Title

The Double-edged Sword of Reverse Triggering: Impact on the Diaphragm.

Journal

American Journal of Respiratory and Critical Care Medicine, 205(6)

ISSN

1073-449X

Authors

Sassoon, Catherine S

Mancebo, Jordi

Publication Date

2022-03-15

DOI

10.1164/rccm.202201-0099ed

Peer reviewed

Author disclosures are available with the text of this article at www.atsjournals.org.

David M. Stieb, M.D., M.Sc.
Environmental Health Science and Research Bureau
Health Canada
Ottawa, Ontario, Canada
and
School of Epidemiology and Public Health
University of Ottawa
Ottawa, Ontario, Canada

References

1. Bozack A, Pierre S, DeFelice N, Colicino E, Jack D, Chillrud SN, *et al.* Long-term air pollution exposure and COVID-19 mortality: a patient-level analysis from New York City. *Am J Respir Crit Care Med* 2022;205: 651–662.
2. Wu X, Nethery RC, Sabath MB, Braun D, Dominici F. Air pollution and COVID-19 mortality in the United States: strengths and limitations of an ecological regression analysis. *Sci Adv* 2020;6:eabd4049.
3. Liang D, Shi L, Zhao J, Liu P, Sarnat JA, Gao S, *et al.* Urban air pollution may enhance COVID-19 case-fatality and mortality rates in the United States. *Innovation (N Y)* 2020;1:100047.
4. Lipsitt J, Chan-Golston AM, Liu J, Su J, Zhu Y, Jerrett M. Spatial analysis of COVID-19 and traffic-related air pollution in Los Angeles. *Environ Int* 2021;153:106531.
5. Stieb DM, Evans GJ, To TM, Lakey PSJ, Shiraiwa M, Hatzopoulou M, *et al.* Within-city variation in reactive oxygen species from fine particle air pollution and COVID-19. *Am J Respir Crit Care Med* 2021;204: 168–177.
6. Villeneuve PJ, Goldberg MS. Methodological considerations for epidemiological studies of air pollution and the SARS and COVID-19 coronavirus outbreaks. *Environ Health Perspect* 2020;128:95001.
7. Khanijahani A, Iezadi S, Gholipour K, Azami-Aghdash S, Naghibi D. A systematic review of racial/ethnic and socioeconomic disparities in COVID-19. *Int J Equity Health* 2021;20:248.
8. Bowe B, Xie Y, Gibson AK, Cai M, van Donkelaar A, Martin RV, *et al.* Ambient fine particulate matter air pollution and the risk of hospitalization among COVID-19 positive individuals: cohort study. *Environ Int* 2021; 154:106564.
9. Kogevinas M, Castaño-Vinyals G, Karachaliou M, Espinosa A, de Cid R, Garcia-Aymerich J, *et al.* Ambient air pollution in relation to SARS-CoV-2 infection, antibody response, and COVID-19 disease: a cohort study in Catalonia, Spain (COVICAT Study). *Environ Health Perspect* 2021;129: 117003.
10. Payne-Sturges DC, Gee GC, Cory-Slechta DA. Confronting racism in environmental health sciences: moving the science forward for eliminating racial inequities. *Environ Health Perspect* 2021; 129:55002.
11. Ciencewicki J, Jaspers I. Air pollution and respiratory viral infection. *Inhal Toxicol* 2007;19:1135–1146.
12. Domingo JL, Rovira J. Effects of air pollutants on the transmission and severity of respiratory viral infections. *Environ Res* 2020;187:109650.
13. Petersen E, Koopmans M, Go U, Hamer DH, Petrosillo N, Castelli F, *et al.* Comparing SARS-CoV-2 with SARS-CoV and influenza pandemics. *Lancet Infect Dis* 2020;20:e238–e244.

The Double-edged Sword of Reverse Triggering: Impact on the Diaphragm

Reverse triggering is a term coined for the unique rhythmic pattern of patient–ventilator interaction observed in deeply sedated, critically ill patients with acute respiratory distress syndrome, in which the ventilator's mechanical inflation triggers inspiratory muscle effort (1). The rhythmic pattern is commonly phase locked at 1:1, in which one inspiratory muscle effort is triggered or preceded by one mechanical inflation, although other patterns (e.g., 1:2, 1:3, 2:3, or chaotic pattern) may occur. Reverse triggering essentially results from the entrainment of respiratory rhythms originating from the central neural oscillators within the respiratory pattern generator in response to external stimulus (2). The stimulus can be in the form of positive pressure ventilation (1); limb somatic afferents (3); locomotor (3), exercise (4), or music (5) rhythms; or arterial carbon dioxide tension (6). Respiratory entrainment in response to mechanical inflation has been observed in humans both under anesthesia (7) and in states of wakefulness and sleep (8), as well as in anesthetized animals (9). In anesthetized animals, the Hering-Breuer reflex, which prevents overinflation of the lung via slowly adapting receptors, rapidly adapting receptors, and vagal-C fibers, all appear to be implicated in respiratory entrainment as vagotomy abolishes the respiratory rhythm (9). However, in humans, vagal feedback is not essential for respiratory entrainment (8), whereas mechanoreceptors in the upper airway, lung, chest wall, and diaphragm may be involved in the generation of respiratory entrainment in response to mechanical inflation (10). Spinal respiratory rhythm generator mediated via spinal reflexes also may be involved in respiratory entrainment; reverse triggering recently was reported in patients who have suffered brain death and are on mechanical ventilation (11, 12).

The prevalence of reverse triggering in critically ill patients with (13) and without (14) acute respiratory distress syndrome, especially those who are under deep sedation and are receiving volume or pressure assist–control mechanical ventilation, is fairly high (~45%). Some reverse-triggered breaths can induce breath stacking, resulting in increased inflation volume and augmented transpulmonary pressure,

Originally Published in Press as DOI: 10.1164/rccm.202201-0099ED on February 9, 2022

which are counterproductive to protective ventilation strategy. In the absence of breath stacking, the inspiratory muscle effort generated may be sufficient to induce pendelluft, resulting in regional stress in the dependent lung (15). However, inspiratory muscle effort during the machine exhalation phase theoretically may attenuate strain in the dependent lung. Depending on the magnitude of inspiratory muscle effort generated, reverse triggering may cause injury to the diaphragm muscle or, alternatively, protect the diaphragm from muscle atrophy when application of mechanical ventilation is prolonged.

In this issue of the *Journal*, from their colossal study in a porcine model of lung injury, Damiani and colleagues (pp. 663–673) reported three novel observations (16): *1*) The development of reverse triggering allowing assessment of inspiratory muscle efforts on diaphragm structure and function. An animal model of reverse triggering will facilitate evaluation of the temporal relationship of phases of ventilator inhalation (concentric contraction) and exhalation (eccentric contraction) to inspiratory muscle efforts. Furthermore, the model is also key for systematically studying the role of ventilator settings (rate, V_T, flow rate, and positive end-expiratory pressure) in mitigating or eliminating the harmful consequences of reverse triggering. *2*) Reverse triggering associated with high inspiratory muscle effort ($\geq$300 cm H_2O/s) induced diaphragm muscle injury and impaired diaphragm muscle function. *3*) Reverse triggering with low inspiratory muscle effort ($\leq$150 cm H_2O/s) protected diaphragm muscle function.

Caveats to the study of Damiani and colleagues (16), however, are as follows: *1*) The study lacked control animals without lung injury that were treated with the same ventilator settings with and without the occurrence of reverse triggering. It is unclear whether the lung injury itself caused systemic inflammations that affected diaphragm muscle function, which then confounded the effect of reverse triggering (17). *2*) The study lacked end-expiratory lung volume measurement. The dependence of muscle force production on its length–force relationship is well known in physiology. Changes in end-expiratory lung volume can potentially occur when a strong inspiratory muscle effort induces pendelluft in the dependent lung region (15). Setting a high respiratory rate in the reverse triggering group may induce intrinsic positive end-expiratory pressure, further shortening the fiber length of the diaphragm muscle. *3*) Unexpectedly, alterations in diaphragm muscle function were discernible at 3 hours. This is in contrast to the study of Jaber and colleagues (18), in which researchers applied controlled mechanical ventilation to smaller piglets (15–20 kg) for both 3 hours and 3 days. Transdiaphragmatic pressure remained intact in the group on short-term ventilation, whereas it did not in the group on long-term ventilation. *4*) Evidence of diaphragm muscle injury was found by means of only light microscopy, which did not detect the disruption of sarcomeres and damage to mitochondria.

How can we translate the observations of Damiani and colleagues (16) to the management of critically ill patients with reverse triggering? Despite the previously mentioned limitations, this study sheds light on the potential harm of high inspiratory muscle efforts on diaphragm function, and hence it is important to, first, identify the presence of reverse triggering, particularly that which results in strong inspiratory muscle efforts, and second, to assess whether modifications of usual supportive treatments (sedatives, opiates, and ventilator settings) change the frequency of reverse triggering. Automated detection of reverse triggering from airway pressure and flow can aid in the care of critically ill patients on mechanical ventilation (19) with the goal of eliminating breath stacking. However, further studies must be performed to determine whether the elimination of reverse triggering associated with high inspiratory muscle effort in critically ill patients with acute respiratory distress syndrome will reduce the duration of mechanical ventilation, length of stay in the ICU, and mortality. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

Catherine S. Sassoon, M.D.
Department of Medicine
University of California
Irvine, California

Jordi Mancebo, M.D.
Servei de Medicina Intensiva
Hospital Universitari Sant Pau
Barcelona, Spain

References

1. Akoumianaki E, Lyazidi A, Rey N, Matamis D, Perez-Martinez N, Giraud R, *et al.* Mechanical ventilation-induced reverse-triggered breaths: a frequently unrecognized form of neuromechanical coupling. *Chest* 2013; 143:927–938.
2. Longobardo G, Evangelisti CJ, Cherniack NS. Introduction of respiratory pattern generators into models of respiratory control. *Respir Physiol Neurobiol* 2005;148:285–301.
3. Potts JT, Rybak IA, Paton JFR. Respiratory rhythm entrainment by somatic afferent stimulation. *J Neurosci* 2005;25:1965–1978.
4. Paterson DJ, Wood GA, Morton AR, Henstridge JD. The entrainment of ventilation frequency to exercise rhythm. *Eur J Appl Physiol Occup Physiol* 1986;55:530–537.
5. Haas F, Distenfeld S, Axen K. Effects of perceived musical rhythm on respiratory pattern. *J Appl Physiol (1985)* 1986;61:1185–1191.
6. Takahashi E, Tejima K, Yamakoshi K. Entrainment of respiratory rhythm to respiratory oscillations of arterial PCO2 in vagotomized dogs. *J Appl Physiol (1985)* 1992;73:1052–1057.
7. Graves C, Glass L, Laporta D, Meloche R, Grassino A. Respiratory phase locking during mechanical ventilation in anesthetized human subjects. *Am J Physiol* 1986;250:R902–R909.
8. Simon PM, Habel AM, Daubenspeck JA, Leiter JC. Vagal feedback in the entrainment of respiration to mechanical ventilation in sleeping humans. *J Appl Physiol (1985)* 2000;89:760–769.
9. Petrillo GA, Glass L, Trippenbach T. Phase locking of the respiratory rhythm in cats to a mechanical ventilator. *Can J Physiol Pharmacol* 1983;61:599–607.
10. de Vries HJ, Jonkman AH, Tuinman PR, Girbes ARJ, Heunks LMA. Respiratory entrainment and reverse triggering in a mechanically ventilated patient. *Ann Am Thorac Soc* 2019;16:499–505.
11. Delisle S, Charbonney E, Albert M, Ouellet P, Marsolais P, Rigollot M, *et al.* Patient-ventilator asynchrony due to reverse triggering occurring in brain-dead patients: clinical implications and physiological meaning. *Am J Respir Crit Care Med* 2016;194:1166–1168.
12. Dubayle D, Viala D. Localization of the spinal respiratory rhythm generator by an in vitro electrophysiological approach. *Neuroreport* 1996;7:1175–1180.

13. Rodriguez PO, Tiribelli N, Fredes S, Gogniat E, Plotnikow G, Fernandez Ceballos I, *et al.*; Grupo Argentino de Estudio de Asincronías en la Ventilación Mecánica Study Group. Prevalence of reverse triggering in early ARDS: results from a multicenter observational study. *Chest* 2021;159:186–195.
14. Mellado Artigas R, Damiani LF, Piraino T, Pham T, Chen L, Rauseo M, *et al.* Reverse triggering dyssynchrony 24 h after initiation of mechanical ventilation. *Anesthesiology* 2021;134:760–769.
15. Yoshida T, Nakamura MAM, Morais CCA, Amato MBP, Kavanagh BP. Reverse triggering causes an injurious inflation pattern during mechanical ventilation. *Am J Respir Crit Care Med* 2018;198: 1096–1099.
16. Damiani LF, Engelberts D, Bastia L, Osada K, Katira BH, Otulakowski G, *et al.* Impact of reverse triggering dyssynchrony during lung-protective ventilation on diaphragm function: an experimental model. *Am J Respir Crit Care Med* 2022;205:663–673.
17. Matthay MA, Ware LB, Zimmerman GA. The acute respiratory distress syndrome. *J Clin Invest* 2012;122:2731–2740.
18. Jaber S, Sebbane M, Koechlin C, Hayot M, Capdevila X, Eledjam JJ, *et al.* Effects of short vs. prolonged mechanical ventilation on antioxidant systems in piglet diaphragm. *Intensive Care Med* 2005;31: 1427–1433.
19. Pham T, Montanya J, Telias I, Piraino T, Magrans R, Coudroy R, *et al.*; BEARDS study investigators. Automated detection and quantification of reverse triggering effort under mechanical ventilation. *Crit Care* 2021; 25:60.

FocuSSced on the Target in Systemic Sclerosis–Interstitial Lung Disease

Another Arrow in the Quiver?

Systemic sclerosis (SSc) is a challenging clinical entity associated with significant morbidity and mortality (1). SSc is characterized by endothelial dysfunction with small vessel vasculopathy, which leads to inflammation and fibrosis of the skin and internal organs, including the lungs (2). Pulmonary manifestations of SSc (pulmonary hypertension and interstitial lung disease [ILD]) account for the majority of deaths in these patients, and ILD alone accounts for a third of the mortality observed in one study of patients with SSc (3). SSc-ILD is a heterogenous disorder with unpredictable clinical course, but in many cases, there is a progressive phenotype typified by a decline in lung function, worsening quality of life, and death (4).

Previous randomized controlled therapeutic trials have demonstrated preservation and improvement of lung function in patients with SSc-ILD (Figure 1) (5–8). Briefly, in 2006, cyclophosphamide was shown to improve FVC compared with placebo in the initial SLS (Scleroderma Lung Study) (7). In SLS II, mycophenolate mofetil (MMF) was compared with cyclophosphamide, and the study demonstrated improvement in FVC during the intervention period with both therapies but a more favorable toxicity profile in those randomized to MMF (6). In the SENSCIS (Safety and Efficacy of Nintedanib in Systemic Sclerosis) trial, nintedanib, an antifibrotic medication approved for the treatment of idiopathic pulmonary fibrosis, was found to slow the decline in FVC over time compared with placebo in a study that allowed for background immunosuppression (5). More recently, the focuSSced trial investigated tocilizumb in SSc, including those with ILD (8). In this 48-week, placebo-controlled, randomized, double-blind study, the primary endpoint (delta in modified Rodnan skin fibrosis score [mRSS]) was not significant between treatment and placebo groups (8). However, a prespecified secondary endpoint analysis revealed preservation in FVC% predicted with tocilizumab compared with placebo at 48 weeks (−0.4 vs. −4.6 change in FVC% predicted), findings that were consistent among patients with SSc with radiologic evidence of ILD (8).

In this issue of the *Journal*, Khanna and colleagues (pp. 674–684) report the results of the 48-week open-label extension period of the focuSSced trial (9). Patients randomized to placebo (PBO) in the initial 48 weeks were transitioned to treatment with tocilizumab (TCZ) for 48 weeks (PBO-TCZ arm), and those patients on tocilizumab in the initial treatment arm continued therapy (Cont-TCZ arm, total of 96 weeks for treatment arm). Patients with SSc were given weekly subcutaneous injections of tocilizumab (162 mg), and the long-term safety and efficacy of tocilizumab was assessed.

From the original randomized cohort, 82/105 from the placebo arm and 85/105 from treatment arm continued into the open-label extension. Of these patients who entered the extension period, 10 withdrew for adverse effects ($n = 4$) or patient decision ($n = 6$). Importantly, of the subjects who entered the open-label extension, the majority (114 out of 181) had ILD on their baseline high-resolution computed tomography scans. Both arms of the open-label extension period had similar preservation of FVC% predicted as that seen in the treatment arm of the parent randomized controlled trial (RCT) among those with SSc, and the findings were consistent among those with SSc-ILD (PBO-TCZ: 0.9 [−0.8, 2.7], Cont-TCZ: −0.4 ml [−2.3, 1.3]; for reference, the results from the parent RCT at 48 weeks were TCZ: −0.4 versus PBO: −4.6 [FVC% predicted at 48 weeks]). These findings support the durability of the effect of tocilizumab on FVC decline in SSc-ILD. The open-label extension period reported similar adverse effects as those observed in the parent RCT and were consistent with the known safety profile of tocilizumab.

The role of an open-label extension trial design is threefold. Primarily, this trial design allows patients randomized to placebo access to the study drug after the initial randomization period ends.

Originally Published in Press as DOI: 10.1164/rccm.202111-2587ED on December 14, 2021