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References

1. Remesar MC, del Pozo AE, Pittis MG, Mangano AM, Sen L, Briones L. Transmission of HTLV-1 by kidney transplant. *Transfusion*. 2000;40:1421.
2. Nakatsuji Y, Sugai F, Watanabe S, Kaido M, Koguchi K, Abe K, et al. HTLV-I-associated myelopathy manifested after renal transplantation. *J Neurol Sci*. 2000;177:154-6.
3. Toro C, Rodés B, Poveda E, Soriano V. Rapid development of subacute myelopathy in three organ transplant recipients after transmission of a human T-cell lymphotropic virus type I from a single donor. *Transplantation*. 2003;75:102-4.
4. Zarranz Imirizaldu JJ, Gomez Esteban JC, Rouco Axpe I, Perez Concha T, Velasco Juanes F, et al. Post-transplantation HTLV-1 myelopathy in three recipients from a single donor. *J Neurol Neurosurg Psychiatry*. 2003;74:1080-4.
5. Date H, Aoe M, Nagahiro I, Sano Y, Andou A, Matsubara H, et al. Living-donor lobar lung transplantation for various lung disease. *J Thorac Cardiovasc Surg*. 2004;126:476-81.

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DOES HYPERCHOLESTEROLEMIA IMPROVE OPERATIVE OUTCOMES IN PATIENTS WITHOUT CORONARY ARTERY DISEASE WHO UNDERGO CARDIAC SURGERY?

To the Editor:

Tabata and colleagues¹ found that preoperative use of statins was associated with lower operative mortality in patients without coronary artery disease who underwent cardiac valve surgery and suggested that the pleiotropic

effects of statins may be an important biological mechanism underlying this beneficial effect.

Although the authors did not include preoperative serum cholesterol levels in the analysis because they were not measured in all patients, they speculated that a beneficial effect of a decreased serum cholesterol might not be ruled out.¹ However, the study suggests that higher baseline cholesterol levels might actually improve operative outcomes in patients without coronary artery disease who undergo cardiac surgery. In fact, baseline total cholesterol levels of statin-treated populations are higher than those of the general population.²

Critical care literature provides strong evidence for a survival advantage associated with higher lipid levels in critically ill surgical patients.³ Furthermore, in surgical patients, hypocholesterolemia, beyond being a strong predictor of in-hospital death, also predicts nosocomial infections and length of hospital stay.⁴ In particular, it has been shown that critically low cholesterol concentrations in patients after cardiothoracic surgery are associated with a significantly increased risk for mortal outcome.⁵

Therefore, we suggest that in individuals studied by Tabata and colleagues,¹ statin use selected the healthy statin user or unselected the unhealthy patients with low cholesterol.

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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 un-

dergo cardiac surgery. *J Thorac Cardiovasc Surg*. 2008;136:1510-3.

2. Thompson R, O'Regan C, Morant S, et al. Measurement of baseline total cholesterol: new data from The Health Improvement Network (THIN) database. *Prim Care Cardiovasc J*. 2008;1:107-11.
3. Gui D, Spada PL, De Gaetano A, Pacelli F. Hypocholesterolemia and risk of death in the critically ill surgical patient. *Intensive Care Med*. 1996;22:790-4.
4. Delgado-Rodríguez M, Medina-Cuadros M, Gómez-Ortega A, et al. Cholesterol and serum albumin levels as predictors of cross infection, death, and length of hospital stay. *Arch Surg*. 2002;137:805-12.
5. Stachon A, Böning A, Weisser H, Laczkovics A, Skipka G, Krieg M. Prognostic significance of low serum cholesterol after cardiothoracic surgery. *Clin Chem*. 2000;46:1114-20.

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Reply to the Editor:

We appreciate the comments from Mascitelli and colleagues. We have shown that preoperative statin use is associated with lower operative mortality in cardiac surgical patients without coronary artery disease.¹ As they pointed out and as we described in the original article,¹ serum cholesterol level could be a potentially confounding factor of the association between preoperative statin use and operative outcomes. However, the effect of baseline hypocholesterolemia on operative outcomes in patients having cardiac surgery remains unknown. The previous studies, including ones that Mascitelli and colleagues referenced, did not reveal an effect. In another study, Horwich and colleagues² have shown that lower serum cholesterol level at the time of admission is associated with increased mortality in patients with heart failure, and that patients with lower serum cholesterol levels were more likely to be on lipid-lowering medication. Although the study population of this study is not patients having surgery, their findings indicate that serum cholesterol level may be a negative confounding factor in our analysis, which would not affect our conclusion. Further investigation is necessary to determine the effect of preoperative statins on operative outcomes in cardiac surgery.

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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.

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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.

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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