Case Reports/Case Series

Case report: Management of immediate post-cardiopulmonary bypass massive intra-cardiac thrombosis

[Prise en charge d'une thrombose intracardiaque majeure immédiatement après la circulation extra-corporelle]

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Purpose: To describe the management of severe acute intracardiac thrombosis in a patient who underwent redo multiple valve replacement and valvular repair. The diagnostic features, associated risk factors, and anesthetic management are reviewed.

Clinical features: A 67-yr-old woman undergoing redo mitral and aortic mechanical valve replacement and tricuspid annuloplasty under aprotinin prophylaxis exhibited severe refractory hypotension that began immediately after protamine reversal of intraoperative heparin anticoagulation following separation from cardiopulmonary bypass. Intraoperative transesophageal echocardiography revealed severe thrombosis in the right atrium, right ventricle and pulmonary artery. The patient was managed by immediate reheparinization and return to cardiopulmonary bypass (CPB), surgical thrombectomy, and intraoperative administration of recombinant tissue-plasminogen activator. After removal of the thrombi, and separation from CPB, no further protamine was given. One hundred units of blood products and two surgical re-explorations were required to manage subsequent massive postoperative bleeding. Acute heparin-induced thrombocytopenia (HIT) was ruled out using sensitive assays for HIT antibodies. After 16 days in the intensive care unit and 30 more days in hospital, the patient was subsequently transferred to a chronic care facility and succumbed several weeks later.

Conclusion: Acute intraoperative thrombosis is a rare and potentially fatal complication of cardiac surgery. Intraoperative transesophageal echocardiography was essential for rapid diagnosis in this case. Multiple interacting prothrombotic factors (e.g., aprotinin use, acquired antithrombin deficiency, long pump time, post-protamine status, transfusion of blood components) were likely contributing factors related to this rare complication.

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Objectif *: Décrire la prise en charge d'une thrombose intracardiaque aiguë sévère chez une patiente subissant une reprise de remplacements valvulaires multiples et de valvuloplastie. Les caractéristiques diagnostiques, les facteurs de risque liés et la prise en charge anesthésique sont passés en revue.*

Éléments cliniques *: Une femme de 67 ans, ré-opérée pour le remplacement de prothèses mécaniques mitrale et aortique et une annuloplastie tricuspidienne sous prophylaxie d'aprotinine, a souffert d'hypotension réfractaire sévère débutant immédiatement après la neutralisation de l'anticoagulation à l'héparine avec la protamine, suivant le sevrage de la circulation extra-corporelle. L'échocardiographie transœsophagienne peropératoire a révélé une thrombose sévère dans l'oreillette droite, le ventricule droit et l'artère pulmonaire. La patiente a été prise en charge par une réhéparinisation immédiate et le retour à la circulation extra-corporelle (CEC), une thrombectomie chirurgicale, et l'administration peropératoire d'un activateur tissulaire du plasminogène obtenu par génie génétique. Après la suppression du thrombus et le sevrage de la CEC, aucune protamine supplémentaire n'a été administrée. Le contrôle du saignement postopératoire massif subséquent a nécessité cent unités de produits sanguins et deux réexplorations*

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chirurgicales. Une thrombocyopénie aiguë induite par l'héparine (HIT) a été évitée en se servant de tests sensibles aux anticorps HIT. Après 16 jours aux soins intensifs et 30 de plus à l'hôpital, la patiente a ensuite été transférée dans un centre de soins chroniques et a succombé plusieurs semaines plus tard.

***Conclusion** : La thrombose peropératoire aiguë est une complication rare et potentiellement fatale de la chirurgie cardiaque. Dans le cas examiné ici, l'échocardiographie transœsophagienne peropératoire a joué un rôle essentiel en permettant un diagnostic rapide. L'interaction de multiples facteurs prothrombotiques (par ex., l'utilisation d'aprotinine, une déficience anti-thrombinique acquise, un temps de CEC long, l'état post-protamine, la transfusion de produits sanguins) a probablement contribué à cette complication rare.*

TABLE I Preoperative laboratory investigations

Variable (reference range)	*Preoperative value*
Hemoglobin (115 – 165 $g \cdot L^{-1}$)	103
Platelets (150 – 400 × $10^{9} \cdot L^{-1}$)	176
INR – PT (0.8 – 1.2)	1.1
aPTT (22 – 35 sec)	36
Anti factor Xa level (0.5 – 1.00 $U \cdot mL^{-1}$)	0.27
Urea (3.0 – 6.5 $mmol \cdot L^{-1}$)	8.9
Creatinine (50 – 100 umol/ L)	84
Albumin (35 – 50 $g \cdot L^{-1}$)	36
Conjugated bilirubin (0 – 5 $umol \cdot L^{-1}$)	12
Total bilirubin (2 – 18 $umol \cdot L^{-1}$)	32
Alkaline phosphatase (4 – 120 $U \cdot L^{-1}$)	219

INR – PT = international normalized ratio prothrombin time; aPTT = activated partial thromboplastin time. Anti-factor Xa level eight hours after the last dose of enoxaparin (prophylactic anticoagulation reference range 0.2–0.4 $U \cdot mL^{-1}$, therapeutic anticoagulation reference range, 0.5–1 $U \cdot mL^{-1}$.

ACUTE intracardiac and pulmonary thrombosis is a rare and potentially fatal complication reported not only during cardiovascular surgery [1,2] but also in non-cardiac surgery.[3,4] Congenital[5,6] and acquired[7] coagulation disorders have been associated with this problem.

We report a case of severe acute intracardiac and pulmonary artery (PA) thrombosis which occurred during the immediate post-cardiopulmonary bypass (CPB) period, following protamine reversal of heparin anticoagulation, in a patient who underwent redo mitral and aortic valve replacement and tricuspid annuloplasty. The diagnosis was made using transesophageal echocardiography (TEE), and treatment consisted of surgical thrombectomy and administration of recombinant tissue-plasminogen activator (rTPA). Several interacting pro-thrombotic risk factors may have contributed to this unusual life-threatening complication. Publication of this report is in accordance with the requirements of the Institutional Research Ethics Board of the Faculty of Medicine at McMaster University.

Case report

A 67-yr-old woman with a history of rheumatic heart disease and previous mitral valve replacement (Starr-Edwards mitral prosthesis in 1967) presented with a six-month history of congestive heart failure (CHF). The heart failure was aggravated by anemia due to bleeding cecal angiodysplasia, and was treated with blood transfusion and tailoring of her anticoagulation treatment. Her past medical history was remarkable for type II diabetes mellitus, atrial fibrillation, hypertension, and two previous transient ischemic attacks without residual neurological deficits. Medications at the time of admission included spironolactone, digoxin, furosemide, ramipril, repaglinide, human insulin, lanzoprazole, ferrous gluconate, folate, aspirin, and lorazepam. Her usual dose of warfarin (5 $mg \cdot day^{-1}$) was discontinued, and she received low-molecular-weight heparin (LMWH), enoxaparin, 30 mg bid by *sc* injection for three days prior to valve replacement, with the last dose being given the morning before the day of surgery.

Key findings on physical examination included a cachectic appearance (weight, 53.3 kg, height 160 cm), irregular pulse with heart rate (HR) at 60 $beats \cdot min^{-1}$, blood pressure (BP) 140/70 mmHg, a systolic aortic murmur and a mitral click, hepatic congestion and ascites. Cardiac angiography showed moderate aortic insufficiency combined with aortic stenosis (mean gradient 24 mmHg), severe tricuspid regurgitation, mitral prosthesis functioning properly, and normal coronary arteries. The transthoracic echocardiogram additionally showed an aortic valve area 1.5 cm^2, with peak and mean gradients of 45 mmHg and 25 mmHg respectively, mild to moderate left ventricular systolic dysfunction, an ejection fraction of 40%, and right ventricular dilatation.

Preoperative laboratory investigations (Table I) revealed mild anemia with a coagulation profile consistent with the effect of recent use of LMWH. There was evidence of mild hepatic and renal dysfunction (calculated creatinine clearance 47 $mL \cdot min^{-1}$), with normal electrolytes. Due to recurrent CHF, urgent redo mitral and aortic valve replacement, and tricuspid valve annuloplasty were recommended.

In the operating room the patient was in slow atrial fibrillation with HR = $60 \cdot min^{-1}$, with BP 140/70 mmHg, and $Sa0_2$ 99% while breathing oxygen 2

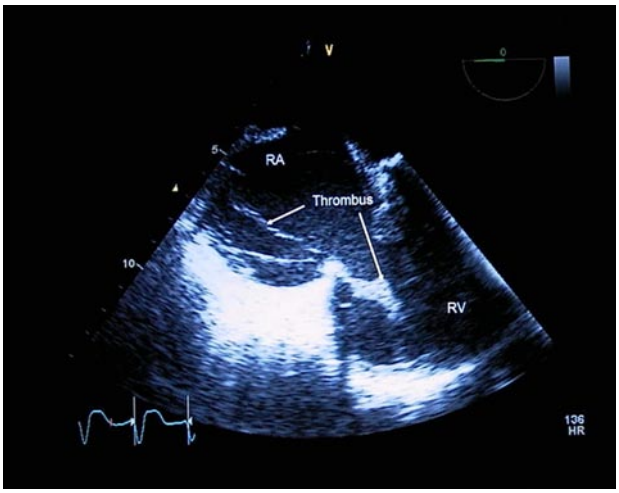

FIGURE 1 Midesophageal four-chamber view showing multiple echodensities (thrombus, arrows) in the right chambers. RA = right atrium; RV = right ventricle.

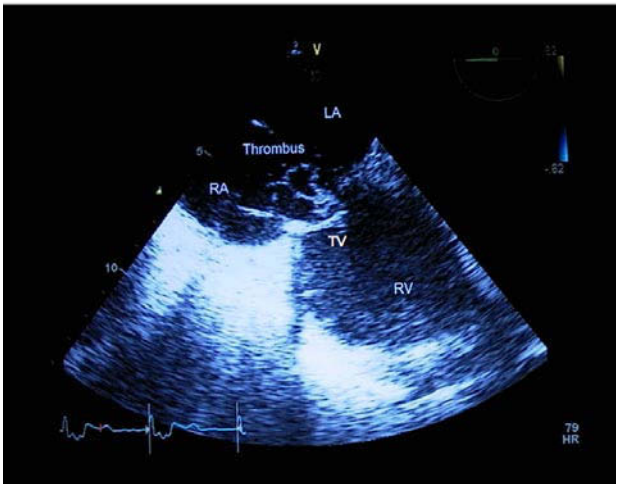

FIGURE 2 Midesophageal four-chamber view showing multiple echodensities (thrombus) in the right chambers and in the tricuspid valve. LA = left atrium; RA = right atrium; RV = right ventricle; TV= tricupid valve.

$L \cdot min^{-1}$ via nasal prongs. Following placement of standard ASA monitors and a radial arterial line, general anesthesia was induced and maintained with midazolam, sufentanil, rocuronium and isoflurane. A right internal jugular PA catheter and TEE probe were inserted after induction of anesthesia. The initial hemodynamic measurements were: central venous pressure (CVP) 13 mmHg, pulmonary artery pressure (PAP) 40/15 mmHg, pulmonary capillary wedge pressure (PCWP) 18 mmHg, and cardiac output (CO) 2.4 $L \cdot min^{-1}$. A high-dose aprotinin regimen (2 million U loading dose and 2 million U in the CPB prime, 0.5 million $U \cdot hr^{-1}$ × four hour infusion) was begun after induction. The pre-CPB period was uneventful, and after porcine heparin 400 $U \cdot kg^{-1}$ (23,000 IU), kaolin activated coagulation time was maintained greater than 480 sec and monitored every 15 to 20 min during CPB [pre-CPB 152 sec; post-heparin 593 sec (minimum 464 sec, maximum 729 sec)] requiring additional heparin 5,000 IU at 130 min of CPB. The patient underwent uncomplicated mitral and aortic mechanical valve replacements and tricuspid annuloplasty. After a clamp time of 156 min and CPB time of 179 min, the patient was separated from CPB without difficulty. Transesophageal echocardiography demonstrated excellent function of all three valves and both ventricles without any pharmacologic support. Protamine 300 mg *iv* was given over five minutes, all cannulae were removed, and hemostasis was secured. Hemoglobin was 74 $g \cdot L^{-1}$ and the platelet count was $97 \times 10^9 \cdot L^{-1}$; 2 U of packed red cells and 5 U of platelets were transfused.

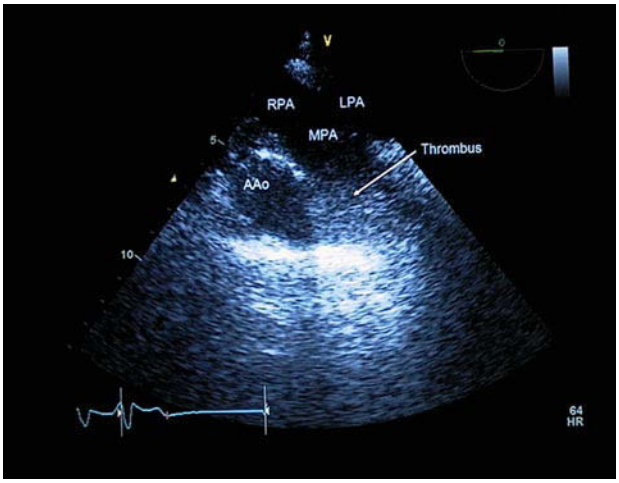

FIGURE 3 Upper midesophageal view showing echodensities (thrombus) in the pulmonary artery. RPA = right pulmonary artery; LPA = left pulmonary artery; MPA = main pulmonary artery; AAo = ascending aorta.

The patient suddenly developed refractory hypotension, with a rapid rise in PA pressures, within ten minutes after infusing the protamine, and while closing the sternum. Intraoperative TEE showed large mobile echodensities in the right atrium (Figure 1) extending across the tricuspid valve (Figure 2) into the right ventricle and the PA (Figure 3). Aprotinin infusion was discontinued and the patient was rapidly re-heparinized and returned to CPB. Opening the right atrium revealed the right heart chambers filled with a large amount of very adherent fresh clots

TABLE II Intraoperative coagulation profiles

Variable (reference range)	*Intraoperative*	*Intraoperative after rTPA*
Platelets (150 – 400 x $10^9 \cdot L^{-1}$)	53	79
Fibrinogen (1.6-4.2 $g \cdot L^{-1}$)	1.2	
TCT (20 – 30 sec)	> 150	>150
TCT protamine (20 – 30 sec)	31	33
Fibrin D-dimer (< 500 $\mu g \cdot L^{-1}$)		> 2000
Antithrombin (0.77-1.25 $U \cdot L^{-1}$)		0.58
Protein C functional ($mg \cdot L^{-1}$)		1.04
APC resistance ratio (> 1.73)		2.5
Free protein S (0.62-1.38 $U \cdot mL^{-1}$)		0.74

TCT = thrombin clotting time; APC resistance ratio = activated protein C resistance ratio, i.e., aPTT with APC divided by aPTT performed without ACP; PTT = activated partial thromboplastin time.

extending through the tricuspid valve into the right ventricle. The PA was also opened and a large clot was removed.

The cause of the intraoperative hypercoagulable state was not immediately apparent. At this time, the coagulation profile was consistent with the effect of high levels of heparin and thrombocytopenia (Table II). Marked reduction in antithrombin (formerly, antithrombin III levels) were also shown, although this result was not available for several days. Normal levels of protein C, free protein S and the test for factor V Leiden (activated protein C (APC) resistance ratio) were documented later. Acute heparin-induced thrombocytopenia (HIT) as an explanation for the acute intracardiac thrombosis was subsequently ruled out by negative testing for HIT antibodies using two sensitive assays (platelet serotonin-release assay and anti-platelet factor 4/heparin enzyme-immunoassay).

Taking into account difficulties separating from CPB due to right ventricular failure, a decision was made to have the surgeon inject rTPA 250 µg directly into the PA to dissolve any residual pulmonary emboli. As protamine had been given shortly before the patient developed intracardiac thrombosis, the hematologist was reluctant to recommend a second protamine dose. Accordingly, no heparin reversal was administered following the second separation from CPB, with a plan to manage the anticipated postoperative hemorrhage with blood products, as required. Subsequent weaning from CPB was difficult (second CPB time 106 min), and required milrinone (2 mg bolus, 0.37 $\mu g \cdot kg^{-1} \cdot min^{-1}$ infusion), epinephrine (0.1 $\mu g \cdot kg^{-1} \cdot min^{-1}$) and nitric oxide (5 ppm). The systolic PA pressure was 65 mmHg, with systemic blood pressure 110/50 mmHg.

Transesophageal echocardiography at this time showed significant right ventricular dysfunction and evidence of high PA pressures, preserved left ventricular function, prosthetic valves functioning properly, and no evidence of left-sided thromboembolism. The patient continued to have microvascular bleeding when transferred to the intensive care unit (ICU). During the immediate postoperative period the chest tube drainage was 700–900 $mL \cdot hr^{-1}$ and massive blood transfusions were required over the ensuing 24 hr: 23 U of packed red cells, 35 U platelets, 21 U fresh frozen plasma, 5 U cryoprecipitate. Transfusion requirements were guided by repeated measurement of CBC and coagulation tests. On postoperative day one, the patient again returned to the operating room for reexploration. No clots were observed within the mediastinum, but diffuse bleeding was noted at all suture lines and exposed surfaces. Those areas were sprayed with Tisseel® (two component fibrin sealant. Baxter AG, Vienna, Austria) and packed with Surgicel® (absorbable hemostat, oxidized regenerated cellulose. Ethicon N INC, Somerville, NJ, USA), the chest was again closed and the patient was transferred back to the ICU. Bilateral upper and lower limbs, and jugular vein Doppler examinations revealed normal blood flow and compressibility of the venous system, and no detectable intralumenal thrombi. After a difficult postoperative course managed with pharmacologic support (milrinone, norepinephrine), four days of mechanical ventilation, hemodialysis, transfusion, and insulin, the patient was discharged from intensive care after five days. At the eighth postoperative day, upon removal of the epicardial wires, the patient suffered cardiac tamponade requiring surgical drainage, and 11 days more of support in the ICU, followed by 30 more days in hospital. The patient was subsequently transferred to a peripheral hospital, in stable condition with limited ambulation due to ongoing right ventricular failure, pulmonary hypertension and renal insufficiency. The patients died several weeks later.

Discussion

This report of acute, massive intracardiac thrombosis beginning abruptly following protamine reversal after separation from CPB after a complex operation, illustrates the importance of TEE for rapid diagnosis of this rare, but life-threatening complication. Echocardiography has proven to be a useful tool in the diagnosis and evaluation of cardiac masses,[8] as it can identify their location, attachment, shape, size and mobility, as well as the presence and extent of any associated hemodynamic derangement. In this case, the key to the echocardiographic diagnosis was the appearance

of new intracardiac mobile echodensities in the right atrium, tricuspid valve, right ventricle and PA.

Acute severe thrombosis during or soon after cardiac surgery employing CPB, while rare, may be associated with high mortality. Similar cases have been reported during cardiovascular surgery, [1,2,5–7,9,10] most of them manifesting as sudden shock in the immediate post-CPB period, and temporally associated with the administration of protamine or blood products. Associated risk factors for thrombosis in those patients may be categorized as congenital, e.g., afibrinogenemia,[6] factor V Leiden,[5,9] or acquired, e.g., bacterial endocarditis,[1,6,9] disseminated intravascular coagulation (DIC),[1] prolonged duration of CPB, deep hypothermic circulatory arrest,[2,9] preoperative CHF,[7,10] liver[6,7] and renal dysfunction,[7,10] use of antifibrinolytics [aprotinin,[1,2, 6,7,11] -aminocaproic acid (EACA)[7,9] and tranexamic acid],[10] biological glue,[10] multiple prosthetic surfaces,[1,2,7,9–11] malignancy and chemotherapy,[1] and recent use of heparin[7,10] (possibly by contributing to acquired antithrombin deficiency).

Cardiopulmonary bypass provokes a systemic inflammatory response characterized by activation of coagulation/fibrinolysis and other systems.[12,13] Numerous investigations have validated the efficacy of antifibrinolytic drugs as prophylactic hemostatic agents in patients requiring cardiac surgery.[14,15] The most widely used antifibrinolytics include the synthetic lysine analogues (EACA, tranexamic acid), and the broad-spectrum protease inhibitor, aprotinin.[16] The use of these drugs has been of apparent benefit to blood conservation practices, but this must be balanced against risks of hypercoagulability, renal, cardiac and cerebrovascular complications.[17,18]

Although recent major surgery has been considered an absolute contraindication to the use of fibrinolytics, there is evidence supporting their use in medical patients with shock resulting from massive pulmonary embolism.[19] One case report describes the successful use of thrombolytics (rTPA) during orthotopic liver transplantation.[3] In the series of nine cases with end-stage CHF,[7] one patient received fibrinolytic therapy (rTPA) which reversed the pulmonary hypertension, but the patient died of exsanguination in the ICU. During cardiac operations with CPB, antithrombin is consumed, and low levels of antithrombin are associated with morbidity (including thromboembolic events) and mortality.[20] Other deficiencies of endogenous anticoagulant factors such as proteins C and S can promote a procoagulant state and DIC.

Considering the specific features of this case (right ventricle failure precluding separation from CPB despite inotropic and vasodilatory therapy in a patient with confirmed fresh adherent thrombus in the right chambers and in the PA) and with the support of the hematology service and the blood bank, we decided to administer low dose rTPA directly into the PA to achieve localized fibrinolysis.[21] Further, given the temporal association between preceding protamine use and development of intracardiac thrombosis, we chose to forgo a second dose of protamine, and to treat the resulting bleeding with transfusion.

The pathophysiology of the postoperative hypercoagulable state in our case is complex and multifactorial. Associated factors include CHF, hepatic and renal dysfunction, preoperative use of LMWH and perioperative hemodilution (with the potential for acquired antithrombin deficiency), and prolonged CPB. In addition, multiple prosthetic surfaces (mechanical mitral and aortic valves), low cardiac output and right ventricular dysfunction, the use of high-dose aprotinin, a post-protamine state with loss of heparin's anticoagulant effect, and transfusion were also likely contributing factors. Immune HIT was excluded using sensitive assays. Other potential risk factors such as congenital or acquired abnormalities in the anticoagulant pathway (factor V Leiden, protein C, protein S) were also ruled out.

This is the second reported case describing the use of rTPA intraoperatively for massive intracardiac thrombosis and pulmonary embolism, and the first case during cardiac surgery. The main clinical challenge was massive bleeding explained by the use of r-TPA, and the decision not to reverse heparin with protamine. Massive intracardiac thrombosis post-separation from CPB is a very rare intraoperative complication with high mortality, that likely represents the result of multiple interacting risk factors. Intraoperative TEE was invaluable for making a rapid diagnosis, and guiding an appropriate therapeutic plan in a life-threatening setting.

References

1 *Augoustides JG, Kilbaugh T, Harris H, Glick JH, Acker M, Savino JS.* Fatal thrombosis after mitral valve replacement for endocarditis: aprotinin and disseminated intravascular coagulation (Letter). Anesthesiology 2006; 104: 213.

2 *Augoustides JG, Lin J, Gambone AJ, Cheung AT.* Fatal thrombosis in an adult after thoracoabdominal aneurysm repair with aprotinin and deep hypothermic circulatory arrest (Letter). Anesthesiology 2005; 103: 215–6.

3 *Jackson D. Botea A, Gubenko Y, Delphin E, Bennett H.* Successful intraoperative use of recombinant tissue plasminogen activator during liver transplantation com-

plicated by massive intracardiac/pulmonary thrombosis. Anesth Analg 2006; 102: 724–8.

4 *Obray JB, Long TR, Rehfeldt KH, Wass CT.* Cardiovascular collapse during elective orthopedic surgery: massive intraoperative pulmonary thromboembolism treated with emergent cardiopulmonary bypass. J Clin Anesth 2005; 17: 205–8.

5 *Shore-Lesserson L, Reich DL.* A case of severe diffuse venous thromboembolism associated with aprotinin and hypothermic circulatory arrest in a cardiac surgical patient with factor V Leiden. Anesthesiology 2006; 105: 219–21.

6 *Chun R, Poon MC, Haigh J, Seal D, Donahue B, Royston D.* Case 1–2005: cardiac surgery in congenital afibrinogenemia with thrombo-occlusive disease. J Cardiothorac Vasc Anesth 2005; 19: 109–17.

7 *Cooper JR Jr, Abrams J, Frazier OH, et al.* Fatal pulmonary microthrombi during surgical therapy for end-stage heart failure: possible association with antifibrinolytic therapy. J Thorac Cardiovasc Surg 2006; 131: 963–8.

8 *Spencer K.* Assessment of cardiac masses. *In*: Savage RM, Aronson S (Eds). Comprehensive Textbook of Intraoperative Transesophageal Echocardiography. Philadelphia: Lippincott Williams & Wilkins; 2005: 271–86.

9 *Fanashawe M, Shore-Lesserson L, Reich DL.* Two cases of fatal thrombosis after aminocaproic acid therapy and deep hypothermic circulatory arrest. Anesthesiology 2001; 95: 1525–7.

10 *Gillham MJ, Tousignant CP.* Diagnosis by intraoperative transesophageal echocardiography of acute thrombosis of mechanical aortic valve prosthesis associated with the use of biological glue. Anesth Analg 2001; 92: 1123–5.

11 *Schmitz A, Hartmann M.* Acute intracardiac thrombus formation during thoracoabdominal aortic surgery. Anesth Analg 2006; 102: 1658–9.

12 *Boyle EM Jr, Pohlman TH, Johnson MC, Verrier ED.* Endothelial cell injury in cardiovascular surgery: the systemic inflammatory response. Ann Thorac Surg 1997; 63: 277–84.

13 *Boyle EM Jr, Verrier ED, Spiess BD.* Endothelial cell injury in cardiovascular surgery: the procoagulant response. Ann Thorac Surg 1996; 62: 1549–57.

14 *Fremes S, Wong BI, Lee E, et al.* Metaanalysis of prophylactic drug treatment in the prevention of postoperative bleeding. Ann Thorac Surg 1994; 58: 1580–8.

15 *Sedrakyan A, Treasure T, Elefteriades JA.* Effect of aprotinin on clinical outcomes in coronary artery bypass graft surgery: a systematic review and meta-analysis of randomized clinical trials. J Thorac Cardiovasc Surg 2004; 128: 442–8.

16 *Green JA, Spiess BD.* Current status of antifibrinolytics in cardiopulmonary bypass and elective deep hypothermic circulatory arrest. Anesthesiol Clin North America 2003; 21: 527–51.

17 *Shore-Lesserson L, Reich DL, Fanshawe MP.* Thrombosis after deep hypothermic circulatory arrest with antifibrinolytic therapy: is factor V Leiden the smoking gun? (Letter reply). Anesthesiology 2002; 97: 760–1.

18 *Mangano DT, Tudor IC, Dietzel C; Multicenter Study of Perioperative Ischemia Research Group; Ischemia Research and Education Foundation.* The risk associated with aprotinin in cardiac surgery. N Engl J Med 2006; 354: 353–65.

19 *Anonymous.* Guidelines on diagnosis and management of acute pulmonary embolism. Task Force on Pulmonary Embolism, European Society of Cardiology. Eur Heart J 2000; 21:1301–36.

20 *Ranucci M, Frigiola A, Menicanti L, Ditta A, Boncilli A, Brozzi S.* Postoperative antithrombin levels and outcome in cardiac operations. Crit Care Med 2005; 33: 355–60.

21 *De Wet CJ, Pearl RG.* Postoperative thrombotic complications. Venous thromboembolism: deep-vein thrombosis and pulmonary embolism. Anesthesiol Clin North America 1999; 17: 895–922.