Impact of Early Passive Exercise With Cycle Ergometer on Ventilator Interaction

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BACKGROUND: Early exercise has been recommended in critically ill patients, but its impact on subject–ventilator interaction is still unclear. Therefore, the aim of this study was to evaluate the occurrence of subject–ventilator asynchrony during passive exercise in mechanically ventilated subjects. METHODS: This study included deeply sedated subjects who were under mechanical ventilation for < 72 h. Subjects were coupled to a cycle ergometer and maintained at rest for 5 min (baseline period). After this period, they started 20 min of passive exercise, followed by 10 min of rest (recovery period). The occurrence of asynchrony was monitored by the analysis of flow and airway pressure waveforms, registered throughout the protocol during the baseline, exercise, and recovery periods. Hemodynamic and respiratory parameters were registered at the end of each period. Finally, arterial blood gas analysis was performed twice, at the end of the baseline period and at the end of the recovery period. RESULTS: 8 subjects were enrolled (63.3 ± 16.7 y old, 50% male). The asynchrony index increased during exercise (median 32.1% [interquartile range (IQR) 18.6–47.6%]), compared to baseline (median 6.6% [IQR 3.9–10.4%]), returning to initial levels during the recovery period (median 2.7% [IQR 0–12.2%]). The most frequent types of asynchrony were ineffective triggering (index of 11.8% [IQR 1.2–22.5%] during exercise, compared to 2.0% [IQR 1.4–4.4%] at baseline), and insufficient flow (index of 11.7% [IQR 4.7–19.3%] during exercise, compared to 2.0% [IQR 1.1 to 3.3%] at baseline). There were no significant changes in the hemodynamic and respiratory variables. CONCLUSIONS: Early cycle ergometer passive exercise in deeply sedated subjects can worsen subject–ventilator interaction, due to ineffective triggering and insufficient flow. Adjustments in the ventilatory parameters may be necessary to avoid asynchrony during exercise. *Key words: mechanical ventilation; early mobilization; exercise therapy; subject–ventilator asynchrony; respiration; hemodynamic monitoring*. [Respir Care 2020;65(10):1547–1554. © 2020 Daedalus Enterprises]

Introduction

ICU-acquired weakness is a common problem among patients receiving mechanical ventilation and is associated with poor outcomes, including prolonged hospitalization and a higher mortality rate.[1,2] Immobility, a common condition in ICU patients, is a risk factor for ICU-acquired weakness and a possible target for therapeutic interventions.[3] Studies have indicated that mechanically ventilated subjects tolerate different levels of physical exercise, and that exercise leads to better functional status at hospital discharge, shorter duration of mechanical ventilation, and decreased ICU and hospital stay.[4,5]

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Because ICU-acquired weakness can start a few hours after the beginning of mechanical ventilation and inactivity, it is suggested that physical activity begin as early as possible.[6,7] In this context, in-bed cycling with a cycle ergometer is a feasible option for patients receiving mechanical ventilation, even those who cannot perform active exercise.[8,9] Passive exercise applied to deeply sedated patients can improve muscle fiber function and attenuate muscle atrophy, suggesting a potential beneficial effect in immobilized ICU subjects.[10,11]

Subject–ventilator asynchrony is common during mechanical ventilation and can have deleterious consequences, such as increased respiratory effort, worsened gas exchange, lower rate of weaning success, longer times on mechanical ventilation, and higher mortality.[12,13] An increase in the ventilatory demand of any individual who is exercising is expected.[14] During mechanical ventilation, it could result in asynchrony with the ventilator with settings that were previously adjusted. Some authors have described the occurrence of asynchronies as adverse effects of exercising during mechanical ventilation.[15,16] To our thinking, however, no study has described the most frequent types of asynchrony in this situation or the frequency in which they occur. Knowing how patients interact with mechanical ventilation during physical activity can be useful for the early detection of asynchronies and for correction by adjusting the ventilatory parameters. Therefore, we conducted this study in subjects who had been on mechanical ventilation for < 72 h to evaluate the occurrence of different types of asynchrony, as well as other respiratory and hemodynamic events, during and after passive exercise performed with a cycle ergometer.

QUICK LOOK

Current knowledge

Patients in the ICU should start exercising as soon as possible. A few studies have indicated that exercise is feasible and safe within the first days of mechanical ventilation in deeply sedated subjects. However, the impact of early exercise on the occurrence of asynchrony has not been addressed.

What this paper contributes to our knowledge

Patient-ventilator interaction worsened among deeply sedated subjects in their first days of mechanical ventilation when they were submitted to passive exercise with a cycle ergometer. The most frequent types of asynchrony were ineffective triggering and insufficient flow. These findings suggest that further studies are necessary to investigate the impact of asynchrony on clinical outcomes and how to manage them during exercise.

Methods

Settings

This study was carried out in the ICU of the University Hospital of the Universidade Federal de Juiz de Fora (Minas Gerais, Brazil), from May 2016 to March 2018, in accordance with the amended Declaration of Helsinki. The ICU is a 9-bed, clinical-surgical unit in a 150-bed teaching hospital. The local ethics committee approved the protocol, and written informed consent was obtained from the subjects' next of kin (University Hospital of the Federal University of Juiz de Fora Research Ethics Committee, protocol number 1.717.952).

Subjects

We included subjects age ≥ 18 y who had received mechanical ventilation for < 72 h, were hemodynamically stable (mean arterial pressure > 60 mm Hg, maximum infusion rate of norepinephrine of 0.1 μg/kg/min), without cardiac arrhythmias during the last 24 h, exhibited respiratory stability (S_{pO_2} > 95%, F_{IO_2} < 0.60, and PEEP < 8 cm H_2O), had a hemoglobin level > 7 g/dL, and were under deep sedation (Richmond Agitation-Sedation Scale [RASS] between –3 and –5).[17]

The exclusion criteria were neurological or osteoarticular disorders affecting the lower limbs that precluded exercise or adaptation to the cycle ergometer, deep vein thrombosis, and attending physician disagreement for enrollment. Subjects whose ventilator data (ie, airway pressure and flow waveforms) could not be recorded were also excluded.

Protocol

The passive exercise was performed with a cycle ergometer (Flexmotor, Cajumoro, São Paulo, Brazil). Deeply sedated subjects (RASS between –3 and –5) were first placed in a semi-recumbent position (30°–60°), had their legs connected to the cycle ergometer, and were maintained at rest for 5 min (ie, the baseline period). The subjects then started 20 min of passive exercise, with a frequency of 30 rpm (ie, the exercise period). Finally, they were kept at rest in the same position for 10 more minutes (ie, the recovery period).

The protocol was performed only once by each subject, and it was supervised by a physician (Dr Pinheiro or Dr Fonseca) and a physiotherapist (Ms Silva, Ms Netto, or Mr Vieira). Subjects were ventilated with the Servo-S ventilator (Maquet, Solna, Sweden) in the pressure-controlled

mode, with the airway pressure adjusted to obtain a tidal volume of 6–8 mL/kg of predicted body weight. The other parameters were set to maintain the S_{pO_2} between 95% and 98% and to keep the subject comfortable. No adjustment in the ventilator parameters was performed throughout the baseline, exercise, and recovery periods of the protocol. The protocol was discontinued in the presence of one of following criteria that indicate an unstable subject: mean arterial pressure > 120 mm Hg or < 60 mm Hg, systolic blood pressure > 200 mm Hg or < 90 mm Hg, heart rate > 120 beats/min or < 50 beats/min, ventricular arrhythmias (except isolated extrasystoles), S_{pO_2} < 88% for > 1 min.

Variables

We collected subjects' demographics and clinical data, such as, age, gender, severity of illness as measured by the Simplified Acute Physiology Score-III (SAPS-III), Sequential Organ Failure Assessment (SOFA), body mass index, the main reason for ICU admission, the use of vasopressors and neuromuscular blockers, and comorbidities. Heart rate, mean arterial pressure, systolic blood pressure, diastolic blood pressure, breathing frequency, tidal volume, and S_{pO_2} were also measured at the end of baseline, exercise, and recovery periods (DX 2020 monitor, Dixtal Biomédica, Amazon, Brazil). A 12-lead electrocardiogram was registered during the whole period to monitor the heart rhythm and the occurrence of ischemic events (DMS 300–7, Compact Flash Card Holter Recorder, DMS, Nevada). Arterial blood samples for gas analysis were obtained at the end of baseline and recovery periods.

Trigger, flow and termination asynchronies were detected by visual inspection of the waveforms by a blinded investigator (Dr Pinheiro). Airway pressure and airway flow signs were acquired by the RS232 serial interface of the ventilator, throughout the protocol (baseline, exercise, and recovery periods) and saved in a portable computer by the software LabVIEW (National Instruments, Austin, Texas). The signs were imported and processed by the software Matlab 2006 (Mathworks, Natick, Massachusetts).

Ineffective triggering was defined by an inspiratory effort (ie, an abrupt airway pressure drop simultaneous with a flow decrease) not followed by a ventilator cycle. Double-triggering was defined as 2 cycles separated by a short expiratory time (< 50% of the mean inspiratory time). Auto-triggering was defined as a cycle delivered by the ventilator without a prior effort performed by the subject (without a prior airway pressure decrease), and that was not expected to occur due to the adjusted breathing frequency.

Two types of flow asynchrony were monitored: insufficient flow or excessive flow to subject's demand. Excessive flow was detected by the presence of pressure-overshoot in the airway pressure waveform or a high peak flow with a steeper flow decrease in the correspondent waveform. Insufficient flow was detected by a decrease of the airway pressure with a simultaneous change of the decelerate pattern of the inspiratory flow in their respective waveforms.

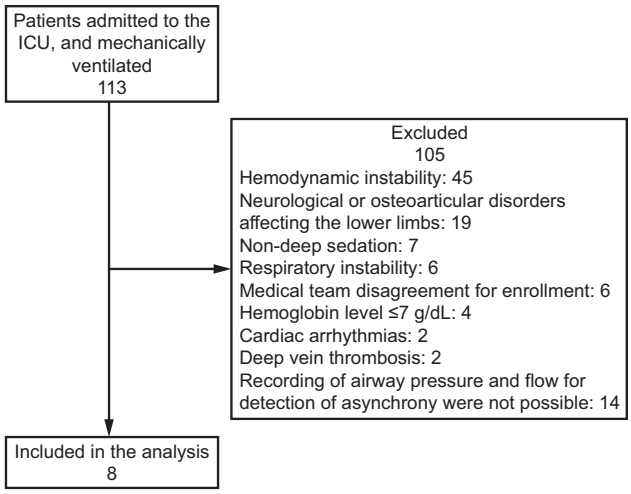

Fig. 1. Flow chart.

Regarding the termination of inspiratory cycling, we monitored premature and delayed cycling. Premature cycling was defined by an abrupt drop of the airway pressure toward the baseline with a simultaneous reversal in the expiratory flow waveform (ie, a rapid return of the expiratory flow to zero). Delayed cycling was identified by a spike in the pressure waveform near the end of the inspiration, accompanied by an abrupt drop of the inspiratory flow.

We calculated the asynchrony index as the number of asynchrony events divided by the total breathing frequency computed as the sum of the ventilator cycles (triggered or not) and of wasted efforts, expressed as percentage. This index was also calculated for each type of asynchrony.[11]

Statistical Analysis

The normality of the data were analyzed by the Kolmogorov-Smirnov test. Data were expressed as mean ± SD or median (interquartile range) for normally and nonnormally distributed data, respectively. One-way analysis of variance followed by the Tukey test was used to compare normally distributed data. For nonnormally distributed data, the Friedman test followed by the Wilcoxon test was used. Adjustments for repeated measures were performed according to the Bonferroni correction. The *t* test was used to compare the difference between gas analysis at baseline and recovery periods. Statistical analyses were performed using STATA 15.1. A P value < .05 was considered statistically significant.

Results

Of the 113 patients admitted in the ICU and mechanically ventilated during the study period, 8 met the inclusion criteria, and 105 were excluded. The main reason for exclusion was hemodynamic instability (42.9%) (Fig. 1). No complications were found during the protocol. Demographic and clinical data of subjects who completed the protocol are shown in Table 1.

Table 1. Demographic and Clinical Data of Subjects

Age, y	63.3 ± 16.7
Male	4 (50.0)
Simplified Acute Physiology Score-III at admission	53.3 ± 8.3
Sequential Organ Failure Assessment at admission	8.3 ± 2.6
Richmond Agitation-Sedation Scale	–5 (–5 to –3)
Body mass index, kg/m^2	2.8 ± 4.6
Cause of ICU admission	
Sepsis	2 (25)
Pneumonia	3 (37.5)
Postoperative	0 (0)
COPD	1 (12.5)
Cardiac failure	1 (12.5)
Central nervous disorder	1 (12.5)
Mechanical ventilation	
F_{IO_2}	0.4 (0.4–0.5)
Breathing frequency, breaths/min	16 (15–20)
Tidal volume, mL	507.9 ± 191.0
Peak pressure, cm H_2O	14 (13–15)
PEEP, cm H_2O	5.5 (5–6)
Vasopressors	7 (87.5)
Neuromuscular blockers	1 (12.5)
Comorbidities	
Hypertension	4 (50.0)
Diabetes	2 (25.0)
COPD	2 (25.0)
Cardiac failure	2 (25.0)
Chronic kidney disease	1 (12.5)
Acquired immunodeficiency syndrome	0 (0)

Data are presented as mean ± SD, *n* (%), or median (interquartile range). $n = 8$ subjects.

Table 2 shows the hemodynamic and respiratory responses at baseline, 20 min after exercise, and 10 min after recovery. These responses did not change significantly after exercise or after the recovery period when compared to baseline.

The incidence of asynchrony increased during exercise and returned to baseline levels during the recovery period. The most frequent types of asynchrony were ineffective triggering and insufficient flow (Table 3). Figure 2 shows the behavior of the global asynchrony index and of the most frequent types of asynchrony in each monitored subject.

Discussion

We observed that subject-ventilator interaction worsened among deeply sedated subjects in their first days of mechanical ventilation while they were submitted to passive exercise with a cycle ergometer. This passive exercise was not associated with deterioration of hemodynamics or oxygenation.

It is well established that early mobilization and exercise can reduce the effects of ICU-acquired weakness; early mobilization and exercise are associated with shorter duration of mechanical ventilation, shorter ICU length of stay, improved quality of life after hospital discharge, and lower rates of hospital readmission.[5,8,18,19] Because of these benefits, it is recommended that exercise should start as soon as possible during mechanical ventilation.[7] However, deeply sedated patients may not be able to do active exercise. Therefore, for these patients, passive exercise may be an alternative.

Table 2. Hemodynamic and Respiratory Characteristics

Variables	Baseline	After 20 Min of Exercise	After 10 Min of Recovery
Systolic blood pressure, mm Hg	117 ± 20	121 ± 22	117 ± 23
Diastolic blood pressure, mm Hg	70 ± 15	70 ± 12	67 ± 12
Mean arterial pressure, mm Hg	86 ± 15	87 ± 15	84 ± 15
Heart rate, beats/min	82 ± 21	80 ± 18	78 ± 19
S_{pO_2}, %	98.3 ± 1.2	97.8 ± 1.6	98.4 ± 1.1
Breathing frequency, breaths/min*	16.0 (15.3–20.0)	19.0 (16.0–21.5)	16.5 (16.0–20.0)
Tidal volume, mL	490 ± 81	494 ± 125	508 ± 96
pH	7.37 ± .06		7.40 ± .08
P_{aCO_2}, mm Hg	35.0 ± 6.0		32.8 ± 5.9
P_{aO_2}, mm Hg	138.1 ± 30.3		129.2 ± 39.0
Bicarbonate level, mEq/L	21.3 ± 4.4		21.4 ± 4.8
Lactate, mmol/L	1.6 ± .6		1.6 ± .4

Data are presented as mean ± SD or median (interquartile range). $n = 8$ in each test period.
* Breathing frequency considered as the cycles by the ventilator.

Table 3. Asynchrony Indexes

Variables	Baseline	After 20 Min of Exercise	After 10 Min of Recovery
Global asynchrony index, %	6.6 (3.9–10.4)	32.1 (18.6–47.6)*	2.7 (0–12.2)
Specific asynchrony indexes, %			
Ineffective triggering	2.0 (1.4–4.4)	11.8 (1.2–22.5)†	0 (0–1.4)
Double-triggering	0 (0–2.2)	0 (0–4.2)	0 (0–4)
Auto-triggering	0 (0)	0 (0)	0 (0)
Excessive flow	0 (0)	0 (0)	0 (0)
Insufficient flow	2.0 (1.1–3.3)	11.7 (4.7–19.3)‡	0.6 (0–3.2)
Premature cycling	0 (0–0.8)	0 (0–2.2)	0 (0–1.5)
Delayed cycling	0 (0–0.9)	0.4 (0–8.1)	0 (0)

Data are presented as median (interquartile range). $n = 8$ in each test period.
* $P < .05$ compared to Baseline and Recovery.
† $P < .05$ compared to Recovery.
‡ $P < .05$ compared to Baseline.

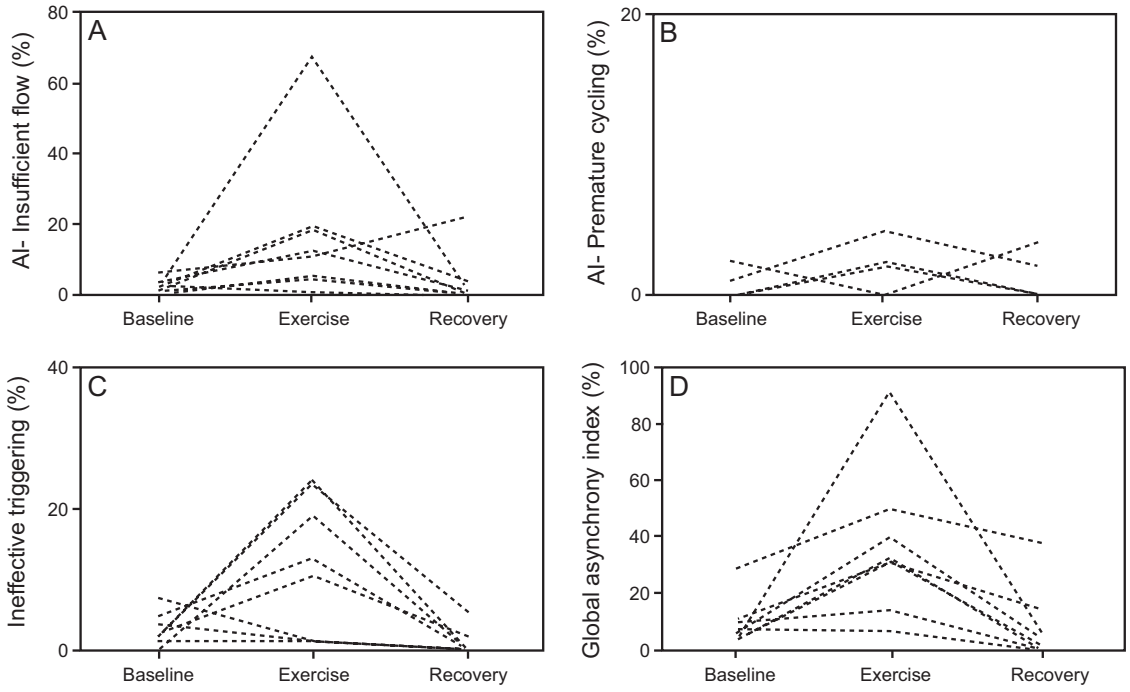

Fig. 2. Insufficient flow, premature cycling, ineffective triggering, and global asynchrony index (AI).

During the exercise, ventilatory demand can increase and the ventilatory support can become insufficient to compensate for the increased demand, raising the risk of asynchrony.[16] Indeed, insufficient flow was the most frequent type of asynchrony observed in our study (Table 3), noted in 7 of the 8 monitored subjects (Fig. 2A, Fig. 3). Moreover, 3 subjects presented premature cycling, a type of asynchrony that is also related to insufficient flow (Fig. 2B).

Akoumianaki et al[16] reported that oxygen consumption by the respiratory muscles increases during physical activity, which is in accordance with our results. The authors also noted that ventilating these subjects with proportional assist ventilation, a ventilatory mode that adjusts the inspiratory flow according to the subject's demand, prevents the increase in oxygen consumption.[16] These results suggest that, during exercise, strategies to improve the interaction between the flow offered by the ventilator and the subject's demand may be necessary. Similar results were reported in another study with subjects performing upper-arm exercise with a cycle ergometer during mechanical ventilation.[20] The authors noted that subjects could exercise for a longer period of time when the pressure support level was increased, suggesting the importance of the adjustments of

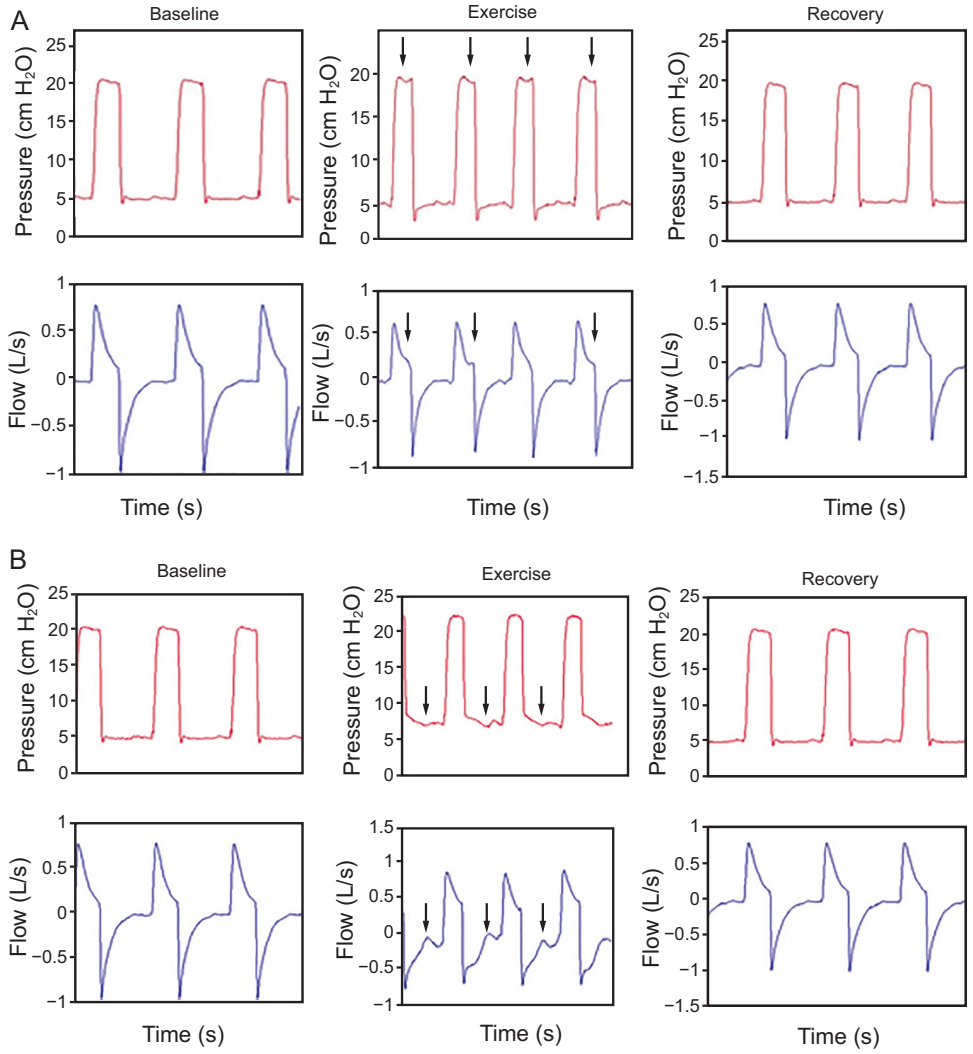

Fig. 3. Airway pressure and flow time waveforms during baseline, exercise, and recovery periods. A: During the exercise period, a decrease of airway pressure (arrows) and a simultaneous change of the decelerate pattern (arrows) of the inspiratory flow indicate contraction of inspiratory muscles to compensate for insufficient ventilatory support offered by the ventilator settings. B: During exercise, ineffective effort can be observed by abrupt airway pressure drop (arrows) simultaneous with expiratory flow decrease (arrows) that is not followed by a ventilator cycle.

ventilatory parameters to improve subject's comfort during physical activity.[20]

In our study, ineffective triggering also increased during exercise (Fig. 2C, Fig. 3). The deep sedation of the subjects may have contributed to the occurrence of this asynchrony. Studies have demonstrated a linear correlation between ineffective triggering and deeper levels of sedation measured with the RASS.[21,22] Deeper sedation levels may decrease respiratory drive and inspiratory muscle efforts, resulting in ineffective triggering even in situations with higher ventilatory demand, including physical activity.[21-23] Among the 8 subjects who were evaluated, 2 presented with COPD, a condition that is often associated with ineffective triggering.[24,25] One subject was admitted due to a COPD exacerbation, and the other subject was admitted with pneumonia. Both subjects exhibited higher numbers of ineffective triggering events during exercise, but the same behavior was also seen among subjects with other diagnoses and comorbidities. Therefore, we think that ineffective triggering during exercise may be a problem regardless of the reason for mechanical ventilation.

The global asynchrony index increased during exercise, and 7 of 8 subjects presented an asynchrony index $> 10\%$ while exercising (Table 3, Fig. 2D). An asynchrony index $> 10\%$, even for short observation periods, has been associated with worse outcomes.[12,26] Thille et al[12] monitored subjects for 30 min to identify the occurrence of major asynchrony (ie, ineffective triggering, double-triggering, auto-triggering, short cycle, and prolonged cycle). The authors reported that subjects with an asynchrony index

> 10% had longer times on mechanical ventilation.[12] In another study, the occurrence of ineffective triggering was observed for 10 min during the first 24 h of mechanical ventilation.[26] Ineffective triggering was associated with longer mechanical ventilation duration and longer ICU stay.[26] In both studies, subjects were monitored at only one point during mechanical ventilatory support. Although recognized as a limitation in both cases, these short periods of monitoring were considered representative of the whole period of mechanical ventilation.

In our study, the asynchrony index increased during exercise but decreased to baseline levels during the recovery period. Although this higher asynchrony index does not represent the scenario throughout mechanical ventilation, it can occur every time the subject exercises. We have not evaluated the impact of this higher asynchrony index during exercise on clinical outcomes, and, to our knowledge, no study has done so yet. However, we have identified this potential problem that can occur frequently, given that ICU patients now exercise more often. Therefore, adjustments in the ventilatory settings can be made to avoid asynchrony.

As previously reported by other authors,[9,27] hemodynamic parameters remained stable during exercise without any clinically relevant deterioration of heart rate, arterial pressure, and lactate levels. Pires-Neto et al[9] also studied hemodynamic behavior in sedated critically ill subjects during passive cycling exercise and reported similar results. During exercise, there was no significant change in heart rate, mean arterial pressure, central venous pressure, and cardiac output. Lactate levels and central venous oxygen saturation did not change either, suggesting that passive cycling exercise in this population did not disturb the balance between oxygen delivery and consumption.[9]

In our study, subjects did not develop hypoxemia during exercise. Moreover, neither tachypnea nor hypocapnia were observed. These results, which are in line with the findings of previous studies, suggest that early physical activity in sedated patients is safe with regard to gas exchange.[9,28]

This study has limitations that should be considered. Asynchronies were detected based on the analysis of flow and airway pressure waveforms. Although this is not the most accurate method to detect asynchrony, we think that it was able to identify the most relevant ones.[29] This was a single-center study, and it should be pointed out that the type of ventilator, the ventilatory parameters, and the sedation strategy may influence subject–ventilator interaction. Moreover, we assessed a small number of subjects, and the study was not designed to infer the impact of asynchrony on more relevant outcomes, such as duration of mechanical ventilation, length of ICU stay, or mortality. Therefore, our findings cannot be extrapolated to every situation.

Conclusions

Our results indicate that passive cycling exercise was feasible and safe in deeply sedated subjects. Nevertheless, the possible occurrence of asynchrony, namely ineffective triggering and insufficient flow, ought to be taken into account. We believe this is relevant due to the increasing popularity of early exercise in ICU practice. Further studies are necessary so that we can have a clearer understanding of how to approach asynchrony during exercise and its impact on clinical outcomes.

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