Fifty Years of Research in ARDS.

Spontaneous Breathing during Mechanical Ventilation. Risks, Mechanisms, and Management

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Abstract

Section:

Spontaneous respiratory effort during mechanical ventilation has long been recognized to improve oxygenation, and because oxygenation is a key management target, such effort may seem beneficial. Also, disuse and loss of peripheral muscle and diaphragm function is increasingly recognized, and thus spontaneous breathing may confer additional advantage. Reflecting this, epidemiologic data suggest that the use of partial (vs. full) support modes of ventilation is increasing. Notwithstanding the central place of spontaneous breathing in mechanical ventilation, accumulating evidence indicates that it may cause—or worsen—acute lung injury, especially if acute respiratory distress syndrome is severe and spontaneous effort is vigorous. This Perspective reviews the evidence for this phenomenon, explores mechanisms of injury, and provides suggestions for clinical management and future research.

Keywords: mechanical ventilation; acute respiratory distress syndrome; spontaneous breathing; ventilator-induced lung injury

Spontaneous Breathing Causes Injury during Mechanical Ventilation

Section:

The most direct evidence comes from experimental studies. In mechanically ventilated rabbits with established lung injury, vigorous spontaneous effort did not change plateau pressure (Pplat) but did worsen injury (8, 9). In a clinical study, strong spontaneous effort can injure not only the injured lung but also the diaphragm (12). Data from three randomized trials support this concept in demonstrating that neuromuscular blockade (to prevent spontaneous effort) results in improved lung function, and increased survival in severe ARDS (13–15). In the largest study (340 patients), early use of neuromuscular blockade in severe ARDS reduced barotrauma (4 vs. 11.7%) and mortality at 90 days (30.8 vs. 44.6%) (15). In addition, mortality in ventilated patients with severe sepsis was up to 12% lower among those who received neuromuscular blockade in the first two hospital days (16). Finally, individual case reports suggest that in pressure-targeted ventilation, spontaneous breathing will increase Vt and can be associated with barotrauma (10, 11).

How Does a Spontaneous Breath Combine with a Ventilator Breath?

Section:

The lung tissue stress during a tidal inhalation is the pressure distending the lung, or the transpulmonary pressure (Pt) (17), that is, the difference between the airway pressure (Paw) and the pleural pressure (Ppl): Pt = Paw - Ppl. In positive-pressure ventilation under muscle paralysis, Paw constitutes the bulk of Pt. (Ppl is a minor contributor) unless chest wall compliance is seriously impaired (17, 18), and at end-inspiration is termed Pplat (19). Also, Pplat is readily recorded, whereas Ppl is not; thus, Pplat is the common indicator of inspiratory lung stress during mechanical ventilation (19). This is sufficiently accurate where changes in Ppl are minor under passive conditions; however, when spontaneous effort occurs during positive-pressure ventilation, Pplat no longer approximates to Pt, and because negative changes in Ppl are far greater with spontaneous effort, the risk of lung injury is increased (8, 9). Several lines of evidence support this reasoning.

Although the Pt (i.e., Paw - Ppl) is the static pressure that holds the lung at any volume, its nature is better understood by decomposing Ppl into two parts: static and dynamic. Paw is zero (atmospheric) during spontaneous ventilation, and has a positive value during mechanical ventilation. However, Ppl is either static (e.g., at end-expiration) or dynamic (the magnitude of its change during inspiration). In the supine position, the static value of Ppl varies according to the vertical height (more negative, nondependent; more positive, dependent), and this is determined by the interaction between the shape of the lung
and the (slightly different) shape of the thorax, as well as by lung density and the weights of mediastinal and abdominal contents (20).

A dynamic change in \( P_l \) results from a change in Paw or a change in Ppl. Inspiration is driven by an increase in Paw (positive pressure) or a decrease in Ppl (spontaneous effort). In the healthy lung, changes in local Ppl are evenly transmitted across the lung surface; this phenomenon is called “fluid-like” behavior (21, 22). Here, the change in \( P_l \) is uniform, and therefore inflation is homogeneous across all lung regions (21, 22). This principle explains, in part, why the changes in esophageal pressure \( (P_{es}) \) are used as a surrogate of overall \( P_l \) changes. In contrast, injured lungs exhibit “solid-like” behavior, where a nonaerated lung region impedes the rapid generalization of a local change in \( P_l \); in such cases, the lung expansion is heterogeneous (Z).

Superimposing a spontaneous effort onto a ventilator breath has an additive effect on the distending \( P_l \) and therefore on the resulting \( V_r \) (Figure 1).

**Figure 1:** Spontaneous effort and transpulmonary and transvascular pressures. During a mechanical breath (left), the transpulmonary pressure \( (Paw - Ppl = P_l) \) distending the lung is \(+20\) \((30 - 10)\); the pulmonary blood vessels are compressed by the positive-pressure breath and the transvascular pressure \( (P_{cap} - Ppl) \) is low \((assume\ 12 - 10 = 2)\). When spontaneous effort is added (right), the \( P_l \) \((30 + 20 = +50)\) is greater, thereby increasing the \( V_r \) and causing lung injury. In addition, the negative Ppl \((-20)\) distends the pulmonary blood vessels and increases perfusion; the transvascular pressure is greater \( (assume\ 12 - 20 = +28)\), increasing fluid shift to the interstitium. In the presence of injury, permeability (and therefore propensity to alveolar edema) is increased. Paw = airway pressure; \( P_{cap} \) = capillary hydrostatic pressure; Ppl = pleural pressure.

**Mechanisms of Injury from Spontaneous Breathing**

Section:

There are several mechanisms whereby spontaneous breathing during mechanical ventilation may worsen lung injury.

**Distending Pressure and Tidal Volumes**

Spontaneous effort during a ventilator breath reduces Ppl and increases \( P_l \) (Figure 1), and if the mechanical properties of the respiratory system have not changed, the resulting \( V_r \) will be increased proportionally (17, 23); this may contribute to lung injury (10, 11). However, the increase in \( V_r \) may be less than predicted from the change in \( P_l \). There are several reasons for this discrepancy. First, if spontaneous effort causes pendelluft (see below), the local inflation is facilitated by corresponding deflation of aerated (nondependent) lung, without a significant increase in overall \( V_r \) (6, 7). Second, intrinsic positive end-expiratory pressure (PEEP) associated with high respiratory drive can lower \( V_r \) (23). Third, \( P_l \) has two components: resistive (generates airflow) and transalveolar (expands alveoli). If \( P_l \) measured during spontaneous breathing includes the resistive pressure due to flow (e.g., incomplete inspiration) and the resistive component of \( P_l \) is high (e.g., status asthmaticus), an elevated \( P_l \) would inflate the alveoli less than predicted from the \( P_l \), and the net \( V_r \) will thus be lower than predicted.

However, airway (inspiratory) resistance is rarely increased in ARDS (24). Finally, if spontaneous effort worsens lung injury over time, the compliance will progressively lessen and the \( V_r \) will be less for a given \( P_l \) (6, 9).

**Pendelluft**

The exchange of air from one lung region to another without causing a significant change in overall \( V_r \) (i.e., pendelluft), has been observed with spontaneous breaths during mechanical ventilation. Although first observed in a patient with ARDS, the mechanisms and characteristics have been determined in a large-animal (pig) model (6, 7). The rapid tissue deformation results in tidal recruitment and local overstretch of the involved dependent region, as well as rapid deflation (followed by reinflation) of the corresponding nondependent region.

This phenomenon occurs because the negative Ppl changes generated by diaphragmatic contraction have localized effects in dependent regions, and the Ppl changes are not uniformly transmitted (i.e., solid-like behavior) (Figure 2). Thus a large vertical pressure gradient of Ppl "swings" from nondependent (less negative) to dependent (more negative) regions causes pendelluft. Although pendelluft has not been proved to cause injury, the rapid inflation–deflation is an injurious pattern.

**Figure 2:** Spontaneous effort and distribution of regional ventilation and pleural pressure. Dynamic computed tomographic scan in end-expiration (left) demonstrates that the aerated lung (blue) is nondependent, while the dependent lung is densely atelectatic (red). At end-inspiration during a spontaneous breath (middle), there is little change in the nondependent aerated lung (blue); the dependent lung, previously densely atelectatic (red), is now partially aerated (green/red) (i.e., tidal recruitment). The inspiratory pleural pressure traces (right), measured at the arrow tips, show the negative deflections ("swings") in regional Ppl and global PES during inspiration. However, the "swing" in regional Ppl is greater (by twofold) than the "swing" in PES, indicating that diaphragm contraction results in greater distending pressure applied to the regional lung near the diaphragm, compared with the pressure transmitted to the remainder of the lung (i.e., PES). A = anterior; HU = Hounsfield units; I = inferior; L = left; P = posterior; PES = esophageal pressure; Ppl = pleural pressure; R = right.

**Increased Lung Perfusion**

Spontaneous effort generates a more negative Ppl, which in turn increases transvascular pressure (difference between intravascular pressure and pressure outside the vessels); this distends thoracic and pulmonary vessels, and increases lung
perfusion (25, 26); in injured lungs it may cause edema (27). Clinical data indicate that inspiratory effort in the setting of volume-controlled ventilation (27) or upper airway obstruction (28) (i.e., no change in Vr or Ptl) can result in elevated transvascular pressure, thereby increasing perfusion and propensity to edema. Finally, because pulmonary edema can reduce lung compliance and increase the heterogeneity of ventilation, it can ultimately contribute to injury (29).

**Patient–Ventilator Asynchrony**

Asynchrony between the patient’s (spontaneous) effort and the ventilator can worsen lung injury. “Double triggering” is the occurrence of two consecutive inspirations after a single respiratory effort (30), and is injurious because the delivered (total) Vr is the sum of the two consecutive tidal volumes (Figure 3). Double triggering may be common (sometimes more than twice per minute) when a protective lung strategy in ARDS is facilitated by heavy sedation, and may lead to higher Vr (>150% preset Vr) (30, 31). Second, in heavily sedated patients reverse triggering (entrainment) can occur, in which the diaphragm is “triggered” by ventilator-driven inspiration (32). Although the mechanism of initiation is unclear, the phenomenon is identified by a slight decrease in Paw and Pes (corresponding to increased Ptl), and an increase in delivered Vr. The increases in Ptl and Vr are potentially harmful. Finally, as noted previously, inability of the patient to receive the desired Vr can result in more negative Ppl, contributing to edema and injury (see above) (27).

**Figure 3.** Impact of double triggering on tidal volume. Double triggering occurs when a spontaneous effort triggers a (second) ventilator breath before the initial breath has been completely exhaled (arrow). The pressure–time trace (top) and flow–time trace (middle) demonstrate the occurrence of the additional breath but do not give a sense that both inspirations are summed; this is apparent from the volume–time trace (bottom) indicating that the double triggering results in a substantially larger (potentially injurious) Vr (red) compared with regular triggering (blue). Adapted by permission from Reference 56.

The adverse impact of these (and other) patient–ventilator asynchronies is increasingly recognized, and data from 50 ventilated patients suggest an association between increased incidence of asynchrony and higher mortality (33).

**Spontaneous Effort: Expiration**

Spontaneous effort activates expiratory (as well as inspiratory) muscles. Forced expiration shifts the diaphragm cephalad and lowers the end-expiratory lung volume; this leads to hypoxemia, and may necessitate more injurious ventilator settings (5, 34). Opioids—frequently used in patients with ARDS with preserved spontaneous effort—may potentially facilitate this phenomenon by increasing abdominal muscle tone (35). Lower lung volume also increases the intrinsic risk of lung injury (36), and because the volume of aerated lung is reduced (36), will increase the injury caused by a given Vr.

**Risk Factors for Injury**

**Severity of ARDS**

Spontaneous effort added to mechanical ventilation in established experimental lung injury significantly worsens the injury if severe to begin with (8, 9); however, in mild lung injury, spontaneous effort improves function (e.g., gas exchange, lung compliance, aeration), but does not worsen injury (2, 9, 37).

This pattern of susceptibility is reflected in clinical studies. In the major clinical trial examining the impact of early neuromuscular blockade in ARDS, only patients with severe disease (PaO2/FIO2 < 150 mm Hg) were recruited (15); by contrast, enrollment in most trials in ARDS specifies a lesser degree of hypoxemia (PaO2/FIO2 < 300 mm Hg) (38). Although the unadjusted analysis suggested benefit from neuromuscular blockade, this was significant in patients with severe disease (PaO2/FIO2 < 120 mm Hg), in whom survival was increased by 13.8% (15).

Of course, increased severity of ARDS is inherently linked to greater loss of lung volume, more injurious ventilator settings (Paw), and increased respiratory drive (and effort); these issues are considered individually.

**Loss of Lung Volume**

Loss of aerated lung volume has two principal effects: less lung available for tidal distension and increased force of diaphragmatic contraction. For any given Vr (or Paw), a lung with lower end-expiratory volume is inherently more susceptible to injury from tidal inflation (36, 39). With mechanical breaths, this is distributed to (and overstretches) already aerated regions (e.g., the “baby” lung) (40); in contrast, a spontaneous breath appears to be distributed mostly to zones of atelectasis lung, resulting in transient (“tidal”) recruitment and local volutrauma in the dependent lung (6, 7) (Figure 2).

Reduced lung volume has important effects on diaphragm position and function. Cephalad displacement results in greater curvature of the diaphragm and an increase in the size of the zone of apposition (41). In addition, diaphragm fibers are lengthened, augmenting its force of contraction; this results in more negative ΔPpl changes to the lung surface, and it increases the positive appositional pressure to the abdominal rib cage (6, 41).

**Increased Respiratory Drive**

Greater respiratory drive is caused by several factors including hypercapnia, acidemia, hypoxemia, pain, fever, and
pulmonary and systemic inflammation—all of which are common in ARDS, and to a greater extent in more severe disease. If respiratory neuromuscular function is intact, then increased drive translates into stronger diaphragm contraction and larger “swings” of Ppl. This has been demonstrated in laboratory studies, in which spontaneous effort (and negative deflections in Pes) was greater in more severe lung injury (9). Stronger spontaneous effort is linearly related to larger degrees of pendelluft, as well as greater tidal recruitment and local volutrauma (6, 7). In addition, strong spontaneous effort can injure not only the injured lung but also the diaphragm (12).

Enhanced respiratory drive also impacts on patient–ventilator interaction. For example, double triggering (breath stacking) is more frequent in patients with higher respiratory drive (42); thus, in more severe disease tidal volumes significantly larger than intended may be delivered.

It is possible (although not proven) that increased respiratory drive explains in part why spontaneous ventilation worsens injury in severe (but not mild) ARDS, because the increased drive results in greater swings in Ppl and these occur at a higher rate.

Injurious Ventilator Settings

Mechanical ventilation in more severe ARDS usually provides higher Pplat and driving pressure (43), and this is probably due to lower respiratory system compliance. When spontaneous effort is added to a higher Pplat, the resultant P, would be injuriously high, reflecting the higher Pplat plus the added negative Ppl (9).

Driving pressure predicts survival in ARDS, but the initial analysis excluded patients with spontaneous effort (18). Conventional calculation of driving pressure takes into account measurement of (positive) airway pressures only (i.e., Pplat - PEEP), and not any contribution from Ppl. However, in the presence of spontaneous effort, two different types of pressure are combined to inflate the respiratory system: positive airway pressure (i.e., Pplat - PEEP) applied by the ventilator, and the negative change in Ppl generated by respiratory muscles. In this case, the true driving pressure across the respiratory system should be calculated as Pplat - PEEP + APpl; thus spontaneous effort preserved in severe ARDS would increase considerably the true driving pressure (9), especially if spontaneous effort is prolonged. Conventional calculation of driving pressure (using an end-inspiratory hold) can be accurately performed provided spontaneous effort has ended before the end of inspiration, and muscle relaxation has occurred (44). It is likely that higher driving pressure due to added spontaneous effort will be associated with greater injury.

In severe ARDS, Pplat may remain elevated (e.g., >30 cm H2O) even after the reduction of Vr to low levels (e.g., 4 ml·kg⁻¹); in such cases, decreasing PEEP to lower Pplat (15), this may increase spontaneous effort and driving pressure, and with spontaneous breathing, may also increase the severity of pendelluft (6).

Benefits of Spontaneous Effort Added to Mechanical Ventilation

Section:

Spontaneous breathing during mechanical ventilation has been recommended for more than four decades because of important short-term benefits (1, 2, 45).

Diaphragm Muscle Tone

Controlled mechanical ventilation (i.e., no spontaneous breathing) induces diaphragmatic muscle dysfunction and atrophy (3). This is a serious problem, especially for subsequent weaning; it is detectable in patients within as little as 18 hours (3), and can be ameliorated by preservation of spontaneous effort (46).

Cardiovascular Effects

Whereas positive-pressure ventilation reduces transvascular pressure and ventricular preload (elevated intrathoracic pressure) (47), as well as reducing ventricular afterload, spontaneous respiration does the opposite. Increased preload and afterload might reduce cardiac output where ventricular function is impaired; this may be important in ARDS where impaired right ventricular function is present in 30% of patients (48). The net effect of spontaneous effort on cardiac output reflects a balance of intrathoracic pressure, baseline ventricular filling, and the ventilator contractile function.

Pulmonary Function

Spontaneous breathing increases aeration in dependent lung (37), as well as increasing lung perfusion (see below) (49). Thus intrapulmonary shunt is reduced and V·V/Q·Q. matching and oxygenation increased (1, 2, 49). Indeed, spontaneous breathing is considered to be the least invasive means to maintain lung recruitment (5).

Although diaphragm movement effectively recruits the lungs, diaphragmatic tone is also important. Continuous phrenic nerve stimulation during general anesthesia (i.e., deep sedation, healthy lungs) lessens the development of atelectasis because transmission of abdominal pressure to the pleural space is impeded by the increased diaphragmatic tone (50).

Benefit from addition of spontaneous breathing has been described in several clinical and laboratory studies, where improved oxygenation is consistently reported; however, in each of these studies the lung injury was mild (modest impairment of oxygenation, low Paw) (1, 2, 9, 37, 49). These data may be the basis for recommendations to preserve
spontaneous breathing in patients with mild ARDS (45).

**Outcome**

In addition to reports of physiological benefit associated with spontaneous ventilation, Putensen and colleagues reported reduced length of intensive care unit stay (2). However, experimental and clinical data suggest a common theme. In severe ARDS, avoidance of spontaneous effort reduces injury (9) and improves outcome (15). By contrast, in milder disease, the presence of spontaneous effort has little impact on outcome, but may prevent worsening of lung injury, improve pulmonary function (1, 2, 9, 37, 49), and in some patients, reduce duration of mechanical ventilation (2).

**Detection of Spontaneous Effort**

Spontaneous effort is usually apparent by observing spontaneous breaths (i.e., chest movement or ventilator waveforms) that are out of sequence with the ventilator breaths. In addition to the timing, it is usually possible to observe the patient effort, which is apparent from accessory muscle use. Although indirect, additional signs of respiratory distress, such as anxiety or nasal flaring, indicate a high likelihood of independent respiratory effort. Standard ventilator monitoring will confirm increased respiratory rate (above the ventilator “set” rate), and demonstrate negative deflection in Paw at the start of inspiration, as well as higher minute ventilation, Vt, and inspiratory flow. It will help us to evaluate whether respiratory drive is vigorous over the appropriate range (e.g., respiratory rate > 35 breaths/min, Vt > 8 ml/kg). Importantly, airway occlusion pressure (i.e., P0.1) can represent a more precise respiratory drive measurement than respiratory rate, Vt, and minute ventilation (51). A high value of P0.1 was observed in the early stage of acute respiratory failure as reflecting vigorous spontaneous effort, but its value decreased as conditions of patients improved (52). Such standard ventilator monitoring is helpful to detect high respiratory drive and, if necessary, further monitoring including esophageal balloon manometry or electrical impedance topography (EIT) will be considered to evaluate P or ventilation pattern. Thus, detection of spontaneous effort is usually straightforward.

However, three aspects of spontaneous breathing during mechanical ventilation might not be appreciated. First, Pes, which is considered to reflect changes in overall Ppl, might not reliably detect changes in regional Ppl in the injured lung. Because atelectatic or consolidated lung regions are solid-like, they poorly transmit dynamic regional changes in Ppl and changes in local Ppl at dependent lung might be underestimated by changes in Pes (7). Thus, esophageal manometry may underestimate spontaneous effort if the lung overlying the diaphragm is densely consolidated or atelectatic (Figure 2).

Second, spontaneous breathing often leads to better oxygenation, and this may be interpreted by the clinician as an improvement in the patient’s status rather than recognized as a potential contributor to worsening lung injury (i.e., tidal recruitment and local volutrauma in the dependent lung). Third, pendelluft cannot be detected by standard monitoring of airway flow, Paw, or Pes, and can be reliably detected only by EIT (accessible) or dynamic CT (less accessible).

**Approach to Management**

**Minimize Spontaneous Effort**

The definitive way to prevent harm from spontaneous effort is to use neuromuscular blockade. Papazian and colleagues demonstrated that early (and short-term) use of neuromuscular blockade reduced mortality and barotrauma in severe ARDS (15). Because most physiological parameters were similar in both groups, the presence of spontaneous effort seems to have been responsible for the difference in outcome (i.e., lung injury); however, the specific mechanism is uncertain. When using neuromuscular blockade it is important to avoid awareness, provide sufficient analgesia, and detect and manage potentially lethal causes of dyspnea (e.g., endotracheal tube displacement). Providing adequate sedation and analgesia (and perhaps buffering acidosis) may reduce breathing effort; indeed, spontaneous effort can be successfully reduced by maintaining normal Paco2 during extracorporeal support (53). In addition, because increased lung volume flattens the curvature of the diaphragm, the diaphragmatic fiber length is lessened and its force of contraction reduced (41). Thus, optimal recruitment may reduce spontaneous effort and lessen pendelluft (6).

**Tidal Volume**

Limitation of Vt might reduce effort-associated lung injury, but this is difficult to accomplish where spontaneous effort is vigorous, especially with pressure-preset modes. If respiratory effort is great, restriction to a small Vt by means of volume-controlled ventilation can cause the patient to develop highly negative Ppl with forced inspiration, and this can contribute to increased pulmonary edema (see above) and increased frequency of double triggering (27, 30, 31).

Limitation of Vt might fail to protect for additional reasons. A ventilator breath is introduced through already aerated lung, thus inflating already aerated lung and the atelectatic lung that borders the aerated lung. In contrast, a spontaneous effort may be introduced largely through atelectatic lung; because this exhibits solid-like behavior, the impact of the diaphragmatic effort may be in part restricted to this atelectatic lung, causing pendelluft and contributing less to the overall Vt (Figure 2). However, the usefulness of Vt limitation during spontaneous effort is unproven.

**Ventilator Mode**
First, in patient–ventilator asynchrony, double triggering is frequently observed during volume-controlled ventilation (30, 31). Switching to ventilator mode with better patient–ventilator interaction such as pressure support may better reduce the frequency of double triggering than increasing sedatives and analgesia (31). Thus, it is important to adapt the ventilator mode to patients to decrease patient–ventilator asynchrony. Second, the presence of spontaneous effort while using inspiratory synchronization (e.g., assist-control, pressure support), is likely to cause high Pt because each spontaneous breath will initiate—and augment—the corresponding positive pressure from the ventilator. In contrast, during nonsynchronized ventilation (e.g., airway pressure release ventilation), a spontaneous breath will infrequently combine with a ventilator breath; when not combined (the usual case), the ventilator and spontaneous volumes are not added and the Vr or Pt, therefore is not increased (54). However, use of nonsynchronized modes has not been associated with improved outcome (55).

**Optimal Lung Recruitment**

Lung recruitment—and maintenance with adequate PEEP—increases compliance, thereby lessening driving pressure for a given Vt. Moreover, optimal lung recruitment can reduce the intensity of respiratory drive (as reflected in reduced negative “swings” in Pes) (6). Recruitment also lessens the degree of solid-like behavior of the lung, and could mitigate injury from spontaneous effort because solid-like behavior contributes to inhomogeneous inflation, and causes underestimation by Pes of swings in Ppl and development of pendelluft (7). Theoretically, optimal recruitment could facilitate benefit from spontaneous breathing (e.g., preservation of muscle tone, less sedation or paralysis), while minimizing injury.

**Conclusions**

There are protective and deleterious consequences of spontaneous breathing during mechanical ventilation in ARDS. Accumulating evidence has revealed that the net impact depends on the severity of lung injury. Ventilator strategies allowing spontaneous breathing and mechanical ventilation with muscle paralysis during ARDS should both be integrated into management strategies. Restoration of ventilated fluid-like lung may be key to preventing the deleterious effects of spontaneous breathing and to render Pes a more accurate reflector of local lung stress.

**References**

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