## COMPARATIVE EFFECTS OF HALOTHANE ON SINGLE SKINNED MUSCLE FIBERS FROM NORMAL PATIENTS AND PATIENTS WITH MALIGNANT HYPERTHERMIA

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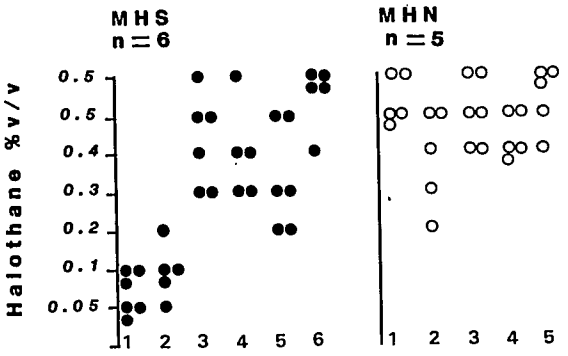
It has been reported that, in single skinned fibers from MH muscle, halothane induced contracture at lower concentrations than in normal muscle. This observation has been the basis for one discriminative method to diagnose MH susceptibility (1). It was of interest to compare it whith the caffeine-halothane contracture test (CHC) recommanded protocol of the North American MH Group (2). Six MH susceptible and 5 MH non susceptible patients were investigated with informed consent and ethical approval. The CHC test has been previously describe for the MH diagnostic procedures (2). Additionnal muscle strips were chemically skinned and single cells were prepared as previously described (3) except that, after loading the sarcoplasmic reticulum, increasing concentrations of halothane were added in the experimental bath. The lowest concentration of halothane was determined as threshold where contraction was first induced in the fiber. For every patient, at least five fibers were assessed. As indicated in table 1, a considerable overlap has been found in the threshold of halothane for tension generation between MH and normal fibers. Only in fibers from 2 MH patients, halothane induced contraction at lower concentrations than in the other patients. These results indicated that the halothane skinned fibre tension test cannot help the in vitro discrimination of MH.

1) Hiroshima, J. Anaesthesia, 16 (suppl):67-69, 1980
2) Anesth. Analg., 69 : 511-515, 1989
3) Can. Anaesth. Soc. J., 6 : 550-562, 1982

TABLE 1 : threshold of halothane concentration for tension generation. Threshold was determined in 33 fibers from 6 MH susceptible patients (MHS) and 26 fibers from 5 normal patients (MHN).




## A354

TITLE: COULD THE TERATOGENICITY OF $N_2O$ IN RATS BE DUE TO ITS SYMPATHOMIMETIC ACTION ON THE EMBRYO?

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Recent evidence casts considerable doubt on the commonly held hypothesis that the reproductive toxicity of $N_2O$ in rats is due to inhibition of methionine synthase.[1,2] An alternative hypothesis based on $N_2O$'s well known sympathomimetic action is that its reproductive toxicity involves an adrenergic mechanism. As a first step in examining this hypothesis, we have compared the teratogenic effects of phenylephrine (PH), an alpha-1 adrenergic agonist, to that of $N_2O$ using an in vitro rat whole embryo culture model.[3,4]

Embryos were explanted on day 9 (plug day = day 0) at 8 a.m. (presomite stage), and were cultured in rotating bottles with a medium containing 0 (control and $N_2O$ groups), 0.01, 0.1, 1, 10, 100, and 500 ug/ml of PH. Embryos in the $N_2O$ group were cultured in the presence of a 75% $N_2O$ atomosphere for the first 24 hours. On day 11 at 10 a.m., culture was terminated and the embryos were examined for gross morphological changes. Data were analyzed by Chi-square test; $p < 0.05$ was considered significant.

$N_2O$ treatment resulted in high incidences of malformed embryos and altered body laterality, i.e., left sided tail (normally right sided) and inverted heart (Table). PH treatment also resulted in a high incidence of altered body laterality but not of malformed embryos. This effect of an alpha-1 agonist on body laterality has not previously been reported.

These results are consistent with the hypothesis that $N_2O$ interferes with the control of body laterality by stimulating alpha-1 adrenergic pathways. Attempts to prevent these changes with alpha-1 antagonists will provide more definitive evidence. However, a different mechanism will have to be found to account for the other morphologic abnormalities.

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References
1. Anesthesiology 67:960-964, 1987.
2. Teratology 38:121-127, 1988.
3. Anesthesiology 69:401-404, 1988.
4. Anesthesiology 71:991-992, 1989.

| | $N_2O$ | | PH (ug/ml) | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Cont | 75% | 0.01 | 0.1 | 1 | 10 | 100 | 500 |
| No. of embryos | 139 | 58 | 49 | 51 | 46 | 47 | 51 | 50 |
| Malform. emb. (%) | 0 | 17* | 0 | 0 | 0 | 4* | 0 | 2 |
| Inverted heart (%) | 2 | 12* | 4 | 4 | 20* | 36* | 35* | 40* |
| Lt. sided tail (%) | 0 | 7* | 0 | 4* | 11* | 13* | 31* | 38* |

* $p < 0.05$ vs. Cont. by Chi-square test