Vander Heide and Reimer [1] recently attempted to evaluate the existence of myocardial reperfusion injury in the open-chest canine model of regional ischemia. Intravenous adenosine was infused for 155 min commencing just before reperfusion utilizing the identical dose reported by Pitarys et al. [2], who showed a marked cardioprotective effect of this agent following 72 h of reperfusion. In addition to a control group, two treatment groups were evaluated in which intravenous adenosine was infused with or without bolus doses of lidocaine given prior to occlusion and reperfusion. Each treatment group failed to demonstrate a reduction in infarct size measured histochemically 3 h after reperfusion, findings in sharp contrast to the study of Pitarys et al. [2] in the closed-chest model.

There are a number of differences between the Vander Heide and Reimer study and previous studies from our laboratory [2–4] that make comparative analysis fraught with difficulty. Review of hemodynamic data in Table 2 from the Vander Heide and Reimer study show that all three groups were tachycardic and were markedly hypertensive, especially the animals in the adenosine plus lidocaine group that had a basal systolic blood pressure of 194 mmHg and a basal heart rate of 174 beats/min. This setting would result in high myocardial oxygen consumption, thereby increasing the endogenous levels of adenosine prior to the ischemic episode [5,6]. This problem is best illustrated by comparing the basal rate × pressure product (RPP) in the groups that received adenosine plus lidocaine. In the study of Pitarys et al. basal RPP was 19.1, whereas in the Vander Heide and Reimer study basal RPP was 34.2—i.e., nearly two-fold elevated in the latter study. Moreover, the Vander Heide and Reimer study did not report whether adenosine affected heart rate and blood pressure following reperfusion.

In the Vander Heide and Reimer study, intravenous adenosine did not increase transmural blood flow measured 35 min after reperfusion. This is in marked contrast to the Pitarys et al. study in which an identical dose of adenosine in the closed chest model increased transmural blood flow three-fold. This suggests that in the Vander Heide and Reimer study either the infused adenosine was pharmacologically inactive at the time of administration or that markedly elevated myocardial oxygen consumption in the animals negated any further effect of exogenous administered adenosine. Numerous studies have demonstrated that reperfusion results in functional and structural changes in the microvasculature resulting in a progressive decrease in blood flow to the reperfused myocardium [7]. Previous studies have demonstrated that adenosine ameliorates these vascular changes, thereby maintaining blood flow in the microvasculature [8]. The absence of a vasodilatory effect of adenosine in the Vander Heide and Reimer study may partially account for the inability of adenosine to enhance myocardial salvage after reperfusion.

The utilization of an open-chest canine model in the Vander Heide and Reimer study is less physiological than the closed-chest model used in the Pitarys et al. study for a number of reasons. Surgical trauma may result in neutrophil activation prior to the onset of myocardial ischemia. Neutrophil activation has been shown in numerous studies to play an important role in the pathogenesis of myocardial reperfusion injury [9]. Adenosine inhibits neutrophil adhesion to endothelial cells and reduces superoxide anion production [10]. In vivo studies have demonstrated that adenosine inhibits neutrophil chemotaxis into the reperfused myocardium [8]. Therefore, the failure of the Vander Heide and Reimer study to demonstrate a cardioprotective effect of adenosine may have been due to the fact that neutrophils were activated prior to the onset of myocardial ischemia. Suspension of the heart in a pericardial cradle in the current study would also result in intense sympathetic activation. Adenosine is known to have anti-
adrenergic effects through its A<sub>1</sub> receptor by decreasing norepinephrine release [11]. Therefore, the potential anti-adrenergic effects of adenosine may have been partially negated in this study.

Infarct size in the Vander Heide and Reimer was measured 3 h after reperfusion. It is plausible that the failure of adenosine to increase salvage in this study may be related to the fact that reperfusion injury may not be fully evolved after a short period of reperfusion. Previous studies showing infarct size reduction with adenosine have utilized reperfusion periods of 24 to 72 h [2–4]. As mentioned by the authors, it is essential that the major determinants of infarct size in the canine model, namely risk region and collateral blood flow, are determined. Comparison of these variables with the study of Pitarys et al. showed that the major determinants of infarct size were comparable. Therefore, it is unlikely that differences in determinants of infarct size could account for the varying results.

In summary, the numerous methodological problems discussed above make interpretation of the data problematic. In our view, the Vander Heide and Reimer study does not definitively refute previous observations that adenosine may ameliorate reperfusion injury in the experimental model of regional ischemia.

References


