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Automatic Diagnosis of Sinus Arrhythmia Using HRV Indices Correlation During Anesthesia State

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Abstract: This study establishes an efficient tool for investigation and automatic diagnosis of sinus arrhythmia and autonomous nervous system (ANS) during anesthesia state. Application is designed to analyze heart rate variability (HRV) based on 3D analysis: PWVT and installed to analyze the behavior of ANS state of anesthesia in surgery service (n=11). PWVT demonstrate that the activity of ANS falls 8'43 after the injection of anesthetic product, while STFT show this activity drops just at the injection, which is physiologically incorrect. An automatic diagnosis method is introduced and it consists in preparing database with set of different cardiac diseases parameters. The LF, HF, LF+HF and LF/HF powers are estimated to reflect the cardiac balance and allow the establishment of parametric database. And estimated the correlation of the above parameters with indices of HRV in time domain: Rri, RRSTD, rMSSD and pNN50. The correlations were significant with p-value<0.001 for most pairs. Our study show, that variables strongly depend on vagal tone (pNN50, rMSSD and LF and HF) were highly correlated ($r > 0.89$). According experimental results, LF/HF powers decrease during anesthesia state and RRi increase.We conclude that some time and frequency domain indices correlate so strongly with each other that they can surrogate each other.

Key words: Rr Series · Correlation analysis · Frequency Analysis · Autonomic Nervous System (Ans) · Sinus Arrhythmia · Wigner-Ville Transform

INTRODUCTION

Autonomic nervous system (ANS) plays an integral role in many aspects of homeostasis and it is affected by a wide variety of pathophysiologic conditions. The fluctuations of heart rate (HR) are the image of the of the ANS activity [1]. The analysis of the heart rate arrhythmia allows the elaboration of quantitative information on the action of ANS and more particularly on the vagal sympathetic scales. This analysis constitutes a simple means and no traumatic method for ANS state exploration. ANS has two branches, namely sympathetic nervous system (SNS) and the parasympathetic nervous system (PNS). The SNS can rapidly increase HR and blood pressure (BP) whereas the PNS functions is the opposite way [2]. The ANS regulate the HR and BP by their interaction. Thus, it can be inferred that the ANS activity mediates the cardiovascular response to anesthesia.

Therefore, we hypothesize that the SNS activity results in the variation of cardiovascular response; in other words, the response of HR and BP during anesthesia is expected to be accompanied by corresponding sympathetic and parasympathetic activity. ANS plays a central role in the maintenance of hemodynamic stability. In this study, we attempted to verify this hypothesis using the heart rate variation (HRV) analysis resulting from the interaction of SNS and PNS to trace the evolution of autonomic activity during anesthesia. It has been widely used as a non-invasive tool to assess the ANS [2].

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While mortality from anesthesia continues to decline, the rate of morbidity is undoubtedly high [3-7]. Damages recorded: neurological damage (40%), complications airway (15%), positioning of the patient (10%), lesions at vascular puncture (7%) and brain injuries (5%) [8].

Satoko *et al*. [9] show that the variation of cardiac activity is affected when the subjects were on duty. They found the LF/HF power ratio was a useful parameter to reflect the balance of cardiac. This power ratio differs significantly between the waking and sleeping times on the off-duty day (P=0.03), while it did not differ between these two states on the on-duty day (P=0.56). Similarly, they proved the normalized HF power ratio [HF/(HF+LF)], was a useful measure of the activity of the PNS. Indeed this ratio differs significantly between the states on the off-duty day (P=0.04), while there is no significant difference in the ratio between the two states on the on duty day (P=0.13) [9].

The literature reports that HRV measurement is a promising method to pre-operatively investigate the integrity of ANS and that it can independently predict post-operative short- and long-term morbidity and mortality mainly for cardiac events, allowing for pre-operative risk stratification [10-14].

Cardiovascular events are the most commonly observed and consist of hypotension not responding to vasopressors, severe hypertensive response to endotracheal intubation, bradycardia, arrythmias, prolonged myocardial ischemia, increased incidence of myocardial infarction (MI) and sudden death, cardiac arrest, altered response to atropine and ephedrine administration [12,15,16].

The possibility to predict hypotension in patients with ANS dysfunction has also been investigated during spinal anesthesia [17-19].

Recently, it was demonstrated that patients with an increased HF component of HRV before spinal anesthesia developed severe bradycardia following sympathetic blockade, suggesting that pre-operative determination of the balance between sympathetic and parasympathetic tone might provide a useful tool to detect patients at risk for severe hemodynamic impairment during spinal anesthesia [14].

Cervical epidural anesthesia produces a significant decrease in HF and LF power without significantly altering the LF/HF ratio, whereas lumbar epidural resulted in a minimal cardiac autonomic effect, with a slight but significant increase in the LF/HF ratio and HR, suggesting sympathetic predominance [20].

Furthermore, in a prospective study in cardiac risk patients undergoing major non-cardiac surgery, a reduced LF/HF ratio before the induction of anesthesia and elevated cardiac Troponin I post-operatively were identified as independent and powerful predictors of 1-year mortality. In particular, an LF/HF ratio less than 2 in the baseline measurement was strongly associated with death after 1 year [11]. However, in Anesthesia condition, the LF component is mostly contributed by the parasympathetic excitation and sympathetic inhibition. This led us to extract the spectral power of LF component to quantify the SNS activity. Also, the conventional spectral analysis approach based on the Fourier transform has two main limitations: the assumption of stationarity and the lack of temporal localization [21].

The LF/HF ratio may also allow identifying patients who will progress to brain death and could be used as a confirmatory test in this diagnosis as it immediately identifies the loss in the spectral power of HR occurring during the transition to brain death [22].

In this study, we applied Time Frequency distribution (TFD) analysis based on Pseudo Wigner-Ville Transform (SPWVT) to characterize HRV of patient exposed to anesthesia. The LF and HF location was determined in terms of instantaneous frequency (IF). The power of LF and HF component was used as a quantification of sympathetic and parasympathetic activity. The evolution of LF and HF power over time are assessed to determine whether the SNS or PNS activity is the source of variation of the cardiovascular response to anesthesia. The discriminant analysis is performed to establish the correlated parameter permitting objective diagnosis and prediction of cardiovascular accident during anesthesia state.

MATERIALS AND METHODS

Experiment and Data Acquisition: A system of the variability analysis of the cardiac rhythm (Rythmotrace) has been installed in surgery block in the goal to observe the behavior of the ANS at anesthesia state. In order to make this study as significant as possible, eleven ECG recorded at rate of 1 kHz, during anesthesia state (˜ 1h44min), were chosen. The registrations of ECG series thus gotten will serve to HRV analysis for 1h44min that we intend to do. We extract the RR series from the ECG signal and study the *tendency curve* of the spectral power in the suitable frequency band to the SNS and PNS. This tendency curve will be calculated for the TFD: the

SPWV transformations. More details about the experiment can be found in Naouar [23]. The tendency curve gives the evolution of the IF of LF and HF activity (Area under the specter of the cardiac variability rhythm in LF or HF) according to the time. This representation is equivalent to the Fourier transform of the function of auto-correlation of the RR series in the spectral band (LF) and (HF). The last studies on the ANS activity showed that the power, on the definite frequency bands (FB), perfectly reflects the activity of the SNS and PNS. The LF is equivalent to the activity of the SNS and PNS whereas the HF is equivalent to the activity of the only PNS.

These parameters are described very well for RR series in the tendency curve representation characterizing the spectral power evolution in time. This tendency curve is also used to test the effect of the pharmacological products injected on the cardiovascular system. It describes the activity of the ANS before and after injection and according to the answer of the ANS we can classify the product in one of two families: cardio - moderator or cardio - accelerator.

This study is concerned with the evolution of the spectral power associated to the FB described previously. We detect the moments where this spectral power presents a change of state to deduct if it is a deceleration or an acceleration of the cardiac rhythm. Therefore an increase of the tendency curve in the HF results from an increase of the activity of the PNS: thus a slowing of the cardiac rhythm. By comparison with the tendency curve in the LF, if there is more important activity of the SNS than an activity of the PNS, then we have an acceleration of the cardiac rhythm.

To determine the most significant parameters in monitoring the HRV state, we choose several parameters called temporal indices of HRV and spectral indices of HRV. Correlation analysis is applied to correlate linear relationship between these parameters and seeks parameters that best reflect the ANS state according to the degree of correlation with RR series. A value with $p \square 0.01$ was considered to be statistically significant. Also, discriminant analysis is used to specify which temporal indices of HRV previously tested better reflect the evolution of the SNS and PNS state.

This approach provide a reliable early assessment of HRV and the effect of ANS state during the anesthesia period to relate the main correlated parameter and perform an objective diagnosis to predict the cardiovascular accident.

Extraction of RR Series from ECG: The spectrum analysis of the cardiac frequency variability is performed from the ECG. The interval time variations between two complexes QRS (RR series) allows to define a representative signal of instantaneous cardiac period. The variability of RR series is owed to irregularity of the cardiac action potential and extra-systoles. The RR series analysis is subjected to different techniques of spectral estimation.

The equivalent spectrum to the HRV is between 0 and 2 Hz [24]. The spectrum analysis requires an equally distant sampling (Te) of the signal expressed according to time [23] but the RR series plotting breaks the sampling. RR series is therefore artificially sampled (fe)at 4 Hz thanks to a method of interpolation perfected by Berger *et al*. [24]. This sampling in 4 Hz allows a step of 0.039 Hz. Moreover, a windowing of 256 seconds allows, according to the theorem of Shannon, to accomplish a spectrum analysis of 0 to 2Hz. Such FB suits perfectly to form the spectrum of cardiac variability [23, 25-27].

In order to avoid that the spectrum folds up regards to the axis of symmetries, it is necessary that the signal includes no upper frequency tofe/2 (Theorem of Shannon $fmax \leq fe/2$). Let us point out that noise can have the upper frequencies tofe/2. To avoid its withdrawal, it is necessary to make an analogical filtration (Who should not therefore distort the signal) cutting in the region fe/2 before coming back into the implement of sampling.

Time-Frequency Distribution: Previous studies showed that the Fourier analysis does not allow the study of non-stationary signals. This method does not allow to notice, really, the alterations of the heart rate variability in an instantaneous manner and therefore does not allow to quantify objectively the activity of the sympathetic and parasympathetic system. Because of this, we are often taken to show the signal spectrum at some points to judge the heart rate variability. Thus FFT algorithm gives only qualitative information not quantitative during the transitional stages of the signal.

As we work on a signal drowned in noise, best manner of discerning the evolution of the activity of the autonomous nervous system is to have the maximum of the energy of the signal and to judge the paces of instantaneous frequency. Such signals require the installation of an analysis allowing a location of the modulation of frequency in time [28]. This led to us to consider a new method of frequency analysis based on

time-frequency representation which allows to discern this evolution [29]. This presentation is more adapted for the detection of energy variations of RR series, in plan time frequency, by allowing to notice the paces of the instantaneous heart rate frequency. In this sense, a smoothed Pseudo Wigner-Ville Transform (PWVT) is used as a time frequency distribution.

Wigner Ville Transformation (WVT) is a bi linear structure which introduces better resolution than the spectrogram [30]. The Wigner-Ville Transform is defined from the analytic signal z (t) associated to a real signal x(t) by equation. With z(t) =x(t) +jH[x(t)] and z* is its complex conjugate of z and H[x(t)] is the Hilbert transform of the real signal x(t) [23].

$$PWVT(t,f)=\int_{-\infty}^{+\infty}\left|w(\frac{T}{2})\right|^2 z\left(t+\frac{\tau}{2}\right)z^*\left(t-\frac{\tau}{2}\right)e^{(-2i\pi f\tau)}d\tau$$

W(t) is the temporal observation window

The discrete formulation of PWVT is:

$$PWVT(m,k)=\frac{1}{2M}\sum_{n=0}^{M-1}w(n)w^*(-n)z(m+n)z^*(m-n)e^{(-2i\pi\frac{kn}{M})}$$

We choose the window of Kaiser w(t) because it answers better demands of the Wigner-Ville transformation and allows having a broad main lobe and a quicker reduction of secondary lobes in µV / Hz. So PWVT is a WVT smoothed version in the frequency direction.

As it saw above, the PWVT has the effect of reducing the small parasitic undulation present in the frequencies direction. However, the parasitic undulation appearing in the PWVT can be reduced again while smoothing the PWVT, in the direction of time of the plan (t, f). We obtain the Smoothed Pseudo Wigner - Ville transformation (SPWVT) which is defined by:

$$SPWVT(t,f)=\int_{-\infty}^{+\infty}\int_{-\infty}^{+\infty}\left|w\left(\frac{\tau}{2}\right)\right|^2 h(u-t)z\left(t+\frac{\tau}{2}\right)z^*\left(t-\frac{\tau}{2}\right)e^{(-2i\pi f\tau)}dud\tau$$

h(u-t) is the smoothing window (Hanning type) in the time domain

So the discrete formulation of SPWVT may be:

$$SPWVT(n,f)=2\sum_{k=-N+1}^{N-1}|w(k)|^2\sum_{m=-M+1}^{M-1}h(m)z(n+m+k)z^*(n+m-k)e^{(-4i\pi fk)}$$

The PWVT smoothed comes back to do a smoothing in the plan (t; f) separable in time and in frequency.

An adequate choice of the type and the size of each windows w(t) and h(t) permits to attenuate the parasitic undulation distinctly often present in the simple WVT without destroying the structure of the signal [31]. This operation of time - frequencies filtering of the SPWVT is a means to make it positive in all point. It facilitates its interpretation like an energizing distribution.

The size of the zone, on which the integration of WVT gives a significant result, is defined by the uncertainty relation of Heisenberg [30]: T_f. $B_f \geq ½$ and T_f is the time length and B_f the spectral band.

The WVT is theoretically an accurate time frequency transformation. However, because of its bilinear structure, the WVT leaves appear interference terms that appear in the form of oscillation related to the interaction between the various frequency and temporal components. We can remove some of these oscillations using a temporal observation window w(t). The resulting new time-frequency representation is the Pseudo-Wigner-Ville-Transformation (PWVT). PWVT is defined by Tacm [31].

Correlation Analysis: 1h44min signals were divided into 1-min epochs. Each epoch was mapped to the time-frequency domain using SPWVT. Tendency curve is calculated for LF power, HF power, combined LF+HF values and LF/HF ratio in the time direction for each epoch. And estimated the correlation of the above parameters with indices of HRV in time domain: consecutive intervals (RRi), standard deviation of all RR intervals over the epoch of analysis (RRSTD), square root of the means of the sum of squares of differences between adjacent RR intervals over the length of the epochs (rMSSD), a percentage of differences between adjacent RR intervals that are greater than 50 ms for the epochs analysis (pNN50) [2] using the correlation coefficient test according to Pearson test. This method was conducted as follows: the RR series for each epoch is extract and TFR is done. The LF power, HF power and LF/HF ratio is calculated and we trace the tendency curve to observe the evolution of the SNS and PNS activity. Then we read the equivalent data and eject them in data analyzer using the SPSS software that delivers us, for each set of data used, the correlation coefficient and the probability significance (p-value). Thus we can deduce whether or not there is a significant correlation between selected parameters.

The standard deviation of normal RR intervals (SDNN) is the root square of the variance mathematically equal to the total power of spectral analysis; however, the total variance depends on the length of recording: usually, 1-min recording and 1h45min recording appear to be equally appropriate [32]. Other HRV parameters can be obtained under different stimuli such as deep breathing, Valsalva maneuver, hyperventilation and postural change [33].

This analysis allows us to deduce the most significant parameter that best reflects the ANS state. Monitoring of this parameter gives the evolution of HRV, therefore the homeostas is state of the patient during anesthesia.

RESULTS AND DISCUSSION

Table 1 presents the correlation matrix between and within time domain and frequency domain measures of HRV. Previously cited HRV indices are all positively correlated with each other, except the RRi which is negatively correlated with LF, HF and LF+HF indices. The correlations were significant with p-value <0.001 for most pairs. However, the strength of correlation varies greatly.

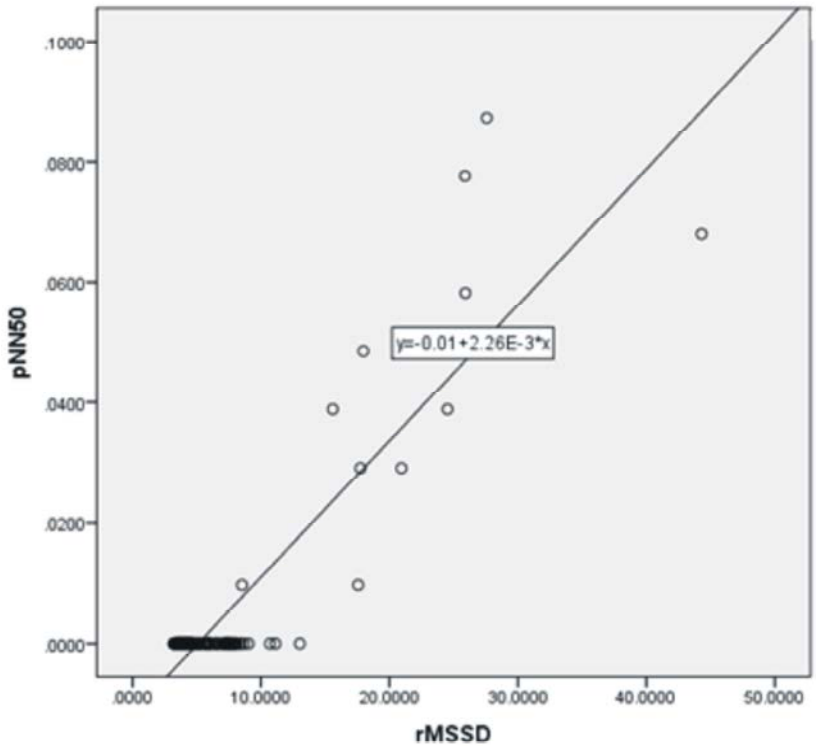

Fig. 1: Correlation between pNN50 and rMSSD for all patients

Table 1: Correlation between HRV indices (r values of the linear regression model)

	RR STD	rMSSD	pNN50	LF	HF	LF/HF	HF+LF
RRi	0.285**	0.272**	0.129	-0.152	-0.143	0.045	-0.148
RR STD		0.749**	0.649**	0.408**	0.425**	0.114	0.417**
rMSSD			0.890**	0.563**	0.549**	0.211*	0.556**
pNN50				0.637**	0.620**	0.165	0.629**
LF					0.996**	0.181*	0.999**
HF						0.157	0.999**
LF/HF							0.169

**. Correlation is significant at the 0.01 level (2-tailed).

*. Correlation is significant at the 0.05 level (2-tailed).

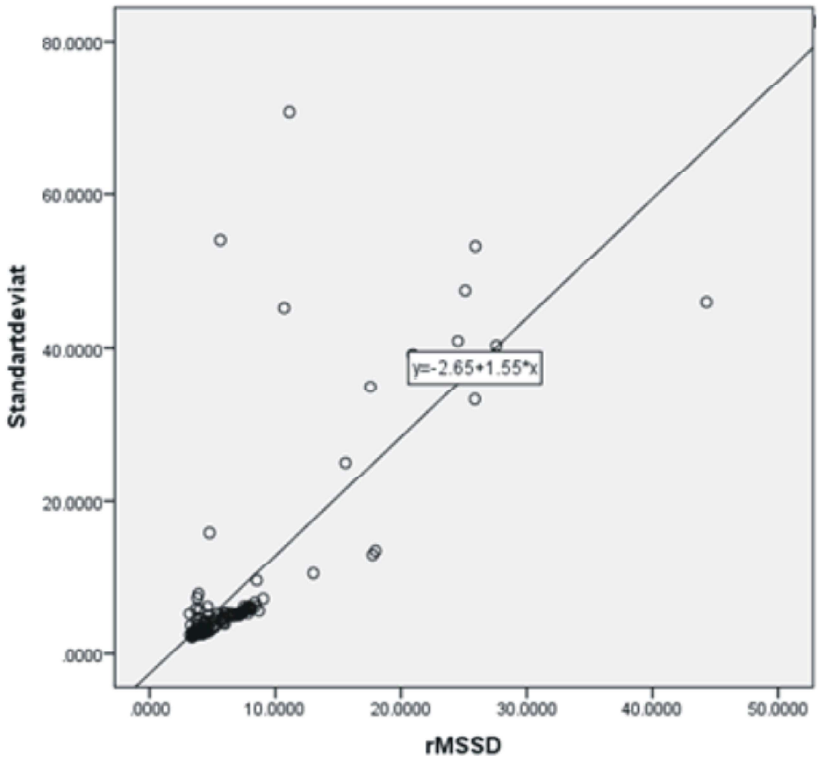

Fig. 2: Correlation between RRSTD and rMSSD for all patients

The variables strongly dependent on vagal tone are highly correlated (r > 0.89): there is a strong correlation between rMSSD and pNN50. A strong positive correlation (r > 0.99) is also found between combined LF+HF with LF and HF. Other very significant correlation was also observed (r > 075): RRSTD with rMSSD, pNN50 with LF and HF and combined LF+HF. And significant correlation was observed (r > 0.55): rMSSD with LF and HF and combined LF+HF. Interestingly, the LF/HF ratio does not strongly correlated with any of the other measures of HRV indices (Table 1).

HRV depends on the influence of sympathetic and vagal activity on the sinus node and variation and variability reflect spontaneous changes in autonomic activity [1].

All previously cited HRV indices are correlated with each other. However, the strength of correlation varies greatly. As might be expected, overall measures of HRV such as rMSSD and pNN50 are so highly correlated that those variables are surrogates for each other. These findings confirm those of previous studies in normal and asthmatic adults [34]. Based on mathematical theory, the squared RRSTD and total spectral power are identical. Therefore, it is not surprising that comparison between frequency and time domain measures show time domain correlates to the bands of the 1h45 min power spectrum. rMSSD and pNN50 have a strong correlation with LF power, a measurement of variance in the range of frequencies associated with breathing. The same strong correlation has been shown between those variables

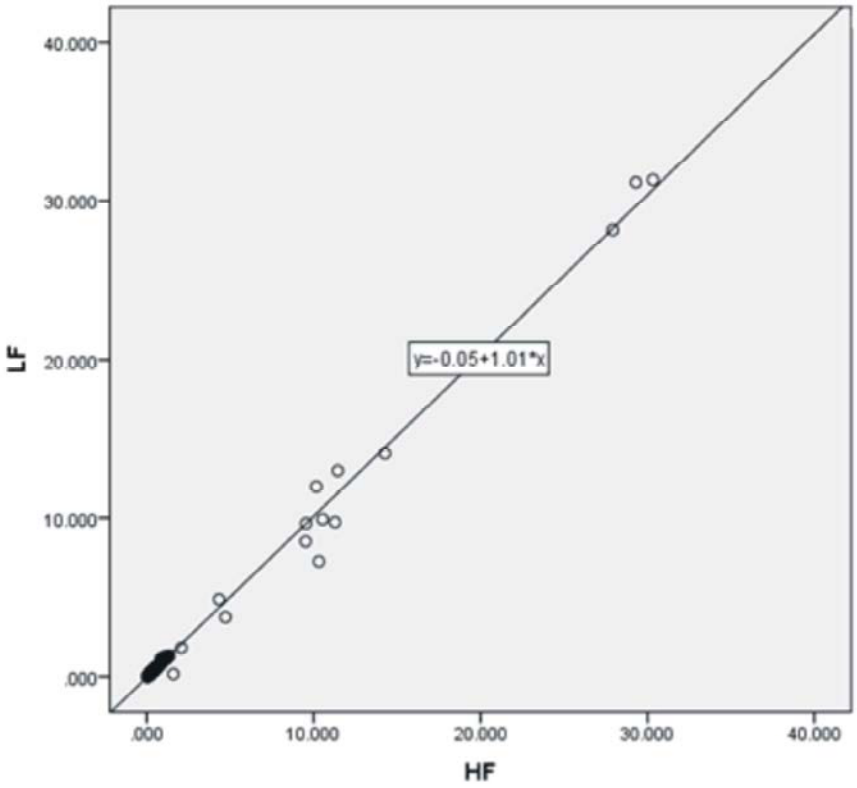

Fig. 3: Correlation between LF and HF and combined LF+HF for all patients

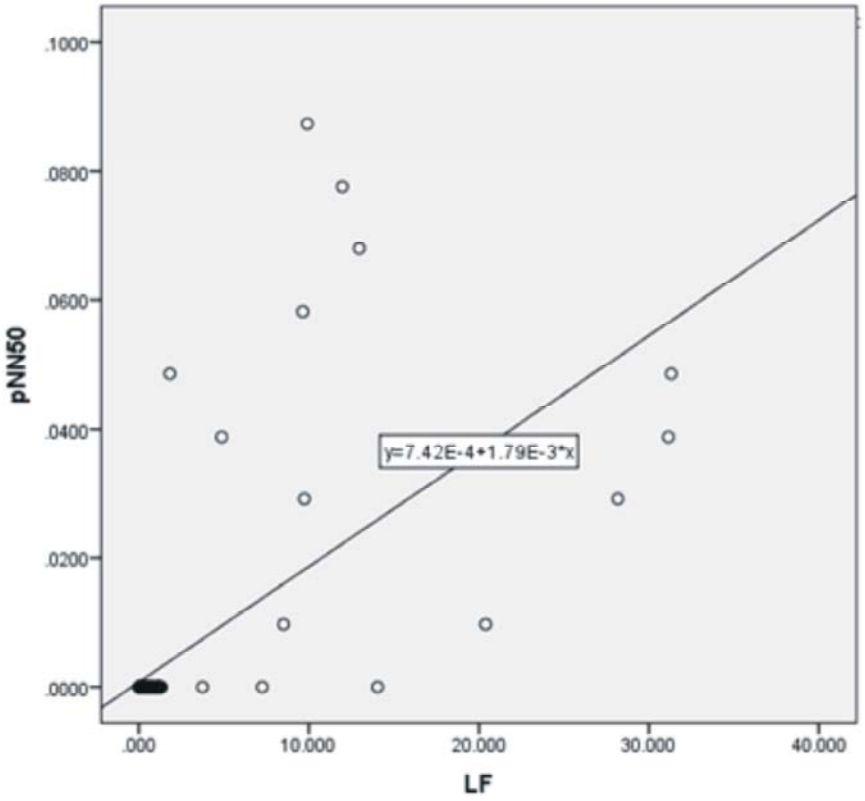

Fig. 4: Correlation between LF and pNN50 for all patients

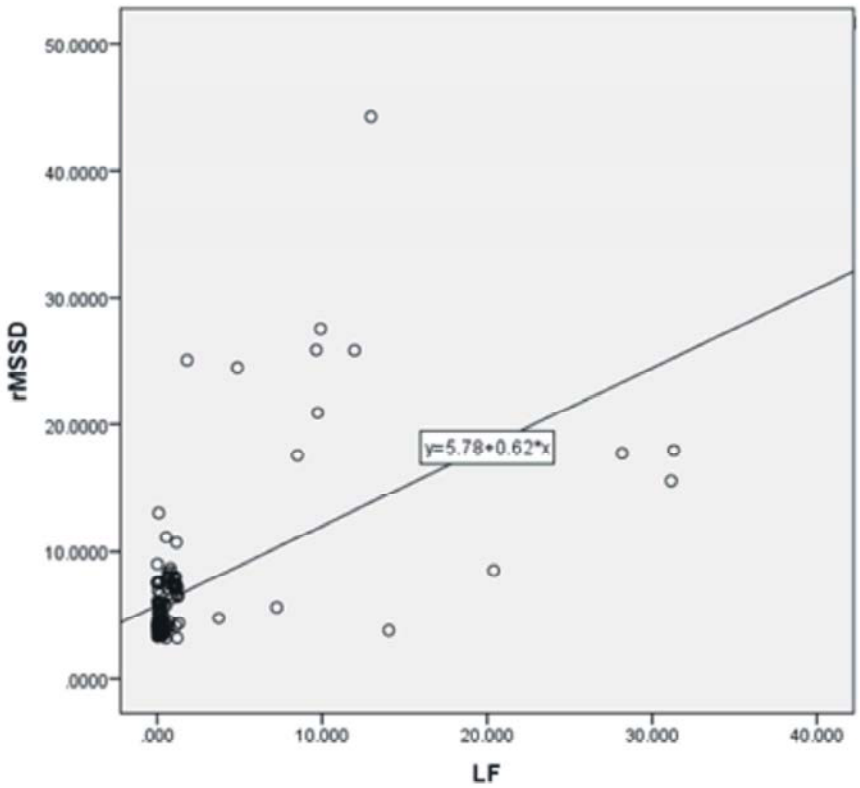

Fig. 5: Correlation between rMSSD and LF for all patients

reflecting vagal tone in previous studies in normal and asthmatic adults [34]. rMSSD and pNN50, have very significant correlations (r between 0.60 and 0.70) with LF and HF measures and with combined LF+HF power. These findings suggest that those bands of the power spectrum are influenced by the same influences such as vagal and sympathetic tones. Interestingly, the LF/HF ratio does not strongly correlate with any of the other measures of HRV, even those that are used to calculate the ratio. Then, HRV allows assessment of overall autonomic dysfunction, but additionally, it can partly separate parasympathetic from sympathetic activity to the heart [1].

However, physiological interpretation of individual components derived from long-term recordings is difficult and to a large extent unknown.

CONCLUSION

The HRV is an important tool for studying the autonomic control of the heart and autonomic disturbance in anesthesia patients with cardiac diseases. In the operative period, the measurement of HRV can be used as a helpful, non-invasive, bedside, low-cost monitoring tool to evaluate the operative risk in patients with suspected autonomic dysfunction, to select individuals who need further cardiac testing and to optimize operative status.

The literature supports a role for HRV monitoring for early prognosis prediction and risk stratification in the critically ill patient, the reduction in HRV generally being associated with the severity of the illness and the restoration of HRV being associated with recovery. HRV analysis may provide additional diagnostic and prognostic information within the context of multiple confounding factors associated with critical illness.

Some time and frequency domain HRV indices are highly correlated, indicating that they may be controlled by similar influences. Time domain indices are simple and inexpensive to compute and do not require any special procedures to correct segments of the Holter recording that contain ectopic complexes or artifact, so that they can act as surrogates for the equivalent frequency domain variables. RRSTD can be used to assess the sympathetic tone and rMSSD, pNN50 and LF to assess the tonic vagal activity over a 1h45min interval in healthy and cardiac patient. However, HRV indices have their own

significance and an interpretation of an alteration must be very carefully done. Finally, clinical benefit will become evident with increasing familiarity with this monitoring tool, which will provide anesthesiologists with indexes that could be used to guide a therapeutic intervention.

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