Myocardial ischaemia during coronary artery bypass graft surgery: a review of intervention strategies (Part 2)

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"There remains a need to document clear clinical benefits from interventions designed to modify the inflammatory response. Modulation of the human inflammatory response has always been difficult, primarily as a result of our incomplete understanding of this response, and may lead to unexpected sequelae. The complexity of the inflammatory response is a significant obstacle to identification of the mechanisms by which alteration of a particular aspect of the response may affect clinical outcome. Indiscriminate inhibition and prevention of the inflammatory response to cardiopulmonary bypass may have detrimental effects, such as loss of appropriate wound healing and defences against infection."
– Laffey JG, et al. Anaesthesiology. 2002;97:243.[1]

Introduction

Low cardiac output syndrome is a common phenomenon in cardiac surgical patients. Myocardial ischaemia, stunning and hibernation often manifest with a low cardiac output state accompanied by segmental wall motion abnormalities.[1] Intracoronary air, direct coronary occlusion due to technical difficulty, hypovolaemia, low systemic vascular resistance, tamponade, diastolic dysfunction, right ventricular dysfunction and intracardiac air may also lead to low cardiac output syndrome.[1] The advent of echocardiography promises to revolutionise the management of this syndrome with early diagnosis and resolution of correctable causes.

Modulation of the stress response

Different modalities for attenuation of the stress response in coronary artery bypass graft (CABG) patients have been extensively investigated.[2] These have ranged from modification of the cardiopulmonary bypass machine, cardioplegia, anaesthetic care, surgical approach and the neuroendocrine response, with mixed results.[2,3] Other strategies to attenuate systemic inflammatory response syndrome (SIRS) response have focused on cell activation,[4] removal of pro-inflammatory mediators by haemofiltration, use of free radical scavengers,[5] complement, endotoxins and cyclooxygenase inhibitors.[5]

Sympathomodulatory therapies

The sympathomodulatory therapies, including β blockers, regional anaesthesia and α_2 adrenergic agonists, have been of particular interest to anaesthetic care givers.[5-8]

Beta blockers

Polderman et al[6] and Mangano et al[6] investigated β blockers in non-cardiac surgery with positive results (Class 1 evidence for β blockers).[6] Currently, the results of the Polderman studies are a subject of controversy and review. It is unclear whether these results could have been extrapolated to patients undergoing cardiac surgery. Devereaux et al, in the PeriOperative Ischaemia Study Evaluation (POISE) trial, highlighted the risk of starting beta blockade in elective cardiac patients on admission for surgery, but emphasised the benefits of these drugs in myocardial protection.[3] It is recommended that patients who are already on β blockers should be maintained on them. In a large observational analysis, Ferguson et al found that preoperative β blockers were associated with a small, but consistent, survival benefit.[9] Current literature suggests a relationship between β receptor antagonist benefit and genetics.[10] It has been suggested that there are common genetic factors in patients who develop cardiac risk factors.

Regional anaesthesia

Regional anaesthesia, in the form of a high spinal or epidural, can offer a sympathetic dernevation that can lead to a decrease in the neurohumoral response to surgery.[8,11-15] The sympatholysis by a spinal is much more extensive and unpredictable than with an epidural. In two small studies, Loick et al and Kirno et al concluded that thoracic epidural during CABG surgery attenuates the stress response to surgery and coronary artery bypass.[13] Contrary to this data, Barrington et al found that thoracic epidural anaesthesia had no effect on troponins.[11] The risk of spinal haematoma, although reported cases are almost non-existent, has to be borne in mind in this patient population where large doses of anticoagulant are administered.[8,13,15]

Alpha-2 agonists

Alpha-2 agonists exert their cardioprotective effects by attenuation of catecholamine release and inhibition of stress-induced tachycardia.[16-20] They lower the central sympathetic tone via activation of α_{2A} adrenergic receptors and the imidazole-1 receptors.[21-24] In addition to their haemodynamic effects, they induce analgesia, anxiolysis and sedation.[16] Prejunctional α_{2B} adrenergic receptors have antiadrenergic effects, while postjunctional α_{2A} adrenergic receptors have anaesthetic and short-term hypertensive effects via inhibition of L type Ca^{++} channels in neurons localised in the locus coeruleus and nucleus reticularis lateralis.[21] Commonly used pharmacological agents in this group include clonidine, mivazerol and dexmedetomidine.[20]

Perioperative mivazerol was found to reduce the occurrence of ischaemic events and cardiac death, but not myocardial infarction in patients undergoing peripheral vessel surgical interventions.[20] Clonidine has also been studied more extensively in non-cardiac patients.[22] Among cardiac surgical patients, a small comparative study by Loick et al showed that clonidine did not cause a significant attenuation of plasma epinephrine release, and there were adverse haemodynamic events.[13]

Dexmedetomidine, a pharmacologically active d-isomer of medetomidine with a high affinity for α_2 adrenoreceptors, has a α_1:α_2 ratio of 1600:1.[21] Dexmedetomidine's alpha half-life is six minutes with an elimination half-life of two hours.[21] It is a hypnotic-anxiolytic with a potential for up to 90% reduction in the anaesthetic dose of isoflurane and halothane at higher doses. Dexmedetomidine prevented changes in contractility, ejection fraction, stoke volume and calculated peripheral resistance.[17,21] At doses of between 0.2- 0.4 µg/kg/hour, it was shown to have minimal haemodynamic adverse effects.[20,23]

Existing data on dexmedetomidine is fragmented and derived largely from non-cardiac surgical patients, as well as patients in intensive care unit (ICU) settings.[22] This makes it difficult to extrapolate results to cardiac surgical patients. In an ICU study by Venn et al,[23] dexmedetomidine was shown to reduce interleukin-6 and to attenuate the haemodynamic response to intubation in cardiac patients. Jalonen et al,[16] in a study of 80 CABG patients, found that it decreases plasma concentrations of norepinephrine by 90%.[16] This study did not show any correlation with a reduction in plasma troponins, mortality and length of ICU and hospital stay. It also did not account for the preconditioning effects of enflurane used in the study.

Administration of anaesthesia

Convincing evidence suggests that volatile anaesthetics have cardioprotective properties.[25,26] Sevoflurane elicits changes in the mitochondrial proteins involved in energetic metabolism.[26,27] The electron transfer chain, including complex II ,III, IV and laden nucleotide translocase II, are increased in delayed preconditioning. Propofol has been found to attenuate free radical mediated lipid peroxidation and systemic inflammation in patients with impaired myocardial function.[28] Fentanyl has a diminished ability to attenuate the inflammatory response.[29] Morphine elicits immunomodulatory actions on lymphocytes, granulocytes and macrophages.[29]

Midazolam has little influence on the host's defence systems.[29] Ketamine attenuates the increase of interleukin-6.[29] Control of blood pressure variations and prevention of systolic excursions could reduce morbidity and mortality. In the Evaluation of CLevidipine In the Perioperative Treatment of Hypertension Assessing Safety Events (ECLIPSE) trial, an association was established between 30-day mortality and the area under the curve of systolic excursions proportionate to systolic blood pressure outside of the range 75-135 mmHg intraoperatively, and 85-145 mmHg pre- and postoperatively.[30] The rate of mortality was greater for high-risk, than low-risk patients.[30]

Reversal of reperfusion ischaemia

Post-cardiac surgery, brief prolongation of cardiopulmonary bypass to rest the heart, as compared to early initiation of inotropic support, was shown to improve myocardial function.[31] Administration of a warm reperfusate cardioplegia during the resting period was shown to further improve myocardial function.[31] The addition of an energy substrate in the reperfusate cardioplegia led to a near-normal recovery of the myocardium.[31] The heart muscle requires energy for both the systolic and diastolic components of the cardiac cycle.

Cardioplegia solutions

In CABG surgery, a combined antegrade and retrograde cardioplegia approach has been seen to improve perfusion.[31-35] The institution of retrograde perfusion at high pressures leads to tissue oedema. In the CABG Patch trial, blood cardioplegia was seen to be superior to crystalloid cardioplegia.[35] Early postoperative left ventricular function is best preserved at tepid cardioplegia temperature, compared with cold or warm.[33-35]

The addition of esmolol in cardioplegia in animal studies was seen to show complete protection in the face of global myocardial ischaemia.[31] Antioxidant addition inactivates free radicals and improves myocardial recovery.[31,32,34] Theoretically, calcium-channel blockers show benefit in cardioplegia.[31] The addition of magnesium into the prime solution reduces the incidence of ventricular arrhythmias and enhances myocardial recovery in paediatric patients.[36]

Cardiac surgical technique

Minimal extracorporeal circuit, off-pump coronary artery bypass and minimally invasive coronary artery bypass has been extensively compared to on-pump bypass CABG over the years. Off-pump cardiac surgery is associated with a reduced increase to stress response.[37,38]

Improvement of the extracorporeal circuit biocompatibility and management of the cardiopulmonary bypass circuit

The spectrum of synthetic material used in extracorporeal circuits (ECCs) is incompatible with blood and tissues.[39] Heparin-coated ECCs improve haemocompatibility and reduce activation of plasma proteins.[40] Biocompatible surfaces have been shown to possess thrombogenic resistance with minimal adhesion of plasma proteins.

Attenuation of the inflammatory response

Nonpharmacological attenuation

Haemofiltration haemoconcentrates and removes some inflammatory mediators and excess body water in tissues.[40] The use of modified ultrafiltration and conventional ultrafiltration , when compared to controls, has shown an increase in total body water of 4%, 15%, and 18% respectively.[40] Ultrafiltration is commonly used in paediatric patients.

Pharmacological attenuation

In a randomised control trial of 21 non-diabetic CABG patients, Visser et al found that patients receiving a glucose-insulin-potassium infusion had significantly reduced markers of SIRS associated with CABG, compared to patients on tight glycaemic control.[41] Pharmacological agents, such as aprotinin and corticosteroids, are fraught with controversy due to their side- effect profile.[29]

Temperature management

Moderate hypothermia serves as a middle ground between the deleterious effects of hypothermia and hyperthermia, and the potential organ protection effects of hypothermia.[42]

Haematocrit management

Haemoglobin concentrations of below 7g/dl in cardiac patients may be associated with poor outcome. Transfusing to a haematocrit of 34% and above has been shown to lead to poor outcome.[44,45] Red cell transfusion is associated with a risk of infection, immunological reactions, immunomodulation and acute lung injury, resulting in multi-organ failure and death.[43] The transfusion of blood components should be guided by evidence of poor tissue perfusion, patient profile and evidence of cardiopulmonary compromise. The principle of a "transfusion trigger" should not be applied as a blanket solution that is applied to all patients. The American Society of Anesthesiologists has developed guidelines for the transfusion of packed red cells in adults (Table I).[43]

Table I: American Society of Anesthesiologists guidelines for the transfusion of packed red cells in adults[45]

Transfusion is indicated in patients on cardiopulmonary bypass with a haemoglobin level ≤ 6g/dl.
A haemoglobin level ≤ 7g/dl in patients older than 65 years, and patients with chronic cardiovascular or respiratory diseases, justifies transfusion.
The benefit of transfusion is unclear in stable patients with a haemoglobin level between 7-10g/dl.
Transfusion is recommended in patients with acute blood loss of more than 1 500 ml or > 30% of blood volume.
Evidence of rapid blood loss, without immediate control, warrants blood transfusion.

The role of echocardiography

Early identification of new wall motion abnormalities, air in the coronaries, air in the heart chambers, tamponade, stunning, hibernation, and any suggestion of mechanical problems with new coronary grafts, may lead to early intervention, thus limiting the advent of prolonged myocardial ischaemia. There is an incidence of new findings in 13% of patients (pre- and post-bypass). The surgical plan has been altered in 5.5% of patients. Patent foramen ovale is the most common incidental finding.[45]

New global deterioration and wall motion abnormalities are associated with in-hospital myocardial infarction, cardiogenic shock and death.[45] Echocardiographic assessment of regional perfusion can be used when making decisions on revascularisation, graft revision and intra-aortic balloon pump use.[45] In a study of non-cardiac surgery, transoesophageal echocardiographic intervention led to a change in drug and fluid therapy, in 47% and 24% of cases, respectively.[46]

Conclusion

Revascularisation in coronary artery disease can be a life-saving intervention. This intervention is not without complications. The addition of a cardiopulmonary bypass circuit increases the burden of injury to blood components, activation of the coagulation cascade and release of vasoactive substances. The sympathetic system, which is meant to be protective to the body in stressful situations, can be harmful in this scenario. Most of the intervention strategies are aimed at attenuating and modulating the neuroendocrine and immunological systems. The question we should be asking, as Roizen did in an editorial, is: "Should we all have a sympathectomy at birth? Or at least preoperatively?"[47] Current data does not equip us with conclusive evidence and guidance in this respect.

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