In regard to the use of concomitant dual antiplatelet therapy, we analyzed the effects of clopidogrel in addition to aspirin in our randomized study, prevention of Coronary artery bypass occlusion After off-pump procedures (CRYSSA).³ Our results indicated that (1) the antiplatelet effect of aspirin is independent of additional clopidogrel administration; (2) the antiplatelet effect of aspirin is independent of clopidogrel resistance; (3) the antiplatelet effect of clopidogrel is independent of aspirin resistance; (4) aspirin and clopidogrel have an additive effect that extends the efficacy of treatment to a larger number of patients; and (5) aspirin in combination with clopidogrel in patients responsive to both drugs displays a synergistic inhibitory effect that potentiates the antithrombotic efficacy of clopidogrel. As a consequence, because of the wide individual variability of clopidogrel or aspirin response, we are in agreement with Petricevic and colleagues,⁴ who suggested the use of platelet function assay devices for the preoperative quantification of platelet function in patients taking aspirin or clopidogrel. We also believe that a relatively cheap and easy to use point-of-care platelet function test could facilitate the individual approach to patients for each antiplatelet agent. This policy would reduce the risk of adverse ischemic events while awaiting surgery and of perioperative bleeding.

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PREVENTING PLEURAL MESOTHELIOMA IN PATIENTS WITH RECOGNIZABLE ASBESTOS-RELATED PLEURAL PLAQUES

To the Editor:

I note the careful "analysis of surgical morbidity and mortality" in the treatment of malignant pleural mesothelioma, published in the July 2014 issue of the *Journal*.¹

This again lists the postoperative complications in what is eventually a lethal disease.

A very large group of individuals exists, those treated with pleurodesis as young adults for complications of spontaneous pneumothorax, who have reportedly never developed malignant pleural mesothelioma.

Many of these individuals have undoubtedly been exposed to asbestos either before or after pleurodesis.

Consideration must surely be given to the value of pleurodesis in preventing pleural mesothelioma in those with evidence of simple asbestos-related pleural change.

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Reply to the Editor:

Mechanical and chemical pleurodesis has been used to treat pneumothorax and malignant pleural effusion. Although good long-term survival after talc pleurodesis as the primary treatment of some patients with pleural effusion associated with mesothelioma has been reported, we are unaware of any link between pleurodesis and the prevention of this disease.¹ In the past, talc preparations contained asbestos and were thought to cause mesothelioma; however, for decades, medical talc preparations have been asbestos free, and the protective antitumor properties of talc have been suggested in the basic science data. For example, talc has been shown to induce apoptosis in human mesothelioma cells² and to promote an angiostatic environment in the pleural space.³ Although using pleurodesis to prevent pleural mesothelioma in individuals with simple asbestos-related pleural change is an interesting idea, we believe that more preclinical

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