Non-linear HRV indices under autonomic nervous system blockade

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Abstract— **Heart rate variability (HRV) has been studied as a non-invasive technique to characterize the autonomic nervous system (ANS) regulation of the heart. Non-linear methods based on chaos theory have been used during the last decades as markers for risk stratification. However, interpretation of these non-linear methods in terms of sympathetic and parasympathetic activity is not fully established. In this work we study linear and non-linear HRV indices during ANS blockades in order to assess their relation with sympathetic and parasympathetic activities.**

Power spectral content in low frequency (0.04-0.15Hz) and high frequency (0.15-0.4Hz) bands of HRV, as well as correlation dimension, sample and approximate entropies were computed in a database of subjects during single and dual ANS blockade with atropine and/or propranolol.

Parasympathetic blockade caused a significant decrease in the low and high frequency power of HRV, as well as in correlation dimension and sample and approximate entropies. Sympathetic blockade caused a significant increase in approximate entropy. Sympathetic activation due to postural change from supine to standing caused a significant decrease in all the investigated non-linear indices and a significant increase in the normalized power in the low frequency band. The other investigated linear indices did not show significant changes. Results suggest that parasympathetic activity has a direct relation with sample and approximate entropies.

I. INTRODUCTION

Heart rate variability (HRV) has been studied as a non-invasive technique to assess autonomic nervous system (ANS) regulation of the heart. Its frequency content evaluated within certain spectral bands has been related with sympathetic and parasympathetic modulation [1].

Non-linear techniques, such as approximate and sample entropy and correlation dimension, derived from chaos theory, have been also applied to HRV signals showing, in some cases, better discriminant power than linear methods, such as spectral analysis [2], [3], [4], [5]. However, their interpretation in terms of sympathetic or parasympathetic dominance is no fully elucidated yet.

In [6] correlation dimension of HRV was investigated under pharmacological blockades with atropine and propranolol and following postural changes from supine to standing. Correlation dimension was found increased with the suppression of sympathetic activity and decreased with the suppression of parasympathetic activity. It was also suggested to decrease with sympathetic predominance.

Classical estimation of correlation dimension presents with some limitations when applied to HRV series, yielding outlier estimates. In [5] a robust estimator of correlation dimension was presented which outperformed classical estimators in simulated and real data.

The goal of this paper is to evaluate the sensitivity of this estimator, as well as of sample and approximate entropies, to changes in autonomic regulation of the heart. Correlation dimension, sample and approximate entropies were estimated from the tachogram series during control and different pharmacological ANS blockades (atropine, propranolol, and both). Frequency indices were also estimated from a HRV signal obtained based on the integral frequency modulation model (IPFM).

II. MATERIALS

The study consists of 78 electrocardiographic (ECG) signals with a sampling frequency of 360Hz, 7 minutes duration each, recorded on 13 male subjects (19-38 years old, mean of 21) with no history of cardiopulmonary disease. These ECGs were acquired at Clinical Research Center at the Massachusetts Institute of Technology under the following protocol which included single and dual pharmacological blockades of the sympathetic and parasympathetic activities (see Fig. 1).

First, ECGs were recorded while subjects were in supine position (no drug administered). Subjects then changed to standing position and after 5 minutes, to allow reaching

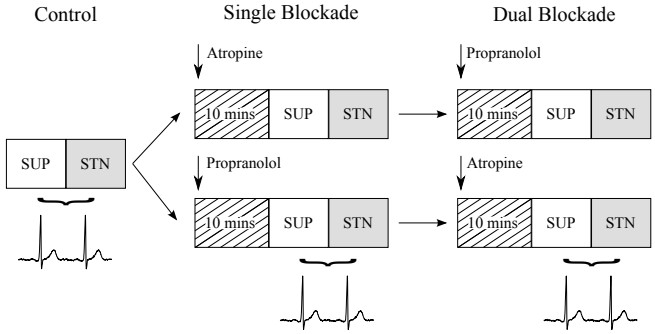

Fig. 1. Database protocol in which two ECG, one during supine (SUP) and other during standing (STN) position were recorded at three different ANS conditions: control, single blockade (by atropine or propranolol) and dual blockade (by atropine+propranolol or vice versa).

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hemodynamic equilibrium, ECGs were recorded in standing position. Second, subjects were divided into two groups. Atropine (0.03 mg/kg) was given in one group (7 subjects, 20.29±1.25 years old) and propranolol (0.2 mg/kg) in the other (6 subjects, 23±6.5 years old). After 10 minutes for equilibration, ECGs were recorded in supine and standing positions. Third, drug administration was exchanged on each group and ECGs at supine and standing position were recorded. Additionally, subjects were asked to practice breathing to irregular sequences of tones for 1-2 minutes at the beginning of each period. Further details of this database can be found in [7].

Among all possible situations of the database protocol, there are two noticeable ones. "Pure parasympathetic" is considered when subjects were in the supine position after propranolol infusion and "pure sympathetic" is considered when subjects were in the standing position after atropine administration.

III. METHODS

The reliability of the HRV analysis can be compromised by low sampling frequency of ECG recordings [8]. In order to increase it, ECGs were interpolated by cubic splines from 360 to 1080Hz and heart beat locations were extracted from these resampled ECGs using a wavelet-based detector [9] to generate the R-R interval time series. Ectopic beat correction was applied [10]. The percentage of ectopic beats with respect to normal beats was 1.15 ± 2.13%. Since the database protocol included 1-2 minutes of irregular breathing at the beginning of each ECG recording, the last 5 minutes were chosen for the analysis.

A. Spectral HRV analysis

HRV was analyzed using the Integrated Pulse Frequency Modulation (IPFM) model [10]. The modulating signal $m(t)$ derived from this model is extracted from the beat occurrence time series and it is assumed that carries information from the ANS. This $m(t)$ signal was interpolated at 4Hz and therefore suitable for spectral analysis.

Power content in low (0.04-0.15Hz) and high (0.15-0.4Hz) frequency bands (PLF and PHF), their normalized values (PLFn and PHFn), and the sympathovagal ratio (LF/HF) were computed.

B. Non-linear HRV analysis

Correlation dimension (D_2), sample and approximate entropy (SampEn and ApEn, respectively), which represent non-linear measurements based on time series complexity and regularity from chaos theory, were investigated.

Correlation dimension: D_2 measures the degree of complexity of the system that generates the time series (R-R interval series) [11]. The more complex the system is, the greater the correlation dimension value. The estimate $\hat{D}_2$ depends, intrinsically, on: the length of the time series, N; the set of thresholds used to compare each pair of reconstructed vectors, r; and the maximum dimension of these reconstructed vectors, m.

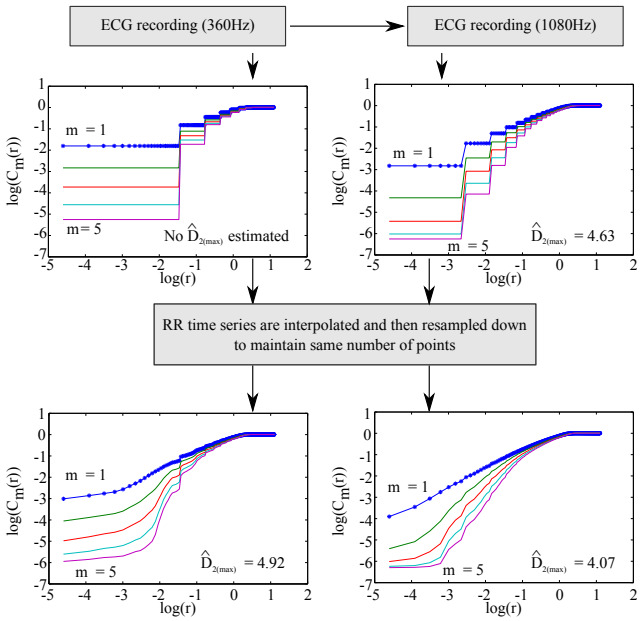

Fig. 2. Log-log curves ($log(C_m(r))$ vs. $log(r)$, where $C_m(r)$ is correlation sum at each embedded dimension m and r are the selected thresholds) for correlation dimension estimation [5]. In the upper part: in the left, log-log curves obtained over RR time series from ECG of 360Hz of sampling rate, whereas in the right log-log curves obtained over RR time series from interpolated ECG at 1080Hz. In the botton, both RR time series were interpolated to be resampled down in order to maintain the same number of points. Data was extracted from a subject in supine position for a dual blockade, where the variability is extremely decreased.

In a previous work, we developed techniques to improve the estimation of correlation dimension [5]. Namely, self-pairs were considered to compute correlation sums and log-log curves (logarithm of correlation sums vs. logarithm of thresholds) were fitted to a sigmoidal curve. Another estimate of correlation dimension, denoted as $\hat{D}_{2(max)}$ was presented based on the points that maximize the difference between each pair of sigmoidal curves. Both $\hat{D}_2$ and $\hat{D}_{2(max)}$ were computed with m = 1 to 16 and with r = 0.01 to 3 in steps of 0.01.

Despite the previous ECG interpolation, the low original sampling frequency limits D_2 estimation, particularly when HRV is very diminished. In these cases, the RR interval series seems to be discretized in a reduced set of values and the estimation of the slope of the log-log curve is unreliable. To solve this problem the RR interval series were interpolated and then resampled maintaining the same number of values.

Sample and approximate entropies: SampEn and ApEn are measurements of the irregularity of the R-R interval series [12], with SampEn having been introduced to overcome the self-pairs-related limitation of ApEn. These entropies also depend on N, r and m. SampEn and ApEn were calculated using a threshold of 0.15 times the standard deviation of the data and $m = 2$. Although both entropy measurements may represent the same phenomena, this is not obvious for short

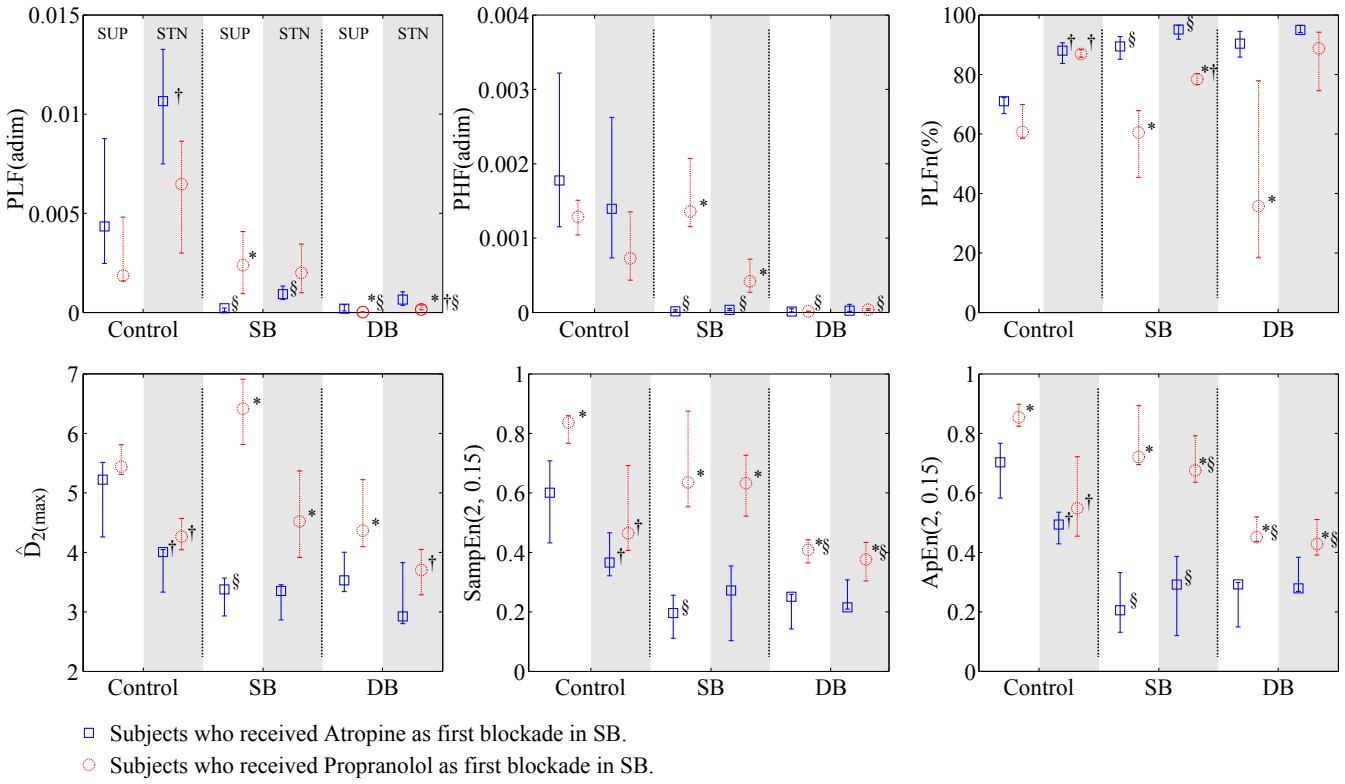

Fig. 3. Linear and non-linear indices evaluated during supine and standing position for conditions of control, one type of drug (SB, single blockade) and with the effect of both drugs (DB, dual blockade). For the sake of comparison, subjects in control conditions were split in order to evaluate their evolution, (□) atropine and (O) propranolol as first blockade, empty markers indicate supine position while full markers indicate standing position. † Supine Vs. Standing, $p < 0.05$. * Atropine Vs. Propranolol, $p < 0.05$. §Vs. previous state same position, $p < 0.05$.

data length and was investigated in this study.

C. Statistical analysis

Prior to the statistical analysis, normality of data was evaluated by Lilliefors test on each group for all positions and conditions and 4 out of 12 of them were found with normal distribution. Therefore, statistical analysis was done by Wilcoxon test to evaluate: the effect of blockades in both groups for all conditions; supine versus standing position for all conditions in the same group; and each group with respect to its previous blockade condition or control during supine and during standing position separately. A p-value < 0.05 was considered as statistically significant.

IV. RESULTS AND DISCUSSION

When ECG is recorded at low sampling frequency and HRV signal presents low variability then, the reliability of correlation dimension estimate may be uncertain. By interpolating the ECG recordings firstly and afterwards by interpolating and sampling down the RR time series the discretization is almost vanished and smooth log-log curves are achieved increasing the reliability of correlation dimension estimate as it is shown in Fig. 2.

Fig. 3 shows the results of evaluating linear (PLFn, PHFn, PLF and PHF) and non-linear ($\hat{D}_{2(max)}$, SampEn(2, 0.15) and ApEn(2, 0.15) indices during supine and standing positions for different conditions. Results are presented separately into two groups, according to the first administered drug, in terms of median($1^{st}|3^{rd}$ quartiles). The sympathovagal ratio (PLF/PHF) was not included due to the very low PHF values reached when atropine was administered. Values of $\hat{D}_2$ were very similar to those of $\hat{D}_{2(max)}$ and are not shown. Furthermore, "Pure" parasympathetic and "pure" sympathetic conditions are pointed out in Tab. I.

When parasympathethic activity is blocked by atropine administration, both linear indices, PLF and PHF suffered a significant decrease in supine as well as in standing position. This result may be associated with the fact that LF and HF bands are influenced by parasympathetic modulation. On the other hand, non-linear indices ($\hat{D}_{2(max)}$, ApEn, SampEn) only showed a notable decrease in supine position, where there is a predominant control of the parasympathetic system.

While sympathetic activity was inhibited via propranolol, no changes in power spectral bands in supine position were found. Nevertheless, a decreased trend was observed in PLF and its normalized value. On the contrary, SampEn and ApEn showed an increase in standing position vs. supine (only significant for ApEn) which is in agreement with the inhibition of the dominant control mechanisms whereas correlation dimension did not change significantly.

Dual blockade by atropine plus propranolol or vice versa caused a significant reduction in PLF and PHF content. A significant reduction was also observed in SampEn and

TABLE I

SPECTRAL AND NON-LINEAR INDICES COMPUTED BY ANALYZING HRV DURING "PURE PARASYMPATHETIC" (SUPINE+PROPRANOLOL) AND "PURE SYMPATHETIC" (STANDING+ATROPINE) CONDITIONS. RESULTS ARE SHOWN AS MEDIAN($1^{st}|3^{rd}$ QUARTILES).

	PLF (adim)	PHF (adim)	PLFn (%)	$\hat{D}_{2(max)}$	SampEn(2, 0.15)	ApEn(2, 0.15)
Supine (Propranolol)	$238(94\|408)\cdot10^{-5}$	$135(115\|207)\cdot10^{-5}$	60(45|68)	6.4(5.8|6.9)	0.64(0.55|0.87)	0.72(0.70|0.89)
Standing (Atropine)	$92(65\|133)\cdot10^{-5}$	$3.5(2.7\|5.3)\cdot10^{-5}$	95(92|97)	3.4(2.9|3.5)	0.27(0.10|0.35)	0.29(0.12|0.39)
$p-value$	0.05	0.001	0.005	0.002	0.005	0.001

ApEn both in supine and standing positions only when propanolol was first administered. Correlation dimension was also reduced when propanolol was first administered, specially during supine position. All the above results suggest that the concept of complexity and regularity of HRV signals may be highly related to parasympathetic activity.

For single blockade conditions, statistical significant differences were also found if both groups are compared in supine as well as in standing position. In supine position PLF and PHF were significantly higher after propanolol than after atropine administration, which is in agreement with the fact that parasympathetic system is the main mechanism control in supine position affecting power in LF and HF bands, but PLFn was significantly lower, supporting its use as a sympathetic marker. Whereas in standing position PHF was also significantly higher and PLFn significantly lower. All non-linear indices studied were significantly higher in both standing and supine conditions after propanolol than after atropine administration.

In control conditions, changing from supine to standing position leads to an increase in the sympathetic activity which is reflected in PLF and PLFn content as well as a decrease in PHF content if all subjects are considered altogether. This natural increase in the sympathetic modulation produced a significant decrease in the non-linear indices. However, this result was not observed after the first blockade (either atropine or propanolol).

All linear and non-linear indices studied are significantly different in the two special conditions called above "pure sympathetic" and "pure parasympathetic". During "pure parasympathetic" condition PLF and PHF were significantly higher, and PLFn significantly lower, than during "pure sympathetic" conditions. Correlation dimension as well as sample and approximate entropies were also significantly higher during "pure parasympathetic" than "pure sympathetic" conditions.

Despite analyzing 5-minutes ECG signals, which implies short data length and therefore lack of reliability in correlation dimension estimation, this index was capable of capturing the physiological changes caused by blockades being in agreement with the results obtained in [6]. The low number of subjects of the analyzed database limits the statistical analysis of this study. The significant differences found in the entropy values at baseline for the two investigated groups may be in relation to such a low number of subjects and the associated intersubject variability.

V. CONCLUSION

In this work, non-linear indices (correlation dimension and sample and approximate entropies) were studied under controlled conditions during single and dual ANS blockade (by means of atropine and propanolol) in supine and standing positions in order to relate these indices to sympathetic and parasympathetic activity.

It was observed that parasympathetic blockade causes a significant decrease in all non-linear indices: Correlation dimension, SampEn and ApEn. Additionally, power in low and high frequency bands of HRV were found to be also significantly reduced, whereas the normalized power of the low frequency band increased. On the other hand, sympathetic blockade caused significant changes only in approximate entropy in standing position. Postural changes from supine to standing caused a decrease in correlation dimension, sample and approximate entropies. These results suggest that parasympathetic activity has a direct relation with sample and approximate entropies.

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