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Reply to the Editor:

Using an in vivo model, we recently demonstrated the superiority of hypocalcemic cardioplegic solutions in protecting the hypoxic neonatal heart. Baker and Olinger have questioned whether these results are transferable to the cyanotic infant, inasmuch as we used a model of acute hypoxia, and chronic cyanosis may allow for the development of compensatory changes. Although this may be a concern, we believe that many similarities exist between the acutely hypoxic animal and the chronically cyanotic infant that make our model of acute hypoxia valid to test cardioplegic solutions. To simulate the chronic adaptive change of erythrocytosis, we gave transfusions to all piglets before hypoxemia. As in the infant with chronic hypoxia, coronary blood flow increases during acute hypoxia to maintain oxygen delivery. This allows ischemia to be avoided, as documented by maintenance of oxygen consumption, lack of lactate production, and preservation of adenosine triphosphate levels. Conversely, the cyanotic infant may become ischemic during periods of stress or exercise, making the chronically hypoxic myocardium more susceptible to a calcium-mediated injury.[1, 2] Although Baker and Olinger also questioned the existence of the reoxygenation injury in cyanotic infants, such injury has been demonstrated even in the absence of aortic clamping.[3, 4] Indeed, the reoxygenation injury after acute hypoxia parallels the findings of several investigators after chronic cyanosis.[5, 6] Furthermore, as we presented at this years' meeting of the Society of Thoracic Surgeons, using the same biochemical test, we[7] have demonstrated that the reoxygenation injury that occurs in cyanotic infants is reproduced by our model of acute hypoxia. Most important, even if an acute hypoxic stress is not exactly like chronic cyanosis in an infant, it allows one to test cardioplegic solutions in stressed neonatal hearts, which we believe is vital, because most infant hearts are not normal at the time of surgery. Baker[8] also recognized the need for including hypoxic (stressed) hearts in studies of myocardial protection and developed his own model of chronic hypoxia by placing newborn rabbits in 9% oxygen from birth. However, the model does not mimic the clinical setting. Unlike cyanotic infants, these animals intermittently become normoxemic, because they are placed in 21% oxygen for every feeding. Since hypoxia and ischemia both subject the tissue to low levels of oxygen, this exposure to frequent intervals of normoxia may be like ischemic preconditioning, in which multiple periods of ischemia followed by reperfusion alter the myocardium, making it more tolerant to subsequent ischemia. This does not happen to infants with cyanosis and may explain why these authors found an increased tolerance to ischemia after hypoxia, whereas others have shown an opposite effect.[9] The authors used an isolated heart preparation perfused by a buffered Krebs solution and documented improvement in myocardial protection by measuring postischemic myocardial flow. As Deng and colleagues[10] recently reported, the use of postischemic myocardial flow measurements in a crystalloid perfused isolated heart preparation is not valid. In addition, as discussed in our manuscript, numerous differences exist between the isolated heart preparation and the intact animal that may affect myocardial protection. Despite these differences, Baker and Olinger, like us, found that low-calcium cardioplegia was superior in preserving hypoxic hearts. Although we recognize the drawbacks to using an acute hypoxic model, cyanotic preparations are usually unattractive because of their high cost and technical difficulty. However, it is important to remember that hypoxia is very common in the clinical setting and may profoundly alter the effect of cardioplegic solutions. Therefore, despite the inherent problems associated with hypoxic models, we believe they are essential if we are to improve myocardial protection in infants with cyanosis.

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