

Effect of Neuromuscular Electrical Stimulation on the Duration of Mechanical Ventilation

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BACKGROUND: It has been proposed that neuromuscular or functional electrical stimulation may have effects on respiratory muscles through its systemic effects, similar to those produced by exercise training. However, its impact on the duration of invasive mechanical ventilation has not been adequately defined. We sought to evaluate the effect of neuromuscular or functional electrical stimulation on the duration of invasive mechanical ventilation in critically ill subjects. **METHODS:** We systematically searched 3 databases up to August 2019 (ie, CENTRAL, MEDLINE, and EMBASE) as well as other resources to identify randomized controlled trials (RCTs) that evaluated the effects of neuromuscular or functional electrical stimulation compared to usual care/rehabilitation or placebo of neuromuscular or functional electrical stimulation on the duration of invasive mechanical ventilation. **RESULTS:** After reviewing 1,200 single records, 12 RCTs ($N = 530$ subjects) fulfilled our eligibility criteria. Three studies included only subjects with COPD ($n = 106$ subjects), whereas the rest considered subjects with different diseases. The most frequently stimulated muscle group was the quadriceps. Neuromuscular or functional electrical stimulation may decrease the duration of invasive mechanical ventilation (mean difference = -2.68 d, 95% CI -4.35 to -1.02 , $I^2 = 50\%$, $P = .002$; 10 RCTs; low quality of evidence), and we are uncertain whether this effect may be more pronounced in subjects with COPD (mean difference = -2.90 d, 95% CI -4.58 to -1.23 , $I^2 = 9\%$, $P < .001$; 3 RCTs; very low quality of evidence). **CONCLUSIONS:** Neuromuscular or functional electrical stimulation may slightly reduce the duration of invasive mechanical ventilation; we are uncertain whether these results are found in subjects with COPD compared to subjects receiving usual care or placebo, and the quality of the body of evidence is low to very low. More RCTs are needed with a larger number of subjects, with more homogeneous diseases and basal conditions, and especially with a more adequate methodological design. *Key words:* neuromuscular electrical stimulation; electric stimulation therapy; artificial respiration; invasive mechanical ventilation; duration of mechanical ventilation; critical illness. [Respir Care 0;0(0):1–●. © 0 Daedalus Enterprises]

Introduction

Advances in medicine in recent decades have led to a decrease in the mortality of patients admitted to an ICU.

However, this decrease has come with a longer time to resolution of critical illness, leading to an increase in neuromuscular and respiratory complications.¹

Among the neuromuscular complications, ICU-acquired weakness occurs frequently and is related to the severity of

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the disease, sepsis, multiple organ failure, hyperglycemia, use of neuromuscular blockers, long periods of immobility, and length of stay in the ICU.² ICU-acquired weakness is directly associated with prolonged invasive mechanical ventilation,³ which also causes undesirable side effects including mechanical ventilation-induced lung injury,⁴ ventilator-associated pneumonia,⁵ and diaphragmatic muscle injury.⁶ That is why, as soon as the conditions that caused the critical illness are controlled or resolved, it is necessary to begin the weaning process to reduce the duration of invasive mechanical ventilation and to achieve extubation and reestablishment of spontaneous ventilation as early as possible.

Several strategies have been proposed to potentially reduce the duration of invasive mechanical ventilation, including early mobilization⁷ and inspiratory muscle training.⁸ Another strategy that could accelerate weaning is neuromuscular electrical stimulation, which is a technique that produces visible muscle contractions through intermittent electrical stimulation on the surface of the skeletal muscles.⁹ This intervention has been shown to decrease anaerobic enzyme levels, increase oxidative capacity, favor the transition from fast to slow muscle fibers,¹⁰ and reduce systemic effects in critically ill patients,¹¹ which by means of an anabolic stimulus could produce effects on the respiratory muscles through the systemic circulation.¹² However, it is not clear whether the cellular effects translate into a decrease in duration of invasive mechanical ventilation. The aim of this study was to summarize and assess the available evidence through a systematic review, and to estimate the impact of neuromuscular or functional electrical stimulation on duration of invasive mechanical ventilation through a meta-analysis.

Methods

This systematic review with meta-analysis was developed and reported in accordance with the PRISMA statement.¹³ The protocol for this review was recorded in the Prospective International Register of Systematic Reviews (PROSPERO) under the number CRD42019145999. We consulted the following databases to identify the primary studies up to August 2019: the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, and EMBASE. The search strategy included MeSH, Emtree, and key words according to the database consulted (see the supplementary materials at <http://www.rcjournal.com>). In addition, we manually searched the references of 3 systematic reviews with broader objectives than our review that secondarily assessed the effect of neuromuscular electrical stimulation on the duration of invasive mechanical ventilation.¹⁴⁻¹⁶ We also contacted authors whose work is related to the objective of our review to identify possible randomized controlled trials (RCTs) that were not identified in our electronic search.

Two reviewers (DG, NN) independently read the titles and abstracts of the database search results to detect potential studies to be included in the review; these articles were classified into included, in doubt, and excluded articles. The same reviewers independently read the full texts of the articles that were classified as included and in doubt to determine whether they met the eligibility criteria to be included in our review. We included studies that were RCTs of adult subjects who were on invasive mechanical ventilation, independent of the disease causing their critical illness and the type of ICU in which they were admitted, and compared neuromuscular or functional electrical stimulation with no intervention (ie, usual care or physical therapy) or placebo of neuromuscular or functional electrical stimulation. We excluded studies published only in conference proceedings and those that applied another intervention (eg, early mobilization or routine treatment) to only 1 of the 2 groups (ie, intervention and control groups). No language restriction was applied. Disagreements were resolved by consensus or ultimately by a third reviewer (RG).

Our primary end point was the duration of invasive mechanical ventilation comparing the group that used neuromuscular or functional electrical stimulation and the control group (ie, the group that did not receive electrical stimulation or was given sham treatment from neuromuscular or functional electrical stimulation). Secondarily, we evaluated the adverse events reported in the different studies. In addition, we performed a subgroup analysis by population type of the duration of invasive mechanical ventilation, separating studies that included adults without distinction of diseases and those that included only subjects with COPD (ie, mixed vs COPD).

Data extraction was performed independently by two reviewers (BP and CZ) using a standard registration form that included general information, study characteristics, intervention characteristics, subjects, and outcomes. Where more than one publication existed for a study, all study reports were pooled and the version with the most complete data was selected for analysis. Any discrepancies were resolved by consensus or ultimately by a third reviewer (RG).

Two reviewers (BP and CZ) independently assessed the risk of bias of studies using the Cochrane Bias Risk Assessment Tool,¹⁷ which considers 6 main domains: random sequence generation, allocation concealment, blinding of subjects and personnel, blinding of outcome assessment, incomplete outcome data, and selective reporting. Any discrepancies were resolved by consensus or ultimately by a third reviewer (RG).

The duration of invasive mechanical ventilation was summarized as mean \pm SD of invasive mechanical ventilation days, so the meta-analysis was performed using the mean difference. The duration of invasive mechanical

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ventilation reported as medians with interquartile ranges or as full ranges were used to estimate the mean and SD.¹⁸ The random-effects model was used for the analyses; the I^2 statistic was used to assess the degree of heterogeneity between the studies, considering low heterogeneity when the I^2 was 25–49%, moderate when it was 50–74%, and high when it was $\geq 75\%$.¹⁹ The results of the studies were combined using Review Manager 5.4 (Cochrane, Oxford, United Kingdom), and the reporting bias was calculated using RStudio 1.2.5001 (RStudio, Boston, Massachusetts).

Results

Our electronic search identified 1,320 records, and our search in other resources added 92 articles. After eliminating duplicate entries, we obtained 1,200 unique records, of which 1,146 were excluded at the title and abstract stage. Of the 53 that underwent full text review, 41 studies were excluded; of the 12 records that fulfilled our eligibility criteria,^{20–31} 10 were included for meta-analysis (Fig. 1). The reasons that studies were excluding after full-text review are provided in the online supplement (see the supplementary materials at <http://www.rcjournal.com>).^{20–29}

Characteristics of Included Studies

The 12 included studies considered a total of 530 subjects; each study involved 20–80 subjects. Two studies were conducted in Turkey,^{24,29} 2 in China,^{25,26} 2 in Greece,^{22,30} 2 in Brazil,^{21,23} and the rest were performed in Egypt,²⁰ Taiwan,²⁷ the United States,²⁸ and Australia.³¹ Three studies included only COPD subjects,^{24,26,29} and the rest considered subjects with different diseases (see the supplementary materials at <http://www.rcjournal.com>).^{20–23,25,27,28,30,31} The quadriceps was the most frequently used muscle group to apply neuromuscular or functional electrical stimulation (see the supplementary materials at <http://www.rcjournal.com>). Due to the nature of the intervention, it is not possible to blind therapists or personnel, so the risk of overall bias of 1 study was considered unclear due to random sequence generation.²⁷ The risk of bias of another study was considered high due to random sequence generation and allocation concealment²⁰; the risk of bias was considered high in 5 studies due to lack of allocation concealment,^{23,25,26,29,30} in 3 studies due to incomplete outcome data,^{21,24,28} and in 2 studies because of both reasons mentioned previously (Fig. 2).^{22,31}

Duration of Invasive Mechanical Ventilation

Of the 12 studies included in this review, 1 study reported that there was no difference in ventilator-free days between the neuromuscular electrical stimulation group and the control group ($P = .32$),³⁰ and another reported a median duration of 6.5 d for the functional electrical

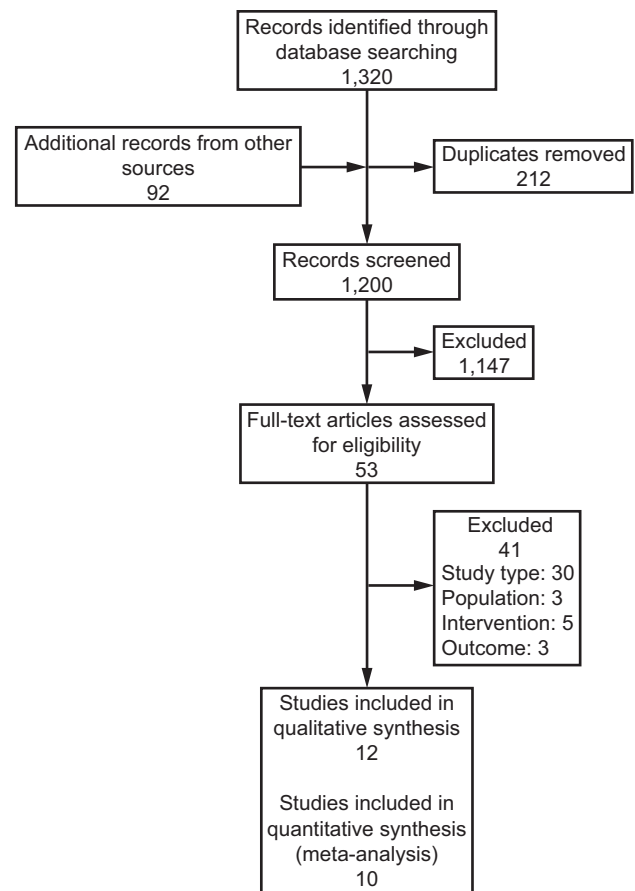


Fig. 1. Flow chart.

stimulation group compared to 34 d for the control group (Gray's test, $P = 0.40$).³¹ Due to the ways in which data were reported, these studies could not be included in the meta-analysis. The 10 studies included in the meta-analyses reported mechanical ventilation time in days ($n = 430$ subjects).^{20–22,24–29} Using a random-effects model, neuromuscular or functional electrical stimulation compared to control intervention (eg, neuromuscular or functional electrical stimulation placebo or usual care/physical therapy) may slightly decreased the time of invasive mechanical ventilation independent of disease that resulted in the need for respiratory support; however, the heterogeneity among the studies was moderate (mean difference = -2.68 d, 95% CI -4.35 to -1.02 , $I^2 = 50\%$, $P = .002$) (Fig. 3).

When studying the heterogeneity derived from the type of disease that resulted in the need for invasive mechanical ventilation, we are uncertain whether neuromuscular or functional electrical stimulation compared to control intervention slightly decreased the duration of invasive mechanical ventilation in subjects with COPD decompensation, decreasing the degree of heterogeneity (mean difference = -2.90 d, 95% CI -4.58 to -1.23 , $I^2 = 9\%$, $P < .001$) (Fig. 4), a decrease that is not significant when studies are

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Random sequence generation (selection bias)

Allocation concealment (selection bias)

Blinding of participants and personnel (performance bias)

Blinding of outcome assessment (detection bias)

Incomplete outcome data (attrition bias)

Selective reporting (reporting bias)

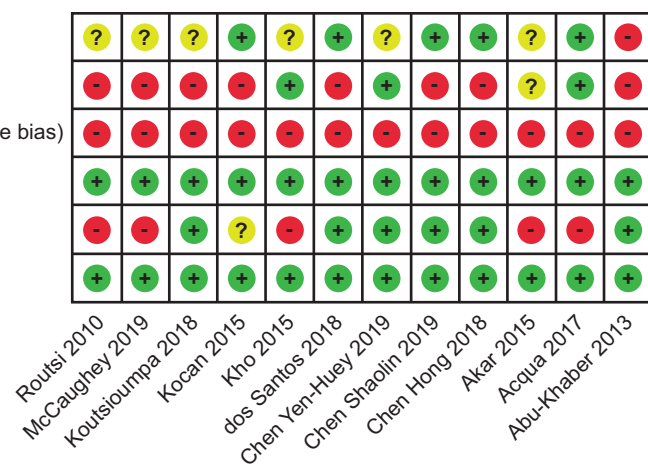


Fig. 2. Risk of bias assessment.

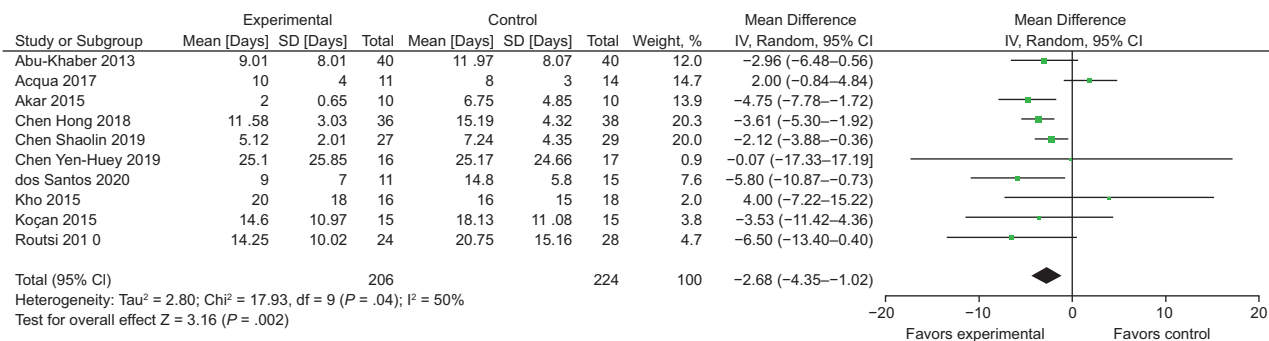


Fig. 3. Effect of neuromuscular or functional electrical stimulation on the duration of invasive mechanical ventilation.

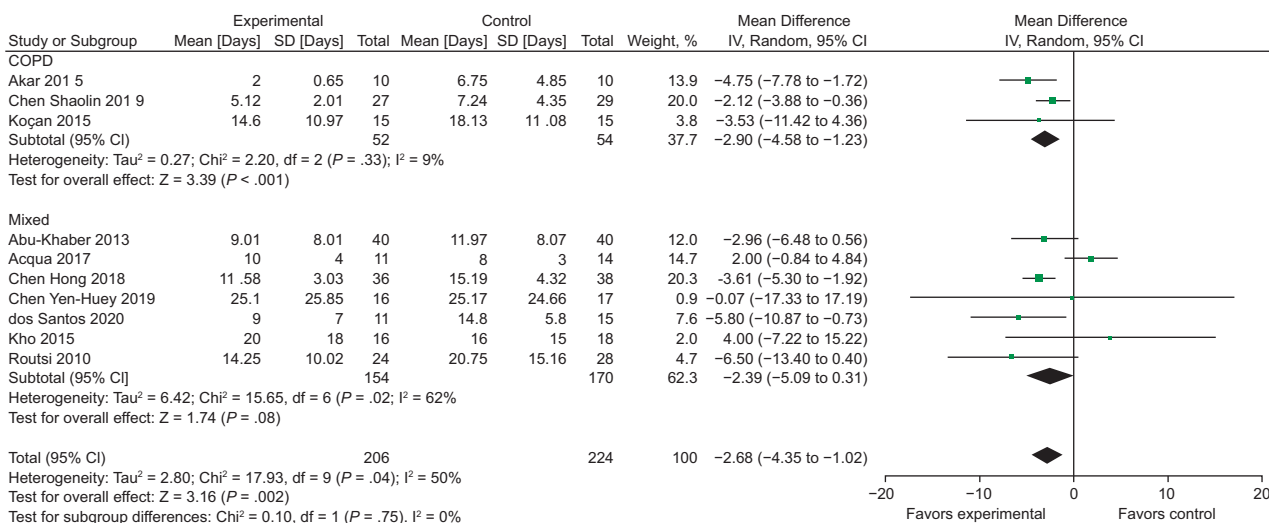


Fig. 4. Effect of neuromuscular or functional electrical stimulation on the duration of invasive mechanical ventilation (COPD vs mixed).

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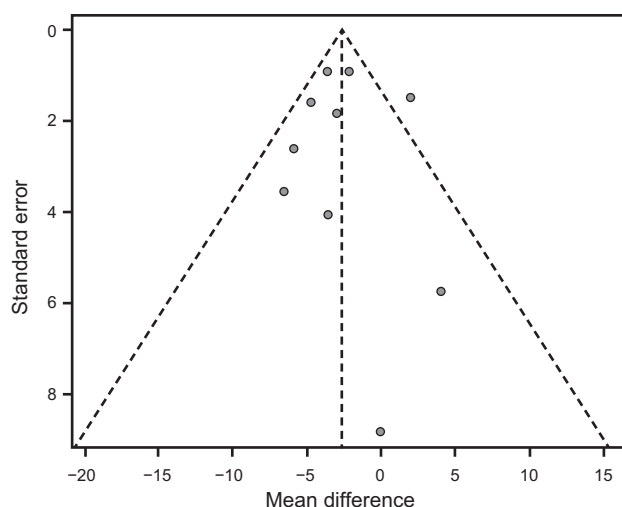


Fig. 5. Funnel plot.

grouped with subjects with different diseases (mean difference = -2.39 d, 95% CI -5.09 to 0.31 , $I^2 = 62\%$, $P = .08$) (Fig. 4). The Begg test ($P = .42$), the Egger test ($P = .98$), and the funnel plot (Fig. 5) indicate that there is no publication bias or small-study effect.

Adverse Events

Only 3 studies mentioned the incidence of adverse effects associated with the application of neuromuscular or functional electrical stimulation.^{20,21,31} It was reported that there were no complications or significant changes in vital signs during the application of neuromuscular electrical stimulation;²¹ 15% of the subjects in the control groups reported an itching sensation (not considered clinically important),²⁰ and there were 8 non-serious adverse events in the intervention groups and 14 adverse events in the control groups, which were not directly related to the application of functional electrical stimulation.³¹

Discussion

This systematic review identified 12 RCTs that evaluated the effect of neuromuscular or functional electrical stimulation on the duration of invasive mechanical ventilation in 530 critically ill subjects, regardless of the disease that led them to need respiratory support and the type of ICU in which they were hospitalized. We observed that the duration of invasive mechanical ventilation may slightly decrease with the use of neuromuscular or functional electrical stimulation compared to placebo or usual care. After grouping studies by disease type, we are still uncertain whether there is a greater therapeutic benefit in subjects with decompensated COPD. Furthermore, although only 3 RCTs mentioned the presence of adverse events associated

with the use of neuromuscular or functional electrical stimulation, these indicate the safety of the application of this intervention, probably related to the correct choice of subjects in terms of contraindications associated with the use of electrostimulation.

This review includes the largest number of RCTs assessing the effect of neuromuscular or functional electrical stimulation on the duration of invasive mechanical ventilation. Three other systematic reviews, considered for manual searching in our study, only included 2 RCTs,¹⁴ 4 RCTs,¹⁵ or 6 RCTs,¹⁶ despite having objectives and eligibility criteria similar to our review. This could be due to the timing of the search for studies¹⁴ or to the fact that the duration of invasive mechanical ventilation was not considered a primary outcome in most of the RCTs included in our review.^{15,16} One of the included RCTs (Fossat et al³²) also incorporated 15-min sessions of leg-limb cycling exercise in addition to neuromuscular electrical stimulation, which makes it difficult to establish a clear relationship of causality related to the duration of invasive ventilation between the 2 techniques. In addition, the most current review¹⁶ included the study by Leite et al,³³ which randomized subjects into 2 groups that received neuromuscular electrical stimulation in different muscle groups and a control group that underwent regular rehabilitation without the application of neuromuscular electrical stimulation. However, controls received treatment prior to recruitment into the study, so it cannot be considered an RCT comparing the application of neuromuscular or functional electrical stimulation with usual care or placebo. Unfortunately, despite the efforts made by our research group, it was not possible to access the study by Sun et al³⁴ to check whether it met our eligibility criteria; however, our review showed no reporting bias in a graphical or statistical manner.

One aspect to consider is that the duration of mechanical ventilation is dependent on when the subjects are able to begin the weaning process, which is not detailed in the studies included in this review, and the type of weaning. As for the type of weaning, only 1 study included subjects with prolonged mechanical ventilation (ie, > 21 d),²⁷ which comprises $< 1\%$ of the overall estimate of the effect of neuromuscular or functional electrical stimulation on the duration of invasive mechanical ventilation. More RCTs are needed in this specific population. In addition, only 1 of the studies included in this review provided respiratory muscle strength values,³¹ an outcome that should be included in future studies because muscle strength would be expected to increase with the application of neuromuscular or functional electrical stimulation, which should be associated with a decrease in duration of invasive mechanical ventilation and thus should confirm the systemic and clinical effect of electrostimulation.

With regard to the certainty or quality of the body of evidence that supports the effectiveness of neuromuscular or

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functional electrical stimulation in reducing the duration of invasive mechanical ventilation, as assessed with the GRADE approach,³⁵ we have shown: (1) several limitations in the body of evidence or serious risk of bias derived from the risk of selection, performance, and attrition bias; (2) study consistency because, although the heterogeneity of the studies was 50% (which dropped to 9% in subjects with COPD when subgroup analyses were performed by disease), the difference in the point estimates of the RCTs was small and the confidence intervals overlapped; (3) there is no indirect evidence because the outcome data came directly from the measurement of the studied outcome; (4) there was no serious imprecision in the overall analysis because we considered a decrease in duration of invasive mechanical ventilation of 1 d clinically relevant, and the upper end of the 95% CI of the mean difference was < -1 (-1.02 d; Fig. 3), which also occurred in the subgroup of subjects with COPD (-1.23 d; Fig. 4) (however, the total number of subjects in this analysis was small, which also determined the presence of serious imprecision for that subgroup); and (5) there was no graphically or statistically verified reporting bias. Thus, the quality of the body of evidence was low when no distinction was made by type of disease due to the very serious risk of bias, and very low for the COPD subgroup due to the very serious risk of bias and serious imprecision. Our findings indicate the need for RCTs with larger sample sizes, specifically for the COPD patient subgroup, and especially with adequate strategies to allocation concealment and decrease loss of subjects from studies or intention-to-treat analyses.

Conclusions

Theoretically, neuromuscular or functional electrical stimulation is an intervention that could influence the duration of invasive mechanical ventilation in critically ill patients. Our review suggests that its use may slightly decrease the duration of invasive mechanical ventilation; we are uncertain whether this therapy provides a greater effect in subjects with COPD compared to usual care or placebo. The quality of the body of evidence is low to very low due to risk of bias and imprecision, so RCTs with larger numbers of subjects, with more homogeneous subjects in terms of the cause that led to the need for invasive respiratory support, and with adequate methodological design are necessary.

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