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Inhaled Nitric Oxide Selectively Decreases Pulmonary Vascular Resistance without Impairing Oxygenation during One-lung Ventilation in Patients Undergoing Cardiac Surgery

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RECENTLY, anesthesiologists and intensive care physicians gained the ability to augment pulmonary blood flow in ventilated lung regions by administering low levels of gaseous nitric oxide to their patients. This is a novel and appealing approach to organ-selective drug delivery, because the vasodilatory properties of nitric oxide are restricted to ventilated regions of the lung. Any nitric oxide that diffuses into the bloodstream is inactivated by rapid binding to hemoglobin, and systemic vasodilation does not occur. Hundreds of patients, adults, children, and newborns have been studied over the past 2 yr, and more than 40 centers in the United States are examining the effects of inhaling nitric oxide in various lung diseases characterized by pulmonary hypertension. In adult respiratory distress syndrome and primary pulmonary hypertension of the newborn, prospective randomized trials are, or soon will be, carried out, and clinicians await those results with keen interest.

In this issue of ANESTHESIOLOGY, Rich *et al.* (page 57) report the results of adding 20 ppm nitric oxide to inhaled gas during one-lung ventilation in supine cardiac surgery patients. In patients without pulmonary hypertension, there were no effects observed upon hemodynamics and gas exchange. In patients with mild pulmonary hypertension, however, inhaling nitric oxide produced selective pulmonary vasodilation, reducing the pulmonary artery pressure and the pulmonary vascular resistance. Thus, there is evidence that, in some cardiac surgery patients, there is a component of increased pulmonary vascular tone in the ventilated lung; and because tone or resistance is reduced by inhaling nitric oxide, this component is reversible.

One might have expected that, if the vascular tone in the ventilated lung were reduced by nitric oxide, then venous blood would be diverted toward this ventilated lung, the right-to-left shunt (\dot{Q}_s/\dot{Q}_t) would decrease, and the P_{aO_2} would increase. This did not occur, and it is unclear to me why. Perhaps the degree of pulmonary tone in the ventilated lung was insufficient to provide adequate flow diversion, or a ventilation/perfusion mismatch developed in the ventilated lung.

Where do we go next? Nitric oxide inhalation should be studied during pulmonary surgery with patients in the lateral decubitus. Many patients undergoing lung surgery have chronic lung disease and various degrees of pulmonary vascular disease. Nitric oxide inhalation may divert more blood to ventilated lung regions and increase the P_{aO_2} . Several inhaled nitric oxide doses should be studied, because we know that lower inhaled nitric oxide levels (60–250 ppb) can, at times, augment arterial oxygenation without significantly reducing the pulmonary artery pressure. Recently, the pulmonary vasoconstrictor almitrine was shown to markedly enhance the P_{aO_2} and reduce \dot{Q}_s/\dot{Q}_t in adult respiratory distress syndrome when combined with nitric oxide breathing. During one-lung anesthesia, almitrine could reduce perfusion to the collapsed lung while nitric oxide augmented flow to the ventilated one. Combining shunt control (almitrine or another vasoconstrictor) with perfusion control (nitric oxide) could make one-lung anesthesia safer. Stand by for more exciting advances in inhalation therapy.

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Safety and Potency of ANQ 9040 in Male Volunteers

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THE search for a nondepolarizing relaxant with an onset/offset profile similar to succinylcholine has preoc-

cupied both clinicians and neuromuscular pharmacologists for several decades. The report on ANQ 9040 by

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Munday *et al.* in this issue (page 97) attests to the fact that progress has been made in our comprehension of at least some of the properties that such a drug is likely to possess. There is substantial evidence that the speed of onset of nondepolarizing blockers is, at least in part, inversely related to their molar potency: the less potent the compound, the faster the onset of action. ANQ 9040, a blocker of the steroidal class with a milligram/kilogram potency less than 1/25th that of vecuronium, is no exception. When subparalyzing doses (ED_{30} – ED_{80}) are administered rapidly, peak neuromuscular block is seen in <90 s, and the train-of-four ratio generally recovers to >0.70 in 10–20 min. When 2.6 mg/kg ($2 \times ED_{95}$) is administered over 30–60 s, complete neuromuscular block ensues within 1 min of completion of drug administration.

Unfortunately, ANQ 9040 also illustrates one of the major problems inherent in the pursuit of a clinically acceptable ultra-short-acting nondepolarizing relaxant. As drug potency decreases, the potential for nonspecific drug actions (side effects) increases. ANQ 9040 not only appears to possess significant vagolytic blocking

activity at 2 times its ED_{95} , but also may trigger considerable histamine liberation at this dosage. This latter action is almost unknown in more potent steroidal relaxants. Finally, as the dose is increased to 2.6 mg/kg, the mean recovery time to a train-of-four ratio >0.70 increases dramatically. Further clinical trials of ANQ 9040 thus appear unlikely based on the narrow margin of safety demonstrated in this study.

However, new and, it is hoped, more promising drugs continue to enter clinical trials. Another steroidal relaxant (Org 9487) with a similar potency ($ED_{90} = 1.15$ mg/kg) has been shown to produce 99% twitch suppression in <90 s when administered at a dose only 1.3 times its ED_{90} ! Onset of this rapidity raises an interesting question: How wide a margin of safety do we need? If a dose equal to 1.5 times the ED_{95} reliably produces complete twitch suppression in <60 s, is the fact that it also may be associated with unacceptable cardiovascular effects at 2.5 times the ED_{95} of great consequence? The quest goes on.

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