CARDIOPULMONARY SUPPORT AND PHYSIOLOGY

DECREASED CEREBRAL EMBOLI DURING DISTAL AORTIC ARCH CANNULATION: A RANDOMIZED CLINICAL TRIAL

Michael A. Borger, MD
Ruth L. Taylor, MSc
Richard D. Weisel, MD
Girish Kulkarni, BSc
Mark Benaroya, BSc
Vivek Rao, MD, PhD
Gideon Cohen, MD
Ludwig Fedorko, MD, PhD
Christopher M. Feindel, MD

Background: Cerebral emboli occur during cardiopulmonary bypass and are a principal cause of postoperative neurologic dysfunction. We hypothesized that arterial cannulation of the distal aortic arch, with placement of the cannula tip beyond the left subclavian artery, will result in fewer cerebral microemboli than conventional cannulation of the ascending aorta. **Methods:** Patients undergoing coronary bypass surgery with a single crossclamp technique were randomized to receive cannulation of the distal aortic arch ($n = 17$) or standard cannulation of the ascending aorta (control group, $n = 17$). Trendelenburg positioning was used whenever possible. Cerebral emboli were quantified by continuous transcranial Doppler monitoring of the middle cerebral artery. **Results:** Baseline demographics were similar for the 2 groups of patients, including cardiopulmonary bypass and crossclamp times. Cerebral microemboli were detected during cardiopulmonary bypass in all patients, with a range of 17 to 627 emboli. The total number of detected emboli was lower in the arch cannulation group (152 ± 33 , mean $\pm$ standard error of the mean) than in the conventional cannulation group (249 ± 35 , $P = .04$). Embolization rates were lower in distal arch patients than in control patients during cardiopulmonary bypass (2.0 ± 0.3 vs 4.2 ± 0.9 per minute, respectively, $P = .03$). Reduction in cerebral emboli by distal arch cannulation was most pronounced during perfusionist interventions. **Conclusions:** Cannulation of the distal aortic arch results in less cerebral microembolism than conventional cannulation of the ascending aorta. Provided it is performed safely, distal arch cannulation may be an important surgical option for patients with severe atherosclerosis of the ascending aorta. (J Thorac Cardiovasc Surg 1999;118:740-5)

Despite continuous improvements in cardiac morbidity and mortality after coronary bypass surgery (CABG), neurologic complications remain an impor-

tant problem.¹ Neurologic injury ranges from neuropsychologic impairment, which is very common but difficult to detect, to stroke, which is infrequent but devastating. Several investigators have demonstrated that neuropsychologic impairment occurs in 50% to 70% of patients undergoing CABG within 1 week after the operation,^{2,3} with 30% to 40% of patients having long-term cognitive deficits.^{4,5}

The introduction of transcranial Doppler ultrasonography in the cardiac operating room has revealed that cerebral microemboli occur in virtually all patients during cardiopulmonary bypass (CPB),^{6,7} a finding that has been verified by retinal fluorescein angiography⁸ and postmortem histologic analysis.⁹ These emboli are thought to be the principal reason for the development of postoperative neuropsychologic impairment.^{10,11}

From the Divisions of Cardiovascular Surgery and Cardiac Anesthesia, The Toronto Hospital, University of Toronto, Toronto, Ontario, Canada.

Supported in part by the Heart and Stroke Foundation of Ontario. M.A.B. is a Research Fellow of the HSFO. R.D.W. is a Career Investigator of the HSFO.

Received for publication Jan 25, 1999; revisions requested April 9, 1999; revisions received June 15, 1999; accepted for publication June 16, 1999.

Address for reprints: Christopher M. Feindel, MD, The Toronto Hospital, EN 14-222, 200 Elizabeth St, Toronto, Ontario, Canada M5G 2C4.

Copyright © 1999 by Mosby, Inc.

0022-5223/99 \$8.00 + 0 12/1/100749

However, few published clinical trials have investigated methods of reducing cerebral embolization during CPB.¹²⁻¹⁵

We have previously demonstrated that the majority of cerebral emboli during CPB consist of air.¹⁶ Since air bubbles ascend in blood, we hypothesized that CPB arterial inflow distal to the carotid arteries, combined with Trendelenburg positioning, will result in delivery of an increased proportion of emboli to the distal circulation and decreased embolization to the cerebral circulation. We therefore conducted a randomized, controlled clinical trial comparing rates of cerebral embolism after cannulation of the distal aortic arch, with positioning of the cannula tip beyond the left subclavian artery, to embolic rates after conventional cannulation of the ascending aorta.

Methods

Patient population. From November 1997 to August 1998, 40 patients undergoing isolated CABG by one surgeon (C.M.F.) consented to participate in this trial. A total of 198 patients underwent CABG by C.M.F. over this same time period. The predominant determinant of whether or not patients were approached to participate was the availability of the transcranial Doppler ultrasonograph and appropriate personnel. Patients were excluded if they had a history of carotid stenosis or carotid bruit ($n = 18$), if they had previous CABG ($n = 20$), or if concomitant surgical procedures were planned ($n = 51$). Patients who consented to participate in the trial were excluded in the operating room if they had evidence of atherosclerosis of the ascending or transverse aorta as determined by digital palpation ($n = 2$). Four patients who consented were also excluded because of an inability to obtain an adequate transcranial Doppler signal of the middle cerebral artery. After these exclusions, 34 randomized patients formed the focus of the remainder of this article. Patients were randomized within the operating room, via an opaque sealed envelope, to one of two aortic cannulation techniques: group I, cannulation of the distal aortic arch ($n = 17$), and group II, standard cannulation of the ascending aorta (control patients, $n = 17$). On the basis of previous data,¹⁶ we determined that a sample size of 17 patients per group would give us an 80% chance of detecting a 25% relative risk reduction in our primary outcome, mean cerebral emboli per minute, with a corresponding α -level of .05.

The experimental protocol was approved by the Human Experimentation Committee of The Toronto Hospital and all participating patients gave informed written consent.

Operative management. Anesthetic management consisted of induction with midazolam, fentanyl, and sodium thiopental, followed by maintenance with isoflurane and propofol. All patients received a Swan-Ganz catheter (Baxter Healthcare Corp, Edwards Division, Santa Ana, Calif) placed through the right internal jugular vein.

Patients were randomized within the operating room to conventional cannulation of the ascending aorta with a 24F standard arterial cannula (model 6672, Sarns/3M Health Care, Ann Arbor, Mich) or to cannulation of the distal aortic arch with a 24F flexible aortic arch cannula (model 4335, Sarns). The aortotomy was located just proximal to the innominate artery in the conventional cannulation group and on the inferolateral aspect of the arch, just proximal to the origin of the left subclavian artery, in the arch cannulation group. The aortic arch cannula was inserted approximately 8 cm and directed into the descending aorta, thus ensuring that the tip was distal to the left subclavian artery. Both cannulas had a single distal aperture for the exit of blood. Trendelenburg positioning of the patient (approximately 20°) was used whenever possible.

Myocardial protection consisted of intermittent cold antegrade blood cardioplegia. All patients received a left internal thoracic artery graft to the left anterior descending coronary artery, plus additional saphenous vein grafts as required. All anastomoses were performed during a single period of aortic crossclamping.

CPB was established with the appropriate randomized arterial cannula and a single 2-stage right atrial cannula. The CPB circuit consisted of a softshell venous reservoir, a hollow-fiber membrane oxygenator, and nonpulsatile roller pumps. A 32- μ m filter was used in the arterial perfusion line. The hematocrit value was maintained between 20% and 25% during CPB, pump flow rates between 2.0 and 2.5 L $\cdot$ min⁻¹ $\cdot$ m⁻², and mean arterial pressure between 50 and 70 mm Hg by use of phenylephrine as required. Systemic body temperature was allowed to drift to a minimum of 34°C, with active rewarming to 37.5°C at the end of CPB.

Transcranial Doppler monitoring. A transcranial Doppler ultrasonograph (MultiDop X4, DWL, Sipplingen, Germany) was used to continuously monitor the middle cerebral artery during the operation. We attempted to monitor both middle cerebral arteries in all patients but were unable to obtain a satisfactory signal from 1 artery in 8 patients. The Doppler sound was turned off during monitoring to keep the operative team blinded to the number and timing of microemboli. A 2-MHz pulsed-wave transducer (diameter = 1.7 cm) was used to simultaneously monitor 2 depths spaced 4.97 mm apart. The mean ($\pm$ standard deviation) insonation depths were 48.9 $\pm$ 1.1 mm and 53.8 $\pm$ 1.1 mm. A 64-point fast Fourier transform was used. In addition, a high-pass filter set at 100 Hz and a low-pass filter at 80 kHz were used.

Detection and analysis of microemboli. We have previously described our method of microembolus detection.¹⁶ In brief, automated software (TCD-8 for MultiDop $\times$ 4, version 8.00q) was used to discriminate between emboli and artifact according to the bigate method.¹⁷ Simultaneous monitoring of 2 different depths of the middle cerebral artery was used. High-intensity signals were considered artifact if they occurred in both depths simultaneously. They were considered emboli if they appeared sequentially in a manner that was consistent with flow velocity and distance between the 2

Table I. Preoperative and intraoperative demographics for the 2 aortic cannulation groups*

Variable	Group I (distal arch, n = 17)	Group II (control, n = 17)	P value
Preoperative			
Female sex	4 (24%)	2 (12%)	.7
Age (y)	59 ± 10	63 ± 8	.3
BSA (m ²)	1.88 ± 0.19	1.93 ± 0.29	.6
Diabetes mellitus	4 (24%)	5 (29%)	.7
Hypertension	12 (71%)	8 (47%)	.16
Hypercholesterolemia	14 (82%)	12 (71%)	.4
Renal insufficiency or failure	3 (18%)	4 (24%)	.8
LVEF <40%	7 (41%)	4 (24%)	.5
CCS angina class 3 or 4	14 (82%)	12 (71%)	.4
NYHA class III or IV	4 (24%)	6 (35%)	.7
Intraoperative			
No. of CABGs	3.5 ± 0.9	3.7 ± 0.7	.4
CPB time (min)	83 ± 25	86 ± 13	.7
Crossclamp time (min)	63 ± 16	65 ± 9	.8

BSA, Body surface area; LV, left ventricle; CCS, Canadian Cardiovascular Society; NYHA, New York Heart Association; CABG, coronary artery bypass grafting; CPB, cardiopulmonary bypass.

*Values are expressed as number of patients, with percentage in parentheses, for categoric variables and mean ± standard deviation for continuous variables.

sample volumes. In addition, manual off-line analysis of all high-intensity signals was performed by an observer blinded to patient group assignment. A detection threshold of 12 dB was used to improve reproducibility while maximizing sensitivity, in accordance with recommendations of an international consensus group.¹⁸

Cerebral embolization rates were calculated as the number of emboli detected per minute. For those patients who had both middle cerebral arteries monitored, we evaluated the artery with the highest quality signal.

Statistical analysis. Data are expressed as mean ± standard deviation for continuous variables and as percentages for categoric variables. Baseline patient demographics were compared by means of the Student *t* test, χ^2 , or Fisher's exact test where appropriate. Embolic rates between the 2 treatment groups were compared by means of the Student *t* test. The effect of perfusionist interventions and treatment group, as well as their interaction, were simultaneously assessed with a 2-way analysis of variance. Analysis of covariance was used to assess for possible confounding variables. All analyses were performed with SAS software (SAS Institute, Inc, Cary, NC).

Results

Baseline and intraoperative demographics for the 2 groups of patients are displayed in Table I. There were no significant differences between the 2 groups for any variable.

Postoperative outcomes for both groups of patients

Table II. Postoperative outcomes for the 2 aortic cannulation groups*

Outcome	Group I (distal arch, n = 17)	Group II (control, n = 17)
Chest tube blood loss (mL/24 h)	524 ± 208	678 ± 279
Re-exploration for bleeding	1 (6%)	0 (0%)
Myocardial infarction	0 (0%)	0 (0%)
Low cardiac output syndrome	1 (6%)	0 (0%)
Arrhythmias		
Atrial fibrillation	3 (18%)	6 (35%)
Other	0 (0%)	0 (0%)
Stroke	0 (0%)	0 (0%)
Other		
Pneumonia, sepsis	1 (6%)	0 (0%)
Intensive care unit length of stay (h)	27 ± 15	31 ± 18
Hospital length of stay (days)	6.6 ± 1.7 [†]	6.2 ± 1.9
Death	0 (0%)	0 (0%)

There was no significant difference between groups for any outcome.

*Values are expressed as number of patients, with percentages in parentheses, for categoric variables and mean ± standard deviation for continuous variables.

[†]Excluding 1 patient with a postoperative length of stay of 64 days (see text).

are presented in Table II. There were no aortic dissections in either group. One patient in the distal arch cannulation group required re-exploration for bleeding. The bleeding site was identified as a mediastinal vein; the arch cannulation site was hemostatic. Postoperative low cardiac output syndrome occurred in a patient who underwent arch cannulation and had preoperative renal failure and a left ventricular ejection fraction of 20%. This patient subsequently developed pneumonia and sepsis but ultimately recovered and was discharged home 2 months after CABG. There were no deaths in either group.

Cerebral microemboli were detected in all patients, with a range of 17 to 509 in the distal arch group and a range of 84 to 627 in the conventional cannulation group. The total number of detected emboli was lower in the arch cannulation group (152 ± 33, mean ± standard error of the mean) than in the conventional cannulation group (249 ± 35, *P* = .04). Fig 1 reveals mean cerebral embolization rates during CPB for the 2 groups of patients. Distal aortic arch cannulation resulted in significantly fewer cerebral microemboli during CPB (2.0 ± 0.3 emboli per minute) than conventional cannulation of the ascending aorta (4.2 ± 0.9, *P* = .03). Similarly, cerebral embolization rates during the entire operative procedure were significantly lower with arch cannulation (1.4 ± 0.3 emboli per minute) than in control patients (2.4 ± 0.5, *P* = .04).

Fig 2 displays the mean embolic rates for both groups of patients during 3 time periods. *Perfusionist events*

were defined as the 2-minute time period after injection of drugs or blood samples into the venous reservoir by the perfusionist, an event that we have previously demonstrated to be the predominant cause of cerebral emboli during CPB.¹⁶ (Injections were made by means of a manifold directly connected to the venous line, just proximal to the venous reservoir.) *Surgical events* were defined as the 2-minute time period after aortic cannulation/decannulation, CPB start/end, crossclamp application/removal, and start of cardiac ejection, events that have previously been described as causes of cerebral emboli.^{7,15,19} *Baseline events* were all time periods excluding perfusionist or surgical events. As Fig 2 reveals, the reduction of cerebral embolization by distal arch cannulation was most pronounced during perfusionist interventions ($P = .01$).

Analysis of covariance failed to identify any confounding variables including individual perfusionist, side of middle cerebral artery monitoring, and patient demographics as listed in Table I.

Discussion

Neurologic morbidity after CABG has received increasing attention in the literature.¹ Stroke is the most thoroughly studied complication but occurs in only a small percentage of patients.^{20,21} Postoperative neuropsychologic impairment, in contrast, is very common. This complication is important because approximately half of patients are aware of their cognitive deficits²² and one third of patients display long-standing impairment.^{4,5}

Cerebral microemboli have been established as the principal cause of postoperative neuropsychologic impairment.^{10,11} Several investigators have documented that cerebral embolization occurs in virtually all patients undergoing CPB and that a reduction in the number of emboli is associated with less cognitive impairment.^{8,11,13,23-25} Hammon and associates¹¹ assessed neuropsychologic impairment in 395 patients undergoing CABG and demonstrated that 100 or more cerebral emboli, as quantified by transcranial Doppler sonography, is an independent predictor of cognitive dysfunction. Pugsley and coworkers²³ found 43% of patients with more than 1000 emboli had neuropsychologic impairment 8 weeks after the operation, compared with only 9% of patients with fewer than 200 emboli. Similarly, Blauth and associates⁸ used retinal fluorescein angiography to demonstrate increased emboli in patients with cognitive deficits compared with those without deficits. Sylivris and coworkers²⁴ recently demonstrated a lower mean embolic rate (number of cerebral emboli per minute of CPB) in

Fig 1. Comparison of cerebral embolization rates during CPB (mean $\pm$ standard error of the mean) between aortic arch cannulation and conventional ascending aorta cannulation groups. There were significantly fewer cerebral emboli per minute in the distal arch group.

patients with neuropsychologic impairment compared with those without impairment.

The precise composition of cerebral microemboli during CPB is not known.⁶ We¹⁶ have previously demonstrated that the vast majority of emboli occur immediately after the injection of drugs, as well as small amounts of air contained within the syringe, into the venous reservoir by the perfusionists. We recorded cerebral embolic rates during CABG and found a 7-fold increase in emboli detection after perfusionist events when compared with other time periods. In addition, we found that careful deairing of the syringe before injection into the CPB circuit resulted in less embolization. These findings would strongly suggest that the majority of cerebral emboli during CPB consist of microbubbles. Further evidence for this conclusion can be found in a randomized trial by Padayachee and associates.¹⁵ These investigators demonstrated that bubble oxygenators result in significantly more cerebral emboli than membrane oxygenators. Because air emboli would be expected to ascend in blood, we hypothesized that cannulation of the distal aortic arch, with placement of the cannula tip into the descending aorta and Trendelenburg positioning, would result in less cerebral embolization than conventional cannulation of the ascending aorta.

The current study assessed 34 patients undergoing CABG in a prospective, randomized trial. We found significantly lower cerebral embolic rates in patients randomized to distal arch cannulation, with the most

Fig 2. Cerebral embolization rates during perfusionist interventions, surgical interventions, and during baseline (see text for definitions). The decrease in cerebral embolization by distal arch cannulation was most pronounced during perfusionist interventions.

pronounced effect during perfusionist interventions. We believe this is an important finding because microembolization is an important cause of postoperative neuropsychologic impairment. Although the majority of emboli in our study probably consisted of microbubbles, which may be less detrimental than atherosclerotic debris because of the ability of air to resorb, we believe that any reduction in cerebral embolic load is clinically significant.

The current study excluded patients with evidence of aortic or carotid atherosclerosis to minimize possible confounding factors. However, we believe that patients with aortic atherosclerosis may also benefit from distal arch cannulation. Although atherosclerosis of the aortic arch is more common than atherosclerosis of the ascending aorta, the disease process is often localized to the superior portion of the arch.²⁶ It is sometimes possible, therefore, to find a disease-free segment of the inferior aortic arch in patients with diffuse atherosclerosis of the ascending aorta. Indeed, our largest experience for this particular cannulation technique is in this patient population. Furthermore, use of a long, straight arterial cannula, as used in the current study for arch cannulation, is associated with lower peak aortic flow velocities than conventional short, right-angled cannulas.²⁷ A decrease in flow velocity, as well as positioning of the cannula tip below the left subclavian artery, may result in decreased embolization from an atherosclerotic aortic wall (known as the “sandblast effect”). Distal arch cannulation, therefore, may be the preferred technique for patients with aortic atherosclerosis.

The benefits of distal arch cannulation would be mitigated if any serious complications arose from this procedure. The small number of patients involved in this study limits conclusions on the safety of this procedure. However, we have previously performed distal arch cannulation in well over 200 patients, predominantly for diffuse atherosclerosis of the ascending aorta. There have been no cases of aortic dissection in this group of patients. In addition, there have been no re-explorations for bleeding from the arch cannulation site. We therefore believe that distal aortic arch cannulation is a safe and effective procedure.

Study limitations

One limitation of this study is that we did not perform neuropsychologic testing in the 2 groups of patients. Because of the small number of patients planned for this study, however, we thought that we would not have the power to comment on neuropsychologic outcomes. Approximately 200 patients per group would be required to detect a 30% relative risk reduction in cognitive impairment. In addition, we thought there was significant evidence in the literature supporting the role of microemboli in the etiology of neuropsychologic impairment.

Another limitation of this study is that we did not use epiaortic ultrasonography or transesophageal echocardiography in the assessment of atherosclerosis of the aorta. The use of digital palpation alone may have resulted in unequal distribution of patients with mild to moderate aortic atherosclerosis to one of the random-

ized groups. However, we have demonstrated that the majority of cerebral emboli during CPB are associated with perfusionist events and therefore probably consist of air. This finding would suggest that the presence of mild to moderate atherosclerosis would not significantly affect our findings of decreased cerebral emboli with arch cannulation.

Conclusions

Distal aortic arch cannulation results in less cerebral microembolism than conventional cannulation of the ascending aorta, particularly during perfusionist interventions. Provided it is performed safely, distal arch cannulation may be an important surgical option in the management of patients with severe atherosclerosis of the ascending aorta.

We acknowledge the help of The Toronto Hospital cardiovascular surgery staff, in particular the anesthesiologists and perfusionists, for their cooperation and support. We also thank DWL Electronics Systems for the use of their transcranial Doppler equipment.

REFERENCES

1. Roach GW, Kanchuger M, Mangano CM, et al. Adverse cerebral outcomes after coronary bypass surgery: multicenter study of Perioperative Ischemia Research and Education Foundation Investigators. *N Engl J Med* 1997;335:1857-63.
2. Shaw PJ, Bates D, Cartlidge NE, et al. Neurologic and neuropsychological morbidity following major surgery: comparison of coronary artery bypass and peripheral vascular surgery. *Stroke* 1987;18:700-7.
3. Wong BI, McLeon RF, Naylor CD, et al. Central nervous system dysfunction after warm or hypothermic cardiopulmonary bypass. *Lancet* 1992;339:1383-4.
4. Shaw PJ, Bates D, Cartlidge NE, et al. Long-term intellectual dysfunction following coronary artery bypass graft surgery: a six month follow-up study. *Q J Med* 1987;62:259-68.
5. Bruggemans EF, Van Dijk JG, Huysmans HA. Residual cognitive dysfunctioning at 6 months following coronary artery bypass graft surgery. *Eur J Cardiothorac Surg* 1995;9:636-43.
6. Barbut D, Yao FF, Lo Y-W, et al. Determination of size of aortic emboli and embolic load during coronary artery bypass grafting. *Ann Thorac Surg* 1997;63:1262-7.
7. Clark RE, Brillman J, Davis DA, Lovell MR, Price TR, Magovern GJ. Microemboli during coronary artery bypass grafting: genesis and effect on outcome. *J Thorac Cardiovasc Surg* 1995;109:249-57.
8. Blauth CI, Arnold JV, Schulenberg WE, McKhann GM, Taylor KM. Cerebral microembolism during cardiopulmonary bypass: retinal microvascular studies in vivo with fluorescein angiography. *J Thorac Cardiovasc Surg* 1988;95:668-76.
9. Moody DM, Bell MA, Challa VR, Johnston WE, Prough DS. Brain microemboli during cardiac surgery or aortography. *Ann Neurol* 1990;28:477-86.
10. Blauth CI. Macroemboli and microemboli during cardiopulmonary bypass. *Ann Thorac Surg* 1995;59:1300-3.
11. Hammon JW, Stump DA, Kon ND, et al. Risk factors and solutions for the development of neurobehavioral changes after coronary artery bypass grafting. *Ann Thorac Surg* 1997;63:1613-8.
12. Padayachee TS, Parsons S, Theobald R, Gosling RG, Deverall PB. The effect of arterial filtration on reduction of gaseous microemboli in the middle cerebral artery during cardiopulmonary bypass. *Ann Thorac Surg* 1988;45:647-9.
13. Pugsley W, Klinger L, Paschalis C, et al. Microemboli and cerebral impairment during cardiac surgery. *Vasc Surg* 1990;24:34-43.
14. Trivedi U, Davies C, Roxburgh J, Cooper G. Cerebral embolization is reduced with the use of the stab technique for aortic cannulation compared with the side-clamp technique. *J Thorac Cardiovasc Surg* 1997;113:215-6.
15. Padayachee TS, Parsons S, Theobald R, Linley J, Gosling RG, Deverall PB. The detection of microemboli in the middle cerebral artery during cardiopulmonary bypass: a transcranial Doppler ultrasound investigation using membrane and bubble oxygenators. *Ann Thorac Surg* 1987;44:298-302.
16. Taylor RL, Borger MA, Weisel RD, Fedorko L, Feindel CM. Cerebral microemboli during cardiopulmonary bypass: increased emboli during perfusionist interventions. *Ann Thorac Surg* 1999;68:89-93.
17. Georgiadis D, Wenzel A, Zerkowski HR, Zierz S, Lindner A. Automated intraoperative detection of Doppler microembolic signals using the bigate approach. *Stroke* 1998;29:137-9.
18. Ringelstein EB, Droste DW, Babikian VL, et al. Consensus on microembolus detection by TCD. International Consensus Group on Microembolus Detection. *Stroke* 1998;29:725-9.
19. Barbut D, Hinton RB, Szatrowski TP, et al. Cerebral emboli detected during bypass surgery are associated with clamp removal. *Stroke* 1994;25:2398-402.
20. Borger MA, Ivanov J, Weisel RD, et al. Decreasing incidence of stroke during valvular surgery. *Circulation* 1998;98(Suppl): III137-43.
21. Borger MA, Fremes SE, Weisel RD, et al. Coronary bypass and carotid endarterectomy: increased risk of combined surgery by meta-analysis. *Ann Thorac Surg* 1999;68:14-21.
22. Shaw PJ, Bates D, Cartlidge NE, et al. Early intellectual dysfunction following coronary bypass surgery. *Q J Med* 1986;58:59-68.
23. Pugsley W, Klinger L, Paschalis C, Treasure T, Harrison M, Newman S. The impact of microemboli during cardiopulmonary bypass on neuropsychological functioning. *Stroke* 1994;25:1393-9.
24. Sylivris S, Levi C, Matalanis G, et al. Pattern and significance of cerebral microemboli during coronary artery bypass grafting. *Ann Thorac Surg* 1998;66:1674-8.
25. Stump DA, Tegeler CH, Rogers AT, et al. Neuropsychological deficits are associated with the number of emboli detected during cardiac surgery. *Stroke* 1993;24:509.
26. Amarencu P, Duyckaerts C, Tzourio C, Henin D, Bousser M-G, Hauw J-J. The prevalence of ulcerated plaques in the aortic arch in patients with stroke. *N Engl J Med* 1992;326:221-5.
27. Grossi EA, Kanchuger MS, Schwartz DS, et al. Effect of cannula length on aortic arch flow: protection of the atheromatous aortic arch. *Ann Thorac Surg* 1995;59:710-2.