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The Effect of Halothane, Isoflurane, and Verapamil on Ischemic-Isolated Rabbit Renal Tubules

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The effects of the volatile anesthetics halothane and isoflurane, and the calcium entry blocker verapamil, were studied in isolated rabbit renal tubules under nonischemic and simulated ischemic conditions. Isolated rabbit renal tubules were subjected to zero (control), 30 (I-30), or 60 (I-60) minutes of simulated ischemia following the method of Weinberg. Following the ischemic period, tubules were reoxygenated in a Gilson respirometer (simulated reperfusion) and treated with either halothane (1%) or isoflurane (1%) in the controls and at I-30, or halothane (1%, 2%, 4%) or verapamil (5 μM, 15 μM, 30 μM) at I-60. Tubules were analyzed for lactate dehydrogenase (LDH) release (measuring cell membrane integrity), intracellular potassium and adenosine triphosphate (ATP), and oxygen consumption (cellular respiratory rate). In nonischemic tubules, exposure to 1% isoflurane caused significantly reduced LDH release compared with that released by controls, indicating cell membrane protection, whereas 1% halothane had no effect on these cells. With 30 min of ischemia, 1% isoflurane was associated with significantly higher cellular LDH release and lower ATP concentration, suggesting increased cellular damage. Halothane (1%) was associated with only an increased ATP concentration in tubules exposed to 30 min of ischemia. Following 60 min of ischemia, halothane (4%) decreased LDH release by 45% (29.2 ± 2.3% *vs.* 47.0 ± 9.6% without halothane). Tubules exposed to halothane also had higher intracellular potassium and ATP concentrations, and increased respiratory rates. Halothane (2%) was less protective and only increased the ATP concentration. The release of LDH was not statistically different with or without 2% halothane. Verapamil (15 μM and 30 μM) was protective to tubular function after 60 min of ischemia. LDH release was less and the intracellular potassium, ATP, and respiration rates were higher in tubules pretreated with verapamil prior to exposure to 60 min of ischemia. It is concluded that halothane (4%) and verapamil (15 μM and 30 μM) are protective, whereas isoflurane (1%) may be detrimental to isolated rabbit kidney tubules after simulated ischemia. Selection of the anesthetic agent may be important for maintaining postischemic renal function. (Key words: Anesthetics, volatile: halothane; isoflurane. Kidney: tubules. Pharmacology, calcium channel blockers: verapamil.)

SURGERY often necessitates partial or complete interruption of blood flow to an organ. Diminished blood flow to the kidney occurs during aortic aneurysm repair, major vascular trauma, renal artery revascularization, and kidney transplantation. The disruption of normal blood flow to the kidney can lead to acute renal failure (ARF) and presents a serious complication to the successful management of these surgical procedures. The role of the anesthetic agent in affecting the extent of ARF following iatrogenic ischemia has not been adequately addressed. In general, currently used anesthetic agents are not particularly injurious to normal renal function, although some of these agents do induce renal vasoconstriction[1] and diminish renal function during surgical procedures. However, except for studies of the effect of fluoride, a major byproduct of the metabolism of methoxyflurane and enflurane,[2,3] it is not known how these anesthetics affect the recovery of function in kidneys exposed to ischemia.

For instance, certain anesthetic agents may exacerbate renal injury following restoration of normal blood flow to a previously ischemic kidney, whereas some agents may be protective and suppress the onset of renal injury. This concern for the role of anesthetic agents in ischemic injury is derived from the fact that many of these drugs have been shown to alter cellular metabolism.[4,5]

Some of the metabolic changes induced by anesthetic agents may affect the postischemic kidney during the initial reperfusion period and can be associated with "reperfusion injury."[6] Reperfusion damage may occur due to the generation of oxygen free radical species,[7,8] alteration in cellular metabolism of calcium,[7,9,10] changes in membrane permeability,[9] cell swelling due to a lack of adenosine triphosphate (ATP) and mitochondrial dysfunction,[9] activation of phospholipases,[11] and the disruption of the cytoskeleton.[7] Anesthetic agents may contribute to reperfusion injury. For instance, anesthetics depress mitochondrial activity,[12] including calcium uptake, which may contribute to increased intracellular cytosolic free calcium and suppress ATP regeneration. The depression of mitochondrial respiration by anesthetics leads to increased lactate formation,[13] which may contribute to cellular acidosis and tissue injury. Anesthetics also alter the structure of cellular membranes, resulting in changes in membrane permeability characteristics.[14] Halothane has been shown to induce lipid peroxidation,[15] due apparently to an oxygen free radical-mediated process. Furthermore, different anesthetics may have varying effects on the rate of recovery of an organ from ischemic injury. Therefore, the anesthetic agent may influence the outcome of organ failure following iatrogenic ischemia.

The study of reperfusion injury *in situ* is complicated by numerous systemic factors that are difficult to control.

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A simpler model involves the use of isolated cells. In this study we have used a model of simulated ischemia and reperfusion in isolated renal tubules, similar to that used by Weinberg.[16] Tubules were exposed to a period of simulated ischemia (anoxic storage), followed by a period of simulated reperfusion (normothermic–oxygenated incubation). To study how anesthetic agents affect recovery from ischemia, tubules were exposed to varying concentrations of anesthetics during the simulated reperfusion period. The results demonstrate that in this model isoflurane can exacerbate ischemic injury, whereas halothane can be protective to the restoration of renal function during simulated reperfusion following ischemia.

Materials and Methods

Isolation of Rabbit Renal Tubules

This study received prior approval from the University of Wisconsin Clinical Health Center Animal Care Committee. Rabbits (3–4 kg) were anesthetized with sodium pentobarbital (18 mg/kg) *via* an ear vein. To ensure adequate surgical anesthesia, lidocaine (1%) was infiltrated in the abdominal midline. Following laparotomy the renal artery and vein of each kidney was dissected, ligated, and divided. A 2-mm cannula was inserted into each renal artery, and the kidneys were flushed *in situ* with 30 ml of heparinized (10 U/ml) solution A (table 1), followed by 30 ml of solution B (table 1) containing collagenase (0.6 mg/ml; Type II, Worthington-Cooper Co., Freehold, New Jersey) and hyaluronidase (4 mg/ml). The cortex was removed, minced with scissors, and suspended in 100 ml of solution B containing collagenase and hyaluronidase. The suspension was stirred (magnetic stirrer) until the cortex was digested (15 min) and filtered through a gauze sponge (16 ply). These procedures were performed at 37° C with solutions equilibrated with O_2–CO_2 (95%–5%).

The filtrate was centrifuged at 60 × *g* for 5 min at 5° C. The sedimented tubules were resuspended in solution B (without collagenase) and washed twice by this same procedure. The tubules were further purified by the procedure of Weinberg[16] using solution B containing Percoll (50 g/100 ml) and centrifuged (37,000 × *g*) at 5° C. The sedimented tubules were suspended in solution B containing 20 mM HEPES (in place of $NaHCO_3$) at a protein concentration of 5.0 ± 1.0 mg/ml (Biuret method). HEPES buffer was substituted for $NaHCO_3$ to lower the concentration of CO_2 in the gas phase of the respirometer flask and reduce the effects of CO_2 on the manometric changes due to O_2 uptake. The *p*H of the HEPES-buffered solution remained at 7.30 ± 0.05 throughout the experiment.

TABLE 1. Solutions for Isolation of Rabbit Renal Tubules

Substance	Solution A (mM)	Solution B (mM)
NaCl	115	115
KCl	2.1	2.1
$NaHCO_3$	25	25
KH_2PO_4	2.5	1.3
$MgSO_4$	2.5	2.5
Dextran	0.6 g/dl	0.6 g/dl
Glucose	5	5
Lactate	4	4
Alanine	1	1
Sucrose	25	25
$CaCl_2$	—	1.3

The microscopic appearance of this tubule preparation was similar to that described by Weinberg[16] and showed short lengths of proximal tubules. The viability of the tubules was judged by determining the extracellular LDH immediately after preparation and suspension in solution B. Only tubule preparations that measured less than 5% extracellular LDH were used for further study. The preparation was warmed to 37° C for 10 min in an Erlenmeyer flask under 100% O_2.

Ischemia

Ischemia was accomplished by gently bubbling the tubule suspension with N_2 (100%) for 10 min at 37° C. The suspension was capped and incubated at 37° C for either 30 or 60 min. The cells immediately settled to the bottom of the flask and remained undisturbed. This method is similar to the simulated ischemia method described previously by Weinberg.[16]

Verapamil

Verapamil (5 μM, 15 μM, or 30 μM) was added to the tubule preparation 5 min prior to the induction of simulated ischemia or 5 min prior to analysis of nonischemic tubules.

Volatile Agents

Tubules (3.5 ml at 5.0 ± 1.0 mg/ml protein) were placed in a respirometer (Warburg) flask and attached to the respirometer (Gilson Differential Respirometer). Either halothane (1%, 2%, or 4%) or isoflurane (1%) was passed through the gassing vent for 5 min while the suspension was continuously shaking. The volatile agent was administered with oxygen (100%) as the carrier gas using a precalibrated (mass spectrometer) vaporizer (Fluotec Mark 2). As shown in figure 1, the volatile agent was administered immediately following the ischemic period.

Functional Analysis

After gassing the tubules with either 100% oxygen or the combination of volatile agent and oxygen for 5 min,

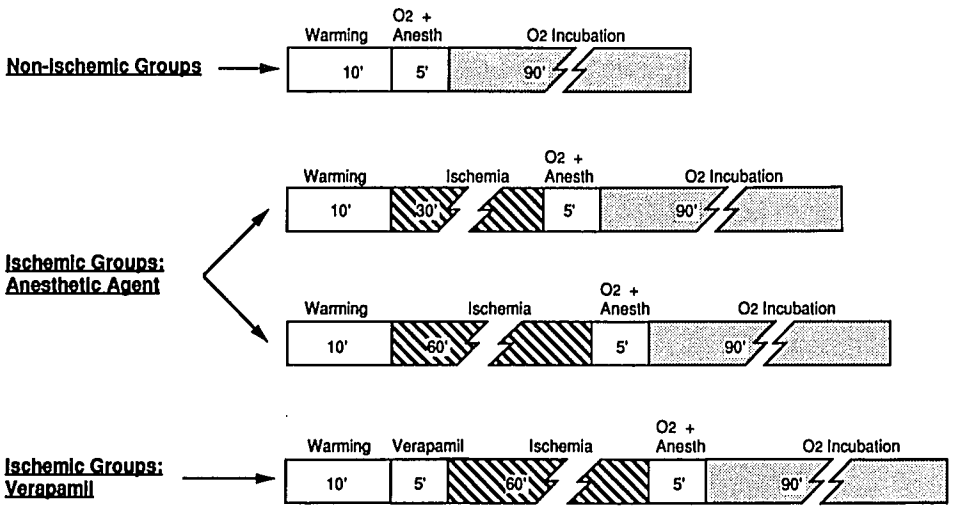

FIG. 1. General protocol used for nonischemic and ischemic groups. Anesthesia represents either halothane or isoflurane.

the respirometer flask was closed to the atmosphere and the suspension equilibrated for an additional 5 min with shaking. The tubules were incubated for a total of 90 min at 37° C under either the 100% oxygen or the oxygen/anesthetic atmosphere. The rate of respiration (nmol oxygen consumed · min^{-1} · mg $protein^{-1}$) was determined manometrically using the respirometer by the method of Umbreit *et al.*[17] Respiration rates were determined at 15-min intervals and remained constant for up to 90 min.

Aliquots of cells were removed at 90 min for determination of extracellular lactate dehydrogenase (LDH), cellular potassium, and ATP concentrations by methods previously described.[16,18]

The following is a brief summary of the methods for metabolite determination:

1. *LDH.* The tubule suspension (0.5 ml) was centrifuged at 13,000 rpm (Eppendorf Microcentrifuge) for 1 min. The LDH activity (Sigma LDH kit #340-UV) was measured in the supernatant and was compared with the total LDH activity in the tubule suspension after disruption of the tubules with sonication. Per cent extracellular LDH (%LDH) = (extracellular LDH divided by total LDH) × 100.

2. *Potassium.* The intracellular potassium concentration was determined by flame photometry after centrifuging the tubules (13,000 rpm) and resuspending the sediment in HNO_3.

3. *ATP.* For determination of ATP, the tubules were pipetted directly into 1 M perchloric acid (4° C), centrifuged at 13,000 rpm, and the supernatant neutralized with KOH. An aliquot of the acid extract was used for separation and quantitation of ATP by high performance liquid chromatography.[19]

Each analysis was done in duplicate and the number of experiments are reported in the legends to the tables. The results shown are the statistical analysis of the 90-min data points following either the conclusion of simulated ischemia or isolation of nonischemic tubules and are expressed as mean ± SD. Statistical analysis was performed using the Mann-Whitney U test between groups. Statistical significance was assumed for $P < 0.05$.

Results

The results shown in table 2 compare the effect of halothane (1%) and isoflurane (1%) on renal tubular cell function following 30 min of simulated warm ischemia. Control tubules (nonischemic) release 17.1% of their intracellular LDH during 90 min of incubation under an atmosphere of 100% oxygen. Potassium concentration remains near normal (227 ± 82 nmol/mg protein), as does the concentration of ATP in the tubules (3.45 ± 1.32 nmol/mg protein). The respiration rate of control tubules was 19.8 ± 5.6 nmol $O_2 \cdot min^{-1} \cdot$ mg $protein^{-1}$. Halothane (1%) had no significant effect on renal tubule function in freshly isolated cells. However, 1% isoflurane decreased LDH release (17.1 ± 7.1% in nonischemic tubules *vs.* 10.5 ± 4.6% in nonischemic tubules with 1% isoflurane).

After 30 min of simulated warm ischemia and simulated reperfusion, renal tubules release more intracellular LDH into the incubation media (34.7%), maintain a lower concentration of cellular potassium (185 ± 62 nmol/mg protein) and ATP (1.24 ± 0.04 nmol/mg protein), and have decreased respiration (10.5 ± 2.4 nmol $O_2 \cdot min^{-1} \cdot$ mg $protein^{-1}$) compared with that in control (nonischemic) isolated tubules. After 30 min of ischemia, tubules incubated in the presence of 1% halothane respond similarly to those incubated in the absence of halothane, except for an increased ATP concentration. Tubules incubated in the presence of 1% isoflurane, however, show an in-

TABLE 2. Comparison of the Effects of 1% Halothane and 1% Isoflurane on Nonischemic and 30-Min Ischemic Tubules

	Nonschemic			30 Min Ischemic		
	Control (n = 4)	Halothane (n = 5)	Isoflurane (n = 4)	Control (n = 5)	Halothane (n = 5)	Isoflurane (n = 4)
LDH (%)	17.1 ± 7.1	16.4 ± 10.2	10.5 ± 4.6*	34.7 ± 12.2*	30.2 ± 5.9	49.1 ± 6.4†
K^+ (nmol/mg protein)	227 ± 82	196 ± 35	199 ± 59	185 ± 62	159 ± 43	136 ± 53
ATP (nmol/mg protein)	3.45 ± 1.32	4.21 ± 1.36	3.21 ± 1.17	1.24 ± 0.04*	3.34 ± 1.81†	0.48 ± 0.46†
Respiration (nmol $O_2 \cdot min^{-1} \cdot mg$ protein^{-1})	19.8 ± 5.6	19.0 ± 7.7	23.0 ± 1.1	10.5 ± 2.4*	12.1 ± 1.4	7.3 ± 2.9

* Value compared with nonischemic control, $P < 0.05$.

† Value compared with ischemic control, $P < 0.05$.

crease in damage. Cellular LDH leakage increased from 30.2% (halothane) to 49.1% (isoflurane), and ATP concentration was decreased to 0.48 ± 0.46 nmol/mg protein (*vs.* 3.34 ± 1.81 nmol/mg protein with 1% halothane). These data demonstrate that at similar concentrations, these two anesthetic agents affect the metabolism of ischemically injured renal tubules differently. Isoflurane appeared somewhat damaging to ischemic renal tubules compared with the effect from halothane. Because only 1% isoflurane exacerbated 30 min of ischemic injury, additional studies were performed with only halothane.

Sixty minutes of simulated warm ischemia induced greater cellular damage than 30 min of ischemia (table 3). LDH release increased from 34.7% to 47.0%, cell potassium was reduced from 185 ± 62 nmol/mg protein to 96 ± 10 nmol/mg protein, ATP concentration was reduced from 1.24 ± 0.04 nmol/mg protein to 0.36 ± 0.15 nmol/mg protein, and respiration was depressed from 10.5 ± 2.4 nmol $O_2 \cdot min^{-1} \cdot mg\ protein^{-1}$ to 6.7 ± 1.8 nmol $O_2 \cdot min^{-1} \cdot mg\ protein^{-1}$. Halothane (1%) had little effect on renal tubule function after 60 min of ischemia. Halothane (2%) stimulated ATP resynthesis (1.12 ± 0.48 *vs.* 0.34 ± 0.21 nmol/mg protein with 1% halothane). However, the amount of LDH released, potassium reaccumulated, and respiratory rates were not different with 2% halothane compared with 1% halothane.

Halothane (4%) after simulated ischemia (60 min) improved cell function after simulated reperfusion. LDH release was reduced from 47.0% (60-min ischemic controls) to 29.2% and cellular potassium was maintained at near-normal concentrations (262 ± 18 nmol/mg protein *vs.* 99 ± 50 and 156 ± 61 nmol/mg protein with 1% and 2% halothane, respectively). ATP concentration was 1.85 ± 0.06 nmol/mg protein *versus* 0.34 ± 0.21 nmol/mg protein (1% halothane). The respiration rate was 12.5 ± 1.0 *versus* 5.4 ± 0.1 and 8.5 ± 1.7 nmol $O_2 \cdot min^{-1} \cdot mg\ protein^{-1}$ for 1% and 2% halothane, respectively.

In addition to determining the effects of halothane on ischemic renal tubule metabolism, we also examined the effects of verapamil (table 4). The addition of verapamil (5 μM) to tubules exposed to 60 min of simulated ischemia had no effect on the rate of recovery of function. However, both 15 μM and 30 μM verapamil appeared to provide protection to the tubules during simulated reperfusion. The presence of verapamil caused a decrease in LDH release from 47.0% (control, 60 min) to 31% (both 15 μM and 30 μM verapamil), and potassium concentrations were elevated from 96 ± 10 nmol/mg protein to 237 ± 49 and 229 ± 11 nmol/mg protein at 15 μM and 30 μM verapamil, respectively. ATP concentration was also increased from 0.36 ± 0.15 to 2.06 ± 0.56 and 1.84 ± 0.26 nmol/mg protein (15 μM and 30 μM verapamil, respectively), and the respiration rate increased from 6.7 ± 1.8 to 11.3 ± 2.9 and 10.7 ± 0.3 nmol $O_2 \cdot min^{-1} \cdot mg\ protein^{-1}$ (15 μM and 30 μM verapamil, respectively).

Discussion

Anesthetic agents, such as halothane and isoflurane, have potent physiologic and biochemical effects but are

TABLE 3. The Effect of 1%, 2%, and 4% Halothane on 60-Min Ischemic Tubules

	60-Min Controls (n = 4)	Halothane 1% (n = 3)	Halothane 2% (n = 4)	Halothane 4% (n = 4)
LDH (%)	47.0 ± 9.6	40.3 ± 6.1	38.4 ± 9.9	29.2 ± 2.3*
K^+ (nmol/mg protein)	96 ± 10	99 ± 50	156 ± 61	262 ± 18*
ATP (nmol/mg protein)	0.36 ± 0.15	0.34 ± 0.21	1.12 ± 0.48*	1.85 ± 0.06*
Respiration (nmol $O_2 \cdot min^{-1} \cdot mg\ protein^{-1}$)	6.7 ± 1.8	5.4 ± 0.1	8.5 ± 1.7	12.5 ± 1.0*

* Value compared with 60-min ischemic control, $P < 0.05$.

TABLE 4. The Effect of 5, 15, and 30 μM Verapamil on 60-Min Ischemic Isolated Tubules

	Controls (n = 4)	Verapamil 5 μM (n = 3)	Verapamil 15 μM (n = 4)	Verapamil 30 μM (n = 4)
LDH (%)	47.0 ± 9.6	41.5 ± 10.2	31.4 ± 4.3*	31.5 ± 8.1*
K^+ (nmol/mg protein)	96 ± 10	104 ± 11	237 ± 49*	229 ± 11*
ATP (nmol/mg protein)	0.36 ± 0.15	0.64 ± 0.33	2.06 ± 0.56*	1.84 ± 0.26*
Respiration (nmol $O_2 \cdot min^{-1} \cdot mg\ protein^{-1}$)	6.7 ± 1.8	5.7 ± 0.2	11.3 ± 2.9*	10.7 ± 0.3*

* Value compared with 60 min ischemic control, $P < 0.05$.

in general relatively safe when administered to various organs under "normal" (nonischemic) surgical situations. It is not clear how these agents affect the biochemistry and physiology of organs previously injured during ischemia. This question has been investigated to some extent in studies in the liver and in isolated hepatocytes,[20,21] but not in the kidney or isolated renal tubules. In this study we have used a renal tubule model of simulated ischemia and reperfusion to determine how two volatile anesthetic agents affect the rate and extent of recovery of function after ischemic damage. This preparation provides a simple model to study the effects of these agents on kidney biochemistry. Unlike an *in situ* model, the renal tubule model allows more control of experimental variables, allows detailed analysis of metabolic reactions at the cellular level, can be readily reproduced, and is not dependent upon differences between systemic factors in whole animal studies. Furthermore, multiple variables can be analyzed using a single preparation of renal tubules from the same experimental animal.

In this study the metabolic parameters measured (ATP concentration, cellular potassium, LDH leakage, and respiratory activity) in nonischemic renal tubules were not affected by halothane. Tubules exposed to simulated warm ischemia showed changes in renal cell function similar to those previously reported; the degree of injury increased with longer warm ischemic times. Warm ischemia caused membrane damage as reflected by the leakage of LDH into the suspending media. After simulated reperfusion, cells were unable to reestablish a normal intracellular potassium concentration and had depression of both respiration rates and ATP concentrations. Tubules exposed to isoflurane (1%) after 30 min of warm ischemia appeared more extensively injured than cells incubated in the absence of the anesthetic agent. This included increased leakage of LDH during simulated reperfusion and decreased ATP concentrations. Although statistical significance (isoflurane plus 30 min warm ischemia *vs.* 30 min warm ischemia) was obtained only for LDH release and ATP concentration, the results suggest that this agent exacerbates warm ischemic injury in tubules. Because increased cellular damage occurred in the presence of 1% isoflurane, higher concentrations were not studied.

In contrast to the results obtained with isoflurane, halothane appeared somewhat protective to renal tubules exposed to 60 min of warm ischemia and reperfusion. The protective effects of halothane, however, required concentrations greater than 1%. In the presence of 2% halothane, increased ATP concentrations were noted in the 60-min ischemic model. All four cellular parameters measured were improved with 4% halothane compared with the 60-min ischemic controls.

It is not clear by what mechanism halothane is protective to ischemic tubules during the simulated reperfusion period. One effect may be to alter calcium metabolism during the reperfusion period. Halothane, in isolated rat ventricular cells, has been shown to inhibit intracellular calcium transport.[4] Hoka *et al.* have demonstrated that halothane reduced calcium uptake into ischemic guinea pig myocardium and have postulated that this property of halothane may be protective to the ischemic tissue.[22] Marijic *et al.* have shown that halothane is protective (increased function of myocardium) to isolated guinea pig hearts after hypoxic injury.[23]

In our study the administration of verapamil to the ischemic tubules suppressed the extent of injury after 60 min of warm ischemia. The effects of verapamil (decreased LDH release, increased uptake of potassium, ATP synthesis, and rate of respiration) were similar to the results obtained with 4% halothane. Thus, both verapamil and halothane suppress ischemic reperfusion injury. This may be accomplished by similar mechanisms related to calcium metabolism.

In this experiment we have chosen to study the effects of volatile anesthetics on reperfusion injury and have not addressed oxygen deprivation injury. The results of this study may be different with the introduction of the anesthetics prior to simulated ischemia, as we did with verapamil.

These results suggest that the selection of an anesthetic agent may be important in determining the rate and extent of recovery of a kidney from ischemia. These data could have important implications in surgical procedures

associated with renal ischemia or in renal transplantation in which the organ is injured by hypothermic storage (cold ischemia). Although in this study the halothane concentration that improved the recovery of ischemic renal tubules is greater than that used clinically, unpublished work in our laboratory has demonstrated that halothane is protective to the ischemic kidney in an *in situ* model at clinically used concentrations (1%).

In the future it will be important to characterize further the effects of the combination of ischemia and the anesthetic agent and to determine the mechanism of protection or damage. These studies may aid the anesthesiologist in determining which agent is indicated for a particular surgical procedure that involves organ ischemia.

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References

1. Cousins MJ, Skowronski G, Plummer JL: Anaesthesia and the kidney. Anaesth Intensive Care 11:292–320, 1983
2. Wickstrom I: Effects of enflurane anesthesia on the function of ischemically damaged kidneys. Acta Anaesthesiol Scand 71:15–19, 1979
3. Mazze RI: Fluorinated anaesthetic nephrotoxicity: An update. Can Anaesth Soc J 31:16–22, 1984
4. Ikemoto Y, Yatani A, Arimura H, Yoshitake J: Reduction of the slow inward current of isolated rat ventricular cells by thiamylal and halothane. Acta Anaesthesiol Scand 29:583–586, 1985
5. Harris RA, Munroe J, Farme B, Kim KC, Jenkins P: Action of halothane upon mitochondrial respiration. Arch Biochem Biophys 142:435–444, 1971
6. Rice MJ: Anesthetics and clinical ischemia, Clinical Ischemic Syndromes: Mechanisms and Consequences of Tissue Injury. Edited by Zelenock GB. St. Louis, CV Mosby, (in press)
7. Bonventre JV: Mediators of ischemic renal injury. Annu Rev Med 39:531–544, 1988
8. Pallar MS, Hoidal JR, Ferris TF: Oxygen free radicals in ischemic acute renal failure in the rat. J Clin Invest 74:1156–1164, 1984
9. Brezis M, Rosen S, Silva P, Epstein FH: Renal ischemia: A new perspective. Kidney Int 26:375–383, 1984
10. Wilson DR, Arnold PE, Burke TJ, Schrier RW: Mitochondrial calcium accumulation and respiration in ischemic acute renal failure in the rat. Kidney Int 25:519–526, 1984
11. Matthys E, Patel Y, Kreisberg J, Stewart JH, Venkatachalam M: Lipid alterations induced by renal ischemia: Pathogenic factor in membrane damage. Kidney Int 26:153–161, 1984
12. Harris RA, Munroe J, Farme B, Kim KC, Jenkins P: Action of halothane upon mitochondrial respiration. Arch Biochem Biophys 142:435–444, 1971
13. Kashimoto S, Tsuji K, Kumazawa T: Effects of halothane and enflurane on myocardial metabolism during post-ischemic reperfusion in the rat. Acta Anaesthesiol Scand 31:44–47, 1987
14. Trudell JR: A unitary theory of anesthesia based on lateral phase separation in nerve membranes. ANESTHESIOLOGY 46:5–10, 1977
15. de Groot H, Noll T: Halothane-induced lipid peroxidation and glucose-6-phosphatase inactivation in microsomes under hypoxic conditions. ANESTHESIOLOGY 62:44–48, 1985
16. Weinberg JM: Oxygen deprivation-induced injury to isolated rabbit kidney tubules. J Clin Invest 76:1193–1208, 1985
17. Umbreit WW, Burris RH, Stauffer JF: Manometric Techniques. Minneapolis, Burgess, 1957, pp 1–17
18. Takano T, Soltoff SP, Murdaugh S, Mandel LJ: Intracellular respiratory dysfunction and cell injury in short-term anoxia of rabbit renal proximal tubules. J Clin Invest 76:2377–2384, 1985
19. Zakaria M, Brown PR: High-performance liquid column chromatography of nucleotides, nucleosides and bases. J Chromatogr 226:267–290, 1981
20. Jee RC, Sipes IG, Gandolfi AJ, Brown BR: Factors influencing halothane hepatotoxicity in the rat hypoxic model. Toxicol Appl Pharmacol 52:267–277, 1980
21. Schieble TM, Costa AK, Heffel DF, Trudell JR: Comparative toxicity of halothane, isoflurane, hypoxia and phenobarbital induction in monolayer cultures of rat hepatocytes. ANESTHESIOLOGY 68:485–494, 1988
22. Hoka S, Bosnjak ZJ, Kampine JP: Halothane inhibits calcium accumulation following myocardial ischemia and calcium paradox in guinea pig hearts. ANESTHESIOLOGY 67:197–202, 1987
23. Marijic J, Bosnjak ZJ, Kampine JP: Protective effect of halothane against hypoxic injury in the isolated guinea pig heart (abstract). ANESTHESIOLOGY 69:A30, 1988