data are required to support its practice.

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IN DISTANT ORGAN ISCHEMIA-REPERFUSION MODEL, WHICH ORGAN'S ISCHEMIA WILL YIELD MORE INJURY?

To the Editor:

We sincerely appreciate the authors of this study.¹ In recent published data, ischemia-reperfusion models have been very popular and widely studied. Especially in these experimental studies, one can create ischemia and examine the very same tissue or examine a distant organ apart from the ischemic one. The basic idea in the distant organ ischemia-reperfusion studies has been that reperfusion has its own systemic effects. Many examples for this type of study have been published. The investigators have sometimes examined distant organs such as the brain and lungs after ischemia of a lower extremity,^{2,3} and sometimes they have examined the lungs after ischemia of mesenteric organs.^{4,5} At this point, we would ask, which organ's ischemia will yield more injury in distant tissues or organs? Another question that should be asked is what type of factors

can play a role—the mass of the ischemic tissue; the perfusion rate; or the distance between the 2 organs or tissues. We would deeply appreciate it if the authors could share their opinions on the matter.

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Reply to the Editor:

We thank Gokalp and colleagues for their interest in our study.¹ By comparing myocardial ischemia-reperfusion injury of patients at different altitude, we found that patients living at a high altitude with congenital heart disease resisted ischemia-reperfusion injury during

cardiac surgery better than did those living at a low altitude. We proposed that the effect of increased tolerance to myocardial ischemia was possibly achieved through elevated basal autophagy induced by chronic hypoxia, which may be different from preconditioning with acute intermittent ischemia or hypoxia.

Acute ischemic preconditioning and chronic hypoxia can protect organs from the ensuing ischemia, whereas ischemia itself produces both local and remote injury.² With respect to the remote organ damage induced by ischemia, there are two common classic models: ischemia of extremity^{3,4} and ischemia of mesenteric organs.^{5,6} The distant crucial organs in which reperfusion injury occurs include the lungs, kidneys, brain, and heart. Although the lungs are regarded as the most vulnerable remote organ injured after intestinal or extremity ischemia and reperfusion, it seems that few studies have compared injuries to distant tissues and organs induced by ischemic insult to different organs.

Relative to ischemia of the extremities, ischemia of mesenteric organs is more critical problem in a sense. In addition to the release of inflammatory mediators from ischemic tissue (such as complement, histamine, interleukin, oxygen free radicals, platelet activating factor, thromboxane, tumor necrosis factor, and so on), ischemia and reperfusion of mesenteric organs may cause gut barrier disruption and endotoxin entry into the circulation, leading to severe systemic inflammation and eventually multiple organ failure.⁷ No matter in which organ, the severity of local and remote injury induced by ischemia and reperfusion certainly depends on the mass and duration of the ischemia. The distance of the two organs or tissues seems to have little impact.

We are grateful for the opportunity to discuss these important issues with you, and we look forward to

further advances in ischemia–reperfusion injury.

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A LIPID NANOEMULSION CARRYING PACLITAXEL IMPROVES THE GENE EXPRESSION OF INFLAMMATORY FACTORS OF HEART GRAFTS IN RABBITS

To the Editor:

In a study by Lourenço-Filho and colleagues,¹ the effects of a paclitaxel derivative—paclitaxel oleate—carried in a lipid nanoemulsion (LDE) was

tested in rabbits undergoing heterotopic heart transplantation.² The preparation was administered intravenously and was shown to concentrate in the grafted hearts and have the ability to strongly ameliorate damage to the grafted tissue. In fact, the treatment (4 mg/kg body weight paclitaxel once a week for 6 weeks) reduced by 50% the degree of coronary stenosis of the grafted hearts consequent to a marked reduction in the width of the arterial intima, and reduced 7-fold the macrophage infiltration. Those results were achieved with minimal observable toxicity and may herald a new therapeutic landmark in the medical management of the posttransplantation period and of cardiac allograft disease.

Here, we report messenger RNA-level analysis data from the tissue of grafted and native hearts. We selected genes related to membrane receptors and inflammatory markers that support the outcome of the treatment tested in that study.

In recipient animals that were not treated with LDE-paclitaxel oleate most of the grafted cardiac tissue was necrotic, so the amount of tissue available for RNA extraction was scarce. As a result we processed tissue pools instead of individual heart samples.

Total RNA was isolated from tissues using Trizol Reagent (Invitrogen, Carlsbad, Calif). After RNA quantification in a Nanodrop2000 Spectrophotometer (Thermo Fisher, Woburn, Mass), 1 µg total RNA of each pool was reverse-transcribed using High Capacity RNA-to-cDNA Master Mix (Applied Biosystems, Foster City, Calif). Polymerase chain reactions were performed in duplicate using the StepOnePlus Real-Time PCR System (Applied Biosystems) and the TaqMan detection system. Relative messenger RNA expression of target genes was normalized to the endogenous *GAPDH* gene. The equation $2^{-\Delta\Delta C_t}$ recommended by Livak and colleagues³ was applied to calculate the relative expression of target genes

comparing the mean of the pool of grafted hearts from the control and LDE-paclitaxel groups versus the mean of the pool of control native hearts. Thus, the comparisons described below on gene expression data of the grafted hearts of both LDE-paclitaxel and nontreated control groups refer to the native hearts of the nontreated group.

In this setting, the gene expression of all lipoprotein cell receptors (low-density lipoprotein receptor [*LDLR*], *LDLR*-related protein 1, and cluster of differentiation 36), all proinflammatory (tumor necrosis factor- α , interleukin-1 β , interleukin-18, monocyte chemoattractant protein-1, vascular cell adhesion molecule-1, matrix metalloproteinase-9, and matrix metalloproteinase-12) and anti-inflammatory (interleukin-10) factors were remarkably upregulated in the heart grafts of the nontreated animals compared with the native hearts. The increase was in the order of 2- to 50-fold for the lipoprotein receptors, which furnishes a strong drug-targeting mechanism for LDE-paclitaxel to concentrate in the grafted heart. The data related to the inflammatory factors in the graft denote a remarkably intense process that could have accounted for the pronouncedly damaged grafts of the nontreated animals, as described in the study by Lourenço-Filho et al.¹ The effects of the LDE-paclitaxel treatment were remarkable, pronouncedly reducing the gene expression of the inflammatory factors (Table 1), which can account for the promising results of this treatment.

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