now and Scheller that the mechanisms underlying sudden cardiac arrest during spinal anesthesia are simple and well-understood. As examples, we cite two case reports. In the first,[2] which appears in this issue of ANESTHESIOLOGY, an athletic young physician underwent knee arthroscopy with epidural anesthesia. He had a sudden asystolic cardiac arrest when his surgeon informed him that the outlook for further sports activity was poor. In the second,[3] which appeared in the May, 1988, issue, a patient with clinically asymptomatic sick sinus syndrome received spinal anesthesia for transurethral prostate resection. During the 10-min interval preceding sudden asystole, he was alert, lucid, and a pulse oximeter gave no indication of hypoxemia. After a brief and successful resuscitation, pinprick testing revealed bilateral sensory blockade to $T_6$.

We direct the reader's attention to several valuable comments contained in these letters. Dr. Brown and colleagues at the Mason Clinic report an impressive record of safety in the conduct of over 10,000 spinal anesthetics. Of note, this group advocates the early use of epinephrine in the management of profound bradycardia during spinal anesthesia. This approach is consistent with the principal hypothesis that we advance. Dr. Abramowitz suggests that the risk of hypoxia may be greater during conscious sedation than during general anesthesia. This is an interesting question that is currently under investigation in the ASA Closed Claims Study. Finally, Dr. Jones offers practical clinical advice about the timing and detection of high spinal anesthesia.

ROBERT A. CAPLAN, M.D.
KAREN POSNER, B.A., M.A.
RICHARD J. WARD, M.D., M.Ed.
FREDERICK W. CHENEY, M.D.

*Department of Anesthesiology*
*University of Washington*
*Seattle, Washington 98195*

*Department of Anesthesiology*
*Virginia Mason Clinic*
*P.O. Box 900*
*Seattle, Washington, 98111*

## REFERENCES

1. Caplan RA, Ward RJ, Posner K, Cheney FW: Unexpected cardiac arrest during spinal anesthesia: A closed claims analysis of predisposing factors. ANESTHESIOLOGY 68:5–11, 1988
2. Frerichs RL, Campbell JJ, Bassell GM: Pyschogenic cardiac arrest during extensive sympathetic blockade. ANESTHESIOLOGY 68:943–944, 1988
3. Cohen LI: Asystole during spinal anesthesia in a patient with sick sinus syndrome. ANESTHESIOLOGY 68:787–788, 1988

*(Accepted for publication March 4, 1988.)*

Anesthesiology
68:974–976, 1988

## Hypoxia and Anesthetic–associated Liver Injury in Guinea Pigs

*To the Editor:*—In the recently published work by Hursh *et al.*[1] concerning hepatic oxygen supply in guinea pigs during anesthesia, it was shown that halothane decreases hepatic oxygen delivery to a much greater extent than does isoflurane. It was also demonstrated that, in the guinea pig, a very small fraction (2%) of the total hepatic blood flow was contributed by the hepatic artery as compared to other species where the fraction is 20–35%.

From these data, it was inferred that the guinea pig is highly susceptible to hypoxic insult to the liver, and that the hepatic lesion observed in guinea pigs following halothane anesthesia[2,3] may be the result of "hepatic oxygen deprivation *per se* without a direct involvement of halothane metabolism."[1] If a hypoxic mechanism is the culprit behind the observed halothane-associated hepatotoxicity in the guinea pig model, then it should be possible to magnify the severity of the lesion and to duplicate it with other anesthetics by utilizing severely hypoxic (8–10% $O_2$) exposure conditions. However, exposure of inbred strain 13 guinea pigs to 1% v/v halothane and 10% $O_2$ for 4 h produced no increases over animals breathing 40% $O_2$ in either the incidence of centrilobular necrosis or the severity of injury (table 1). The hypoxic stress to the livers of guinea pigs breathing 10% $O_2$ during halothane exposure was obviously much greater, as indicated by halothane metabolite levels in the plasma. With hypoxia, plasma concentrations of fluoride ion, indicative of reductive (lack of oxygen) biotransformation of halothane, increased four-fold, while levels of the oxidative metabolite, trifluroacetic acid (TFA), decreased three-fold. Total halothane metabolism, indicated by plasma levels of bromide ion, was identical between the groups. An additional indication of the severity of hypoxic stress to the livers of animals breathing halothane and 10% $O_2$ is that three of eight animals demonstrated extensive areas of panlobular coagulative necrosis within the

TABLE 1. Plasma Metabolite Levels and Indices of Hepatic Necrosis following Halothane Exposure* in Guinea Pigs

| Strain† | %$O_2$‡ | Plasma Metabolites§ (μm) | | | Plasma ALT‡‡ (units/ml) | Incidence of Necrosis§§ |
|---|---|---|---|---|---|---|
| | | F¶ | TFA** | Br†† | | |
| Strain 13 | 40 | 3.4 ± 1.5 | 422 ± 118 | 409 ± 98 | 118 ± 60††† | 8/12 |
| Strain 13 | 10 | 14.5 ± 4.0¶¶ | 148 ± 63¶¶ | 429 ± 51 | 145 ± 58††† | 4/8 |
| Inbred Hartley | 40 | 4.1 ± 1.9 | 316 ± 59 | 426 ± 97 | 55 ± 71*** | 0/6 |

All values are $\bar{x}$ ± SD, N = 4–12. All analyses carried out as previously described.[5]* Statistical analysis by ANOVA with a Newman-Keuls multiple comparison.

* 1% v/v halothane, 4h.

† Strain 13 exposures include male and female animals. Inbred Hartley, males only (570–1000 g).

‡ Oxygen concentration during halothane exposure.

§ Immediately after exposure.

¶ Fluoride ion.

** Trifluoroacetic acid.

†† Bromide ion.

‡‡ 48 h after exposure.

§§ Number of animals with centrilobular necrosis/N value.

¶¶ $P < 0.01$ *versus* other treatment groups.

*** $P < 0.05$ *versus* control (ALT = 22 ± 7 units/ml; N = 6) values.

††† $P < 0.05$ *versus* control and inbred Hartley group.

liver. This type of necrosis is a hallmark of hypoxic/anoxic or ischemic injury, and is morphologically and chronologically distinct from the centrilobular necrosis normally observed in the model.[3]

Genetic factors appear to be involved in susceptibility, since an inbred Hartley strain has been shown to be refractory to the lesion,[3] and a breeding study has indicated an inheritable susceptibility.[4] Hursh *et al.* speculated that these observed differences may be due to a "higher hepatic oxygen demand and/or . . . a more severe reduction in hepatic oxygen supply due to a particular sensitivity of the arterial hepatic vasculature to halothane."[1] Our resistant inbred Hartley strain exhibited plasma levels of halothane metabolites that were no different from our susceptible inbred strain 13 animals (table 1). Thus, it can be assumed that there were no large differences in hepatic oxygen supply between the groups, and that this potential mechanism is not adequate to explain the observed differences in susceptibility to injury.

Our efforts to produce an intentional hypoxic/anoxic hepatic lesion in the guinea pig with enflurane and isoflurane have been frustrating at best. We have previously reported little hepatic injury with exposure of guinea pigs to 1.7% enflurane, 8% $O_2$, for 4 h.[3] We have also attempted to expose overnight fasted strain 13 guinea pigs to 1.7% isoflurane and 10% $O_2$. These exposure conditions proved so stressful that animals began dying within 3 h, yet none of these animals developed any hepatic necrosis. This lack of injury differs greatly from the rat models based on hypoxia-related hepatotoxicity, which report extensive necrosis after shorter hypoxic exposure periods.[5,6]

The inability to intensify halothane-associated centrilobular necrosis with hypoxia, or to mimic the lesion with exposure to other anesthetics, would indicate that hypoxia *per se* is not the mechanism behind the halothane guinea pig model. In fact, the guinea pig would appear to be very resistant to hypoxia/anoxia induced liver damage when compared to the rat.[5,6] The data of Hursh *et al.*[1] indicating that the hepatic artery of the guinea pig supplies only 2% of total hepatic blood flow can be interpreted in another way. Such a low fraction could indicate that the liver is less dependent upon the arterial portion of blood flow for oxygen delivery, and is thus more resistant to hypoxic stress or decrease in arterial supply than other species. Of course, the lack of intensification of the halothane-associated hepatic lesion with hypoxic exposure conditions in the guinea pig is also damning of the free-radical, reductive metabolism mechanism of injury.

Unless it can be shown that mimicking reported halothane-induced reductions in hepatic blood flow and oxygenation[1] produces a centrilobular lesion as seen in the guinea pig model,[2,3] other mechanisms must be at work. Observed genetic variations in susceptibility to the model[3,4] could be the result of intrinsic differences in susceptibility to injury or subsequent subcellular reparative abilities.

RICHARD C. LIND, M.S.
A. JAY GANDOLFI, PH.D.
*Department of Anesthesiology*
*College of Medicine*
*University of Arizona*
*Tucson, Arizona 85724*

* Maiorino RM, Gandolfi AJ, Sipes IG: Gas chromatographic method for the halothane metabolites, trifluoracetic acid and bromide in biological fluids. Analyt Toxicol 4:250–254, 1980

## REFERENCES

1. Hursh D, Gelman S, Bradley EL: Hepatic oxygen supply during halothane or isoflurane anesthesia in guinea pigs. ANESTHESIOLOGY 67:701–706, 1987

2. Lunam CA, Cousins MJ, Hall PM: Guinea-pig model of halothane associated hepatotoxicity in the absence of enzyme induction and hypoxia. J Pharmacol Exp Ther 232:802–809, 1985
3. Lind RC, Gandolfi AJ, Brown BR, Hall P: Halothane hepatotoxicity in guinea pigs. Anesth Analg 66:222–228, 1987
4. Lunam CA, Cousins M, Hall P: Genetic predisposition to liver damage after halothane anesthesia in guinea pigs. Anesth Analg 65:1143–1148, 1986
5. Lind RC, Gandolfi AJ, Sipes IG, Brown BR: Comparison of the requirements for hepatic injury with halothane and enflurane in rats. Anesth Analg 64:955–963, 1985
6. Van Dyke RA: Hepatic centrilobular necrosis in rats after exposure to halothane, enflurane, or isoflurane. Anesth Analg 61:812–819, 1982

*(Accepted for publication March 4, 1988.)*

Anesthesiology
68:976, 1988



*In Reply:*—The fact that the severity of hepatic injury could not be magnified nor duplicated by utilizing severely hypoxic conditions does not rule out hepatic oxygen deprivation as the main cause of hepatic injury. Severe hypoxic hypoxia might be, to a great extent, compensated by an increase in cardiac output with subsequent maintenance of minimally needed hepatic blood and oxygen supply. Since hepatic blood flow and oxygen supply were not determined in the mentioned experiments, their assumption might be incorrect.

Regarding the possible role of genetic factors (which are obviously very important), Lind and Gandolfi speculate that, since inbred Hartley strain had approximately the same intensity of reductive metabolism as strain 13, hepatic oxygen supply was the same. Such an assumption might turn out to be incorrect, as did the assumption that similar hypotension is associated with similar reductions in hepatic oxygen supply. Only studies measuring hepatic oxygen supply *per se* would answer this question.

It is impossible to interpret the data the authors describe with respect to exposure of guinea pigs to 1.7% isoflurane at 10% $O_2$. The observation that these "animals began dying within 3 h, yet none of these animals developed any hepatic necrosis" is not surprising, nor does it prove anything regarding the mechanisms of hepatotoxicity: these animals died from myocardial and/or cerebral oxygen deprivation before hepatic necrosis could develop.

I agree with Lind and Gandolfi that a very low hepatic arterial blood flow in the guinea pig "could indicate that the liver is less dependent upon the arterial portion of blood flow for oxygen delivery . . . ." However, it does not necessarily make the liver "more resistant to hypoxic stress:" to the contrary, a decrease in portal blood flow and/or in portal blood oxygen content may be particularly harmful, since such a decrease cannot be compensated by an increase in hepatic arterial blood flow.

In our study,[1] we did not prove, nor did we claim, that hepatic oxygen deprivation *per se,* without an involvement of halothane metabolism, causes hepatic injury. We even stated that "the present study does not exclude the possibility that liver damage in a guinea pig model is related to the reductive metabolism of halothane . . . ." The results of our study just "demonstrate that halothane produces more severe hepatic oxygen deprivation than isoflurane when administered in doses accompanied by similar decreases in MAP." Therefore, it is clear that any developments in this area of knowledge are welcomed.

The new data presented by Lind and Gandolfi in their letter are very exciting, and call for interpretation. The table shows that reductive metabolism of halothane increased four-fold during 10% $O_2$ exposure *versus* 40% $O_2$. However, this substantial increase in halothane reductive metabolites was not associated with a more prominent hepatic damage (increase in ALT or an increase in incidence of hepatic necrosis). In addition, inbred Hartley strain and strain 13 at 40% $O_2$ had a similar intensity of reductive metabolism of halothane as strain 13 at 40% $O_2$. If hepatic injury were due to the reductive metabolism of halothane, the injury should have been similar in these two groups. In reality, however, more prominent damage was observed in strain 13 (table, line 1 *versus* line 3, last 2 columns).

Thus, the data presented in the table do not say anything about the possible role of hepatic oxygen supply, but strongly suggest that liver damage in guinea pigs may result from factors other then reductive metabolism of halothane.

SIMON GELMAN, M.D., PH.D.
*Professor of Anesthesiology and Vice Chairman for Research*
*Department of Anesthesiology*
*The University of Alabama at Birmingham*
*Birmingham, Alabama 35294*

*(Accepted for publication March 4, 1988.)*