patient requires vasodilatation as well as inotropic support.

2. If an arterial graft is suspected to be in spasm or the patient has symptoms of hypoperfusion syndrome, possibly caused by graft constriction (manifested by low cardiac output, left ventricular failure, rising pulmonary wedge pressure, and hypotension¹), milrinone may be given as a vasodilator in combination with other therapies in an attempt to dilate the possibly constricted graft or coronary artery. It is particularly indicated when other traditional vasodilators such as nitroglycerin have been used and found to be of little help. In this situation, milrinone is probably well indicated because tolerance to nitroglycerin is suspected.

3. When milrinone is used in combination with nitroglycerin, these two vasodilators may have a synergistic vasorelaxant effect. Reduced doses of the vasodilators may be sufficient to obtain the desirable vasorelaxant effect either in bypass grafts or in the systemic (or coronary) circulation.

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12/8/82352

Hyperoxic cardiopulmonary bypass causes reoxygenation injury and lipid peroxidation

To the Editor:

With great interest I read the brief communication "Contribution of Hyperoxia to Lipid Peroxidation in Coronary Artery Operations: Should We Keep a Low Oxygen Tension?" by Hadjinikolaou and colleagues (*J Thorac Cardiovasc Surg* 1997;113:212-3). However, I have to disagree with several of their statements.

First, the comment that "the contribution of hyperoxia to oxygen free radical generation and consequent lipid peroxidation in cardiac operations has to date not been addressed" is wrong. We intensively studied the effect of hyperoxic cardiopulmonary bypass (CPB) on oxygen-derived free radical-induced lipid peroxidation in hypoxic immature hearts^{1-4,6} and in normoxic adult hearts.⁵

Fig. 1. Malondialdehyde (MDA) as a measure of lipid peroxidation from systemic venous blood at the start and end of CPB. The hyperoxic group included 10 patients during coronary artery bypass graft operations in which CPB was conducted in a hyperoxic fashion ($PO_2 = 450$ mm Hg). The normoxic group consisted of 10 patients also undergoing coronary artery bypass graft operations in which CPB was run with reduced oxygen levels (PO_2 150 mm Hg). The groups did not differ in terms of age, sex, severity of disease, contractility, number of grafts, length of CPB, or ischemic time. * $p < 0.05$ versus hyperoxic group (analysis of variance).

The results show that hyperoxic CPB causes reoxygenation damage, leading to lipid peroxidation, reduced antioxidant reserve capacity, creatine kinase release, and impaired postbypass contractility in hypoxic immature hearts.^{1-4,6} Reports by other groups also address the issue.⁷ Additionally, in normoxic adult hearts, hyperoxic CPB causes lipid peroxidation, creatine kinase and lactate dehydrogenase release, and an increase in polymorphonuclear leukocyte elastase.⁵

Second, the authors further state that lipid peroxidation is absent during CPB. Additionally, they did not find a relationship between the degree of hyperoxia and levels of lipid peroxidation. The results of our studies clearly indicate the existence of lipid peroxidation as early as 5 minutes after the start of CPB. We measured conjugated dienes as a marker of lipid peroxidation. Compared with results in control subjects without hypoxia, hyperoxic CPB (oxygen tension [PO_2] = 400 mm Hg) caused a 13-fold increase in myocardial conjugated diene production during cardioplegic induction (5 minutes after the start of CPB) in hypoxic immature hearts.^{2,3} Reduction of PO_2 during CPB to normoxic levels (100 mm Hg) resulted in significantly (73%) lower production of myocardial conjugated dienes.^{2,3}

Furthermore, for the first time, we described a new

method of "controlled reoxygenation," in which CPB is started with ambient Po_2 (30 mm Hg) and normoxic reoxygenation is begun at the time of cardioplegic arrest.⁴ Applying this method, we were able to avoid biochemical evidence of reoxygenation injury and to present almost complete functional recovery in previously hypoxic hearts.⁴

In normoxic adult hearts we demonstrated a beneficial effect in terms of enzyme release, polymorphonuclear leukocyte elastase production, and especially lipid peroxidation, by lowering oxygen levels (150 mm Hg) in the extracorporeal circuit⁵ (Fig. 1).

We were also able to show that treatment with oxygen-derived free radical scavengers can limit reoxygenation injury and avoid lipid peroxidation during CPB.⁶ I therefore partly agree with the authors, although we found convincing evidence that reduced Po_2 during CPB is more important and is indeed absolutely vital. Hyperoxia is not physiologic, it is damaging to all organs, and above all it is absolutely not necessary. I truly believe that within 5 to 10 years, CPB in hypoxic immature hearts, as well as in normoxic adult hearts, will be instituted only in a normoxic fashion to avoid oxygenation damage and lipid peroxidation.

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Reply to the Editor:

We studied lipid peroxidation in adult patients undergoing cardiopulmonary bypass (CPB) for routine coronary artery bypass grafting (CABG). Assumptions about lipid peroxidation based on observations in immature piglets and cyanotic children with tetralogy of Fallot¹ may not be reliably transferred to adult human beings. During CPB, lipid peroxidation may well vary in different settings. Morita,² Ihnken,³ and their associates measured conjugated dienes and malondialdehyde as markers of lipid peroxidation in the myocardium of immature piglets and found a significant increase 5 minutes after the start of CPB. However, Davies and coworkers⁴ measured lipid peroxidation in the coronary sinus in adult patients undergoing routine CABG and found no significant changes during CPB. The only related study seems to be an abstract reporting the results of a comparison between hyperoxic (Po_2 400 mm Hg) and normoxic (Po_2 150 mm Hg) CPB in 20 adult patients (63 ± 8 years) undergoing CABG.⁵ Unfortunately, several questions arise from this report. Apart from being a very small study, the number of patients in each of the two groups was not stated. Crossclamp times and CPB times between the two groups were not compared, although their significance in lipid peroxidation is beyond question. Longer ischemic damage in the normoxic group might well have resulted in higher creatine kinase and malondialdehyde levels. Therefore our comment that "the contribution of hyperoxia to free radical generation and consequent lipid peroxidation in adult cardiac operations has to date not been addressed" should not be dismissed lightly.

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