PRESSURE ANTAGONISM OF ANAESTHETIC-INDUCED CONDUCTION FAILURE IN FROG PERIPHERAL NERVE

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SUMMARY
Experiments to investigate pressure-induced antagonism of the effects of general anaesthetics in isolated peripheral nerve from the frog are described. The doses of four gaseous general anaesthetic agents required to reduce electrically evoked action potentials by 50% (mean ± SEM) were nitrous oxide 490 ± 40.4 kPa, ethylene 665 ± 212 kPa, dichlorodifluoromethane 108 ± 17.2 kPa and cyclopropane 70 ± 5 kPa. The combination of high pressure and the anaesthetic agent partially or completely restored the action potential amplitudes for the gaseous and some of the volatile agents (chloroform, diethyl ether, halothane). However, reversal of the effects of other volatile agents (ethanol, butanol), sodium pentobarbitone and two local anaesthetic agents (procaine, dibucaine) did not occur. The pressures used to effect a reversal were less than anticipated. This apparent inconsistency with the critical volume hypothesis for anaesthesia is discussed.

There have been many extensions of the classical Meyer-Overton (Meyer, 1899; Overton, 1901) theory of anaesthesia, perhaps the most explicit being that of Mullins (1954) who suggested that the potency of an anaesthetic agent is not related simply to the concentration in the membrane phase, but rather to the increase in the volume of the site of action: that some neuronal membrane crucial to a state of consciousness is expanded by a certain critical volume as a result of the absorption of the anaesthetic molecules. Although not a mechanistic explanation, in the biochemical or even physiological sense, the suggestion links membrane expansion with the state of anaesthesia, rather than simply acknowledging that the two are concurrent events. Consistent with this view of anaesthetic action are the observations that membranes are expanded by anaesthetic agents (Roth and Seeman, 1971; Seeman and Roth, 1972), and that the effects of certain anaesthetics may be antagonized by an increased pressure sufficient to compress an "expanded" membrane to its original dimensions (Lever et al., 1971; Miller et al., 1973).

Antagonism of anaesthesia by pressure was originally reported by Johnson, who showed that increased hydrostatic pressure could reverse the depressant effects of various anaesthetic agents on luminescent bacteria (Johnson, Brown and Marsland, 1942a, b). Later, it was observed that tadpoles anaesthetized with ethanol regained normal swimming when they were exposed to pressures in the range 15 150-35 350 kPa (Johnson and Flagler, 1950, 1951). Several workers have since observed that pressure will antagonize the effects of certain anaesthetic agents on the squid axon (Spyropoulos, 1957a), model membranes (Johnson and Miller, 1970; Trudell et al., 1973) and whole animals (Halsey and Eger, 1971; Lever et al., 1971; Miller et al., 1972).

A quantitative study on newts demonstrated that 10 100 kPa of helium pressure completely reversed the anaesthetic effect, and it was calculated that this pressure counteracted an expansion of about 0.5% in membranes (Miller et al., 1973). Similarly anaesthetic agents at surgical concentrations expand erythrocyte membranes (Roth and Seeman, 1971) by an amount calculated to be approximately 0.5% (Seeman et al., 1969).

The concept of pressure reversal is implied rather than explained by the critical volume hypothesis. This study was undertaken to investigate the effects of pressure and anaesthetic agents on a peripheral nerve structure and to determine whether the expansion hypothesis may be advanced for such a system.

METHODS
The sciatic nerve from pithed frogs (Rana temporaria) was dissected from close to the vertebral column to
a point beyond the knee, including both the peroneal and tibial branches. The excised nerves were immediately placed in oxygenated frog Ringer solution at 21 ± 1 °C, buffered at pH 7.0 with Tris buffer. They were maintained in this solution for a minimum of 1 h before testing.

The nerves were placed in one of two types of specially designed Perspex chambers. In the first chamber, used with gaseous and volatile anaesthetic agents, the nerve was suspended on platinum electrodes and extended slightly by fastening silk thread attached to the nerve ends in miniature clamps at each end of the chamber. Sufficient humidity was maintained by placing absorbent cotton-wool soaked in Ringer solution along the bottom of the chamber.

In the other chamber the nerve was laid in position across narrow electrode wells which were then sealed and insulated from each other with petroleum jelly. The wells were then filled with Ringer solution and platinum electrodes provided electrical contact between the solution and the stimulating and recording apparatus. Between the pairs of stimulating and recording electrodes, the nerve passed through a larger well containing either Ringer solution or anaesthetic solution.

The nerve chamber was placed into a cylindrical stainless steel pressure vessel of 300 ml capacity. Temperature was monitored by a miniature glass bead thermistor, approximately 5 mm above the nerve, and was maintained at 21 ± 1 °C.

Square-wave impulses from a stimulator (Bell and Stein, 1971) were applied via an isolation transformer to the spinal end of the nerve, the cathode being distal to the anode to avoid anodal block. A supermaximal stimulus of 0.05-ms duration was delivered once per second throughout the experiment. The evoked action potential was displayed on an oscilloscope (Tektronix) and photographed (Grass Kymograph Camera).

The threshold to electrical stimulation, height of action potential, and conduction time were measured. Conduction velocities were determined from measurements made between the peak heights of two action potentials recorded from two pairs of electrodes spaced approximately 10 mm apart. Diphasic action potentials were compared with monophasic action potentials recorded with the distal electrode placed either on a crushed portion of the nerve or on a portion of the nerve immersed in isotonic potassium chloride solution. Since there appeared to be no significant difference in these responses, diphasic action potentials were recorded as a rule.

Gaseous anaesthetic agents were introduced into the sealed vessel to the desired pressure after flushing with oxygen for 1 min; volatile anaesthetic vapours were carried in oxygen through the vessel for a period of 2–5 min, their concentration being measured by gas chromatography. The anaesthetic solution pH was 7.1 units except when the amines were introduced, when pH was 8.5. All control measurements were made immediately before the addition of the anaesthetic and an interval of not less than 15 min was allowed for equilibration, the length of time chosen depending on the particular anaesthetic agent used. The release of the anaesthetic gas or vapour or removal of the local anaesthetic solution, followed by washing with Ringer solution, always restored the threshold action potential amplitude and conduction velocity to the control values. After equilibration, the pressure was increased by introducing helium and subsequent measurements were made after transient increases in temperature (up to 5 °C), resulting from increasing pressure, had returned to control value.

To determine the role of temperature, a small heating element was constructed to enable the environmental temperature inside the pressure vessel to be increased at a rate identical to that occurring during compression. The 5 °C increase in temperature had no effect on the depressed action potentials.

To test the effect of pressure alone, nerves were maintained at pressure for a brief period only (5 min); these nerves were still viable with unchanged action potentials after decompression. Following longer periods at pressure (3 h) there was no difference in the recorded action potential compared with the original response. However, in these nerves, severe drying and "decompression sickness" occurred on returning to ambient pressure.

In some experiments nitrous oxide was used as the anaesthetic agent and the pressure was increased by the addition of nitrogen to show that reversal was not an artefact of helium gas.

To demonstrate the antagonism in mammalian nerve, experiments were performed on isolated non-myelinated C fibres of desheathed rabbit vagus nerve. These nerves were bathed with oxygenated Krebs' solution at 20 °C after removal and were stimulated thereafter at 20 V for 0.2 ms once per second. Diphasic action potentials were recorded from two electrodes separated by a sucrose well. The effect of pressure alone and nitrous oxide plus pressure were studied as described above.

Four gases, capable of producing conduction blockade in peripheral nerve below their saturated...
vapour pressures at room temperature, were chosen for this study: nitrous oxide (N$_2$O), ethylene (C$_2$H$_4$), dichlorodifluoromethane (CF$_2$Cl$_2$) and cyclopropane (C$_3$H$_6$). Dose–response curves for these agents in peripheral nerve were determined. The volatile agents studied were chloroform, diethyl ether, halothane, ethanol and butanol; the non-volatile agents were dibucaine hydrochloride, procaine hydrochloride and sodium pentobarbitone.

RESULTS

The mean partial pressures (± SEM) required to reduce action potentials to 50% of control (ED$_{50}$) were 490 ± 40.4 kPa for N$_2$O, 665 ± 212 kPa for C$_2$H$_4$, 108 ± 17.2 kPa for CF$_2$Cl$_2$ and 70 ± 5 kPa for C$_3$H$_6$.

The effect of 6868 kPa of helium on the evoked action potential in frog sciatic nerve is shown in the stimulus response curves in figure 1. In 14 experiments with helium alone, the threshold was unchanged and action potentials remained constant, or decreased by not more than 5% of the control value at pressures up to 10 100 kPa.

Table I summarizes the action potential data for all the compounds tested in this way. The response at a specified dose of anaesthetic agent is compared with the responses at the same dose in the presence of helium at total pressures of 6868 and 10 302 kPa. The level of significance reached for the difference between the height of action potential in the presence of anaesthetic agent, both with and without applied pressure, is quoted where $P<0.05$. Although significance can, in general, be attached to the antagonism
of anaesthesia by pressure for the gases and vapours, this does not apply for the local anaesthetics following which an enhancement of their action by pressure may have occurred.

The mean conduction velocity of 40 of the nerves tested was $21.8 \pm 1.2 \text{ m s}^{-1}$. This is in agreement with the value of $23.5 \text{ m s}^{-1}$ quoted by Meyer and Hegmann (1971) for the conduction velocity measured at 20 °C in frog sciatic nerves from North American frogs acclimatized at 23 °C. Helium, 6868 kPa for 15 min, decreased conduction velocities in 12 nerves by a mean of 3%. Table II shows comparative changes in the conduction velocity of nerves tested with the gaseous anaesthetic agents and then subjected to pressure. The changes in the conduction velocity reflect the changes in the action potential amplitude, but to a less marked degree.

In two nerves exposed to 6868 kPa of nitrogen for 15 min, action potentials were depressed to a mean of 80% of the control values. In two other nerves the action potential amplitude was depressed to a mean of 30% of control by 545 kPa of nitrous oxide. The latter pair of nerves was then exposed to nitrogen at 6868 kPa for 15 min, which restored their action potential amplitudes to a mean of 55% of control values. If the slight depressant effect of nitrogen alone is discounted, this approaches the degree of reversal caused by helium. If there were no reversing effect of pressure per se, such a mixture of nitrous oxide and nitrogen would be expected to

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### Table I. Effects of gaseous, volatile and local anaesthetic agents alone and with pressure on the action potential in frog peripheral nerve. Mean ± SEM (no. of experiments)

<table>
<thead>
<tr>
<th>Anaesthetic</th>
<th>Dose</th>
<th>Height of action potential (% of control height)</th>
<th>Under dose of anaesthetic stated</th>
<th>Under anaesthetic at a total pressure of</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>6868 kPa</td>
</tr>
<tr>
<td></td>
<td>kPa</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nitrous oxide</td>
<td>545</td>
<td>$56 \pm 7$ (12)</td>
<td>$98 \pm 1$ (6)</td>
<td>$100 \pm 0$ (3)</td>
</tr>
<tr>
<td></td>
<td>686</td>
<td>$32 \pm 8$ (17)</td>
<td>$69 \pm 8$ (2)</td>
<td>$71 \pm 3$ (2)</td>
</tr>
<tr>
<td></td>
<td>828</td>
<td>$7 \pm 2$ (29)</td>
<td>$32$</td>
<td>$36 \pm 7$ (4)</td>
</tr>
<tr>
<td>Ethylene</td>
<td>616</td>
<td>$53 \pm 3$ (15)</td>
<td>$63 \pm 6$ (4)</td>
<td>$64 \pm 8$ (3)</td>
</tr>
<tr>
<td>Dichlorodifluoromethane</td>
<td>121</td>
<td>$43 \pm 7$ (5)</td>
<td>$77 \pm 5$ (5)</td>
<td>$71 \pm 6$ (3)</td>
</tr>
<tr>
<td>Cyclopropane</td>
<td>69</td>
<td>$54 \pm 2$ (23)</td>
<td>$74$</td>
<td>$74 \pm 10$ (5)</td>
</tr>
<tr>
<td>Chloroform</td>
<td>2</td>
<td>$58 \pm 5$ (4)</td>
<td>$65 \pm 10$ (3)</td>
<td>$71 \pm 1$ (2)</td>
</tr>
<tr>
<td>Diethylether</td>
<td>5.7</td>
<td>$68 \pm 4$ (6)</td>
<td>$86 \pm 3$ (4)</td>
<td>$89 \pm 3$ (3)</td>
</tr>
<tr>
<td>Halothane</td>
<td>3.6</td>
<td>$50 \pm 6$ (4)</td>
<td>$74 \pm 7$ (4)</td>
<td>$P&lt;0.05$</td>
</tr>
<tr>
<td></td>
<td>5.6</td>
<td>$25 \pm 1$ (2)</td>
<td>$23 \pm 9$ (3)</td>
<td>$P&lt;0.05$</td>
</tr>
<tr>
<td>Ethanol</td>
<td>mol/litre</td>
<td>$5.1 \times 10^{-1}$</td>
<td>$72 \pm 10$ (5)</td>
<td>$46 \pm 14$ (5)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$6.0 \times 10^{-1}$</td>
<td>$60$</td>
<td>$51 \pm 4$ (2)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$6.9 \times 10^{-1}$</td>
<td>$43 \pm 16$ (4)</td>
<td>$26 \pm 12$ (3)</td>
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<tr>
<td>Butanol</td>
<td>mol/litre</td>
<td>$6.8 \times 10^{-2}$</td>
<td>$70 \pm 4$ (2)</td>
<td>$59$ (1)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$2.0 \times 10^{-5}$</td>
<td>$48 \pm 11$ (3)</td>
<td>$48 \pm 8$ (3)</td>
</tr>
<tr>
<td>Dibucaine</td>
<td></td>
<td>$1.0 \times 10^{-2}$</td>
<td>$6 \pm 6$ (4)</td>
<td>$0 \pm 0$ (2)</td>
</tr>
<tr>
<td>Procaine</td>
<td></td>
<td>$5.0 \times 10^{-3}$</td>
<td>$58$</td>
<td>$57 \pm 9$ (3)</td>
</tr>
</tbody>
</table>

* The variance ratio test indicated that the null hypothesis on which Student's $t$ test is based is invalid in this case. Although the means are clearly different, the variances about these means are also very different.
† Interpolated from the pressure-response curve.
‡ Interpolated from the dose-response curve.
produce a depression of action potential amplitude greater, at least, than the same partial pressures of nitrous oxide or nitrogen alone.

Helium at 6868-10 302 kPa for 1 h had no effect on the action potential in the rabbit vagus nerve. Nitrous oxide at 828 kPa depressed the action potential to 72% of its control. When pressurized to 6868 kPa the action potential was restored to 96% of its original value; 10 302 kPa caused a complete restoration.

**DISCUSSION**

The results demonstrate that, notwithstanding the high doses of anaesthetic agents and correspondingly high membrane concentrations or membrane volume expansions, pressures of less than 10 100 kPa may produce a reversal of anaesthesia in both mammalian vagus and frog sciatic nerve.

The effects of helium pressure alone on threshold, action potential amplitude and conduction velocity are similar to those reported by Marshall (1951) and Spyropoulos (1957b), although, in squid axon, Spyropoulos (1957a) detected a reduction in threshold at this order of pressures.

Kendig, Trudell and Cohen (1975) have shown antagonism of the effects of halothane and, to a lesser extent, of ethanol on the compound action potential of directly stimulated preganglionic sympathetic nerve trunk in rats by pressures of 3535-17 271 kPa. Spyropoulos (1957a) reversed the depression caused by 3% ethanol on squid axon at pressures ranging from 20 604 to 48 076 kPa, but we were unable to reverse the effects of ethanol and, indeed, of all the other agents we studied in solution. It is possible that our pressures were too low or that our technique with solutions introduced an artefact which we could neither eliminate nor explain. With the gases and vapours the whole nerve was anaesthetized, whereas with the solutions only a portion of nerve was exposed to the drug. In an experiment in which, except for a 10-mm section in the middle, a nerve was sealed with a thick layer of petroleum jelly and exposed to nitrous oxide, successful reversal was achieved. Nevertheless, the difference in technique may be important when solutions are used.

The finding that the threshold to electrical stimulation of the nerve is increased by all the gaseous anaesthetic agents but that this increase cannot be reversed significantly by high pressure is most interesting. An increase in resistance between the stimulating electrodes could explain the increase in threshold but, although this resistance was not measured, nerves under helium pressure for 3 h showed no changes in threshold. This suggests that pressure did not alter the contact between electrodes and tissue, and that the increases in threshold were not a result of artefacts. The implication is that the anaesthetic "stabilizes" the nerve membranes and pressure does not act on those same membranes in a reciprocal manner. Therefore pressure does not act at the same site as the anaesthetic agent.

If expansion of the membrane were the only requisite for depression of peripheral nerve activity, then pressure should counteract equally the effects of all the anaesthetic agents studied. Despite the difficulties, mentioned above, with anaesthetic solutions, it seems that pressure is not equally effective over the range of agents studied. Again, this suggests an independent stimulatory action of pressure. Recent studies in mice suggest different degrees of pressure...
reversal for nitrous oxide, argon and nitrogen (Smith et al., 1975), and that the dose–response curve for phenobarbitone anaesthesia in mice is steeper at 10 100 kPa than at 101 kPa (Winter et al., 1975). All these findings tend to suggest that pressure is acting independently and at a different site from the anaesthetic agents.

However, such circumstantial evidence against the mechanistic reciprocity between pressure and anaesthesia does not preclude the critical volume hypothesis from consideration in the mechanism of anaesthesia or its interaction with pressure. Considering expansion alone, a dose of anaesthetic required to abolish rolling response in 50% of newts indicates a membrane expansion of about 0.5%. This expansion is opposed by 10 100 kPa pressure which implies a membrane compressibility of the order of 505 x 10^{-10} kPa^{-1}. For peripheral nerve a pressure of 6868 kPa can change the required dose of nitrous oxide by at least 303 kPa which, based on olive oil, indicates an expansion of at least 1%. This suggests a membrane compressibility of at least 152 x 10^{-10} kPa^{-1}, that is a fluid more compressible than most organic liquids at 20 °C. Although such large compressibilities are unexpected classically, it is not inconceivable that in a biological membrane, where condensed and expanded liquid phases may coexist with a range of phase transition temperatures (Ueda, Shieh and Eyring, 1974), a pressure-induced volume change may take place with a low free energy change and an abnormally high compressibility (Wisnieski et al., 1974). Thus, although the observation of pressures used in this system may be surprising in view of the critical volume model using conventional compressibilities, the possibility of high membrane compressibilities implies that the critical volume model cannot be excluded.

Observations on spin-labelled phospholipid vesicles (Trudell et al., 1973) indicate that exclusion of the anaesthetic molecule from the membrane phase is unlikely to provide an explanation of the pressure antagonism of gaseous anaesthetic agents. Alternatively, displacement within the membrane, that is relocation of the anaesthetic agent to a pressure-induced site, may be important. An active pressure-induced site would explain pressure enhancement, and an inactive site pressure reversal. The work of Hsia and Boggs (1973) gives some support to this concept. TEMPO (2,2,6,6-tetramethyl piperidine-1-oxyl), a water soluble lipophilic spin label with nerve-blocking properties, appears to be relocated preferentially to an active pressure-induced polar site within the membrane under conditions of minimal excess aqueous free TEMPO at pressure. The observed enhancement of the nerve-blocking effect of TEMPO under pressure (Roth, 1975) is consistent with the interpretation of the electron spin resonance data. Conceivably, the differential efficacy of different anaesthetic molecules at particular pressure-induced sites could lead to the observation of antagonism, enhancement or independence of anaesthetic effects on pressure over a range of agents, although the nature of such specific differentiation cannot be explained readily.

In conclusion it may be inferred that, for our simple system, the mode of action is unlikely to be described simply by the critical volume model without modification. Whilst this study cannot differentiate between a direct mechanism of antagonism or, for example, a fortuitous coincidence of anaesthetic depression and pressure stimulation these results tend to support the latter view. The interaction between anaesthesia and pressure, observed in whole animal systems, may also be agent dependent and it is necessary to examine further the pressure-dependence of the effects of non-gaseous, non-volatile anaesthetic agents in whole animals.

ACKNOWLEDGEMENTS

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REFERENCES


**ANTAGONISMO DE LA PRESION SOBRE EL NERF PERIPHERICO DE LA GRENOUNILLE PAR SUITE DE L'INSUFFISANCE DE CONDUCTION DUE A L'ANESTHESIE**

**RESUME**

On décrit dans ce document les expériences qui ont été faites pour étudier l'antagonisme des effets des agents anesthésiques généraux, antagonisme provoqué par la pression sur le nerf périphérique isolé de la grenouille. Les doses de quatre agents anesthésiques généraux gazeux requises pour réduire de 50% (moyenne ± erreur standard des moyennes) les possibilités d'action provoquées électriquement, ont été les suivantes: Protoxyde d'azote 490 ± 40,4 kPa, éthylène 665 ± 212 kPa, dichlordifluorométhane 108 ± 17,2 kPa et cyclopropane 70 ± 5 kPa. La combinaison de la haute pression et de l'agent anesthésique a partiellement ou complètement restauré les amplitudes potentielles d'action des agents gazeux et de certains agents volatils (chloroforme, éther diéthyl, halothane). Cependant, il ne s'est produit aucune inversion des effets des autres agents volatils (éthanol, butanol), du pentobarbitone de sodium et de deux agents anesthésiques locaux (procaïne, dibucaine). Les pressions exercées pour provoquer l'inversion ont été inférieures à celles auxquelles on s'attendait. On discute dans ce document de cette inconsistence apparente de l'hypothèse du volume critique pour l'anesthésie.

**DRUCK-ANTAGONISMUS DES LEITUNGSVERSAGENS AUFGRUND VON NARKOSE IN DEN PERIPHEREN NERVERN VON FRÖSCHEN**

**ZUSAMMENFASSUNG**

Der durch Druck hervorgerufene Antagonismus der Auswirkungen einer allgemeinen Narkose in isolierten peripheren Nerven beim Frosch wird beschrieben. Die Dosen von vier gasförmigen allgemeinen Narkosemitteln, benötigt zur Verringerung der elektrisch hervorgerufenen Aktionspotentiale um 50%, waren 490 ± 40,4 kPa Protoxyd, 665 ± 212 kPa Äthylen, 108 ± 17,2 kPa Dichlordifluormethan und 70 ± 5 kPa Cyclopropan. Die Kombination von hohem Druck mit dem Narkosemittel stellte ganz oder teilweise die Aktionspotentiale der gasförmigen und mancher flüchtiger Narkosemittel (Chloroform, Diäthyäther, Halothan) wieder her. Dagegen trat eine Wirkungs-umkehr anderer flüchtiger Mittel (Äthanol, Butanol), Sodium Pentobarbiton und zweier Lokalanästhesiemittel (Procain, Dibucain) nicht auf. Die verwendeten Drucke zur Erzielung einer Umkehrung waren niedriger als erwartet, und diese scheinbare Gegensätzlichkeit zur Hypothese des kritischen Volumens für Narkose wird diskutiert.

**ANTAGONISMO POR PRESION, DE FRACASO EN LA CONDUCCION DE NERVIOS PERIFERICO EN LA RANA, INDUCIDO POR ANESTESICO**

**SUMARIO**

Se describen experimentos para investigar antagonismo inducido por presión de los efectos de anestésicos generales
en el nervio periférico aislado de la rana. Las dosis de cuatro agentes anestésicos generales gaseosos requeridas para reducir potenciales de acción provocados eléctricamente a un 50% (promedio ± SEM) fueron: oxido nitroso 490 ± 40,4 kPa, etileno 665 ± 212 kPa, diclorodifluorometano 108 ± 17,2 kPa, y ciclopropano 70 ± 5 kPa. La combinación de presión elevada y agente anestésico restableció parcial o totalmente las amplitudes de potencial de acción para los agentes gaseosos y algunos de los volátiles (cloroformo, éter dietilico, halotano). Sin embargo, no se produjo inversión de los efectos de otros agentes volátiles (etanol, butanol), pentobarbitona sódica, y de dos anestésicos locales (procaína, dibucaina). Las presiones usadas para efectuar una inversión fueron menores de lo anticipado. Esta aparente inconsistencia respecto a la hipótesis del volumen crítico para anestesia es comentada aquí.