could emphasize. Second is the increasing life-saving role of these devices as access to transplants decreases. Third is the fact that all LVADs are still subject to the same entry criteria that were used in the 1970s for patients with acute failure-to-wean-from-bypass. These hemodynamic entry criteria should be reassessed in view of the changing medical therapy and the fact that these implantable pumps are for patients with chronic heart failure on transplant waiting lists who experience worsening of heart failure made manifest primarily by end-organ failure and not by acute hemodynamic compromise.

O. H. Frazier, MD

Director, Cardiopulmonary Transplantation
Texas Heart Institute
PO Box 20345
Houston, TX 77225-0345

References

1. Copeland J. Multicenter bridge to transplantation with the HeartMate assist device: Evaluation from another perspective. *J Thorac Cardiovasc Surg.* 2003; 125:228-30.
2. Frazier OH, Rose EA, Oz MC, Dembitsky W, McCarthy P, Radovancevic B, et al. Multicenter clinical evaluation of the HeartMate vented electric left ventricular assist system in patients awaiting heart transplantation. *J Thorac Cardiovasc Surg.* 2001; 122:1186-95.

doi:10.1067/mtc.2003.69

Cerebral protection with retrograde cerebral perfusion

To the Editor:

In their article Bonser and colleagues¹ claim that the cerebral flow resulting from retrograde cerebral perfusion (RCP) is insufficient to make a major contribution to cerebral oxygenation and that the brain remains ischemic. In the discussion of their impressive work, the authors stated correctly that current data suggest that RCP might provide only little brain perfusion in human subjects compared with antegrade baseline cerebral flow. Should we abandon this adjunct to hypothermic circulatory arrest, or should we explore methods to maximize the benefits from its application? The effort to improve the effectiveness of RCP during hypothermic circulatory arrest should combine reduction of the metabolic activity with simultaneous increase of blood flow to fulfill the residual metabolic requirements of the brain. In a small series

my colleagues and I² demonstrated that the introduction of vasodilators and anesthetics into the retrograde perfusate tripled RCP flow without increase in pressure and with concomitant suppression of electric activity. In the present study it is not stated whether brain electric activity was monitored, and the individual RCP flow is not specified. Simple pharmacologic manipulations might augment RCP to 20% or 30% of cerebral flow instead of only 10%. The administration of potent anesthetics or other neuroprotective agents might mitigate the metabolic needs of the brain. Such maneuvers will render the brain less ischemic, allowing safer circulatory arrest.

Amir Elami, MD

Department of Cardiothoracic Surgery
Hadassah University Hospital
PO Box 12000
Jerusalem 91120, Israel

References

1. Bonser RS, Wong CH, Harrington D, Pagano D, Wilkes M, Clutton-Brock T, et al. Failure of retrograde cerebral perfusion to attenuate metabolic changes associated with hypothermic circulatory arrest. *J Thorac Cardiovasc Surg.* 2002;123:943-50.
2. Shenkman Z, Elami A, Weiss YG, Glantz L, Milgalter E, Drenger B, et al. Cerebral protection using retrograde cerebral perfusion during profound hypothermic circulatory arrest. *Can J Anaesth.* 1997;44:1096-101.

doi:10.1067/mtc.2003.246

Reply to the Editor:

We thank Elami for his comments concerning our work on retrograde cerebral perfusion (RCP).¹ We acknowledged in our discussion that RCP could contribute to metabolic support during hypothermic circulatory arrest and that this contribution could be increased by the use of vasodilators. It is also possible that the use of anesthetics or neuroprotective agents during RCP might afford neuroprotection. The series quoted by Elami, however, describes only anecdotal evidence from 3 patients undergoing differing pharmacologic interventions.² This report described no monitoring of cerebral metabolism or perfusion, therefore making inferences regarding cerebral metabolic activity and blood flow unreliable. We have previously reported that RCP can provide some brain perfusion, but we have questioned what fraction of retrograde flow provides true brain perfusion.^{3,4} It is quite possible that increased

flow achieved by means of vasodilator administration bypasses the brain through venovenous and venoarterial collaterals.⁴ Any assumption that increasing flow increases true brain perfusion and neuroprotection requires rigorous enquiry. We would agree that the jury remains out on RCP and that a beneficial clinical effect remains to be proven. Such therapeutic interventions therefore require assessment as part of randomized controlled trials if their efficacy is to be completely investigated.

Robert Bonser, FRCP, FRCS

Deborah Harrington, MRCS

Domenico Pagano, MD, FRCS

Department of Cardiothoracic Surgery
Queen Elizabeth Hospital
Edgbaston

Birmingham B15 2TH, United Kingdom

References

1. Bonser RS, Wong CH, Harrington D, Pagano D, Wilkes M, Clutton-Brock T, et al. Failure of retrograde cerebral perfusion to attenuate metabolic changes associated with hypothermic circulatory arrest. *J Thorac Cardiovasc Surg.* 2002;123:943-50.
2. Shenkman Z, Elami A, Weiss YG, Glantz L, Milgalter E, Drenger B, et al. Cerebral protection using retrograde cerebral perfusion during profound hypothermic circulatory arrest. *Can J Anaesth.* 1997;44:1096-101.
3. Pagano D, Boivin CM, Farouqi MH, Bonser RS. Retrograde perfusion through the superior vena cava perfuses the brain in human beings. *J Thorac Cardiovasc Surg.* 1996; 111:270-2.
4. Wong C, Bonser RS. Retrograde perfusion and true reverse brain blood flow in humans. *Eur J Cardiothorac Surg.* 2000;17: 597-601.

doi:10.1067/mtc.2003.245

Angiogenesis by means of endothelial cell transplantation

To the Editor:

In their article, "Angiogenesis by Endothelial Cell Transplantation," Kim and associates¹ present results of a novel and intriguing approach to angiogenic therapy. Their preliminary report that endothelial cell transplantation into a myocardial scar accelerates angiogenesis suggests a promising alternative to angiogenic gene or protein therapy. About the same time that their article was published, we² presented similar results before the American Heart Association at our annual scientific session (Anaheim, Calif) in November 2001.

Interestingly, we created our model of ischemic cardiomyopathy by placing an ameroid constrictor on the branch of the circumflex artery in 12 adult sheep.

In our experiment, 4 weeks after constriction, we randomly assigned 3 groups (4 animals per group) to transpericardial injection (3 sites per animal): sham treatment (saline solution with denatured cells), control (no injections), and endothelial cell fibrin meshwork groups (autologous mature endothelial cells, 5×10^5 per injection site harvested from jugular veins). Eight weeks after transepicardial treatment, animals were assessed for myocardial function (by means of echocardiography), myocardial blood flow (MBF), and capillary area (by means of histology).

We demonstrated improved capillary density and MBF in keeping with their speculation that, "A coronary ligation model of myocardial infarction, in which a more extensive peri-infarct border zone could harbor viable but hypoperfused cardiomyocytes and endothelial cells, might result in greater angiogenesis."

One month after constriction, MBF in the ischemic myocardium decreased to 70% of baseline value ($P < .001$). Two months after reoperation and the beginning of treatment, animals were killed, and MBF was found to have decreased to 28% versus baseline values in the control and saline solution groups ($P < .001$). MBF in the endothelial cell group significantly increased to 108%.

In normal nonischemic myocardium in all 3 groups, there were 205.54 ± 12.31 capillaries/mm². Three months after constriction (and 2 months after reoperation and beginning of treatment) in the control and saline solution groups, there was a decrease up to 51% in capillaries per square millimeter ($P < .001$ vs baseline). However, although this decreased significantly in the control and saline solution groups versus baseline values, in the endothelial cell group this increased to 146% ($P < .001$). Hence all of our results confirmed those in the report of Kim and associates.¹

However, they also concluded that "increasing blood flow by endothelial cell transplantation in this model did not improve contractility or prevent ventricular dilatation," and "we plan to perform autol-

ogous endothelial cell transplantation in our clinically relevant porcine model of occlusion of the left anterior descending coronary artery. We anticipate that angiogenesis may improve regional and global function."

In our investigation, 4 weeks after constriction, left ventricular ejection fraction (LVEF) decreased to 75% ($P < .001$). Two months later, LVEF decreased to 57% in the control and saline groups ($P < .001$ vs 4 weeks and baseline). In the endothelial cell group LVEF increased to 89% of baseline values but continued to be less than baseline value ($P < .05$). However, LVEF in this group was significantly better than in the control and saline solution groups ($P < .001$).

On the basis of our data, we think that use of endothelial cell transplantation within a 3-dimensional matrix system can be used to induce angiogenesis in patients who cannot be adequately revascularized by using standard techniques. Exploring autologous mature endothelial cell transplantation might become a useful alternative to gene and protein therapy. We recently completed studies involving a large number of animals; these results are pending.

Valeri Chekanov, MD, PhD^a

Nicholas Kipshidze, MD, PhD^b

Milwaukee Heart Institute

Aurora/Sinai Medical Center

Milwaukee, Wis^a

Lenox Hill Heart & Vascular Institute

Cardiovascular Research Foundation

Lenox Hill Hospital

New York, NY^b

References

1. Kim E-J, Li R-K, Weisel RD, Mickle DA, Jia ZQ, Tomita S, et al. Angiogenesis by endothelial cell transplantation. *J Thorac Cardiovasc Surg.* 2001;122:963-71.
2. Chekanov V, Nikolaychik V, Tchekanov G, Dargas G, Roubin G, Leon M, et al. Transplantation of autologous endothelial cells in a fibrin meshwork induces angiogenesis and improves myocardial function in an animal model of ischemic cardiomyopathy [abstract]. *Circulation.* 2001;104(suppl 17):II260.

doi:10.1067/mtc.2003.248

Reply to the Editor:

Chekanov and Kipshidze performed a series of experiments that appear to confirm our findings that endothelial cell transplan-

tation improved perfusion after myocardial injury. Recently, a variety of techniques have been used to induce angiogenesis to treat patients who are not candidates for conventional methods of revascularization. Cell transplantation has the advantage of inducing angiogenesis by a variety of mechanisms because the technique is not limited to the release of a single protein.

Chekanov and Kipshidze used an endothelial cell fibrin meshwork applied to the epicardial surface of an ischemic region. They found that this technique induced angiogenesis. The mode of delivery and the number of cells engrafted might critically affect the benefits achieved with cell transplantation. The optimal conditions have not been well defined. In addition, the cell type that induces the most beneficial response has not been adequately established. Endothelial cells induce an extensive capillary network, but they might not induce the formation of sufficient conduit vessels. Further research into this important area might establish which cell type, which cell number, and which mode of delivery are optimal to induce angiogenesis.

Ren-Ke Li, MD

Richard D. Weisel, MD

Department of Cardiovascular Surgery

Toronto General Hospital

200 Elizabeth St

Toronto, Ontario M5G 2C4, Canada

doi:10.1067/mtc.2003.249

Missing data from mesothelioma study

To the Editor:

The phase II trial of surgery and radiation of malignant mesothelioma by Rusch and colleagues¹ is an important addition to the literature, documenting contemporary efforts to control and eventually cure this so far incurable malignant process. The 8% mortality after extrapleural pneumonectomy reflects the tremendous strides in surgical techniques effected in recent decades. The rigorous staging confirms a major attempt to bring better science to this capricious disease.

Nevertheless, Rusch and colleagues¹ have excluded a host of important information from their publication. I hope that they will be able to strengthen the report by rectifying some of these omissions: