◇ This Month in

ANESTHESIOLOGY

■ Accuracy of Cardiac Output Monitoring Methods Compared. Tachibana *et al.* (page 830)

To investigate the accuracy of partial carbon dioxide rebreathing measurements compared with those obtained using thermodilution methods, Tachibana *et al.* enrolled 25 post–cardiac surgery patients to undergo two serial protocols. On admission to the intensive care unit, each patient was mechanically ventilated, with initial settings of inspired tidal volume (V_T) of 10 ml/kg, respiratory rate of 10 breaths/min, inspiratory time of 1.0 s, positive end-expiratory pressure of 4 cm H_2O, and pressure support of 10 cm H_2O. The team began cardiac output (CO) measurements 1 to 2 h after surgery, with patients in the supine position and sedated with continuous intravenous injections of propofol.

In the first protocol, the team applied three settings of volume-controlled ventilation in random order: a V_T of 12 ml/kg and a respiratory rate of 10 breaths/min, a V_T of 6 ml/kg and a respiratory rate of 20 breaths/min, and a V_T of 6 ml/kg and a respiratory rate of 10 breaths/min. The second protocol involved measurement of CO during spontaneous breathing effort, initiated after the patients had recovered spontaneous breathing and satisfied extubation criteria. In random order, the team applied three settings of partial ventilatory support: synchronized intermittent mandatory ventilation plus pressure support ventilation (PSV), PSV with an appropriately adjusted rebreathing loop, and PSV with the shortest available loop. During both sets of experiments, CO was measured using two methods: thermodilution (CO_{TD}) and noninvasive partial carbon dioxide rebreathing technique (CO_{NI}). The values of expired V_T and small minute ventilation were recorded, arterial blood samples were analyzed, and dead space and venous admixture fraction were calculated. The correlation between the data yielded by CO_{TD} and CO_{NI} methods was determined by Bland-Altman analysis and linear regression.

The investigators found that, when minute ventilation was set to maintain normocapnia, CO measured with the carbon dioxide rebreathing technique moderately correlated with that measured by thermodilution, regardless of tidal volumes. When minute ventilation was set low, the carbon dioxide rebreathing technique underreported CO. During spontaneous breathing, correlation between the two CO measurements worsened. Specifically, the carbon dioxide rebreathing technique was less accurate and increased spontaneous tidal volume and respiratory rate (20 and 30%, respectively, during PSV) when the rebreathing loop was adjusted for large tidal volume. Because CO_{NI} is derived from changes in carbon dioxide output and end-tidal pressure of carbon dioxide during synchronized intermittent mandatory ventilation–PSV, the presence of breath-by-breath changes in carbon dioxide output and end-tidal pressure of carbon dioxide may affect accuracy of measurements. The partial carbon dioxide rebreathing technique warrants further investigation to evaluate its accuracy and reproducibility under various hemodynamic conditions.

■ Computer Model Evaluates Partial Rebreathing as Pulmonary Blood Flow Measurement Technique. Yem *et al.* (page 881)

Using a comprehensive mathematical model of the cardiorespiratory system of a healthy, 70-kg man, Yem *et al.* sought to identify and quantify potential sources of error in measurements of pulmonary blood flow (PBF) by the partial rebreathing technique. The model simulates tidal breathing through a branched respiratory tree and incorporates the effects on carbon dioxide dynamics of lung tissue mass, vascular transport delays, multiple body compartments, and realistic blood–gas dissociation curves. For purposes of this study, an additional variable, dead space, switched in and out to simulate the rebreathing process, was incorporated into the model.

The authors ran the model using four different sets of parameters. During the first simulations, the model was run for 6,000 s using standard conditions. Then, to examine the effects of changes in mixed venous P_{CO_2} caused by recirculation, the model was modified by removing body compartments components, while mixed venous P_{CO_2} and P_{O_2} inputs to the pulmonary capillaries were kept constant at values appropriate to the cardiac output. The third series of simulations evaluated the effects of alveolar–proximal airway differences in P_{CO_2} and carbon dioxide flux. The fourth series of simulations included three investigations to examine the effects of rebreathing time: PBF values calculated using an extended rebreathing time of 300 s, without the inclusion of recirculation; the percentage of the step change in end-tidal pressure of carbon dioxide completed during 50 s of rebreathing determined using results from the first investigation; and rebreathing times necessary for end-tidal pressure of carbon dioxide to

change through 95% of the change achieved after 300 s of rebreathing, also determined for each PBF using results from the first investigation.

The authors found that systematic errors are less than 10% when the simulated PBF is between 3 and 6 l/min. At 2 l/min, PBF is overestimated by approximately 35%. At 14 l/min, PBF is underestimated by 40%. At PBF greater than 6 l/min, recirculation causes 60% of the systematic error, while alveolar–proximal airway differences account for 20% and alveolar–arterial differences account for 20%. The standard rebreathing time of 50 s was excessive for a PBF greater than 6 l/min. At PBF less than 3 l/min, errors are caused by inadequate rebreathing time and alveolar–arterial gradients. The systematic errors in partial rebreathing cardiac measurements have multiple causes. The authors suggest that errors could be reduced by using a variable rebreathing time, which should be increased at low PBF so that quasi equilibrium in the alveoli can be achieved. Rebreathing should be decreased at high PBF to reduce the effects of recirculation.

■ Exploring Mechanisms of Rapacuronium-induced Fatal Bronchospasm. Jooste *et al.* (page 906)

Rapacuronium has been withdrawn from clinical practice because of its association with a high incidence of bronchospasm, a few cases of which have been fatal. Since rapacuronium selectively inhibits M2 muscarinic receptors, Jooste *et al.* deemed further investigation of its mechanisms to be potentially useful for the design and assessment of other nondepolarizing agents. They hypothesized that inhibition of M2 muscarinic receptors by relaxants such as rapacuronium during intubation may result in acetylcholine release, which, in turn, acts on unopposed M3 muscarinic receptors, leading to bronchoconstriction.

To test their hypothesis, the team used Chinese hamster ovary cells transfected with either the M2 or M3 muscarinic receptors to determine the binding affinities of rapacuronium, vecuronium, cisatracurium, methoctramine (selective M2 antagonist) and 4-diphenylacetoxy-*N*-methylpiperidine methiodide (selective M3 antagonist) for M2 and M3 muscarinic receptors. The researchers found that, in clinically relevant concentrations, rapacuronium competitively displaced ^{3}H-QNB from the M2 muscarinic receptors but not from the M3 muscarinic receptors expressed in Chines hamster ovary cells. Cisatracurium and vecuronium also competitively displaced ^{3}H-QNB binding from M2 and M3 muscarinic receptors but not at clinically achieved concentrations. It may be, conclude the authors, that rapacuronium potentiates bronchoconstriction by blocking the M2 muscarinic receptor on prejunctional parasympathetic nerves, leading to continued release of acetylcholine and, ultimately, M3 muscarinic receptor–mediated airway smooth muscle constriction. In light of these results, it may be prudent to evaluate all newly designed muscle relaxants for their potential to selectively inhibit M2 muscarinic receptors, especially if their intended use is to facilitate intubation, a procedure requiring large doses of relaxants and coinciding with activation of the vagal reflex.

■ Is Increased Analgesic Requirement Associated with Dysfunctional Labor? Panni *et al.* (page 957)

To determine whether severity of pain during early labor is associated with dystocia (difficult labor) and subsequent cesarean section, Panni *et al.* approached 148 nulliparous women who requested epidural analgesia to participate in their study. Investigators assigned women to one of four study groups, prior to knowledge of actual mode of delivery: spontaneous vaginal delivery, receiving oxytocin at time of epidural placement; spontaneous vaginal delivery, not receiving oxytocin; cesarean section for dystocia, receiving oxytocin; or cesarean section, not receiving oxytocin. Group assignments were made without the knowledge of how each woman would actually deliver, and epidural analgesia was provided before a diagnosis of dystocia was made. The minimum local anesthetic concentration was calculated, and only patients who delivered *via* their assigned delivery mode influenced the up–down sequence of drug delivery, and, thus, determination of minimum local anesthetic concentration, in each of the four study arms. That is, if a participant's delivery was the same as her assigned mode, her data were used to determine the next patient's anesthetic concentration. The total number of women included in the study's final analysis was 57. The authors found that women who delivered vaginally had 25 and 31% lower minimum local anesthetic concentration values (for those who received oxytocin and those who did not, respectively). The minimum local anesthetic concentration values were higher for those who eventually experienced dystocia and required cesarean sections. The authors state that further research will be necessary to delineate the mechanisms by which dystocia increases pain.

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