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## High-frequency ventilation

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Modes of high-frequency ventilation (HFV) are characterized by high respiratory rates and tidal volumes that are lower than those used in conventional mechanical ventilation (CMV). The tidal volumes are often less than anatomic dead space and gas exchange is maintained by increasing respiratory rates to supra-physiologic frequencies. Gas exchange under these conditions occurs through a number of mechanisms that are related to the given mode of HFV. The most common modes of HFV include:

- high-frequency positive-pressure ventilation
- high-frequency percussive ventilation
- high-frequency jet ventilation
- high-frequency oscillatory ventilation.

Lung-protective mechanical ventilation strategies can reduce these injurious forces and subsequent lung damage, while providing adequate ventilation and oxygenation. The mechanics of HFV make it particularly suitable for protecting the lung and there is increasing physiologic support and growing clinical experience with HFV as an alternative to conventional mechanical ventilation or as salvage therapy in patients failing conventional ventilation strategies.

### Description and classification

**High-frequency positive pressure-ventilation (HFPPV)** delivers small volumes (approximately 3-4 cc/kg) of conditioned gas at high frequencies (60-100 breaths/min), using a conventional mechanical ventilator. Valves in the inspiratory and expiratory limbs of the ventilator circuit allow for control of inspiratory flow rates (which are generally high) and positive end-expiratory pressure (PEEP), respectively. Expiration is passive and relies on the elastic recoil of the patient's respiratory system. The clinician applying HFPPV controls the respiratory rate, inspiratory flow rates and driving pressures, and PEEP. Because high respiratory rates leave little time for passive expiration, there is the risk of gas trapping with hyperinflation and resultant overdistention injury.

**High-frequency percussive ventilation (HFPIV)** represents a hybrid mode of high-frequency ventilation that attempts to combine the principles of HFV with CMV using a proprietary mechanical ventilator.<sup>1</sup> A conventional ventilation circuit is fitted with a gas-driven piston at the end of the endotracheal tube. The reciprocating piston generates pressure oscillations at 3-15 Hz with short expiratory times that are superimposed on the conventional inspiratory-expiratory pressure waves. The high-frequency beats are delivered in bursts to generate auto-PEEP through breath-stacking; they are then stopped to allow alveolar pressure to fall back to baseline. It has been hypothesized that generated auto-PEEP may improve alveolar recruitment without exposing alveoli to high peak airway pressures that would be generated with comparable CMV. High-frequency percussion also provides some internal mucokinesis, improving pulmonary toilet and reducing the requirement for endotracheal suctioning, which could have deleterious effects on blood pressure, intracranial pressure, and alveolar recruitment, particularly in patients with head trauma. Although the high-frequency pressure oscillations are driven actively in both directions, bulk exhalation from underlying CMV breaths is passive. Clinicians control all aspects of the underlying CMV breaths, as well as the frequency and pressure of the high-frequency beats.

**High-frequency jet ventilation (HFJV)** employs a small-aperture nozzle to direct a high-pressure stream of gas into the lung. Gas flow through the nozzle is controlled by a solenoid valve that allows control of frequency and inspiratory time. During inspiration, a high-pressure jet streams into the proximal airways, entraining air from the circuit. Tidal volumes in HFJV are largely dependent on the momentum of the jet and entrainment of gas from the surrounding circuit. Expiration is passive, relying on respiratory system recoil. PEEP is determined by changing the flow of fresh gas through



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the circuit and the resistance to flow through the expiratory limb. The small size of the injector nozzles (2-3 mm) allows for their placement in the endotracheal tube or proximal trachea, which not only decreases dead space, but also allows for better visualization and access during surgical procedures involving the upper airway.

The clinician using HFJV can control frequency, inspiratory-time, driving pressure, and the mean airway pressure applied through the ventilator circuit. Larger tidal volumes can be delivered by increasing driving pressure and inspiratory time. Larger jet catheters and ET tubes also augment  $V_T$  by increasing the jet volume and gas entrainment, respectively. Because expiration is passive, gas trapping with intrinsic-PEEP may occur at high frequencies when expiration is limited by progressively shorter expiratory times.

Complications specific to HFJV include traumatic upper airway injury. The high velocity inspiratory jet may cause direct trauma to the proximal airways. Necrotizing tracheobronchitis is a well-established complication of HFJV in both infants and adults.<sup>2,3</sup> Gas conditioning in HFJV, particularly humidification and warming, is also problematic. Although the gas entrained from the proximal circuit is warmed and humidified, the gas projecting from the jet nozzle expands and cools, compromising the overall conditioning of the inspired gas. It has also been hypothesized that high gas flow rates and rapid increases in lung volume can cause lung injury through the generation of shear forces at the interface between adjacent compliant and atelectatic lung units.

In *high-frequency oscillatory ventilation (HFOV)*, an oscillating diaphragm creates pressure waves in the ventilator circuit. Because the excursion of the diaphragm is active in both directions, both inspiration and expiration are active in HFOV, although the actual tidal volumes generated by HFOV are thought to be very small. Mean airway pressure is determined by adjusting the resistance to the flow of fresh gas (bias flow) across the circuit.

Clinicians using HFOV set the bias flow rate, mean airway pressure, frequency, inspiratory/expiratory ratio, and the power applied to the oscillating diaphragm. The generation of pressure oscillations in HFOV is controlled, in part, by the frequency and the energy applied to the moving diaphragm (power). The excursion of the diaphragm (and presumably the delivered tidal volumes) is inversely related to the frequency. High frequencies result in a short inspiratory period that limits the time during which the diaphragm can move. This can be overcome by increasing the power, which increases diaphragm excursion at a given frequency.

HFOV is distinguished from other modes of HFV in that it has an active expiratory phase. Because the diaphragm is actively driven in both directions, the ventilator creates both inspiratory and expiratory pressure waves; in other forms of HFV, expiration is passive and dependent on the elastic recoil of the respiratory system. Active expiration may be advantageous in controlling lung volumes and preventing hyperinflation. Although all modes of HFV may generate some degree of auto-PEEP that may be beneficial in increasing alveolar recruitment, high levels of auto-PEEP can cause hyperinflation and lung injury. HFOV has been shown to be associated with less gas trapping than other forms of HFV.<sup>4</sup>

### Mechanisms of gas transport during HFV

HFV is thought to generate tidal volumes that are smaller than anatomic dead space. Adequate ventilation under these

conditions relies on alternative gas exchange mechanisms. A number of proposed mechanisms may contribute to gas transport during HFV.<sup>5</sup> When  $V_T$  approximates anatomic dead-space, the leading edge of the gas front may actually reach a number of proximal alveoli and thus contribute to some gas exchange through bulk flow.<sup>5</sup> Although it is thought that HFV generally generates  $V_T$  levels that are lower than anatomical dead space, recent experimental data suggest that larger tidal volumes may be generated under some conditions. One study evaluating HFOV – usually considered to have the smallest tidal volumes of the different HFV modes – demonstrated that a  $V_T$  significantly greater than anatomic dead space is generated when HFOV is applied to a large-animal model using settings similar to those traditionally used in adults (frequency of 3-6 Hz,  $\Delta P$  60-90 cm H<sub>2</sub>O).<sup>6</sup> The *in vitro* characteristics of pediatric HFOVs have been studied, revealing a  $V_T$  of 3 to 11 ml.<sup>7</sup> Thus, bulk flow may still contribute to gas exchange during HFV, although to a much lesser degree than during CMV.

Pendelluft is a phenomenon of regional gas movement that is the result of heterogeneity in alveolar filling rates. The filling rate of a lung unit is dependent on its time constant ( $\tau$ ), a property related to the product of compliance and resistance.<sup>8</sup> Adjacent lung units with different time constants may fill at different rates during inspiration. Following inspiration, there is redistribution of inspired gas from full fast-filling units to slower-filling units, augmenting gas exchange.<sup>9</sup>

Convective streaming occurs as a result of the asymmetric velocity profile of the inspired gas front as it moves through the bronchial tree. When inspired gas flows down the bifurcating bronchial tree, the gas front is skewed so that inspired gas streams down the inside wall of distal airways. During exhalation, the velocity profile of the gas front is flat across the airway cross-section. The asymmetry in gas velocity between the inspiratory and expiratory phases of breathing results in a net streaming of fresh gas down the inside walls of distal airways and carbon dioxide-laden gas back along the outside walls.<sup>10,11</sup> This asymmetrical streaming of fresh gas down airways creates a radial concentration gradient (augmented diffusion) that may contribute significantly to gas mixing.<sup>12</sup> In addition, the beating heart may also enhance gas exchange through agitation of surrounding lung tissue (cardiogenic mixing) in these lung units and molecular diffusion.

The extent to which each of these mechanisms contributes to gas exchange at any one moment in a given patient is unknown and it is perhaps of questionable clinical relevance beyond the fact that adequate gas exchange can be achieved with HFV. Experimental models have shown that CO<sub>2</sub> elimination is a product of the frequency and the square of the tidal volume ( $V_{CO_2} \propto f \times V_T^2$ ),<sup>13</sup> suggesting that adequate CO<sub>2</sub> elimination may become problematic in the clinical setting when tidal volumes are very small. Regardless, clinical experience has demonstrated that adequate gas exchange can be achieved with mechanical ventilation using tidal volumes that are less than anatomical dead space.

### Rationale for high-frequency ventilation

#### *Ventilator-induced lung injury and lung protection*

Over the past 20 years, there has been a greater appreciation of the potential for lung injury caused by mechanical ventilation (ventilator-induced lung injury [VILI]). Mechanical ventilation uses high inspired oxygen concentrations, high pressure, and large volumes and is widely accepted as being harmful. Although

the pathogenesis of VILI is complex and remains incompletely elucidated, current data support several injurious mechanisms including volutrauma, atelectrauma, and biotrauma.

**Volutrauma:** Supporting evidence reveals that ventilation with excessive tidal volumes, even using negative pressure ventilators, results in pathologic abnormalities similar to those seen in acute respiratory distress syndrome (ARDS); mechanical restriction of lung volume mitigates this damage even when extremely high inflation pressures are applied.<sup>14,15</sup> This understanding has led to the adoption of the term “volutrauma”.<sup>16</sup> The exact mechanism by which large volumes cause lung injury is not clear, but it may be related to alveolar wall stretch, stress failure of the lung ultrastructure, and cellular mechanotransduction leading to release of inflammatory mediators.<sup>17</sup>

**Atelectrauma:** Mechanical ventilation at low end-expiratory volumes may also be injurious. Atelectrauma occurs when end-expiratory volume is insufficient to maintain inflation of lung units throughout the respiratory cycle. Under these conditions, lung units collapse at end-expiration, only to be forced open during inspiration. Shear forces generated during this cyclical collapse and re-inflation injure the alveolar walls, contributing to VILI.<sup>18</sup> Similar forces may also be generated at the interface between aerated and atelectatic lung units during the respiratory cycle, stressing the connecting alveolar walls.<sup>19</sup> Furthermore, underlying lung pathology may predispose to or exacerbate atelectrauma-type injury. Although cyclical collapse can be tolerated for short periods in healthy lungs,<sup>20</sup> the shear forces are intensified when lung mechanics are altered by surfactant depletion and underlying lung injury.<sup>21</sup>

**Biotrauma:** The end-organ effects of VILI are not isolated to the lung. Biotrauma refers to the contribution of VILI to systemic inflammation.<sup>22</sup> Injurious mechanical ventilation is associated with increases in circulating inflammatory mediators and these increases can be attenuated through the use of mechanical ventilation strategies that avoid these injurious forces.<sup>23</sup> The production of systemic inflammatory mediators may contribute to multiple-organ dysfunction and mortality.

## Reducing VILI

The mechanical ventilation strategies that have been designed to reduce VILI have been termed lung-protective. The current goals of lung protection are threefold:

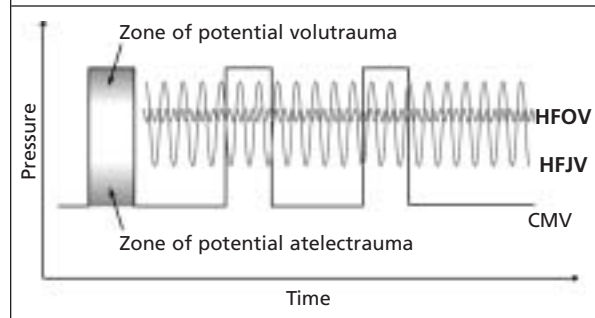
- 1) prevention of overdistention related lung injury by reduction of tidal volumes
- 2) maintenance of lung volume to prevent cyclical collapse and atelectrauma-type lung injury
- 3) reduction of FiO<sub>2</sub> (fraction of inspired oxygen) requirements through a variety of mechanisms to reduce oxygen toxicity.

The hope is that reduction of these injurious mechanical forces will translate into a decrease in systemic inflammation and subsequent end-organ dysfunction and mortality.

## Successes and limitations of lung-protective CMV

The principles of lung-protective ventilation have been applied successfully in the clinical setting using CMV. Approaches to minimize VILI include limiting tidal volumes to prevent volutrauma and using PEEP and recruitment maneuvers to maintain end-expiratory lung volume, thereby preventing cyclical collapse.<sup>24</sup> The landmark ARDS Network trial evaluated a lung-protective CMV strategy based on low tidal volumes and reduced airway pressures, and reported a 9% absolute reduction in mortality.<sup>25</sup> Lung-protective CMV is also associated with

**Figure 1: Theoretic comparison of the alveolar pressure swings seen with high-frequency ventilation versus CMV**



HFOV = high-frequency oscillatory ventilation;  
 HFJV = high-frequency jet ventilation  
 CMV = conventional mechanical ventilation

lower levels of circulating inflammatory mediators, supporting the hypothesis that the mitigation of injurious mechanical forces during mechanical ventilation may help to decrease biotrauma and its contribution to multisystem organ failure.<sup>23,25</sup>

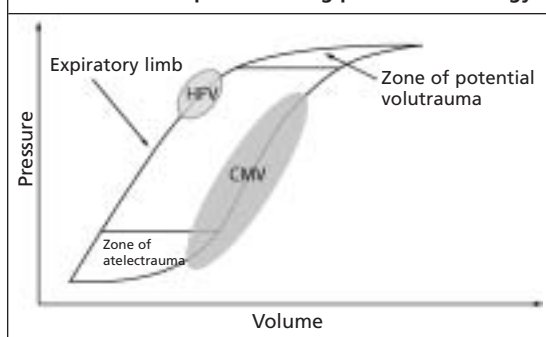
The clinical application of these ventilation protocols, however, is often complicated by impaired ventilation. The use of lower tidal volumes results in a decrease in alveolar ventilation that is not always completely offset by increases in respiratory rate. Consequently, clinicians may be forced to accept hypoventilation and respiratory acidosis, so-called “permissive hypercapnea,” if they wish to maintain low tidal volumes. In addition, even the best possible lung-protective CMV may still contribute to the injury of some lung units. Computerized tomographic imaging studies have demonstrated that lung injury in ARDS is heterogeneous,<sup>26</sup> resulting in local differences in lung mechanics and variable susceptibility to VILI. Relatively healthy lung units may have higher compliance and lower time constants than their more severely-injured neighbours, potentially making them more prone to volutrauma-type lung injury. Relatively non-compliant lung units, conversely, may be more prone to atelectrauma-type injury if allowed to collapse at end-expiration. Thus, even when CMV is applied with low “lung-protective” tidal volumes (4-6 cm/kg), patients may still suffer atelectrauma-type injury in diseased, non-compliant lung units, while adjacent healthy lung units are injured by overdistention. Furthermore, determining the ideal level of PEEP to prevent end-expiratory collapse may be difficult. One study found that alveolar recruitment occurred progressively over the entire inflation limb of the PV curve, making reliable identification of the lower inflection point difficult.<sup>27</sup>

## Theoretical advantages of HFV

HFV may be well-suited to accomplish all the goals of lung-protection. By the nature of its low tidal volumes, HFV may decrease the risk of overdistention injury, even to relatively healthy, compliant lung units. In addition, because these tidal volumes are delivered using relatively small pressure swings at high rates, mean airway pressure can be maintained at higher levels than are generally used during CMV. This high mean airway pressure may optimize end-expiratory lung volume, leading to improved oxygenation, and prevent cyclical collapse and resultant atelectrauma (Figure 1).

The ideal application of HFV might involve “opening” the lung, using sustained inflation maneuvers and appropriate levels of PEEP/mean airway pressure, pushing the lung onto the

**Figure 2: Illustration of the optimal application of HFV as part of a lung protection strategy**



HFV = high-frequency ventilation;  
CMV = conventional mechanical ventilation

“expiratory” limb of the curve, and optimizing oxygenation and lung compliance (Figure 2). The “open lung” is then ventilated using small tidal volumes and pressure swings, minimizing alveolar overdistention and collapse throughout the respiratory cycle. In animal models comparing HFOV to lung-protective CMV, such a strategy has been found to decrease pulmonary inflammation and attenuate the increase in levels of systemic inflammatory mediators observed during CMV.<sup>28,29</sup>

### Clinical experience with HFV

#### *High-frequency positive-pressure ventilation*

First described in 1969 as an experimental technique,<sup>30</sup> high-frequency positive-pressure ventilation (HFPPV) has found limited clinical use in specialized upper airway surgical procedures and bronchoscopy.<sup>31</sup> Published clinical experience with HFPPV has been largely limited to neonatal populations. One meta-analysis found that synchronized mechanical ventilation delivered via HFPPV was associated with decreased barotrauma events and shorter length of stay when compared to CMV.<sup>32</sup> The effect of HFPPV on mortality or chronic oxygen dependency was not clear after analysis of the published studies. In adult patients, HFPPV has found only limited popularity in specialized applications.<sup>33-35</sup>

#### *High-frequency percussive ventilation*

The existing literature evaluating HFPV in patients with acute respiratory failure remains limited to one case series in pediatric patients<sup>36</sup> and several case reports and case series in adults.<sup>37-42</sup> In most of these series, the investigators observed improvements in oxygenation after switching from CMV to HFPV, without a significant rise in peak or mean airway pressure. These series were small, however, and were not adequately powered to detect a difference in mortality or evaluate other clinical outcomes.

#### *High-frequency jet ventilation*

HFJV has been commonly used in specific clinical settings, particularly pulmonary air leak syndromes where the ability to achieve adequate gas exchange with lower peak airway pressures may be advantageous.<sup>43</sup> Additionally, the decreased reliance on bulk flow using HFJV may improve gas distribution and gas exchange in large air leaks. HFJV has also been used intraoperatively during surgical procedures involving the airway and upper trachea; the

small tidal volumes minimize movement of the proximal airways and the small jet catheter and lack of a cuffed endotracheal tube improve visualization of the operative field. HFJV has also been used for acute respiratory failure in both adults and infants, where it was generally found to improve gas exchange while decreasing peak airway pressures. Published clinical experience with HFJV in acute respiratory failure remains small compared to that of CMV and, to date, the most extensive clinical experience is in neonatal and pediatric populations.

Several comparative studies comparing HFJV with CMV in premature infants with respiratory distress syndrome and pulmonary interstitial emphysema have shown that HFJV is safe and provides improved ventilation at lower peak airway pressures. Although one study demonstrated improved outcomes (decreased incidence of bronchopulmonary dysplasia and home oxygen use at 36 weeks),<sup>44</sup> the majority of studies have not demonstrated a significant advantage of HFJV over CMV with respect to long-term outcome or mortality, despite short-term improvements in gas exchange and respiratory parameters.<sup>45-47</sup> One study evaluating the early use of HFJV in 73 premature infants found that infants ventilated with HFJV were more likely to suffer adverse outcomes (cystic periventricular leukomalacia, intraventricular hemorrhage, and death) than infants receiving CMV.<sup>48</sup>

Published experience with HFJV in adult respiratory failure is limited, although many ICUs have sizable anecdotal experience. Comparative clinical trials have demonstrated that HFJV is safe, improves oxygenation and ventilation compared with CMV, improves respiratory parameters, and decreases required peak pressures.<sup>49-51</sup> None of these trials, however, demonstrated any significant clinical advantage to HFJV compared to CMV.

#### *High-frequency oscillatory ventilation*

HFOV has recently been the subject of renewed interest for use in acute respiratory failure. HFOV has the potential to achieve all of the goals of lung protection; ie, the small, high-frequency pressure oscillations allow the application of high mean airway pressures to optimize lung volume recruitment and prevent end-expiratory collapse without exposing the lung to injurious peak airway pressures during inflation. In addition, the circuit allows for optimal gas conditioning, reducing the likelihood of airway trauma and inspissation of secretions.

Similar to HFJV, the most extensive published clinical evaluation of HFOV has been in neonatal and pediatric populations.<sup>52-61</sup> In neonates, safe and effective application of HFOV appears to require lung volume recruitment maneuvers and possibly exogenous surfactant. The majority of studies using HFOV in this manner have demonstrated that HFOV is safe, improves oxygenation, and may reduce the risk of air-leak and barotrauma.<sup>53-57</sup> Whether HFOV reduces infant mortality and morbidity is contentious, although 2 recent studies suggest that it is beneficial in carefully controlled clinical settings.<sup>56,60</sup> A current meta-analysis of the existing trials evaluating pediatric HFOV revealed no mortality difference between CMV and HFOV, although HFOV may have been associated with a modest reduction in chronic lung disease compared to CMV.<sup>62</sup>

Because the cause and pathophysiology of respiratory failure in preterm neonates and adults is different, the results of neonatal HFOV trials cannot be extrapolated to older children or adult populations. Clinical application of HFOV in adult subjects was initially hampered by technical failures and a lack of adequately powered ventilators. With the development of more robust ventilators that could generate sufficient power to oscillate an adult patient, there has been a resurgence of interest in HFOV as part of a lung-protective ventilation strategy in ARDS. Two published case series described ARDS patients who were ventilated with HFOV after failing CMV; they found improved oxygenation with decreased  $\text{FiO}_2$  requirements.<sup>63,64</sup> The mortality rate in these uncontrolled series was high (32%-53%). However, this is not surprising since HFOV was used as salvage therapy, pre-selecting patients with a risk of high mortality. Other small case series have described the use of HFOV in burn and trauma patients, both with similar improvements in oxygenation.<sup>65,66</sup>

The best evidence for the use of HFOV in ARDS comes from 2 prospective series<sup>67,68</sup> and a prospective clinical trial.<sup>69</sup> Both Mehta et al and David et al reported experiences with HFOV in patients with oxygenation failure after CMV, and found significant improvements in oxygenation compared to baseline.<sup>67,68</sup> HFOV was safe and well-tolerated, without significant hemodynamic compromise. Although the series by Mehta observed a very high mortality rate, their patient population included very high-risk patients (hematologic malignancy and burn victims). Derdak et al published the first, prospective, randomized trial comparing HFOV to CMV in early ARDS and found that HFOV was safe and improved oxygenation.<sup>69</sup> Although not statistically significant, there was a trend towards decreased mortality in patients receiving HFOV. Of interest, all 3 of these prospective studies found that a longer duration of CMV prior to HFOV was predictive of poor outcome. This has led some investigators to propose early application of HFOV in an attempt to attenuate VILI and possible mortality.

In summary, HFOV has been found safe and effective in pediatric patients with hypoxic respiratory failure and in adult patients failing CMV. In children, in carefully selected cases, HFOV may be superior to CMV. Despite the paucity of published HFOV experience in adults, it is suggested that early use of HFOV in adults may be of additional benefit, although this approach has yet to be borne out by rigorous clinical trials.

### Future of high-frequency ventilation

Despite several decades of research into the principles and clinical applications of HFV, many issues remain unresolved, particularly regarding its use in adults. In fact, the very mechanical characteristics of HFV (tidal volumes, gas exchange mechanisms) remain incompletely understood. The optimal settings that maximize lung protection and gas exchange remain unknown for several modes of HFV. It has been theorized that optimization of HFV modes would involve minimizing tidal volumes to reduce the risk of overdistention-injury and cyclical lung unit collapse, and maximizing alternative gas transport mechanisms. Furthermore, the timing of initiating HFV is not clear; eg, does

early HFV outweigh the risks of increased sedation, paralysis, and patient discomfort?

These questions are not purely semantic, since inappropriate HFV use may be associated with increased morbidity. The early negative trials evaluating HFOV in neonatal populations without the use of aggressive lung-volume recruitment are testament to the importance of a proper HFOV ventilation protocol. It is important to resolve these questions prior to embarking on comparative trials, lest HFV be dismissed not because of a lack of benefit, but because of inappropriate application. Despite these unknowns, HFV possesses many theoretical advantages over CMV in the mechanical ventilation of the injured lung, especially regarding the principles of lung protection.

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