References

1. Tabata M, Khalpey Z, Cohn LH, Chen FY, Bolman RM 3rd, Rawn JD. Effect of preoperative statins in patients without coronary artery disease who undergo cardiac surgery. *J Thorac Cardiovasc Surg.* 2008;136:1510-3.
2. Horwich TB, Hernandez AF, Dai D, Yancy CW, Fonarow GC. Cholesterol levels and in-hospital mortality in patients with acute decompensated heart failure. *Am Heart J.* 2008;156:1170-6.

doi:10.1016/j.jtcvs.2009.03.027

HYPOXIA-INDUCIBLE FACTOR-1 α IN STEM CELL PRECONDITIONING: MECHANISTIC ROLE OF HYPOXIA-RELATED MICRO-RNAs

To the Editor:

Since its inception more than 2 decades ago, ischemic preconditioning (IP) is considered as the most powerful cytoprotective stimulus and is being devised as a potent strategy to promote stem cell survival post-engraftment in the infarcted heart.¹ The elegant study from Hu and colleagues² is a step forward toward the use of low oxygen culture conditions to trigger activation of survival signaling pathways in the cells before their engraftment in vivo. The authors showed significantly improved survival of the hypoxia-treated (0.5% oxygen for 24 hours) mesenchymal stem cells after engraftment in the infarcted heart. Unlike many of the previous studies, an important aspect of the study protocol was cell engraftment during the acute phase of myocardial infarction to assess the effectiveness of a preconditioning approach. Acute phase engraftment exposed the engrafted cells to the harsh, cytokine-rich microenvironment of the infarcted myocardium, which was aggravated even more because of the infiltration of inflammatory and progenitor cells as a part of the intrinsic repair process. The authors attributed the effectiveness of the hypoxic preconditioning approach to up-regulation of hypoxia inducible factor (HIF)-1 α , a heterodimeric master switch of a hypoxia-responsive array of genes

that enable the cells to acclimatize and survive in low oxygen conditions. Although a low-level presence of HIF-1 α has been reported in the cytoplasmic compartment of cells grown under normoxia, hypoxia stabilizes HIF-1 α against degradation and promotes its translocation to the nucleus, where it forms functional complexes for gain of functions. As a part of our continuing endeavor to precondition donor cells for their better survival in the infarcted heart and that too with clinical relevance,³ we share our experience of extrapolating the classic IP strategy of exposing the cells to multiple sublethal ischemia/reoxygenation cycles of short duration to promote mesenchymal stem cell survival (unpublished data). This approach represents an extension of the one-time, long-term exposure to sublethal hypoxia approach suggested by Hu and colleagues.² Our results showed significant up-regulation of HIF-1 α in an Akt-dependent manner in the cells preconditioned by 2 cycles of ischemia-reperfusion of 30 minutes each. These molecular events successfully attenuated donor cell attrition on subsequent exposure to lethal ischemic insult. The participation of hypoxia-associated micro RNAs (miR), miR-107 and miR-210,⁴ downstream of HIF-1 α in translation of cytoprotective effects of IP was another important observation in our study. HIF-1 α -specific RNA interference abrogated both miR-107 and miR-210 in the preconditioned cells transfected with HIF-1 α -specific siRNA with a concomitant increase in preponderance of apoptotic cells. Our in vivo experimental results in a rodent model of acute myocardial infarction showed that transplanted preconditioned cells survived significantly better compared with their nonpreconditioned counterparts. Moreover, transplantation of preconditioned cells promoted miR-107 and -210 expression in the infarcted heart at the site of the cell graft. These novel findings necessitate more in-depth studies to elucidate whether

the effect of IP can be duplicated by manipulation of the cells for hypoxia-related miRNAs to promote donor cell survival.

Khawaja Husnain Haider, MPharm,
PhD
Ha Won Kim, PhD
Muhammad Ashraf, PhD
Department of Pathology and
Laboratory Medicine
University of Cincinnati Medical
Center
Cincinnati, Ohio

References

1. Haider H, Ashraf M. Strategies to promote donor cell survival: combining preconditioning approach with stem cell transplantation. *J Mol Cell Cardiol.* 2008;45:554-66.
2. Hu X, Yu SP, Fraser JL, Lu Z, Ogle ME, Wang JA, et al. Transplantation of hypoxia-preconditioned mesenchymal stem cells improves infarcted heart function via enhanced survival of implanted cells and angiogenesis. *J Thorac Cardiovasc Surg.* 2008;135:799-808.
3. Niagara MI, Haider H, Jiang S, Ashraf M. Pharmacologically preconditioned skeletal myoblasts are resistant to oxidative stress and promote angiomyogenesis via release of paracrine factors in the infarcted heart. *Circ Res.* 2007;100:545-55.
4. Kulshreshtha R, Davuluri RV, Calin GA, Ivan M. A microRNA component of the hypoxic response. *Cell Death Differ.* 2008;15:667-71.

doi:10.1016/j.jtcvs.2009.01.028

THE IMPLICATIONS OF OUTCOME PREDICTORS WHEN TRANSITIONING FROM ARTERIAL TO DOUBLE-SWITCH SURGERY

To the Editor:

I read with great interest the fate of the systemic ventricle after double-switch surgery among those who had left ventricle (LV) training.¹ The authors concluded that LV training with pulmonary artery (PA) banding resulted in a worse outcome after the double-switch procedure. I would like to add a few potential explanations for their findings. One of the important aspects of the decline in function can be related to the coronary circulation and its aberrant network in patients with corrected transposition of the great arteries.² This has been

documented in the literature in the context of simple transposition of the great vessels but was not discussed further in this study. The arterial switch component of the double-switch procedure carries all the known risk hazards as in any arterial switch and long-term complications, including fatal arrhythmias, neo-aortic regurgitation, and left ventricular dysfunction.³ These risks can be higher among those with a single orifice coronary artery.

Training is a relative term and is tailored to the individual patient. Excessive training leading to LV pressures more than 75% systemic is a well-known association with late ventricular dysfunction. Although the study states that LV pressures were 65% to 80%, it would be more informative to the reader if the authors explained the target pressures for the 24 patients after PA banding in the nontrained subgroup. Furthermore, approximately 46% (n = 5) of the trained subgroup had more than 1 PA band to properly prepare the morphologic LV (mLV) for the double switch. It would be important to know whether such patients' ventricles fared better than the application of singleton pressure load PA banding, especially when not all LV training is detrimental in older patients.

It is interesting to note that the mLV/mRV pressure ratio was similar in the trained and nontrained groups at the time of their anatomic repair. However, those older patients with LV dysfunction achieved mLV/mRV pressure in less time (436 vs 730 days) than those without dysfunction. This may imply that the LV was generating the same pressure at the time of the double switch as in those with ventricular defect physiology (increased end-diastolic volume, reduced afterload) but fared better than in the trained group. This may illustrate that the PA band is a confounder, whereas the morphology (congenitally corrected transposition of the great arteries with small restrictive ventricular septal defect or no ventricular septal defect) is an independent predictor, especially when the authors state in

Table 1 that 20% of the nontrained group had good mLV versus 60% in the trained group ($P = .04$, statistically significant). Furthermore, in support of this is the well-known association of worsening survival in the older infant with transposition of the great arteries and an intact ventricular septum after the arterial switch compared with transposition of the great arteries and a ventricular septal defect.⁴ The additional benefit of ventricle volume load via a systemic circulation to PA shunt to the pressure load PA band afterload has been described and could be of benefit in corrected transposition.⁵ Finally, the ventricular activation time period (QRS) has been a strong marker of ventricular function.⁶ The authors did not state its respective duration for the 2 groups before and after the double switch. I would appreciate the authors' response based on their vast experience when managing this unique group of patients.

Jeffrey Shuhaiber, MD

Loyola University Stritch School of
Medicine
Maywood, Ill

References

1. Quinn DW, McGuirk SP, Metha C, Nightingale P, de Giovanni JV, Dhillon R, et al. The morphologic left ventricle that requires training by means of pulmonary artery banding before the double-switch procedure for congenitally corrected transposition of the great arteries is at risk of late dysfunction. *J Thorac Cardiovasc Surg*. 2008;135:1137-44.
2. Chiu IS, Wu SJ, Chen SJ, Wang JK, Wu MH, Lue HC. Sequential diagnosis of coronary arterial anatomy in congenitally corrected transposition of the great arteries. *Ann Thorac Surg*. 2003;75:422-9.
3. Angeli E, Raisky O, Bonnet D, Sidi D, Vouhé PR. Late reoperations after neonatal arterial switch operation for transposition of the great arteries. *Eur J Cardiothorac Surg*. 2008;34:32-6. Epub 2008 May 8.
4. Prêtre R, Tamisier D, Bonhoeffer P, Mauriat P, Pouard P, Sidi D, et al. Results of the arterial switch operation in neonates with transposed great arteries. *Lancet*. 2001;357:1826-30.
5. Ilbawi MN, Idriss FS, DeLeon SY, Muster AJ, Gidding SS, Duffy CE, et al. Preparation of the left ventricle for anatomical correction in patients with simple transposition of the great arteries. Surgical guidelines. *J Thorac Cardiovasc Surg*. 1987;94:87-94.
6. Bautista-Hernandez V, Marx GR, Gauvreau K, Mayer JE Jr, Cecchin F, del Nido PJ. Determinants of left ventricular dysfunction after anatomic repair of congenitally corrected transposition of the great arteries. *Ann Thorac Surg*. 2006;82:2059-65.

doi:10.1016/j.jtcvs.2008.07.076

CONTEGRA AND EXTRACARDIAC FONTAN

To the Editor:

We read with great interest the letter to the editor by Sersar and Jamjoom¹ in the *Journal* of November 2008, describing the use of the Contegra (Medtronic Inc, Minneapolis, MN) bovine jugular vein as a possible alternative extracardiac conduit in total cavopulmonary connection (TCPC).

We want to emphasize our bad experience with this particular conduit in patients undergoing the Fontan procedure, which was published in the *Journal* 7 years ago.²

The only 3 patients in whom the Contegra conduit was used for TCPC all experienced serious complications of conduit thrombosis; 2 of them died and 1 survived, but with major neurologic injury. The Contegra implantation was carried out at different institutions by different surgeons.

Evidence has meanwhile accumulated that thrombogenicity is indeed an inherent characteristic of the Contegra bovine jugular venous conduit. Thrombus formation has been shown to occur even in high-flow right ventricular to pulmonary artery conditions.^{3,4}

A fatal case of conduit thrombosis also occurred at the authors' institution. This was published by Baslaim⁵ in 2008 (1 of 18 patients undergoing operation between 2002 and 2005). An "operative technical cause" is suggested by the author as a possible cause.

We are looking forward to the structured clinical and echocardiographic follow-up in their patients. For the present, we continue to discourage the use of the Contegra bovine jugular vein as an extracardiac conduit in TCPC.

Paul Schoof, MD, PhD

Tjalling Waterbolk, MD

Divisions of Cardiothoracic Surgery
University Medical Center Nijmegen
and Groningen
The Netherlands

References

1. Sersar SI, Jamjoom AA. Contegra and extracardiac Fontan. *J Thorac Surg*. 2008;136:1393.