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REVIEW ARTICLE

Autonomic nervous system assessment using heart rate variability

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ABSTRACT

The role of the autonomic nervous system in the onset of supraventricular and ventricular arrhythmias is well established. It can be analysed by the spontaneous behaviour of the heart rate with ambulatory ECG recordings, through heart rate variability measurements. Input of heart rate variability parameters into artificial intelligence models to make predictions regarding the detection or forecast of rhythm disorders is becoming routine and neuromodulation techniques are now increasingly used for their treatment. All this warrants a reappraisal of the use of heart rate variability for autonomic nervous system assessment.

Measurements performed over long periods such as 24H-variance, total power, deceleration capacity, and turbulence are suitable for estimating the individual basal autonomic status. Spectral measurements performed over short periods provide information on the dynamics of systems that disrupt this basal balance and may be part of the triggers of arrhythmias, as well as premature atrial or ventricular beats. All heart rate variability measurements essentially reflect the modulations of the parasympathetic nervous system which are superimposed on the impulses of the adrenergic system. Although heart rate variability parameters have been shown to be useful for risk stratification in patients with myocardial infarction and patients with heart failure, they are not part of the criteria for prophylactic implantation of an intracardiac defibrillator, because of their high variability and the improved treatment of myocardial infarction. Graphical methods such as Poincaré plots allow quick screening of atrial fibrillation and are set to play an important role in the e-cardiology networks. Although mathematical and computational techniques allow manipulation of the ECG signal to extract information and permit their use in predictive models for individual cardiac risk stratification, their explicability remains difficult and making inferences about the activity of the ANS from these models must remain cautious.

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1. Introduction

The role of the autonomic nervous system (ANS) in the onset of supraventricular and ventricular arrhythmias is well established [1]. The ANS can be studied by selective blockade of its action in the electrophysiology laboratory. The multiple facets of cardiac arrhythmias and their relationship with the ANS can also be analysed by the spontaneous behaviour of the heart rate (HR) with ambulatory ECG recordings, through heart rate variability (HRV) measurements. This approach is allowed over an extended time frame and is totally non-invasive. Multiple studies have shown the usefulness of HRV for risk stratification in coronary artery disease, heart failure, and supraventricular and ventricular tachyarrhythmias.

Despite their apparent simplicity, HRV study techniques require a high degree of rigour to be used for clinical practice. Moreover, there is a notable gap between the biomedical engineering literature and the medical literature dealing with HRV assessment. Neuromodulation techniques are now increasingly used for the treatment of arrhythmias [2]. Therefore, it seems appropriate to review the different methods of HRV for the ANS assessment.

2. Heart rate variability-heart rate correlation

The cardiac rhythm is the final and easily accessible result of multiple regulatory systems, not only cardiac but also cerebral, metabolic, and endocrine. However, the well-known "adrenergic paradox" makes it difficult to use HRV in pathological situations, precisely when it would be most useful [3]. Although atrial depolarizations precede ventricular depolarizations, and the atrioventricular interval is variable, interbeats normal intervals (NN or RR) are used as a reference for purely technical reasons. These allow very precise temporal

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measurements, of the order of a thousandth of a second, while P waves do not allow the same precision.

Nollo et al. showed that the variation in PR intervals is negligible in 17 normal subjects and that NN or RR intervals give a satisfactory estimate of variations in sinus cycle length [4]. However, it is not so obvious that this conclusion can be extrapolated in patients with various pathologies. The variation of atrioventricular delay with changes in heart rate (HR) is, moreover, exploited for the optimisation of hemodynamics in electro-stimulated patients [5].

All HRV parameters showed significant correlations with HR in mice [6] and have been quantified in rabbits [7]. A corrective method has also been proposed [8]. Kleiger who gave HRV its true credentials with his study of 788 patients with myocardial infarction had already highlighted the existing correlation between mean HR and 24-hour standard deviation of normal intervals (SDNN) [9]. Coumel et al. established a correlation coefficient of 0.79 between SDNN and HR in 17 normal 20-year-old subjects [10]. We obtained a weaker but significant correlation in 126 normal subjects of both sexes (156 males and 94 females) and all ages (7 to 90 years, mean: 54 ± 17.8) (Figure 1). However, the relationship between HR and HRV continues to be underestimated, and many published studies do not report HRs associated with HRV.

3. Statistical methods

Statistical methods, also called temporal, are the most obvious to use. The calculations are based on the NN complexes. The basic parameters of the HRV are estimated by the SDNN, which is the calculation of the standard deviation of the sequence of sinus intervals measured by the NN distance during a certain period. The SDNN reflects the entirety of the components responsible for HRV during the recording period. Sinus intervals should be clearly differentiated from premature intervals because the existence of premature beats distorts the results of calculations, especially if they are numerous (more than 1%). Indeed, RR intervals include both sinus and premature beats of supraventricular origin. However, most published papers report only RR intervals without further specification.

A detailed history of the evolution of the concepts of the HRV can be found in Bilman [11]. In 1987, Kleiger et al. published a landmark study for postinfarction risk stratification [9]. Despite the plethora of studies that have confirmed the value of the SDNN for risk stratification and the fact that it has a complementary and almost equivalent value to the ejection fraction, the SDNN is not part of the criteria for implantable defibrillator (ICD) implantation [12–14]. Indeed, improved treatment methods for both acute myocardial infarction and its revalidation have greatly reduced the value of SDNN as a predictive value in this patient group. Second, there is a very high inter- and intra-individual HRV in measurements, despite high statistical significance obtained when analysing groups of patients. Third, changes in HRV parameters predict mortality but are not associated with a specific mode of death in patients with stable CAD [15]. Fourth, there is a lack of reliable reference values, and in addition, the values reported for normal subjects in the literature are highly divergent [16]. Lastly, the evolution of the ANS with age makes it even more difficult to use SDNN as a criterion for implantation of an ICD [17,18]. SDANN is the standard deviation of the average NN interval calculated over short periods, usually 5 min. It can help to discriminate patients with paroxysmal atrial fibrillation (AF) in whom SDNN can be extremely elevated and meaningless.

4. Spectral analysis

Spectral methods allow the extraction and analysis of additional information contained in the sequence of RR intervals. The sequence of RR intervals is not strictly speaking a time series because the sequence of RRs is not uniform. It is necessary to perform mathematical manipulations to transform this series of variable intervals into amplitude variations on a time scale with fixed intervals [19]. The sequence of RR intervals must first be resampled to make the transition from time to frequency. The integral of the curve obtained as a function of the frequencies then allows the different power bands of the signal to be highlighted and measured. The meaning of the different frequency bands thus obtained remains to be established.

The first use of the frequency spectrum corresponding to the oscillations of cardiac control systems was made by Sayers in a remarkable pioneering work performed to quantify the physiological origins of sinus rhythm variability [20]. Using periods of 256 RR intervals, he showed that sinus rhythm responds to both linear and nonlinear laws and that the three main influences were the respiratory rhythm, blood pressure and temperature variations. Akselrod et al. performed autonomic blockade in dogs to show the action of the two branches of the ANS and the action of the renin-angiotensin system. Using 5-minute stationary recordings, she obtained three frequency zones between

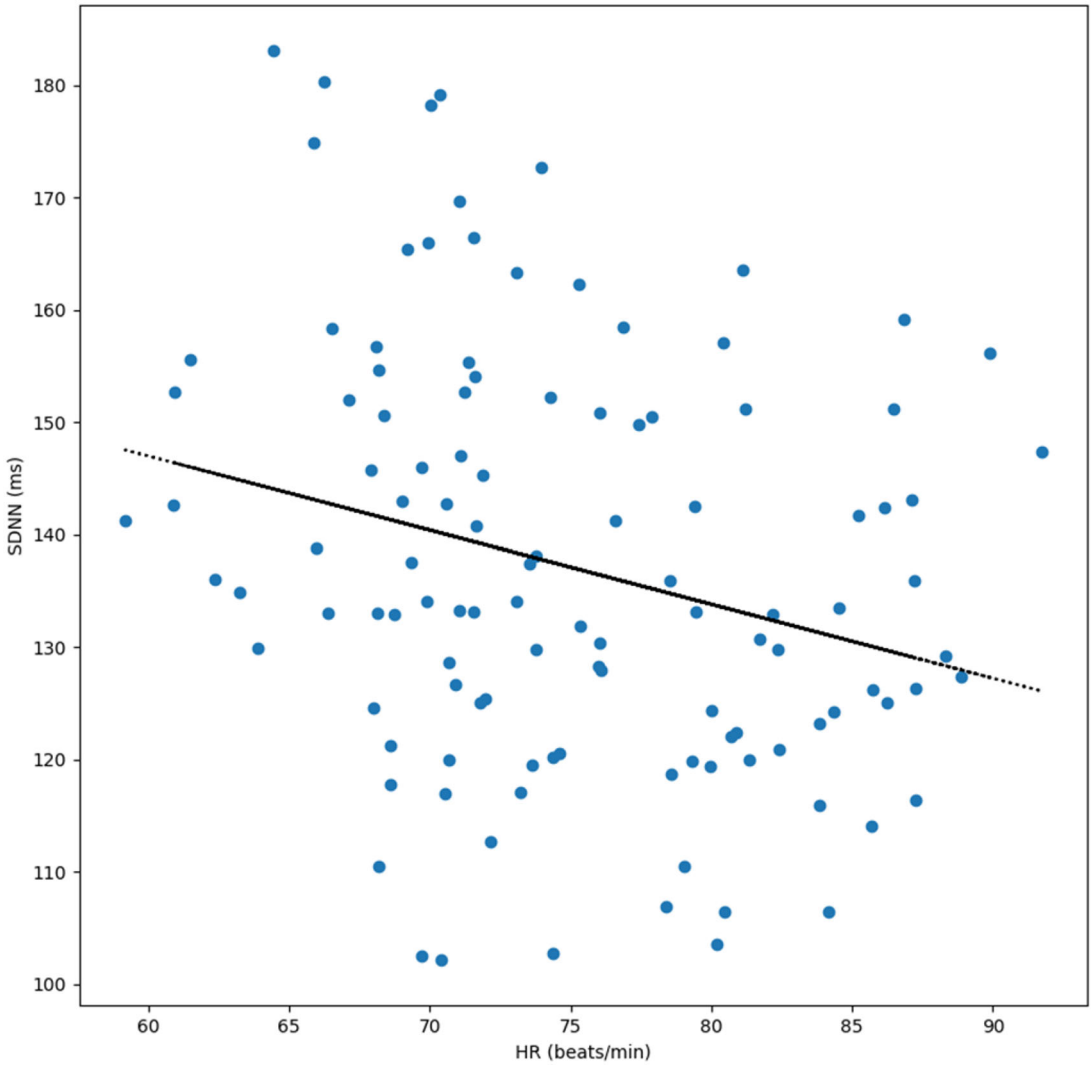

Figure 1. Relationship between standard deviation (SDNN) and heart rate from 24H ECG recordings in 126 normal human subjects ($r = 0.26$ $p < 0.005$): increased heart rate is associated with a decrease in variance value.

0.02 and 1 Hz, which she called low, medium, and high frequency [21]. In parasympathetic blockade, the high-frequency and mid-frequency peaks (corresponding to high frequency (HF) and low frequency (LF) in humans, respectively) were abolished, whereas what she called the low-frequency peak (corresponding approximately to very low frequency (VLF) in humans) was of lower amplitude. The complete autonomic blockade resulted in the abolition of all peaks and a metronomic beat. Selective blockade of the renin-angiotensin system resulted in a decrease in the low-frequency peak (the VLFs in humans).

One of the keys to understanding the activity of the ANS lies in the greater speed of action of vagal activity (of the order of 500 msec, which allows it to exert beat-to-beat control) compared with adrenergic reactivity (of the order of several seconds). It should be noted that there are permanent interactions between the two parts of the ANS, which complicates the interpretation of the results obtained. The relationships between the ANS and the spectral parameters of the HRV have been demonstrated by experimental protocols in animals under controlled conditions. Spectral analysis allows inferences about the state of the ANS, but simplistic equivalences should be avoided [22].

Spectral analysis can be performed by non-parametric and parametric methods. The advantages of nonparametric methods are mainly the simplicity of the algorithm used, most often fast Fourier transforms (FFT) and the high processing speed, whereas parametric methods have smoother spectral components and facilitate postprocessing of the spectrum due to automatic calculation of LF and HF power components and easy identification of the centre frequency of each component [23,24]. The normalisation process allows a

direct comparison between frequency and autoregressive methods. In addition, it allows a degree of interpretability between studies, since the proportional change between the defined frequency bands can be considered roughly equivalent, regardless of the spectral method used [25].

a. The normalisation process

The normalised HRV values (LFnu, HFnu) are calculated from the raw values of either short-term frequency band (LF or HF) divided by the total spectral power. For recordings of a few minutes, we usually divide by LF + HF. In this case, the use of normalised values has significant redundancies, since LFnu and HFnu are trivially equivalent, and the individual normalised values do not contain more information than the individual values of the LF/HF ratio. On this basis, it is not possible to justify how "sympathetic balance" (LFnu) is mathematically different from "parasympathetic modulation" (HFnu) or how they would be conceptually different from "sympathovagal balance" (LF/HF) [26]. From recording durations of at least 5 min to 24 h or longer, normalised values are calculated from an expanded power spectrum, thus including VLF. These are included in the denominator, which avoids the redundancies described above. The distribution of the spectral values does not follow a normal distribution and it is preferable to report their frequency bands as a natural logarithm (Ln) of the original units to obtain a distribution closer to the normal distribution.

b. Technical limitations

i. Aliasing

Aliasing, a well-known phenomenon in signal theory, occurs when a time-continuous signal is sampled at a frequency less than twice the maximum frequency of the sampled signal. The sampling frequency divided by two is called the Nyquist frequency. When the frequency of the sampled signal exceeds the Nyquist limit, it appears at an erroneously lower position. Because of the limitation provided by the Nyquist frequency, the frequency of 0.4 Hz is the acceptable upper limit of HFs. Although the frequency bands and parameters of the HRV have been standardised, the method to be used to calculate the spectral density is not standardised. The differences between the methods are not critically important in standard situations, but under certain conditions, different methods can give radically different results. Aliasing is caused by a synchronous respiratory rate greater than 24/′ [27]. A mean HR greater than 48/′ and a respiratory rate less than 24/′ are therefore essential for reliable spectral analysis [28]. If aliasing occurs, it becomes possible to find frequencies above the Nyquist frequency in the VLF and VHF frequency bands.

ii. Ectopic beats

HRV results in ANS assessments may be biased if HRV is analysed without eliminating ectopic beats. Interpolation is the recommended method of correction. It consists of replacing abnormal RR intervals with an interpolated RR interval. Interpolation methods include zero-order, first-order, spline, and nonlinear predictive interpolation [29]. Many papers using spectral parameters of HRV to make predictions about the onset of AF episodes do not mention how the authors treated premature beats.

c. Spectral bands from 0.04 to 0.40 Hz

The HF and LF bands form the largest part of the signal for short recording times (of the order of a few minutes) (Figure 2). Frequencies above 0.04 Hz are mainly due to sympathetic or parasympathetic control mechanisms. Mechanical couplings also exist causing small but unequivocal fluctuations in the low frequency (LF) and high frequency (HF) bands. These mechanical influences are thought to be generally negligible except in transplanted hearts and if there is significant cardiac denervation as in some neurodegenerative diseases [30].

i. The LF band: 0.04–0.15 Hz

The interpretation of the LF band (0.04–0.15 Hz) is more complex. Sympathetically mediated blood pressure oscillations (Mayer waves) are slower than respiration and are reflected in the HRV spectrum [31]. As a result, the LF band indirectly represents at least part of the adrenergic activity. It is related to the baroreceptor reflex. Thus, part of the LFs comes from vagal activity because this reflex is mediated by the vagus nerve. As a result, vagal or adrenergic participation in the LF band is highly variable depending on the position and activity of the subjects. This variable participation complicates interpretation and invalidates the fact that LFs can be considered solely representative of adrenergic activity. Eckberg also suggested that central mechanisms may play a role in addition to the baroreflex [32]. Thus, the interpretation of LFs as solely representative of adrenergic activity should be avoided.

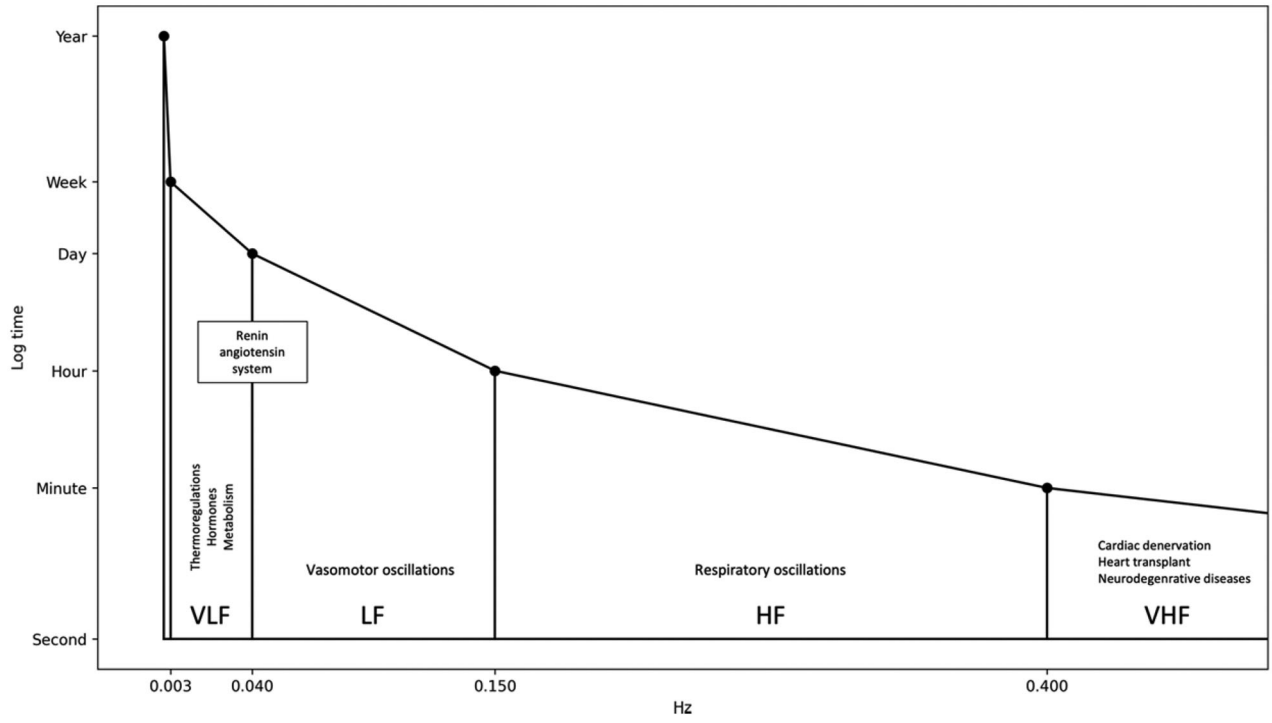

Figure 2. Theoretical plot of spectral frequencies versus log recording time, showing the influence of the recording time on the results to be expected for the frequency bands.

ii. The HF band: 0.15–0.40 Hz

Because the sympathetic system is relatively slow, it cannot generate significant fluctuations at frequencies higher than 0.15–0.20 Hz and therefore all neural contributions to the HR spectra at higher frequencies are essentially parasympathetic in origin. Most authors agree that the HF band represents respiratory-related vagal activity [33]. Respiratory rhythm, therefore, plays an important role in its interpretation. The significance of the HF band is questionable when the respiratory rate is less than 9 per min and greater than 24 per minute [28]. Other frequency limits for the HF band have been proposed for infants because of the difference in the physiological range of their respiratory rate [33]. Similar problems have been reported in adults during exercise. Evidence suggests greater vagal activation at lower respiratory rates, Eckberg et al. report that this may be due to more complete hydrolysis of acetylcholine. According to this theory, acetylcholine hydrolysis is a relatively slow process and is therefore more complete at lower respiratory rates before subsequent inhalation blocks its excretion [34].

iii. The LF/HF ratio

The low frequency/high frequency (LF/HF) ratio was once used as an index of sympatho-vagal interaction. It is hazardous to draw conclusions from this ratio alone because of the complexity of the relationship between the vagus nerve and the adrenergic system [35]. For this reason, the expressions "autonomic modulations" and "responsiveness of the ANS to different influences" are used instead [36,37]. Furthermore, the value of this ratio depends on the normalisation process and provides additional information only if VLFs are used in addition to LFs and HFs to perform normalisation.

d. The VLF band: 0.003–0.04 Hz

The meaning of VLFs is not clear: these frequencies could correspond to slower influencing rhythms such as hormonal rhythms and thermoregulation. It could also be aliasing and artefacts due to non-stationarity of the signal over longer periods. In his pioneering experimental study, Akselrod et al. showed that, in dogs, VLFs automatically occur with renin-angiotensin system blockade or LFs and HFs increase [21]. The observed increase in VLFs could then be a simple consequence of the increase in LFs and HFs because of the mathematical procedure used for its calculation. Another hypothesis suggests that VLFs may be generated by stimulation of afferent sensory neurons in the heart. This stimulation would in turn activate various levels of feedback and feedforward loops in the heart's intrinsic cardiac nervous system (ICNS), as well

as between the heart, extrinsic cardiac ganglia, and the spinal cord. Experimental evidence suggests that the heart generates the VLF rhythm intrinsically and that efferent activity of the CNS due to physical activity and stress responses modulates its amplitude and frequency [38,39]. When complete isolation of the pulmonary veins is achieved the VLFs disappear, which would be in favour of the latter hypothesis. (Figure 3). VLFs would therefore reflect the state of the ICNS.

VLFs have been used to discriminate high-risk patients in patients with congestive heart failure [40]. Reconnection after isolation of the pulmonary veins is responsible for most AF recurrences. Calburean et al. showed that an absolute VLF power value greater than 160 ms^2 was associated with a 5-fold higher probability of pulmonary vein reconnection [41]. In patients with obstructive sleep apnoea, the VLF power spectral density index correlates with the severity of obstructive apnoeas and is also associated with Cheyne–Stokes in congestive heart failure [42].

e. The VHF band: (0.40.9 Hz)

The literature concerning the very high frequency (VHF) of 0.4-0.9 Hz in HRV is scarce. After heart transplantation the new sinus node is completely denervated. The HF peak is markedly reduced and is attributed solely to mechanical coupling in the cardiorespiratory system. Because parasympathetic reinnervation does not occur after standard transplantation surgery, the mechanically mediated peak HF remains low in transplanted patients regardless of the time after transplantation. Toledo et al. showed the existence of marked VHF peaks in transplant patients [30]. The VHF band occurs at frequencies well above the respiratory frequency, ruling out aliasing as an explanation. Toledo logically proposed the existence of VHF as a test proving cardiac denervation. Estévez-Báez et al. suggested that activity in the VHF could be related to the intensity of a reduction in parasympathetic influence because of alterations in autonomic fibres with possible involvement of the ICNS [43].

5. Heart rate turbulence (HRT)

The turbulence phenomenon is a biphasic baroreflex-mediated HR response manifested by changes in HR in response to ventricular premature beats [44,45]. It is quantified by two indices: turbulence onset (TO), which reflects the initial acceleration of the HR after a premature ventricular beat (PVB), and turbulence slope (TS), which corresponds to the subsequent deceleration of the HR. A consensus regarding turbulence measurement techniques has been published [44]. It is explained by an increase in systolic blood pressure following the PVB, thereby activating a spontaneous baroreflex mechanism, with initial sympathetic inhibition followed by predominantly transient vagal activation. The TO is calculated by determining the percentage differences between the 2 RR intervals following the compensatory pause and the 2 RR intervals immediately preceding the coupling interval of the premature beat. TS is defined as the maximum regression slope measured over 5 consecutive sinus cycles in the first 15 sinus intervals following the compensatory pause. At least 5 ventricular premature beats are required to calculate turbulence. Unlike HRV, which shows autonomic activity during sinus rhythm, HRT reflects

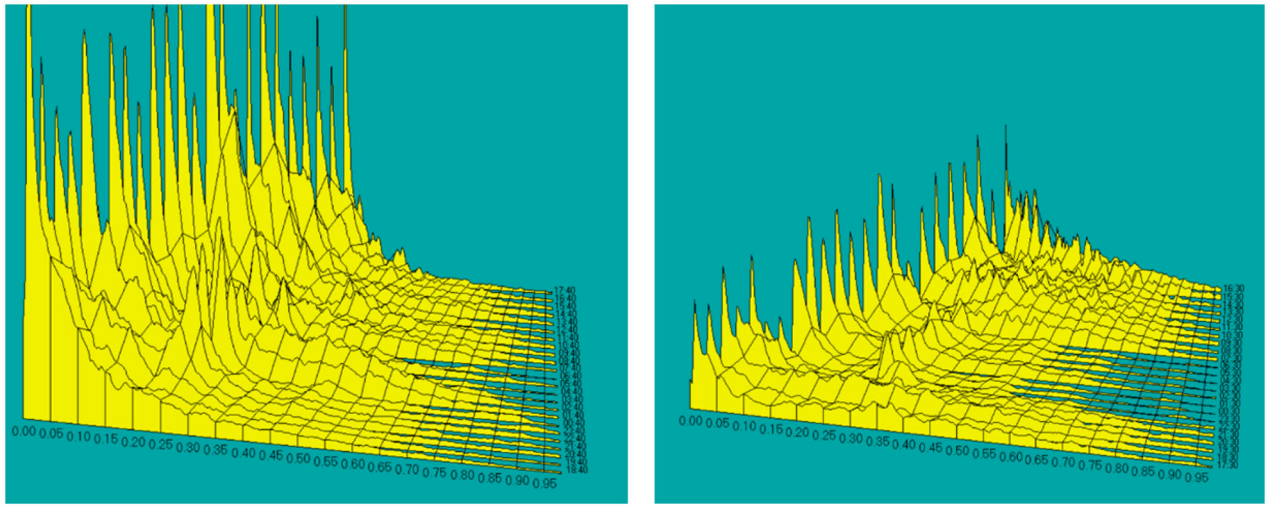

Figure 3. Example of the effect of ablation on the ICNS: VLFs are almost completely suppressed after the procedure (3D plot of 24H hour-by-hour recordings, same scale). (1) before pulmonary vein isolation for AF in a paroxysmal AF patient. (2) after pulmonary vein isolation in the same patient.

autonomic responses to endogenous interference. TO $>$ or $=$ 0% and TS $<$ or $=$ 2.5 ms/RR are considered abnormal. Both TO and TS were moderately but significantly correlated with baroreflex sensitivity and SDNN. Several large clinical studies and numerous smaller studies have demonstrated the prognostic value of abnormal HRT in predicting adverse outcome in different populations, particularly in postinfarction patients and patients with heart failure [46]. A recent study of 240 articles highlighted the methodological difficulties of calculating these indices. In these publications, HRT assessment was often performed in a variety of ways and important specifications of the methodology were not always reported [47].

A retrospective analysis of turbulence in the ATRAMI study had shown that abnormal HRT discriminated postinfarction patients at risk for arrhythmic events defined as fatal or nonfatal cardiac arrest [48]. The ISAR-Risk study demonstrated that the presence of altered ANS, composed of abnormal HRT and deceleration capacity (DC), identified a subset of postinfarction patients with left ventricular ejection fraction (LVEF) $>$30% with a mortality risk compared to a high-risk group of patients with significantly depressed LVEF [49]. Turbulence could therefore be useful for risk stratification of developing malignant tachyarrhythmia in patients with partially preserved left ventricular function [46], but is not currently included in the criteria for an ICD placement [50]. This is partly due to the difficulty of giving a precise individualised risk from observations made from risk groups. The results of two prospective studies evaluating the efficacy of HRT (and other stratifiers such as percentage of ventricular extrasystoles and other HRV parameters) are waiting for the classification of patients who may benefit from prophylactic ICD implantation. The REFINE ICD (Risk Estimation Following Infarction Non-invasive Evaluation - ICD Efficacy) study involves myocardial infarction survivors with LVEF $>$35%). http//clinicaltrials.gov/ct2/show/NCT00673842. The EU-CERT-ICD study involved patients with ischaemic or non-ischaemic dilated cardiomyopathy with LVEF) $\leq$35%. http://clinicaltrials.gov/show/NCT02064192. Elevated values of TO and decreased values of TS and SDNN are associated with worse 1-year prognosis in heart failure with preserved ejection fraction patients [51].

The CARISMA study showed that abnormal TS was associated with an increased risk of new-onset AF as documented by implantable loop recorders [52]. Early AF onset after cardioversion can be predicted by a multivariate model consisting of TO, DC, and spectral and nonlinear HRV indices reflecting the ANS tone [53].

6. Deceleration capacity: phase-rectified signal averaging algorithm

One of the problems of spectral analysis is the non-stationarity of long-duration ECG recordings. Mathematical methods exist to overcome this but are complex and difficult to implement, such as empirical modal decomposition [54]. Indeed, the many internal and external physiological disturbances continuously influence the control systems and cause interruptions in the periodic behaviour. These interruptions have the effect of "resetting" the control processes, resulting in phase desynchronisation of the oscillations. The signal then becomes quasi-periodic. This risk becomes important for recordings longer than 5 min. Bauer et al. proposed to overcome this problem by averaging phase-rectified signals (PRSA for Bivariate phase-rectified signal averaging) [55]. This algorithm allows separate characterisation of HR deceleration (DC) and acceleration (AC) over long recording times. The idea is to align parts of ECGs with respect to anchor points. These anchor points are selected according to the AC or DC of the signal. Then windows of intervals are delimited around these anchor points and the values obtained from all the windows are averaged. The PRSA thus offers the possibility of selectively analysing periodic behaviours related to HR, which could provide more differentiated information about the autonomic regulation processes of the heart.

Age, sex, and circadian rhythm may be useful in the assessment of cardiac autonomic function and should be considered in the assessment of DC and HRV in clinical and scientific research. Zou et al. showed that DC capacity is an independent risk factor for dilated cardiomyopathy, and a predictor of heart failure exacerbation in patients with dilated cardiomyopathy [56]. The REFINE ICD study and the EU-CERT-ICD study discussed above should clarify the value of DC as a criterion for ICD placement.

Chen et al. suggested that AC and DC could distinguish and quantify the roles of the vagal and sympathetic nervous systems in discriminating AF recurrence before and after ablation. They showed that DC $<$4.8 ms or AC $>$ or $=$ $-$5.1 ms had significantly higher AF recurrence-free rates, that traditional HRV parameters were unable to distinguish [57]. Pan et al. investigated the correlation between DC and AC and ANS activity using an experimental model and showed that DC and AC reflect the same aspect of ANS activity and

depend exclusively on vagal activity [58]. High parasympathetic activity, reflected by DC capacity greater than 6.45 ms, allows for predicting the recurrence of AF after a repeated catheter ablation procedure [59].

7. Non-linear methods

The sequence of heartbeats can be considered a dynamic system that responds to linear and nonlinear laws [60]. Although non-linear methods have contributed to the technical understanding of the characteristics of the HRV signal, their success in developing new clinical tools, such as those to identify high-risk patients, remains very limited [61]. These methods are based on the demonstration that the heart rhythm exhibits deterministic chaotic behaviour. Although powerful, techniques for studying nonlinear dynamics remain research tools. These dynamic methods must be used with extreme caution because errors can be introduced at several stages of their implementation. Indeed, noise, nonstationary data, and sampling methods can distort the results.

a. High order spectra

The bispectrum provides information on the phase relationships between frequencies [62]. Higher order spectra (HOS) can be defined for deterministic signals but also random processes. They can detect deviations from Gaussianity and thus identify nonlinear systems [63]. Their main interest lies in their ability to extract information not revealed by spectral methods. As with the latter, two main approaches can be used: conventional non-parametric methods (FFT) and the parametric approach, based on an autoregressive model. They allow a qualitative assessment facilitating the differentiation between normal subjects and subjects with different pathologies. However, their added clinical value has not yet been demonstrated.

b. ECG and RR intervals series considered as non-linear dynamic systems

The term dynamic simply refers to phenomena that evolve over time. The cardiac cycle can thus be modelled from about 15 non-linear differential equations [64]. The surface ECG recording results from the set of ionic currents responsible for cardiac depolarisation and repolarization. Goldberger hypothesised the anatomic structure of the His Purkinje network is responsible for the chaotic nature of the resulting signal [65]. The decrease in autocorrelation function values overtime rules out periodic dynamics for the ECG signal, since for a periodic function, there is no time decay. Nonlinear dynamic analysis techniques begin with the reconstruction of the phase space portrait. The dimension of the reconstructed phase space is sufficient dimension to recover the object without distorting any of its topological properties [66]. The dimension of what physicists call the cardiac attractor is between 3.6 ± 0.1 and 5.2 ± 0.1 in young and healthy subjects [60]. The Lyapunov exponent is a measure of the exponential divergence of the trajectories of the attractor. It allows us to define a predictability horizon.

The succession of heartbeats presents a temporal evolution and as such, follows the laws of dynamic, deterministic, non-linear systems. The dimension of the RR intervals is between 5.5 and 6.1 in the normal young subject [60]. The approximate entropy (ApEn) measures the rate of generation of new information. A deterministic signal of high regularity has a very low value, unlike a random signal. The Sample Entropy (SampEn) algorithm is also used as a measure of complexity instead of the ApEn. The decay of ApEn is the only parameter that has been consistently reported in cardiological studies in search of pathophysiology [61]. It has been shown that the SampEn, progressively decreases during the sympathetic activation induced by the gradual head-up tilt test, thus providing an alternative measure of sympathovagal balance. Detrended fluctuation analysis (DFA) quantifies the short-term self-similar properties of the R-R interval time series: The short-term fractal scaling exponent (DFA1) is determined for 4–11 beat sequences of R-R interval data. DFA1 of 0.5 indicates a totally random signal and a DFA1 of 1.5 indicates one that is totally correlated [67]. The combination of low DFA1 and an abnormal HRT is a strong risk factor for cardiovascular death among older adults [68]. The link between nonlinear dynamics and fractals does not seem obvious but they are mathematical relatives because they both deal with irregularity. Nonlinear dynamics are part of mathematical analysis while fractals are geometrical techniques. Fractals allow us to understand the form of chaos. A strange attractor is now usually defined as a fractal object.

c. Linear and non-linear dynamics of ECG RR interval sequences analysis by geometric methods

The main advantage of geometric methods is their relative insensitivity to the analytical quality of the series of intervals between heartbeats. They are not very sensitive to noise. Their implementation in an

algorithm is easy and they have low algorithmic complexity. The interval sequence can first be converted into histograms, which already gives a good visual idea of the HRV. It is also possible to measure a triangular index that is computed as the integral of the density distribution of all NN intervals divided by the maximum distribution of that density [69]. Although theoretically appealing, it is only readily applicable for recordings in which the difference between mean nocturnal and diurnal HR is small. Indeed, in normal subjects, there is a clear difference between the daytime and night-time histogram, so that not one but two triangles can be distinguished. The two triangles merge in pathological cases. Finally, this triangular index has not really kept its promises and is not widely used.

i. Poincaré plots

There is some confusion in the literature about the name of these graphs, which are indifferently called Lorenz or Poincaré plots, first return maps, and recurrence graphs. These are scatter diagrams that show the R-R intervals as a function of the previous R-R intervals (Figure 4). Their use has been proposed to easily visualise the HRV. Nevertheless, quantitative analysis allows the calculation of the standard deviation of the instantaneous beat-to-beat HRV and the standard deviation of the long-term continuous beat-to-beat HRV. Although many authors report Poincaré plots as indicative of nonlinear dynamics, this is not the case because the correlation between them and the linear temporal and frequency parameters is almost perfect [70]. Hourly Poincaré plots from N-N intervals allow quantification of "erratic" sinus rhythm pattern (ESR). In elderly patients, they make it possible to discriminate between an increase in vagal tone and the appearance of a disorganisation of the rhythm preceding AF. ESR is associated with an increased risk of mortality [71] and this risk is getting higher after antiarrhythmic therapy among MI patients [72]. Poincaré plots have recently shown their usefulness for systematic AF screening by a convolutional neural network algorithm in Holter recordings [73]. These graphs allow visualisation of the global aspect of the rhythm, and their automatic recognition is likely to be used to facilitate the analysis of the big data of ECG recordings received by mobile health applications [74].

ii. Higher order difference plots

The interval variation diagram second-order difference plot (SODP) is constituted by the differences of the RRs compared to the previous differences [75]. It allows appreciating the VHFs since it reflects the dynamics over 2 beats by giving the percentage of ACs, DCs, immediate ACs-DCs and immediate DCs-ACs (Figure 5). The different number of points in the four quadrants clearly shows that there is a heartbeat dynamic that escapes traditional spectral analysis. Quadrant I indicates the DC of the HR over three successive RR intervals. An AC of the HR over three successive intervals gives quadrant III. Quadrant II is the location of all three intervals such that one long interval is surrounded by two short intervals. The opposite situation occurs in quadrant IV where a short interval is surrounded by two long intervals. SODPs can selectively measure parasympathetic activity over short durations of recordings, a difference from the PRSA algorithm which measures parasympathetic activity over longer periods of time on the order of 24H. The SODPs provide information on very rapid variations in HR, selectively linked to the vagal system and without the disadvantages associated with the aliasing phenomenon of spectral methods. The fact that the range of correlations in HRV plots extends over several data points provides a more accurate view of the dynamics compared with first-return maps, which allows discrimination of apparently identical dynamics. Sarkar et al. proposed to implement them in an implantable loop recorder. This algorithm is used to screen for AF in patients with cryptogenic stroke and to provide daily information on rhythm and rate control in patients with AF over a long period of time [76]. Thuraisingham et al. proposed a classification system to distinguish patients with congestive heart failure from normal patients using SODPs. The algorithm derived from SODPs showed a 100% correct classification score based on a small series of 36 patients [77].

8. Conclusions

All HRV measurements essentially reflect the modulations of the parasympathetic nervous system which superimposed on the impulses of the adrenergic system. Measurements performed over long periods such as 24H-SDNN, 24H-total spectrum power, DC capacity, and HRT provide information on the individual basal autonomic status. Spectral measurements performed over short periods (usually 5 min) provide information on the dynamics of systems that disrupt this basal balance and may be part of the triggers of arrhythmias, as well as premature beats. Graphical methods such as Poincaré plots allow quick screening of AF and are set to play an important role in the e-cardiology networks. Although mathematical and computational techniques allow manipulation of the ECG signal to extract

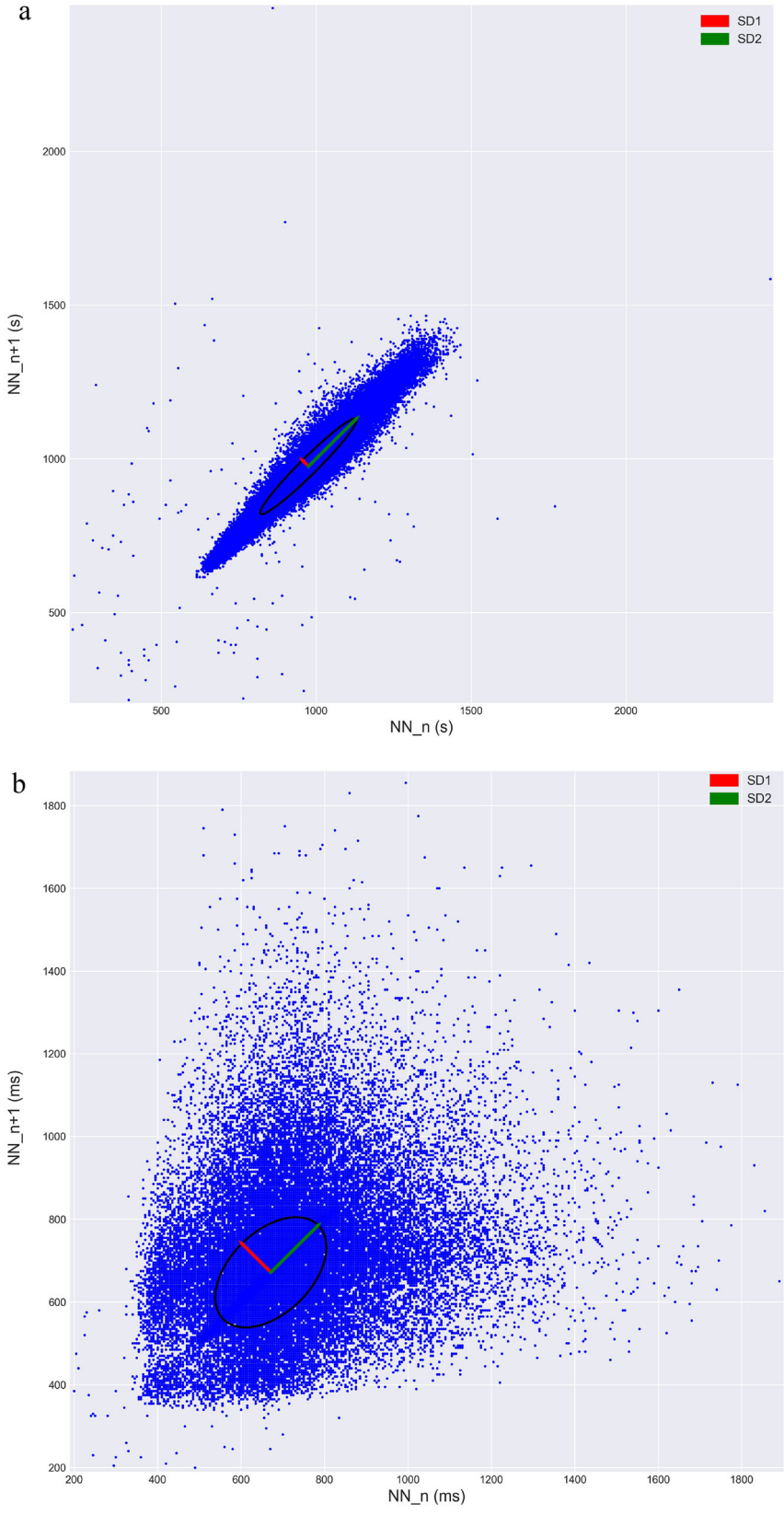

Figure 4. Poincaré plots: SD1 is the standard deviation of the instantaneous beat-to-beat variability and SD2 the standard deviation of the long-term continuous beat-to-beat variability. (a) normal patient. (b) AF patient.

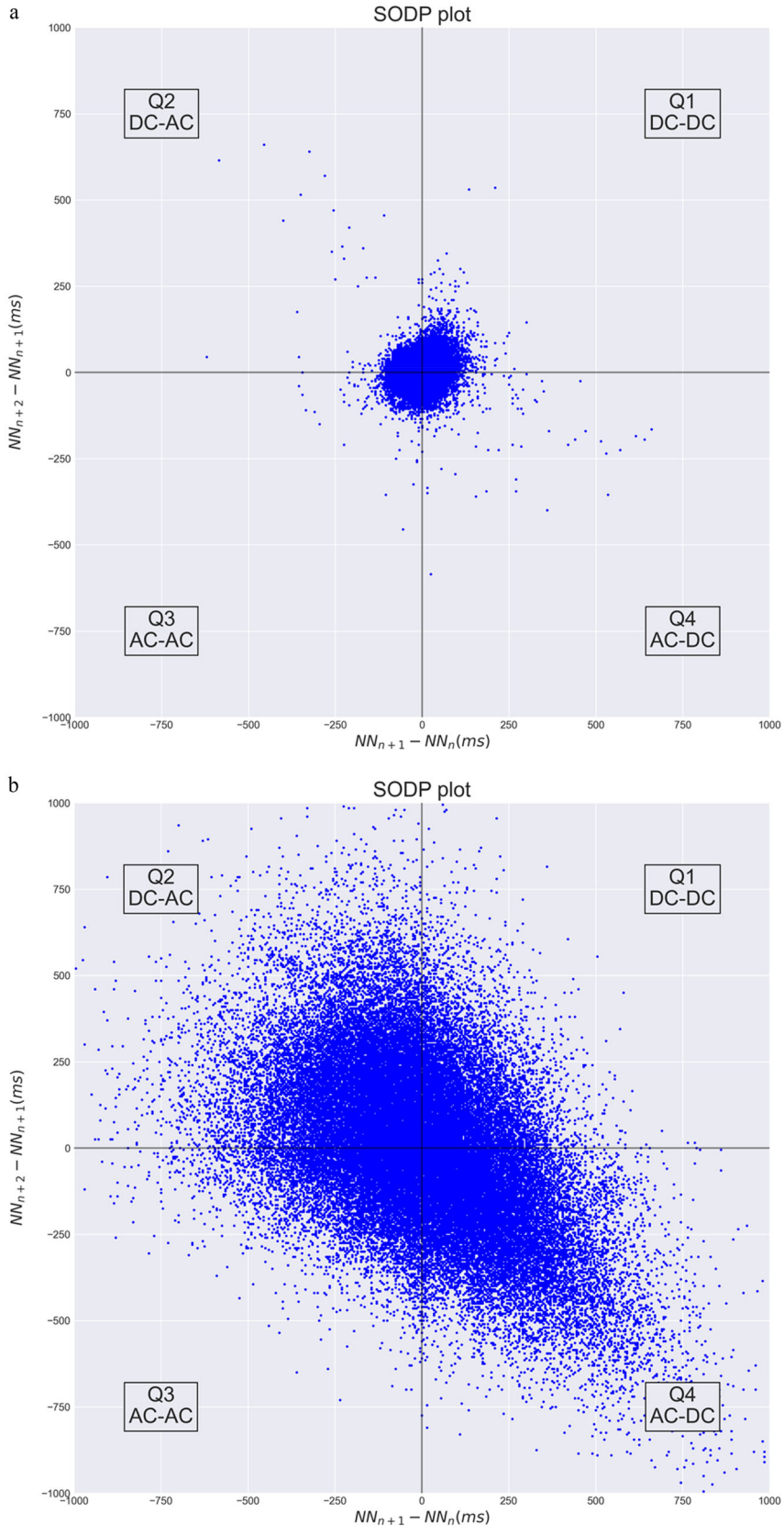

Figure 5. Second Order Difference Plots. (a) Normal subject: Division into 4 quadrants: Q1: DCs, Q2: DC/AC, Q3: ACs; Q4: AC/DC (DC: deceleration of the instantaneous heart rate; AC: acceleration). (b) Subject in persistent AF. (c) Subject in persistent AF: same scale and larger cloud when compared to the normal subject, showing larger points dispersion.

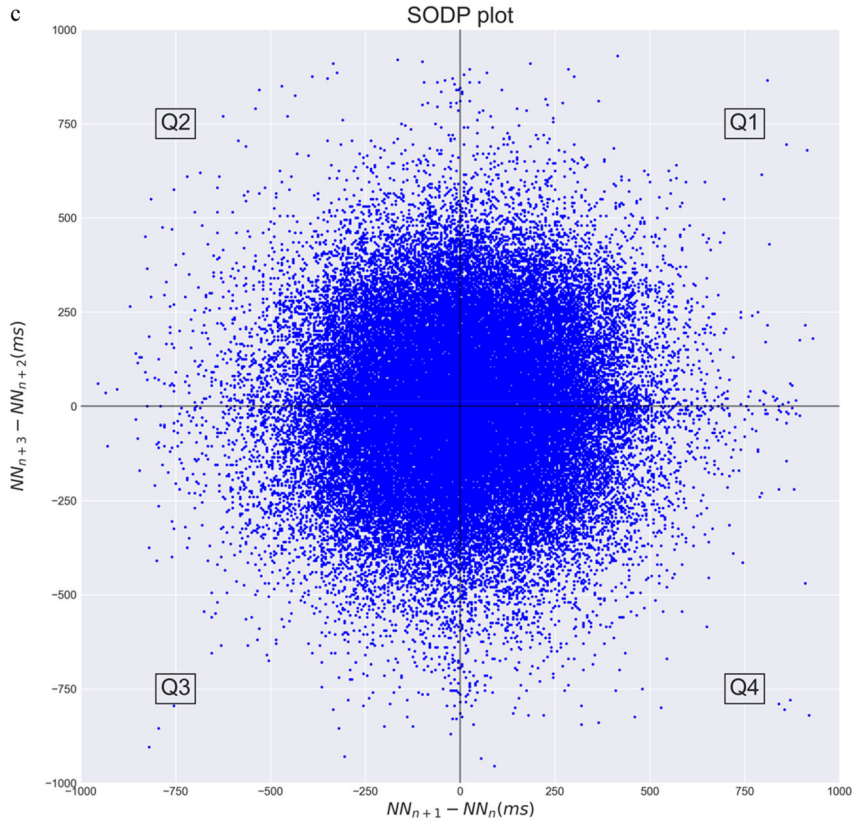

Figure 5. Continued.

information and permit their use in predictive models for individual cardiac risk stratification, their explicability remains difficult. Making inferences about the activity of the ANS from these models must remain cautious.

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