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The Effects of Halothane on Pregnant and Nonpregnant Human Myometrium

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Strips of myometrium were obtained at operation from eight nonpregnant and ten pregnant patients. The tissues were immediately suspended in a muscle bath and induced to contract isometrically with K_2SO_4 in the presence and absence of halothane (0.5 to 2.0 vol per cent). The anesthetic produced significant dose-related depression of developed tension and rates of increase and decrease of tension in both pregnant and nonpregnant muscles. Time to peak tension was increased in the nonpregnant but not in the pregnant muscles. The depressant effect of the lower halothane concentrations (<1.1 vol per cent) was significantly greater in the pregnant muscles. (Key words: Anesthetics, volatile, halothane; Uterus, contractility; Anesthesia, obstetric.)

THE DEPRESSANT EFFECTS of halothane on uterine contractility and the associated intra- and postpartum hemorrhage have been established in numerous clinical reports.[1–8] In consequence, halothane is often not recommended for use in obstetrical practice[9–10] except in those circumstances where uterine relaxation is desired. Nonetheless, halothane, because of its ease of administration, patient acceptance, and safety in surgical areas, is still widely used in obstetrical practice.[10] Indeed, some recent reports[11] have failed to confirm its deleterious effects on the uterus.

Several investigators[12–14] have examined *in vitro* the depressant effect of halothane on uterine-muscle contractility. However, variations in the definitions of contractility and in the methods of administration and measurement of halothane concentration make evaluation of these data difficult. No detailed analysis of a single contraction of an isolated strip of human myometrium in the presence of halothane has been described, and no statistically significant dose–response relationship has been established.

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This study was undertaken to provide data on the effect of halothane on the isometric myogram of isolated human myometrium, to describe dose–response relationships for various contraction modalities, and to compare the results in pregnant and nonpregnant tissues.

Methods and Materials

Eighteen specimens of human myometrium were obtained from the operating room and immediately transported to the laboratory in an ice-cold solution (S). The composition of S in mM was: NaCl, 120; $NaHPO_4$, 1.38; $NaHCO_3$, 25; KCl, 5.0; $MgSO_4\,7\,H_2O$, 1.2; $CaCl_2$, 2.25; glucose, 11.1. Eight of the specimens were cut longitudinally from the upper anterior segment of the uterus during abdominal hysterectomy and were obtained before the uterine arteries were clamped. The remaining ten were excised during elective cesarean section and came from the edge of the lower segment incision.

The muscles were divided into two groups: pregnant (cesarean section) and nonpregnant (hysterectomy). The mean age of the ten pregnant patients was 23 years (range 14–37) and the mean parity was 3. These patients were undergoing either primary or first repeat cesarean section.

The mean age of the eight nonpregnant patients was 45 years (range 34–61) and the mean parity was also 3. Every patient in this group had a proliferative endometrium. In four patients undergoing hysterectomy for fibroids, the tumors were small and the myometrial strips were taken well away from the affected areas. Three patients had pelvic inflammatory disease and one had dysfunctional bleeding. There was no myometrial abnormality in these last four cases.

ABBREVIATIONS

S = a modified Krebs-bicarbonate solution
S + K = S + 125 mM K_2SO_4
S − Ca = S − $CaCl_2$ + 1 mM EGTA
EGTA = ethylene glycol bis (B-amino ethyl ether),N,N − tetraacetic acid
T_{pd} = peak developed tension, the tension produced above resting tension in response to a stimulus
TPT = time to peak tension, the time from onset of contraction to T_{pd}
+dP/dt = maximum rate of tension development
−dP/dt = maximum rate of tension relaxation

TABLE 1. Control Data Obtained from Pregnant and Nonpregnant Muscles

	Pregnant (n = 9)	Nonpregnant (n = 7)	Significance of Difference*
Muscle length (mm)	8.1 ± 0.5	7.8 ± 0.6	*NS*
Muscle cross-sectional area (mm^2)	1.66 ± 0.45	1.94 ± 0.25	*NS*
T_{pd} (g)	3.8 ± 0.7	3.9 ± 1.0	*NS*
TPT (sec)	33.1 ± 1.1	30.9 ± 0.9	*NS*
+dP/dt (g/sec × 10^{-2})	19.5 ± 2.1	21.6 ± 2.9	*NS*
−dP/dt (g/sec × 10^{-2})	2.0 ± 0.23	1.6 ± 0.17	*NS*

*NS = not significant.

All specimens were trimmed to approximately the same size (8 × 2 × 1 mm). Each strip was suspended between ring clamps in a 12-ml muscle bath containing solution S oxygenated with 95 per cent O_2–5 per cent CO_2 and maintained at *p*H 7.4 and a temperature of 30 C. Throughout the experiment, the bathing solution was changed every 15 minutes.

Each muscle was allowed to equilibrate for 30 minutes with an initial resting tension of 0.5 g. At the end of this period, the bathing solution was replaced with a high-potassium (hi-K) solution (S + K: same composition as S but with 125 mM K_2SO_4 added) to induce a single contraction. Two muscles that failed to generate at least 1.0 g developed tension were removed from the study.

Each muscle was studied at a comparable non-calcium-dependent resting tension. This was achieved by replacing solution S with one (S − Ca), which was identical except for the absence of Ca^{2+} and the addition of 1 mM EGTA (which binds calcium by chelation). After 20 minutes in this solution, no muscle developed any tension in response to depolarization with a calcium-free S + K solution. The specimens were then considered to have lost calcium-dependent resting tension and to be functionally calcium-free. When necessary, small increases in length were made to increase non-calcium-dependent resting tension to 0.3 g. Length was then held constant for the remainder of the experiment.

Each muscle was then re-equilibrated in solution S for 30 minutes, during which time full contractile capacity was regained.

Substituting S + K solution for 5 minutes resulted in a control muscle contraction. During the next 30 minutes, halothane was added to the gas mixture; this was followed by 30 minutes without this anesthetic. A myogram was obtained at the conclusion of each of these periods. This sequence was then repeated with another halothane concentration. The order of administering the concentrations of halothane (range: 0.13 to 2.75 per cent measured by gas chromatography) was based on a table of random numbers. Thirteen muscles each received two to four exposures to halothane; three muscles received five exposures. Anesthetic effects were calculated as the differences between measurements obtained with halothane and the means of the two control myograms obtained just prior to and after halothane.

In each isometric myogram, the following were measured: peak developed tension (T_{pd}), the tension produced above resting tension in response to a stimulus; time to peak tension (TPT), the time from onset of the contraction to T_{pd}; and the maximum rates of tension development (+dP/dt) and relaxation (−dP/dt). Isometric tension was detected with a transducer (Statham UC3), displayed on an oscilloscope, and recorded on light-sensitive paper.

At the conclusion of each experiment, muscle length and least diameter were measured. Each muscle was dried overnight and then weighed. Cross-sectional area was calculated based on a specific gravity of 1.054.[15] There was no muscle in which the least diameter exceeded 1.5 mm, the limiting thickness for diffusion of halothane and oxygen in human myometrial strips.[16]

Least-squares regression lines for all modalities examined were calculated from individual changes from control values with halothane. The halothane concentrations were combined around five mean values (0.5, 0.7, 1.1, 1.5 and 2 per cent). Calculations of halothane-induced percentage changes for all modalities were based on group data. The level of significance (Student's *t* test) for the regressions and for differences between the pregnant and nonpregnant muscles at the various anesthetic concentrations was taken as $P < 0.05$.

Results

Control data obtained from the pregnant and nonpregnant muscles are listed in table 1. There was no significant difference between the two groups in either the dimensions of the muscles or their mechanical properties. Thus, although the mean ages of the patients in the two groups differed, the physiologic states of their uterine muscles were comparable.

The regression of change in T_{pd} in relation to halothane concentration was significant for both pregnant and nonpregnant groups (fig. 1*a*). The 0.5 vol per cent halothane concentration reduced T_{pd} 25 per cent in the pregnant muscles, but had no effect in the nonpregnant muscles. However, 2 per cent halothane reduced T_{pd} 60 and 44 per cent in the pregnant and nonpregnant muscles, respectively. The difference between the effects of halothane on pregnant and nonpregnant muscles was significant ($P < 0.01$) with concentrations to 1.1 vol per cent, but not with higher concentrations.

TPT was generally increased by halothane (fig. 1*b*). This increase was dose-related for the nonpregnant muscles but the regression did not achieve statistical significance in the pregnant group. Comparisons between pregnant and nonpregnant mus-

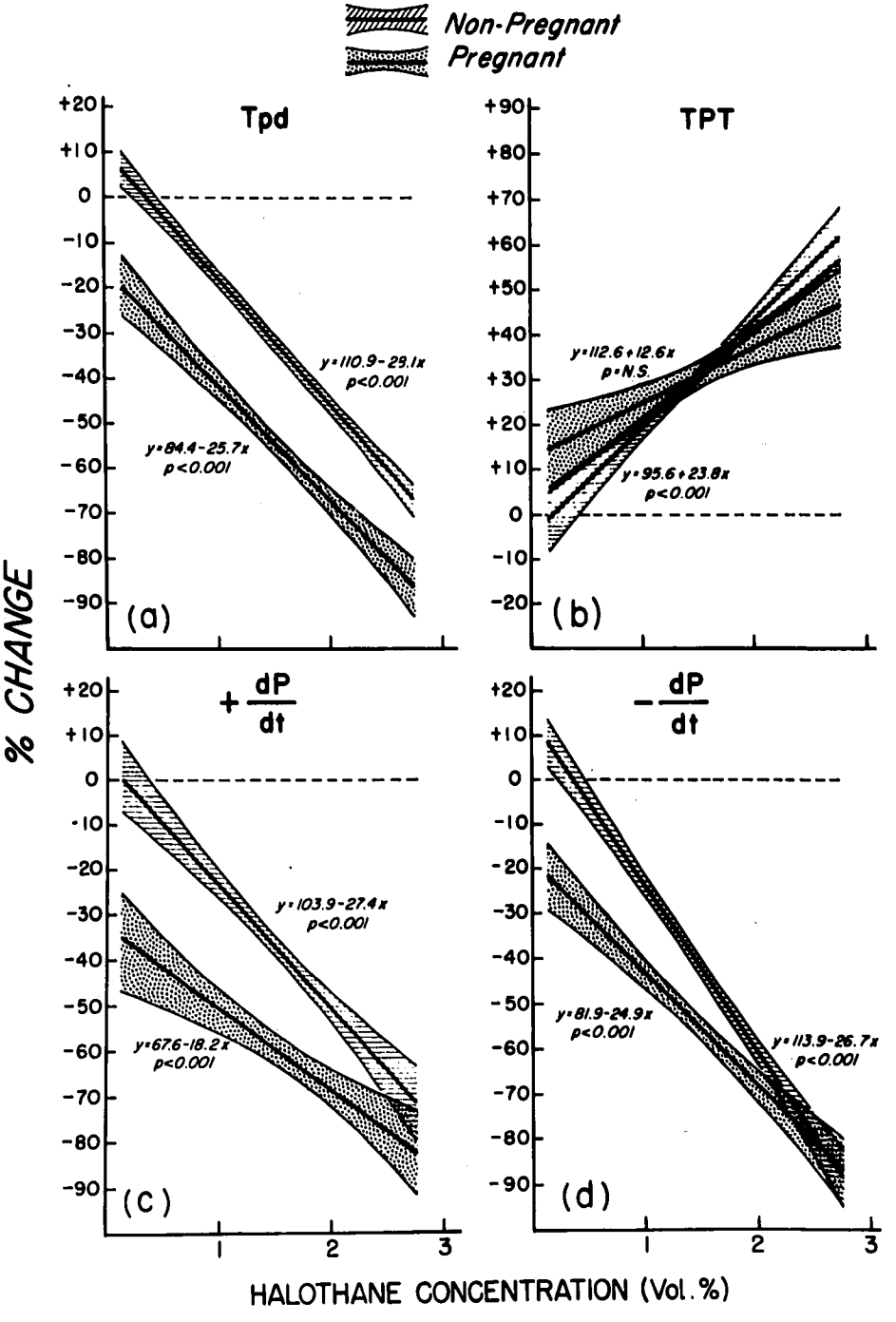

FIG. 1. Least-squares regressions of four modalities of the isometric myograms of pregnant and nonpregnant muscles in relation to halothane concentration. Shaded areas indicate 95 per cent confidence limits.

cles (at each of the five halothane concentrations) showed no significant difference in prolongations of TPT.

The depression in the rate of increase of tension (+dP/dt) was dose-related in both pregnant and nonpregnant muscles (fig. 1*c*). With 0.5 vol per cent halothane, the average depression was 45 per cent for the pregnant and 10 per cent for the nonpregnant muscles, and the difference was significant ($P < 0.05$). However, as the halothane concentration increased, this difference diminished, and with 2 vol per cent halothane reductions of 55 to 65 per cent were found in both groups.

Halothane also reduced −dP/dt in a dose-related manner (fig. 1*d*). Halothane, 0.5 vol per cent, had no effect in the nonpregnant group but reduced −dP/dt by 35 per cent in the pregnant group. With 2 vol per cent halothane, depressions of 60 and 65 per cent occurred in the nonpregnant and pregnant groups, respectively. The difference between the two groups was significant ($P < 0.02$) at the lowest halothane concentration studied only.

Discussion

Evaluation of the pharmacologic effect of a drug *in vitro* is dependent upon steady-state experimental conditions. This situation cannot be achieved with spontaneously contracting myometrium, in which contractility varies from one moment to the next, especially when one compares specimens from different uteri, and even in studying any particular muscle strip.[17] Reduction of the muscle bath temperature to 30 C can abolish spontaneous contractions without significantly altering length–tension characteristics.[17] This reduction in temperature together with chemical depolarization of the muscle in this study provided an adequate steady state, in which the effects of halothane could be recorded. In reviewing the literature, we failed to find any previous work on the effects of halothane on human myometrium in which a similar steady state was obtained.

In order to ensure that our experiments were conducted on the ascending portion of the length–tension curves, a small non-calcium-dependent resting tension was placed on each muscle. That the cross-sectional areas of the muscle strips were fairly uniform and tension developments did not show great variation indicated that all muscles were studied at approximately the same length relative to their length–tension relationships.

Halothane produced significant dose-related depression of human myometrial contractility, as measured by its effects on T_{pd} and +dP/dt in the isometric myogram. These results are compatible with those obtained in previous studies of spontaneously contracting pregnant[12] and nonpregnant[13] myometria. However, Miller *et al.*[12] presented no statistical analysis of their data. Munson's studies[13] are also difficult to evaluate as the modalities measured could have been subject to considerable observer interpretation. In addition, although changes from control were reported, there was no indication of the extent of variation within the control group. Examination of their illustrations suggests that such variation may have been considerable. Although Munson *et al.*[13] described severe, progressive depression of contractility with increasing halothane concentrations, statistically significant changes occurred only with their lowest halothane concentration (0.37 per cent), and the regression of contractility in relation to halothane concentration was not reported as being significant.

In the present study, 0.5 per cent halothane depressed pregnant muscles to a greater extent than nonpregnant muscles, but there was no major difference between the responses of the two groups when the halothane concentration exceeded 1.1 vol per cent. Miller *et al.*,[12] measuring the concentration of halothane necessary to inhibit contractility *in vitro* completely, observed that pregnant muscles were more sensitive to halothane than nonpregnant muscles. There is no indication of how many muscles were studied, nor were graded responses obtained until inhibition occurred.

McDonald-Gibson[14] reported that pregnant myometrium is less sensitive to halothane than nonpregnant myometrium. Since he did not state how he measured changes in contractility in spontaneously contracting muscles, and since he performed no statistical analysis, this claim is difficult to evaluate. Although dose–response curves relating depression of contractility to halothane concentration were constructed, the methods of anesthetic administration and bath concentration measurement prevent comparison with other studies.

By virtue of its tourniquet effect on placental-bed vessels, contraction of uterine muscle limits peripartum bleeding. Depression of this mechanism by halothane may result in hemorrhage. The increased sensitivity of pregnant myometrium, as reported in this study, may compound this problem. These results support restriction on the use of halothane in obstetrics to conditions such as internal podalic version or other intrauterine manipulative procedures where uterine relaxation is desired.[9,10]

Since the process of retraction that occurs during labor and the contracted state of the uterus post partum are tonic states, it is important that the effects of halothane on resting tension—both passive and calcium-dependent—be studied. In previous work on pregnant rat myometrium reported from this laboratory,[18] a 26 per cent reduction of T_{pd} occurred with 1.5 vol per cent halothane and was associated with complete removal of calcium-dependent tone. In the present study of human tissue, similar changes in T_{pd} occurred with 0.5 per cent halothane. This may indicate a shift of the dose–response curve to the left in human myometrium compared with rat myometrium.

In conclusion, these results demonstrate the depressent effects of halothane on pregnant human myometrium and support a limitation of the use of this anesthetic in obstetrical practice.

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The protocol was approved by the Human Studies Committee of the Boston City Hospital prior to this study.

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