A Possible Method to Predict Response to Non-Pharmacological Insomnia Therapy

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Study Objectives: To determine if electrocardiographic parameters are predictive of response to non-pharmacological insomnia therapy.

Design: Secondary analysis of heart rate parameters from a double blind, randomized, sham-controlled trial at multiple study sites.

Setting: Six sites in the United States were used for the data collection.

Participants: One hundred ninety-eight healthy subjects with no sleep disorders.

Interventions: Subjects were studied on 2 consecutive nights, a baseline night and a therapy night. On the therapy night, subjects were phase advanced 4 h and randomized to receive either sham or vestibular stimulation, an experimental therapy for insomnia.

Measurements and Results: ECG data were recorded and analyzed for the 5-min periods preceding and following sleep onset. Analyses were conducted on those who did and did not respond to therapy, as defined by latency from bedtime to per-

sistent sleep (LPS). Responders to therapy were found to have higher low-frequency (LF) power at baseline during wakefulness than non-responders, and responders had higher high-frequency (HF) power during therapy than non-responders on therapy. Furthermore, responders > 35 y had elevated LF power at baseline than non-responders > 35 y ($p < 0.05$). No differences were seen in the sham group in identical analyses, ruling out a nonspecific effect of sleep onset.

Conclusions: Heart rate variability analyses indicate that differences exist between those who respond to insomnia therapy and those that do not, particularly in an older subset of subjects. Further research into the use of ECG and other physiological parameters to stratify response to therapeutic interventions is warranted.

Keywords: Heart rate variability, aging

Citation: Campana LM; Clifford GD; Trinder J; Pittman SD; Malhotra A. A possible method to predict response to non-pharmacological insomnia therapy. *J Clin Sleep Med* 2011;7(4):370-375.

Insomnia is a heterogeneous disorder, with multiple possible causes that result in a common symptom. For example, insomnia can result from a variety of medical or psychiatric disorders, medications, or be the result of heightened arousal.^{1,2} An intervention targeted at only one possible cause of insomnia will require a considerable sample size to show a treatment effect. Better patient characterization and selection might help limit interventions to those patients most likely to respond. If such a technique could be developed, therapeutic approaches to insomnia could be investigated in a more cost-effective and focused manner, while minimizing risk and expense for probable non-responders. Some investigators have suggested that physiological parameters may be a useful method to classify insomnia patients (particularly those with psychophysiological insomnia) and thus may be used to stratify responsiveness to therapy.²

Bonnet et al.^{2,3} have suggested that electrocardiographic (ECG) parameters may be markers of hyperarousal in insomnia patients. Although heart rate variability (HRV) analyses have been widely mistrusted regarding their ability to define sympathetic and parasympathetic activity,^{4,6} most investigators believe that these parameters have some physiological significance.⁷ While low-frequency (LF) and high-frequency

BRIEF SUMMARY

Current Knowledge/Study Rationale: One potential cause of insomnia is hyperarousal, and it has been hypothesized that heart rate variability (HRV) measurements can be used as markers of hyperarousal. We propose that physiological variables may be useful in stratifying response to insomnia therapy.

Study Impact: This study found that HRV metrics were different between those who responded to the insomnia therapy and those who did not, particularly in an older subset of subjects. HRV may be useful in identifying the subset of insomnia patients likely to respond to efforts that reduce hyperarousal.

(HF) power in the spectrum of the beat-to-beat (RR) interval tachogram may not directly or completely reflect sympathetic and parasympathetic activity, respectively, they are quantifiable parameters which are likely modulated by the autonomic nervous system.⁷ It has been hypothesized that HF power in the spectrum may represent a component of vagal tone, while LF power represents a combination of vagal and sympathetic activity. Therefore an increase in HF would indicate some increase in vagal activity, but an increase in LF would be harder to interpret in isolation. Though the true relationship between LF and HF power and autonomic function is unclear, insomnia pa-

tients with changes in these values may reflect a specific subset of patients most likely to respond to a given intervention. We therefore propose the use of these physiological parameters for the purpose of reducing variance in response to therapy among patient populations.

Behavioral therapies and pharmacotherapy have important roles in the treatment of insomnia; however, some investigators have suggested other approaches. We and others have investigated the role of vestibular stimulation as an interventional strategy.⁸ We have recently tested the hypothesis that electrical stimulation of the vestibular nerve would reduce sleep onset latency to a greater extent than sham stimulation. Vestibular stimulation can create a rocking sensation, which was predicted to shorten the latency from bedtime to persistent sleep (LPS) in an established insomnia model.

In the parent study, vestibular stimulation did not significantly shorten LPS time as compared to sham when examining the entire cohort. However, the authors speculated that vestibular stimulation was effective in specific subsets of patients. We hypothesized that HRV markers may be a predictor of response to treatment, specifically that increased levels in LF and LF/HF ratio are suggestive of increased estimated sympathetic activity, which may make one more likely to respond to therapy. The therapy is hypothesized to decrease arousal and sympathetic activity, as measured by a decrease in LF and LF/HF ratio.

METHODS

Subjects

All subjects gave informed consent prior to participation in the study. Subjects were enrolled at 6 sites in the United States, with each site receiving approval of the protocol by their local institutional review board (IRB) or a central IRB. Study subjects were healthy volunteers, aged 21-60 years old, with no report of sleep problems. History, physical examination, drug testing, and screening polysomnogram were performed to eliminate subjects with insomnia due to a medical or psychiatric cause, medication, or other substance (see complete listing of exclusion criteria in Krystal et al.⁸) Subsequently, all subjects completed a 5-nap multiple sleep latency test (MSLT).⁹ Only those with an average sleep onset latency (> 8 min) were recruited for the study; those with a sleep onset latency < 8 min were thought to have excessive daytime sleepiness, which may be associated with sleep disorders or chronic partial sleep deprivation.

Study Protocol

Detailed study design procedures have been described in the parent study.⁸ Briefly, subjects were recruited for 2 consecutive overnight studies. On the first night, subjects were allowed to sleep at their normal bedtime. The following night, subjects were phase advanced 4 h and randomized to receive either 1 h of vestibular stimulation or sham therapy, beginning at lights out. In an attempt to qualify the subjective experience of subjects with stimulation, subjects were asked whether they had a physical (skin) or vestibular (sway) sensation on the treatment night.

HRV Analysis

ECG data from standard polysomnogram leads were recorded for the entire night with a sampling rate of 500 Hz with 16-bit amplitude resolution. Data were analyzed from the 5 min before persistent sleep until at least 5 min after the onset of persistent sleep on each study night. Polysomnographic latency to persistent sleep (LPS) was defined as the time from lights out to the first 20 consecutive 30-sec epochs of any stage of sleep.

To eliminate noise in ECG data and to detect RR intervals more accurately, the ECG was filtered using a bandpass phase-preserving finite impulse response (FIR) filter with cutoffs at 2 and 30 Hz. From the filtered ECG data, RR intervals were found using a standard peak detection program,¹⁰ with all irregular and ectopic beats removed from the analysis. Non-sinus beats were identified for removal when an RR interval had changed > 20% from the previous interval.

The power spectral density of the RR intervals was calculated for each 5-min window using the Lomb periodogram,^{11,12} which obviates the need for resampling and interpolation of missing data. LF power was defined as the total power in the spectra 0.04-0.1499 Hz.⁷ HF power was defined as the total power in the spectra from 0.15 Hz-0.4 Hz.⁷ We normalized LF and HF by the total power in the spectra from 0.0-0.5 Hz after linear detrending. The LF/HF ratio was calculated, together with the average heart rate (HR) and standard deviation of HR before and after sleep onset. The relative change of each variable between baseline night and therapy night, as a percent difference from the baseline night, was calculated. All metrics were calculated for each individual subject and averaged over each treatment group. In the parent study, it was found that a long baseline MSLT time predicted shorter LPS when on therapy.⁸ We therefore analyzed the HRV data to assess whether sleep onset latency times correlated with increased LF at baseline. Furthermore, because HRV is age-dependent, we assessed any age effects on HRV data at baseline and on therapy/sham.¹³⁻¹⁶

Another commonly used HRV metric, the pNN50, was also calculated. The pNN50 is defined as the percent of normal beat-to-beat RR intervals in which the change in consecutive normal sinus (NN) intervals exceeds 50 milliseconds and is thought to reflect parasympathetic activity.^{17,18}

Responders vs. Non-Responders

"Responders" to therapy were pre-specified (prior to the analyses of the present study) as those whose LPS time was decreased by 25% or more on the therapy night relative to the baseline night, or if LPS time was ≤ 8 min when on therapy. All subjects who did not meet these criteria were defined as "non-responders."

We also separated the sham group (who received no active therapy) into responders and non-responders as well. While this is somewhat counterintuitive, we wanted to eliminate the possibility that any changes in HRV metrics were simply due to a shortened LPS time (i.e., nonspecific/behavioral effects of sleep onset) or due to random variations that may occur night to night.

Statistics

Since the HRV estimates were non-Gaussian, we performed a Mann-Whitney U test for all comparisons of HRV metrics be-

tween groups. We also used a Spearman rank order correlation to determine the correlation between parameters such as age and HRV measures.

RESULTS

One hundred one subjects underwent treatment with vestibular stimulation, and 97 subjects underwent sham treatment. Subjects were excluded from this analysis due to major ECG artifacts ($n = 14$), interruptions in treatment ($n = 7$), or missing data ($n = 9$).

Full demographic data and sufficient quality ECG data were available from 75 treated subjects and 93 sham subjects. Treatment and sham groups were well matched for age, sex, MSLT, and baseline LPS (**Table 1**). With vestibular stimulation, most subjects reported feeling a swaying sensation (65%), while some reported a skin sensation (40%).

We found no statistically significant differences in HRV between treatment and sham groups either at baseline or on the treatment night during wakefulness (**Table 2**).

As stated, subjects receiving the stimulation treatment were separated into responders or non-responders. When separated in this manner we found a significantly higher LF power ($p < 0.02$) during wakefulness on the baseline night in people who responded to therapy ($n = 26$), compared to those who did not respond to the therapy ($n = 49$) (**Figure 1A**). When we separated the sham group in a similar manner, we did not see any difference in LF power between those who had a shortened LPS time ($LF = 0.18 \pm 0.09$, $n = 33$) and those with no change in LPS ($LF = 0.19 \pm 0.08$, $n = 67$; **Figure 1B**).

Although responders and non-responders had similar levels of HF power at baseline, in the therapy group responders exhibited elevated HF power relative to non-responders when on therapy ($p < 0.05$; **Figure 2A**). In the sham control, there were no differences seen in HF power (**Figure 2B**). During the 5-min period following onset of persistent sleep, no differences in any tested HRV metrics were detected between responders and non-responders or between therapy and sham.

When separating the sham group by LPS, we did not find any statistically significant differences in any of the HRV metrics we evaluated. Furthermore, we found no statistically significant

differences in pNN50 between responders and non-responders in either the sham or therapy group.

One exploratory aim of the study was to determine if other factors such as age or MSLT had an impact on the HRV characteristics. We found that age negatively correlated with LF power during therapy (correlation coefficient = -0.26 , $p < 0.03$); however, age did not correlate with LF power at baseline or during sham treatment. Furthermore, age correlated with a decrease in LF power from baseline to therapy in the treatment group (correlation coefficient = -0.29 , $p < 0.01$) but not in the sham cohort (correlation coefficient = -0.02 , $p = 0.84$). Mean sleep onset latency was not correlated with any HRV characteristics.

As an alternative way to analyze age differences, we chose a cutoff age of 35 years and analyzed older vs. younger responders and non-responders to therapy. When stratifying by age, we found that responders aged > 35 years ($n = 11$) had significantly elevated LF power at baseline as compared to non-responders ($n = 18$) aged > 35 years ($p < 0.01$). However, in those ≤ 35 years of age, there was no statistically significant difference in LF power between responders ($n = 15$) and non-responders in this age group ($n = 31$) at baseline or during therapy (**Figure 3A**). Furthermore, we found that older responders (aged > 35 y) had significantly higher LF power at baseline than when they were on therapy ($p < 0.005$). Again, none of these statistically significant differences was observed when we stratified the sham group in the same manner (**Figure 3B**).

Table 1—Subject demographics

	Treated	Sham
N	75	93
Age (y)	34.2 ± 10.8	33.6 ± 10.9
Sex (%male)	32	39
MSLT (min)	15.6 ± 3.4	15.3 ± 3.1
Baseline LPS (min)	21.5 ± 24.1	21.1 ± 21.4
Therapy/sham LPS (min)	31.6 ± 39.6	40.8 ± 52.4
Sway sensation (%)	65.3	18.3
Skin sensation (%)	40.0	9.7

Table 2—Heart rate variability results

	LF Power (normalized)	HF Power (normalized)	LF/HF	HR (beats/min)	SD of HR
Treated (N = 75)					
Baseline	0.168 ± 0.060	0.232 ± 0.088	0.958 ± 1.120	65.0 ± 9.45	0.133 ± 0.072
Therapy	0.170 ± 0.062	0.247 ± 0.102	0.850 ± 0.649	67.2 ± 9.75	0.130 ± 0.093
%Change	15.3 ± 59.6	24.1 ± 86.5	23.0 ± 94.4	3.9 ± 10.7	17.2 ± 95.8
Sham (n = 93)					
Baseline	0.185 ± 0.083	0.245 ± 0.102	0.933 ± 0.706	65.0 ± 9.17	0.148 ± 0.086
Sham	0.178 ± 0.080	0.246 ± 0.091	0.848 ± 0.660	65.8 ± 8.35	0.126 ± 0.087
%Change	12.9 ± 68.3	20.6 ± 74.2	13.2 ± 72.9	2.2 ± 12.9	11.6 ± 108.0

Summary of average mean and standard deviations of LF power, HF power, LF/HF ratio, heart rate (HR), and standard deviation of HR during wakefulness prior to sleep onset. The percent change (% change) from baseline is calculated for each individual subject and averaged across each group.

Figure 1

(A) Normalized LF power during wake in responders and non-responders to therapy. Median LF power is represented by the solid white line, while mean LF power is represented by the dashed line. Error bars represent the 10th and 90th percentile; the triangles/circles are the points outside this range. On the baseline night, responders had a statistically significant ($p < 0.02$) increase in LF power relative to non-responders at baseline. (B) Normalized LF power during wake in responders and non-responders on sham treatment.

Figure 2

(A) Normalized HF power during wake in responders and non-responders to therapy. During therapy, responders had statistically significant ($p < 0.05$) higher levels of HF power relative to non-responders (indicated by *). (B) Normalized HF power during wake in responders and non-responders on sham treatment.

DISCUSSION

Our results add to the literature in an important manner as they provide proof for the concept that physiological markers may be used to classify people in terms of their probability of response to insomnia therapy. Although LPS time and HRV measures were not significantly different between therapy and sham groups, we have shown that the HRV data are different in those subjects who responded to therapy as compared to those that did not respond. Responders to therapy had an elevated baseline LF power, possibly indicative of heightened

arousal at baseline and amenable to this type of stimulation therapy. Given that baseline HF levels were similar in responders and non-responders, it seems possible that responders to therapy may have had increased estimated sympathetic activity at baseline leading to increased LF power. This relationship is driven by the older cohort of subjects (> 35 years). Older subjects were more likely to have lower LF power during therapy, independent of LPS time, while the effect was not seen in sham groups. When stratified by age we observed that older responders had a clear elevation in LF power at baseline as compared to other groups and to themselves on therapy,

Figure 3

(A) Normalized LF power during wake in responders and non-responders to therapy segregated by age (young ≤ 35 y, older > 35 y). Statistically significant differences between baseline and therapy are indicated by * $p < 0.005$, and between older responders and non-responders on baseline night are indicated by † $p < 0.01$. (B) Normalized LF power during wake in responders and non-responders to sham treatment segregated by age.

indicating this group may be the most responsive to treatment. The differences seen in the HRV characteristics of the therapy group were not replicated within the sham group and lead one to speculate that the therapy does play some role in altering the autonomic output of the therapy subjects. We speculate that the vestibular stimulation may work to decrease sympathetic activity as estimated by LF power. An older group of subjects with high baseline LF (possibly indicative of high sympathetic activation) would be the most likely group to respond to this therapy. If HRV differences were just due to shortened LPS time or age, they should also appear in the sham cohort.

Our paper has a number of limitations. First, we analyzed ECG data only in the five minutes before and after sleep onset. However, we believe this approach would bias the data toward the null hypothesis, as we would expect subjects to be extremely sleepy in the five minutes before sleep onset occurs, rather than hyperaroused. Furthermore, there is considerable overlap in the range of LF and HF power of responders and non-responders, indicating that HRV in isolation may not be perfect in predicting response. Of note, since we did not see any differences in HRV variables during sleep, only during wakefulness, we hypothesize that the hyperaroused state before sleep onset does not persist during sleep. This finding is consistent with prior reports that patients with insomnia tend to have normal heart rate variability characteristics during sleep.^{19,20}

Although considerable controversy exists regarding how closely HRV metrics correspond with actual autonomic parameters,²¹ for the purpose of our analyses this debate is largely academic. Future studies looking more closely at the relationship between autonomic function and sleep would be useful in determining important markers which can help predict response to various insomnia therapies. We hypothesize that this therapy

may see the most benefit in a population of hyperaroused (as estimated by increased LF power) people over the age of 35 years. Further research (employing gold standard measures of muscle sympathetic nerve activity or pharmacological studies, for example) would be required to test mechanistic hypotheses such as the role of the sympathetic nervous system *per se* in mediating insomnia therapy response.

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ACKNOWLEDGMENTS

The authors thank the primary study authors for their work in collecting the data used in this study: Andrew D. Krystal, Gary K. Zammit, James K. Wyatt, Stuart F. Quan, Jack D. Edinger, David P. White, Richard P. Chiacchierini, and Atul Malhotra. Mary Macdonald and Pam DeYoung provided technical support for the parent study at the Boston site.

SUBMISSION & CORRESPONDENCE INFORMATION

Submitted for publication August, 2010

Submitted in final revised form January, 2011

Accepted for publication March, 2011

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DISCLOSURE STATEMENT

Dr. Malhotra has consulting and/or research income from Philips, Ethicon, Medtronic, SHC, SGS, Pfizer, Novartis, Sepracor, Cephalon, Apnex, Itamar, Merck, Apnicure. He is funded by NIH P01 HL095491, R01 HL085188, R01 HL090897, K24 HL 093218 and AHA. Dr. Clifford has received consulting and/or research income from Philips. Dr. Pittman is employed by Philips.