (and the specific committee identified)?</td>
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<td></td>
<td>17. Is the process of informed consent explained</td>
<td>+</td>
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<tr>
<td></td>
<td>18. Are inclusion and exclusion criteria described?</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>19. Are the interventions described?</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>20. Are the outcome measures described?</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>21. Is the primary outcome specified?</td>
<td>+</td>
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</table>
Table 2. Continued

<table>
<thead>
<tr>
<th>Section</th>
<th>Item</th>
<th>Consort</th>
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<tbody>
<tr>
<td>Title</td>
<td>21. Is the primary outcome specified?</td>
<td>+</td>
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<tr>
<td></td>
<td>22. Is a minimum important difference for the primary outcome reported?</td>
<td>+</td>
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<td></td>
<td>23. Are power calculations described?</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>24. Is the rationale for the statistical analyses explained?</td>
<td>+</td>
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<tr>
<td></td>
<td>25. Are the methods for statistical analyses described?</td>
<td>+</td>
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<td></td>
<td>26. Are stopping rules described?</td>
<td>+</td>
</tr>
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<td></td>
<td>27. Were any interim analyses carried out?</td>
<td>+</td>
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<td></td>
<td>28. Was a safety monitoring committee used?</td>
<td>+</td>
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<td></td>
<td>29. Is the unit of randomization described?</td>
<td>+</td>
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<tr>
<td></td>
<td>30. Is the method used to generate the allocation schedule described?</td>
<td>+</td>
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<td></td>
<td>31. Is the method of allocation concealment described?</td>
<td>+</td>
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<tr>
<td></td>
<td>32. Is the timing of assignment described?</td>
<td>+</td>
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<tr>
<td></td>
<td>33. Is the method to separate those generating the allocation sequence from those assigning participants to groups described?</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>34. Are the mechanisms of blinding described?</td>
<td>+</td>
</tr>
<tr>
<td>Results</td>
<td>35. Is the number of randomized patients reported?</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>36. Is the number of randomized patients reported for each comparison group?</td>
<td>+</td>
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<tr>
<td></td>
<td>37. Are prognostic variables by treatment and control group described?</td>
<td>+</td>
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<td></td>
<td>38. Have confounding influences been considered (note: these should not be the subject of statistical testing)?</td>
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<tr>
<td></td>
<td>39. Is the number of patients receiving intervention as allocated reported for each comparison group?</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>40. Is the number of patients analyzed reported for each comparison group?</td>
<td>+</td>
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<tr>
<td></td>
<td>41. Are withdrawals and dropouts described for each comparison group?</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>42. Are protocol deviations described for each comparison group?</td>
<td>+</td>
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<tr>
<td></td>
<td>43. Is the estimated effect of the intervention on primary and secondary outcomes stated, including a point estimate and measure of precision (confidence interval)?</td>
<td>+</td>
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<tr>
<td></td>
<td>44. Are the results stated in absolute numbers?</td>
<td>+</td>
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<tr>
<td></td>
<td>45. Are summary data and inferential statistics presented in sufficient detail to permit alternative analyses and replication?</td>
<td>+</td>
</tr>
<tr>
<td>Discussion</td>
<td>46. Are the key findings summarised?</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>47. Are these findings related to the literature?</td>
<td>+</td>
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<tr>
<td></td>
<td>48. Are the limitations of the study explained?</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>49. Are the strengths of the study outlined?</td>
<td>+</td>
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<tr>
<td></td>
<td>50. Is the significance of the findings explained?</td>
<td>+</td>
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<tr>
<td></td>
<td>51. Are possibilities for future work outlined?</td>
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</tbody>
</table>

Forms

Data should be collected on pre-designed case record forms (CRFs). Most clinical trials should include adverse event reporting. A predefined grading system and specific forms for adverse events are needed.

COMPLIANCE

Table 3 lists compliance requirements typical of a current clinical study. There is a great deal of time and work in meeting these regulatory requirements. Research must be conducted strictly with ethics committee approval and involvement, but the Ethics Committee is in fact the researcher’s friend, and should be seen as a source of advice in the face of difficulty. If in doubt about any aspect of the research ask the Ethics Committee.

Table 3. Some compliance requirements for clinical studies

<table>
<thead>
<tr>
<th>Item</th>
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<tbody>
<tr>
<td>1. Compliance with good clinical practice guidelines (see Box 2)</td>
</tr>
<tr>
<td>2. Ethics committee approval</td>
</tr>
<tr>
<td>3. Written, informed consent from all participants</td>
</tr>
<tr>
<td>4. Consultation with Maori (probably Pacific Island populations should also be consulted)</td>
</tr>
<tr>
<td>5. Contractual agreement with host hospital</td>
</tr>
<tr>
<td>6. Contractual agreement with sponsor, whether a funding agency or company</td>
</tr>
<tr>
<td>7. Reporting requirements</td>
</tr>
<tr>
<td>a. To ethics committee</td>
</tr>
<tr>
<td>b. To funding organisations</td>
</tr>
<tr>
<td>c. To patients at the end of the study</td>
</tr>
<tr>
<td>8. Retention of data (typically 10 or 15 years)</td>
</tr>
<tr>
<td>9. Compliance with security requirements for document storage</td>
</tr>
<tr>
<td>10. Compliance with privacy requirements for all aspects for the research</td>
</tr>
<tr>
<td>11. Compliance with confidentiality requirements for industry sponsored research</td>
</tr>
</tbody>
</table>

JECC. 2006;38:49–80
WRITING THE PAPER

The scientific report of a research project should follow a highly structured format (Box 3 and Table 2). Writing a scientific paper becomes much easier once one realises what should and should not be included. In writing a paper it is important to keep material in its correct section. It is a very common mistake to put discussion into the methods and results sections or to include new results into a discussion section. This is confusing and should be avoided. Each journal has its own guidelines for authors, and these should be followed explicitly. Reviewers are busy researchers, who give their time free - make sure the paper has been carefully proofed and internally reviewed before sending it to the journal. It is disrespectful to submit shoddy work.

INSPIRATIONAL ASPECTS OF RESEARCH

This outline might suggest that the primary requirement of research is a recipe. Nothing could be further from the truth. However, despite the fact that every project is unique and represents its own challenges, there are a large number of issues that need to be considered and dealt with on a routine basis. In this paper, I have tried to give an overview of some of the more important aspects of any research project.

Ultimately, however, good research arises out of an inquiring mind. A good research project is underpinned by a good question. Researchers are sceptics who question everything. Typically they differ from good teachers, who tend to be clearer at expounding currently accepted knowledge. The researcher, by contrast, doubts the validity of currently accepted knowledge, and questions it. This in itself is only the first step, but it is a key defining characteristic of the good researcher. The fascination with knowledge and the thrill of the pursuit of new information is what drives research.

REFERENCES

5. Merry AF, Davies JM, Maltby JR. Qualitative research in health care. BJA. 2000;84:552–5.

Pericardial Suction Blood—What Are We Doing About It?

Tim Willcox, Dip Perf, CCP; Gillian Chase, Dip Perf, CCP; Jean-Luc Charlier, BSc, ECP; Katherine Place, BSc, Dip Perf, CCP; Jude Clark, Dip Perf, CCP; Nathan Ibbott, BSc, Dip Perf, CCP; Tom Hick, BSc, ACPS; Rach van Uden, ECP; Jennie O’Shea, CCP

Green Lane Perfusion, Auckland City Hospital, Auckland, New Zealand

INTRODUCTION

In August 2004 we introduced the Dideco 903 Avant hard-shell membrane oxygenator (Mirandola, Italy) into our practice that incorporates a cardiotomy reservoir integral to the venous reservoir that enables pericardial suction blood (PSB) to be separated from the circulation and sequestered.

METHODS

Following ethics committee approval, a prospective audit of the treatment of PSB was conducted on 58 adult patients undergoing elective cardiopulmonary bypass (CPB) at Auckland City Hospital. A sheet was filled out for each procedure to include patient demographics, whether unprocessed PSB was reinfused and reason for reinfusion, use of the blood cell processor, and perioperative hematology, blood product transfusion and blood loss.

RESULTS

Pericardial suction blood was reinfused unprocessed in 28% of patients (group R) and sequestered and not returned in 72% (group S). The reason for reinfusion of PSB unprocessed in Group R was “excessive volume” in all cases.

While the age and weight of patients both groups were similar (62.8 yrs vs. 65.5 yrs and 81.5 Kg vs. 76.8 Kg) the case mix and CPB times were different. The operating room (OR) discard suction was variably used regardless of whether PSB was sequestered or reinfused.

Where blood was not processed (n = 45), in 53% no processor disposables were used. A cell processor reservoir plus aspiration line was used and wasted in 13% of cases, the majority of these being CABG where there was insufficient PSB volume to process.

BLOOD PRODUCT USE

Table 1. Discarded OR suction and sequestered PSB volumes.

<table>
<thead>
<tr>
<th></th>
<th>Group R</th>
<th>Group S</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean OR discard suction (ml)</td>
<td>545</td>
<td>439</td>
<td>ns</td>
</tr>
<tr>
<td>Mean OR discard equated units</td>
<td>0.86</td>
<td>0.35</td>
<td>0.02</td>
</tr>
<tr>
<td>Mean sequestered PSB discarded</td>
<td>249</td>
<td>125</td>
<td>ns</td>
</tr>
<tr>
<td>Mean sequestered PSB equated units discarded</td>
<td>1.7</td>
<td>0.4</td>
<td>ns</td>
</tr>
</tbody>
</table>

There was no difference post operative chest drainage (24 hour) between Group R and Group S (770ml and 716ml respectively).

CONCLUSION

These limited data show the Avant 903 cardiotomy to enabled improved avoidance of reinfusion of cardiotomy blood with an open system (72% vs. 4% for the year prior to its introduction). Discarded blood in group R yielded a significantly greater red cell mass (and hence equated units of blood) than group S and this should have been directed to a blood processor. While there is level 1 evidence that PSB contains deleterious elements there is currently no strong evidence on the impact of avoidance of reinfusion of PSB on patient outcome. Further prospective clinical trials are warranted.
The OXICAB Trial: Cerebral Oximetry in Adult Cardiac Surgical Patients

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INTRODUCTION

Decreased cerebral oxygenation has been demonstrated to be associated with adverse outcomes after surgery. Observational studies have demonstrated advantages in continually monitoring cerebral oxygenation with near infra-red spectroscopy with respect to incidence of stroke, intensive care and hospital stays. We are evaluating the influence of continuous cerebral oximetry to guide interventions to determine the effect on clinical endpoints in a prospective randomized study.

METHODS

Patients undergoing coronary artery bypass graft (CABG) surgery were invited to participate in this study (approved Flinders Clinical Research Ethics Committee). We present an interim report of 87 patients (final sample 300 patients). Patients were stratified for surgeon and diabetic status, then randomly assigned to either a control arm (n = 45, cerebral oximetry (INVOS-4100) recorded, but operating room blinded to output) or an intervention arm (n = 42, active measures taken to increase regional cerebral oxygen saturation (rSO2) if either a fall from baseline of greater than 20% or rSO2 of less than 50%). Intervention consisted of a combination of increased; FiO2 (if <100%), perfusion pressure, flow, CO2 (if <pCO2 < 35) and Hct (if <21%).

RESULTS

Intervention patients had shorter intubation times (12.2 hours (5–75) vs. 14.4 hours (6–140), p = 0.12, Wilcoxon Rank Sums), ICU stays (22.9 hours (4–101) vs. 25.3 hours (6–191), p < 0.05) and hospital stay (5 (4–15) vs. 6 (4–12), p = 0.057). There were no differences in combined clinical endpoint (19% vs. 22.2%, p = 0.7).

CONCLUSION

These results support previous data suggesting a benefit associated for CABG surgery patients with cerebral oximetry.

Perioperative Temperature and Cardiac Surgery

Hilary P. Grocott, MD, FRCPC

Associate Professor of Anesthesiology and Critical Care Medicine, Duke University Medical Center, Durham, North Carolina USA

Perioperative thermoregulation encompasses a very broad field in anesthesia and surgery. This review focuses principally on issues surrounding intraoperative temperature management, with particular emphasis on cardiopulmonary bypass (CPB) temperature issues. The implications of temperature during the postoperative period and its relationship to outcome after cardiac surgery will also be addressed. Temperature in the setting of cardiac surgery has been a major research focus for a number of decades. The judicious use of hypothermia remains a mainstay of perioperative management in the cardiac surgical patient with its putative, though far from definitively proven, global organ protective effects having led to its continued use. Although it has effects on most organ systems, this review will principally focus on the effects of temperature on the brain.

Although hypothermia has a defined and measurable effect of suppressing cerebral metabolism (approximately 6%–7% decline per °C) (1), it is likely that its other neuroprotective effect(s) may be mediated by non-metabolic actions. In the ischemic
brain, for example, moderate hypothermia has been demonstrated to block the release of excitotoxic glutamate (2), reduce calcium influx (3), hasten recovery of protein synthesis (4), diminish membrane-bound protein kinase C activity (5), slow time to onset of depolarization (6), reduce formation of reactive oxygen species (7), and suppress nitric oxide synthase activity (8). It is likely that some or all of these effects in combination convey some of the neuroprotective effects of hypothermia. Although experimental demonstrations of this are abundant, clinical examples of hypothermia neuroprotection, until recently (9,10), have been elusive (11,12).

The past ten years have seen some definitive work in the field of temperature management during CPB. Although much of this work is centered on the effects of temperature on the brain, this work was initiated because of a developing body of evidence focused on optimizing temperature-mediated myocardial preservation during CPB. In the late 80’s and early 90’s, the judicious use of warm CPB was used because of its putative myocardial salvaging effects when used with continuous warm cardioplegia (13). However, because CPB was being carried out at a higher temperature than what was considered conventional, the implications on the brain were also studied. Several large studies were undertaken to elucidate the effects of temperature management on cerebral outcome after cardiac surgery. These were the Warm Heart Investigators trial (13), a trial performed at Emory University (14), and a later trial at Duke University (15). Although there were several differences between these trials, there were some very similar results with respect to neurocognitive outcome (16,17), but some very divergent results with respect to stroke. In short, none of the studies demonstrated any neuroprotective effect of hypothermia on neurocognitive outcome after cardiac surgery. What the Emory trial did demonstrate, however, was an apparent injurious effect (as manifest by a worse stroke outcome) of what was most likely mild degrees of cerebral hyperthermia during CPB. Neither the Warm Heart Investigators trial nor the Duke trial showed any effect of temperature on stroke per se. However, one of the issues raised from these trials related to how temperature was defined, monitored, and managed–of paramount importance when trying to understand the effects of temperature on the brain. The Warm Heart Investigators trial was in actual fact a comparison of moderate hypothermia to mild hypothermia, the Emory trial compared mild hypothermia to mild hyperthermia, and the Duke trial examined hypothermia vs. normothermia. In addition to these differences in temperature management, there were some fundamental differences with respect to cardioplegia management and intraoperative glucose management.

Although there are numerous sites for monitoring temperature during cardiac surgery, several warrant special consideration. The take home message from the three warm vs. cold trials above, as well as other information regarding temperature gradients between the bypass circuit, nasopharyngeal and brain (18), is that it is very important to monitor (and use as a target) a temperature site relevant to the organ of interest. If it is the body, then a core temperature measured in the bladder, rectum, pulmonary artery, or esophagus would be appropriate. However, if one wants to measure the temperature of the brain, barring implantation of a thermistor directly into the brain (which has been done) (19), one needs to look at surrogates of brain temperature. These include nasopharyngeal temperature as well as tympanic membrane temperature. However, more invasive surrogates of brain temperature have also been obtained using a jugular bulb thermistor (18,20). What is clear from these different temperature sites is that vast gradients appear across the body and across the brain with respect to temperature. It is likely that during periods of rapid flux (such as during rewarming), that these temperature gradients are maximal.

Just as hypothermia likely has some protective effects on the brain, hyperthermia, in an opposite and disproportionate fashion, has some injurious effects. Although one can argue whether hypothermia in the setting of cardiac surgery has any definitive neuroprotective effect, there is emerging evidence that whatever neuroprotection can be afforded by hypothermia may be negated by the obligatory rewarming period that must ensue (21). Indeed, Grigore et al. (21), demonstrated that when compared to conventional “fast” rewarming, slower rewarming resulted in a lower incidence of neurocognitive dysfunction six weeks after cardiac surgery. These lower rewarming rates led to lower peak cerebral temperatures during rewarming, consistent with past observations that rapid rewarming can lead to an overshoot in cerebral temperature resulting in inadvertent cerebral hyperthermia. By reducing this rewarming rate, one reduces the overshoot in temperature and prevents the negative effects of cerebral hyperthermia. Consistent with the concept that preventing some of the rewarming may be protective was a study by Nathan et al. (22) that similarly demonstrated an avoidance of cerebral hyperthermia during rewarming and improvement of cognitive outcome after cardiac surgery.

There are several mechanisms by which hyperthermia may adversely affect the brain. Metabolically, cerebral hyperthermia has been shown to increase intracellular acidosis after ischemic reperfusion; the recovery of ATP and other high-energy phosphates is also attenuated by hyperthermia (23). Sternau et al. have demonstrated that the release of neurotransmitters (in excitotoxic quantities) is accentuated by hyperthermia (24). A greater increase in oxygen-derived free radical production after hyperthermic reperfusion after global ischemia has also been demonstrated (7). Exaggerated increases in blood-brain barrier permeability occur during ischemia under hyperthermic conditions compared with normothermia (25). Additionally, hyperthermia during ischemia increases ischemic depolarizations in the peri-infarct region and, as a consequence, increases infarct size (26). Lastly, the cytoskeleton is sensitive to hyperthermia, with decreases in microtubule-associated protein (a cytoskeletal protein) that are due to calpain degradation (27).

Although a great deal of work has focused on trying to avoid hypothermia in the perioperative period, to prevent some of its associated complications (28), several studies have demonstrated not only the safety of hypothermia but also a neurologic benefit (22). This was demonstrated in the study from the Ottawa Heart Institute by Nathan et al. (22) which demonstrated a neurocognitive benefit for patients who were maintained between 34 and 36° for a prolonged (12 hours) period postoperatively. Studies by Kurz et al. (28) have eloquently outlined the potential serious side effects of hypothermia, such as perioperative infection. This may be particularly important in the setting of cardiac surgery where mediastinitis can be a very serious complication leading to increased morbidity and mortality. However, no cardiac surgery studies have addressed any links to perioperative temperature and infection. Most of the links between perioperative hypothermia and infection have been in the setting of general surgery such as bowel resection (28). Another concern regarding postoperative hypothermia relates to the
potential for increased blood loss. Interestingly, despite an intuitive argument to the contrary, this has not been thus far demonstrated (29).

Although a great deal of interest and focus has been placed on intraoperative temperature, one must not ignore postoperative temperature. Several studies have linked postoperative hyperthermia to adverse outcomes. We have previously demonstrated that maximum postoperative temperature within 24 hours after cardiac surgery was associated with adverse neurocognitive outcome six weeks after cardiac surgery (30). In addition, a recent study has shown a further link between adverse outcomes and the peak temperature on admission to the intensive care unit (31). Although these studies suggest that postoperative hyperthermia is important, what they do not demonstrate is whether intervening to prevent postoperative hyperthermia can prevent some of the adverse complications seen with cardiac surgery.

In summary, much has been learned in the recent decades regarding optimizing perioperative thermoregulation. We have learned that although hypothermia may not be as beneficial as was once thought, hyperthermia is particularly detrimental. The likely best approach in this regard is to allow for some mild hypothermia but to prevent aggressive rewarming which may lead to an overshoot in cerebral temperature. In addition, additional work needs to be done to determine whether intervening to prevent postoperative hyperthermia can be protective. Perioperative thermoregulation remains a fruitful area for perioperative research.

REFERENCES


