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Reverse Triggering, the Rhythm Dyssynchrony: Potential Implications for Lung and Diaphragm Protection

Patient–ventilator dyssynchrony occurs when mechanical support from the ventilator does not match the neuromechanical output from the patient's respiratory center. Classically, dyssynchrony subtypes have been characterized breath to breath by mismatch in the timing and/or force of patient effort relative to machine support (e.g., ineffective efforts, double triggering, delayed cycling, flow dyssynchrony, etc.) (1). The concept of reverse triggering does not fit within this construct but rather describes one or more overarching mechanisms by which many of these breath-to-breath dyssynchronies can occur.

Reverse triggering is a patient inspiratory effort that is delayed in timing relative to the passive expansion of the lungs and chest wall by machine-initiated breaths (2). It often occurs in a repetitive, stereotyped pattern. Thus, reverse triggering might best be understood as a *rhythm dyssynchrony*, a recurring time lag between the ventilator and the patient's inspiratory effort, with the patient effort initiated slightly "off-beat" and appearing as though it was "triggered" by the ventilator.

In this issue of the *Journal*, Baedorf Kassis and colleagues (pp. 67–77) evaluate the effects of reverse triggering on lung mechanics in patients with acute respiratory distress syndrome (ARDS) (3). Using the Campbell diagram (pressure–volume loop of the chest wall), they detected reverse triggering in 25 of 55 patients with early ARDS, with waveform recordings with a mean of 7 minutes in duration. During reverse triggering, the maximum pressure generated by the respiratory muscles averaged between 4 and 10 cm H_2O, which is comparable with that of healthy subjects breathing at rest, although more extreme values were observed. They further classified reverse triggering into four subtypes distinguished by the timing of reverse triggering relative to mechanical insufflation and deflation. Lung mechanical effects varied by subtype. Reverse trigger–associated effort occurring during insufflation increased V_T and inspiratory transpulmonary pressures. When reverse trigger–associated effort occurred during deflation, mean expiratory transpulmonary pressure was increased.

Several findings of this study have potential clinical relevance. Patient effort during inspiration can increase global lung stress and strain in pressure-targeted modes or when breath stacking results (4) and might increase regional stress and strain from Pendelluft (5). If occurring frequently for prolonged periods, such efforts may be injurious in lungs primed for mechanical trauma. Patient inspiratory effort during exhalation might attenuate atelectrauma. Considering diaphragm protection, reverse triggering may preserve muscle activity in patients otherwise predisposed to completely passive ventilation, but eccentric contraction (during exhalation) or excessive load may cause injury. Whether the net effect is protective or injurious to the lungs and diaphragm likely depends on the timing and force of muscle activity and the patient's predisposition to injury.

Some caveats need to be considered when interpreting this study. The short duration of the recordings and use of few breaths to evaluate respiratory mechanics make it unclear as to whether data are representative of individual patient exposure. For instance, all reverse triggering might not occur within the range of effort comparable with that of healthy subjects. The durability of reverse triggering patterns over time and generalizability across patient populations are also uncertain. All patients were supported on pressure-regulated assist-control modes, and physiological consequences will vary according to the set mode. For example, V_T will not increase on volume assist control without breath stacking.

Several potential mechanisms may underlie reverse triggering. Most often, reverse triggering is believed to result from entrainment of the patient's respiratory rhythm to ventilator-induced insufflation. Entrainment occurs when a biological rhythm (e.g., respiration) is aligned in phase and period (phase-locked) to an external oscillator. Respiratory entrainment normally occurs during locomotion and can be induced via positive pressure ventilation during quiet wakefulness, during sleep (6), or under anesthesia (7) in humans. Vagal afferents influencing the respiratory rhythm generator mediate entrainment in animals (8), whereas in humans, they increase the strength of phase-locking during sleep (9). Possible alternative entrainment cues in humans include activation of intercostal (10) or phrenic nerve afferents as well as suprapontine stimuli triggered by auditory or respiratory sensations.

Alternatively, reverse triggering may result from a reflex contraction of the respiratory muscles after insufflation. Reverse triggering was reported in brain-dead patients lacking brainstem function (11), suggesting that spinal reflexes (12), such as the intercostal-to-phrenic nerve reflex described in animals (13), might be responsible. An alternative mechanism is respiratory muscle contraction entrained through the hiccup reflex arc (14). Quite possibly, several of these mechanistic pathways may contribute to reverse triggering under different conditions in critically ill patients.

In the study by Baedorf Kassis and colleagues (3), 16 of 25 patients exhibited reverse triggering with a fixed temporal relationship after insufflation at integral ratios (1:1, 2:1, or a combination), which is consistent with earlier descriptions characterized by a stereotyped, phase-locked pattern (2). In eight patients, reverse triggering at integral ratios was intermixed with spontaneous effort triggering the ventilator. Intermittent patient-triggered breaths could result from preset respiratory rate near the patient's intrinsic rate if slight variability in patient rate or rhythm and a lower strength of coupling occur. In one patient, reverse triggering without a specific pattern was observed. The lack of a fixed temporal relationship between the ventilator and patient's respiratory rhythm can be secondary to aperiodic behavior (when neural respiratory activity is still influenced by lung inflation) or complete dissociation between the two oscillators. Differentiating between the two might require long recordings and complex analysis (9).

Understanding predisposing factors and clinical effects will be essential to determining the clinical relevance of reverse triggering

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(injurious and beneficial) and possible management strategies. Modifiable factors such as ventilator settings (3), respiratory drive (4), level of consciousness, and prescribed sedatives and opiates may predispose differentially to reverse triggering depending on the mechanism. Regarding clinical significance, some degree of permissive dyssynchrony is probably benign or even beneficial for patients at low risk of lung or diaphragm injury. For patients at highest risk, including those with moderate and severe ARDS, clinical consequences of reverse triggering likely depend on the subtype, duration of exposure, and tradeoffs of interventions such as neuromuscular blockade.

Despite the uncertainties surrounding reverse triggering, the following is clear: a rapidly expanding literature indicates reverse triggering occurs often in mechanically ventilated patients at risk of injury and might be underrecognized at the bedside. What, if anything, should be done clinically remains to be determined. ■

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Molecular Imaging of Pulmonary Fibrosis: Another Step Forward

Molecular imaging enables *in vivo* visualization of molecular processes within a tissue or organ of interest using targeted molecular probes. Because of advancements in molecular imaging in fields ranging from neurology to oncology, there are now multiple U.S. Food and Drug Administration–approved molecular probes for use in clinical care. Within the field of fibrotic diseases, the application of molecular imaging in the preclinical arena and early-phase clinical trials is growing (1, 2). Over the past year, the results of the first in-human studies using the αvβ6 integrin–targeted positron emission technology (PET) probes [^{18}F]FB-A20FMDV2 and [^{18}F]FP-R$_0$1-MG-F2 and the type 1 collagen–targeted PET probe ^{68}Ga-CBP8 demonstrated increased PET signal in patients with pulmonary fibrosis consistent with increased αvβ6 integrin expression and type 1 collagen, respectively (3–5). In addition, ^{18}F-fluorodeoxyglucose

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