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CLINICAL REVIEW

Heart rate variability, sleep and sleep disorders

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SUMMARY

Heart rate (HR) is modulated by the combined effects of the sympathetic and parasympathetic nervous systems. Therefore, measurement of changes in HR over time (heart rate variability or HRV) provides information about autonomic functioning. HRV has been used to identify high risk people, understand the autonomic components of different disorders and to evaluate the effect of different interventions, etc. Since the signal required to measure HRV is already being collected on the electrocardiogram (ECG) channel of the polysomnogram (PSG), collecting data for research on HRV and sleep is straightforward, but applications have been limited. As reviewed here, HRV has been applied to understand autonomic changes during different sleep stages. It has also been applied to understand the effect of sleep-disordered breathing, periodic limb movements and insomnia both during sleep and during the daytime. HRV has been successfully used to screen people for possible referral to a Sleep Lab. It has also been used to monitor the effects of continuous positive airway pressure (CPAP). A novel HRV measure, cardiopulmonary coupling (CPC) has been proposed for sleep quality. Evidence also suggests that HRV collected during a PSG can be used in risk stratification models, at least for older adults. Caveats for accurate interpretation of HRV are also presented.

Introduction

Heart rate (HR) is modulated on a beat-to-beat basis by the combined effects of the sympathetic (SNS) and parasympathetic (PNS) nervous systems on the sino-atrial node. Therefore, analysis of changes in HR over time (heart rate variability or HRV) provides information about autonomic functioning. In clinical conditions associated with autonomic dysfunction, (e.g., congestive heart failure, diabetes, end-stage renal disease, etc.), abnormal, usually decreased, HRV is generally found. Moreover, abnormal HRV is an independent risk factor for mortality both in clinical and population studies.[1] It should be noted that HRV cannot reflect autonomic "tone" which can only be measured using pharmacological blockade. Moreover, HRV is a black box with HR as the output. Hence the cause of decreased HRV, whether a lack of central signaling, lack of reflex feedback to the central nervous system or lack of responsiveness of the heart itself, cannot be determined.

HRV is generally derived from mathematical analyses of intervals between normal heart beats (NN intervals) and requires patients to be in sinus rhythm for most measures to be meaningful from HRV alone. However, one HRV measure, HR turbulence, is based on the NN interval response to ventricular ectopic beats.

Although millions of continuous polysomnogram (PSG) electronic electrocardiogram (ECG) signals from which HRV could potentially be calculated have been stored, the potential for obtaining additional, clinically relevant information from them has scarcely been tapped. At the same time, there are a huge number of 24-h Holter recordings, and increasingly, multi-day telemetry recordings from which not only HRV, but clinically relevant information about sleep could be derived, yet these important data are generally ignored. Thus, in the current review, we will focus on a basic understanding of HRV and then on potential sleep-related clinical applications of HRV from both PSG ECGs and 24-h ambulatory recordings. For each section, a table will be provided that describes the population and methods for citations.

Measurement of HRV

The starting point for HRV analysis is a list (a "beat file") of the intervals in milliseconds between heart beats on the ECG recording that includes the morphology of each heart beat so that normal, ectopic, paced beats and artifact can immediately be identified. Although beat files (or RR interval files) can be exported from many

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Table 1
Time-domain HRV measures.

AVNN (ms)	Average of NN intervals for period of interest	Can convert to average HR of NN intervals (HR = 60,000/AVNN)
SDNN (ms)	Standard deviation of NN intervals for period of interest	Reflects total HRV
SDANN (ms)	Standard deviation of AVNN for 5-min intervals for period of interest	Reflects primarily circadian HRV
SDNNIDX (ms)	Average of 5-min standard deviations of N–N intervals for period of interest	Reflects average short-term HRV and combined SNS and PNS influences
pNN50 (%)	Percent of NN intervals > 50 ms different from previous (NN) for period of interest	With normal sinus rhythm reflects vagal activity
pNN625 (%)	Percent of NN intervals different from previous by 6.25% or more of local AVNN (NN) for period of interest	With normal sinus rhythm reflects vagal activity normalized by HR
rMSSD (ms)	Root mean square of successive differences of NN intervals for period of interest	With normal sinus rhythm reflects vagal activity
CV	Average coefficient of variance (SD/Mean) for 5-min intervals for period of interest	Reflects average short-term HRV normalized by HR

HR: heart rate.
HRV: heart rate variability
PNS: parasympathetic nervous system
SNS: sympathetic nervous system

PSGs, they usually do not have morphology annotations. Thus generating an accurate beat file generally requires some form of Holter scanning, just as PSG software determinations of sleep parameters need to be over read to provide an accurate sleep study. The ECG channel can easily be exported to a Holter scanner for accurate beat detection and annotation. However, because certain HRV measures are relatively insensitive to scanning error when calculated over a longer period of time, the clinical utility of HRV parameters derived from PSG RR interval files, perhaps with appropriate filtering for clearly ectopic beats, bears investigation.

Traditionally, HRV is measured in the "time domain" and the "frequency domain." Time-domain HRV (Table 1) is a set of statistical measures derived from the beat file. The most commonly used ones are described below. The most global HRV measure is SDNN (the standard deviation of all NN intervals). SDNN is usually measured on the entire recording, but it can be measured on any segment (e.g., every 5 min) or during specific sleep stages. It captures total HRV and is one of the measures that are relatively insensitive to small errors in scanning. In the late 1980s, 24-h SDNN < 50 ms was shown to identify post-myocardial infarction (MI) patients at an adjusted risk of 5.3 for mortality over a mean of 31 months follow-up compared to patients with SDNN > 100 ms.[2] Adjustment for covariates did not explain this association, although relative risk declined to 2.8. However, in the era of modern therapy, the utility of SDNN *per se* to predict survival has been attenuated because of the markedly reduced prevalence of very low SDNN, although other HRV measures continue to risk stratify post-MI patients.[3]

A similar measure to SDNN is SDANN, which is the standard deviation of the 5-min averages of interbeat intervals. It is insensitive to scanning error. However, because low global values for these measures are primarily driven by a lack of circadian rhythm, it is unclear how useful they would be as global measures of HRV during PSGs.

Other time-domain HRV measures capture more short-term variations in HR. SDNN index is the average of the 5-min standard deviations of NN intervals. The degree to which HRV changes on a beat-to-beat basis is reflected in two common time-domain measures, pNN50 (the % of beats where the change from one beat to the next is > 50 ms) and rMSSD (the average change in interbeat interval between beats). These are measured over the entire recording, but can easily be measured over specific time periods (e.g., for each 5 min) or by sleep stage.

When patients are in truly normal sinus rhythm, both rMSSD and pNN50 reflect PNS control of HR, and changes in these parameters, e.g., between sleep stages, serve as markers of changing PNS activity. This is because changes in PNS nerve traffic mediate HR through changes in acetylcholine binding, which is instantaneous, whereas changes in SNS nerve traffic are mediated by a complex signaling cascade that is initiated by the binding of norepinephrine, resulting in a time delay before they can be affected. Thus, changes in HR at (faster) respiratory frequencies (respiratory sinus arrhythmia or RSA) are due to PNS signaling, although when breathing gets slower than ~9 breaths/min, HR changes will reflect both SNS and PNS nerve traffic.

Sleep is an excellent time to measure PNS function because HR is primarily under PNS control during supine rest and RSA becomes prominent. As will be described in more detail in a later section, however, rMSSD and pNN50 measures are problematic, because they cannot differentiate between increased HRV due to RSA and HRV due to scanning error (uneven beat detection, missed or misclassified beats) or from irregular HR patterns (erratic rhythm) that are not reflective of better PNS functioning.[4] This phenomenon is illustrated in Fig. 1 which shows the HR tachogram and the HR tachogram integrated with PSG respiratory signals during a period of normal sinus rhythm and one of erratic rhythm in the same subject. As can be seen, HR fluctuations correlate poorly with respiration during erratic rhythm and closely track them during true sinus rhythm. On the other hand, markedly decreased values for PNS HRV measures, whether from a PSG RR interval file or from Holter scanning, would reliably reflect severely blunted autonomic control of HR.

Frequency domain HRV (Table 2) parses out the variance in beat-to-beat HR into its underlying components at different frequencies using fast-Fourier transforms (FFTs) or equivalent techniques. It should be emphasized that calculation of most frequency domain HRV requires a condition called "stationarity," i.e., that the mean and variance of the signal do not change significantly at different points in the recording. In order to roughly meet this requirement, some frequency domain HRV measures are calculated over shorter intervals, e,g., 5 min or less, and averaged as needed but this also means that some frequency domain measures are less useful when the HR is changing rapidly. Frequency domain HRV measures have their counterparts in the time domain but often perform better in risk models. Values are generally skewed and most analyses are performed on natural log-transformed values. Total power, when measured over 24 h, should be very similar to SDNN squared, since the variance is mathematically the square of the standard deviation. Ultra low frequency power (ULF) is mathematically similar to SDANN.[5] It reflects