

## Heparin Nitroglycerin Interaction

*To the Editor:*—Resistance to the anticoagulant effect of heparin rightly concerns all anesthesiologists who administer the drug intraoperatively. Recently, an interaction between heparin and nitroglycerin (NTG) has been described in the medical literature. This interaction has been reported in at least three studies.<sup>1-3</sup>

Col *et al.*<sup>1</sup> were the first to describe this drug interaction and studied it *in vitro* by examining the effect of heparin and NTG or propylene glycol on the aPTT. They describe a decreasing clotting time associated with increasing concentrations of NTG or propylene glycol. They also examined this interaction *in vivo* in five normal subjects by measuring the effect on the aPTT of the injection of heparin 30 IU/kg alone (control) and mixed in a syringe with NTG 0.2 ml (0.3 mg) or its diluent propylene glycol 0.2 ml. At 30 min there was a 70% reduction in aPTT with heparin and NTG, and a 49% reduction with heparin and propylene glycol. A further investigation in a group of eight patients with coronary disease, treated with iv NTG infusing at 50  $\mu$ g/min (0.33 ml/min propylene glycol), revealed similar results. Two hours after the initiation of the NTG infusion, heparin 30 IU/kg was injected intravenously, and 30 min after that injection the aPTT was measured. The aPTT increased to  $66 \pm 7$  s, which was only 61% of the increase obtained with this dose of heparin in normal subjects ( $P < 0.05$ ).

Habbab and Haft<sup>2</sup> examined whether this resistance to the action of heparin was present with simultaneous NTG and heparin infusions. In a study of seven patients, their observations, presented graphically, indicated that an increase in the infusion rate of NTG causes the aPTT to decrease in spite of a constant heparin infusion rate. Conversely, slowing the NTG infusion led to an increase in aPTT. These effects were seen regardless of whether propylene glycol was included in the preparation. Though their results were not subjected to statistical analysis they concluded that the addition of NTG and not propylene glycol is responsible for heparin resistance.

Pizzulli *et al.*<sup>3</sup> conducted a clinical study with patients receiving simultaneous heparin and NTG infusions. In this study the heparin infusion was titrated to achieve an aPTT  $> 100$  s; then while continuing to infuse heparin, NTG was begun intravenously at 2–5 mg/h. During these simultaneous infusions aPTT decreased significantly from 130

$\pm 28$  s to  $60 \pm 23$  s ( $P < 0.01$ ). Following termination of the NTG infusion the aPTT returned to the initial value ( $126 \pm 30$  s). In nine of the 27 patients studied, heparin concentrations were also measured. Interestingly, the heparin concentration found during infusion of heparin alone ( $0.31 \pm 0.1$  IU/ml) was unchanged from the heparin concentration discovered during concurrent infusion of NTG and heparin ( $0.28 \pm 0.18$  IU/ml), leading these investigators to conclude that the NTG induced a reversible heparin resistance. They recommended adequate testing of aPTT and appropriate adjustment of heparin infusion whenever NTG is simultaneously being infused.

Due to the increasing number of intravascular and surgical procedures that require the concomitant use of parenteral heparin and NTG we believe this newly reported drug interaction has obvious importance to all practicing anesthesiologists and is worthy of further investigation.

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## Effects of Nitrous Oxide on Rat Embryos Grown in Culture

*To the Editor:*—We previously reported that “the rat whole embryo culture system” is a useful *in vitro* model for studying the mechanisms of nitrous oxide ( $N_2O$ ) teratogenicity.<sup>1</sup> The system that we described involved explanting embryos on the morning of gestational day 10 (early organogenesis stage; approximately 10 somites), and culturing them in an atmosphere of 75%  $N_2O$  for 22 h. Morphologic and biochemical abnormalities were seen. The reviewers of the paper correctly commented, however, that the total number of morphologic abnormalities (7/54) among  $N_2O$  exposed embryos was only just different ( $P = 0.02$ ) from controls (0/46). Furthermore, specific types of ab-

normalities were present in too few a number to be statistically significant. We have now performed additional experiments which demonstrate that rat embryos are more sensitive to the adverse effects of  $N_2O$  when exposed on gestational day 9. Specifically, we cultured embryos in an atmosphere of 50–75%  $N_2O$  for 24 h starting on the morning of day 9 (early somite stage; 0–1 somites), and we have found that when examined on day 11 there was a highly significant increase in malformations, in general, and in left-sided tail and inverted heart, in particular (table 1). These results, together with the decreased protein content in embryos exposed to  $N_2O$  on day 9 (table 1), provide more

TABLE 1. Morphologic and Biochemical Effects of Nitrous Oxide (N<sub>2</sub>O) on Embryos Treated for 24 Hours on Day 9 and Examined on Day 11

	Control	50-75% N <sub>2</sub> O
Number of embryos cultured	96	106
Number of viable embryos	94	93
Number of malformed embryos (Percent of viable embryos)	6 (6.3)	66* (71.0)
Number of embryos with left-sided tail (Percent of viable embryos)	2 (2.1)	14* (15.1)
Number of embryos with inverted heart (Percent of viable embryos)	1 (1.1)	18* (19.4)
Protein content (μg/embryo ± SD)	422 ± 80 (n = 36)	183 ± 108† (n = 39)

\*  $P < 0.01$  versus control by chi-square analysis.

†  $P < 0.01$  versus control by Student's *t* test.

convincing evidence than in our previous report. We are now in a position to use this more robust day-9 *in vitro* model to establish dose-response relationships and mechanisms of N<sub>2</sub>O teratogenicity.

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## Unusual Cause of an Absent Capnogram

*To the Editor:*—The capnogram is taken to be a valuable adjunct in identifying proper endotracheal tube placement; inability to detect exhaled CO<sub>2</sub> following intubation represents esophageal intubation until proven otherwise. Herein we report an unusual cause of abrupt capnography failure in a pediatric patient.

A 5-yr-old ASA physical status 1 patient presented for elective strabismus repair. After inhalation induction with nitrous oxide and halothane in oxygen, an iv infusion was begun, vecuronium administered, and the trachea was intubated without difficulty with a 5.0-uncuffed oral RAE tube. Bilateral breath sounds were confirmed. A large leak at less than 5 cm H<sub>2</sub>O was evident around the endotracheal tube. A 5-l fresh gas flow was used and the lungs were easily ventilated when mechanical ventilation was initiated (the bellows failed to refill fully with a lower flow). Capnography (Life Watch/Perkin-Elmer mass spectrometer, aspiration rate ~240 ml/min), however, failed to demonstrate expired CO<sub>2</sub> previously evident on induction. Breath sounds were reconfirmed bilaterally with good chest wall excursion; peripheral oxyhemoglobin saturation remained at 100% on an inspired F<sub>I</sub>O<sub>2</sub> of 0.3. The ventilator bellows (Omeda 7000) emptied and filled appropriately with a peak inspiratory pressure of 20 cm H<sub>2</sub>O and an end-expiratory pressure of approximately 2 cm H<sub>2</sub>O (the lowest resting position of the aneroid manometer). The aspirating tubing of the mass spectrometer had no obvious loose connections or kinks. When tested, CO<sub>2</sub> was immediately evident upon exhalation into this tubing by an anesthesiologist. Suspecting the large leak to be the culprit, we briefly manually sealed the patient's mouth and nose and a CO<sub>2</sub> tracing appeared on the screen. We then checked the circle system for other obstruction to exhaled volume and found the Omeda GMS PEEP valve to be minimally engaged. Upon loosening the valve one-half turn counterclockwise, CO<sub>2</sub> appeared on the capnogram. Reinstating minimal PEEP again resulted in no observable CO<sub>2</sub> on the capnogram, despite the manometer registering only 2 cm H<sub>2</sub>O at end-expiration.

The valve was then opened fully, with the manometer needle still resting on 2 cm H<sub>2</sub>O, and the case proceeded uneventfully.

In this child with a large leak around the endotracheal tube, the small resistance to flow through the expiratory limb of the circle system offered by partial engagement of the PEEP valve was enough to divert total expiratory flow around the tracheal tube. The leak, however, prevented the development of PEEP, and the manometer correctly determined end-expiratory pressure to be low. We do not believe that the Omeda GMS PEEP valve, which provides a spring-loaded obstruction to the circle's exhalation valve, was faulty; nonetheless it was difficult to determine by simple visual inspection if it was engaged. The mechanism consists of a knob atop a spring over the exhalation valve of the circle system; progressive clockwise turns provides a graded obstruction to gas flow. The valve is disengaged when turned fully counterclockwise. A click-lock position when disengaged might prevent accidental turning of the knob; more importantly, its evaluation should be part of the machine check-out before each case.

Although practice differs among anesthesiologists, significant leaks around the endotracheal tube are often accepted for short cases if gas exchange appears adequate and excessive fresh gas flow (>5 l) is not needed to ensure proper bellows refilling. The maneuver of sealing the patient's mouth and nose was merely demonstrative and is not to be condoned as an alternative to placing an appropriately larger-size tube. High fresh gas flow, particularly with small tidal volumes, may also result in significant attenuation of the capnogram. As we were unable to reduce the fresh gas flow, we do not know how a lower flow would have affected the capnography in this case.

Capnography is currently felt to be the most reliable means of detecting esophageal intubation, and there have been no documented failures of the technique, *i.e.*, the false-negative rate is zero.<sup>1</sup> The converse is not true, however, and this event represents the equivalent of a false-positive; the lack of end-tidal CO<sub>2</sub> does not necessarily imply