Power spectral and Poincaré plot characteristics in sinus node dysfunction

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The pacemaker cells of the sinoatrial node (hereafter sinus node) are usually regarded as a population of electrically coupled oscillators, synchronized by a mechanism of mutual entrainment or phase-locking (24, 29). A salient feature of the normal sinus rhythm is its variability at rest, which is dominated by respiratory and baroreceptor-related reflexes, can be described by differential equations, and can be almost completely abolished by parasympathetic blockade with atropine (4, 15, 22, 35).

Analysis of heart rate variability (HRV) attracts increasing interest on the assumption that it contains important information concerning the interaction between the cardiovascular and neurological systems. Different methods of HRV analysis are used, but power spectral analysis is a major one (21). All methods have one thing in common: the sinus node is the effector organ, the function of which therefore is crucial but rarely questioned. Although symptomatic sinus node dysfunction, often referred to as sinus node disease (sick sinus syndrome), is a common cause of permanent pacemaker treatment (34), the prevalence of asymptomatic sinus node dysfunction, which might affect HRV analysis, is virtually unknown, owing primarily to lack of reliable screening methods. Numerous previous studies on HRV have addressed any of three main issues: 1) the diagnosis of autonomic dysfunction or neuropathy by the reduction or absence of HRV; 2) the prognostic information contained in the HRV as a reflection of the overall activity of the autonomic nervous system in particular the magnitude of sympathetic stress; and 3) whether the normal HRV shows chaotic (nonlinear deterministic, aperiodic) behavior.

Whereas the power spectrum of the normal sinus node-related HRV characteristically shows an inverse power law relationship (1/f, where f is frequency) with a negative slope around −1, independent of time scale (20, 37, 42), the behavior in sinus node dysfunction is incompletely known. We have previously described seemingly haphazard variations around the mean sinus cycle length in patients with sinus node disease (7, 9). The hypothesis of this study was therefore that these variations would be reflected by the short-term spectral power and Poincaré plot characteristics.

METHODS

Subjects

Three groups were included: 1) thirty patients with the sick sinus syndrome (20 women; mean age ± SD: 73 ± 8 yr; range 54–88). All had sinus bradycardias and symptoms with a proven or strongly suspected relation. Twenty-six had sinus bradycardia ≤40 beats/min, and 19 had sinus pauses ≥2.5 s. Syncope was the dominating symptom in 14 patients and presyncope or dizzy spells in the remainder. They all had time series suggesting sinoatrial node dysfunction (9), and all 27 patients who had been catheterized also had abnormal sinus node recovery times (28) (see Methods for Defining Study Groups). These patients were therefore diagnosed as suffering from the sick sinus syndrome and constitute the study group. Eighteen patients had evidence of concomitant cardiovascular disease such as hypertension, congestive heart failure, ischemic heart disease, or radiographic cardiomegaly. 2) Another group of 30 patients (24...
men; mean age ± SD: 56 ± 10 yr; range 35–77) with clinically significant ischemic and/or valvular heart disease, of whom 11 had received surgical treatment, was recruited to serve as a control group for comparison with the study group. To be included they should neither have any clinical evidence of sick sinus syndrome, i.e., symptoms of slow or rapid heart rates or brief, sudden episodes of syncope or presyncope, nor should they have any treatment with negative chronotropic drugs that could suppress sinus node function. They were studied when coming for routine exercise tests or standard ECG recording. Four of them were found to have asymptomatic sinus node dysfunction according to the preceding analysis of sinus cycle variations in their time series, but the remaining patients had no evidence of such dysfunction. 3) A third group consisted of 10 younger individuals (6 men; mean age 28 yr; range 22–34), who were considered healthy on the basis of clinical history, physical examination, laboratory screening tests, and a standard surface ECG. They had previously participated in a comparative study of the antiarrhythmic substance disopyramide and its main metabolite (10). Their sinus cycle variations, as assessed from the time series, were within the age-stratified reference values, and their baseline sinus node recovery times were normal. They were included as an “internal control” of the method, showing that short-term samples provide similar information to more extended sampling periods in healthy individuals used in previous studies, in accordance with the concept of self-similarity on different scales. In addition, they were studied repeatedly and therefore provide information on the short- and long-term time-dependent variations (8).

The invasive procedure was part of the clinical evaluation for pacemaker treatment in the sick sinus patients and part of a pharmacology study protocol approved by the Ethics Committee of Karolinska Institutet in the healthy subjects (10). All individuals gave their consent before participation.

Data Collection

The atrial myocardial electrical activity, reflected by the P wave on surface ECG and by the A wave in invasive endocardial recordings from the right atrium, was used to monitor the overall output of the sinus node. To ensure sinus node origin of this activity and exclude ectopic origin, both the P wave morphology and vector in the frontal as well as in the sagittal plane of surface ECG recordings or simultaneous endocavitary recordings from two positions in the right atrium were used in healthy subjects and sick sinus patients. Six surface standard ECG leads were used in control patients with cardiovascular disease. Recordings were made in a standardized fashion with a multichannel ink-jet recorder (Siemens-Elema, Solna, Sweden) at a paper speed of 50 or 100 mm/s for a period of between 1 and 2 min, preceded by supine resting with closed eyes for ≥5 min. All cardiac cycles including either atrial or ventricular ectopic activity were excluded to reduce noise (37). The remaining cycles of sinus node origin were then treated as a sequence of consecutive intervals, because we have previously shown that single ectopic beats do not cause significant perturbations of sinus node activity (9), and interpolation with an average cycle might introduce an artifact in the variability in sinus node disease. All cycles were then measured with a digitizing equipment (Calcomp 2000, Digitizer Products Division, Anaheim, CA), working in point mode (10 lines/mm, accuracy ± 0.635 mm). They were then analyzed in the time and frequency domains by construction of time series, Poincaré plots (return maps), power spectra, and the logarithmic transformation of power spectra.

Methods for Defining Study Groups

Long-term ECG recording was used to document sinus bradycardia (<50 beats/min) and sinus pauses (here: ≥1.8 s) and to prove their relation to symptoms in sick sinus patients, the “Golden standard” for diagnosis (5). Sinus node recovery time assessment was performed by measuring the return cycle after abruptly terminated atrial overdrive pacing delivered via an endocavitary catheter (28). Our routine protocol has been described elsewhere (11). It has a sensitivity of >70% in patients with proven sick sinus and a specificity close to 100%, and it is comparable to other protocols (5). The reproducibility of sinus node recovery time assessment is ~70% in sick sinus patients, higher in healthy subjects (1, 17). Analysis of short-term sinus cycle variations is a new noninvasive screening method, which has been

![Fig. 1. Recordings from a young healthy individual obtained on 4 occasions, 2 baseline recordings separated >20 min at each study separated at least 14 days, presented superimposed. A: time series. B: Poincaré plots (sometimes referred to as Lorentz plots, or return maps). C: Poincaré plots corrected or normalized for the mean of all R-R intervals.](http://jap.physiology.org/)
described in detail elsewhere (7, 9) and was used together with the recovery time assessment to diagnose sinus node dysfunction. In summary, the sinus cycle variations of 1-min time series were defined from two variables: the sinus cycle variation range around the mean cycle length (in %) and the maximal change in cycle length between any two consecutive intervals (in ms), which were then compared with age-stratified reference limits defined from a healthy population (7, 9). Abnormal sinus node function was diagnosed when both variables were increased. This method also has a sensitivity of 70%, a specificity of 100%, a reproducibility of 70%, and an excellent diagnostic concordance with recovery time assessment in sick sinus patients (9).

Methods for Analysis of Dynamical Behavior of the Sinus Node

**Time domain analysis.** Poincaré plots (return maps), correlating observation \( n \) on the \( x \)-axis with observation \( n + 1 \) on the \( y \)-axis, were used to study the sinus node activity as a series of discrete events. Each interval in the sequence is first \( n \) and then \( n + 1 \) until each interval in the time series has been plotted against its successor. This method was introduced by Shaw to differentiate between random nonperiodic behavior and chaotic activity of the dripping faucet (38), and its usefulness has since been demonstrated in different systems (6). Return maps can be modified in different ways. In

Fig. 2. Recording from a patient with the sick sinus syndrome. All cycles are of verified sinus node origin. A: time series with very exaggerated beat-to-beat-variations. B: Poincaré plot. C: Poincaré plot corrected for the mean R-R interval.

Fig. 3. Recording from another sick sinus patient showing an intermediate pattern compared with Figs. 1 and 2. All cycles are of verified sinus node origin. A: time series with most cycles with small variations typical for the aged sinus node behavior interspersed with exaggerated sinus node variations. B: Poincaré plot. C: Poincaré plot corrected for the mean R-R interval, which in this case appears very similar.
this study, “normalization” by division with the mean R-R interval was employed to allow between subject comparisons of the plots, i.e., the variation around the mean R-R interval (Fig. 1).

**Frequency domain analysis.** Power spectra were obtained by a customized software for discrete Fourier transform (DFT) of the time series. The program was written in Microsoft Quick BASIC for Macintosh. Fast Fourier transform (FFT) is often preferred to DFT because of its shorter calculation time. However, the number of data calculated by the FFT needs to be 2"(2, 4, 8, 16, 32, 64, 128, 256, . . .). In this study, the number of the measured intervals (cardiac cycles) in a data set was ~100 (corresponding to a sampling time of ~2 min), and DFT was employed instead of FFT to utilize limited numbers of data. The power spectra were further arranged in logarithm to analyze whether they followed 1/f distribution.

**Statistical Analysis**

Comparisons were made between the two groups of sick sinus and control patients, because they were closer in age and HRV is strongly inversely related to age, although with only minor additional changes above 50 yr of age (7). Because of the skewed distribution of data, a nonparametric test (Mann-Whitney rank sum test) was used for between-group comparisons of correlation and regression coefficients as well as for the ranges of the return map plots. The $\chi^2$ test was used for comparing the distribution of the three different patterns of the return maps. Standard definitions were used for sensitivity and specificity. Calculations were made with StatView 4.01.

**RESULTS**

**Poincaré Plots**

In the young, healthy individuals, all plots had a similar ellipsoid pattern of points gathered along the identity line (Fig. 1), in accordance with previous observations using a 24-h sampling time (40). This pattern was reproducible when results from recordings obtained 20–30 min apart, as well as an average 25 days apart (range: 14–63 days), were compared in overlay graphs. In three individuals, some points were detached from the main group, suggesting the presence of strong, probably parasympathetic (vagal) perturbations. In the sick sinus patients, three different patterns were observed: 3 patients had a pattern that appeared completely normal (type 1); 9 patients had a randomlike pattern (suggesting although not proving random behavior; see Limitations) (type 2) (Fig. 2); and the remaining 18 patients had a pattern that represented a transition between types 1 and 2 with one well-defined group of points along the identity line as in healthy individuals, whereas a varying number of points were scattered (type 3) (Fig. 3). In the control patients, the normal pattern was observed in 27 (90%) of the cases, but generally with a more concentrated or circular group of points than in the younger, healthy individuals, consistent with the well-known decreased variability with increasing age (Table 1). In three of the four patients with asymptomatic sinus node dysfunction in this control group, a “transitional” type 3 pattern was observed. The pattern distribution was significantly different when the sick sinus patients were compared with the control patients ($\chi^2$ test, overall analysis $P < 0.0001$, with Bonferroni correction $P < 0.01$).

Expressed as the correlation coefficient of the return map, these were $\geq 0.6$ in the great majority of the recordings from the healthy subjects and the control patients, $\geq 0.5$ in 90 and 80%, respectively. In contrast, it was $<0.5$ in 75% of the sick sinus patients; 11 of them actually had negative correlation coefficients (Table 1).

In the healthy subjects and the control patients the points of the plots were concentrated within $\pm 20\%$ of the mean R-R interval, corresponding to a range of the normalized plot between 0.8 and 1.2. In sick sinus patients the average spread around the mean interval was between two and three times that in the other two groups (Table 1).

**Frequency Domain (Power Spectral) Analysis**

In healthy individuals, a high-frequency peak indicating respiratory sinus arrhythmia and a low-frequency component corresponding to the Mayer wave were recognizable between 0.1 and 0.3 cycles/beat in the time domain (Fig. 4A). In control patients, the respiratory component and the Mayer wave were still recognizable in most of the cases. However, in sick sinus patients the spectra were closer to the white

<table>
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<tr>
<th>Table 1. Correlation coefficients and the variability ranges around the mean R-R interval of the Poincaré plots</th>
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<tr>
<td>Poincaré Plot (return map)</td>
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<tr>
<td><strong>Correlation coefficient</strong></td>
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<td>Range</td>
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<td><strong>Variability range around mean R-R interval</strong></td>
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<td>range</td>
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The same data sets were used as in Table 2. In addition, all healthy subjects were assessed 4 times, and the means, standard deviations, and ranges based on the individual average value of the 4 observations are included within parentheses to allow comparison. *The statistical comparison was performed for sick sinus vs. control patients, $P < 0.0001$, Mann-Whitney’s rank sum test.
noise than in the other two groups, and peaks corresponding to respiration and Mayer wave were indistinguishable in the majority of cases (Fig. 4B).

**Power Law Relationship**

Logarithmic arrangement of the frequency spectra disclosed that the healthy subjects and control patients had patterns close to $1/f$ distribution, in agreement with previous observations (20, 23, 37, 42), whereas the sick sinus patients had lost this pattern and the spectra were more like those for white noise (Fig. 5, A and B). Linear regression analysis including the definition of the slope (normally around $-1$) showed the highest correlation in the healthy subjects and lowest in the sick sinus patients; the control patients were in between but closer to the healthy subjects. Thus the regression lines had negative slopes in healthy subjects and control patients, but the slope was close to zero or even positive ($>-0.2$) in 16 of 29 sick sinus patients (one excluded for technical reasons) (Table 2).

**DISCUSSION**

According to our results, the very complex dynamic behavior of the healthy sinus node, which shows $1/f$
that large peaks of noise masked normal 1/f sinus patients. An explanation for the mechanism is that intrinsic cardiac events. Precisely those peaks should therefore not be regarded as meaningless noise, and the apparent loss of 1/f distribution pattern in sick sinus patients may well be considered as the loss of normal biological fluctuation in cardiac intervals.

Methods of Analysis

The use of Poincaré plots (return maps) was introduced by Shaw to differentiate between random non-periodic behavior and chaotic activity of the dripping faucet (38). Because the interaction between the sinus node and the atrium and the resulting heart beats also are discrete events, the Poincaré map was applied in this study. Both the Poincaré plots and the power spectral analysis suggest a randomlike pattern of behavior of the sinoatrial activity in nine of our sick sinus patients. A randomlike behavior of the ventricular response in atrial fibrillation has also been observed in serial autocorrelation analyses of data series of ~2,000 intervals (12) and in the short-term component in a 24-h study (23). When the result of the studies on the ventricular response in atrial fibrillation, the analysis of ventricular fibrillation (26), and our own data on sick sinus patients are considered, a general feature of arrhythmia development seems to appear.

Spectral analysis with the Fourier transform thus failed to show 1/f distribution in the majority of the sick sinus patients. An explanation for the mechanism is that large peaks of noise masked normal 1/f fluctuation, of which amplitude is small in higher frequency domains. This can be paraphrased that the noise in cardiac R-R interval distribution increased and signal-to-noise ratio decreased in patients with sick sinus. However, the noisy peaks in the spectra of such patients do not derive from extrinsic noise, but they reflect intrinsic cardiac events. Precisely those peaks should therefore not be regarded as meaningless noise, and the apparent loss of 1/f distribution pattern in sick sinus patients may well be considered as the loss of normal biological fluctuation in cardiac intervals.

Normal and Abnormal Sinus Node Behavior

On the whole, the normal sinoatrial activity reflects a stable, oscillating system, which after perturbations will return rapidly to the main trajectory (24, 29). It is unclear whether the normal vagally mediated perturbations mainly serve a homeostatic physiological purpose or also have a trophic effect on the pacemaker cells. Neural input to a skeletal muscle is essential for its persistent normal function. There is evidence suggesting that this is the case also for the sinus node pacemaker cells. Thus spectral analysis of the sinus node activity has shown patterns of broad-band or white noise in most recipients of a completely denervated heart (transplant patients), just as in our sick sinus patients, but in one case a normal pattern was observed, suggesting reinnervation (19, 36). Furthermore, symptomatic sinus node dysfunction is the main indication for treatment with artificial pacemaker in heart transplant patients, although other mechanisms for the arrhythmia than denervation might exist (18). There are several factors influencing both the automaticity of the pacemaker cells and the conduction of the sinus impulse, knowledge of which is limited (5). Coupling of pacemaker cells is a prerequisite for regular beating (25, 32), and it can be assumed that uncoupling by fibrosis, fatty infiltration, and so forth might form the histopathological background to the beat-to-beat irregularities observed in sick sinus patients.

Clinical Implications

Because 27 of 30 sick sinus patients (90%) and 3 of 4 control patients with asymptomatic sinus node dysfunction had abnormal patterns, the use of Poincaré plots based on short-term recordings offers a diagnostic method based on pattern recognition. Spectral analysis might be an alternative. The correlation coefficient and the range around the average of the Poincaré plot are both parameters expressing beat-to-beat relations in the return map. Although they came out significantly different at group comparisons (Table 1), they do not offer significant diagnostic advantages compared with the graphs because of overlap between the groups. Low coefficients were observed not only in sick sinus patients with randomlike or transitional patterns but also in healthy individuals with strong (probably vagal) perturbations as well as in control patients with low heart rate variability. Generally, the same conclusions apply to the correlation and regression coefficients from the frequency domain analysis (Table 2). Although analysis of HRV might be applied with confidence in studies of the activity of the autonomic nervous influence in healthy individuals, the possibility of sinus node dysfunction, whether symptomatic or asymptomatic, should as far as possible be ruled out before such analysis is attempted in patients with cardiovascular disease, because the results otherwise might become significantly distorted.

As to the physiological consequences of the change in dynamical behavior observed in sick sinus patients, the evidence is circumstantial. Atrial fibrillation is com-

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<th>Logarithms of Power Spectra</th>
<th>Healthy subjects (n = 10)</th>
<th>Control patients (n = 30)</th>
<th>Sick sinus patients (n = 29)</th>
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<tr>
<td>Correlation coefficient</td>
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<tr>
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<td>−0.59</td>
<td>−0.09*</td>
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<tr>
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<td>0.25</td>
<td>0.32</td>
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<tr>
<td>Range</td>
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<td>−0.98 to −0.03</td>
<td>−0.81 to −0.56</td>
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</tbody>
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*The statistical comparison was performed for sick sinus vs. control patients, P < 0.0001, Mann-Whitney’s rank sum test.
mon in patients with sick sinus. Because cardiac pacing from the atrium reduces not only bradycardia-related symptoms but also the risk for atrial fibrillation and the related thromboembolic events, the functional disturbance of the sinus node behavior has deep impact on morbidity (2, 3). Thus it is of note that loss of 1/4 sinus node behavior predisposes for atrial fibrillation, which is characterized by a similar pattern (12, 23). Regarding the physiological consequences of the irregularity per se, we also need to refer to studies (12, 23). Regarding the physiological consequences of bradycardia, which is characterized by a similar pattern (14, 16, 27, 30, 31, 39). Whether the random-like distribution of cardiac cycles in sinus node disease, which results in highly variable stroke volumes, pulse wave amplitudes, and shear stress on the vessel walls, impairs endothelial function remains to be studied. Nitric oxide synthase is regulated by flow-mediated shear stress, and in an experimental model it was recently shown that atrial fibrillation is associated with endocardial changes that might promote the occurrence of thromboembolic phenomena (15). It is therefore conceivable that sick sinus-associated variations in shear stress also might have importance for nitric oxide synthase expression and nitric oxide production.

**Limitations**

The atrial electrical activity reflects the overall sequence when a sinus node impulse reaches and propagates through the atrial myocardium, which undoubtedly is the biologically important sequence of events. By direct recording techniques of the sinus node activity, it has been shown that sinus pauses after tachycardias or after electrical atrial stimulation in sick sinus patients might be due either to impaired automaticity of the sinus node, to impaired sinoatrial conduction, or to a combination (41), which possibly was reflected by the different patterns we observed in sick sinus patients. Direct recording techniques might therefore disclose more about the dynamics of the transition from the healthy to the malfunctioning sinus node. The study and control groups were not perfectly matched for age and gender; the study group had more women and somewhat higher age. This would, however, lead to a relative decrease rather than increase in the beat-to-beat variability in the study group, and the opposite in the control group, consisting of slightly younger patients and more men, bringing the two groups closer to each other. As a result, the observed differences in this study would rather be less than for perfectly age and gender matched groups. Furthermore, there are certain problems inherent in the study of the dynamical behavior of cardiac arrhythmias. One is the salient feature of instability. The size of the data sample is also crucial, but the requirements vary depending on the method. Expanded data series are desirable but in the setting of clinical arrhythmias are bought at the expense of increased instability. Normally and for most arrhythmias, the heart beat is a discrete event and might be studied as such. However, in certain types of ventricular arrhythmias such as ventricular fibrillation, also characterized by severe global hemodynamic consequences and a very short time course, there are no discrete ECG events and other methods of analysis must be used (26). Different arrhythmias therefore need to be studied according to their specific features and circumstances, and comparisons are risky. Thus we do not claim to present definite proofs of random behavior as sinus node dysfunction develops. We do, however, demonstrate the loss of the inverse power law relationship (1/4) and the discriminative power of the analysis of the dynamical behavior for separating normal and abnormal sinus node behavior.

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