



Classifying reverse triggering breaths: A clinically oriented approach

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Abstract

Asynchronies during mechanical ventilation, particularly reverse triggering (RT), is a common phenomenon in critically ill patients, with prevalence estimates between 30% and 60%. RT is characterized by the activation of respiratory muscles induced by the passive insufflation, which can impact pulmonary physiology and diaphragmatic function, increasing the risk of lung injury and muscle damage. The proposed classification of RT in this article is based on five key criteria which suppose a structured evaluation of RT phenotypes.

This classification criteria would allow differentiation between events that may be beneficial, such as maintaining diaphragm activity and improving oxygenation, and injurious episodes, including breath stacking and high efforts that exacerbate pulmonary and muscular injury.

Understanding and classifying RT in detail enables clinicians to make more precise decisions and implement personalized interventions, thereby improving the safety and effectiveness of mechanical ventilation in critical care settings. This comprehensive approach provides a foundation for future research to validate its clinical utility, identify high-risk patient phenotypes, and develop targeted therapies.

Keywords: reverse trigger, phenotypes, classification, timing

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Introduction

Asynchronies in patients undergoing invasive mechanical ventilation are common and have been correlated with increased duration of ventilation and mortality.¹ Their prevalence, though variable, may be underestimated due to the challenges in their identification.^{2,3} Reverse triggering (RT) is a type of asynchrony resulting from inspiratory muscle activation induced by passive insufflation of the thorax (whether leading to ventilator assistance or not). Although first documented in adults in 2013,⁴ its existence has been recognized for some time.⁵ The prevalence of RT ranges from 30% to 60% in sedated patients undergoing mechanical ventilation, and its physiological repercussions are not yet fully understood.^{4,5}

Reverse activation with and without entrainment: Physiological mechanisms

This phenomenon can be classified based on the presence of an intrinsic respiratory pattern (entrainment)^{6,7} or its absence, where RT may manifest as a response to local reflexes without involvement of vagal reflexes or the respiratory rhythm generator in the brainstem.^{8,9}

These contractions can occur with varying frequencies (1:1; 1:2; 1:3) and at different points in the inspiratory cycle.⁴ In this regard, Baedorf Kassis et al.¹⁰ proposed a classification based on the temporality of its occurrence during the cycle. The main phenotypes are described according to the timing of onset and the relaxation pattern: 1) rapid activation and rapid relaxation, 2) rapid activation and slow relaxation, 3) mid-activation and late relaxation, and finally, 4) late activation (which is observed entirely during the expiratory phase).

These different temporal phenotypes have been associated with diverse physiological consequences, such as varying degrees of post-inspiratory contraction. For example, if the effort of reverse triggering exceeds the mechanical time (e.g., early/mid-activation and late relaxation), an alteration in expiratory flow will be observed because of this post-inspiratory contraction. In some cases, the work shifting will be sufficient to trigger another ventilator insufflation, producing a second respiratory cycle and an additional mandatory tidal volume. This latter situation leads to the loss of protective ventilation and an increase in inspiratory transpulmonary pressure. In this regard, Hashimoto et al.¹¹ showed in an animal model that breath stacking can impair pulmonary compliance, oxygenation, and cytokine concentrations because of the excessive increase in volume and pulmonary stress. Furthermore, pendelluft may be more

frequent during breaths with RT than in those triggered by the patient.¹²

Reverse triggering (RT), with or without entrainment, is a complex phenomenon involving the interaction of neural and mechanical mechanisms, and can manifest in different physiological states, from sleep to anesthesia.⁶ Various investigations have confirmed that this phenomenon occurs both in anesthetized animals and in humans in various states of consciousness.^{6,13-15} Entrainment can facilitate ventilatory synchronization, reflecting the nervous system's ability to adjust respiration in response to external stimuli, which may involve the participation of the frontal cortex and other higher centers.⁸

The prevailing theory holds that the flow and pressure applied by the ventilator activate stretch receptors in the airways, lungs, muscles, and chest wall. The feedback from these receptors would adjust the activity of the respiratory center, producing a repetitive and synchronized pattern.⁴ However, RT has also been detected in patients with bilateral lung transplants, even after resection of vagal afferents,⁸ suggesting that vagal feedback is not essential for its development. Furthermore, it has been reported in patients with brain death,⁹ who lack brainstem reflexes, indicating that other afferents such as thoracic mechanoreceptors, phrenic reflexes, intercostal reflexes, or even supra-pontine pathways may be involved.¹⁶⁻¹⁸ On the other hand, stimuli originating from higher centers of the nervous system, including auditory stimuli such as background noise or music, can also influence the appearance of respiratory entrainment.¹⁵ Sensory information processed by these centers can synchronize with the activity of the respiratory center, producing entrainment and breathing patterns related to the frequency of the external stimulus.

Thus, predisposing factors can be categorized as either related to environmental characteristics (external stimuli such as periodic insufflation dictated by mechanical ventilator settings, auditory, or sensory stimuli); intrinsic patient factors, which modify susceptibility to entrainment and/or facilitate the appearance of local reflexes (characteristics of the respiratory drive, sleep stages, CO₂ level, system compliance, and/or sedation); or a combination of both.

Predisposing Factors (in the era of lung-protective ventilation)

The tidal volume and respiratory rate set on the ventilator modulate the intensity and characteristics of the respiratory

entrainment induced by the stimulus. In general, there is a frequency range within which the respiratory rhythm can be entrained, related to the intrinsic frequency of the central pattern generator neurons.^{6,8} Reducing the ventilator rate can modify the entrainment relationship or abolish reverse triggering if the set frequency falls below the patient's intrinsic frequency, and the patient begins to trigger the ventilator.¹⁹

Tidal volume plays an important role; in fact, most of the recent observations described referred to patients on lung-protective ventilation with tidal volumes around 6 mL/kg of predicted body weight, a singular characteristic of the lung-protective ventilation era.⁵ In this regard, in the experimental work of Damiani et al.²⁰ in animals with lung injury, reverse triggering was induced by reducing tidal volume.

Sedation, on the other hand, is associated with reverse triggering and is typically observed during the transition from deep sedation to the resumption of spontaneous ventilation. Furthermore, certain drugs may increase susceptibility to reverse triggering, although this is not fully elucidated. In this regard, higher doses of opioids and benzodiazepines have been associated with greater susceptibility to reverse triggering in adult patients with ARDS.¹⁹

Discussion

Although reverse triggering has been classically associated with mandatory ventilation, it is increasingly evident that it can also occur during partial support modes. In fact, a recent study associated reverse breaths with PSV mode compared to NAVA when propofol was administered at various incremental doses.²¹ While this area warrants further study, the role of drive-modulating drugs such as opioids or propofol in the emergence of the phenomenon is noteworthy.

On the other hand, auto-triggered breaths, for example, do not originate from the respiratory control center and have the potential to function as mandatory ventilator insufflations, which, in turn, can trigger reverse breaths. These unsought ventilator triggers can influence airway pressure (Paw) or the flow signal and may be produced by condensations in the ventilator circuit,²² tracheobronchial secretions,²² cardiac oscillations,²³⁻²⁵ myoclonus,^{26,27} air leaks,²⁸ or relaxation of the expiratory muscles.²⁹

In some small case series, auto-triggered breaths due to cardiac oscillations are observed, followed by inspiratory

effort with an apparently regular pattern.^{28,29} However, these reverse breaths do not respond, at least in these case series, to a fixed pattern with phase angles that suggest entrainment. Nevertheless, given the intricate physiology of RT, it does not seem prudent to rule out that these external stimuli (auto-trigger) could provoke entrainment in certain patients. However, we acknowledge the difficulty of studying and demonstrating this without advanced equipment.

The presence of myoclonus, on the other hand, implies activation of the patient's inspiratory or expiratory musculature, which can trigger the ventilator outside of the respiratory center's control. In terms of patient-ventilator interaction, this is problematic because, while it is an effort that triggers the ventilator, it is not the patient's real or conscious effort. Even more problematic is the fact that the patient's real effort occurs just after the ventilator has triggered, potentially generating the sensation of entrained reverse breaths.

Furthermore, expiratory muscle activity and subsequent relaxation can trigger the ventilator (ERIT).²⁷ This interaction poses some difficulty in detection unless esophageal and gastric catheters or EAdi are available. The scenario can be more difficult if the patient produces a real inspiratory effort after (with some delay) the ventilator trigger. In fact, prior to the publication of the article regarding ventilator triggering due to expiratory muscle relaxation,²⁵ interactions had been demonstrated suggesting the presence of triggers generated by expiratory muscle activity and/or cardiac oscillations followed by patient efforts without a fixed phase angle, suggesting that there is no entrainment,²⁷ which the authors called false RT.

In our opinion, calling it false RT does not seem appropriate, since it is the patient who follows the ventilator in a reverse manner, although without entrainment. In this sense, the term "early trigger" seems more appropriate to highlight when the ventilator precedes the patient (whether due to auto-triggers, ERIT, or simply being at a higher frequency than the patient's neural drive). However, this term, by not referring to the origin of the auto-trigger, does not help the clinician at the bedside resolve the situation.

The confounding factor of double triggering origins

Double triggering is an asynchrony characterized by being generated by the patient's inspiratory effort, which, when sustained over time (exceeding the mechanical time), produces an additional insufflation.²² It is exclusively developed by the patient's inspiratory effort beyond the

mechanical time, but many times it could lead to misunderstanding about its origin and subjacent mechanisms.

Expiratory Muscle Relaxation Induced Triggering (ERIT), can also cause double triggering; however, the originating mechanisms of this interaction are different. On the other hand, an auto-trigger can cause a double trigger if the patient is activated during the insufflation period, exceeding the mechanical time. Likewise, late RT or mid-activation and prolonged relaxation can also cause double triggers. In the past, these interactions were called automatic double triggers or false RT.³⁰ Double triggers where the first insufflation is triggered by the patient's inspiratory effort (double trigger due to premature cycling) and that generated by ERIT (triggered by the relaxation of the expiratory muscles) have distinct clinical implications and resolutions. All the interactions are different in their origins, although any of them can cause double triggers and be potentially injurious (figure 1).

To facilitate the identification and management of reverse breaths, we propose the following classification based on five key criteria (figure 1):

- **Nature of Trigger:** This criterion classifies the origin of the stimulus that initiates respiration. We distinguish three main categories: 1) Ventilator-Induced (Reverse Trigger): Ventilator insufflation triggers a diaphragmatic contraction. 2) Patient-Initiated: Contraction and relaxation of the expiratory muscles prior to diaphragmatic contraction triggers the ventilator. 3) Auto-trigger: Trigger not related to patient effort or ventilator assistance, but generated by cardiac oscillations, circuit leaks, myoclonus, or secretions.
- **Mechanism of Action:** This criterion includes the identification of entrained or non-entrained breaths by the analysis of the phase angle and entrainment pattern. The phase angle expresses the relationship between the phase difference, defined as the time between the onset of the mechanical cycle (mandatory cycle) the onset of the patient's inspiratory activity, and the total duration of the mechanical ventilatory cycle (mechanical Ttot), divided by 360°, which represents a complete cycle of a nonlinear oscillatory system ($\Delta t \times T_{tot} / 360^\circ$)
- **Frequency and Pattern of Occurrence:** This criterion evaluates the frequency with which reverse breaths

occur and whether they follow a regular or irregular pattern. The presence of a regular pattern (e.g., reverse breaths that occur with each ventilator cycle) suggests a strong coupling between the patient and the ventilator (entrainment), while an irregular pattern may indicate a more random response to internal or external stimuli.

- **Timing of Occurrence During the Cycle:** Introduced by the work of Baedorf Kassis et al.¹⁰
- **Potential for Diaphragm and/or Lung Injury/Benefit:** This criterion evaluates the risk of pulmonary or diaphragmatic injury associated with reverse breathing, considering factors such as the magnitude of inspiratory effort, the presence of post-inspiratory contractions, and double triggering, as these are associated with the risk of overdistension, pendelluft, and the potential for myotrauma. On the other hand, when the RT contraction is low, occurs in the expiratory phase, and keeps the diaphragm active, improving blood flow, oxygenation, and preventing end-expiratory lung collapse, it might not be detrimental.

This classification proposes a novel approach by emphasizing the evaluation of the nature of the trigger, allowing for consideration of other mechanisms, both related to the patient and the ventilator, which can directly influence the patient-ventilator interaction. This is complemented by the evaluation of entrainment, through the analysis of the phase angle and the entrainment pattern, which facilitates a more precise understanding of the occurrence and behavior of the RT phenomenon, since the absence of entrainment makes it difficult to identify potential approaches. By considering the origin and frequency of the appearance of reverse breaths, solutions are proposed that go beyond adjusting tidal volume or pressure support. In this sense, the identification and correction of the underlying cause of auto-trigger or the administration of specific therapies (including pharmacological therapies) become more relevant.

This proposal complements the valuable contribution of Baedorf Kassis et al.¹⁰ by incorporating consideration of the injurious (or beneficial) potential of reverse breaths. We recognize that both breath stacking (BS) and work shifting can exacerbate pulmonary injury, so their early identification and management are essential to minimize the risk of ventilator-induced lung and diaphragmatic injury.

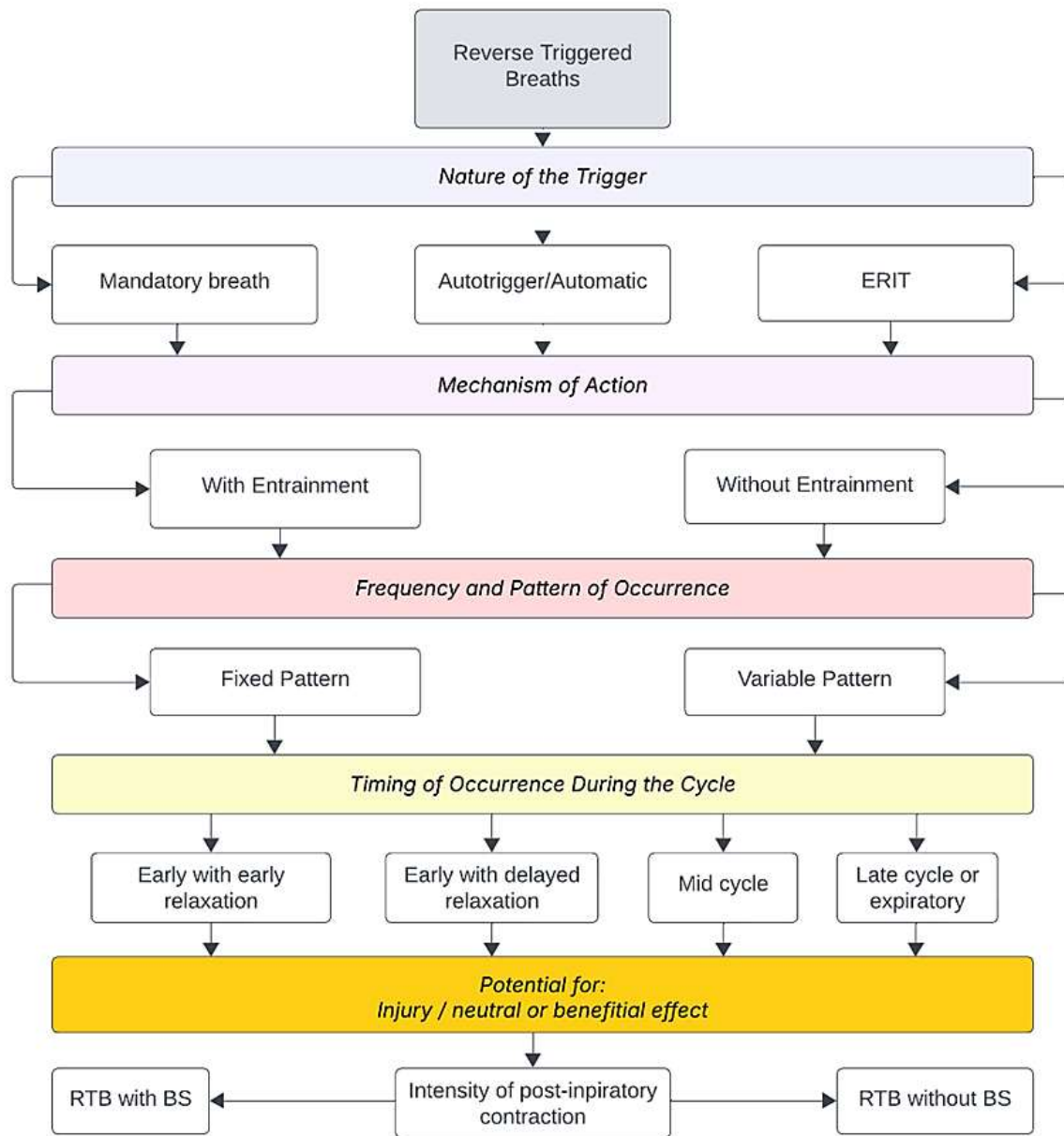


Figure 1: Comprehensive classification of reverse triggered breaths. BS: breath stacking, ERIT: Expiratory Muscle Relaxation Induced Triggering, RTB: reverse triggering breath

Conclusion

Reverse triggering is a common asynchrony in critically ill patients undergoing mechanical ventilation that demands a comprehensive understanding of the origins and predisposing factors involved to address it at the bedside. The proposed classification, by considering the nature of the trigger, the mechanism of action, the pattern of occurrence,

the timing, and the potential for injury, facilitates a structured evaluation of reverse breaths, optimizing the management strategy and minimizing the risk of ventilator-induced pulmonary and diaphragmatic damage. Furthermore, this classification could lay the foundation for future research to validate its clinical utility, identify phenotypes of patients at higher risk and develop more personalized and effective intervention.

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