Original Research

Correlates of Therapeutic Response in Panic Disorder Presenting With Palpitations: Heart Rate Variability, Sleep, and Placebo Effect

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Objective: To examine the correlates of therapeutic response of patients with panic disorder presenting with palpitations, we hypothesized that therapeutic response would correlate with heart rate variability (HRV) and sleep measures.

Methods: After a 1-week placebo washout, 27 patients free of structural heart disease and not on cardioactive drugs were randomized in a double-blinded fashion to 4 weeks of treatment with clonazepam (a known antipanic agent) or placebo. We performed standard sleep measures and recorded HRV from 24-hour Holter acquisitions at baseline and end of study. We defined response to therapy as a 50% improvement in the Hamilton Anxiety Rating Scale (HARS) score, confirmed by questionnaires and reaction to sodium lactate infusion.

Results: There were 12 responders and 15 nonresponders. Normalization of sleep pattern (including less stage 1 and rapid eye movement [REM] sleep) was observed in both drug and placebo responders ($P = 0.011$ and $P = 0.05$, respectively) and in placebo responders alone, compared with nonresponders ($P = 0.006$ and $P = 0.013$, respectively). Placebo responders were more likely to show less depression, but even after we controlled for depression, main sleep effects remained. None of the HRV measures correlated with response, but compared with placebo, clonazepam led to a decrease in all the time and frequency domain measures of HRV (all $P < 0.05$).

Conclusions: Central mechanisms are related to the therapeutic response of patients with panic disorder presenting with palpitations, but this does not directly correlate with HRV. Larger and longer studies may allow objective explanations of placebo response in panic disorder.

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Clinical Implications

- Therapeutic response is not directly correlated with heart rate variability (HRV) and is likely related to central rather than autonomic factors.
- Therapeutic response on placebo or clonazepam is associated with normalization of sleep.
- Depression and illness intrusiveness are associated with clinical nonresponse in patients on placebo.
- Larger and longer studies on HRV, sleep, and placebo effect are required.

Limitations

- The whole sample size was small.
- The clonazepam group was small.
- Clinical response is arbitrarily defined.

Key Words: *placebo, sleep, heart rate variability, palpitations, panic disorder*

Palpitations are the commonest presentation of panic disorder, a condition occurring in 4% of the general population and about 15% of cardiac outpatients (1,2). Many of the symptoms in these patients with palpitations suggest a disorder of autonomic stability; nonetheless, the response to betadrenoreceptor blockers is inconsistent, and these medications are often not tolerated. These patients generally do not have structural heart disease. There is poor symptom–rhythm correlation, and the identification of ectopy as a cause of symptoms is suspect: up to 48% of normal control subjects may have a similar degree of ectopy, compared with those having a specific history of palpitations (1–6).

Heart rate variability (HRV) has been recommended as a noninvasive probe of the autonomic nervous system modulation of the heart rate, as represented by its cumulative effect on sinus node automaticity, which is the control parameter for heart rate (7,8). HRV may also be a clinically useful marker to assess the risk of serious arrhythmias or cardiovascular events in patients with cardiac disease (9). The association between panic disorder and HRV has come under increased scrutiny with the repeated findings of low HRV in patients with panic disorder (10,11). There is also some evidence that panic or phobic anxiety in men may increase cardiac mortality risk over time (12–14). Evaluating HRV in panic disorder may thus be important with respect to a neurobiological mechanism in panic disorder (2,14). Previous studies have tended to use abbreviated measures (11,33); however, HRV measurement may be enhanced with the use of 24-hour recordings. We hypothesized that therapeutic response in panic disorder with palpitations would directly correlate with HRV.

To enhance the evaluation of therapeutic response to clonazepam or placebo, we included objectively derived assessments such as sleep measures and sodium lactate infusion. Various sleep disturbances have been found in panic disorder (15–17). The infusion of sodium lactate has been found to be related to increased panic symptoms (18). Clonazepam is an established and well-tolerated antipanic medication with few cardiac side effects (19,20). There are varying reports of placebo effect in panic disorder patients (21,22).

To determine whether therapeutic response in patients with panic disorder presenting with palpitations was directly correlated with changes in HRV, we examined the association of therapeutic response (including assessments of sleep and sodium lactate infusion) to clonazepam or placebo and standard 24-hour measures of HRV.

Methods

Subjects were referred by general practitioners, psychiatrists, and cardiologists and also obtained from local advertising. Male and female patients who participated in the trial gave written consent; were aged 18 to 65 years; and had a normal physical examination, with no focal or global systolic wall motion abnormalities on an echocardiogram. All patients underwent 24-hour ambulatory monitoring for ectopy documentation and symptom–rhythm correlation. Patients were independently interviewed with the Structured Clinical Interview for DSM-IV (SCID) and diagnosed with panic disorder according to DSM-IV criteria (23), with the following modification: recurrent DSM-IV defined panic attacks for 1 month or more and recurrent panic attacks (that is, 2 or more) for a minimum of each of the past 2 weeks. This modification replaces the DSM-IV criteria of recurrent panic attacks with 1 month or more of persistent concern, worry about implications, or change of behaviour. This change was instituted because of the presence of “nonfear” panic noted in medical patients (24). Eligible patients also scored more than 20 on the Hamilton Anxiety Rating Scale (HARS) (25), and this score did not diminish by more than 25% by the end of the 1-week placebo phase, after which there was a 4-week, double-blind, randomized clinical trial of clonazepam or placebo.

At baseline and at the end of the trial, patients completed the following psychosocial questionnaires: the Symptom Checklist-90-R (SCL-90-R) (26), the Somatosensory Amplification Scale (SAS) (27), and the Illness Intrusiveness Scale (IIS) (28). Patients completed daily diaries and were evaluated weekly with the HARS. In addition, they were evaluated with the Hamilton Depression Rating Scale (HDRS) (29) at the beginning and end of the trial. No psychotropic medications were permitted for 7 days prior to the start of the study.

We performed HRV and sleep studies at baseline and at the end of the trial. HRV measures were recorded from 24-hour Holter acquisitions at baseline and end of study. The measures assessed were the standard deviation of all normal RR intervals (SDANN), the standard deviation of the mean of all 5-minute segments of normal RR intervals (SDNN), power in the low-frequency (LF, 0.04 Hz to 0.15 Hz) and high-frequency (HF, 0.15 Hz to 0.40 Hz) domains, and total power (TP, 0.01 Hz to 1.0 Hz). We used a commerical software package (30) to obtain a standard fast fourier transform of the RR interval data expressed as power.

We ascertained the standard measures of sleep, including latency of sleep onset and rapid eye movement (REM), sleep cycle length, slow wave sleep pattern, number of arousals, and standard sleep architecture. The morning after the sleep study, a standardized lactate infusion was performed. This procedure consisted of a 20-minute saline infusion (the control period) followed by a 20-minute infusion of sodium lactate (see 18). The number and intensity of symptoms during the infusion was recorded. Clonazepam (a known antipanic medication) or placebo was administered, starting at 0.5 mg twice daily. A psychiatrist assessed patients weekly for symptoms and side effects (see 19). The participating hospital review boards approved this study. Cardiology assessments were performed at St Michael's Hospital, and all remaining procedures took place at the Toronto Western Hospital.

Statistical Analyses

Patients meeting the entry criteria of an initial HARS score greater than 20 and a change in HARS score over the placebo week of less than 25% were included in the analysis. We used the change in HARS scores from baseline (that is, the end of the placebo week) to the end of the study to classify patients as responders or nonresponders. A responder had at least a 50% decrease in scores at study completion after 4 weeks of treatment. We analyzed changes from baseline to the end of the study by treatment and by response, using covariance analysis. We used the baseline data as the covariate and the data reported at the end of study as the outcome variable. Interactions among these variables, treatment, and response were tested in the model. We tested baseline differences between the 2 groups using *t*-tests for all variables except the HARS. We also calculated changes from baseline to the end of the study for the HARS .

Results

At the end of the placebo week, 28 patients met the entry criteria. At the end of the study, 1 patient lacked a HARS score, leaving 27 patients for analysis.

There were 12 responders (7 on placebo and 5 on clonazepam) and 15 nonresponders (10 on placebo and 5 on clonazepam). Women comprised 56% of the placebo group and 30% of the clonazepam group. They represented 50% of the responders and 40% of the nonresponders. The average age and standard error for each group are as follows: placebo (44.4 years, SE 1.87), clonazepam (47.3 years, SE 2.76), responders (47.8 years, SE 2.14), and nonresponders (43.0 years, SE 2.06).

On the psychosocial scales, there was a difference between the responders and nonresponders for the IIS total score ($P = 0.027$) and for the SAS total score ($P = 0.023$).

When we tested for differences between the responders and nonresponders in the number and intensity of panic symptoms during lactate infusion, we found a significant difference between the responders and nonresponders ($P = 0.022$) for the number, but not the intensity, of panic symptoms.

There were no differences between responders and nonresponders on any of the HRV measures. However, clonazepam consistently decreased HRV for all time and frequency domain measures (all $P < 0.05$). Table 1 shows the effects of clonazepam and placebo on HRV. Each patient treated with clonazepam showed a decrease in all HRV measures from baseline to 4 weeks.

Table 1 The effects of clonazepam and placebo on heart rate variability (% change from baseline)

	Clonazepam Mean (SD)	Placebo Mean (SD)
Total power (TP)	–5.3 (3.8)	1.5 (4.8)[a]
Low frequency (LF)	–6.4 (4.9)	1.9 (7.2)[a]
High frequency (HF)	–8.2 (6.4)	1.7 (7.7)[a]
SDANN	–17.2 (19.7)	10.3 (22.2)[a]
SDNN	–13.0 (15.5)	7.9 (20.2)[a]

[a]$P < 0.05$ (*t*-test)

TP , LF, and HF refer to heart rate variability (HRV) measures in the frequency domain related to TP, and its components of HF and LF.

SDANN and SDNN refer to HRV measures in the temporal domain expressed as the standard deviation of all normal beats (SDANN) or beats assessed in 5-minute segments (SDNN). HF and SDNN are considered as markers of predominantly vagal tone on HRV. (See text and [9] for more details).

Regarding sleep measures, there were significant differences between the responders and nonresponders for percentage of stage 1 sleep and percentage of REM sleep ($P = 0.011$ and $P = 0.05$, respectively). There were borderline differences between the responders and nonresponders for percentage of time awake ($P = 0.07$), sleep-onset latency ($P = 0.07$), and sleep efficiency ($P = 0.08$). There were no differences for total defined sleep, total sleep time, percentage of stage 2 sleep, percentage of stage 3 sleep, percentage of stage 4 sleep, movement time, REM latency, number of REM episodes, respiratory disturbance index, movement arousal index, leg movement index, and number of minutes to panic. There were no differences between placebo and clonazepam responders and between placebo and clonazepam nonresponders.

When we examinined the placebo patients alone during lactate infusion, by the end of the study the nonresponders reported an average of 13.13 symptoms and the responders reported an average of 9.9 symptoms ($P = 0.047$). Table 2 compares sleep variables of placebo responders and nonresponders. There were differences in the percentage of stage 1 sleep ($P = 0.006$): at the end of study, the average was higher for the nonresponders (5.7%) than for the responders (2.0%). There were also differences in the percentage of REM sleep ($P = 0.013$): the nonresponders had a higher average (17.76%) than the responders (14.06%).

We compared variables to clarify any differences between placebo responders and nonresponders at baseline: The HDRS total scores (with 23 items) differed significantly between the responders and nonresponders ($P = 0.008$): the nonresponders had a higher mean than did the responders.

Table 2 Placebo responders and nonresponders: sleep variables

Group	Statistic	% Stage 1 sleep	% REM sleep	% Awake	Sleep-onset latency	Sleep efficiency
Responders	Mean[a]	1.99	14.67	9.69	14.28	89.61
	Standard Error[b]	2.22	2.96	2.83	4.59	2.97
Nonresponders	Mean	5.71	17.76	12.27	16.02	83.90
	Standard Error	2.73	3.46	2.50	4.04	2.62
	P-value[c]	0.006	0.013	ns	ns	ns

REM = rapid eye movement

[a]Mean is the estimated end-of-study mean adjusted for the baseline covariate.

[b]Standard error is the estimated standard error of the adjusted mean.

[c]The *P*-value tests differences between the responders and nonresponders using analysis of covariance where the baseline values are the covariates.

The IIS scores also differed significantly ($P = 0.036$), with the nonresponders having a higher average than the responders.

When we used analysis of covariance to examine the changes from baseline to end of study, HDRS scores differed between responders and nonresponders ($P = 0.02$). Of the SCL-90 scales, anxiety ($P = 0.02$) and positive symptom distress index ($P = 0.02$) differed significantly. Using chi-square and Spearman's nonparametric method to test the relation between the end of study HDRS scores and response to treatment, we found a highly significant effect for percentage of stage 1 and REM sleep ($P = 0.009$ and 0.0001, respectively). Testing baseline HDRS scores and responder status indicated no significant effect with chi-square ($P = 0.11$) and a borderline effect with Spearman's coefficient ($P = 0.05$).

Discussion

This study has 2 main findings. First, therapeutic response in patients with panic disorder presenting with palpitations was not correlated with HRV; however, clonazepam was consistently related to decreased HRV. Second, therapeutic response was associated with normalization of sleep, regardless of clonazepam or placebo status.

HRV and Therapeutic Response

Therapeutic response in these subjects was not coincident with HRV change, which instead correlated more with clonazepam than with placebo. This suggests that therapeutic response is not directly related to autonomic change, even though this study may have lacked power to demonstrate HRV changes between responders and nonresponders. Clonazepam presumably causes sedation, which may suppress autonomic modulation of HRV—effects described previously with anxiolytics, usually in the setting of anesthesia (31–33), but not in outpatients treated for panic. Imipramine, another antipanic agent, has been shown to reduce HRV (34); however, after discontinuation of treatment, HRV can return to normal (35). Patients with panic disorder have shown increased HRV measures after treatment with paroxetine (36). These preliminary data suggest that antipanic agents work centrally and may have variable autonomic effects.

The dissociation of a drug effect from a therapeutic response found with HRV measures underscores the importance of placebo-controlled data in the assessment of HRV correlates of response. It also suggests that the neurobiological mechanisms of placebo response may differ in unknown ways from drug-mediated mechanisms of efficacy. Interestingly, this dissociation of effect is not seen with sleep-related parameters, which in our dataset track a therapeutic, rather than a medication, effect. It is important to emphasize that HRV measures are not static and, at best, approximate prevailing autonomic tone. It is therefore also possible that the therapy-independent effects of clonazepam on HRV measures may be related to a nonspecific sedating effect or simply to a decrease in daily activity caused by low-dosage clonazepam (37,38). Future studies using less sedating antipanic medication and 24-hour HRV measures are needed to assess whether our observed clonazepam effect on HRV represents a real dissociation of an effect different from a placebo effect.

Sleep Parameters and Therapeutic Response

This study found that responders and nonresponders differed with respect to the certain sleep variables. Responders generally showed normalization of sleep patterns, although several sleep parameters showed no change. Thus, it appears that nonresponders had more disrupted sleep, as evidenced by increased wakefulness, more stage 1 sleep, and longer sleep-onset latency. However, these observations will need a larger sample size for confirmation. Panic disorder patients have been shown to have multiple but inconsistent changes in sleep architecture, compared with control subjects (15,16), as well as expected normalization of sleep following treatment with alprazolam, an antipanic medication (39). Our study examines the sleep effects of placebo as well as of clonazepam. Of note are the sleep effects of placebo responders: when all variables were controlled, sleep variables such as percentage of stage 1 sleep and REM sleep remained reduced in the placebo responders, compared with the nonresponders. While the sleep changes were relatively small with respect to change in REM sleep, the change in stage 1 sleep, which is often associated with improved sleep quality, is notable and merits replication.

Placebo Effect in Panic Disorder

Placebo effect is reported in panic disorder (21). For example, with more strict definitions of response, between 23% and 34% of panic disorder patients showed placebo response (22). While a subject of debate (40), the placebo effect is a recognized phenomenon and a component of any double-blind, placebo-controlled study (41). It has long been suggested that anxiety is one of the conditions believed to predispose people to the placebo effect (42). Our understanding of the placebo effect has been enhanced by recent findings using positron emission tomography to study depression patients treated with the antidepressant fluoxetine or with placebo (43). Both placebo and antidepressant treatment were associated with metabolic changes in cortical areas, but fluoxetine response showed additional subcortical and limbic changes, suggesting advantages "in maintaining long-term clinical response" (43). The placebo effect in cortical regions is consistent with the frequent finding of clinical response, especially in short trials. The restoration of balance suggested by the aforementioned study may be associated with a concomitant effect regarding neuroanatomic correlates of sleep, including REM sleep (44).

We found that increasing severity of depression and illness intrusiveness were associated with clinical nonresponse to the placebo effect. Depression is common in panic disorder and has been shown to impair the response to panic disorder treatment (45–47). Illness intrusiveness is importantly related to a wide range of subjective indices, quality of life, and symptoms of psychopathology (28). The changes in illness intrusiveness observed among responders is consistent with the interpretation that psychosocial benefits included improved quality of life.

Limitations

While the definition of 50% response on the Hamilton scales is common, therapeutic response is arbitrarily defined; however, correlates of response suggest a consistent and persistent demarcation of responders and nonresponders. The finding that responders reported fewer panic symptoms during sodium lactate infusion is objective confirmation of the response categorization of responders vs nonresponders. As mentioned, this study may have lacked power to show a therapeutic response associated with HRV; however, the consistent correlation of clonazepam with HRV demonstrates that HRV status is not directly correlated with therapeutic response.

To rule out the first-night effect, it would have been desirable to have more than a single night of sleep recording at both the beginning and end of the study (48; for dissent, see 49): with a whole month separating the 2 recordings, the adaptation effect is lost. To this extent, the effect is consistent on the 2 occasions. It would have been more problematic to have the recordings closer in time, because the adaptation effect of the first sleep study would have affected the second sleep study. The fact that some patients responded to treatment and others did not argues against the sleep studies' being subject to an ordering effect. This sample is small, and the results must be regarded as preliminary. Further, because the course of panic disorder may become persistent (50), this study only indicates the initial phase of treatment.

Clinical Implications and Conclusions

In a group of patients with panic disorder presenting with palpitations, therapeutic response as defined here is a central (brain) phenomenon and is not coincident with HRV change. Medications such as clonazepam and imipramine are thus effective in treating panic disorder, even though HRV may be low owing to mechanisms related to their specific pharmacologic actions (such as sedation or anticholinergic effects). This study also provides confirmation of objective changes in patients with panic disorder presenting with palpitations who have been given placebo, although it is important to establish whether such changes(for example, normalization of sleep) are sustained over time, in the light of recent findings with depression patients, for whom it was hypothesized that medication may confer more long-lasting effects than placebo (43). We also demonstrated that depression and illness intrusiveness are factors that mitigate against a placebo effect. The clinical significance of our observations is not known. Autonomic effects are dissociated from therapeutic response and provide a tool to further assess drug actions and clinical response. This study explores new avenues in the nature of therapeutic and placebo response and contributes to the literature on HRV as a tool for psychosomatic research. However, given the limitations, larger and longer studies of HRV, sleep, and placebo effects in panic disorder are now required.

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Résumé : Corrélations de réaction thérapeutique dans le trouble panique accompagné de palpitations : variabilité de la fréquence cardiaque, sommeil et effet placebo

Objectif : Pour examiner les corrélations de la réaction thérapeutique des patients souffrant de trouble panique accompagné de palpitations, nous avons émis l'hypothèse que la réaction thérapeutique serait en corrélation avec la variabilité de la fréquence cardiaque (VFC) et les mesures du sommeil.

Méthodes : Après 1 semaine d'élimination du placebo, 27 patients exempts de maladie cardiaque structurelle et ne prenant pas de médicaments agissant sur le coeur ont été affectés au hasard, à double insu, à 4 semaines de traitement à la clonazépam (agent anti-panique reconnu) ou à un placebo. Nous avons effectué des mesures du sommeil régulières et enregistré la VFC selon la méthode de Holter de 24 heures, au début et à la fin de l'étude. Nous avons défini la réaction au traitement comme une amélioration de 50 % du score à l'échelle d'anxiété de Hamilton (HAMA), confirmée par des questionnaires et la réaction à une infusion de lactate de sodium.

Résultats : Il y a eu 12 sujets répondants et 15 non-répondants. La normalisation de la structure du sommeil (incluant moins de sommeil de la phase 1 et de sommeil paradoxal) a été observée chez les sujets répondants tant au médicament qu'au placebo ($P = 0{,}011$ et $P = 0{,}05$, respectivement) et chez les répondants au placebo seulement, comparativement aux non-répondants ($P = 0{,}006$ et $P = 0{,}013$, respectivement). Les répondants au placebo étaient plus susceptibles de présenter moins de dépression, mais même en contrôlant la dépression, les principaux effets sur le sommeil demeuraient. Aucune des mesures de la VFC ne corrélait avec la réaction, mais comparée au placebo, la clonazépam entraînait une diminution dans toutes les mesures du temps et de la fréquence de la variabilité de la fréquence cardiaque (tous, $P < 0{,}05$).

Conclusions : Les mécanismes centraux sont reliés à la réaction thérapeutique des patients souffrant de trouble panique accompagné de palpitations, mais cela n'est pas en corrélation directe avec la VFC. Des études plus vastes et plus longues pourraient permettre des explications objectives de la réaction au placebo dans le trouble panique.