may involve antiapoptotic effects. The discussion about this study focused on the neuroprotective balance between the degree of hypothermia and the duration of circulatory arrest.¹

An important consideration is that the 75-minute duration of circulatory arrest in this animal study exceeds the typical clinical range of minutes (30–50 minutes).^{2–4} Why not study the effects of profound hypothermia in an experimental model that includes clinically relevant durations of circulatory arrest? Why not study brain apoptosis during profound hypothermia at time intervals of 10 minutes within the clinical range to calibrate the degree of hypothermia with the duration of ischemia? The answers to this series of questions would provide additional laboratory evidence that could perhaps guide clinical conduct of hypothermia for optimal neuroprotection.

This kind of pitfall may be a theme in experimental circulatory arrest: The conduct of hypothermic circulatory arrest in the laboratory setting is significantly different from that in the clinical setting. As a consequence, the laboratory findings are diluted in translation, resulting in a laboratory–clinical divide that may slow progress toward the optimal clinical conduct of circulatory arrest.

Perhaps it is time for the development of guidelines for the laboratory study of circulatory arrest and regional cerebral perfusion, given the considerable current controversy in infant perfusion management.^{2–4} To my knowledge, no such guidelines have been published. The guidelines could follow a series of deliberations among both clinical and laboratory experts in this area to develop answers to questions such as the following:

1. What is the recommended study interval of circulatory arrest?
2. What depths of hypothermia should be studied at which durations of circulatory arrest?
3. What neuroprotective interventions require further laboratory study in a clinically relevant model?
4. How should a particular neuroprotective intervention best be studied in the laboratory for maximal clinical utility?
5. Which is the most clinically relevant laboratory model of regional cerebral perfusion?

6. Which are the most important questions for further study with respect to optimizing the practice of regional cerebral perfusion?

I congratulate Dr Ananiadou and colleagues¹ on their excellent study that has raised many thought-provoking questions. I look forward to their feedback and the ongoing progress in this area.

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doi:10.1016/j.jtcvs.2007.05.068

Reply to the Editor:

Although the deleterious effects of prolonged exposure to cardiopulmonary bypass on brain function and structure have been demonstrated, neuroprotective strategies, particularly deep hypothermia and circulatory arrest (DHCA), remain an issue of debate. This is related in part to the gap between the experimental understanding of brain injury and the clinical application of various neuroprotective strategies. As suggested by Dr Augoustides, this gap can be attributed to the lack of clinically relevant guidelines for effective laboratory study of circulatory arrest.

Our goal was to assess one possible mechanism of neuronal injury after DHCA. Because apoptosis seems to involve a subtle and complex cascade of events, the paradigm applied, although not totally clinically relevant, would allow a robust response for assessment. Further study is clearly warranted to unravel relevant mechanisms and sensitive markers, which in turn would allow us to appreciate the potential clinical relevance of these experimental findings. Dr Augoustides makes a valid point for the need to develop appropriate guidelines that would enhance this investigative process.

Evaluating various strategies in animal studies to determine clinical feasibility has been limited to large-animal models (porcine, canine, and ovine). These are expensive, demanding, and usually performed without neuropsychologic assessment. Each model system, however, from cell cultures to rats, large animals, and ultimately clinical trials, has its advantages and disadvantages, and its place in these investigations.

Most animal models require an extended period of arrest to produce a reproducible level of neuronal injury that would facilitate elucidating the mechanisms of injury and efficacy of neuroprotective interventions. Many large animal models require DHCA for at least 90 to 120 minutes to demonstrate neurologic deficits.^{1,2} Although such prolonged DHCA intervals might not be considered clinically realistic, they may be more appropriate for demonstrating the molecular pathways behind acute neuronal injury and thus modes of intervention.

Study of a neuroprotective strategy includes the appropriate selection of an animal model and functional indices. The model is selected with respect to the relevance and feasibility of assessing the parameters of interest. Investigations of promising neuroprotective methods require validation (validation study), use in experimental settings to optimize cerebral protection during cardiopulmonary bypass and DHCA (performance study), and test during routine cardiac surgery (clinical study).

A clearer understanding of the consequences of DHCA will be pivotal in clinical decision-making, including when to initiate circulatory arrest and the appropriate interval. Delayed cell death is of

special interest because of the potential for intervention. Although apoptosis is believed to play a part in cerebral injury, its role has generally been identified through histologic techniques. These snapshots do not permit a clear delineation of the timeline of apoptosis. Because the role of apoptosis is not clear, therapies have yet to be designed for the specific purpose of inhibiting apoptosis.

There are still many gaps in our knowledge about how to best study cerebral outcome. Investigations require coordinated efforts by multiple groups, pursuing systematic, multilevel research, spanning from cell cultures, to various animal models, and ultimately to clinical trials.

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Interventional techniques in cardiovascular surgery

To the Editor:

We appreciate the thoughtful editorial written by Dr Mitchell¹ concerning our brief report.²

Aortic stenting is a new procedure. We agree that any problems with this technology should be discussed openly, as we tried to do in our report. Likewise, Dr Mitchell's comments add to a vivid exchange of opinions.

Please allow us to answer the questions posed in his first paragraph at the beginning: The left carotid was accidentally overstented for 2 mm, as said in the text, and obviously it was an open web design; otherwise placement of a stent in this position would have resulted in almost complete overstenting of the left carotid artery. The length of the neck is always a crucial issue; we considered it to be longer than 2 cm both at the lesser and the greater curvatures.

These technical details may be an important, but secondary, issue. However, we doubt whether conventional open surgery is still the method of choice in many elective operations on the descending aorta. The sentence "In my opinion stent grafting should be viewed as an additional surgical strategy rather than an alternative one" brilliantly describes the attitude surgeons should have toward this new technology. In contrast with the reactions to coronary stenting decades ago that were characterized by rejection and opposition, we should eagerly learn to adopt the interventional techniques to expand the traditional surgical armamentarium for the best of our patients. In our center, the decision for aortic stent grafting is exclusively made by 3 cardiovascular surgeons with extensive experience in open aortic procedures. We believed stent grafting to be superior in this special case because of the significant calcifications of the aortic wall, which may be visible in Figure 1.¹ Meanwhile, we changed our policy in comparable cases to one that may combine the advantages of open surgery and stent grafting while avoiding the majority of drawbacks of

both methods. In several similar cases in the last months, we implanted stent grafts through an open approach via the aortic arch. This procedure allows perfect control of the supraaortic vessels and secure fixation of the graft inside the arch by sutures, thus avoiding endoleaks and migration. The cumbersome distal aortic anastomosis is omitted, minimizing the operation time and risks of spinal ischemia and bleeding. Correct expansion of the graft and aortic pathology at the distal end of the stent are assessed by intraluminal endoscopy. Short circulatory arrest with antegrade cerebral perfusion required for this operation was well tolerated by all patients.

This may be just one example how methods developed by interventionalists may help surgeons make a hazardous procedure a simple one. Others, most probably in the field of interventional treatment of valve disease, will follow. We strongly believe that surgeons should face the progress of interventional technology critically, but with an open mind, and try to extract the best of these methods.

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doi:10.1016/j.jtcvs.2007.01.101