doi:10.1510/mmcts.2004.000745

MULTIMEDIA MANUAL OF CARDIOTHORACIC SURGERY MMCTS

Blood cardioplegia

Jürgen Martin*, Christoph Benk

University Hospital Freiburg, Department of Cardiovascular Surgery, Hugstetter Strasse 44, D-79106 Freiburg, Germany

We present the technical details of blood cardioplegia as the standard clinical practice in most centers today. In addition, the contribution refers to the advanced strategies using blood cardioplegia in specific situations, including warm cardioplegia induction, controlled reperfusion in acute myocardial infarction, and the application of leucocyte filtration.

Keywords: Myocardial protection; Blood cardioplegia; Controlled reperfusion

Introduction

Currently, blood cardioplegia is the preferred cardioprotective strategy in the United States and in most West European countries. The technical details of blood cardioplegia have evolved as a consequence of experimental studies and clinical application, including multidose cold blood cardioplegia, warm blood cardioplegic reperfusion, warm induction, antegrade and retrograde delivery, continuous cold blood perfusion, and intermittent warm blood cardioplegia.

The fact that blood cardioplegia has emerged as the preferred cardioprotective strategy is based on its versatility, because a blood vehicle for cardioplegic delivery blends onconicity, buffering, rheology, and antioxidant benefits with its capacity to augment oxygen delivery and ability to 'resuscitate' the heart, prevent ischemic injury, and limit reperfusion damage.

In detail, the cardioprotective potential of blood cardioplegia is represented by the synergistic effect of its different components:

- Hyperkalemia: induction and maintenance of cardioplegic arrest
- Hypocalcemia: avoidance of mitochondrial calcium overload and prevention of irreversible myocyte injury.
- Tris buffer: prevention of tissue acidosis
- Hyperosmolarity and hyperglycemia: prevention of myocardial edema
- Glutamate and aspartate: these amino acids replenish key Krebs-cycle depleted during ischemia by enhancing aerobic metabolism and reparative processes.

In this chapter we describe the so-called 'standard blood cardioplegia' that is based on the intensive experimental and clinical investigations of Gerald Buckberg's research group and has been proven in leading cardiac centers worldwide over the last 20 years.

Blood cardioplegia is provided by a mixture of native blood and a commercially-available crystalloid solution (Köhler-Chemie, Alsbach-Hähnlein, Germany, www.koehler-chemie.de) at a ratio of 4:1.

Surgical technique

Arterial and venous cannulation is performed according to the planned surgical procedure. The cannulas are connected to the heart-lung machine. Insertion of a combined antegrade cardioplegia-vent catheter [1], cannulation of the coronary sinus [2], and connection of the cardioplegia-catheters to a manifold cardioplegia delivery system and the pressure monitoring lines are performed thereafter.

* Corresponding author: Tel.: +49-761-270 2818; fax: +49-761-270 2550
E-mail: martin@ch11.ukl.uni-freiburg.de

© 2006 European Association for Cardio-thoracic Surgery

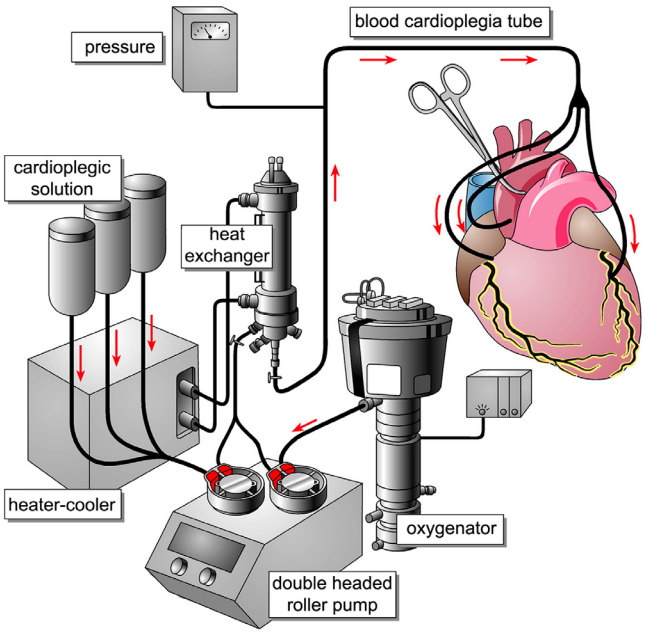
Cardiopulmonary bypass is commenced and the perfusionist initiates delivery of blood cardioplegia by mixing oxygenated blood with a crystalloid solution at a ratio of 4:1 using a double-headed roller pump (Schematic 1). The blood cardioplegic solution is guided through a special heat exchanger (i.e. Sidus – MMCTSLink 107) before it is applied to the patient's heart. Careful de-airing of the delivery system and of the aortic root is necessary to avoid coronary artery air embolism.

Cardiopulmonary bypass for routine cardiac surgery is instituted with linear flow at 2.6 l/min per m^2, maintaining perfusion pressure of 60–80 mmHg and systemic blood temperature at 35 °C.

Application of standard blood cardioplegia

The following phases of myocardial protection can be differentiated during routine open heart operations (i.e. coronary artery bypass procedures) according to our institutional protocol:

1. *Cold induction.* Reduction in extracorporeal circulation flow and aortic cross-clamping. Delivery of cold cardioplegic solution (8–12 °C) antegrade and retrograde for 2 min each until complete cardioplegic arrest is achieved (flow 200 ml/min, in hypertrophied hearts increase to 300 ml/min) (Video 1).



Schematic 1. Delivery system for blood cardioplegia using a double headed roller pump. The different cross section area of the two tubes provides a constant ratio of blood and crystalloid solution of 4:1 regardless of different flow rates. A special heat exchanger is required to adjust the temperature of the blood cardioplegic solution.

Video 1. After starting the cardiopulmonary bypass the blood cardioplegia is mixed by a double headed roller pump using 4 parts arterialized autologous blood from the oxygenator and one part of crystalloid cardioplegic solution. Thereafter the admixture is passed through a heat exchanger and then infused into the patient's heart with the pressure and flow controlled.

2. *Reinfusions with cold blood cardioplegia.* During aortic cross-clamping, multidose cold blood cardioplegia is applied at intervals of 20 min to maintain cardioplegic arrest and myocardial hypothermia. Cold blood cardioplegic infusions are routinely delivered retrograde and simultaneously via vein grafts for 1 min (flow 200 ml/min). Antegrade administration via the aortic root or direct cannulation of the coronary ostia is also applicable in specific situations.
3. *Warm terminal reperfusion ('hot shot').* Normothermic, substrate-enriched blood cardioplegia is applied before aortic unclamping. This warm reperfusate is usually delivered via the coronary sinus and the vein grafts for 1 min. This is followed by a brief (20–30 s) retrograde administration of normothermic blood. Retrograde blood delivery is stopped when spontaneous electrical and mechanical activity of the heart is visible, and the aortic clamp is released.

This method usually allows discontinuation of bypass within 5 min of releasing the aortic clamp.

Advanced strategies using blood cardioplegia in specific situations

Warm cardioplegic induction The concept of warm cardioplegic induction was introduced to 'actively resuscitate' the ischemically-damaged, energy- and substrate-depleted heart by maximizing the kinetics of repair and minimizing O_2 demands by maintaining arrest [3]. Therefore, blood cardioplegia is supplemented with the amino acids glutamate and aspartate to replenish Krebs' cycle intermediates that are depleted in compromised hearts. Warm cardioplegic induction is applied to patients in cardiogenic shock, with severely impaired ejection fraction, or in acute myocardial infarction.

Normothermic blood cardioplegia (solution for warm induction, Table 1) is administered initially at 250–

Table 1. Composition of blood cardioplegia (Buckberg/Beyersdorf)

Compound	Principle (unit)	Cold induction	Warm induction	Warm terminal reperfusion ('hot shot')	Controlled reperfusion
Tromethamin	Buffer (pH)	7.7–7.8	7.5–7.6	7.5–7.6	7.6–7.8
Citrate-phosphate-Dextrose	Ca-reduction (mmol/l)	0.5–0.6	0.15–0.25	0.15–0.25	0.15–0.20
Glucose	Osmolarity (mOsmol/l)	340–360	380–400	380–400	350–400
KCl	Cardioplegic arrest (mmol/l)	18–20	20–25	8–10	10–14
Glutamate/aspartate	Substrate of Krebs' cycle	–	13 mmol/l each	13 mmol/l each	13 mmol/l each

300 ml/min via the aortic root until cardioplegic arrest is achieved. Thereafter, cardioplegic flow is reduced to 150 ml/min (antegrade perfusion pressure 40–60 mmHg). Warm cardioplegic perfusion is applied ante- and retrogradely (1 min each). This is followed by cold cardioplegic standard blood cardioplegia.

Controlled reperfusion Controlled reperfusion is a strategy to reduce reperfusion injury after acute coronary occlusion. After completion of the final distal anastomosis and release of the aortic clamp, the controlled blood cardioplegic solution (Table 1) is given at a flow rate of up to 50 ml/min per graft with a perfusion pressure not exceeding 50 mmHg for 20 min into the grafts only. Cannulation of a side branch of the vein graft makes delivery of the reperfusate possible while the proximal anastomosis is being performed (Schematic 2) [4]. In a multicenter trial, the results of controlled reperfusion were evaluated in 156 consecutive patients with acute coronary occlusion and compared to 1203 patients who underwent PTCA as the primary therapy [5]. Controlled reperfusion reduced overall mortality from 8.7% to 3.9%.

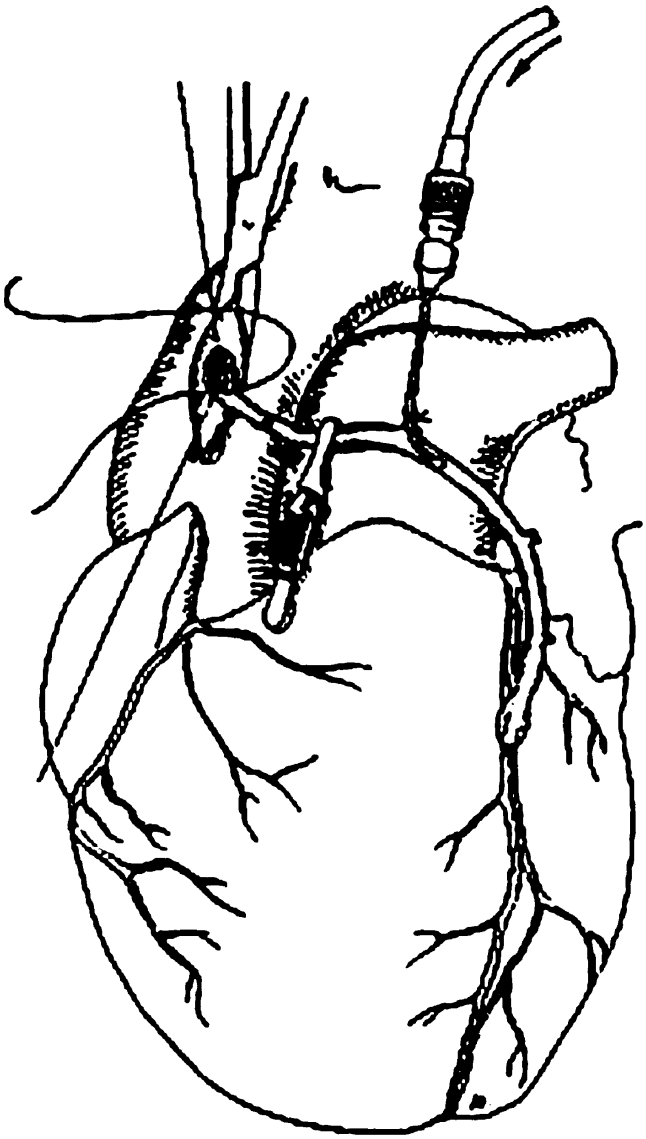
Blood cardioplegia leucocyte filtration Myocardial ischemia and reperfusion are associated with activation of neutrophils and expression of adhesion molecules on the myocardial endothelium surface. In the case of long cross-clamp time, acute myocardial infarction, or in heart transplantation, activated leucocytes in blood cardioplegia or initial reperfusate may cause significant myocardial damage. Clinical studies have demonstrated the benefit of blood cardioplegia filtration in patients undergoing emergency coronary bypass surgery or prolonged crossclamping, in patients with depressed ejection fraction, and in heart transplantation [6–8]. Experimental studies have shown that at least 90% of leucocytes must be removed to attenuate reperfusion injury markedly. In addition, leucocyte depletion should be maintained for 5–10 min after the start of initial reperfusion prior to aortic clamp release. Commercially available blood cardioplegia filters remove more than 90% of the leucocytes up to a total volume of 1500 ml of blood cardioplegia (i.e. Pall BC1B – MMCTSLink 108).

Blood cardioplegia in heart transplantation We use leucocyte-depleted blood cardioplegia and start with the first retrograde administration after the heart is removed from the storage solution. The coronary sinus catheter is introduced and secured with a prolene pursestring suture using a tourniquet. Initially, cold blood cardioplegia is administered for 3 min. The second application of cold blood cardioplegia (2 min) is performed after 20 min (end of right atrial anastomosis). The third application is a warm terminal reperfusion with leucocyte-depleted and substrate-enriched blood cardioplegia for 45 s. Retrograde perfusion is continued with normothermic leucocyte-filtrated blood. The aortic clamp is released as the first contractions of the transplanted heart become visible.

Other current techniques using blood cardioplegia

In addition to the classic 'standard technique' of blood cardioplegia, several modifications have evolved and are used in different centers.

Continuous warm blood cardioplegia The goal of this technique is to prevent any myocardial ischemia during aortic cross-clamping by continuous retrograde delivery of warm blood cardioplegia [9]. However, most surgeons discontinue cardioplegic flow for a few minutes during construction of the distal anas-



Schematic 2. Delivery of blood cardioplegic solution for controlled reperfusion after cannulation of the vein graft's side branch permits simultaneous completion of proximal anastomoses. (Reprinted from Ref. [4] with the permission of Landes Company.)

tomoses leading to 'unintentional' myocardial ischemia. In addition, cardioplegic overdose is a potential problem using this technique.

Intermittent antegrade warm blood cardioplegia This concept was first published by Calafiore in 1995 and had been developed to eliminate the problem of blood in the operative field when using continuous warm blood cardioplegia [10]. Normothermic blood is mixed with a K+ solution using a syringe pump. Repeated doses are delivered after 15 min. Hypothermia is completely avoided. The presence of critical coronary stenoses limits the delivery of antegrade cardioplegia to ischemic regions of the heart, particularly when revascularization with the internal mammary artery prevents vein graft infusions to the left anterior descending artery. This inadequate cardioplegic delivery using only the antegrade route may induce warm ischemic injury.

Tepid blood cardioplegia Antegrade tepid blood cardioplegia was introduced by the Toronto group to combine the advantages of warm and cold blood cardioplegia and to minimize the detrimental effects of blood cardioplegia [11]. Reducing the heart's temperature from 37 °C to 29 °C did not alter myocardial oxygen consumption but did reduce myocardial lactate release.

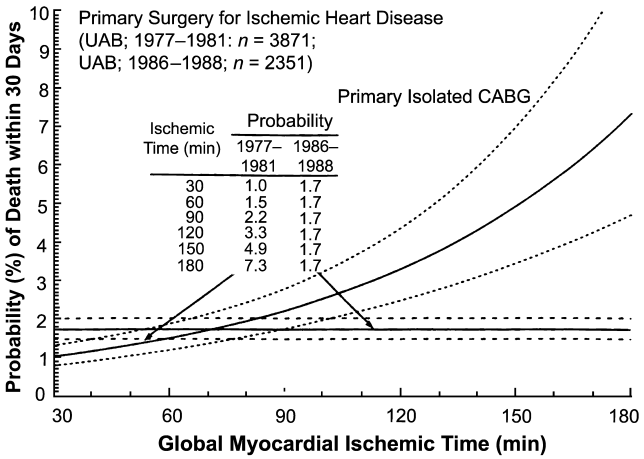
Results

Since its initial description, blood cardioplegia has become the preferred tool to arrest the heart for open heart surgery. This shift from crystalloid-type to blood cardioplegia occurred because experimental and clinical studies demonstrated superior protection of the arrested myocardium by blood cardioplegia [12–14].

The efficacy of myocardial protection with a single aortic crossclamp and blood cardioplegia was evaluated in a clinical study including 819 consecutive patients (stratified for risk profile) and compared with antegrade crystalloid cardioplegia in 2582 patients [13]. The use of combined antegrade/retrograde blood cardioplegia resulted in lower postoperative morbidity by significantly reducing perioperative myocardial infarction, wound complications, and length of stay in patients having reoperations. However, there was no significant difference in one-year mortality between the two groups.

Kirklin compared the results of primary isolated coronary bypass operations in the 1977–1981 era (crystalloid cardioplegic solution) with those from 1986–1988. During the latter era cold blood cardioplegic perfusions and warm reinfusions were used in patients with longer clamping times [14] (Graph 1). There was a significant drop in 30-day mortality after introduction of blood cardioplegia, i.e. after 180 min cross-clamping from 7.3% to 1.7%. These clinical results confirm the experimental findings and demonstrate that warm, controlled reperfusion provides a powerful tool to limit reperfusion damage and minimize the adverse effects of prolonged aortic clamping.

In a multicenter trial patients were randomized to receive either continuous warm blood cardioplegia or intermittent cold blood cardioplegia [15]. The investi-



Graph 1. Relation between global myocardial ischemic time (in minutes) and the probability of death within 30 days of operation. The two depictions describe the results with isolated primary coronary artery bypass grafting from 1967 to 1981 and from 1986 to 1988. In both eras, cold cardioplegia was used, but in the latter era controlled aortic root reperfusion was used in patients with longer global myocardial ischemic times. The solid lines depict the continuous estimate of probability, and the dashed lines enclose the 70% confidence intervals around the estimate. (Reproduced from Ref. [14] with the permission of Elsevier.)

gators found similar myocardial preservation (mortality, postoperative incidence of myocardial infarction, need for intraaortic balloon counterpulsation).

Another randomized study in 1001 patients compared continuous warm blood cardioplegia with intermittent cold crystalloid cardioplegia [16]. The data showed no difference in the postoperative rates of myocardial infarction, death or need for intraaortic balloon counterpulsation. Of substantial concern was an unexpected increased rate of perioperative stroke and overall neurologic events in the warm cardioplegic group. Systemic body temperature was actively maintained >35 °C in the warm blood cardioplegia group.

The 'CABG patch trial' enrolled a high-risk group of 885 coronary artery disease patients with an ejection fraction of $<36\%$ [17]. The patients were randomized with respect to the use of blood and crystalloid cardioplegia. Patients receiving crystalloid cardioplegia versus those receiving blood cardioplegia were found to have significantly more operative deaths (2% vs. 0.3%), postoperative myocardial infarctions (10% vs. 2%), shock (13% vs. 7%), and postoperative conduction defects (21.6% vs. 12.4%). Despite this, there was no significant difference in early or late survival.

Cardiogenic shock is the leading cause of death after acute myocardial infarction. Modern myocardial preservation strategies using blood cardioplegia have been used with promising results for surgical revascularization in acute myocardial infarction [18]. Recent analyses of the New York State Cardiac Surgery Registry revealed that there is a significant correlation between hospital mortality and time interval from acute myocardial infarction to time of operation. Coronary bypass operation within the first 24 h was associated with an in-hospital mortality of 14% in transmural infarction. In contrast, mortality had decreased to 3% after a time interval of more than 7 days [19]. Despite of these good results logistic and economic constraints relegate surgical revascularization to a third option behind thrombolysis and PTCA for the primary treatment of acute myocardial infarction.

The SHOCK (should we emergently revascularize occluded coronaries for cardiogenic shock) trial found clear survival benefits for early revascularization by PTCA or CABG over initial medical stabilization by thrombolytic therapy [20].

Excellent recovery of myocardial contractility after intermittent warm blood cardioplegia could be demonstrated in elective coronary artery bypass patients. The analysis of pressure-volume-loops after cardiopulmonary bypass revealed no change in end-systolic elastance while the diastolic chamber stiffness was significantly increased indicating impaired diastolic function [21].

Discussion

The versatility of blood cardioplegia provides the cardiac surgeon with a tool to actively treat the jeopardized myocardium as well as to prevent ischemic damage. The known benefits of using blood as the vehicle for delivering oxygenated cardioplegia include oxygen carrying capacity, active resuscitation of myocardium, avoidance of reperfusion damage, limitation of hemodilution, provision of onconicity, buffering, rheologic effects, and endogenous oxygen free radical scavengers. The major prerequisite to provide these benefits to the patient is ensuring adequate delivery of the cardioplegic solutions.

Current standard of myocardial protection using blood cardioplegia has evolved as a consequence of experimental studies and their subsequent clinical application over the last decades. It combines different principles, such as cold blood cardioplegia, warm blood cardioplegic reperfusion, warm induction, and alternating and simultaneous ante- and retrograde delivery to compensate for the individual shortcomings of each procedure and permit optimum myocardial preservation.

It is essential to understand and use the various techniques to obtain the desired protective effect. Some surgeons who are not familiar with blood cardioplegia criticize it as cumbersome and overly complicated compared to the simpler administration of crystalloid cardioplegia. However, in this case, simplicity and safety are not synonymous [22]. Cardiac damage from inadequate myocardial protection leading to low-output syndrome can prolong hospital stay and cost, and may result in delayed myocardial fibrosis.

References

[1] Siegenthaler MP. Antegrade administration of cardioplegia. Multimed Man Cardiothorac Surg doi:10.1510/mmcts.2004.000695.

[2] Bothe W. Retrograde administration. Multimed Man Cardiothorac Surg. doi:10.1510/mmcts.2004.000711.

[3] Rosenkranz ER, Okamoto F, Buckberg GD, Robertson JM, Vinten-Johansen J, Bugyi HI. Safety of prolonged aortic clamping with blood cardioplegia. III. Aspartate enrichment of glutamate-blood cardioplegia in energy-depleted hearts after ischemic and reperfusion injury. J Thorac Cardiovasc Surg 1986;91:428–435.

[4] Beyersdorf F. Coronary sinus interventions during surgical treatment of acute myocardial infarction in Mohl W, editor. Coronary sinus interventions in cardiac surgery, R.G. Landes Company, 1994.

[5] Allen BS, Buckberg GD, Fontan FM, Kirsh MM, Popoff G, Beyersdorf F, Fabiani JN, Acar C. Superiority of controlled surgical reperfusion versus percutaneous transluminal coronary angioplasty in acute coronary occlusion. J Thorac Cardiovasc Surg 1993;105:864–879.

[6] Hayashi Y, Sawa Y, Fukuyama N, Miyamoto Y, Takahashi T, Nakazawa H, Matsuda H. Leukocyte-depleted terminal blood cardioplegia provides superior myocardial protective effects in association with myocardium-derived nitric oxide and peroxynitrite production for patients undergoing prolonged aortic crossclamping for more than 120 min. J Thorac Cardiovasc Surg 2003; 126:1813–1821.

[7] Pearl JM, Drinkwater DC, Laks H, Capouya ER, Gates RN. Leukocyte-depleted reperfusion of transplanted hearts: a randomized, double-blind clinical trial. J Heart Lung Transplant 1992;11: 1082–1092.

[8] Martin J, Krause M, Benk C, Lutter G, Siegenthaler MP, Beyersdorf F. Blood cardioplegia filtration. Perfusion 2003;18(Suppl 1)75–80.

[9] Salerno TA, Houck JP, Barrozo CAM, Panos A, Christakis GT, Abel JG, Lichtenstein SV. Retrograde continuous warm blood cardioplegia: a new concept in myocardial protection. Ann Thorac Surg 1991;51:245–247.

[10] Calafiore AM, Teodori G, Mezzetti A, Bosco G, Verna AM, Di Giammarco G, Lapenna D. Intermittent antegrade warm blood cardioplegia. Ann Thorac Surg 1995;59:398–402.

[11] Hayashida N, Ikonomidis JS, Weisel RD, Shirai T, Ivanov J, Carson SM, Mohabeer MK, Tumiati LC, Mickle DA. The optimal cardioplegic temperature. Ann Thorac Surg 1994;58:961–971.

[12] Schlensak C, Doenst T, Beyersdorf F. Clinical experience with blood cardioplegia. Thorac Cardiovasc Surg 1998;46(Suppl 2):282–285.

[13] Loop FD, Higgins TL, Panda R, Pearce G, Estafanous FG. Myocardial protection during cardiac operations. Decreased morbidity and lower cost with blood cardioplegia and coronary sinus perfusion. J Thorac Cardiovasc Surg 1992; 104:608–618.

[14] Kirklin JW. The science of cardiac surgery. Eur J Cardiothorac Surg 1990;4:63–71.

[15] Naylor CK, Lichtenstein SV, Fremes SE, Warm Heart Investigators. Randomized trial of normothermic versus hypothermic coronary bypass surgery. Lancet 1994;343:559–563.

[16] Martin TD, Craver JM, Gott JP, Weintraub WS, Ramsay J, Mora CT, Guyton RA. Prospective, randomized trial of retrograde warm blood cardioplegia: myocardial benefit and neurologic threat. Ann Thorac Surg 1994:57:298–304.

[17] Flack JE, Cook JR, May SJ, Lemeshow S, Engelman RM, Rousou JA, Deaton DW. Does cardioplegia type affect outcome and survival in patients with advanced left ventricular dysfunction? Results from the CABG trial. Circulation 2000;102(Suppl 3):III84–89.

[18] Lee DC, Ting W, Oz MC. Myocardial revascularization after acute myocardial infarction. In: Cohn LH, Edmunds LH Jr, editors. Cardiac surgery in the adult. New York: McGraw-Hill, 2003, Chapter 24, 639–658.

[19] Lee DC, Oz MC, Weinberg AD, Ting W. Appropriate timing of surgical intervention after transmural acute myocardial infarction. J Thorac Cardiovasc Surg 2003;125:115–120.

[20] Hochman JS, Sleeper LA, White HD, Dzavik V, Wong SC, Menon V, Webb JG, Steingart R, Picard MH, Menegus MA, Boland J, Sanborn T, Buller CE, Modur S, Forman R, Desvigne-Nickens P, Jacobs AK, Slater JN, LeJemtel TH. One-year

survival following early revascularization for cardiogenic shock. J Am Med Assoc 2001;285: 190–192.

[21] Tulner SA, Klautz RJ, Engbers FH, Bax JJ, Baan J, van der Wall EE, Dion RA, Steendijk P. Left ventricular function and chronotropic responses after normothermic cardiopulmonary bypass with intermittent antegrade warm blood cardioplegia in patients undergoing coronary artery bypass grafting. Eur J Cardiothorac Surg 2005;27:599–605.

[22] Buckberg GD. Update on current techniques of myocardial protection. Ann Thorac Surg 1995;60: 805–814.