

## Cardioprotective Effects of Propofol and Sevoflurane in Ischemic and Reperfused Rat Hearts

### Role of $K_{ATP}$ Channels and Interaction with the Sodium-Hydrogen Exchange Inhibitor HOE 642 (Cariporide)

Sanjiv Mathur, M.D.,\* Parviz Farhangkhgoee, D.V.M.,† Morris Karmazyn, Ph.D.‡

**Background:** Sodium ion-hydrogen ion ( $Na^+H^+$ ) exchange inhibitors are effective cardioprotective agents. The  $Na^+H^+$  exchange inhibitor HOE 642 (cariporide) has undergone clinical trials in acute coronary syndromes, including bypass surgery. Propofol and sevoflurane are also cardioprotective *via* unknown mechanisms. The authors investigated the interaction between propofol and HOE 642 in the ischemic reperfused rat heart and studied the role of adenosine triphosphate-sensitive potassium ( $K_{ATP}$ ) channels in the myocardial protection associated with propofol and sevoflurane.

**Methods:** Isolated rat hearts were perfused by the Langendorff method at a constant flow rate, and left ventricular function and coronary pressures were assessed using standard methods. Energy metabolites were also determined. To assess the role of  $K_{ATP}$  channels, hearts were pretreated with the  $K_{ATP}$  blocker glyburide (10  $\mu M$ ). Hearts were then exposed to either control buffer or buffer containing HOE 642 (5  $\mu M$ ), propofol (35  $\mu M$ ), sevoflurane (2.15 vol%), the  $K_{ATP}$  opener pinacidil (1  $\mu M$ ), or the combination of propofol and HOE 642. Each heart was then subjected to 1 h of global ischemia followed by 1 h of reperfusion.

**Results:** Hearts treated with propofol, sevoflurane, pinacidil, or HOE 642 showed significantly higher recovery of left ventricular developed pressure and reduced end-diastolic pressures compared with controls. The combination of propofol and HOE 642 provided superior protection toward the end of

the reperfusion period. Propofol, sevoflurane, and HOE 642 also attenuated the onset and magnitude of ischemic contracture and preserved high-energy phosphates (HEPs) compared with controls. Glyburide attenuated the cardioprotective effects of sevoflurane and abolished the protection observed with pinacidil. In contrast, glyburide had no effect on the cardioprotection associated with propofol treatment.

**Conclusion:** HOE 642, propofol, and sevoflurane provide cardioprotection *via* different mechanisms. These distinct mechanisms may allow for the additive and superior protection observed with the combination of these anesthetics and HOE 642. (Key words: Anesthetics; cardioprotection; ischemia;  $Na^+H^+$  exchange; reperfusion.)

SODIUM ion-hydrogen ion ( $Na^+H^+$ ) exchange (NHE) inhibitors have been identified as effective cardioprotective agents against myocardial ischemic reperfusion injury in various experimental models.<sup>1-3</sup> The NHE functions to extrude protons after an ischemia-induced intracellular acidosis, resulting in the entry of sodium ions.<sup>4,5</sup> However, the  $Na^+$  influx cannot be effectively removed because of the impaired  $Na^+K^+$  adenosine triphosphatase activity in the ischemic myocardium. It is proposed that the increase in intracellular [ $Na^+$ ] then results in an elevation in intracellular [ $Ca^{2+}$ ] because of increased entry of  $Ca^{2+}$  or decreased removal of intracellular  $Ca^{2+}$  *via* the Na-Ca exchange.<sup>1,3,6</sup> This intracellular  $Ca^{2+}$  overload and metabolic imbalance contributes to cell injury,<sup>6</sup> contracture,<sup>7</sup> and myocardial stunning.<sup>1</sup> HOE 642 (cariporide) is an NHE inhibitor that acts primarily against the isoform-1 subtype (NHE-1), which is the predominant if not sole type found in the myocardium. This agent has recently undergone clinical evaluation (GUARDIAN study [Guard during Ischemia Against Necrosis]) as a potential cardioprotective agent in patients with acute coronary syndromes, including high-risk patients undergoing coronary artery bypass surgery. We recently reported the interaction between HOE 642 and isoflurane, sevoflurane, and sufentanil in the isolated

\* Resident, Department of Anesthesia, University of Western Ontario, London, Ontario, Canada.

† Research Technician, Department of Pharmacology and Toxicology, University of Western Ontario, London, Ontario, Canada.

‡ Professor, Department of Pharmacology and Toxicology, University of Western Ontario, London; and Career Investigator, Heart and Stroke Foundation of Ontario, Toronto, Ontario, Canada.

Received from the Departments of Pharmacology and Toxicology and Anaesthesia, University of Western Ontario, London, Ontario, Canada. Submitted for publication July 15, 1998. Accepted for publication May 7, 1999. Supported by the Medical Research Council of Canada, Ottawa, Ontario, Canada; and the Department of Anaesthesia, University of Western Ontario, London, Ontario, Canada.

Address reprint requests to Dr. Karmazyn: Department of Pharmacology and Toxicology, University of Western Ontario, Medical Sciences Building, London, Ontario, Canada N6A 5C1. Address electronic mail to: mkarm@julian.uwo.ca.

ischemic reperfused rat heart<sup>8</sup>; however, the interaction with propofol has never been reported. This is of importance given the recent documentation of propofol as being cardioprotective against myocardial injury induced by both ischemia-reperfusion<sup>9</sup> and exogenous hydrogen peroxide administration.<sup>10</sup> However, these results contrast those of the study by Coetzee,<sup>11</sup> who reported that propofol failed to provide functional benefit on the reperfused pig myocardium after left anterior descending coronary artery occlusion.

The exact mechanisms of cardioprotection provided by volatile anesthetics and propofol are not fully understood; however, recent literature has identified a role for the adenosine triphosphate-sensitive potassium ( $K_{ATP}$ ) channel in isoflurane-induced myocardial protection.<sup>12,13</sup> Indeed, activation of  $K_{ATP}$  channels with agents such as pinacidil has been proposed as a potentially effective pharmacologic approach toward myocardial protection.<sup>14,15</sup> The role of the  $K_{ATP}$  channel in cardioprotection with sevoflurane and propofol has not been studied. Therefore, the purpose of the present study was to determine the functional and metabolic effects of propofol on the ischemic reperfused rat heart in the presence or absence of HOE 642 and to assess the role of the  $K_{ATP}$  channel in the cardioprotection afforded by sevoflurane and propofol.

## Materials and Methods

### Animals

Male Sprague Dawley rats (250–300 g) were purchased from Charles-River Canada Ltd (St Constant, Quebec, Canada) or Harland Sprague-Dawley Inc (Indianapolis, IN). The animals were maintained in the Health Sciences Animal Care Facility of the University of Western Ontario in accordance with the guidelines of the Canadian Council on Animal Care (Ottawa, Ontario, Canada).

### Heart Perfusion

Rats were killed by decapitation, and the hearts were immediately excised and placed in cold Krebs-Henseleit buffer to stop contractions. Hearts were gently squeezed to remove any blood to prevent clotting. The hearts were picked up by the aorta and prepared for retrograde perfusion using a modified Langendorff method at a constant flow rate of 10 ml/min using a peristaltic pump. The perfusion fluid (pH 7.4; temperature, 37°C) was Krebs-Henseleit buffer that contained 120 mM NaCl, 4.63

mM KCl, 1.17 mM  $KH_2PO_4$ , 1.25 mM  $CaCl_2$ , 1.2 mM  $MgCl_2$ , 20 mM  $NaHCO_3$ , and 8 mM glucose. The buffer was vigorously gassed with 95%  $O_2$ /5%  $CO_2$  before drug addition. Coronary pressure was measured *via* a side arm of the perfusion cannula connected to a pressure transducer (Spectramed P23XL, Oxnard, CA). A latex water-filled balloon fixed to a pressure transducer was inserted through the mitral valve into the left ventricle for the determination of left ventricular developed pressure. Rates of pressure development and relaxation (positive and negative dP/dt, respectively) were calculated with a differentiator. Left ventricular end-diastolic pressure was adjusted to approximately 5 mmHg before the start of the experiment by adjusting the volume in the intraventricular balloon with the aid of a micrometer-equipped syringe. Hearts were electrically paced at a rate of 325 beats/min with a stimulator. Pacing was also maintained during the ischemic period. All determinations of ventricular and coronary pressures were obtained on-line on a Pentium 586 computer using a Biopac data analysis system (Biolynx Scientific Equipment, Montreal, Quebec, Canada).

### Experimental Protocol

Hearts were initially equilibrated for 15 min, after which either glyburide (10  $\mu M$ ) or its drug vehicle dimethyl sulfoxide (100  $\mu l$  in 1.2 l perfusate) was added for an additional 5 min. Hearts were then exposed to either propofol (6.2  $\mu g/ml$  [35  $\mu M$ ]), sevoflurane (delivery and concentration discussed in the following section), pinacidil (1  $\mu M$ ), HOE 642 (5  $\mu M$ ), propofol in combination with HOE 642, or control buffer for an additional 15 min. The glyburide or vehicle was present during this 15 min of drug treatment. Control hearts were perfused with vehicle-containing buffer for 20 min after the 15-min equilibration period. Six hearts were studied in each of the experimental groups.

At the end of the 15-min drug-treatment period, hearts were rendered globally ischemic by stopping the flow for 60 min (zero-flow ischemia), after which reperfusion at the normal flow rate was initiated for an additional 60 min. Recording of left ventricular end-diastolic pressure was taken during the 1-h ischemia. The respective drug treatment was maintained throughout the reperfusion period.

### Anesthetic Delivery and Determination of Concentrations

Sevoflurane was injected directly into sealed 4-l glass bottles, each containing 1 l of preoxygenated perfusate

## CARDIOPROTECTIVE EFFECTS OF PROPOFOL AND SEVOFLURANE

**Table 1. Baseline Values of Left Ventricular Developed Pressure (mmHg)**

|           | Cont        | Sevo        | Ppf         | HOE 642     | Ppf+ HOE    | Glyb        | Glyb+ Sevo | Glyb+ Ppf   |
|-----------|-------------|-------------|-------------|-------------|-------------|-------------|------------|-------------|
| BL1       | 62.4 ± 22.0 | 57.7 ± 12.2 | 57.5 ± 21.8 | 58.0 ± 13.7 | 52.5 ± 6.9  | 59.3 ± 18.6 | 56.5 ± 9.1 | 58.5 ± 19.1 |
| BL2       | 61.1 ± 21.1 | 55.1 ± 10.0 | 59.9 ± 23.0 | 55.9 ± 13.5 | 51.4 ± 5.9  | 58.8 ± 20.8 | 57.5 ± 9.8 | 54.5 ± 16.9 |
| % change1 | -2.08       | -4.51       | +4.26       | -3.62       | -2.03       | -0.84       | +1.77      | -6.89       |
| BL3       | 65.6 ± 22.3 | 48.9 ± 4.9  | 43.6 ± 13.7 | 53.4 ± 10.5 | 34.7* ± 8.6 | 59.2 ± 17.6 | 51.4 ± 8.1 | 46.5 ± 10.5 |
| % change2 | 7.37        | -11.3       | -27.3       | -4.47       | -32.6       | +0.68       | -10.6      | -14.8       |

Values are mean ± SD (n = 6 for each group). There were no significant differences in BL1, BL2, or % change1 between the groups. Left ventricular end-diastolic remained at 5 mmHg at BL1, BL2, and BL3 in all groups.

BL1 = baseline left ventricular pressure development after 15 min equilibration period with no drugs present; BL2 = baseline left ventricular pressure development after 5 min exposure to glyburide or drug vehicle DMSO; BL3 = baseline left ventricular pressure development after 15 min exposure to the drugs indicated and just prior to ischemia; % change1 = the effect of drug vehicle or glyburide; % change2 = the effect of the drug treatment in the presence of vehicle or glyburide; Cont = controls; Sevo = sevoflurane; Ppf = propofol; Glyb = glyburide; HOE = HOE 642.

\*P < 0.05 versus BL1 and BL2 within the group and versus BL3 of controls.

(pH 7.39 ± 0.02, carbon dioxide partial pressure 30 ± 5 mmHg, and oxygen partial pressure 818 ± 31 mmHg) as described by Boban *et al.*<sup>16</sup> A gas-tight syringe equipped with a gas-tight stainless steel valve (Hamilton 1000 series syringe, Hamilton GTS valve H86560; VWR, Mississauga, Ontario, Canada) was used for aspiration and injection of the volatile anesthetic. Specific volumes of sevoflurane were injected immediately into the designated sealed glass bottle using a double stopcock system to avoid leakage and volatilization of the anesthetics before and during injection. The sealed perfusate was stirred continuously to facilitate equilibration of the volatile anesthetics between the liquid and gas phases.

To ensure that sevoflurane concentrations were maintained throughout the complete perfusion period, samples of perfusate were collected at the aortic outlet just before ischemia and 60 min after reperfusion for determination of anesthetic concentrations by gas chromatography using a Varian 3300 gas chromatograph (Mississauga, Ontario, Canada) equipped with a J+W Scientific DB-1 High Resolution Gas Chromatography Column (VWR). Effective volume percent concentrations were calculated as 2.15 vol% for sevoflurane (0.304 mm) before ischemia and 2.14 vol% (0.303 mm) at the end of reperfusion using Krebs-Ringer's solution/gas partition coefficients of 0.36 for sevoflurane at 37°C and 1 atm as described previously.<sup>8</sup>

#### Metabolite Assays

At the end of the reperfusion period, hearts were clamped with Wollenberger tongs precooled in liquid nitrogen, removed from the cannula, and stored in liquid nitrogen until enzymatic determination for energy metabolites, as previously described.<sup>17</sup> Studies were also conducted to determine basal HEP levels before ischemia after the addition of various drug combinations.

#### Data Analysis

All values are given as mean ± SD. One-way analysis of variance and Tukey's post-test for multiple comparisons were used to determine the effects of glyburide, vehicle, propofol, sevoflurane, and HOE 642 on ischemic contracture and metabolite content. Repeated-measures analysis of variance and Tukey's post-test were used to compare the effects on hemodynamic function at each baseline (BL) period and each time interval during post-ischemic reperfusion. Differences were considered significant at P < 0.05.

## Results

#### Basal Hemodynamic Function

Table 1 shows no significant differences among the experimental groups with respect to BL left ventricular developed pressure after the initial 15-min equilibration period (BL1). In addition, BL2 shows there was no significant effect of vehicle nor glyburide exposure in any of the groups. BL3 represents the effect of the vehicle or glyburide in the presence of either control buffer, sevoflurane, propofol, or the combination of propofol with HOE 642. Propofol treatment resulted in a 27.3% reduction in left ventricular developed pressure, although this did not reach statistical significance from BL1 or BL2. The combination of propofol and HOE 642 resulted in a 32.6% reduction in left ventricular developed pressure that was significantly lower than that for BL1 and BL2. BL3 for propofol plus HOE 642 was significantly less than the BL3 for controls and glyburide groups; however, there was no further significant differences in the values of BL3 between the remaining groups.

The effect of the drugs on the baseline values of left

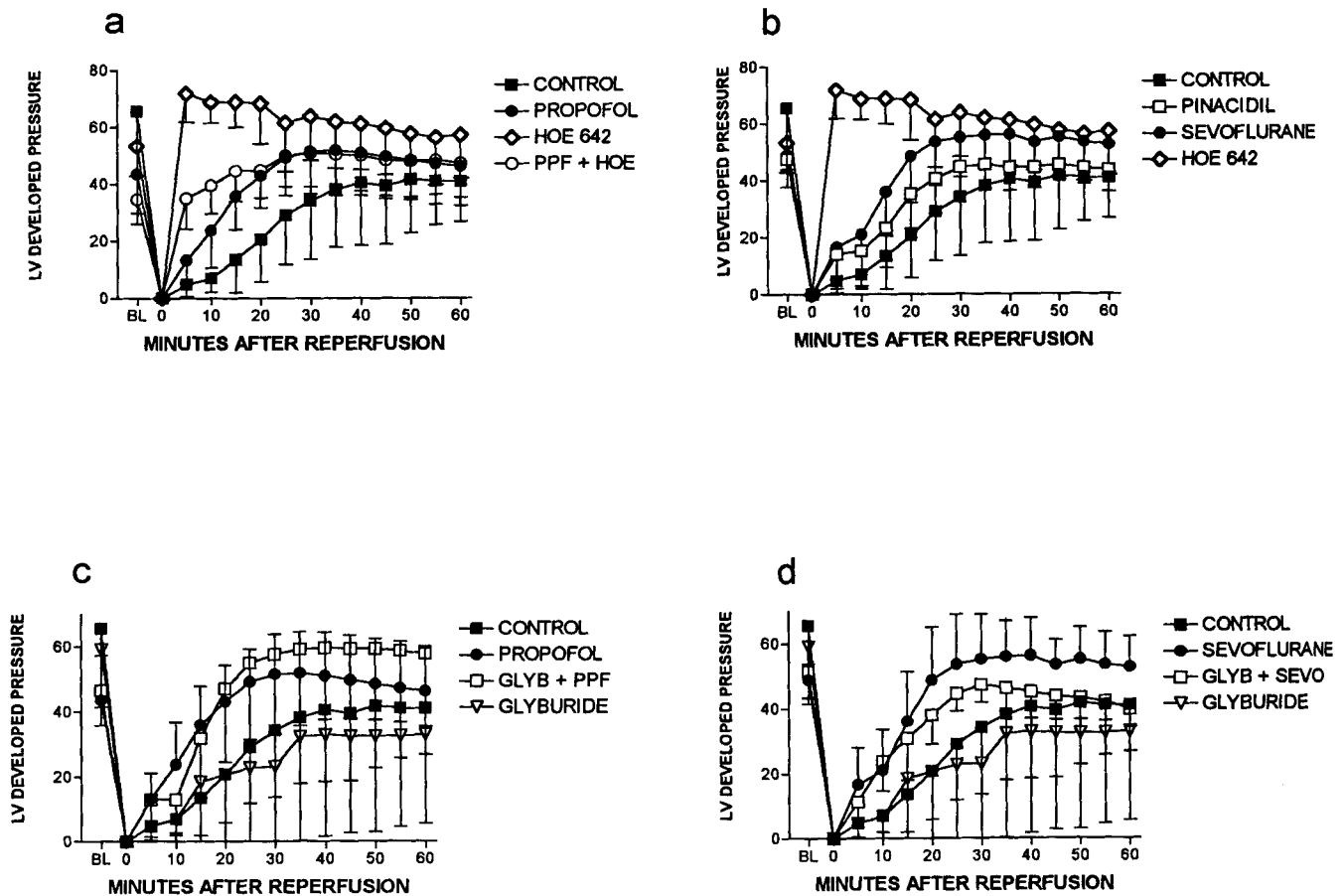


Fig. 1. (A-D) The recovery of left ventricular developed pressure (mmHg) during reperfusion compared with baseline (BL) preischemic values (BL3 in table 1) for each drug. Drugs were present for 15 min before ischemia and throughout the reperfusion period. Values are mean  $\pm$  SD and  $n = 6$  for all groups.

ventricular pressure development (+dP/dt) and left ventricular relaxation (-dP/dt) paralleled the responses observed with left ventricular developed pressure (data not shown). The left ventricular end-diastolic pressure was initially set at 5 mmHg and was unaffected by any of the drug exposures (data not shown).

Sevoflurane and propofol treatment resulted in a reduction in coronary perfusion pressure (9.5% and 28.3%, respectively); however, there was no significant difference between the groups in the value of the coronary perfusion pressure during the preischemic period (data not shown).

#### *Functional Response to 60 min of Ischemia followed by 60 min of Reperfusion*

Figure 1 depicts the recovery of left ventricular developed pressure during reperfusion. The BL values shown are BL3 from table 1 and represent the value of left

ventricular developed pressure after 15-min exposure to the agents noted, which were present during the entire reperfusion period. The BL values (BL3 in table 1) were reduced in the hearts exposed to propofol, sevoflurane, and propofol plus HOE 642, making interpretation of recovery difficult. To normalize the data, we calculated the recovery of left ventricular developed pressure as a percentage of the BL value obtained just before ischemia (BL3) for each individual heart. Thus, the recovery of left ventricular developed pressure function in figures 2-5 is in the presence of ongoing effect of the agents. The left ventricular end-diastolic pressure was 5 mmHg for all groups just before ischemia; therefore, the recovery of end-diastolic pressure was not normalized, and it is presented as the actual values recorded in figures 2-5.

The effect of propofol and HOE 642 on recovery of left ventricular developed pressure and elevation in left ventricular end-diastolic pressure is presented in figure 2.

## CARDIOPROTECTIVE EFFECTS OF PROPOFOL AND SEVOFLURANE

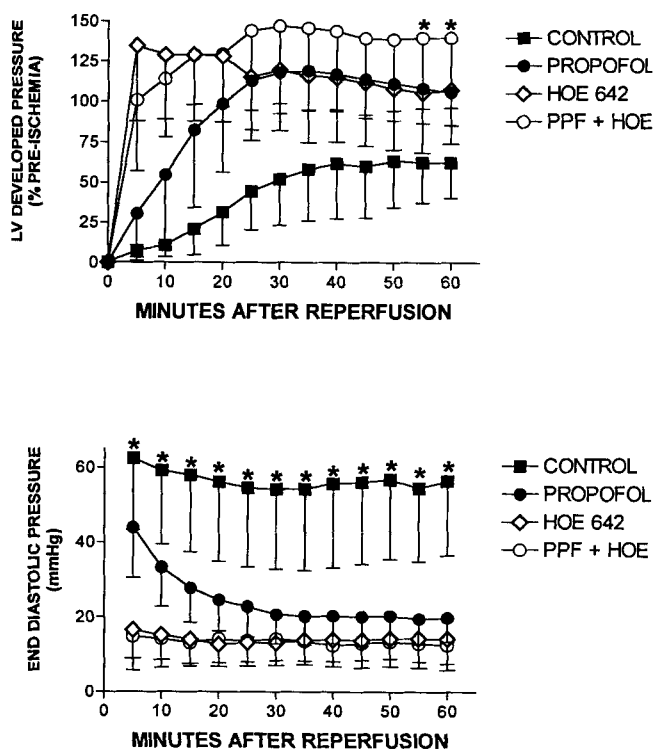


Fig. 2. Effects of propofol (PPF) or HOE 642 alone or in combination on left ventricular developed pressure and left ventricular end-diastolic pressure (EDP) during reperfusion after 60 min of global ischemia in rat hearts. Drugs were present for 15 min before ischemia and throughout the reperfusion period. Values are mean  $\pm$  SD and  $n = 6$  for all groups. (Top) Values depict percentage of preischemic values (BL3 in table 1). Values for HOE 642 alone were significantly greater than for controls at all times during reperfusion and from propofol alone for the first 15 min. Values for the propofol-alone group were significantly higher than those for controls from 10 min until the end of reperfusion. Values for the combination of PPF and HOE 642 were greater than those for all other groups for the final 5 min of reperfusion.  $*P < 0.05$  compared with all other groups. (Bottom) The EDP was set at 5 mmHg before ischemia. Values depict the recorded EDP. Values for HOE 642, PPF, and PPF plus HOE 642 are significantly less than those for controls during the entire reperfusion. For the first 10 min, the groups that received HOE 642 had significantly less increase in EDP than did the PPF group.  $*P < 0.05$  compared with all other groups.

These results show that propofol improved recovery of left ventricular developed pressure compared with control hearts after 10 min of reperfusion until the end of the reperfusion period. Hearts treated with HOE 642 showed significantly greater recovery than controls at all times during reperfusion, as well as hearts treated with propofol alone for the first 15 min. The group that received the combination of propofol and HOE 642 showed a greater recovery than all other groups for the final 5 min of reperfusion. Propofol, HOE 642, and a

combination of these drugs significantly attenuated the increase in left ventricular end-diastolic pressure compared with controls during the entire reperfusion period. For the first 10 min of reperfusion, the groups that received HOE 642 had significantly less increase in left ventricular end-diastolic pressure than did the propofol group. Thus, although recovery associated with propofol and HOE 642 was identical at 60 min of reperfusion, there was clearly a different profile because HOE 642

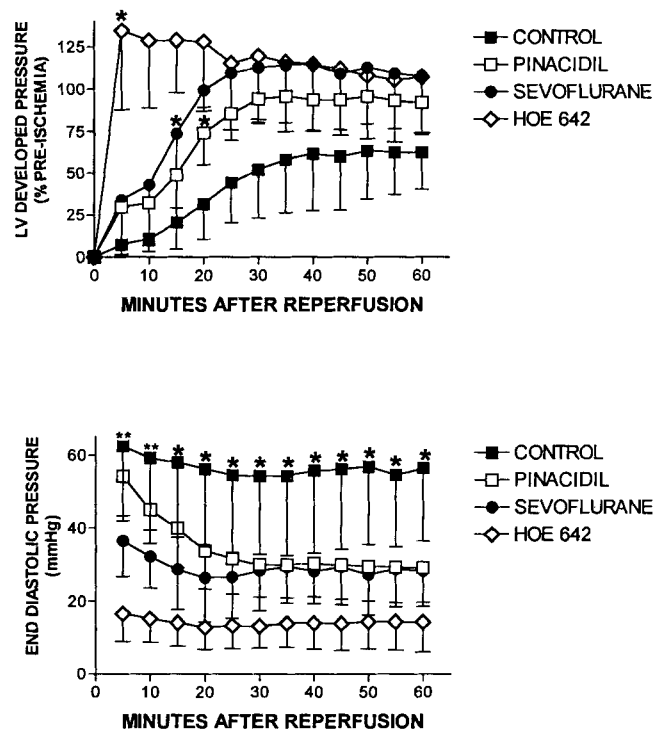


Fig. 3. Effects of pinacidil (PIN; a  $K_{ATP}$  channel agonist), sevoflurane (SEVO), or HOE 642 on left ventricular developed pressure and left ventricular end-diastolic pressure (EDP) during reperfusion after 60 min of global ischemia in rat hearts. Drugs were present for 15 min before ischemia and throughout the reperfusion period. Values are mean  $\pm$  SD and  $n = 6$  for all groups. (Top) Values depict percentage of preischemic values (BL3 in table 1). Values for HOE 642 alone were significantly greater than those for controls at all times during reperfusion, greater than those for SEVO for the first 15 min, and greater than those for PIN for the first 20 min. Values for the SEVO group were significantly higher than those for controls from 15 min until the end of reperfusion. Values for the PIN group were significantly higher than those for controls from 20 min until the end of reperfusion.  $*P < 0.05$  indicates the onset of significance from controls; significance continued from this point until the end of reperfusion. (Bottom) The EDP was set at 5 mmHg before ischemia. Values depict the recorded EDP. Values for HOE and SEVO were significantly less than those for controls during the entire reperfusion. Values for PIN were significantly less than those for controls during the final 50 min of reperfusion.  $*P < 0.05$  compared with all other groups.  $**P < 0.05$  compared with SEVO and HOE 642 groups.

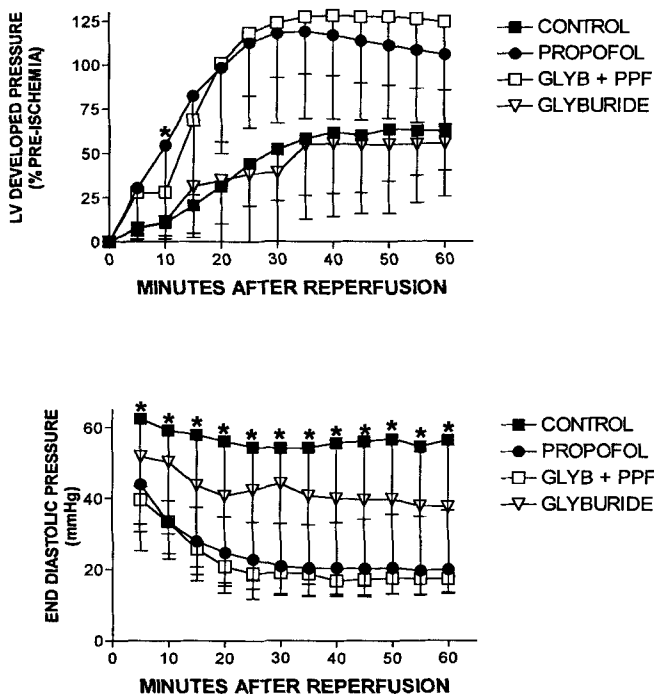


Fig. 4. Effects of propofol (PPF) or glyburide (GLYB) alone or in combination on left ventricular developed pressure and left ventricular end-diastolic pressure (EDP) during reperfusion after 60 min of global ischemia in rat hearts. Drugs were present for 15 min before ischemia and throughout the reperfusion period. Values are mean  $\pm$  SD and n = 6 for all groups. (Top) Values depict percentage of preischemic values (BL3 in table 1). Values for the propofol-alone group were significantly higher than those for controls from 10 min until the end of reperfusion. Values for the GLYB group were not significantly different from those for controls over the whole reperfusion period. Values for the combination of PPF and GLYB were not significantly different from those for the PPF-alone group for the entire reperfusion period. \*P < 0.05 indicates the onset of significance from controls for both PPF and GLYB plus PPF; significance continues from this point until the end of reperfusion. (Bottom) The EDP was set at 5 mmHg before ischemia. Values depict the recorded EDP. Values for PPF and GLYB plus PPF were significantly less than those for controls during the entire reperfusion period. Values for the GLYB group were not significantly different from those for controls. \*P < 0.05 compared with PPF and GLYB plus PPF.

provided a dramatic recovery of left ventricular developed pressure (preischemic value, 134.6%) as early as 5 min compared with the delay in recovery associated with propofol. In addition, propofol did not attenuate the increase in left ventricular end-diastolic pressure to the same degree as HOE 642 for the initial 10 min of reperfusion.

Figure 3 demonstrates the effect of  $K_{ATP}$  channel opener pinacidil, HOE 642, or sevoflurane on recovery of left ventricular developed pressure and elevation in

left ventricular end-diastolic pressure. The left ventricular developed pressure in the sevoflurane group was significantly greater than in controls from 15 min until the end of reperfusion. The left ventricular developed pressure in the pinacidil group was significantly higher than in controls from 20 min until the end of reperfusion. Neither pinacidil nor sevoflurane demonstrated the rapid recovery of left ventricular developed pressure as provided by HOE 642. With respect to left ventricular end-diastolic pressure, groups treated with HOE 642 and sevoflurane significantly attenuated the elevation of left ventricular end-diastolic pressure compared with con-

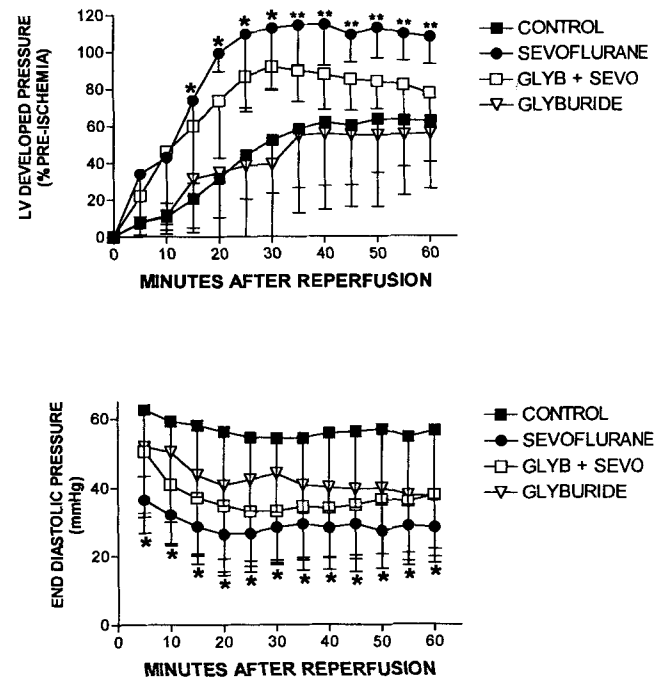


Fig. 5. Effects of sevoflurane (SEVO) or glyburide (GLYB) alone or in combination on left ventricular developed pressure and left ventricular end-diastolic pressure (EDP) during reperfusion after 60 min of global ischemia in rat hearts. Drugs were present for 15 min before ischemia and throughout the reperfusion period. Values are mean  $\pm$  SD and n = 6 for all groups. (Top) Values depict percentage of preischemic values (BL3 in table 1). Values for the SEVO-alone group were significantly higher than those for controls from 15 min until the end of reperfusion. Values for the GLYB group were not significantly different from those for controls over the whole reperfusion period. Values for the combination of SEVO and GLYB were significantly less than those for the SEVO group for the final 25 min of reperfusion and were not statistically different from those for controls or the GLYB group over this period. \*P < 0.05 compared with controls. \*\*P < 0.05 compared with all other groups. (Bottom) The EDP was set at 5 mmHg before ischemia. Values depict the recorded EDP. Only values for the SEVO group were significantly less than those for controls during the entire reperfusion period. \*P < 0.05 compared with controls.

## CARDIOPROTECTIVE EFFECTS OF PROPOFOL AND SEVOFLURANE

**Table 2. Rates of Left Ventricular Pressure Development (+dP/dt) and Left Ventricular Relaxation (-dP/dt) during Reperfusion (5, 30, and 60 min)**

|                            | +dP/dt (mmHg/s) |                |                | -dP/dt (mmHg/s) |                |                |
|----------------------------|-----------------|----------------|----------------|-----------------|----------------|----------------|
|                            | 5 min           | 30 min         | 60 min         | 5 min           | 30 min         | 60 min         |
| Controls                   | 39.1 ± 36.7     | 335.1 ± 223.4  | 333.1 ± 225.1  | 35.7 ± 26.5     | 327.7 ± 201.6  | 341.2 ± 204.8  |
| % preischemia              | 5.8             | 49.7           | 49.4           | 5.3             | 48.6           | 50.6           |
| Sevoflurane                | 340.2 ± 301.9   | 1167.9 ± 306.6 | 1160.7 ± 168.2 | 330.7 ± 300.0   | 1106.1 ± 351.5 | 1045.7 ± 158.5 |
| % preischemia              | 33.0            | 113.3*         | 112.6*         | 34.5            | 115.4*         | 109.1*         |
| Propofol                   | 298.7 ± 244.0   | 1222.3 ± 253.3 | 1135.5 ± 210.9 | 252.9 ± 214.4   | 1115.1 ± 224.9 | 1021.0 ± 195.4 |
| % preischemia              | 28.2            | 115.4*         | 107.2*         | 26.9            | 118.6*         | 108.6*         |
| HOE 642                    | 1345.7 ± 392.4  | 1277.0 ± 371.9 | 1154.8 ± 298.3 | 1219.0 ± 347.0  | 1154.8 ± 289.4 | 1043.6 ± 291.4 |
| % preischemia              | 131.1*          | 124.4*         | 112.5*         | 127.2*          | 120.5*         | 108.9*         |
| Propofol +<br>HOE 642      | 1087.8 ± 432.7  | 1569.4 ± 399.4 | 1461.0 ± 235.5 | 957.2 ± 420.2   | 1482.2 ± 457.7 | 1377.4 ± 205.7 |
| % preischemia              | 102.3*          | 147.6*         | 137.4*         | 96.8*           | 149.9*         | 139.3*         |
| Glyburide +<br>sevoflurane | 167.6 ± 175.5   | 692.3 ± 109.7  | 591.9 ± 119.9  | 153.6 ± 168.6   | 652.9 ± 101.8  | 549.0 ± 112.9  |
| % preischemia              | 22.2            | 91.7*          | 78.4           | 21.6            | 91.8*          | 77.2           |
| Glyburide +<br>propofol    | 363.2 ± 224.8   | 1625.7 ± 863.1 | 1641.7 ± 419.5 | 320.3 ± 219.1   | 1469.9 ± 780.3 | 1472.2 ± 376.8 |
| % preischemia              | 27.1            | 121.3*         | 122.5*         | 26.8            | 123.0*         | 123.2*         |

Values are mean ± SD; 5, 30, and 60 min refer to time after onset of reperfusion. The percentage of preischemic (BL3) values is reported. Six animals were recorded in each group.

\*  $P < 0.05$  versus controls.

trols throughout reperfusion. The left ventricular end-diastolic pressure for pinacidil was significantly less than that for controls during the final 50 min of reperfusion.

As shown in figure 4, pretreatment with glyburide had no effect on the ability of propofol to improve recovery of function. On its own, glyburide had no effect on recovery of left ventricular developed pressure, nor did it prevent the elevation in left ventricular end-diastolic pressure.

Figure 5 displays the effect of glyburide pretreatment on the functional recovery provided by sevoflurane. As shown in figure 3, sevoflurane improved the recovery of left ventricular developed pressure above that in controls from 15 min until the end of reperfusion. Glyburide had no significant effect on recovery of left ventricular developed pressure. However, glyburide pretreatment attenuated the recovery of left ventricular developed pressure afforded by sevoflurane. The left ventricular developed pressure of hearts exposed to both glyburide and sevoflurane was not significantly different from that of controls for the final 25 min of reperfusion. Glyburide pretreatment also eliminated the protective influence of sevoflurane on the increase in left ventricular end-diastolic pressure observed in reperfusion (fig. 5). As expected, glyburide pretreatment completely eliminated all of the effects of pinacidil on the ischemic reperfused rat hearts (data not shown).

As summarized in table 2, recovery as a percentage of BL3 of the rates of left ventricular pressure development (+dP/dt) and left ventricular relaxation (-dP/dt) paralleled the responses observed with left ventricular developed pressure in all treatment groups. There was no significant differences in coronary perfusion pressure between any of the treatment groups during reperfusion (table 3).

#### *Effect of Treatments on Contracture Development during Ischemia*

Figure 6 demonstrates the effect of cardioprotective treatments (see figs. 2 and 3) on the contracture profile during ischemia *per se*, that is, before the restoration of flow. Propofol, sevoflurane, HOE 642, and the combination of propofol and HOE 642 significantly reduced the maximum left ventricular end-diastolic pressure reached during ischemia. In addition, these agents significantly delayed the time to reach peak elevation of left ventricular end-diastolic pressure. As shown in the bottom panel of figure 6, the propofol and HOE 642 combination provided a significant additive delay in the time to maximum left ventricular end-diastolic pressure. Interestingly, pinacidil treatment failed to alter the contracture profile when compared with controls.

Figure 7 shows the effect of glyburide pretreatment on contracture development during ischemia in hearts ex-

**Table 3. Drug Effect on Coronary Perfusion Pressures (mmHg) prior to Ischemia and during Reperfusion (30 and 60 min)**

|                    | Cont         | Sevo         | Ppf          | HOE 642      | Ppf+ HOE     | Glyb         |
|--------------------|--------------|--------------|--------------|--------------|--------------|--------------|
| BL1                | 112.4 ± 30.1 | 114.4 ± 39.7 | 98.2 ± 24.7  | 94.0 ± 22.3  | 98.9 ± 18.1  | 93.8 ± 28.9  |
| BL2                | 120.2 ± 35.3 | 110.1 ± 37.0 | 93.7 ± 27.9  | 89.9 ± 17.6  | 99.7 ± 23.5  | 93.6 ± 26.5  |
| % change1          | +6.9         | -4.51        | -4.6         | -4.4         | -1.8         | -0.21        |
| BL3                | 117.9 ± 51.1 | 99.6 ± 24.2  | 67.2* ± 22.5 | 91.3 ± 24.7  | 91.5 ± 28.7  | 92.0 ± 32.6  |
| % change2          | -1.9         | -9.5         | -28.3*       | +1.6         | -8.2         | -1.7         |
| 30 min reperfusion | 107.6 ± 27.2 | 93.8 ± 28.9  | 91.8 ± 22.3  | 97.4 ± 23.3  | 98.7 ± 25.0  | 108.0 ± 42.1 |
| 60 min reperfusion | 122.3 ± 31.8 | 116.9 ± 44.3 | 103.4 ± 30.4 | 105.0 ± 26.9 | 101.7 ± 26.2 | 121.7 ± 71.5 |

Values are mean ± SD (n = 6 for each group). See table 1 for abbreviations. There were no significant differences in BL1, BL2, or % change1 between the groups. There were no significant differences in coronary perfusion pressure through the reperfusion period.

\*  $P < 0.05$  versus BL1 and BL2 within the group and versus controls.

posed to propofol and sevoflurane. Glyburide had no effect on either maximum left ventricular end-diastolic pressure or the time to reach peak left ventricular end-diastolic pressure (data not shown). Moreover, glyburide pretreatment did not affect the influence of propofol on ischemic contracture. However, glyburide did abolish the effects of sevoflurane on maximum left ventricular end-diastolic pressure and the time to reach peak left ventricular end-diastolic pressure.

#### Energy Metabolite Contents

Table 4 summarizes the energy metabolite content in the rat hearts at the end of 60 min of reperfusion. Treatment with propofol, sevoflurane, HOE 642, and propofol plus HOE 642 all resulted in significant sparing of ATP, total HEP, and energy charge compared with controls. Glyburide pretreatment did not affect the metabolite content as compared with controls; however, it eliminated the preservation of ATP, HEP, and energy charge in rat hearts treated with sevoflurane. Moreover, glyburide did not influence the effects of propofol on energy metabolite content.

None of the treatments that preserved ATP or total HEP contents in the reperfused myocardium had any direct effects on these parameters before initiating ischemia (BL3). Thus, basal preischemia values ( $\mu\text{M/g}$  dry weight, mean ± SD; n = 4) for these groups for ATP and HEP, respectively, were as follows: controls, 24.1 ± 2.3 and 50.1 ± 2.8; propofol, 27.7 ± 5.6 and 53.7 ± 11.9; sevoflurane, 24.5 ± 5.4 and 49.3 ± 11.6; HOE 642 alone, 24.1 ± 5.6 and 48.5 ± 11.6; propofol plus HOE 642, 21.2 ± 4.8 and 44.4 ± 12.8.

#### Discussion

The goal of the first part of our study was to clarify the effects of propofol on the ischemic reperfused myocar-

dium. Our study shows that propofol at clinically relevant concentrations (35  $\mu\text{M}$ ) delays the onset and magnitude of ischemic contracture produced by ischemia *per se* before reperfusion, allows complete recovery of left ventricular developed pressure during reperfusion after 60 min of ischemia compared with controls, attenuates the increase in left ventricular end-diastolic pressure associated with reperfusion, and preserves HEP levels in reperfused hearts. In addition, we have demonstrated that these effects were not influenced by the pretreatment of glyburide at concentrations that have been shown to effectively inhibit  $K_{\text{ATP}}$ ,<sup>18,19</sup> suggesting that propofol does not provide cardioprotection *via* the  $K_{\text{ATP}}$  channel.

This study also included an evaluation of the interaction between propofol and HOE 642 in the ischemic myocardium. Although a number of NHE inhibitors have been developed, HOE 642 is of particular interest in that it specifically inhibits the NHE-1 isoform, the predominant NHE subtype in the heart that provides excellent cardioprotection.<sup>20</sup> Moreover, HOE 642 has recently undergone clinical evaluation in a multicentered international study in high-risk patients with acute coronary syndromes, including those undergoing coronary artery bypass surgery. We have proposed that NHE inhibition represents a potentially safe and effective adjunct in cardiac surgery<sup>21</sup> and is therefore of significant importance to the anesthesiologist. We recently reported the interaction between isoflurane, sevoflurane, and sufentanil with HOE 642<sup>8</sup>; however, the combination with propofol has not been previously studied. Our results suggest distinct and separate mechanisms of protection elicited by these drugs. HOE 642 and propofol provided an equal magnitude of recovery of left ventricular developed pressure and end-diastolic pressure; however, the onset of recovery with HOE 642 was significantly faster than with propofol-treated hearts. Both treatments atten-



## CARDIOPROTECTIVE EFFECTS OF PROPOFOL AND SEVOFLURANE

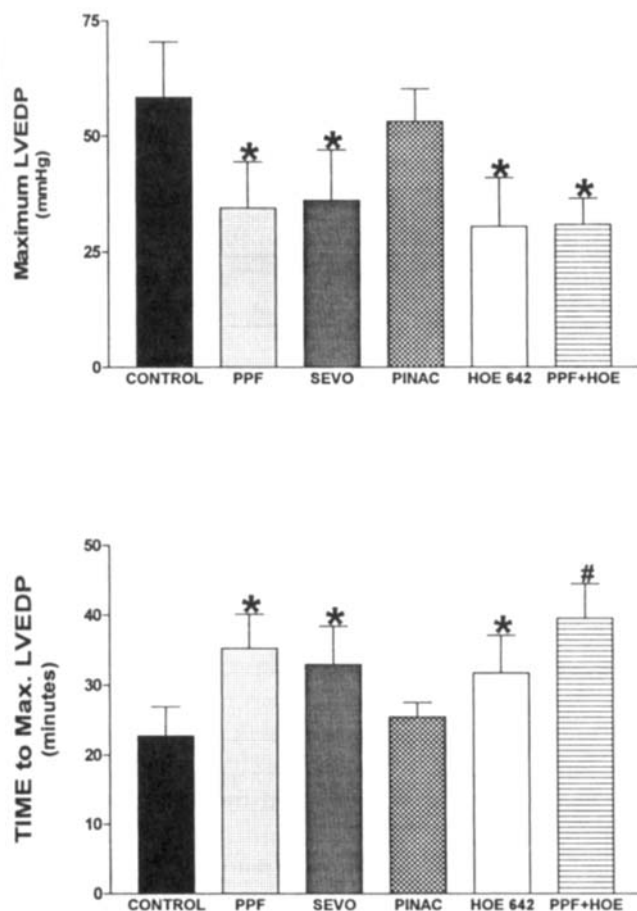


Fig. 6. Changes in maximum left ventricular end-diastolic pressure (LVEDP) and the time to peak LVEDP during the 60 min of global ischemia. Values are mean  $\pm$  SD and  $n = 6$  for each group. PPF = propofol; SEVO = sevoflurane; PINAC = pinacidil; HOE = HOE 642. \* $P < 0.05$  vs. unlabeled groups. # $P < 0.05$  vs. all other groups.

uated the onset and magnitude of contracture during ischemia and reperfusion and preserved ATP content at the end of the reperfusion period. The combination of propofol and HOE 642 provided a superior recovery of left ventricular developed pressure at the end of reperfusion and further delayed the onset of peak contracture, suggesting an additive benefit of separate cardioprotective mechanisms. Indeed, with this drug combination, function after reperfusion was higher than baseline values before ischemia. These results are similar to those obtained with the combination of isoflurane or sevoflurane with HOE 642,<sup>8</sup> suggesting that the excellent protection reflects the net effect of two distinct mechanisms. The underlying mechanism for the  $> 100\%$  recovery in function is unknown at present, but a plausible explanation may involve a sensitizing effect in the

reperfused myocardium; however, this needs to be assessed with further studies.

Recently, the  $K_{ATP}$  channel has been identified as a potentially distinct mechanism for the myocardial protection observed with isoflurane based on the ability of glyburide to attenuate the isoflurane-induced cardioprotection.<sup>12,13</sup> Moreover, glyburide has been demonstrated to eliminate the ATP-preserving effect of isoflurane on ischemic reperfused myocardium.<sup>22</sup> In the present study, we report for the first time that glyburide pretreatment significantly attenuated the cardioprotection associated with sevoflurane but not propofol. Glyburide eliminated the HEP-sparing effect in sevoflurane-treated hearts after reperfusion. Glyburide also nullified the protective influence of sevoflurane on ischemic contracture and the recovery of left ventricular end-diastolic pressure during reperfusion. Glyburide pretreatment significantly attenuated the recovery of left ventricular developed pressure observed with sevoflurane, but did not

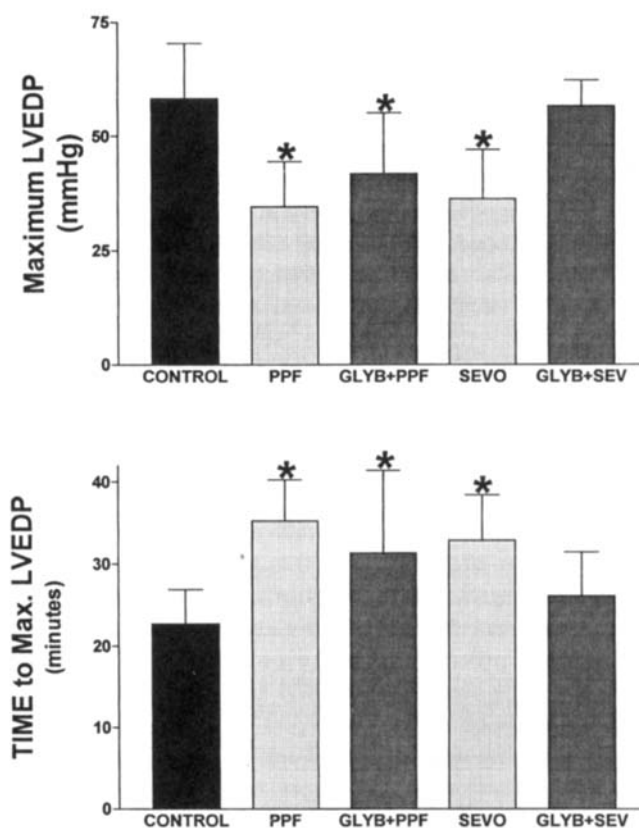


Fig. 7. Changes in maximum left ventricular end-diastolic pressure (LVEDP) and the time to peak LVEDP during the 60 min of global ischemia. Values are mean  $\pm$  SD and  $n = 6$  for each group. CNTRL = control; PPF = propofol; SEVO = sevoflurane; GLYB = glyburide. \* $P < 0.05$  vs. unlabeled groups.

**Table 4. Energy Metabolite Concentrations ( $\mu\text{mol/g}$  Dry Weight) at the End of Reperfusion**

|                   | ATP              | CrP               | LAC             | ADP             | AMP             | HEP               | TAN               | EC               |
|-------------------|------------------|-------------------|-----------------|-----------------|-----------------|-------------------|-------------------|------------------|
| Cont              | 4.13 $\pm$ 0.51  | 10.30 $\pm$ 2.03  | 4.84 $\pm$ 4.75 | 3.99 $\pm$ 0.78 | 1.52 $\pm$ 0.44 | 14.43 $\pm$ 2.42  | 9.64 $\pm$ 1.35   | 0.64 $\pm$ 0.02  |
| Ppf               | 8.49* $\pm$ 2.38 | 16.73* $\pm$ 7.54 | 6.78 $\pm$ 6.96 | 4.76 $\pm$ 1.57 | 2.29 $\pm$ 0.96 | 25.22* $\pm$ 9.50 | 15.54* $\pm$ 3.77 | 0.70* $\pm$ 0.04 |
| Sevo              | 8.70* $\pm$ 1.54 | 16.96* $\pm$ 2.35 | 7.00 $\pm$ 5.56 | 6.53 $\pm$ 3.21 | 1.77 $\pm$ 0.34 | 26.32* $\pm$ 3.82 | 17.66* $\pm$ 5.27 | 0.71* $\pm$ 0.02 |
| Hoe 642           | 9.42* $\pm$ 2.91 | 22.75* $\pm$ 8.77 | 9.72 $\pm$ 4.75 | 5.76 $\pm$ 1.98 | 2.32 $\pm$ 0.78 | 32.17* $\pm$ 11.6 | 17.50* $\pm$ 4.92 | 0.71* $\pm$ 0.04 |
| Ppf+ Hoe<br>642   | 8.64* $\pm$ 2.06 | 19.99* $\pm$ 2.20 | 2.99 $\pm$ 1.74 | 3.39 $\pm$ 1.22 | 1.58 $\pm$ 0.34 | 28.63* $\pm$ 4.14 | 13.61 $\pm$ 2.57  | 0.76* $\pm$ 0.04 |
| Glyb              | 5.61 $\pm$ 2.13  | 14.62 $\pm$ 5.19  | 3.56 $\pm$ 2.03 | 3.35 $\pm$ 0.64 | 1.48 $\pm$ 0.29 | 20.23 $\pm$ 7.30  | 10.44 $\pm$ 2.13  | 0.68 $\pm$ 0.07  |
| Glyb+<br>Sevoflur | 6.64 $\pm$ 2.33  | 15.06 $\pm$ 5.12  | 9.81 $\pm$ 9.97 | 3.68 $\pm$ 1.25 | 1.92 $\pm$ 0.66 | 21.71 $\pm$ 7.45  | 12.25 $\pm$ 2.28  | 0.68 $\pm$ 0.12  |
| Glyb+<br>Propofol | 11.7* $\pm$ 6.44 | 24.62* $\pm$ 10.2 | 6.47 $\pm$ 8.87 | 4.76 $\pm$ 1.94 | 1.70 $\pm$ 0.88 | 36.34* $\pm$ 16.5 | 18.18* $\pm$ 6.64 | 0.76* $\pm$ 0.09 |

Values are mean  $\pm$  SD (n = 6 for each group).

ATP = adenosine triphosphate; CrP = creatinine phosphate; LAC = lactate; ADP = adenosine diphosphate; AMP = adenosine monophosphate; HEP = high energy phosphate; TAN = total adenine nucleotide; EC = energy charge. See table 1 for other abbreviations.

\*  $P < 0.05$  versus controls.

abolish the cardioprotection. As noted previously, in view of the fact that we used a glyburide concentration that would be expected to completely block the  $K_{ATP}$  channel,<sup>18,19</sup> the findings suggest that the  $K_{ATP}$  channel is unlikely to represent the sole mechanism of protection produced with sevoflurane. In addition, our study confirms that a  $K_{ATP}$  channel agonist, pinacidil, provides functional cardioprotection in the ischemic reperfused heart, as demonstrated by other investigators.<sup>14,15</sup> The profile of recovery was somewhat different to that produced by sevoflurane in that the recovery of left ventricular developed pressure and end-diastolic pressure in pinacidil-treated hearts was slightly delayed in onset as compared with sevoflurane. Moreover, pinacidil was unable to mimic the HEP-sparing effect of sevoflurane, nor did pinacidil attenuate the onset and magnitude of peak ischemic contracture, as did sevoflurane. It should be noted that in our previous study, sevoflurane failed to significantly preserve HEPs as compared with controls.<sup>8</sup> The values of ATP content in sevoflurane-treated hearts in this study were similar to those of the previous report; however, the ATP content of controls was significantly lower in the present study. This was surprising but may be a result of the somewhat higher pacing frequency of 325 beats/min used in the present study compared with 300 beats/min used previously, resulting in greater ATP depletion. It is interesting that pinacidil alone failed to preserve HEPs despite the ability of glyburide to reverse sevoflurane-induced preservation of ATP content. Taken together, these findings suggest that although  $K_{ATP}$  channel activation likely plays an important role in sevoflurane-induced cardioprotection, other mechanisms may contribute to these

effects. The failure of glyburide to modulate any parameters in propofol-treated groups suggests that the  $K_{ATP}$  channel is not involved in the cardioprotection by propofol. The underlying mechanisms for the protective effects of propofol are not known with certainty. However, propofol has been shown to possess antioxidant properties *in vitro*<sup>23</sup> and has been demonstrated to inhibit lipid peroxidation induced by oxidative stress in isolated organelles.<sup>24,25</sup> In addition, propofol inhibits the trans-sarcolemmal calcium current in ventricular myocytes.<sup>26-28</sup> This is important because lipid peroxidation and calcium overload are associated with myocardial stunning and ischemic reperfusion injury.<sup>29,30</sup> However, Coetzee<sup>11</sup> reported that propofol failed to protect the pig heart from ischemic reperfusion injury induced by left anterior descending coronary artery occlusion. Recent studies have now demonstrated that propofol attenuates the mechanical derangements and lipid peroxidation induced by hydrogen peroxide and preserves the ATP content.<sup>10</sup> Moreover, there has been clinical evidence that propofol reduces lipid peroxidation in ischemic reperfusion injury.<sup>31</sup> In addition, a high concentration (100  $\mu\text{M}$ ) of propofol has been reported to attenuate ischemic contracture, mechanical dysfunction, lactate dehydrogenase release, and histologic damage in isolated ischemia-reperfused rat hearts.<sup>9</sup> Thus, the additive benefits of propofol and HOE 642 may be the result of the combined antioxidant effects of propofol and the reduced calcium overload associated with HOE 642 treatment. Another potential contribution has been suggested in a study involving assessment of coronary artery vasoactivity in which the dilatory effect of propofol was

## CARDIOPROTECTIVE EFFECTS OF PROPOFOL AND SEVOFLURANE

attenuated with nitric oxide synthase and cyclooxygenase inhibitors.<sup>32</sup>

In summary, our study using the isolated rat heart suggests that  $K_{ATP}$  channel activation, NHE inhibition, and antioxidant effects may all represent distinct pathways of myocardial protection that can be exploited under clinical settings by the anesthesiologist. Our study should be interpreted with some degree of caution, particularly because it was performed using rat hearts, which may not be completely applicable to human tissue. Moreover, we did not study concentration-response relationships for each drug but, instead, relied on concentrations that have been established to produce the relevant effect for the respective agent. It cannot be excluded that different concentrations of these agents could produce other effects. Taken together, however, it is nonetheless attractive to suggest that the different agents used may provide additive protection if used in combination; however, further studies are required to verify these observations in this model of ischemic injury as well as in other animal species.

The authors thank Dr. Wolfgang Scholz, formerly of Hoechst-Marion-Roussel, Frankfurt, Germany, for the generous gift of HOE 642 (cariporide), and Dr. Adrian W. Gelb for his interest in this study and for helpful discussion.

## References

- Karmazyn M: The sodium-hydrogen exchange system in the heart: Its role in ischemic and reperfusion injury and therapeutic implications. *Can J Cardiol* 1996; 12:1074-82
- Karmazyn M, Moffat MP: Role of Na/H exchange in cardiac physiology and pathophysiology: Mediation of myocardial reperfusion injury by the pH paradox. *Cardiovasc Res* 1993; 27:915-24
- Karmazyn M: Role of sodium-hydrogen exchange in mediating myocardial ischemic and reperfusion injury: Mechanisms and therapeutic implications, The Na/H Exchange. Edited by Fliegel L. Austin, Landes Bioscience Publishers, 1996, pp 189-215
- Fröhlich O, Karmazyn M: The Na-H exchanger revisited: An update on Na-H exchange regulation and the role of the exchanger in hypertension and cardiac function in health and disease. *Cardiovasc Res* 1997; 36:138-48
- Lazdunski M, Frélin C, Vigne P: The sodium/hydrogen exchange system in cardiac cells: Its biochemical and pharmacological properties and its role in regulating internal concentrations of sodium and internal pH. *J Mol Cell Cardiol* 1985; 17:1029-42
- Pierce GN, Czubyrt MP: The contribution of ionic imbalance to ischemia/reperfusion-induced injury. *J Mol Cell Cardiol* 1995; 27:53-63
- Ventura-Clapier R, Veksler V: Myocardial ischemic contracture: Metabolites affect rigor tension development and stiffness. *Circ Res* 1994; 74:920-9
- Mathur S, Karmazyn M: Interaction between anesthetics and sodium-hydrogen exchange inhibitor HOE 642 (cariporide) in ischemic and reperfused rat hearts. *ANESTHESIOLOGY* 1997; 87:1460-9
- Ko SH, Yu CW, Lee SK, Choe H, Chung MJ, Kwak YG, Chae SW, Song HS: Propofol attenuates ischemia-reperfusion injury in the isolated rat heart. *Anesth Analg* 1997; 85:719-24
- Kokita N, Hara A: Propofol attenuates hydrogen peroxide-induced mechanical and metabolic derangements in the isolated rat heart. *ANESTHESIOLOGY* 1996; 84:117-27
- Coetzee A: Comparison of the effects of propofol and halothane on acute myocardial ischaemia and myocardial reperfusion injury. *S Afr Med J* 1996; 86(Cardiovasc Suppl 2):5-90
- Kersten JR, Lowe D, Hettrick DA, Pagel PS, Gross GJ, Wartier DC: Glyburide, a K-ATP channel antagonist, attenuates the cardioprotective effects of isoflurane in stunned myocardium. *Anesth Analg* 1996; 83:27-33
- Kersten JR, Schmeling TJ, Hettrick DA, Pagel PS, Gross GJ, Wartier DC: Mechanism of myocardial protection by isoflurane: Role of adenosine triphosphate-regulated potassium ( $K_{ATP}$ ) channels. *ANESTHESIOLOGY* 1996; 85:794-807
- Grover GJ, McCullough JR, Henry DE, Conder ML, Sleph PG: Anti-ischemic effects of the potassium channel activators pinacidil and cromakalim and the reversal of these effects with the potassium channel blocker glibenclamide. *J Pharmacol Exp Ther* 1989; 251:98-104
- Grover GJ: Pharmacology of ATP-sensitive potassium channel ( $K_{ATP}$ ) openers in models of myocardial ischemia. *Can J Physiol Pharmacol* 1997; 75:309-15
- Boban M, Stowe DF, Buljubasic N, Kampine JP, Bosnjak ZJ: Direct comparative effects of isoflurane and desflurane in isolated guinea pig hearts. *ANESTHESIOLOGY* 1992; 76:775-80
- Bergmeyer HU: *Methods in Enzymatic Analysis*. New York, Academic Press, 1963, pp 539-616
- Findlay I: Inhibition of ATP-sensitive  $K^+$  channels in cardiac muscle by the sulphonylurea drug glibenclamide. *J Pharmacol Exp Ther* 1992; 261:540-5
- Jovanovic A, Jovanovic S, Lorenz E, Terzic A: Recombinant cardiac ATP-sensitive  $K^+$  channel subunits confer resistance to chemical hypoxia-reoxygenation injury. *Circulation* 1998; 98:1548-55
- Scholz W, Albus U, Counillon L, Gögelein H, Lang HJ, Linz W, Weichert A, Schölkens BA: Protective effect of HOE 642, a selective sodium-hydrogen exchange subtype 1 inhibitor, on cardiac ischaemia and reperfusion. *Cardiovasc Res* 1995; 29:260-8
- Karmazyn M: Sodium-hydrogen exchange inhibition: A superior cardioprotective strategy. *J Thorac Cardiovasc Surg* 1996; 112:776-7
- Nakayama M, Fujita S, Kanaya N, Tsuchida H, Namiki A: Blockade of ATP-sensitive  $K^+$  channel abolishes the anti-ischemic effects of isoflurane in dog hearts. *Acta Anaesthesiologica Scand* 1997; 41:531-5
- Murphy PG, Myers DS, Davies MJ, Webster NR, Jones JG: The antioxidant potential of propofol (2,6-diisopropylphenol). *Br J Anaesth* 1992; 68:613-8
- Eriksson O, Pollesello P, Saris N-EL: Inhibition of lipid peroxidation in isolated rat liver mitochondria by the general anaesthetic propofol. *Biochem Pharmacol* 1992; 44:391-3
- Musacchio E, Rizzoli V, Bianchi M, Bindoli A, Galzigna L: Antioxidant action of propofol on liver microsomes, mitochondria and brain synaptosomes in the rat. *Pharmacol Toxicol* 1991; 69:75-7
- Zhou W, Fontenot HJ, Liu S, Kennedy RH: Modulation of cardiac calcium channels by propofol. *ANESTHESIOLOGY* 1997; 86:670-5

27. Yang CY, Wong CS, Yu CC, Luk HN, Lin CI: Propofol inhibits cardiac L-type calcium current in guinea pig ventricular myocytes. *ANESTHESIOLOGY* 1996; 84:626-35
28. Cook DJ, Housmans PR: Mechanism of the negative inotropic effect of propofol in isolated ferret ventricular myocardium. *ANESTHESIOLOGY* 1994; 80:859-71
29. Karmazyn M: Ischemic and reperfusion injury in the heart: Cellular mechanisms and pharmacological interventions. *Can J Physiol Pharmacol* 1991; 69:719-31
30. Bolli R: Mechanism of myocardial "stunning." *Circulation* 1990; 82:723-31
31. Kahraman S, Kilinc K, Dal D, Erdem K: Propofol attenuates formation of lipid peroxides in tourniquet-induced ischaemia-reperfusion injury. *Br J Anaesth* 1997; 78:279-81
32. Park KW, Dai HB, Lowenstein E, Sellke FW: Propofol-associated dilation of rat distal coronary arteries is mediate by multiple substances, including endothelium derived nitric oxide. *Anesth Analg* 1995; 81:1191-6