Turk J Intensive Care
DOI: 10.4274/tybd.galenos.2022.95914

ORIGINAL RESEARCH / *ÖZGÜN ARAŞTIRMA*

Analysis of Heart Rate Variability in Patients Undergoing Mechanical Ventilation

Mekanik Ventilasyon Uygulanan Hastalardaki Kalp Hızı Değişkenliğinin İncelenmesi

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Received/Geliş Tarihi : 10.03.2022
Accepted/Kabul Tarihi : 14.06.2022

ÖZ *Objective:* In this study, the purpose was to determine the changes in the activity of the autonomic nervous system by analyzing the parameters of heart rate variability among patients who underwent invasive mechanical ventilation.

Materials and Methods: A total of 83 patients who had been followed up in the intensive care unit for at least 24 h, without a diagnosis of any known heart disease or arrhythmia, and aged over 18 years were included in the study. Mechanically ventilated patients were included in Group M (n=41) and others in Group K (n=42). The electrocardiography (ECGs) of the patients was recorded for 24 h through a Holter device, which records ambulatory ECG with 3 channels.

Results: There was no significant difference between the groups regarding the heart rate variability parameters, atrial arrhythmia numbers, heart rates, RR times, as well as intervals of QT and QTc. It was found that the number of ventricular arrhythmias was significantly higher in the mechanically ventilated group compared to the non-mechanically ventilated group (p=0.0083).

Conclusion: In conclusion, based on the results of this study, we believe that invasive mechanical ventilation did not lead to changes in the heart rate variability parameters of the patients who were hemodynamically stable without any cardiac disease.

Keywords: Ventilation, respiration, intensive care unit, heart rate, electrocardiography

ABSTRACT *Amaç:* Bu çalışmada, invaziv mekanik ventilasyon uygulanan hastalarda kalp hızı değişkenliği parametrelerini analiz ederek otonom sinir sistemi aktivitesindeki değişiklikleri belirlemeyi amaçladık.

Gereç ve Yöntem: Bilinen herhangi bir kalp hastalığı veya aritmi tanısı olmayan, en az 24 saat yoğun bakımda izlenmiş olan 18 yaş üstü toplam 83 hasta çalışmaya dahil edildi. Mekanik ventilasyon uygulanan hastalar Grup M'ye (n=41), uygulanmayanlar Grup K'ye (n=42) dahil edildi. Hastaların elektrokardiyografileri (EKG), 3 kanallı EKG kaydeden Holter cihazı ile 24 saat boyunca kaydedildi.

Bulgular: Kalp hızı değişkenlik parametreleri, atriyal aritmi sayıları, kalp hızları, RR süreleri, QT ve QTc aralıkları açısından gruplar arasında anlamlı fark yoktu. Ventriküler aritmi sayısının mekanik ventilasyon uygulanan grupta mekanik ventilasyon uygulanmayan gruba göre anlamlı derecede yüksek olduğu saptandı (p=0,0083).

Sonuç: Çalışmamızın sonuçlarına dayanarak, herhangi bir kalp hastalığı olmayan hemodinamik olarak stabil olan hastalarda invaziv mekanik ventilasyonun kalp hızı değişkenlik parametrelerinde değişikliğe yol açmadığına inanıyoruz.

Anahtar Kelimeler: Ventilasyon, solunum, yoğun bakım, kalp hızı, elektrokardiyografi

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Presented in: The summary of this study was orally presented at the Balkan States Anesthesia Days-II Congress (Tirana, Albenia, May 2015).

Introduction

Mechanical ventilation may cause changes in cardiac parameters such as heart rate, preload, contraction, and afterload by affecting parameters such as lung volume, intrathoracic pressure, and autonomic nervous system tone (1). Changes in lung volume during invasive mechanical ventilation can cause sinus arrhythmia, decreased heart rate, and reflex arterial vasodilation (2). These changes might not be determined through standard monitoring techniques unless they cause severe arrhythmias.

Heart rate variability (HRV) consists of very low frequency (VLF), low frequency (LF), high frequency (HF), and total power (TP) components. HRV analysis is a simple and non-invasive technique, which is utilized to assess autonomic function and sympathovagal balance at the sino-atrial level (3). In this regard, an increase in sympathetic activity or a decrease in vagal activity on cardiac functions can be assessed through HRV. Values of the normalized high frequency (HFn), which is one of the autonomic nervous system parameters, account for parasympathetic activity, while normalized low frequency (LFn) are considered to be the indicators of sympathetic activity (4). The decrease in HRV is considered to be correlated with increased sympathetic modulation and has been associated with an increased risk of cardiovascular disease, arrhythmia, and sudden cardiac death (3,4). Moreover, decreased HRV and autonomic changes are correlated with an increase in malignant ventricular arrhythmias (3). Thanks to Holter monitoring, electrocardiography (ECG) parameters can be recorded for 24 hours, and these records can be analyzed by a computer. In our study, we aimed to investigate comparatively the parameters of HRV and activities of the autonomic nervous system among intensive care patients who had undergone invasive mechanical ventilation and those who had not through continuous Holter monitoring technique.

Materials and Methods

After obtaining ethics committee approval (Ankara Training and Research Hospital, Ethics Committee 520/4325), patients who met the study criteria in Ankara Training and Research Hospital tertiary intensive care unit (ICU) within two years were included in the study. Written consent was taken to participate in the study of the patient's relatives. The study was performed according to the Declaration of Helsinki. Patients aged over 18 who had undergone invasive mechanical ventilation and those who had not were divided into two groups, each of which consisting of 50 patients. The demographic characteristics of the patients, their pre-admission characteristics to the ICU, and the duration of intensive care hospitalization until they were included in the study were recorded. Patients aged under 18, pregnant, patients who stayed in the ICU for less than 24 hours, and those who had been receiving medications that affect the interval of corrected QT (QTc) (antiarrhythmic drugs, beta-blockers, tricyclic antidepressants, phenothiazines), who had arrhythmias, bundle branch blocks or preexcitation, as well as those who had not normal sinus rhythm, who had a medical history of myocardial infarction, congestive heart failure, and the patients with the diagnosis of secondary or idiopathic long QT syndrome were excluded from the study. In addition, patients who had been receiving sedation and inotropic support were excluded from the study. Intubated patients who underwent mechanical ventilation for at least 24 hours were included in the study.

In the study, the mechanical ventilator mode had been set as Pressure-Synchronized Intermittent Mandatory Ventilation, and parameters of the patients who underwent mechanical ventilation throughout the follow-up period had been set to generate a frequency of 14/min, positive end-expiratory pressure (PEEP): 5 cm H_2O and tidal volume of 6-8 mL/kg. The same brand and model of mechanical ventilators were used in all patients (Galileo Classic, Hamilton Medical AG, Switzerland). To exclude the changes, which occurred during the weaning period, patients who did not undergo mechanical ventilation in Group K were selected from those who had never been intubated since admission to the ICU. The ECGs of the patients in both groups were recorded for 24 hours with a Holter device (NorthEast's DR200/HE, NorthEast Monitoring, Inc., USA.), which recorded a 3-channel ambulatory ECG and transferred to the Holter analysis system (NorthEast's Holter LX Analysis Software New Version 5.4). For the analysis of the Holter records, the minimal, maximal and mean heart rates of the patients, as well as the heart rate variability parameters, HFn and LFn measurements, the LF/HF ratios, and the measurements of the RR durations were assessed. Corrected-QT intervals were calculated by using Bazett's formula ($QTc=QT\sqrt{RR}$). Global sympathetic index (GSI) calculations were performed using the formula of LF + VLF/HF (5). The QRS complexes were automatically classified as normal sinus rhythm, atrial or ventricular premature beats, and manually verified. Normal intervals of RR (N-N intervals) were measured based on the normal sinus beats. Analysis of the HRV was conducted based on the records. Values of VLF (VLF, 0.01-0.04 Hz), LF (LF, 0.04-0.15 Hz), HF (HF, 0.15-0.4 Hz), and TP (total power) (0.01-0.4 Hz) were obtained from the sum of the areas within their range through performing power spectrum density analysis. "Normalized HF" and "LF" components, which are expressions of these components in percentage, were calculated by proportioning these components to the total power.

The sample size was calculated for the student t-test, which was used to test the primary hypothesis of our study. As a result of the sample size analysis performed using Cohen's effect size value of 0.58 (determined by expert opinion as a result of the pilot study) with a minimum of 80% power (1-β=0.20) and β=0.05 error (95% confidence interval), it was found that a minimum of 74 patients (37 patients in both groups) should be included in the study to reveal significant differences between the HRV parameters of two independent research groups. However, it was decided to include 80 patients (an additional 10%) in the study, taking into account the patients who could leave the study during the research process. The G*power software (Version 3.1.9.7, Heinrich-Heine-Universität Düsseldorf, Düsseldorf, Germany) was used for sample size estimation.

Holter recordings were assessed by a cardiologist who did not know which group the patients belonged to. Patients who had normal sinus beats as >85% at the time of analysis were included and recordings with intense artifacts were excluded from the study. As a result, the study was performed with 42 patients from the group, which had not undergone mechanical ventilation, and 41 patients from the intubated group, which had undergone mechanical ventilation.

Statistical Analysis

To determine the normality of the distribution, the Kolmogorov-Smirnov test was used for the statistical analysis of all quantitative data. T-test was used for intergroup comparison of quantitative data, which conformed to the normal distribution, and Mann-Whitney U test was used for comparing quantitative data, which did not conform to normal distribution between the groups. Results were presented as the mean +/- standard deviation. The chi-square test was used to compare qualitative data between groups. Results were presented as percentages and were considered statistically significant at p≤0.05.

Results

When the demographic data were examined, it was determined that there was no statistically significant difference between the groups, which had undergone mechanical ventilation and those that had not (Table 1).

It was found that there was no significant difference between the groups concerning the HRV variables including the LF, HF, HFn, LFn, LF/HF ratios, VLF, TP, and GSI values (Table 2).

Table 1. Demographic data

Group	Group M	Group K
Age	58.14±19.94	57.73±15.96
Number of patients	41	42
Gender M/F	27/14	23/19
Reason of admission to intensive care		
Pneumonia	14	7
GIS surgery	8	4
Trauma	6	6
Other	7	14

Group M: Mechanical ventilated group, Group K: non-mechanical ventilated group

Table 2. Mean and standard deviation values of heart rate variability components

HRV	Group M	Group K	p-value
Total Power (msn^2) Mean ± SD	3.77±2.34	3.47±2.06	0.421
VLF[a](msn^2) Mean ± SD	4.23±2.60	3.25±2.03	0.0974
LF[b](msn^2) Mean ± SD	4.72±2.69	3.95±2.29	0.2071
HF[c](msn^2) Mean ± SD	3.65±2.40	3.64±2.69	0.6068
LF/HF ratio	1.91±1.57	2.10±1.99	0.9274
LF nu[d]	53.98±25.79	63.57±29.06	0.0699
HF nu[e]	46.51±25.93	36.87±28.95	0.0735
Global sympathetic index	3.56±2.44	3.27±3.16	0.2088

[a]Very low frequency, [b]low frequency, [c]high frequency, [d]normalized low frequency, [e]normalized high frequency, SD: standard deviation, LF: low frequency, HF: high frequency, HRV: heart rate variability

The normalized HF and LF percentages of both groups are shown in Figure 1.

It was determined that there was no statistically significant difference between the atrial arrhythmia numbers, maximal, minimal, and mean values of the heart rates, durations of RR, as well as durations of QT and QTc. Durations of RR, QT, and QTc of both groups are shown in Figure 2.

When the number of ventricular arrhythmias was examined between the two groups, it was found to be higher in the group that had undergone mechanical ventilation compared to the group, which had no mechanical ventilation (Table 3). It was determined that the mean number of ventricular arrhythmias was 59.537±107.460 in the mechanically ventilated group, while it was 54.952±185 in the group that had not undergone mechanical ventilation (p=0.0083).

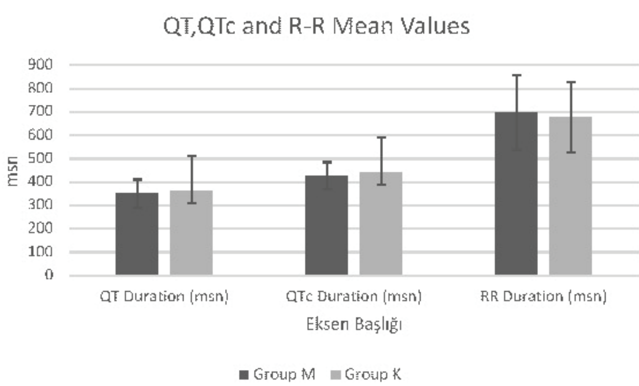

Figure 1. Mean values of HFn and LFn, and standard deviation values in the group
HFn: Normalized high frequency, LFn: Normalized low frequency

Discussion

In this study, which investigated the effect of mechanical ventilation on HRV between two demographically similar groups, no significant differences were found between the two groups. There was no significant difference between the groups concerning the HRV variables including the LF, HF, HFn, LFn, LF/HF ratios, VLF, TP, and GSI values. Also, there was no statistically significant difference between the atrial arrhythmia numbers, maximal, minimal, and mean values of the heart rates, durations of RR, as well as durations of QT and QTc. Different from these results, the number of ventricular arrhythmias was found to be higher in the group that had undergone mechanical ventilation compared to the group which had no mechanical ventilation. It was determined that the mean number of ventricular arrhythmias was 59.537±107.460 in the mechanically ventilated group,

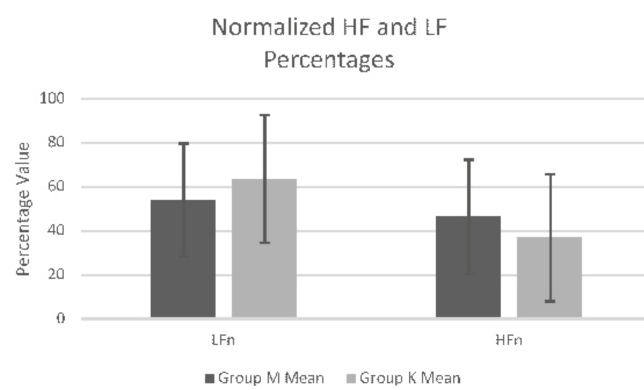

Figure 2. Mean ± SD values for QT, QTc, and RR durations of the groups
SD: Standard deviation, HFn: normalized high frequency, LFn: normalized low frequency

Table 3. Mean values of heart rate, QT durations, and arrhythmia numbers for the groups

	Mechanical ventilation group	Non-mechanical ventilation group	p-value
Maximum heart rate	131.70±31.77	138.97±27.31	0.1282
Minimum heart rate	61.09±15.52	60.57±18.46	0.6099
Average heart rate	89.90±18.51	86.23±18.64	0.3718
QT duration (msn)	351.22±59.37	360.95±51.02	0.4252
QTc duration (msn)	425.70±58.67	438.78±48.94	0.2730
RR duration (sn)	0.696±0.16	0.677±0.15	0.4661
Ventricular arrhythmia (VES)	59.53±107.46	54.95±185.14	0.0083
Atrial arrhythmia (AES)	34.58±90.56	40.78±120.84	0.1282
Number of supraventricular tachycardia attacks	1.17±3.54	0.35±1.26	0.3249
Number of ventricular tachycardia attacks	0.56±1.76	0.14±0.92	0.1124

while it was 54.952±185 in the group that had not undergone mechanical ventilation (p=0.0083).

The HF component of HRV primarily indicates parasympathetic modulation (4,6-9). Although the LF component is thought to demonstrate both sympathetic and parasympathetic activity, recent studies are showing that the LF component is not a measure of cardiac sympathetic tone (4,6,8,10,11). Moreover, the LF/HF ratio is regarded to demonstrate the sympathetic-parasympathetic balance (5). However, due to the complex and uncertain situation in the LF component, the accuracy of the thought that the LF/HF ratio indicates sympathovagal balance is controversial (12). No significant difference was determined in this study regarding the HRV variability and GSI components among patients who underwent ventilation and control groups. In this respect, our study contradicts the results of Macefield (13,14). who revealed that high intrathoracic pressure caused an increased sympathetic response in the muscles, and the results of Garet et al. (15). which indicated that positive pressure ventilation causes a decrease in the LF band and an increase in the HF band.

Increases in respiratory frequency and tidal volume may affect both high and low-frequency spectral components (16). In a study carried out by Thungton et al. (17) in a rat model with acute lung injury, biological variable ventilation (BVV) and continuous mechanical ventilation (CMV) modes were compared and no HRV variability was detected. In this study, when the RR intervals were examined, no change was observed, but when the periodic repetitions (periodicity) of the intervals were examined, it was determined that there were more RR interval changes in BVV mode than in the CMV mode. Variable lung volumes in BVV mode have been noted to lead to this result. It was found in the study that there was no statistically significant difference when the two groups were compared in this regard by making RR measurements, which is the indicator of parasympathetic tone. Based on the results of Thungton et al.'s (17) study, it was thought that the reason why HRV changes were not observed in our study may be due to the low volume changes in the selected mode and settings. The results of our research are in line with the study of Elinoff et al. (18), which demonstrated that there are no major ECG changes in mechanically ventilated patients.

In hemodynamically unstable critically ill patients in whom heart rate can change rapidly, erroneous conclusions about HRV are possible if the heart rate is not taken into account (16). The results of studies on this subject show that changes in HRV and autonomic nervous system during mechanical ventilation are dependent on the current cardiovascular status (19). According to the general opinion revealed in the results of studies on this subject, HRV changes are not expected in hemodynamically stable patients, like the patients in our study.

There are reports in the literature stating that there may be changes in HRV and autonomic nervous system function depending on the level of sedation (20,21). According to the results of one of them, deep sedation, especially with benzodiazepines, may be associated with suppression of parasympathetic function in patients receiving mechanical ventilation (21). Similarly, Kasaoka et al. (22), suggested that mechanical ventilation combined with sedation could reduce autonomic nervous system function in intensive care patients. To exclude HRV changes due to sedation, patients were not sedated in our study.

It was found in the study of Güntzel Chiappa et al. (23), which compared the acute effects of spontaneous breathing with T-piece and ventilation with pressure support ventilation in intensive care patients, that there was an increase in LF values among patients who spontaneously breathing with a T-piece, whereas there was a decrease in HF values, and hence an increased LF/HF ratio (23). In a different study, Crescimanno et al. (24) compared the same ventilator parameters and different PEEP values, and higher sympathetic activity was observed in the examination of HRV in patients who underwent PEEP. Based on this result, it was thought that different ventilator settings may increase sympathetic activity. Besides different ventilator settings, the weaning process also changes the normal ventilation mechanics. Studies on this subject have shown that HRV changes that occur in weaning failure are a decrease in HRV and vagal withdrawal in autonomic nervous system activity (25). A recent study examined the relationship between HRV change and weaning outcomes in critically ill patients. The results of this study showed that HRV changes can be used as a guide for successful extubation (26). To exclude these changes, patients in the weaning period were not included in our study. It was determined in our study that there was no significant difference between the two groups regarding the HRV variables.

GSI is one of the sympathovagal balance indicators and has a positive correlation with the increase in sympathetic tone, as in the LF/HF ratio (5). The GSI was calculated in our study as well, and there was no difference in GSI values because there was no difference between the two groups in HRV values.

The prolongation of the QT (QTc) interval, which is corrected based on the heart rate, is considered to be pathological (27). Arai et al. (28) investigated the correlation between the QT interval and HRV among youngsters, and they found out that the QTc interval was negatively correlated with parasympathetic activity. In our study, there was no statistically significant difference between the two groups, regarding the QTc intervals.

The impacts of the autonomic nervous system on ventricular arrhythmias have been examined both in various heart diseases and in individuals without structural heart disease. Ventricular tachycardias, which occur typically during sympathetic tone increase or isoproterenol infusion, are considered to be the result of the triggered activity (29). In the study by Shen et al. (30), which investigates the relationship between the autonomic nervous system and arrhythmias, it was revealed that the sympathetic activity was proarrhythmic and the parasympathetic effect was antiarrhythmic. In our study, the number of ventricular arrhythmias (VES) was determined to be significantly higher (p=0.0083) in the mechanically ventilated group; the publications, demonstrate that ventricular arrhythmias are associated with sympathetic activity (29,30), and the publications, which put forwards that HRV has deficiencies in showing the sympathetic effect (31), made us think that sympathetic activity could not be monitored thoroughly in our study.

Our failure to detect HRV changes, which are linked to mechanical ventilation in our study, might be resulting from various reasons and limitations. First, positive pressure ventilation might not generate consistent HRV changes in individuals who are hemodynamically stable and have no active cardiac disease. The second likelihood is that the difference between the tidal volume of the patients and the tidal volume, which was applied in our study, may not be great enough to reveal the ECG and HRV changes, which were specified previously, that occur with hyperinflation. When compared with the studies consisting of different patient groups that we examined due to the design of the study, it was found that our patient group was more stable in terms of hemodynamically than the other groups; and there was no active cardiac disease in our group. Even though including patients who had no active cardiac disease seems to limit the study, it strengthened our study since it enabled us to determine the impact of mechanical ventilation by isolating other variables that might be encountered. Another limiting factor was that we used only a single ventilator parameter. Various tidal volumes and PEEP applications could induce ECG and HRV changes that we could not detect. Given that the ventilator settings, which we preferred, are often used clinically, we consider that these settings do not have a major impact, but we cannot state the same for other ventilator settings.

Consequently, we believe that there is no significant change in the activity of the autonomic nervous system and HRV variables during invasive mechanical ventilation in ICU patients who have not any active cardiac disease and who are hemodynamically stable.

Ethics

Ethics Committee Approval: After obtaining ethics committee approval (Ankara Training and Research Hospital, Ethics Committee 520/4325), patients who met the study criteria in Ankara Training and Research Hospital tertiary intensive care unit (ICU) within two years were included in the study.

Informed Consent: Written consent was taken to participate in the study of the patient's relatives.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: R.Y., Ç.K., N.N.Ö., H.B., Concept: R.Y., Ç.K., S.N.M., H.B., A.Ö., Design: R.Y., Ç.K., H.B., A.Ö., M.K., Data Collection or Processing: R.Y., N.N.Ö., A.Ö., M.K., Analysis or Interpretation: R.Y., Ç.K., N.N.Ö., S.N.M., H.B., A.Ö., A.K., M.K., Literature Search: R.Y., Ç.K., N.N.Ö., A.K., M.K., Writing: R.Y., Ç.K., N.N.Ö., S.N.M., H.B., A.Ö., A.K., M.K.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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