Administering Inhaled Nitric Oxide: Still More to Understand

Inhaled nitric oxide (INO) is a selective pulmonary vasodilator used to manage pulmonary arterial hypertension and ventilation-perfusion mismatch associated with cardiac and pulmonary conditions.[1] In 1999, the Food and Drug Administration approved INO for the treatment of hypoxic respiratory failure in term and near-term newborns, which remains the only on-label application. The safe and accurate administration of this medical gas has been achieved predominantly with the INOmax DS_{IR} Plus (Mallinckrodt, Madison, Wisconsin), a delivery and monitoring device now in its fourth iteration. In this issue of RESPIRATORY CARE, Ranallo et al[2] report on a bench evaluation of the previous iteration of the INOmax DS_{IR} and its effect on monitored tidal volume (V_T). As described in their study, the device measures air flow by means of a pneumotachometer and proportionally injects nitric oxide gas throughout inspiration based on a set dose while simultaneously providing continuous sidestream sampling at a rate of 230 mL/min. The impetus for this experiment was clinical observations of discrepancies between monitored inspired and expired V_T when using this device with the Servo-i ventilator (Getinge, Fort Wayne, New Jersey), particularly with low V_T.

Ranallo et al[2] suggest that discrepancies between set inspiratory V_T and percentage error in measured expiratory V_T are inversely proportional during INO administration, with the smallest set V_T of 18 mL/kg resulting in the percentage error in observed exhaled V_T. Compared to the expired V_T displayed on the Servo-i, the expiratory V_T, as measured at the simulated airway with a pneumotachometer, was 34% lower. This is an expected effect because more volume is lost through sampling than is being injected; this can be predicted, as described by the authors, with the manufacturer's provided formula: INO flow = [INO dose (ppm) × $\dot{V}_E$ (L/min)] ÷ [cylinder concentration (ppm) – INO dose (ppm)]. The minute volume ($\dot{V}_E$) with a set V_T of 18 mL/kg and a breathing frequency of 30 breaths/min is 540 mL/min, and at a dose of 20 ppm results in an INO flow of 14 mL/min; when the sample rate of 230 mL/min is subtracted, there is a net loss of 216 mL/min, or 40% of the $\dot{V}_E$. These results are consistent with a previous bench study by Clark et al,[3] who reported $\dot{V}_E$ reductions of

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19–56% using the Servo-i infant pressure-regulated volume control mode with set V_T values of 9–30 mL. Clinically speaking, this could be a significant decrease in $\dot{V}_E$ and, as the manufacturer recommends, may need to be compensated for. However, the current study by Ranallo et al[2] indicates that volume loss occurs primarily during exhalation because the measured inspired and expired V_T values were similar, which would not matter clinically.

When the Servo-i is operating in the pressure-regulated volume control mode, V_T is set and peak inspiratory pressure is adjusted by the ventilator to ensure the inspiratory volume target is achieved. Therefore, it makes sense that inspiratory V_T is accurate because the INOmax DS_{IR} is proportionally adding flow to the circuit and the Servo-i is targeting V_T at the flow valve during inspiration. However, when the Servo-i cycles into exhalation, exhaled V_T is not corrected for leak, and the effect of sampling becomes noticeable on the Servo-i flow scalar. In the infant configuration, the Servo-i provides a bias flow of 0.5 L/min during exhalation to affect flow-triggering, which theoretically should be a sufficient amount of flow to counteract the loss of 230 mL/min from the continuous sampling. In a bench study of imposed expiratory resistance, DiBlasi et al[4] reported that the Servo-i had a higher degree of imposed resistance when compared to other ventilators studied. They also observed that bias flow was introduced variably and did not instantaneously turn on the moment the expiratory phase begins. In their letter of response to the manufacturer, this is further supported by airway graphics that show bias flow re-established at 120 ms after exhalation is initiated.[5] It seems possible that exhaled V_T is measured and displayed prior to the return of bias flow, which may account for the observed error in expired volume.

This study is the first published account of how the injection of INO and sampling affect V_T measurements when using the INOmax DS_{IR}, and the suggestion that a proximal flow sensor be used to ensure accurate monitoring of volumes is valid. We encounter the same inspiratory-expiratory discrepancies in managing infants with small V_T, but

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we have to balance our standard of monitoring P_{ETCO_2} versus proximal volume measurements because coupling these airway sensors potentially increases dead space and is heavy on small endotracheal tubes. However, we do occasionally utilize a standalone volumetric CO_2 monitor to measure and adjust V_T.

Ranallo and colleagues[2] have conducted a sound bench trial with one brand of ventilator set in the pressure-regulated volume control mode. Their findings may be unique to the Servo-i and, as they have suggested, evaluating other ventilator brands and modes may yield different results. Expanding on this work might also include studying ventilators with leak compensation, as well as neonatal-specific ventilators with NICU to adult ICU capabilities. Additional questions to answer include: (1) To what extent are the observed discrepancies in exhaled V_T or $\dot{V}_E$ measurement clinically relevant to smaller infants, and what is the optimal method of assessing this phenomenon clinically?; and (2) Is an animal study evaluating several modern ventilators warranted to determine whether this phenomenon is related solely to measurement error or if a critical threshold exists in which gas exchange is negatively affected?

While INO has been used for more than 3 decades, the technical aspects of monitoring and delivery could be explored further, particularly as new devices become available such as the $NOxBOX_i$ (Praxair, Danbury, Connecticut), an INO delivery and monitoring system recently introduced to the United States that also utilizes a pneumotachometer for INO injection and allows simultaneous sidestream sampling. Another new device is the GENOSYL DS (Vero Biotech, Atlanta, Georgia), which utilizes an ascorbic acid cartridge to convert nitrogen dioxide to nitic oxide.[6] This device is purported to provide more consistent dosing throughout inspiration; while it does not use gas cylinders as the NO source, it still relies on continuous sidestream sampling for gas monitoring. Also in development is a miniaturized system that electrically generates nitric oxide, which may make INO delivery in the home more accessible and be a more economical option for developing countries.[7] Undoubtedly, there are bench-to-bedside research opportunities for understanding how these devices will interact with various ventilators.

Respiratory therapists who deploy INO delivery systems should have a firm understanding of the effect on ventilation, particularly when used in small infants. Moreover, the continuous sidestream sample rate of 230 mL/min can result in auto-triggering, which may also pose patient safety risks. Therefore, it is imperative that respiratory therapists provide close monitoring of the system to ensure safety, assess and refine ventilator parameters accordingly, and evaluate blood gases and hemodynamics to gauge the response to and titration of INO.

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