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Anesthesiology
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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.

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