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ORIGINAL ARTICLE

ANALYSIS OF HEART RATE VARIABILITY AND CARDIOVASCULAR RESPONSE IN THE ALVEOLAR RECRUITMENT MANOEUVER IN ACUTE RESPIRATORY DISTRESS SYNDROME

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KEYWORDS: Heart rate variability; alveolar recruitment manoeuvre; acute respiratory distress syndrome; positive end-expiratory pressure

Objective: To assess the cardiac autonomic modulation through heart rate variability (HRV) in response to alveolar recruitment manoeuvre (ARM) of patients with acute respiratory distress syndrome (ARDS). **Methods:** We have studied four patients with ARDS. The RR intervals were recorded before, during and after alveolar recruitment manoeuvre (ARM), along with blood pressure (BP), oxygen arterial pressure (PaO_2), oxygen inspired fraction (FiO_2) heart rate (HR), oxygen peripheral saturation (SpO_2), compliance (Comp), resistance (Res), and PaO_2/FiO_2 ratio. HRV was analyzed by using linear time-domain (TD) and non-linear methods. The former consisted of RMSSD (root mean square of squares of differences between successive R-Ri values) and SDNN (standard deviation of the mean of normal R-Ri values) in the frequency domain (FD) regarding low (LF) and high frequency (HF) bands as well as LF/HF ratio, whereas the latter consisted of short- (SD1) and long-term (SD2) records, and de-trended fluctuation analysis of short- (DFAα1) and long-term (DFAα2) duration. **Results:** We found significant increases in the variables Comp and PaO_2/FiO_2 compared to the rest period, and in $SatO_2$ at the end of ARM. In addition, recovery and decreased Res were also found at the end of ARM compared to the rest period. HRV showed a significant increase in index DFAα1 during ARM as well as a tendency of decrease in RMSSD and increase in SDNN, including increase in SD1, SD2, and DFAα2 as well. **Conclusion:** HRV undergoes changes in response to ARM with a tendency of decrease in the parasympathetic activity and increase in the total variability during ARM.

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INTRODUCTION

The acute respiratory distress syndrome (ARDS) is defined as an acute inflammatory pulmonary syndrome of varied etiologies involving risk factors for lung lesions such as sepsis and pneumonia, evolving to severe hypoxemia, bilateral pulmonary infiltrate on chest x-ray and reduction in pulmonary compliance. The majority of patients in this situation will eventually need mechanical ventilation[1-3]. Both incidence and diagnostic criteria for patients with ARDS are controversial[4]. In 1994, however, the American-European Consensus Conference Committee (AECC) defined these criteria as being acute respiratory insufficiency with bilateral pulmonary infiltrate on chest x-ray, severe hypoxemia with the ratio of oxygen arterial pressure (PaO_2) and oxygen inspired fraction (FiO_2) lower than 200 mmHg, and absence of clinical signs of left cardiac insufficiency[2].

Although there is a consensus on the strategic use of mechanical ventilation to protect the lungs of patients with ARDS at low current volume (4-6 mL/Kg) and plateau pressure below 35 cmH_2O[3], pulmonary failure and lesions resulting from the cyclic alveolar opening and closing in patients with ARDS on mechanical ventilation are still of concern during their treatment[5], including poor positive end-expiratory pressure (PEEP), which makes it difficult to keep lungs open during the whole respiratory cycle [6]. Within this context, the alveolar recruitment manoeuvre (ARM) is aimed at eliminating any pulmonary collapse[7]. Despite its controversial use[8-10], ARM is indicated as a helpful method for pulmonary protection[7], being defined as a re-expansion of previously collapsed lung tissues by increasing the intra-pulmonary pressure to decrease the cyclic opening and closing of different alveolar regions and to improve the pulmonary volume in non-ventilated areas [11]. When correctly performed, ARM may play a crucial role in re-establishing ventilation and perfusion in recruited areas, thus improving gas exchange [7, 10].

The high intra-thoracic pressures promoted by ARM can have a significant hemodynamic repercussion, with decrease in cardiac output and venous return as a result [3, 10, 12, 13]. However, literature on the ARM impact on cardiac function is scanty. The heart rate variability (HRV), representing one of the most important non-invasive markers for assessment of the sympathetic-vagal modulation of the heart[14, 15], has been shown to be useful in reflecting the cardiovascular adjustments promoted by new demands. In this sense, our hypothesis is that HRV might reflect the modifications in the cardiac function promoted by ARM. In view of this, the objective of the present study was to assess the cardiac autonomic modulation during ARM in patients diagnosed with ARDS.

MATERIALS AND METHODS

Study

This is a quantitative analytic study with cross-sectional characteristic in which 17 adult patients who had early-onset (less than 24 h) moderate or severe ARDS and were hospitalized in the Federal University of Uberlândia Clinic Hospital's Intensive Care Unit between June and October 2011, were evaluated. All patients were over 18 years old, sedated, and on mechanical ventilation as they presented oxygen deficit according to PaO_2 and SpO_2.

According to resolution number 196/96 established by the National Health Council, their legal caregivers signed an informed consent form after explanation about the objectives of the study. The study was approved by the Human Research Ethics Committee of the Federal University of Uberlândia through protocol number 052/11.

Inclusion and Exclusion Criteria

The patients who took part in the present study were clinically diagnosed with ARDS based on diagnostic criteria established by the AECC[2]. Patients with cardiac pacemaker, presenting with significant arrhythmia (more than 15% of total sinus beats), heart-transplanted or treated for intracranial pressure control were excluded. In addition, exclusion criteria included potential contraindications for ARM such as haemodynamic instability (mean arterial pressure <65 mmHg), bronchopleural fistula, significant pleural effusion, pneumothorax or history of pneumothorax, emphysema, and pulmonary arterial hypertension.

Experimental Procedure

After clinical and radiological indication for ARM procedure, the patients were previously sedated before 30 minutes of the manoeuvre, positioned in dorsal decubitus, and put on mechanical ventilation. Prior to the ARM, bronchial hygiene was performed with aspiration of lung secretion and leak-check procedure done, including adequacy of the endotracheal cuff pressure to maintain the pressure of 30 mmHg in order to prevent leakage around the cuff. Next, a 10-minute rest period was allowed so that cardiovascular and pulmonary functions could return to their same conditions before bronchial hygiene.

In order to decrease the error margin of the ventilation variables, all patients included in the study were ventilated with the same mechanical ventilation device, that is, a Dixtal DX3010 (Dixtal Biomédica Ind. & Com. Ltda,, São Paulo. Brazil).

Heart rate (HR) and R-R intervals (R-Ri) were recorded by using a heart-rate monitor (Polar, model PS800CX, Proximus, Finland) on a continuous basis, starting 10 minutes before, during 7 minutes and finishing 10 minutes after the ARM procedure. This allowed three different monitoring periods to be recorded for data analysis, namely, beginning of ARM, during ARM, and 10 minutes after ARM. The variables HR, SpO_2, systolic arterial pressure (SAP), diastolic arterial pressure (DAP) were recorded in all three monitoring periods, whereas static pulmonary compliance (Comp), respiratory system resistance (Res), and gasometry were recorded 10 minutes before ARM and immediately after it. The experimental design in Figure 1 illustrates the whole phase of data collection.

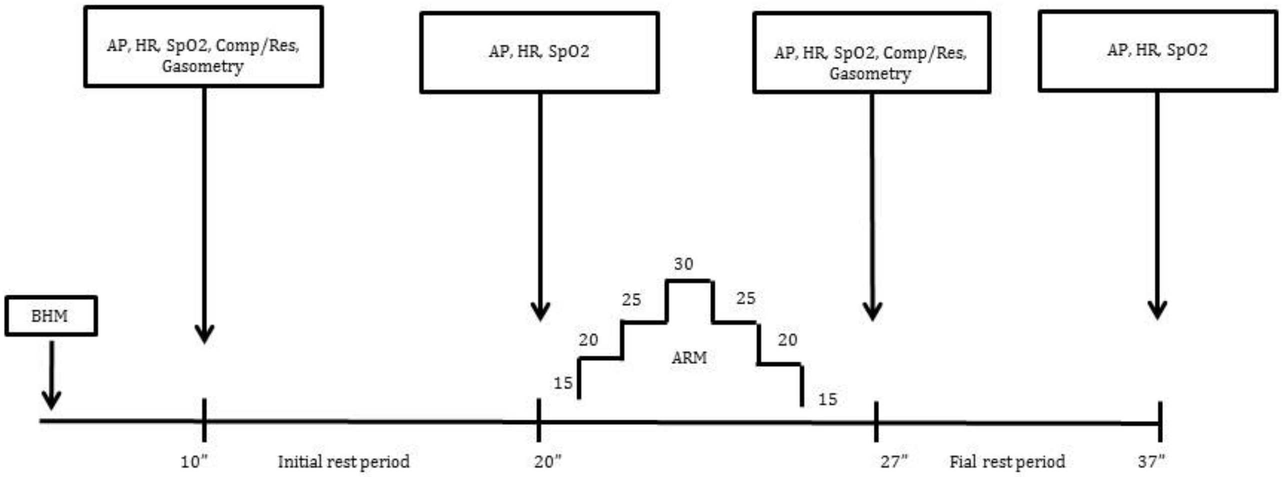

Figure1. Experimental design of data collection. AP (arterial pressure); HR (heart rate); SpO_2 (oxygen arterial saturation); Comp (compliance); Res (Resistance); BHM (bronchial hygiene manoeuvre); ARM (alveolar recruitment manoeuvre).

The ARM procedure was incrementally performed by one of the researchers based on Lim et al.[13] and recommendations set by the Third Brazilian Council for Mechanical Ventilation[3], with the patient being pressure-controlled ventilated. PEEP was progressively increased at 15, 20, 25, and up to 30 cmH_2O and then decreased at the same proportion up to the initial value. Each PEEP value was kept for 1 minute, totalizing seven minutes of ARM. The total inspiratory pressure was limited to 15 cmH_2O above the PEEP, allowing a maximum value of 45 cmH_2O to be obtained. FiO_2 was not changed, but it was adjusted to 10 respirations per minute

(RPM) so that the real effectiveness of ARM on gas exchange and heart rate could be assessed.

Arterial gasometry was collected by the adult ICU nursing staff of the Clinic Hospital before and immediately after the end of ARM in order to compare the initial and final PaO_2 values as well as the acute efficacy of ARM on arterial oxygen.

Data Analysis

HRV was analyzed by using linear time-domain (TD), including frequency domain (FD), and non-linear methods at different experimental periods of time. In the time domain, HRV was analyzed from R-Ri (ms) and the following indexes were used: mean R-Ri (ms), RMSSD (corresponding to the root mean square of squares of differences between successive R-Ri values) and SDNN (corresponding to the standard deviation of the mean of normal R-Ri values)[16, 17].

In the frequency domain, data were analyzed by using power spectral density from high (HF) and low (LF) frequency bands in Hz (absolute and normalized units). Low frequency was measured for sympathetic and parasympathetic nervous systems, whereas high frequency was measured for the parasympathetic system only. The HF/LF ratio was represented by the sympathetic-vagal balance[16, 17]. This analysis is performed by applying the Fourier quick transformation to the data[16, 17].

The non-linear methods were analyzed by using the Poincaré plot for dynamic analysis of HRV, both qualitatively by means of the evaluation of the figure formed and quantitatively by means of indexes SD1 and SD2, with the former representing instantaneous record of the beat-to-beat variability and parasympathetic autonomic activity and the latter representing HRV in long-term recordings, that is, the total variability [16, 18].

Another non-linear method was the de-trended fluctuation analysis, measured by correlations of different time scales between R-R signals using indexes DFAα1 for short-term fluctuations and DFAα2 for long-term fluctuations [18].

All analyses involving HRV were performed by means of specific routine from the Kubios HRV software (version 2.0, Finland) developed for this purpose.

The results obtained were shown in tables containing the values of means and standard-deviations. HRV, ventilation and hemodynamic data were submitted to a test of frequency distribution (ANOVA) for analysis of repeated measures and to parametric tests (Tukey's test) to know how they represent a normal distribution. All tests were performed by using the SigmaPlot for Windows software (version 11.0; Build 11.0.0.77, Germany) at significance level of 5%.

RESULTS

Out of the 17 patients evaluated, only four took part in the study as they were clinically diagnosed with ARDS. Among the patients who were excluded, one was being treated for intracranial pressure control and another had cardiac pacemaker, and all the 13 patients did not meet the AECC criteria either. Figure 2 shows the flowchart for patient screening. The mean age of the patients included in the study were 53±24 years, with half being men.

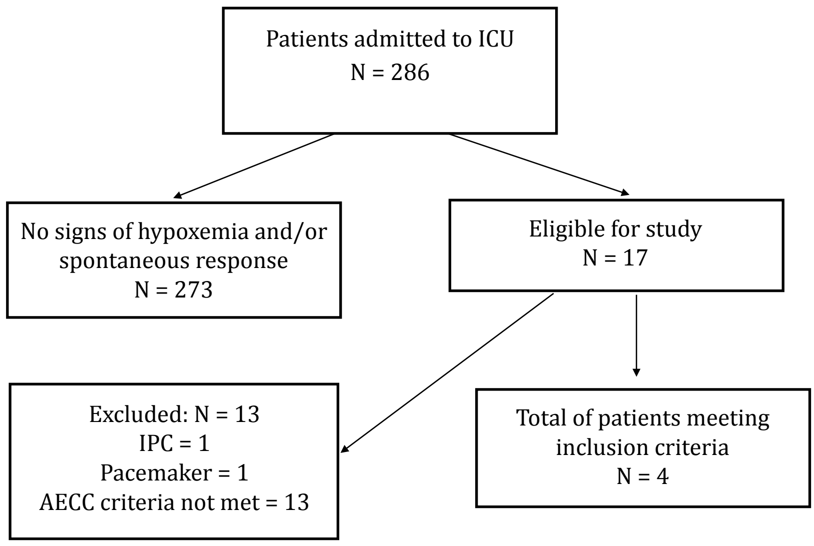

Figure 2. Flowchart for patient screening. Patients included in the study sample corresponding the period between June to October 2011

All were receiving antibiotic therapy and sedation still containing propophol (n = 100%), fentanyl (n = 100%) and midazolam (n = 75%). The initial diagnoses were pneumonia (50%) and ARDS (50%). Clinical and demographic characteristics as well as medications used by patients during data collection.

Table 1. Clinical and demographic characteristics and medications used by patients (mean ± SD).

	Age (years)	Gender	Initial Diagnosis	Sedatuion	Neuromuscular blocker	PEEP (cmH	FiO
Pt.1	19	Male	Pneumonia	P, F, M	Rocuronium	14	0.6
Pt.2	56	Male	Sepsis	P, F, M	Rocuronium	12	0.8
Pt.3	62	Female	Sepsis	P, F, M	-	13	0.7
Pt.4	74	Female	Pneumonia	P, F	-	12	0.45
Mean		-	-	-	-	12.7 ± 0.9	0.63 ± 14.9

Pt: Patient; P: Propofol; F: Fentanyl; M: Midazolam

The variables SAP, DAP, HR, SpO_2, Comp, Res, PaO_2 and PaO_2/FiO_2 ratio are presented in Table 2. Statistically significant differences were found for variables Comp, Res and PaO_2/FiO_2 ($P<0.05$) ratio regarding initial rest and for recovery regarding initial rest. No significant differences were found for the other variables ($P>0.05$).

Table 2. Values of hemodynamic and ventilation variables (mean ± SD).

	Initial rest	Beginning of ARM	End of ARM	Recovery
Systolic AP (mmHg)	12.8 ± 10.8	130.7 ± 25.6	126.5 ± 24.4	131.7 ± 24.5
Diastolic AP (mmHg)	63 ± 12.8	63.2 ± 6.6	55.5 ± 6.3	66.2 ± 12.7
Heart rate (bpm)	90.7 ± 18.4	87.5 ± 16.8	87.7 ± 19.8	88.5 ± 18.1
O_2 saturation (%)	92% ± 0.04	91% ± 0.04	94% ± 0.02*	93% ± 0.03**
Compliance (mL/cmH_2O)	27.25 ± 5.7	-	30 ± 5.7	-
Resistence ($cmH_2O/L/min$)	15 ± 6.1	-	13.2 ± 5.5*	-
PaO_2 (mmHg)	81.8 ± 11.1	-	94.4 ± 17.2	-
PaO_2/FiO_2 ratio	132.1 ± 24.4	-	147.5 ± 21.7*	

AP: arterial pressure; PaO_2; Oxygen arterial pressure; *=p<0.05 for final ARM vs. initial rest ; **=p<0,05 for recovery vs. initial rest

Table 3 shows data obtained from linear (TD and FD domains) and non-linear analyses. No significant differences were found for linear method between mean values of rest, ARM and recovery (P>0.05). However, a significant difference was observed in the non-linear method regarding the index DFAα1 for ARM versus rest (P<0.05). Although only one index showed data significance, one can observe a tendency (P=0.06) of ARM on TD (SDNN) and non-linear variables of HRV (SD2, P=0.06).

Table 3. Values of HRV for time domain (TD), frequency domain (FD), and non-linear variables during and after AMR (mean ± SD).

HRV	Rest period	ARM	Recovery
R-Ri mean (ms)	692.9 ± 134.9	713.2 ± 174.9	679.3 ± 156.8
RMSSD (ms)	8.2 ± 6.3	4.2 ± 3.7	3.8 ± 3.1
SDNN (ms)	11.0 ± 9.1	19.5 ± 9.5	10.7 ± 9.5
LF (nu)	39.5 ± 32.6	40.7 ± 6.7	38.4 ± 19.0
HF (nu)	60.4 ± 32.6	59.2 ± 6.7	61.5 ± 19.0
LF/HF	1.3 ± 1.7	0.7 ± 0.2	0.7 ± 0.5
SD1 (ms)	5.8 ± 4.4	3.0 ± 2.6	2.7 ± 2.2
SD2 (ms)	14.0 ± 12.7	27.3 ± 13.3	14.9 ± 13.2
DFAα1	0.7 ± 0.3	1.1 ± 0.2*	0.8 ± 0.3
DFAα2	1.0 ± 0.1	1.5 ± 0.1	1.2 ± 0.2

Linear variables in TD: R-Ri mean: mean of the r-r intervals in ms; RMSSD: root mean square of squares of differences between successive R-Ri values; SDNN: standard deviation of the mean of normal R-Ri values. Linear variables in FD: LF: low frequency in normalised units; HF: high frequency in normalised units. Non-linear variables: SD1: short-term dispersion; SD2: long-term dispersion; DFAα1: short-term de-trended fluctuation analysis; DFAα2: long-term de-trended fluctuation analysis. *=p<0.05 vs. Rest

Figure 3 illustrates the Poincaré plot behavior for a patient. A represents the initial rest period; B represents the ARM period, and C represents recovery following ARM.

An increase in SD2 (P=0.06) and a decrease in SD1 were observed during ARM, however, without statistical significance (P>0.05)

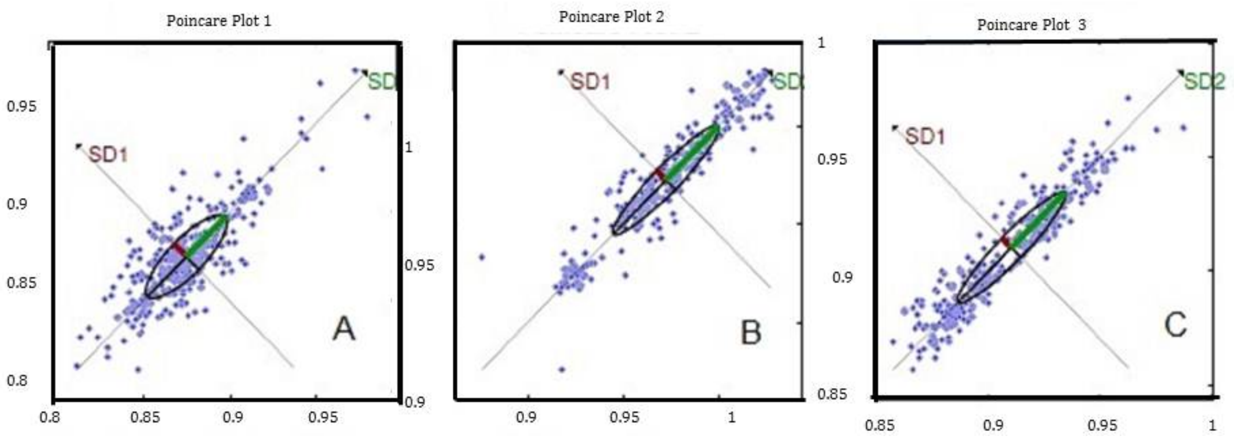

Figure 3. Poincare plots of a patient during initial rest (A), during ARM (B), and recovery (C).

DISCUSSION

The present study has shown that ARM caused modifications in the cardiac autonomic modulation in patients with ARDS, which was more evident in TD linear indexes and non-linear variables of HRV.

With regard to the sample studied, the mean age of the patients was 52.7±23.7 years old. The elevated standard deviation reflects the great age difference between the patients, possibly influencing some HRV indexes, a finding also described by Paschoal et al.[19] in their results as they found that HRV decreases with age.

The ALIEN study by Villar et al.[4] demonstrates a fall in the incidence of ARDS among patients in Europe, which was the first study in the literature on the incidence of ARDS following consolidation of lung-protective ventilation. In fact, this finding can be related to the low number of patients in our study as only four ones were found in a period of five months. The possible explanation for this may be the advanced strategies and optimal care of critically ill patients in the last decades[1, 4].

By analyzing the results of hemodynamic and ventilation variables, one can observe an improvement in compliance, SpO_2, PaO_2/FiO_2 ratio, and a decrease in resistance. Increased compliance[3, 20] and decreased resistance[21] are indicative of an efficient recruitment and adequate adjustment of PEEP, thus preventing excessive hyper-distension or alveolar collapse[22].

Despite the lack of observable significant difference, it was observed a fall in SAP and DAP values during ARM. This finding may be related to a decrease in cardiac output during ARM caused by the compression of ventricles and inferior vena cava due to the high thoracic pressures resulting from the recruitment[12].

It was also observed an improvement in oxygenation of the patient when the SpO_2 was analyzed, with ARM being very efficient in promoting quick oxygenation[20]. The decrease in alveolar collapse has an immediate effect on the oxygenation[7]. Most studies, however, report that when strategies for maintaining the alveolar stability are not taken[6,23], only a transitory improvement of the oxygenation is achieved[24]. In fact, as observed in the present study, SpO_2 had a gradual decrease during recovery following ARM.

With regard to the PaO_2/FiO_2 ratio, it was possible to observe an improvement following ARM. Similarly, it was noted an increase in PaO_2 despite not being statistically significant. The lack of consensus in the literature regarding the improvement of the PaO_2/FiO_2 ratio makes it difficult to evaluate and compare the effectiveness of ARM [7].

In the same way, the improvement of PaO_2 can be interpreted depending on the age, with older individuals being more hypoxemic than the younger ones[25] although lower oxygenations are tolerated by patients with ARDS[20].

It is very important to emphasize that FiO_2 of the patients was not changed in any of the experimental periods of ARM. Based on this, one can relate hemodynamic and ventilation responses only to the effects of the pressures generated by ARM. The great majority of the studies on ARM and its responses are conducted with FiO_2 set to 1, which may directly influence the gas exchanges. In addition, the use of high values of FiO_2 can produce absorption atelectasis in a short period of time[26].

No significant changes were found in HR during our study. In the study conducted by Nielsen et al[12], short-duration ARM (10-20 seconds) was performed immediately after a cardiac surgery, promoting falls in HR values although the previous use of beta-blockers might have influenced the results. However, there is no study evaluating AMR in terms of cardiac analysis and few ones assess its hemodynamic effects[12, 13, 27].

By analysing the HRV, we were able to evaluate the subtle autonomic cardiac alterations promoted by ARM. In fact, this is the first study assessing the effects of ARM on HRV in patients with ARDS on mechanical ventilation.

The results found in the time domain (TD) using indexes RMSSD and SDNN as well as in the frequency domain using LF and HF bands and HF/LF ration showed no statistically significant differences. However, it was observed a tendency of decrease in RMSSD and increase in SDNN during ARM, suggesting a decrease in parasympathetic activity[28].

Additionally, Borghi-Silva et al[29] studied the effect of non-invasive ventilation (NIV) on HRV in patients with chronic obstructive pulmonary disease (COPD) and they also observed a decrease in parasympathetic activity influenced by acute application of intrapulmonary pressures.

The advance in the research on HRV has shown that the statistical analyses of the linear biological signs do not directly characterize its complexity, irregularity or predictability. Methods based on non-linear dynamics and on chaos theory can reveal subtle abnormalities in the cardiovascular regulating mechanisms, whereas the traditional linear methods cannot detect them[30].

In the present study, it was observed a significant increase in the index DFAα1, considered the best predictive index for adverse heart events as the decrease in DFAα1 values has been attributed to a higher incidence of ventricular tachyarrhythmia and death by arrhythmia[31].

Although no statistical difference was observed in the values of SD1, SD2 and DFAα2, it was possible to notice a clear alteration in them during ARM, with a tendency of decrease in SD1 and increase in both SD2 and DFAα2. According to these results, one can infer that there is a tendency of decrease in the parasympathetic activity during ARM. In fact, this was demonstrated by the decrease in SD1 and increase in SD2, DFAα2, and DFAα1, thus leading to an actual increase in total variability. However, DFAα1 significantly increased during ARM, showing to be a powerful strategy to improve the complexity of HRV. The increase in DFA indexes may be associated with a lower likelihood of cardiac events and mortality. Ksela et al.[32] showed that the decline of non-linear indexes (DFA) promotes higher susceptibility to the development of cardiac arrhythmias. In this context, it was shown that ARM that increases the oxygen saturation, which protects against the arrhythmogenic effects in ARDS patients.

Some studies found a reduction in the cardiac output during ARM in patients under different conditions[5,12,13,21-24]. Some authors suggest that the decrease in cardiac output is influenced by the reflexive sympathetic activity, which is opposed to the tendency found in our study. However, Campagna and Carter[33] state that distention of lung tissue can activate a reflexive vagal response.

Interdependence between respiratory and cardiovascular systems is established during mechanical ventilation, with the mechanical effects on the latter and autonomic activity seeming to be more evident. However, the lack of related studies impedes such effects from being consistently demonstrated[34].

Among the limitations of the present study, we can cite the small number of patients in our sample. Our sample was limited to changes in the main outcomes observed in the literature (RMSSD and SDNN). However, we found that DFAα1 index was sensitive to changes due to ARM. In this context, the generalization of our findings may be restricted secondarily to the limited characteristics of the patient recruitment. In view of the seasonable characteristic of ARDS, the worldwide fall of its incidence, and the trauma profile involving the adult intensive care therapy unit of the Federal University of Uberlândia, there was a difficulty in finding patients meeting the inclusion criteria for our study. Another limitation was the great difference in the age of the patients, which had been already mentioned in the Discussion section. This fact may have influenced the cardiovascular responses in relation to ARM.

All patients participating in the study were sedated, and it was not possible to know the influence of drug treatment and its discontinuation on HRV. Nevertheless, this is the reality in which the patients were studied as ARM can only be done under sedation. Moreover, a study using dogs sedated with propophol and sufentanil showed no alteration in HRV[34].

In conclusion, we showed that heart rate variability is changed in response to ARM. We demonstrated that non-linear dynamics of heart rate improved when ARM was applied. In addition, we showed that there is a tendency of increase in total variability during ARM, with no increase in the risk of adverse cardiac events. Therefore, further studies are needed to confirm that HRV can be used for obtaining parameters to stratify this population in terms of cardiovascular risk and to evaluate different interventions for these patients.

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