Cardiology in the Young

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Dead space ratio as a tool in nitric oxide weaning: a study in pulmonary hypertensive disease

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Original Article

Cite this article: Garcia AD, Liu W, Agarwal H, and Hanna WJ (2022) Dead space ratio as a tool in nitric oxide weaning: a study in pulmonary hypertensive disease. *Cardiology in the Young* **32**: 1603–1607. doi: 10.1017/S1047951121004662

Received: 3 July 2021
Revised: 3 November 2021
Accepted: 3 November 2021
First published online: 9 December 2021

Keywords:
Pulmonary hypertension; dead space fraction; inhaled nitric oxide

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*The online version of this article has been updated since original publication. A notice detailing the change has also been published.

Abstract

Objectives: To describe the association between successful weaning of inhaled nitric oxide and trends in dead space ratio during such weans in patients empirically initiated on nitric oxide therapy out of concern of pulmonary hypertensive crisis. *Patients:* Children in a cardiac intensive care unit initiated on inhaled nitric oxide out of clinical concern for pulmonary hypertensive crisis retrospectively over 2 years. *Measurements and Main Results:* Twenty-seven patients were included, and nitric oxide was successfully discontinued in 23/27. These patients exhibited decreases in dead space ratio (0.18 versus 0.11, $p = 0.047$) during nitric oxide weaning, and with no changes in dead space ratio between pre- and post-nitric oxide initiation ($p = 0.88$) and discontinuation ($p = 0.63$) phases. These successful patients had a median age of 10 months [4.0, 57.0] and had a pre-existent diagnosis of CHD in 6/23 and pulmonary hypertension in 2/23. Those who failed nitric oxide discontinuation trended with a higher dead space ratio at presentation (0.24 versus 0.10), were more likely to carry a prior diagnosis of pulmonary hypertension (50% versus 8.7%), and had longer mechanical ventilation days (5 versus 12). *Conclusions:* Patients empirically placed on nitric oxide out of concern of pulmonary hypertensive crisis and successfully weaned off showed unchanged or decreased dead space ratio throughout the initiation to discontinuation phases of nitric oxide therapy. Trends in dead space ratio may aid in determining true need for nitric oxide and facilitate effective weaning. Further studies are needed to directly compare trends between success and failure groups.

Background

During a pulmonary hypertensive crisis, acute elevations in pulmonary vascular resistance trigger ventricular dysfunction and a low cardiac output state which can be lethal when not recognised and treated early.[1–3] Inhaled nitric oxide, a selective pulmonary vasodilator, has been shown to effectively reverse this process in many patients, and is currently used as a first-line agent in children with known or suspected pulmonary hypertensive crises.[4–10]

In acutely deteriorating patients however, reliably diagnosing a decompensation as a pulmonary hypertensive crisis and recognising the need for and response to nitric oxide remains an ongoing challenge at the bedside. In patients who have been empirically started on inhaled nitric oxide, titration is often is dictated by institution-based guidelines that include arbitrary time-based weaning strategies and/or changes in biomarkers such as PaO_2 that lack strong physiologic justification as surrogates for changes in pulmonary blood flow.[11,12] The increasing implementation of stewardship programmes' in centres using inhaled nitric oxide may reflect the extent of this problem.[11]

Of existing biomarkers that reflect changes in pulmonary blood flow, use of the dead space ratio has a strong physiologic basis and has shown some promise in the existing literature. Measured using the Enghoff modification of the Bohr equation $((PaCO_2 - PeCO_2)/PaCO_2)$, the dead space ratio and its derivatives have been used for the last 30 years in the paediatric population.[13] Available literature includes its use as a prognostic indicator in patients with compromised pulmonary blood flow such as congenital diaphragmatic hernia or with Fontan circulation, and as a tool in evaluating for ECMO decannulation readiness, reflecting increases in pulmonary blood flow as a surrogate for increased native cardiac output.[14–18]

Changes in dead space ratio, as a reflection of changes in pulmonary blood flow, may thus prove novel as an effective bedside tool in guiding the appropriate initiation and titration of inhaled nitric oxide in patients with suspected pulmonary hypertension. We thus seek to describe trends in dead space ratio during initiation and weaning phases of inhaled nitric oxide in patients placed on it out of concern of pulmonary hypertensive crisis.

Table 1. Characteristics by overall success and failure of iNO therapy wean

Variable	Success group (n = 23)	Failure group (n = 4)	p-value
Age (months)	10 [4.0, 57]	11 [2.0, 30]	0.52[b]
Gender (female)	15/23 (65%)	1/4 (25%)	0.27[d]
Pre-existing congenital heart disease	9/23 (26%)	2/4 (50%)	0.72[d]
Pre-existent diagnosis of pulmonary hypertension	2/23 (8.7%)	2/4 (50%)	0.092[d]
Dead space ratio before iNO initiation	0.10 [0.060, 0.27]	0.24 [0.15, 0.37]	0.22[b]
Initiated on additional pulmonary vasodilating agents	9/23 (39%)	3/4 (75%)	0.29[d]
Total hours on iNO	53 [26, 121]	74 [65, 81]	0.42[b]
Mechanical ventilation (days)	5 [2.0, 8.0]	13 [8.5, 17]	0.12[b]

p-values: b = Wilcoxon rank sum test; d = Fisher's exact test.

Methods

Patients and settings

This single centre retrospective cohort study was approved by the Institutional Review Board of Cleveland Clinic. We included children admitted to the PICU between January 2018 and June 2020 who were started on inhaled nitric oxide out of clinical concern for pulmonary hypertensive crisis and had documented continuous capnography and arterial blood gas data at time points of ≥20 ppm and ≤5 ppm nitric oxide during weaning.

Study procedures

The database of patients initiated on inhaled nitric oxide was obtained from the Respiratory Therapy Department. Charts were individually reviewed, and we included the patients that met the eligibility criteria. Dead space ratio was calculated using the Enghoff modification of the Bohr equation ($Vd/Vt = (PaC0_2 - PetCO_2)/PaCO_2$). iNOmax® was used for iNO delivery. Servo-i® and Servo-U® mechanical ventilators with in-line $ETCO_2$ monitoring and GE® E-mini-CO_2 modules were used for continuous wave capnography measurements.

Data collection

In addition to arterial CO_2 and $ETCO_2$, relevant demographic data were collected, including age, gender, cardiac anatomy, presence of co-morbidities, and chromosomal defects. Additional variables collected included vasoactive infusion score, minute ventilation, oxygenation index, and hours on iNO.

Determination of pulmonary hypertensive crisis

After identification of the patients that were started on inhaled nitric oxide from the database, we excluded the patients that had been started on inhaled nitric oxide for other reasons besides clinicians concerns of pulmonary hypertensive crisis. This criterion was taken based on the documentation in the patient's chart. Patients included in the study were started on inhaled nitric oxide either in the PICU or the cardiac OR and subsequently transferred to the PICU and had either documented history of pulmonary hypertension or had cardiac lesions with risk of developing a pulmonary hypertensive crisis.

Determination of success or failure to wean from inhaled nitric oxide

Failure to wean from inhaled nitric oxide was defined as reinitiating it within 72 hours of discontinuation.

Statistical analysis

Continuous variables were described using medians and interquartile ranges; categorical variables were described using counts and percentages. Between-group comparisons of demographic and clinical characteristics by inhaled nitric oxide success were assessed by using Wilcoxon rank sum test for continuous data and Fisher's exact test for categorical data, as appropriate. Dead space ratios, as well as FiO_2, vasoactive infusion score, oxygenation index, and minute ventilation, in different time points of inhaled nitric oxide procedure were compared by Wilcoxon signed rank test. Pearson's correlation coefficient was used to explore associations between dead space ratio and vasoactive infusion scores and oxygenation indexes.

All analyses were performed on a complete case basis; subjects with missing data on particular variables were only excluded for analyses in which those variables were used. All tests were two-tailed and performed at a significance level of 0.05. SAS 9.4 software (SAS Institute, Cary, NC, USA) was used for all analyses.

Results

Patient demographics and characteristics

Table 1 shows demographic and clinic characteristics of the success and failure groups. In total, 27 patients were included (see Fig 1), of which 23 (85%) were in the success group and 5 (15%) in the failure group. Patients in the success group had a median age of 10 months [4.0, 57], had pre-existing CHD in 9/23 (39%), and had a pre-existent diagnosis of pulmonary hypertension in 2/23 (8.7%). Dead space ratio before inhaled nitric oxide initiation was 0.1 [0.06, 0.27] in this group, with 9/23 (39%) initiated on additional pulmonary vasodilators during the weaning process, and with a median total time on inhaled nitric oxide of 53.0 hours [26.0, 121.0]. Patients in the failure group had a median age of 10.5 months [2, 29.5], had pre-existing CHD in 2/4 (50%), had a pre-existent diagnosis of pulmonary hypertension in 2/4 (50%), had a dead space ratio before inhaled nitric oxide initiation of 0.24 [0.15, 0.37], with 3/4 (75%) initiated on additional

https://doi.org/10.1017/S1047951121004662 Published online by Cambridge University Press

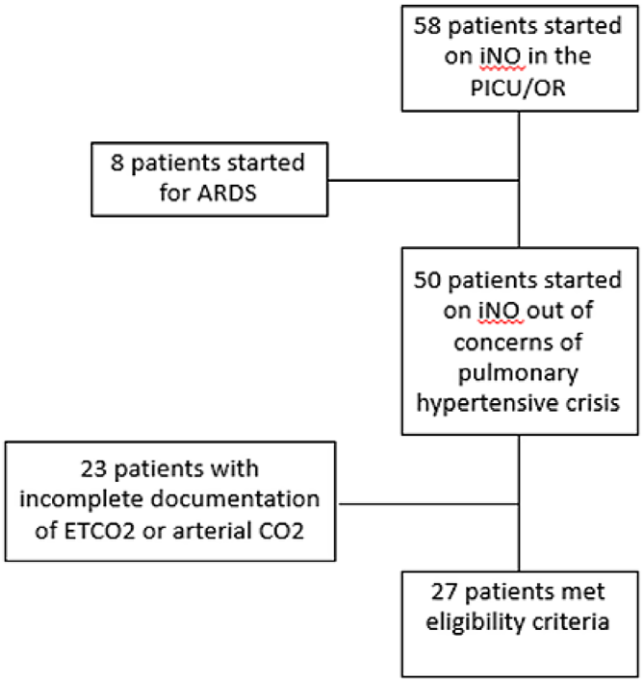

Figure 1. Inclusion and exclusion criteria.

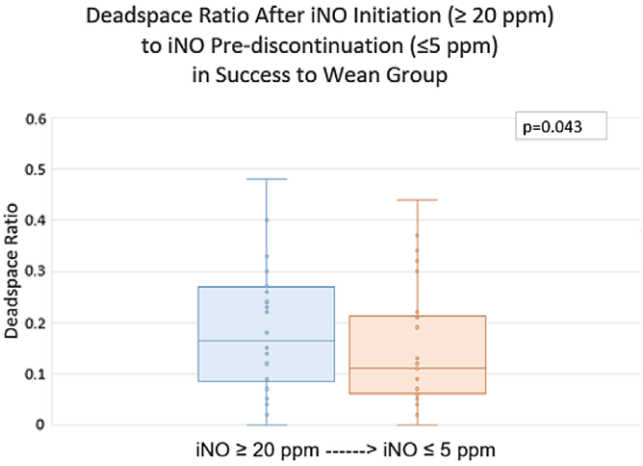

Figure 2. Dead space ratio success to wean group.

pulmonary vasodilators during weaning, and with a median time on iNO of 74.0 hours [65.3, 80.5].

Primary analysis

Given the small sample size of the failure group (Supplemental Data, Figure 1), further quantitative analysis focused upon trends in dead space within the success group. In this group, the median dead space ratio after initiation of inhaled nitric oxide (>20 ppm) was 0.18 [0.09, 0.27] and prior to inhaled nitric oxide discontinuation (<5 ppm) decreased to 0.11 [0.060, 0.22], $p = 0.043$ (Figure 2). No significant differences were noted between dead space ratio pre- and post-inhaled nitric oxide initiation ($p = 0.88$) and pre- and post-inhaled nitric oxide discontinuation ($p = 0.63$). The PaO_2 after initiation (>20 ppm) was 82 mmHg [40, 157], and prior discontinuation was 90 mmHg [47, 129], $p = 0.34$. Vasoactive infusion score after initiation (>20 ppm) and prior to discontinuation (<5 ppm) were 12 [7.5, 17] and 8 [5.3, 8.5], respectively ($p < 0.001$).

Secondary analysis

Using alternative outcome measures of changes in vasoactive infusion score and changes in oxygenation index in all subjects ($N = 27$), no significant correlation was found between changes in dead space ratio and changes in vasoactive infusion score ($r = -0.23$, $p = 0.25$) or oxygenation index ($r = 0.30$, $p = 0.16$) during the weaning process.

Discussion

In this retrospective review, we studied the utility of dead space ratio trends as a novel tool in predicting ongoing need for inhaled nitric oxide in patients with clinical concern for pulmonary hypertensive crisis. For those successfully weaned off, we found that dead space ratio decreased during the weaning process and that no significant differences in dead space ratio existed between pre- and post-inhaled nitric oxide initiation and pre- and post-inhaled nitric oxide discontinuation phases. These results suggest that trends in dead space ratio, as a surrogate for changes in pulmonary blood flow, may aid in determining true need for inhaled nitric oxide and facilitate effective inhaled nitric oxide weaning using a physiologically based and target-driven approach.

Continuous waveform capnography has been recognised as a powerful tool in assessing changes in pulmonary blood flow and hence as a surrogate of left ventricular cardiac output.[19] Most notably, it has been incorporated into AHA resuscitation guidelines as a marker of adequate cardiopulmonary resuscitation and a reflection of return of spontaneous circulation.[20–23] In isolation, however, end-tidal capnography ($ETCO_2$), being one component of the dead space equation, may not be an accurate reflection of pulmonary blood flow, given that changes in minute ventilation may also affect its result. Incorporating changes between alveolar and arterial $C0_2$ content as a more accurate surrogate for changes in pulmonary blood flow, an early proof-of-concept study by Askrog investigated changes in arterial-alveolar $C0_2$ difference ($\Delta C0_2$) among healthy post-operative adult patients following a 1L rapid infusion IV bolus. Directly measured mean pulmonary artery pressures immediately increased by 5 mm Hg, and a clear inverse linear relationship was found between mean pulmonary artery pressures and $\Delta C0_2$.[24] A more recent study by Chauhan and Deb found that use of alveolar functional fraction ($ETCO_2/PaCO_2$) can accurately reflect changes in the ratio pulmonary to systemic blood flow (Qp:Qs) in those CHD patients with intracardiac shunting, data validated by comparing this metric to direct catheterisation measurements of Qp:Qs ($r = 0.83$, $p < 0.0001$).[25]

To date, dead space ratio using the modified Bohr equation has been studied extensively in patients as a prognosticator in acute lung injury, and it has been recently highlighted in patients with single ventricle physiology.[26] Shostak et al[27] described that in patients with Fontan physiology (a population with potentially compromised pulmonary blood flow) and those with increased dead space values had higher morbidity, with increased duration of mechanical ventilation, severity of illness, and ICU length of stay. Likewise, Cigarroa et al[28] described that in patients following bidirectional cavo-pulmonary anastomosis, a dead space more

https://doi.org/10.1017/S1047951121004662 Published online by Cambridge University Press

than 0.28 upon ICU admission increased the risk of requiring reintervention or death during admission. Little focus has been placed on its primary use as a surrogate for changes in pulmonary blood flow in conditions such as an acute pulmonary hypertensive crisis. In many pulmonary hypertension-related inhaled nitric oxide protocols, biomarkers with less physiologic plausibility such as PaO_2 are commonly used to help guide weans of inhaled nitric oxide.[29,30] To this point, Schindler et al[12] described the clinical characteristics of 15 children during acute pulmonary hypertensive crises using invasive monitoring, finding that only 1/15 patients exhibited hypoxaemia in the midst of these episodes, with that 1 patient having an intracardiac shunt. While the gold standard in monitoring for real-time changes in pulmonary blood flow may involve pulmonary artery catheters, their placement is often technically challenging in the paediatric population and has a higher risk of bleeding during removal, in addition to their inability to assess hemodynamic data in the face of intracardiac shunting, a condition that many children with pulmonary hypertension exhibit.[31–33] The need for non-invasive, readily available, and accurate markers of pulmonary blood flow remain an ongoing need in this population.

Comparing those patients failing inhaled nitric oxide discontinuation in our cohort to the success group, a trend appears of a higher dead space ratio prior to inhaled nitric oxide initiation, along with increased pre-existing documentation of a pulmonary hypertension diagnosis, longer times on inhaled nitric oxide, higher FiO_2 need after inhaled nitric oxide discontinuation, and longer need for mechanical ventilation. This higher dead space ratio may thus serve as a prognostic marker of pulmonary HTN disease severity, although reaching further conclusions on this failure group and its trends requires a larger population.

Limitations

One of the main limitations of our study was the low number of patients in the inhaled nitric oxide failure group, which hindered our ability to quantitatively compare the success and failure to wean groups. In addition, the outcome variable of success/failure was dependent on physician's clinical judgment to reinitiate inhaled nitric oxide without including supportive echocardiographic or catheterisation-based hemodynamic data, data not consistently available within our studied population. Using the alternative outcome measures of changes in vasoactive infusion score or oxygenation index during nitric oxide weaning, no significant correlations were found between decreases in dead space ratio and decreases in these variables. While this may reflect limitations in dead space ratio as a tool in weaning inhaled nitric oxide, it must also be recognised that the vasoactive infusion score as an outcome measure may be influenced by other hemodynamic perturbations not related to pulmonary hypertension and that worsening oxygenation both may not be a primary manifestation of worsening pulmonary hypertension and may also be influenced by other primary pulmonary pathology.[12]

An additional limitation in our analysis is that in the success to wean group, 9/23 (39%) were started on an additional pulmonary vasodilator during the weaning process. However, it should be mentioned that the question of our study is centred more on the relationship of dead space ratio changes and inhaled nitric oxide weaning per se, independently of the use of additional vasodilators during this weaning process. With this in mind, we reviewed the dead space ratio trends in the remaining 14 patients without finding significant changes (0.25–0.17, $p = 0.25$) in this group. Another limitation of our study involves not including the presence of ETT leak as a variable in the analysis of dead space ratio. In our unit, it is standard of care to use cuffed ETT, but we acknowledge that in patients with ETT leak, the calculated dead space ratio may be falsely overestimated.

Conclusions

Children empirically placed on inhaled nitric oxide out of concern of pulmonary hypertensive crisis and then successfully weaned off exhibited an unchanged or decreased dead space ratio throughout the initiation to discontinuation phases of inhaled nitric oxide therapy, suggesting that trends in dead space ratio may aid in determining true need for inhaled nitric oxide and facilitate effective weaning. Further studies with both larger sample sizes and thoughtful outcome measures are needed to directly compare trends between success and failure groups.

Supplementary material. To view supplementary material for this article, please visit https://doi.org/10.1017/S1047951121004662

Acknowledgements. None.

Conflicts of Interest. None.

Author Contribution. ADG: Literature search, Study design, Data collection, Analysis of data, Manuscript preparation, Review of manuscript. WL: Statistical method development, Analysis of data. HA: Study design, Review of Manuscript. WJH: Study design, Analysis of data, Review of manuscript.

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