

# The prolonged effect of pneumoperitoneum on cardiac autonomic functions during laparoscopic surgery; are we aware?

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**Abstract. – BACKGROUND:** The gynecological laparoscopic surgery requires pneumoperitoneum (PP) with CO<sub>2</sub> gas insufflation. CO<sub>2</sub> PP may influence cardiac autonomic function (CAF). This study was conducted to assess its significance and the prolonged effects of CO<sub>2</sub> PP on the activity of the cardiac autonomic function 24 hours after the operation by heart rate turbulence (HRT) and heart rate variability (HRV), first time in the literature.

**PATIENTS AND METHODS:** Fifty patients scheduled for elective gynecologic laparoscopy were evaluated. The patients had no preexisting lung or heart disease or pathologic lung function. Conventional general anesthesia with midazolam, propofol, fentanyl, rocuronium, and sevoflurane was administered. ECG recordings were carried out between before 4 h from surgery and the beginning of anesthesia (T1), induction of PP and CO<sub>2</sub> evacuation (T2) and a 24-h period postoperatively (T3). The Holter recordings of all patients were analyzed by HRT and HRV.

**RESULTS:** There were significant reductions in in HRV and HRT parameters peri-op period compared to the pre-op values ( $p < 0.05$ ). In the first 3 h of post-op period, were calculated all HRT and some HRV (SDNN, LF) parameters were also found to be significantly reduced than the values of pre-op period ( $p < 0.05$ ).

**CONCLUSIONS:** This study described adverse effects of CO<sub>2</sub> PP on cardiac autonomic regulation in the early postoperative period according to the long-term HRV and HRT frequency analysis, for the first time in the literature. The early postoperative monitorization may supply efficacious information for arrhythmic complications.

#### Key Words:

Pneumoperitoneum, Laparoscopy, Cardiac autonomic function, Heart rate turbulence, Heart rate variability.

## Introduction

The gynecological laparoscopic surgery has been progressively and successfully introduced into woman practice because, safe invasive surgery is associated with a low morbidity, less postoperative pain, and better cosmetics. However, numerous manuscripts showed that high intraperitoneal pressure due to CO<sub>2</sub> pneumoperitoneum (PP) affects cardiopulmonary function significantly<sup>1,2</sup>. The reduced venous return, increased systemic vascular resistance, decreased cardiac output (CO), increased heart rate, and mean arterial blood pressure are the main hemodynamic changes associated with CO<sub>2</sub> PP<sup>3-5</sup>. In addition, CO<sub>2</sub> absorption causes respiratory and hemodynamic changes during the operation<sup>6,7</sup>. Combined with all these adverse cardiogenic effects of CO<sub>2</sub> PP, previous researches showed that there is a compensatory increase in baroreceptor activity and serious alteration to the cardiac autonomic function (CAF)<sup>8,9</sup>. The results of all these previous studies showed that the appearance of cardiac arrhythmia is increased with CO<sub>2</sub> PP during operation. However, best of our knowledge to evaluate the prolonged effects of CO<sub>2</sub> PP on the activity of the CAF in the postoperative period has not been reported in the literature previously.

In addition, the CAF in the patients with CO<sub>2</sub> PP can be evaluated by using different parameters, such as heart rate variability (HRV), signal-averaged P-wave duration and QT interval dispersion<sup>10-12</sup>. However, in our best knowledge, the technique using Heart rate turbulence (HRT) during PP has not been published previously. HRT is a non-invasive method for detecting impaired CAF by 24 h electrocardiogram (ECG) holter.

This method is based on the physiological sinus node response to a premature ventricular beat<sup>13</sup>.

Therefore, the primary aim of the present study is to investigate the prolonged effects of CO<sub>2</sub> PP on the activity of the CAF in early post-operative period. The secondary aim of our study is to evaluate possible effects of PP by HRT and HRV.

## Patients and Methods

### *Study Design and Patients*

After obtaining approval from our Institutional Ethics Committee and informed consent, we studied patients undergoing an elective gynecologic surgery, recruited for a prospective study. We included 50 patients with American Society of Anesthesiologists (ASA) physical status I or II; age over 18 years and body mass index (BMI) 30 kg.m<sup>2</sup> or less, undergoing elective laparoscopic intervention who successfully completed the surgery with no immediate apparent surgical complications. Specifically, the patients with known significant systemic or cardiopulmonary disease such as coronary artery disease, chronic obstructive lung disease, congestive heart failure, moderate or severe degrees of any valvular regurgitation or co-existent valvular stenosis, hypertension, hyperlipidemia, diabetes mellitus, obstructive sleep apnea and being on any medical therapy at the time of clinical evaluation were not included in the analysis. Those patients with pacemaker rhythm, atrial fibrillation (AF), left bundle branch block, right bundle branch block, any sign of ischemia on the initial ECG and echocardiographic evidence of LV hypertrophy, systolic dysfunction, wall motion abnormalities, pericardial disease or who have serious hemodynamic instability because of large fluid shifts, and/or blood loss were also excluded from the study. None of the patients was receiving beta-adrenergic-blocking drugs, calcium-channel blockers, digitalis, diuretics, antihypertensive, or vasodilators preoperatively.

All patients were premedicated with i.v. midazolam 0.02 mg.kg<sup>-1</sup> Following routine monitoring including ECG, blood pressure, oxygen saturation (SatO<sub>2</sub>), end-Tidal CO<sub>2</sub>, and temperature, induction was initiated. Anesthesia was started following induction using propofol 2 mg.kg<sup>-1</sup>, fentanyl 1 mcg.kg<sup>-1</sup> and 0.5 mg.kg<sup>-1</sup> rocuronium bromide. Anesthesia was maintained with a standard general anesthesia protocol using 2% sevoflurane

in a mixture of 50% air and 50% oxygen. Tidal volume was set at 8 mg.kg<sup>-1</sup> initially and then adjusted to achieve an end-Tidal (ETCO<sub>2</sub>) concentration of 35 ± 5 mmHg at a respiratory rate (RR) of 12 breaths per minute. None of the patients received medications aimed to control blood pressure or heart rate (i.e. antihypertensive drugs, beta-blockers) at any time during the study period. Technically, a laparoscopic elective gynecologic surgery was performed as commonly accepted, while maintaining a PP CO<sub>2</sub> pressure of 14 mmHg. Pneumoperitoneum was established by introduction of a Veress needle into the navel, insufflating CO<sub>2</sub> using an Olympus CO<sub>2</sub> insufflator.

### *ECG Recordings, HRV and HRT Analysis*

ECG recordings were carried out between before 4 h from surgery and the beginning of anesthesia (T1), induction of PP and CO<sub>2</sub> evacuation (T2) and a 24-h period postoperatively (T3). Recordings were performed with a GE Marquette SEER system digitizing at 125 samples per second (GE Marquette, Milwaukee, WI, USA). Both time- and frequency-domain analyses were performed for four hours before, 24 hours after and during operation. For the time-domain, the Standard Deviation of all Normal-to Normal intervals (SDNN), the root mean square of the difference between successive NN intervals (RMSSD) and the proportion of adjacent normal NN intervals differing by > 50 ms (pNN50) were calculated. SDNN reflects both the sympathetic and parasympathetic function as an estimate of overall heart rate variability (HRV). RMSSD is an estimate of short-term components of HRV. PNN50 is a parameter indicating increased relaxation by increasing values. For the frequency-domain analysis, power spectral analysis based on the fast Fourier transformation algorithm was used. Two components of power spectrum were computed following bandwidths: high frequency (HF) (0.15-0.4 Hz) and low frequency (LF) (0.04-0.15 Hz). The LF/HF ratio was also calculated. LF is known to relate to both sympathetic and parasympathetic modulation [20]. HF band (0.15-0.40 Hz) is affected almost exclusively by parasympathetic afferents. The LF/HF ratio is used as a metric of sympathetic-parasympathetic balance. A non-significant reduction of LF/HF ratio is apparently associated with a decrease in sympathetic tone<sup>14</sup>.

The Holter recordings of all patients were also analyzed to obtain the HRT parameters of turbulence onset (TO) and turbulence slope (TS). QRS

detection, morphology classification (normal, aberrant, premature aberrant) and measurement of the RR interval were automatically performed by the system. All Holter files were reviewed and manually corrected. HRT analysis was performed on sequences of sinus RR intervals after VPB (Ventricular Premature Beat). The evaluated sinus rhythm immediately before and after the VPB was free from any arrhythmia or other artifacts. The HRT after a VPB comprises two parameters: TO, which represents the initial acceleration (shortening of R-R intervals); and TS, which represents the subsequent deceleration (prolongation of R-R intervals)<sup>15</sup>. In mathematical terms, TO (%) (normal < 0) is the difference between the sum of the first two R-R intervals after the compensatory pause following a VPB and the sum of the last two R-R intervals preceding the VPB, divided by the sum of the last two R-R intervals preceding the VPB. The TS (normal > 2.5 ms/R-R interval number) was accepted as the steepest slope of a regression line over any sequence of five consecutive RR intervals. The average of HRT values, measured for all convenient VPBs, was accepted as the final HRT value to characterize the patient<sup>13</sup>.

### Statistical Analysis

A sample size of 50 patients per group was required to detect anticipated effect size 0.1 with 95% power at a significance level of < 0.05. Calculations were done by using SPSS version 15.0 software (SPSS Inc., Chicago, IL, USA). The data are presented as a means and standard deviation, as median and range for quantitative parameters, and as frequency and percentage for qualitative parameters. We used the paired *t*-test or alternatively the Wilcoxon signed rank test to evaluate the significance in the different changes in HRV and HRT parameters, between the different stages of the operation. We used a 95% confidence interval to evaluate the proportion of patients that expressed a considerable difference in HRV and HRT parameters between two successive operational stages. The Wilcoxon signed rank test was used to verify the type of change, meaning an increased or decreased HRT and HRV parameters. Pearson's and Spearman's correlation coefficients were used to test the relationship between the all HRT-HRV values and operation parameters. A statistical significance was established when the *p* value was equal to or less than 0.05.

## Results

Demographic characteristics of study participants are shown in Table I. The age range of the patients was 24 to 36 years (mean = 27 years). The BMI range was 21.7 to 27.3 kg.m<sup>-2</sup> (mean = 24 kg.m<sup>-2</sup>). The operative time was 35 to 75 minutes (mean 47 minutes). Operative time varied depending on the types of the operation. There were no episodes of cardiac arrhythmias during surgery in the study population and all patients survived to discharge. Heart rate (HR) significantly increased in T2 more than T1 and T3 period; also mean arterial pressure (MAP) was significantly higher in T2 period than other period. (HR T1, 76.9 ± 9.43; T2, 95.2 ± 12.1; T3, 89.4 ± 9.1/min *p* = 0.012; MAP T1, 69.7 ± 1.55; T2, 82.9 ± 3.05; T3, 79.4 ± 2.18 mmHg *p* = 0.033). The end tidal CO<sub>2</sub> (ECO<sub>2</sub> mmHg) had significant change during the first 10 minutes of CO<sub>2</sub> insufflation compared to base line and to evacuation of CO<sub>2</sub> from peritoneum. There was no significant change in SatO<sub>2</sub> at any stage of the operation. The observed changes were not accompanied by any serious clinical signs of cardiovascular deterioration.

We found a high significant differences in HRV in both of the time period and frequency domain indices, compared to T1-T2 values, which was sustained throughout the 24-h post-op period, were just statistically significant in first 3 h (Table II). The LF/HF ratio was significantly increased compared to T1-T2-T3 (*p* < 0.05).

There was a negative correlation between pNN50, SDNN and duration of operation (*r* = 0.657, *r* = 761; *p* = 0.003, *p* = 0.001 respectively). There were significant reductions in all time domain measures of HRV at all-time point's periop period compared to the pre-op values (Table I). Also, there were significant reductions in SDNN and LF at post-op first 3h period com-

**Table I.** Demographic and clinical characteristics of patients.

Age (year)	27 [24-36]
ASA physical status (I/II)	34/16
BMI [kg/m <sup>2</sup> ]	24 [21.7-27.3]
Preoperative ejection fraction (%)	66 [50-73]
Body surface area (m <sup>2</sup> )	1.81 (0.19)
Duration of operation (min)	47 (35-75)
Duration of anesthesia (min)	55 (42-83)

\*Data are given as mean (range), mean (SD) or absolute numbers.

**Table II.** Comparison of HRT and HRV parameters values in different period.

	T1 period (mean±SD)	T2 period (mean±SD)	T3 period (mean±SD)	Postop in first 3h (mean±SD)	p values
HRT onset (%)	-0.26 ± 0.19	0.79 ± 0.16	-0.17 ± 0.53	0.31 ± 0.42	*0.013 **0.041
HRT slope [ms/beat]	4.04 ± 1.61	1.73 ± 1.06	3.01 ± 1.36	1.98 ± 1.12	*0.021 **0.031
SDNN [ms]	171.56 ± 25.43	141.71 ± 71.94	168.53 ± 84.67	152.28 ± 68.31	*0.013 **0.034
RMSDD [ms]	110.14 ± 75.61	101.32 ± 67.52	108.42 ± 72.14	104.85 ± 71.24	*0.044 **0.098
pNN50 (%)	16.51 ± 13.62	12.01 ± 11.31	15.11 ± 11.65	13.65 ± 10.42	*0.041 **0.092
LF	39.41 ± 28.32	71.14 ± 35.16	40.11 ± 33.12	55.13 ± 37.31	*0.012 **0.033
HF	19.81 ± 11.42	39.55 ± 19.34	21.65 ± 13.41	29.81 ± 17.56	*0.001 *0.102
LF/HF	3.31 ± 1.47	2.11 ± 1.52	3.24 ± 1.22	2.68 ± 1.14	*0.003 *0.112

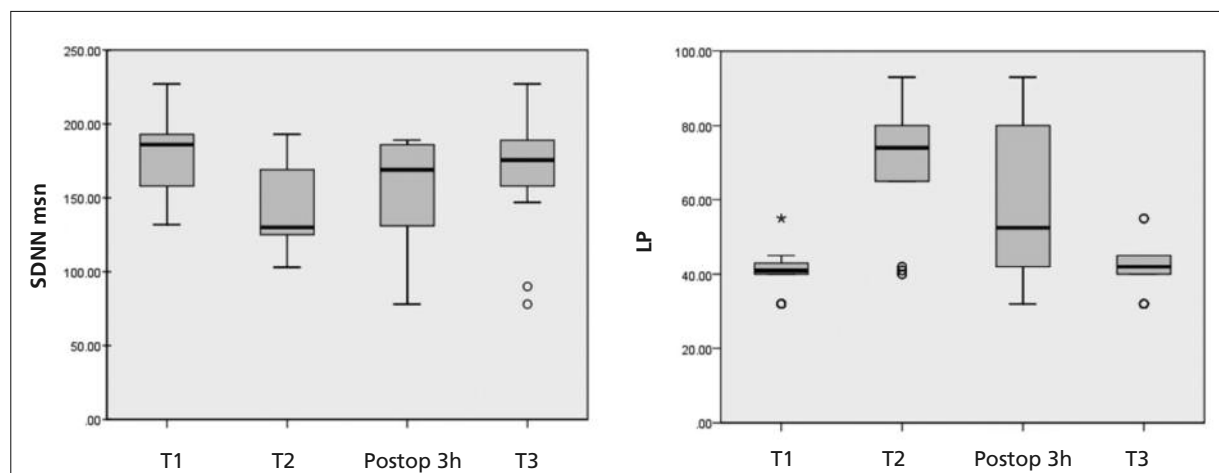
\*p values between T1, T2 and T3; \*\*p values between T1 and postop in first 3h (mean ± SD).

pared to the pre-op values (SDNN post 3h: 152.28 ± 68.31, pre: 171.56 ± 25.43  $p = 0.001$ ; LF post 3h: 55.13 ± 37.31 pre: 39.41 ± 28.32  $p = 0.023$ , Figure 1). These values returned to baseline at the end of post-op 3 h. which demonstrates impaired autonomic regulation in the early postoperative period (SDNN post: 168.53 ± 84.67, SDNN pre: 171.56 ± 25.43  $p = 0.121$ ; LF post: 40.11 ± 33.12 LF pre: 39.41 ± 28.32  $p = 0.213$  respectively).

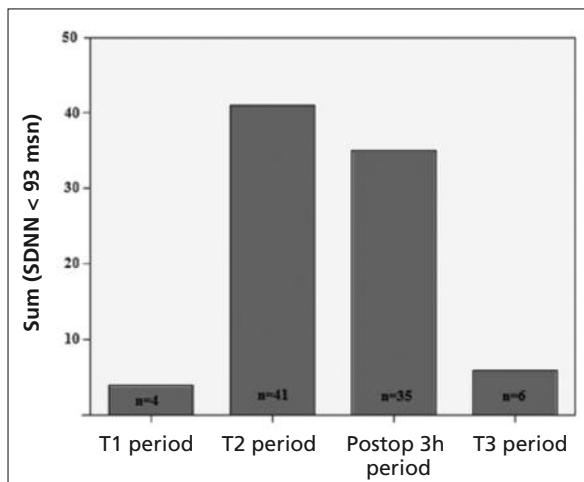
The cut-off point for normal overall HRV in general cardiology patient population was 93 ms for SDNN<sup>16</sup>. The four patients in T1 period, 41 patient in T2 period, 35 patient in first 3 h post-

op period and 6 patients in last 21 h post-op period had abnormal HRV (SDNN < 93 ms,  $p < 0.05$ , Figure 2). There were significant positive correlation between abnormal SDNN number and duration of operation ( $r = 0.654$ ;  $p < 0.001$ ).

When HRT parameters were compared, Total onset was observed significantly higher in T2 period than T1 and T3 period (T1, -0.26 ± 0.19 T2 0.79 ± 0.16, T3 -0.17 ± 0.53;  $p < 0.005$  respectively). Total slope values were also found significantly different between T1, T2 and T3 period (T1, T2 1.73 ± 1.06, T3 3.01 ± 1.36;  $p < 0.005$  respectively). Abnormal Total onset and Total slopes were observed higher in T2 period



**Figure 1.** SDNN and LF values in different period.



**Figure 2.** Comparison of the patients number who had abnormal HRV (SDNN < 93 ms between periods).

than T1 and T3 period ( $p < 0.05$ , Table II). TO and TS values were found to be significantly different than the preoperative baseline when HRT parameters were calculated in the first post-op 3 h period (TO  $-0.26 \pm 0.19$ ,  $0.31 \pm 0.42$ ,  $p = 0.041$ ; TS  $4.04 \pm 1.61$ ,  $1.98 \pm 1.12$ ,  $p = 0.031$  respectively). In addition percent of abnormal TO and TS's were observed higher in first 3 h of post-op period than preoperative baseline values ( $p < 0.05$ ).

## Discussion

We aimed to evaluate the effect of CO<sub>2</sub> PP on CAF in patients with elective gynecologic surgeries during per- and post-operative period in this study. We revealed that CO<sub>2</sub> PP significantly affects the CAF during operation and also the early postoperative time. The cardiac autonomic regulation has a reduction in the early postoperative time and all parameters return to baseline after the first 3 h of postoperative period. To our knowledge, this is the first study to monitor cardiac autonomic function in the first 24 h post-op period. We found a significant deterioration in CAF. This deterioration occurred during CO<sub>2</sub> PP period and continued in the first 3 h of post-op period. Furthermore, this is the first work that evaluates the relationship between CO<sub>2</sub> PP and impaired CAF by using HRT and HRV.

The heart is highly innervated by vagal and sympathetic fibers and is very sensitive to autonomic influences<sup>17</sup>. The autonomic nervous system responds to all changes sensed by barorecep-

tors and chemoreceptors to maintain cardiovascular (CV) homeostasis<sup>18</sup>. The result of the many studies showed that sympathetic-parasympathetic imbalance, due to disturbance in cardiac autonomic function, causes cardiac arrhythmia and can lead to sudden cardiac death in both of the risk group and normal healthy subjects<sup>19-21</sup>. Because of this, impacts on CAF in the patients who underwent surgery with general anesthesia were evaluated by using different methods. Some of these methods are HRV, ST segment analysis, QT interval dispersion, filtered signal-averaged P-wave duration and intermittent sequential pneumatic compression device but among these HRV is the most common<sup>9,12,22,23</sup>. However, best of our knowledge, HRT has not been used in this situation and this is the first study establishing the relationship between CO<sub>2</sub> PP and impaired CAF by HRT. HRT is a non-invasive method for detecting impaired CAF by ECG holter. This evaluation method is based on the physiological sinus node response to PVB<sup>13</sup>. Cardiac autonomic imbalance, manifested by impaired HRT, is a powerful risk factor for sudden cardiac death and malignant cardiac arrhythmias in healthy individuals<sup>13,21</sup>.

Previous investigations showed that HRT parameters were closely correlated with HR<sup>24-26</sup>. This study concluded that HRT parameters (TO and TS) were correlated significantly with almost all heart rate variability parameters. As a result, the combination of HRV and HRT parameters may be valuable and can be used as a simple ways of evaluating cardiac autonomic functions during operative period. A combination like this may increase the positive predictively and provide a more accurate identification of high risk patients for cardiac arrhythmias during peri- and postoperative periods.

CO<sub>2</sub> is a normal product of human metabolism and at physiological levels non-toxic. Because of its solubility in blood and being inexpensive, chemically stable, physically inert and also because it is rapidly eliminated, CO<sub>2</sub> is the preferred gas for the creation of PP<sup>27</sup>. Previous studies showed that CO<sub>2</sub> PP induces significant hemodynamic changes: increase in heart rate, arterial blood pressures and systemic vascular resistance<sup>1,2,6</sup>. Beside these cardiac effects of CO<sub>2</sub> PP, it was also found in the previous articles that CO<sub>2</sub> PP causes disturbance in cardiac autonomic function<sup>8-10</sup>. Iorio et al<sup>28</sup> showed that LF/HF ratio, one of the HRV parameters, decreased significantly from the third minute of

CO<sub>2</sub> PP in the patients who underwent laparoscopic cholecystectomy with CO<sub>2</sub> PP. They also found statistically significant increase in QT interval dispersion and corrected QT interval dispersion. Previous studies on this topic agree that CO<sub>2</sub> PP causes sympathetic tone activation and because of that strict monitorization is needed in high risk patients<sup>1,6,9,12</sup>. Shin et al<sup>29</sup> concluded that the negative affects of CO<sub>2</sub> PP on the ANS may be more remarkable in the patients with underlying cardiovascular problems, renal or hepatic failure, and those undergoing lengthy procedures. In a similar research, Sato et al<sup>9</sup> suggested that pneumoperitoneum increases sympathetic cardiac activity and that the choice of general anesthetic did not seem to have a major influence on the change in the cardiac autonomic nervous system after induction of pneumoperitoneum for laparoscopic cholecystectomy. Barczyk et al<sup>1</sup> showed that pneumoperitoneum leads to sympathetic activation of the CAF. We also found that CO<sub>2</sub> PP caused sympathetic hyper-activation by effecting CAF in the patients who are not in the risk group for cardiac disorders. It is detected that this impact starts after four minutes from induction of CO<sub>2</sub> PP and causes an increase in blood pressure and heart rate. We hypothesis that all of these cardiac effects can cause severe problems especially in the patients at risk group. It is well known that there is a problem in detection the patients that have risk factors in some special groups. Previous reports showed that some patients with congenital long QT syndrome have normal QT interval in symptom-free period and in the some part of life. Precipitating factors like electrolyte imbalances, surgical stress and interactions with anesthetic agents prolonging QT interval can cause life threatening arrhythmias in congenital or acquired long QT syndrome<sup>30-32</sup>. So, it is thought that more careful and continuous cardiac monitorization is needed during CO<sub>2</sub> PP even for the patients who are thought to be cardiovascular healthy, because of the precipitating factors like physical-emotional stress and the additional risk of CO<sub>2</sub> PP.

The most important difference of this work from previous reports is that it is the first study showed the effect of CO<sub>2</sub> PP in prolonged post-operative period. Many investigations about this issue evaluated CAF during CO<sub>2</sub> evacuation, termination of the operation or awakening from anesthesia. Bickel et al showed that the disturbance on CAF was noted during anesthesia and

the middle of PP<sup>8,12,22</sup>. But in these studies patients' measurements were taken from 2 h before induction of anesthesia up to 2 h following the end of the surgery. Nelskyla et al<sup>33</sup> referred that there were no differences in HRV as far concerns the median values before anesthesia and 15 and 75 min after anesthesia. However, they recorded ECG from patients before anesthesia, and 15 and 75 min after extubation to evaluate changes in the sympathetic-parasympathetic balance of ANS. Also in the two of the similar studies, Sato et al<sup>9</sup> and Iorio et al<sup>28</sup>, a continuous 256-s ECG recorded for HRV analysis was terminated at awake stage. Instead in our study, a continuous 256-s ECG recorded up to twenty-fourth hour of post-op period. However, there are reports that support our findings. Several Authors concluded that autonomic deterioration during the post-operative period, occurs because of anesthesia and surgery stress<sup>34,35</sup>. Ushiyama et al<sup>35</sup> referred that most indices of HRV decreased postoperatively and correlated significantly to the factors of surgical stresses. Zhang et al<sup>36</sup> confirmed that CAF decreased in the postoperative 1.st day not only in DM patients, but also in the NDM ones. We hypothesis that the effect of CO<sub>2</sub> PP on CAF in prolonged third hour of post-op period should take into account seriously, and strict cardiac monitorization during first four hours of post-op period should be done in all patients, especially in the ones who have risk. By the means of that a valuable method can be obtained in early detection of arrhythmic complications.

A small sample size we observed may result in a low statistical power for equivalency testing, leading to false-negative results. However, establishing a study group without comorbidities (e.g. diabetes mellitus, hypertension, and cardiovascular or renal disorders) is difficult. Moreover, we did not assess the impact of circadian variation.

## Conclusions

This is the first study in the literature evaluating the relationship between CO<sub>2</sub> PP and impaired CAF by using HRT and HRV. In brief, the present report described adverse effects of PP on cardiac autonomic regulation in the early postoperative period according to the long-term HRV and HRT frequency analysis. The early postoperative monitorization may supply efficacious information for arrhythmic complications.

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