Myocardial ischaemia during coronary artery bypass graft surgery: a review of the pathophysiology (Part 1)

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Keywords: myocardial ischaemia; coronary artery bypass surgery; troponin; systemic inflammatory response syndrome

Abstract

Myocardial mortality and morbidity during cardiac surgery is a devastating emotional phenomenon for both the medical team and the patient's family, often leading to dire financial consequences. Multiorgan dysfunction as a result of the effects of the neurohumoral system, triggered by surgery, anaesthesia, cardiopulmonary bypass, hypothermia and blood transfusion, can lead to prolonged intensive care unit and hospital stay. In this article, a literature review was embarked upon, to understand the pathophysiology and to find ways for early detection, of perioperative cardiac surgery-specific myocardial damage. It is important to appropriately understand and interpret the pattern of enzyme leakage as a marker of myocardial injury during cardiac surgery. Supplemented by clinical findings and echocardiographic evidence of possible causes of low cardiac output, earlier diagnosis may mean more prompt and goal-directed intervention, with a better outcome. A multidisciplinary approach to improve outcomes in this patient population is an absolute necessity. This can lead to modifications in surgical, anaesthetic, perfusion, and postoperative care strategies targeted at attenuating the effects of the neurohumoral insult. Often, the side-effect profile of pharmacological agents limits their use in this patient population, due to their labile haemodynamic profiles. More research is necessary to continue to interrogate the available information, and to produce new information, both in understanding the pathophysiology, and with regard to intervention strategies.

Ⓟ **Peer reviewed. (Submitted: 2011-12-05. Accepted: 2012-03-01.)** **South Afr J Anaesth Analg 2012;18(2):70-74**

"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-prevention of the inflammatory response to cardiopulmonary bypass may have detrimental effects, such as loss of appropriate wound healing and defences against infection."[1]

Introduction

Myocardial ischaemia remains the major cause of death, following both elective and emergency cardiac surgery. However, the classic sign of chest pain is masked in the perioperative period.[1,2] During this period, myocardial ischaemia often presents with pulmonary oedema, a low cardiac output state requiring an increase in inotropic support, new onset arrhythmias, new wall motion abnormalities, raised cardiac enzymes, multi-organ dysfunction, and death.[2-4]

During coronary artery bypass graft surgery (CABG), there is an imbalance in oxygen demand and supply to the myocardium.[4] Surgery leads to the amelioration of ischaemia, and an improvement in symptoms in the long term.[4,5] However, the operative period is highly important as a determinant of short- and long-term outcome.[4,6] This is a period of increased vulnerability to coronary events.[6,7] A previous review has estimated the postoperative myocardial infarction rate to be in the range of 1-25%, with mortality ranging from 0.5-14%.[6,7]

The aetiology of mortality and morbidity is multifactorial, and includes hemodynamic instability, graft anatomical and functional failure, myocardial ischaemia during aortic cross-clamp, reperfusion injury, cardioplegia-induced myocardial dysfunction, and activation of the inflammatory

and coagulation cascades.[3,5,8] The period of increased risk is the early postoperative period.[3]

The role of the stress response

There is an established stress response to surgery and anaesthesia. This stress response is mediated by the neuro-endocrine system with the release of catabolic and immunosuppressive hormones, and the activation of the sympathetic nervous system.[5,9] CABG surgery, blood transfusion, hypothermia, cardiopulmonary bypass (CPB) and anaesthesia, trigger this response equally.[1,10] The stress response is characterised by increased secretion by the pituitary hormones, and activation of the sympathetic nervous system.[9] Hypothalamic activation of the sympathetic autonomic system results in increased secretion of catecholamines from the adrenal medulla, and the release of norepinephrine from the presynaptic nerve terminals.[9] Norepinephrine is a primary neurotransmitter, but there is some spillover from nerve terminals into the circulation.[9]

The increased sympathetic activity results in adverse cardiovascular events of tachycardia and hypertension.[11] During CABG surgery, the periods of highest risk include the peri-induction and postoperative period, when anaesthesia is lighter, and the sympathetic output is the highest.[11] Catecholamines released by the neuroendocrine response lead to shear stress in the already compromised coronary vasculature.[11,12] This may lead to plaque fissuring and rupture.[3,12]

The acute stress of surgery and mechanical injury induces a hypercoagulable inflammatory state, that increases the risk of coronary thrombus formation.[12] The sympathetic hyperactivity promotes hypercoagulability by upregulating coagulation and platelet function, and downregulating fibrinolysis.[12-14] In addition, excess sheer stress during cardiopulmonary bypass may cause damage to blood constituents, contributing to endothelial injury and platelet activation.[13] Increased platelet activation secondary to epinephrine, in conjunction with decreased fibrinolysis, may lead to venous graft occlusion within the first month after surgery.[12-14] Endothelial damage, with expression of tissue factor, also leads to increased coagulation and decreased fibrinolysis.[15] This further compromises oxygen supply.[12]

The overall result of the activation of the neuroendocrine system is twofold. It increases catabolism, which mobilises substrates to provide energy sources, and it also activates a mechanism to retain salt and water, and maintain fluid volume and cardiovascular homeostasis.[10] These responses evolved as survival mechanisms to allow sustenance until healing has taken place, but may cause more harm in the perioperative period.[10] The question we probably should ask ourselves, as Roizen did in an editorial in 1988,[16] is: "Should we all have a sympathectomy at birth? Or at least perioperatively?" Although this concept may appear desirable, it has to be dealt with cautiously, bearing in mind the positive effect of the sympathetic system on transmural coronary perfusion.

The role of the inflammatory response

Tissue and peripheral nerve injury lead to a local inflammatory reaction, accompanied by elevated concentrations of various mediators.[1,17] Although there are inconsistencies in the literature, the release of pro-inflammatory markers, such as tumour necrosis factor alpha (TNF α) and interleukin-1 (IL-1), and anti-inflammatory markers such as IL-6 and IL-8 have been shown to be of particular significance.[1,17,18] Tissue injury and oedema follow a number of humoural and cellular inflammatory pathways. Different cytokines, complement, bradykinin and kallikrein stimulate the endothelium, and activate platelets and leukocytes. This results in a procoagulant state. Drugs used in anaesthesia and intensive care may modulate the stress response by influencing and modifying these intercellular communications.[19,20] The cardiopulmonary bypass machine, through complement activation, is a major contributor to the inflammatory response.[1,21]

Although blood component transfusion enhances oxygen-carrying capacity, volume support of cardiac output and haemostasis, it is associated with immunomodulation, that may lead to multi-organ failure.[22]

Hibernation, stunning and preconditioning

Episodes of deficient coronary arterial blood supply can manifest in hibernation, stunning, or preconditioning.[23] Hibernation is a state of myocardial acontractility with downregulated metabolism, due to depressed flow and function.[23,24] Stunning is a transient reversible dysfunction, provided sufficient time is allowed for recovery.[23,24] It is characterised by a flow-function mismatch. The two phenomena can be differentiated by radionuclear scans.[23]

Contrary to hibernation and stunning, episodes of transient ischaemia can lead to protection of the myocardium from extensive necrosis through ischaemic preconditioning. These episodes need to be short, followed by episodes of reperfusion (Figure 1). A preconditioned myocardium exhibits metabolic and physiological changes attributed to the activation of G protein-coupled receptors, multiple protein kinases and adenosine triphosphate (ATP) sensitive potassium channels.[23] Preconditioning can also be elicited pharmacologically, and at remote anatomical tissues.[24]

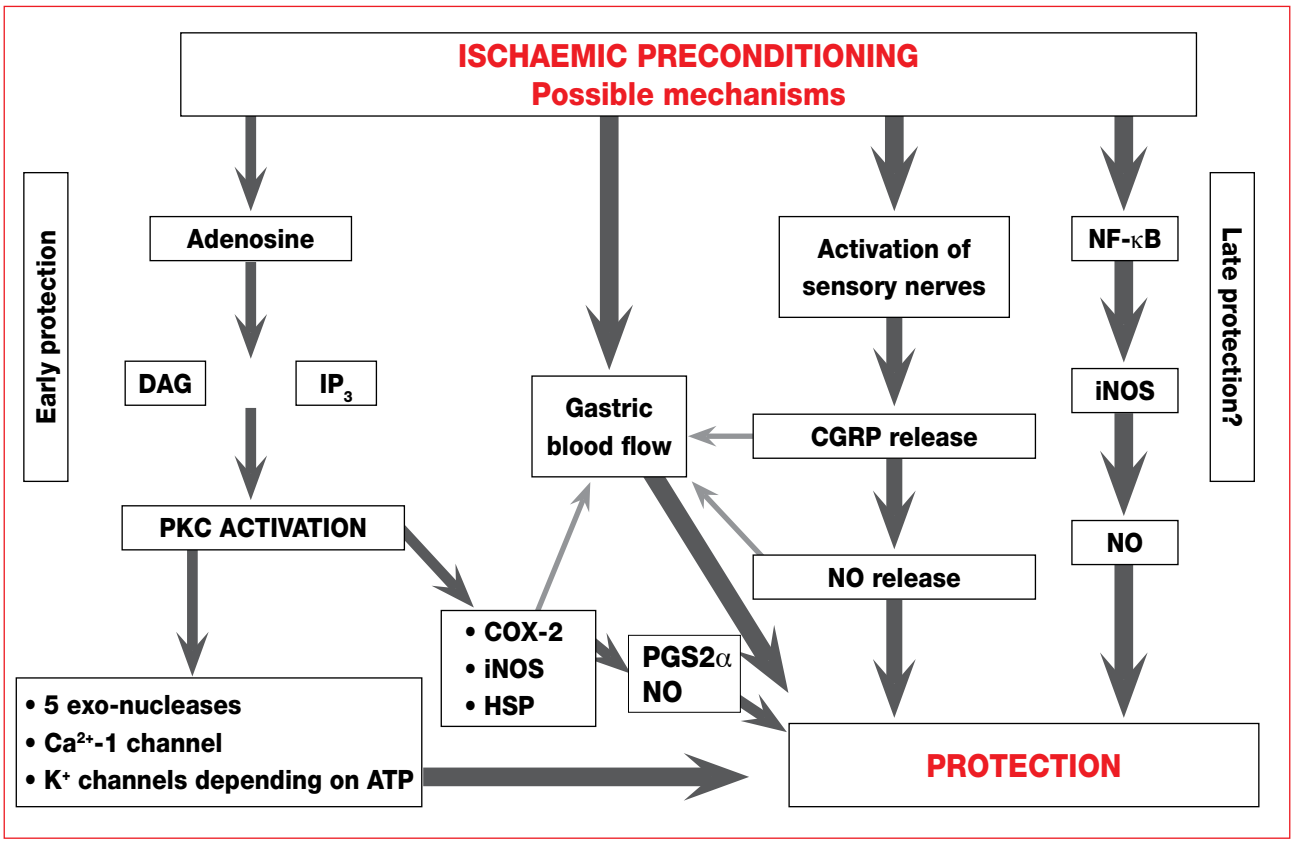

Figure 1: Possible mechanisms of ischaemic preconditioning

Ischaemia reperfusion

Myocardial ischaemia results in a state of anaerobic glycolysis. This leads to the accumulation of products such as lactate, dihydronicotinamide adenine dinucleotide and hydrogen ions.[24,25] The Na^+/H^+ pump fails. The increase in intracellular sodium serves to drive the Na^+/Ca^{2+} pump. The result of this is increased accumulation of calcium in the cells, and failure of the integrity of the membrane lipids and oedema.[25,26] Reperfusion is followed by the generation of cytotoxic oxygen metabolites. The failing heart is deficient in antioxidant enzymes, and therefore fails to respond to oxygen-free radicals.[26]

The cardiac enzymes

Cardiac enzymes are elevated within 24 hours in 90% of patients who have undergone cardiac surgery.[27] Cardiac troponin (cT) isoforms, either T or I, are proteins belonging to the thin filament regulatory system of the contractile complex.[28] Cardiac troponin I is a 24-kd protein, uniquely expressed in the human heart, and is thus not confounded by skeletal muscle proteins in the interpretation of laboratory values.[28] Compared to creatine kinase MB, troponins have been shown to be more specific and sensitive to myocardial injury.[28]

A comparison of troponins in cardiac surgery vs. myocardial infarction

Cardiac troponins, particularly cTn I, have a short half-life in the myocardium.[29] During ischaemia, progressive intracellular degradation takes place.[29] To allow preservation, the enzymes are released as complexes, viz. troponin I-troponin C, troponin I-troponin T, troponin I-troponin T and C covalent complexes. This enhances their sensitivity.[29] Troponin covalent complexes with troponin T and C appear with mild ischaemia, and disappear with more severe injury.[29] The elimination of these enzymes takes place in the liver, pancreas, kidney and reticuloendothelial system.[29] Impaired clearance, in particular during multi-organ failure, may lead to prolonged increases.

In acute coronary syndrome, plasma troponin levels correlate strongly with the extent of myocardial injury, as well as with morbidity and mortality.[28-30] Cardiac surgery also leads to an increase in plasma troponin levels.[29,30] The pattern of this increase, when compared to that of myocardial infarction with or without reperfusion, is suggestive of different pathophysiological mechanisms.[28]

An evaluation of the wash-in and washout curves of troponin post-surgery and post-myocardial infarction (MI), have shown a steeper upslope and slower downslope in post-surgical patients (Figure 2).[28] It is believed that the

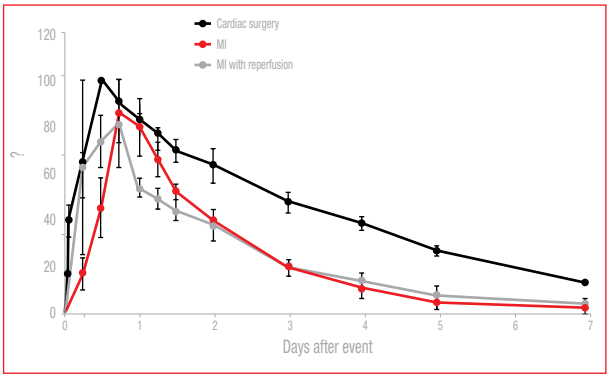

Figure 2: Mean plasma troponin-I changes after cardiac surgery and myocardial infarction, with and without reperfusion[29]

fast peak observed with surgery is due to enhanced cell membrane permeability, rather than permanent cellular damage, as seen in MI.[23] Plasma troponin levels reach a peak seven hours after cardiac surgery, and peak 18 hours post-MI, which has been confirmed by electrocardiographic criteria.[28] The slow washout may be attributed to the fact that the ischaemic insult after surgery may be milder than post-MI, with troponin appearing as a complex, rather than a free form, rendering it less vulnerable to degradation.[29]

The relationship between ischaemic markers and outcome

The troponin level, measured 20-24 hours postoperatively, is an independent predictor of in-hospital death after cardiac surgery.[28,30,31] In addition, it is associated with major postoperative complications.[7,27,28,30-34] There is no correlation of peak troponin T with the preoperative ejection fraction.[28] Although there is some heterogeneity in the cut-off points, there was a highly significant association between cardiac events and clinical end-points, with troponin levels of > 60 ng/ml, and hospital deaths of up to 44% in one study.[28] Alternatively, Nesher et al suggested an association between major adverse cardiac events and troponin levels eight times the upper range of normal.[27] Troponin levels below 40 ng/ml are associated with no cardiac events.[28]

Summary

In the CABG surgery patient, the impact of ischaemia-reperfusion, systemic inflammatory response syndrome, postoperative organ dysfunction and auto-transfusion of shed mediastinal blood rich in troponins, may complicate the correlation of enzyme level to myocardial injury.[29] Blood transfusion, CPB and cross-clamp times have also been shown to have an effect on troponin levels.[33] Enzyme levels rise less in CABG and aortic valve surgery, than in intracardiac and combined procedures.[31,32] This is due to the direct injury of myocardial cells in the latter.

These mechanisms of myocardial injury are a subject of particular interest to anaesthetic care givers. Intervention strategies to attenuate these are being investigated regularly by different clinical disciplines.

References

1. Laffey JG, Boylan JF, Chang DCH. The systematic inflammatory response to cardiac surgery. Anaesthesiology. 2002;97:251-252.
2. Miller AL, Beckman JA. Which patient should have a preoperative cardiac evaluation (stress test)? In: Lee E, Fleisher LA, editors. 2nd ed. Evidence based practice of anaesthesiology. Philadelphia: Saunders; 2004.
3. Priebe HJ. Triggers of perioperative myocardial ischaemia and infarction. Br J Anaesth. 2004;93(1):9-20.
4. Gillies M, Bellomo R, Doolan L, et al. Bench-to-bedside review: inotropic drug therapy after adult cardiac surgery: a systematic literature review. Crit Care. 2005;9(3):266-279.
5. Hirsch WS, Ledley GS, et al. Acute ischemic syndromes following coronary artery bypass graft surgery. Clin Cardiol. 1998;21(9):625-632.
6. Kirno K, Friberg P, Grzegorczyk A, et al. Thoracic epidural anesthesia during coronary artery bypass surgery: effects on cardiac sympathetic activity, myocardial blood flow and metabolism, and central hermodyanamics. Anesth Analg. 1994;79(6):1075-1081.
7. Mohammed AA, Agnihorti AK, van Kimmenade RR, et al. Prospective, comprehensive assessment of cardiac troponin T testing after coronary artery bypass graft surgery. Circulation. 2009;120(10):843-850.
8. Mentzer RM, Jahania MS, Lasley RD. Myocardial protection. Cardiac surgery in the adult. 3rd ed. In: Cohn L, editor. New York: McGraw-Hill Professional, 2003; p. 413-438.
9. Golubovska I, Vanags I. Anaesthesia and stress response to surgery. Proceedings of the Latvian Academy of Sciences. 2008;62(4/5):141-147.
10. Desborough JP. The stress response to trauma and surgery. Br J Anaesth. 2000;85(1):109-117.
11. Sablotzki A, Friedrich I, Mühling J, et al. The systematic inflammatory response syndrome following cardiac surgery: different expression of proinflammatory cytokines and procalcitonin in patients with and without multiorgan dysfunctions. Perfusion. 2002;17(2):103-109.
12. Menda F, Köner O, Sayin M, et al. Dexmedetomidine as an adjunct to anaesthetic induction to attenuate hemodynamic response to endotracheal intubation in patients undergoing fast-track CABG. Ann Card Anaesth. 2010;13(1):16-21.
13. Devereaux PJ, Golman L, Cook DJ, et al. Perioperative cardiac events in patients undergoing noncardiac surgery: a review of the magnitude of the problem, the pathophysiology of the events and methods to estimate and communicate risk. CMAJ. 2005;173(6):627-634.
14. Preibe HJ. Perioperative myocardial infarction: aetiology and prevention. Br J Anaesth. 2005;95(1):3-19.
15. PeriOperative Ischemic Evaluation-2 Trial (POISE-2 Trial). Population Health Research Institute. Hamilton: Canada; 2010.
16. Roizen MF. Should we all have a sympathectomy at birth? Or at least preoperatively? Anesthesiology.1988;68(4):482-484.
17. Burdette ASD. Systematic inflammatory response syndrome. Medscape reference [homepage on the Internet]. c2010. Available

from: http://emedicine.medscape.com/article/168943-overview

18. Talmor M, Hydo L, Barie PS. Relationship of systemic inflammatory response syndrome to organ dysfunction, length of stay and mortality in critical surgical illness. Arch Surg. 1999;134(1):81-87.
19. Zaugg M, Schulz C, Wacker J, et al. Sympatho-modulatory therapies in perioperative medicine. Br J Anaesth. 2004;93(1):53-62.
20. Raja S, Dreyfus GD. Modulation of systemic inflammatory response after cardiac surgery. Asian Cardiovasc Thorac Ann. 2005;13(4):382-395.
21. Asimakopoulos G, Taylor KM. Effects of cardiopulmonary bypass on leukocyte and endothelial adhesion molecules. Ann Thorac Surg. 1998;66(6):2135-2144.
22. Society of Thoracic Surgeons Blood Conservation Guideline Task Force, Ferraris VA, Sasha SP, et al. Perioperative blood transfusion and blood conservation in cardiac surgery: the Society of Thoracic Surgeons and the Society of Cardiovascular Anaesthesiologists clinical practice guideline. Ann Thorac Surg. 2007;83(5 Suppl):S27-86.
23. Kloner RA, Jennings RB. Consequences of brief ischaemia: stunning, preconditioning, and their clinical implications: part 1. Circulation. 2001;104(24):2981-2989.
24. Kloner RA, Jennings RB. Consequences of brief ischaemia: stunning, preconditioning, and their clinical implications: part 2. Circulation. 2001;104(24):3158-3167.
25. Rosenkranz ER, Buckberg GD. Myocardial protection during surgical coronary reperfusion. J Am Coll Cardiol. 1983;1(5):1235-1246.
26. Ferrari R, Ceconi C, Curello S, et al. Different outcomes of the reperfused myocardium: insights into the comments of stunning and hibernation. Int J Cardiol. 1998;65(1):S7-16.
27. Nesher N, Alghamdi AA, Singh SK, et al. Troponin after cardiac surgery: a predictor or a phenomenon? The Society of Thoracic Surgeons. Ann Thorac Surg. 2008;85(4):1348-1354.
28. Greenson N, Macoviak J, Krishnaswamy P, et al. Usefulness of cardiac troponin I in patients undergoing open heart surgery. Am Heart J. 2001:141(3)447-455.
29. Abramov D, Abu-Tailakh M, Frieger M, et al. Plasma troponin levels after cardiac surgery vs after myocardial infarction. Asian Cardiovasc Thorac Ann. 2006;14(6):530-535.
30. Domanaski M, Mahaffey K, Hasselblad V, et al. Association of myocardial enzyme elevation and survival following coronary artery bypass graft surgery. JAMA. 2011;305(6):585-591.
31. Lasocki S, Provenchere S, Bénessiano J, et al. Cardiac troponin I is an independent predictor of in-hospital death after adult cardiac surgery. Anesthesiology. 2002;97(2):405-410.
32. Croal BL, Hillis GS, Gibson PH, et al. Relationship between postoperative cardiac troponin I levels and outcome of cardiac surgery. Circulation. 2006;114(14):1468-1475.
33. Fellahi J, Le Menach Y, Daccache G, et al. Combination of EuroSCORE and cardiac troponin I improves the prediction of adverse outcome after cardiac surgery. Anesthesiology. 2011;114(2):330-339.
34. Lurati Buse GA, Koller MT, et al. The prognostic value of troponin release after adult cardiac surgery: a meta-analysis. Eur J Cardiothorac Surg. 2010;37(2):399-406.