

Hyperglycemia Prevents Isoflurane-induced Preconditioning against Myocardial Infarction

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Background: Volatile anesthetics stimulate but hyperglycemia attenuates activity of mitochondrial adenosine triphosphate-regulated potassium channels. The authors tested the hypothesis that acute hyperglycemia interferes with isoflurane-induced preconditioning *in vivo*.

Methods: Barbiturate-anesthetized dogs (n = 79) were instrumented for measurement of hemodynamics. Myocardial infarct size and collateral blood flow were assessed with triphenyltetrazolium chloride staining and radioactive microspheres, respectively. All dogs were subjected to a 60-min left anterior descending coronary artery occlusion followed by 3 h of reperfusion. Dogs were randomly assigned to receive an infusion of normal saline (normoglycemic controls) or 15% dextrose in water to increase blood glucose concentrations to 300 or 600 mg/dl in the absence or presence of isoflurane (0.5 or 1.0 minimum alveolar concentration [MAC]) in separate experimental groups. Isoflurane was discontinued, and blood glucose concentrations were allowed to return to baseline values before left anterior descending coronary artery occlusion.

Results: Myocardial infarct size was $26 \pm 1\%$ of the left ventricular area at risk in control experiments. Isoflurane reduced infarct size (15 ± 2 and $13 \pm 1\%$ during 0.5 and 1.0 MAC, respectively). Hyperglycemia alone did not alter infarct size (26 ± 2 and $33 \pm 4\%$ during 300 and 600 mg/dl, respectively). Moderate hyperglycemia blocked the protective effects of 0.5 MAC ($25 \pm 2\%$) but not 1.0 MAC isoflurane ($13 \pm 2\%$). In contrast, severe hyperglycemia prevented reductions of infarct size during both 0.5 MAC ($29 \pm 3\%$) and 1.0 MAC isoflurane ($28 \pm 4\%$).

Conclusions: Acute hyperglycemia attenuates reductions in myocardial infarct size produced by isoflurane in dogs.

PERIOPERATIVE myocardial infarction is an important complication of noncardiac surgery associated with significant morbidity and mortality.¹ Identification of patients at greatest risk for infarction is the subject of intense investigation. Diabetes mellitus is an independent predictor of cardiovascular complications or death in patients undergoing major noncardiac surgery.¹⁻³ The relative risk of sustaining an adverse event is increased more than threefold in patients with diabetes.⁴ Hyperglycemia alone, independent of diabetes, may also in-

crease postoperative cardiovascular risk.^{5,6} The mechanisms by which diabetes or hyperglycemia increase cardiovascular risk are unknown. We recently demonstrated that diabetes and hyperglycemia impair activation of mitochondrial adenosine triphosphate-regulated potassium (K_{ATP}) channels.⁷ Activation of these channels plays a central role in myocardial protection produced by ischemic preconditioning, and hyperglycemia abolishes this protective effect. Volatile anesthetics also protect ischemic myocardium by activation of mitochondrial K_{ATP} channels.⁸ Thus, we tested the hypothesis that acute hyperglycemia impairs isoflurane-induced preconditioning in a canine model of experimental myocardial infarction.

Materials and Methods

All experimental procedures and protocols used in this investigation were reviewed and approved by the Animal Care and Use Committee of the Medical College of Wisconsin. Furthermore, all conformed to the *Guiding Principles in the Care and Use of Animals* of the American Physiologic Society and were in accordance with the *Guide for the Care and Use of Laboratory Animals* (National Academy Press, Washington, DC, 1996).

General Preparation

Implantation of instruments has been previously described in detail.⁹ Briefly, mongrel dogs of either sex were anesthetized with sodium barbitol (200 mg/kg) and sodium pentobarbital (15 mg/kg) and ventilated using positive pressure with an air and oxygen mixture after tracheal intubation. Arterial blood pH was maintained within a physiologic range by adjustment of tidal volume and respiratory rate. End-tidal concentrations of isoflurane were measured at the tip of the endotracheal tube by an infrared anesthetic analyzer that was calibrated with known standards before and during experimentation. The canine minimum alveolar concentration (MAC) of isoflurane used in the current investigation was 1.28%. Temperature was maintained with a heating blanket. A 7-French dual micromanometer-tipped catheter was inserted into the aorta and left ventricle (LV) for measurement of aortic and LV pressures and the maximum rate of increase of LV pressure ($+dP/dt_{max}$). Heparin-filled catheters were inserted into the left atrial appendage and the right femoral artery for administration of radioactive microspheres and withdrawal of reference blood flow samples, respectively. A catheter was also inserted in the

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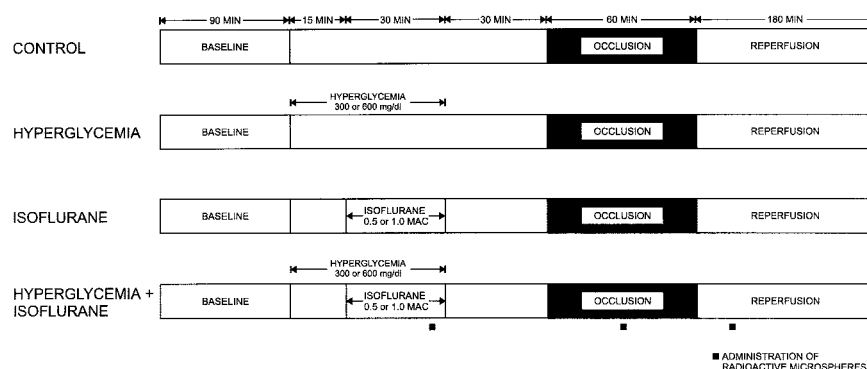


Fig. 1. Schematic diagram illustrating the experimental protocol.

right femoral vein for fluid or drug administration. A 1-cm segment of the left anterior descending coronary artery (LAD) was isolated, immediately distal to the first diagonal branch, and a silk ligature was placed around the vessel for production of coronary artery occlusion and reperfusion. Hemodynamics were continuously monitored on a polygraph during experimentation and digitized using a computer interfaced with an analog-to-digital converter.

Experimental Protocol

Ninety minutes after instrumentation was completed and calibrated, baseline systemic hemodynamics were recorded. All dogs were subjected to a 60-min LAD occlusion followed by 3 h of reperfusion (fig. 1). Dogs were randomly assigned to receive saline or 15% dextrose in water to increase blood glucose concentrations to 300 or 600 mg/dl (moderate or severe hyperglycemia, respectively) in the absence or presence of isoflurane (0.5 or 1.0 MAC) in separate experimental groups. Isoflurane was administered for 30 min followed by 30 min of washout, a procedure previously shown to precondition myocardium against infarction.¹⁰ Blood glucose concentrations were allowed to return to baseline values 30 min before LAD occlusion and reperfusion to evaluate the effects of hyperglycemia, specifically, on isoflurane-induced preconditioning. Regional myocardial blood flow was measured at baseline, during LAD occlusion, and after 1 h of reperfusion. Dogs that developed intractable ventricular fibrillation and those with a subendocardial coronary collateral blood flow greater than $0.15 \text{ ml} \cdot \text{min}^{-1} \cdot \text{g}^{-1}$ were excluded from the analysis.¹¹

Measurement of Myocardial Infarct Size

At the end of each experiment, myocardial infarct size was measured as previously described.¹² Briefly, the LV area at risk for infarction (AAR) was separated from the normal area, and the two regions were incubated at 37°C for 20–30 min in 1% 2,3,5-triphenyltetrazolium chloride in 0.1 M phosphate buffer adjusted to pH 7.4. After overnight storage in 10% formaldehyde, infarcted and noninfarcted myocardium within the AAR were carefully separated and weighed. Infarct size was expressed as a percentage of the AAR.

Determination of Regional Myocardial Blood Flow

Carbonized plastic microspheres ($15 \pm 2 \mu\text{m}$ [SD] in diameter) labeled with ^{141}Ce , ^{103}Ru , or ^{95}Nb were used to measure regional myocardial perfusion as previously described.⁹ Transmural tissue samples were selected from the ischemic region (distal to the LAD occlusion) and were subdivided into subepicardial, midmyocardial, and subendocardial layers of approximately equal thickness. Samples were weighed, placed in scintillation vials, and the activity of each isotope was determined. Similarly, the activity of each isotope in the reference blood flow sample was assessed. Tissue blood flow (milliliters per minute per gram) was calculated as $Q_r \cdot C_m \cdot C_r^{-1}$, where Q_r indicates rate of withdrawal of the reference blood flow sample (milliliters per minute), C_m indicates the activity (counts per minute per gram) of the myocardial tissue sample, and C_r indicates the activity (counts per minute) of the reference blood flow sample. Transmural blood flow was considered as the average of subepicardial, midmyocardial, and subendocardial blood flows.

Statistical Analysis

Statistical analysis of data within and between groups was performed with analysis of variance for repeated measures followed by the Student-Newman-Keuls test. Changes within and between groups were considered statistically significant when the P value was < 0.05 . All data are expressed as mean \pm SEM.

Results

Seventy-nine dogs were instrumented to obtain 71 successful experiments. Six dogs were excluded because subendocardial collateral blood flow exceeded $0.15 \text{ ml} \cdot \text{min}^{-1} \cdot \text{g}^{-1}$ (three in the 0.5-MAC isoflurane group, one in the 1.0-MAC isoflurane group, and two in the 0.5-MAC isoflurane + moderate hyperglycemia group). Two dogs receiving 0.5 MAC isoflurane during moderate hyperglycemia were excluded because myocardium could not be reperfused. Blood glucose concentrations (table 1) were similar among groups at baseline, during LAD occlusion, and after reperfusion.

Table 1. Blood Glucose Concentration (mg/dl)

	Baseline	Intervention	30 min CAO	Reperfusion (h)	
				1	3
CON	78 ± 3	—	67 ± 4	66 ± 1	70 ± 1
H ₃₀₀	76 ± 4	316 ± 9*	83 ± 12	73 ± 6	73 ± 7
H ₆₀₀	61 ± 5	579 ± 7*	90 ± 16	61 ± 7	81 ± 9
ISO _{0.5} MAC	68 ± 3	68 ± 2	66 ± 2	64 ± 1	61 ± 2
ISO _{1.0} MAC	72 ± 5	71 ± 6	67 ± 3	62 ± 5	61 ± 6
H ₃₀₀ + ISO _{0.5} MAC	81 ± 3	277 ± 20*	56 ± 10	68 ± 5	67 ± 6
H ₃₀₀ + ISO _{1.0} MAC	69 ± 2	291 ± 22*	85 ± 30	73 ± 2	78 ± 3
H ₆₀₀ + ISO _{0.5} MAC	73 ± 2	581 ± 7*	61 ± 10	68 ± 7	67 ± 1
H ₆₀₀ + ISO _{1.0} MAC	65 ± 7	558 ± 24*	83 ± 15	51 ± 5	57 ± 5

Data are mean ± SEM.

* Significantly ($P < 0.05$) different from baseline.

CAO = coronary artery occlusion; CON = control; H₃₀₀ and H₆₀₀ = target blood glucose concentrations of 300 and 600 mg/dl, respectively; ISO_{0.5} MAC and ISO_{1.0} MAC = isoflurane 0.5 and 1.0 minimum alveolar concentration, respectively.

Systemic Hemodynamics

There were no differences in hemodynamics between experimental groups during control conditions, during LAD occlusion, or during reperfusion (table 2). Elevation of blood glucose concentration to 600 mg/dl alone transiently increased LV end-diastolic pressure and LV +dP/dt_{max} but had no other hemodynamic effects. Isoflurane decreased heart rate, mean arterial and LV systolic pressures, and LV +dP/dt_{max} in the presence or absence of hyperglycemia. Hemodynamics returned to baseline values within 30 min after isoflurane was discontinued. LAD occlusion and reperfusion produced similar increases in LV end-diastolic pressure and decreases in LV +dP/dt_{max} in all experimental groups.

Myocardial Infarct Size

The LV AAR was similar between groups (control, 38 ± 2%; 0.5 MAC isoflurane, 40 ± 3%; 1.0 MAC isoflurane, 37 ± 1%; moderate hyperglycemia, 39 ± 2%; severe hyperglycemia, 37 ± 1%; 0.5 MAC isoflurane + moderate hyperglycemia, 35 ± 3%; 0.5 MAC isoflurane + severe hyperglycemia, 37 ± 2%; 1.0 MAC isoflurane + moderate hyperglycemia, 40 ± 2%; 1.0 MAC isoflurane + severe hyperglycemia, 35 ± 1%). Myocardial infarct size expressed as a percentage of the AAR was 26 ± 1% (n = 7) in control dogs. Isoflurane (0.5 and 1.0 MAC) reduced infarct size to 15 ± 2 (n = 7) and 13 ± 1% (n = 7) of the AAR, respectively (fig. 2). Moderate (n = 8) or severe hyperglycemia (n = 8) alone did not alter myocardial infarct size (26 ± 2 and 33 ± 4%, respectively). Moderate hyperglycemia blocked the protective effect of 0.5 MAC but not of 1.0 MAC isoflurane (25 ± 2 and 13 ± 2%, respectively; n = 7 in each group). In contrast, severe hyperglycemia blocked the protective effect of both isoflurane concentrations (29 ± 3 and 28 ± 4%, respectively; n = 6 and 7 in the 0.5- and 1.0-MAC groups). Coronary artery occlusion caused significant decreases in transmural myocardial perfusion in each group, and there were

no differences in coronary collateral blood flow between groups (table 3).

Discussion

Hyperglycemia is a substantial contributor to and an independent predictor of increased short- and long-term cardiovascular mortality.^{13,14} A strong correlation between blood glucose concentrations at the time of hospital admission and long-term mortality was recently observed in a study of diabetic patients with acute myocardial infarction.¹⁵ A meta-regression analysis of data published in 20 studies of more than 95,000 patients also demonstrated a relation between fasting blood glucose concentration and the relative risk of sustaining a cardiovascular event.¹⁶ The mechanisms responsible for the increased morbidity and mortality in these patients are poorly understood, but recent evidence implicates impairment of signal transduction pathways mediating endogenous myocardial protection against ischemic injury as a potential cause.^{7,17,18}

Adenosine triphosphate-regulated potassium channels mediate the protective effects of ischemic^{19,20} and volatile anesthetic-induced^{8-10,21-24} preconditioning. Reductions of myocardial infarct size produced by ischemic preconditioning²⁵ and volatile anesthetics^{10,22,23,26} are blocked by the nonselective K_{ATP} channel antagonist glyburide (glibenclamide) or the selective mitochondrial K_{ATP} channel antagonist sodium 5-hydroxydecanoate.^{8,24} Increases in mortality were observed in diabetic patients treated with the sulfonylurea hypoglycemic agent tolbutamide more than 30 yr ago,²⁷ thus indirectly implicating impaired K_{ATP} channel activation as a potential mechanism for increased cardiovascular risk. K_{ATP} channels are regulated in part by binding of antagonists to the sulfonylurea receptor.²⁸ The activity of these channels in myocardium may also be affected by glucose concentration. K_{ATP} channels in pancreatic β cells close

Table 2. Systemic Hemodynamics

	Baseline	Intervention	30 min CAO	Reperfusion (h)		
				1	2	3
HR (beats/min)						
CON	134 ± 6	136 ± 8	128 ± 7	135 ± 10	131 ± 8	135 ± 8
H ₃₀₀	131 ± 8	129 ± 8	133 ± 8	131 ± 10	135 ± 11	137 ± 11
H ₆₀₀	137 ± 10	140 ± 11	144 ± 12	133 ± 11	137 ± 12	139 ± 12
ISO _{0.5} MAC	133 ± 6	121 ± 6	125 ± 7	122 ± 8	123 ± 9	125 ± 11
ISO _{1.0} MAC	137 ± 5	110 ± 4*	126 ± 5*	121 ± 6*	123 ± 7*	127 ± 9*
H ₃₀₀ + ISO _{0.5} MAC	131 ± 8	113 ± 7*	131 ± 8	130 ± 8	132 ± 9	133 ± 9
H ₃₀₀ + ISO _{1.0} MAC	123 ± 6	100 ± 6*†	109 ± 6*	105 ± 5*	105 ± 5*	105 ± 5*
H ₆₀₀ + ISO _{0.5} MAC	132 ± 7	117 ± 8*	124 ± 6	126 ± 8	128 ± 9	132 ± 8
H ₆₀₀ + ISO _{1.0} MAC	133 ± 4	113 ± 2*	134 ± 4	126 ± 2	127 ± 3	127 ± 4
MAP (mmHg)						
CON	95 ± 3	99 ± 3	94 ± 5	110 ± 8	111 ± 6	109 ± 7
H ₃₀₀	101 ± 4	106 ± 4	96 ± 6	99 ± 4	103 ± 3	99 ± 4
H ₆₀₀	104 ± 3	105 ± 7	87 ± 7*	96 ± 3	98 ± 3	96 ± 4
ISO _{0.5} MAC	97 ± 3	76 ± 4*†	92 ± 4	99 ± 3	96 ± 5	101 ± 3
ISO _{1.0} MAC	102 ± 4	67 ± 2*†	95 ± 4	97 ± 2	99 ± 3	99 ± 5
H ₃₀₀ + ISO _{0.5} MAC	92 ± 4	85 ± 5	100 ± 7	100 ± 5	101 ± 5	102 ± 6
H ₃₀₀ + ISO _{1.0} MAC	90 ± 4	64 ± 4*†	80 ± 4*	93 ± 3	90 ± 3	90 ± 4
H ₆₀₀ + ISO _{0.5} MAC	101 ± 5	93 ± 10	84 ± 4*	91 ± 6	93 ± 8	96 ± 6
H ₆₀₀ + ISO _{1.0} MAC	90 ± 3	71 ± 4*†	85 ± 6	91 ± 4	91 ± 5	92 ± 5
LVSP (mmHg)						
CON	108 ± 4	112 ± 3	101 ± 6	114 ± 10	117 ± 7	118 ± 7
H ₃₀₀	110 ± 4	115 ± 4	101 ± 7	106 ± 5	109 ± 6	108 ± 7
H ₆₀₀	111 ± 3	114 ± 7	93 ± 9*	97 ± 4*	103 ± 4	102 ± 5
ISO _{0.5} MAC	108 ± 5	83 ± 5*†	97 ± 4	104 ± 4	106 ± 4	111 ± 3
ISO _{1.0} MAC	110 ± 4	74 ± 2*†	101 ± 4	101 ± 3	104 ± 4	102 ± 5
H ₃₀₀ + ISO _{0.5} MAC	105 ± 4	97 ± 5	108 ± 7	106 ± 6	108 ± 5	110 ± 5
H ₃₀₀ + ISO _{1.0} MAC	100 ± 4	74 ± 4*†	84 ± 5*	96 ± 4	93 ± 3†	93 ± 5
H ₆₀₀ + ISO _{0.5} MAC	110 ± 5	104 ± 10	87 ± 3*	96 ± 5	98 ± 7	101 ± 7
H ₆₀₀ + ISO _{1.0} MAC	103 ± 3	82 ± 3*†	90 ± 6	96 ± 4	96 ± 5	95 ± 5
LVEDP (mmHg)						
CON	8 ± 1	5 ± 2	14 ± 4*	18 ± 4*	17 ± 3*	19 ± 5*
H ₃₀₀	4 ± 1	4 ± 1	9 ± 1*	11 ± 2*	10 ± 2*	9 ± 2*†
H ₆₀₀	7 ± 2	10 ± 2*	10 ± 2*	12 ± 1*	12 ± 2*	12 ± 2*
ISO _{0.5} MAC	6 ± 2	8 ± 1	12 ± 2	14 ± 3	13 ± 1	16 ± 3*
ISO _{1.0} MAC	6 ± 1	9 ± 1*	14 ± 2*	14 ± 2*	13 ± 1*	12 ± 1*
H ₃₀₀ + ISO _{0.5} MAC	7 ± 1	8 ± 2	12 ± 2*	12 ± 3*	12 ± 3*	12 ± 3*
H ₃₀₀ + ISO _{1.0} MAC	6 ± 1	8 ± 1	13 ± 2*	15 ± 2*	11 ± 2*	11 ± 2*
H ₆₀₀ + ISO _{0.5} MAC	5 ± 2	6 ± 2	11 ± 2*	12 ± 2*	10 ± 2	10 ± 2
H ₆₀₀ + ISO _{1.0} MAC	5 ± 1	7 ± 1	8 ± 1*	10 ± 1*	10 ± 1*	9 ± 1*
+dP/dt _{max} (mmHg/s)						
CON	2,000 ± 210	2,140 ± 310	1,600 ± 160	1,570 ± 170	1,520 ± 110	1,470 ± 100
H ₃₀₀	1,940 ± 110	2,200 ± 120	1,750 ± 150	1,680 ± 80	1,670 ± 90	1,620 ± 120
H ₆₀₀	1,710 ± 120	2,220 ± 210*	1,580 ± 150	1,590 ± 40	1,550 ± 40	1,500 ± 50
ISO _{0.5} MAC	1,810 ± 140	1,230 ± 70*†	1,590 ± 130	1,500 ± 70*	1,450 ± 40*	1,440 ± 80*
ISO _{1.0} MAC	2,080 ± 150	1,120 ± 70*†	1,690 ± 100*	1,580 ± 80*	1,560 ± 60*	1,550 ± 70*
H ₃₀₀ + ISO _{0.5} MAC	1,790 ± 150	1,540 ± 100*†	1,650 ± 120	1,540 ± 110*	1,540 ± 130*	1,530 ± 110*
H ₃₀₀ + ISO _{1.0} MAC	1,680 ± 110	1,160 ± 70*†	1,370 ± 70*	1,450 ± 70*	1,320 ± 40*	1,280 ± 40*
H ₆₀₀ + ISO _{0.5} MAC	1,820 ± 110	1,730 ± 110†	1,490 ± 100*	1,580 ± 120	1,570 ± 110	1,540 ± 140
H ₆₀₀ + ISO _{1.0} MAC	1,720 ± 110	1,250 ± 50*†	1,450 ± 150*	1,420 ± 100*	1,330 ± 80*	1,280 ± 60*

Data are mean ± SEM.

* Significantly ($P < 0.05$) different from baseline. † Significantly ($P < 0.05$) different from the respective value in control experiments.CAO = coronary artery occlusion; HR = heart rate; MAP = mean aortic blood pressure; LVSP = left ventricular systolic pressure; LVEDP = left ventricular end-diastolic pressure; +dP/dt_{max} = maximal rate of increase of left ventricular pressure; CON = control; H₃₀₀ and H₆₀₀ = target blood glucose concentrations of 300 and 600 mg/dl, respectively; ISO_{0.5} MAC and ISO_{1.0} MAC = isoflurane 0.5 and 1.0 MAC, respectively.

after generation of ATP by glucose metabolism,^{29,30} and elevated blood glucose concentrations attenuate activation of mitochondrial K_{ATP} channels in myocardium.⁷ These findings suggest that treatment with sulfonylurea drugs or the presence of hyperglycemia may attenuate or

abolish K_{ATP} channel activity in diabetic patients and increase the risk of myocardial ischemic injury by eliminating this important endogenous protective mechanism.

The current results confirm previous findings demonstrating that isoflurane preconditions myocardium

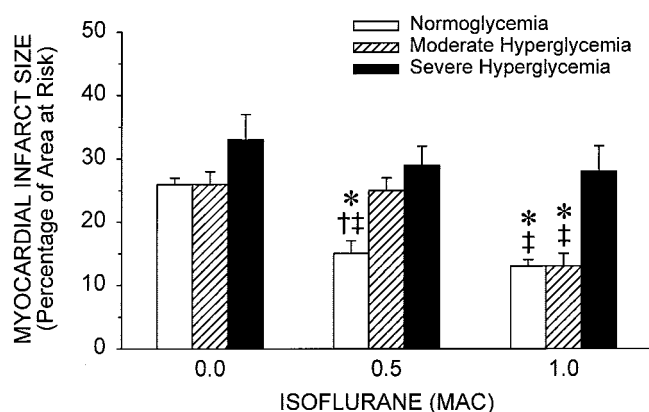


Fig. 2. Histograms illustrating myocardial infarct size expressed as a percentage of the left ventricular area at risk in dogs receiving saline (normoglycemia) or 15% dextrose in water to increase blood glucose concentrations to 300 (moderate hyperglycemia) or 600 mg/dl (severe hyperglycemia) in the absence or presence of isoflurane (0.5 or 1.0 minimum alveolar concentration [MAC]). All data are mean \pm SEM. *Significantly ($P < 0.05$) different from control experiments (0.0 MAC). †Significantly ($P < 0.05$) different from the respective value during moderate hyperglycemia. ‡Significantly ($P < 0.05$) different from the respective value during severe hyperglycemia.

against infarction. Isoflurane at 0.5- or 1.0-MAC concentrations produced equivalent reductions of myocardial infarct size (15 ± 2 and $13 \pm 1\%$, respectively) in the current investigation. This degree of protection was nearly identical to that afforded by the selective mitochondrial K_{ATP} channel agonist diazoxide (10 ± 1 and $11 \pm 2\%$ at doses of 2.5 and 5.0 mg/kg, respectively).⁷ The current results demonstrate that hyperglycemia attenuates or completely abolishes the protective effects of isoflurane in a dose-related manner. These results are strikingly similar to our previous findings indicating that hyperglycemia antagonizes the effects of diazoxide to decrease myocardial infarct size.⁷ The interaction between the concentration of isoflurane and severity of hyperglycemia demonstrated in the current investigation suggests that volatile anesthetics and glucose exert opposing actions on K_{ATP} channel-mediated modulation of myocardial injury *in vivo*. The results also indirectly support our previous hypothesis that blood glucose concentration may be an important determinant of the functional status of signal transduction mechanisms responsible for myocardial protection.

Impairment of cardioprotective signal transduction during disease states, including diabetes, has previously been identified. Diabetes prevented ischemic preconditioning in patients with acute myocardial infarction.¹⁸ The presence of prodromal angina, thought to be a correlate of ischemic preconditioning, was associated with a reduction in mortality in normal patients but not those with diabetes.¹⁸ Atrial trabeculae collected from diabetic patients could not be preconditioned with diazoxide, again implicating dysfunctional mitochondrial K_{ATP} channels in this disease.³¹ Chemically induced dia-

betes¹⁷ or moderate hyperglycemia alone³² abolished ischemic preconditioning in a canine model of experimental myocardial infarction. Moreover, infarct size was directly related to the severity of hyperglycemia produced by the exogenous administration of 15% dextrose or diabetes itself.¹⁷ In the current investigation, infarct size was not affected by moderate or severe hyperglycemia because blood glucose concentrations were only transiently increased and were allowed to return to baseline levels before LAD occlusion.

The current results should be interpreted within the constraints of several potential limitations. The LV AAR and coronary collateral blood flow are important determinants of the extent of myocardial infarction, but no differences in these variables were observed among experimental groups that would account for the current findings. Isoflurane caused similar hemodynamic effects in the presence or absence of hyperglycemia, and there were no differences in hemodynamics between groups after discontinuation of isoflurane. Hyperglycemia alone caused minimal hemodynamic effects. Thus, it is unlikely that the hemodynamic effects of isoflurane or hyperglycemia are responsible for the observed differences in infarct size. Nevertheless, coronary venous oxygen tension was not measured, and myocardial oxygen consumption was not directly quantified in the current investigation. Thus, changes in myocardial metabolism during the administration of isoflurane in the presence or absence of hyperglycemia cannot be completely excluded from the analysis. Acute administration of dextrose produces hyperinsulinemia and hyperosmolality in addition to increases in blood glucose concentration. We previously demonstrated that glucose-induced alterations in cardioprotective signal transduction occur independent of changes in insulin concentration or serum osmolality.¹⁷ The possibility exists that chronic elevation in blood glucose concentrations observed during diabetes may produce different effects on anesthetic-induced

Table 3. Transmural Myocardial Perfusion in the Ischemic (LAD) Region ($\text{ml} \cdot \text{min}^{-1} \cdot \text{g}^{-1}$)

	Baseline	30 min CAO	1 h Reperfusion
CON	0.98 ± 0.13	$0.08 \pm 0.01^*$	$1.61 \pm 0.10^*$
H ₃₀₀	1.06 ± 0.14	$0.09 \pm 0.01^*$	$2.05 \pm 0.25^*$
H ₆₀₀	1.24 ± 0.09	$0.07 \pm 0.01^*$	1.81 ± 0.24
ISO _{0.5} MAC	0.70 ± 0.10	$0.06 \pm 0.01^*$	$1.79 \pm 0.17^*$
ISO _{1.0} MAC	0.68 ± 0.08	$0.06 \pm 0.01^*$	$1.68 \pm 0.33^*$
H ₃₀₀ + ISO _{0.5} MAC	1.14 ± 0.17	$0.08 \pm 0.01^*$	$1.99 \pm 0.23^*$
H ₃₀₀ + ISO _{1.0} MAC	0.80 ± 0.09	$0.06 \pm 0.01^*$	$1.57 \pm 0.18^*$
H ₆₀₀ + ISO _{0.5} MAC	1.11 ± 0.07	$0.06 \pm 0.01^*$	1.26 ± 0.10
H ₆₀₀ + ISO _{1.0} MAC	1.17 ± 0.10	$0.05 \pm 0.01^*$	$1.98 \pm 0.19^*$

Data are mean \pm SEM.

* Significantly ($P < 0.05$) different from baseline.

LAD = left anterior descending coronary artery; CAO = coronary artery occlusion; CON = control; H₃₀₀ and H₆₀₀ = target blood glucose concentrations of 300 and 600 mg/dl, respectively; ISO_{0.5} MAC and ISO_{1.0} MAC = isoflurane 0.5 and 1.0 minimum alveolar concentration, respectively.

preconditioning compared with those observed during acute hyperglycemia. However, we previously showed that both acute hyperglycemia and diabetes prevent ischemic preconditioning³² and pharmacologic protection with diazoxide⁷ to similar degrees. Administration of supplemental oxygen during experimentation could contribute to coronary vasoconstriction by closing vascular smooth muscle K_{ATP} channels.³³ However, arterial oxygen tension measured during these *in vivo* experiments (190 ± 20 mmHg) was well below that level previously shown *in vitro* to cause coronary vasoconstriction (approximately 500 mmHg). Experiments were conducted in an established model of myocardial infarction using acutely instrumented, barbiturate-anesthetized dogs. However, the results obtained in dogs may not be directly comparable to that in anesthetized patients.

In summary, the current results demonstrate that hyperglycemia attenuates or abolishes the myocardial protection produced by isoflurane. The results also demonstrate that anesthetic concentration and severity of hyperglycemia are interactive determinants of myocardial infarct size *in vivo*. Hyperglycemia predicts mortality after myocardial infarction and may contribute to perioperative risk by impairing activation of K_{ATP} channels during ischemic- or anesthetic-induced preconditioning. These findings suggest that perioperative management of blood glucose concentrations may influence cardiovascular risk in humans. Additional investigation will be required to confirm this intriguing hypothesis.

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