Diurnal Heart Rate Patterns in Inappropriate Sinus Tachycardia

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Background: *Inappropriate sinus tachycardia (IAST) is a supraventricular tachycardia originating from the sinus node. Proposed etiologies for this symptom complex include autonomic dysfunction, abnormal automaticity, or hypersensitivity of the sinus node.*

Methods: *Patients with IAST were identified by symptomatic tachycardia, with P-wave morphology consistent with origination from a sinus location. A matched set of control subjects was included. Hourly heart rate (HR) was measured as the average HR during each one hour period on an ambulatory 24-hour Holter monitor. Patients were further divided into two subgroups based on average daily HR $\leq$ 80 and $>$80 bpm. Harmonic analysis was used to evaluate diurnal variation.*

Results: *The mean HR was 86.0 $\pm$ 12.8 beats per minute (bpm) in the IAST group and 73.9 $\pm$ 8.6 bpm in the control group ($P = 0.056$). There was an increased overall heart rate for the IAST group, which appeared to be more prominent in the morning hours. In the IAST subgroup with average daily HR $\leq$ 80, hourly HR appears similar to controls for the period 8 pm–8 am. However, in the late AM, the IAST group had an increase in HR not seen in the control subjects. In the IAST subgroup with average HR $>$ 80, there appeared to be a fixed difference in HR compared to the control group, without hourly change.*

Conclusions: *Patients with IAST and elevated average daily HR exhibit normal diurnal variation around a higher mean HR. In contrast, patients with IAST and lower average daily HR had an exaggerated morning rise in HR. These diurnal patterns may be useful to classify the pathophysiology of IAST. (PACE 2010; 33:911–919)*

tachycardia, diurnal, sinus, circadian, heart rate

Introduction

Inappropriate sinus tachycardia (IAST) is a supraventricular tachycardia originating from the SA node and characterized by P-wave morphology indistinguishable from sinus rhythm, with tachycardia at rest or disproportional to the physiologic needs.[1–4] This syndrome is often a diagnostic and treatment dilemma for clinicians, and may have a prevalence as high as 1.1% in a middle-aged population.[5] The mechanism for the exaggerated response of the sinus node is incompletely understood. Proposed etiologies for this symptom complex include autonomic dysfunction,[1,6–8] abnormal automaticity or hypersensitivity of the sinus node,[6,8] or an automatic atrial tachycardia with a focus near the sinus node. Several investigations have yielded conflicting results.[2,6,8,9] It has been reported that individual patients with IAST may demonstrate different patterns of heart rate variation.[10] Among the three patients reported in this study,[10] there were those with normal average daily heart rates and those with persistently elevated heart rates. Because of these observed differences in IAST patients, some authors have suggested that inappropriate sinus tachycardia may be made up of several disorders with divergent etiologies.[2,7]

The purpose of this study was to evaluate the diurnal variation in heart rate in patients with IAST to assess the response of the sinus node to the daily variation in autonomic tone. The subjects were stratified by average daily heart rate to assess if the diurnal variation in daily heart rate was influenced by average resting heart rate.

Methods

Study Population

Patients with IAST were identified by screening the outpatient records of the cardiology department of Northwestern Memorial Hospital. Inclusion criteria were age between 18 and 60 years and symptomatic sinus tachycardia. IAST was defined by symptomatic tachycardia, with a P-wave morphology consistent with origination from a

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sinus location, of greater than 100 beats per minute (bpm) at rest or with minimal exertion. A matched set of control subjects was included who were also aged 18–60 years and had a Holter monitor performed for any clinical indication, with no identifiable heart disease, and who did not meet criteria for IAST. Matching was performed to identify patients with similar 24-hour average heart rates. Patients were excluded if they were on autonomically active medications at the time of the Holter monitor, were not euthyroid, or had other explanations for sinus tachycardia. Also excluded were patients with more than 1% premature beats, runs of sustained or nonsustained ventricular tachycardia, or less than 22 hours of recorded data. This study was approved by the Northwestern University Institutional Review Board.

Ambulatory ECG Data Analysis

The average daily heart rate was calculated using the Marquette Holter system by dividing the total number of beats in the recording by the duration of the Holter in minutes. Average hourly rates were also calculated for patients with at least 20 minutes of data in that hour. Hours that did not have sufficient data had interpolated values used if they were preceded and followed by hours with more than 20 minutes of data. Subjects were required to have at least 22 hours of recorded time to be included in this study.

Patients were divided into two groups based on their mean daily heart rate, initially chosen as the median heart rate of the group (80 bpm).[11] Both the IAST group and control group were stratified into subgroups with mean heart rates above and below 80 bpm. Mean hourly heart rates were then calculated for each subgroup and plotted over a 24-hour period.

Data Analysis

Data are expressed as mean ± standard deviation. The primary analysis focused on harmonic regression analysis of the heart rate.[12,13] The circadian variation in heart rate measurements was assessed using first and second-order harmonic least-squares regression analysis. Results were fit to an equation of the form

$$HR(t) = A + \sum_{i=1}^{2}\left(B_i \sin\left(\frac{2\pi it}{24}\right) + C_i \cos\left(\frac{2\pi it}{24}\right)\right) + IASTx\left(\sum_{i=1}^{2}\left(IB_i \sin\left(\frac{2\pi it}{24}\right) + IC_i \cos\left(\frac{2\pi it}{24}\right)\right)\right)$$

where HR(t) is the heart rate at hour t, and A, B_i, C_i, IAST, IB_i, and IC_i are constants.

The first summation includes the first and second harmonics of a 24-hour diurnal variation and the second summation includes terms specific for the groups with IAST. Harmonic regression analysis was performed for all subjects and then in each of the heart rate subgroups—those with heart rate ≤80 bpm and those with heart rate >80 bpm. A total of five diurnal models were predetermined prior to data collection, and each was evaluated in these three groupings:

Model #1 incorporated only the first harmonic term and set IAST to zero (this model would be appropriate if diurnal variation in IAST patients did not differ from controls);
Model #2 incorporated the first and second harmonic and set IAST to zero;
Model #3 incorporated only the first harmonic term and the IAST term with only the first harmonic;
Model #4 incorporated the first and second harmonic and the IAST term with the first and second harmonic;
Model #5 incorporated the first and second harmonic and the IAST term with the first harmonic.

For each model the log likelihood ratio and Akaike Information Criterion were calculated. Model #4 was superior to the others for all patients ($P < 0.0001$), for those with heart rate ≤80 bpm ($P < 0.0001$), and those with heart rate >80 bpm ($P < 0.03$ vs model #2, $P < 0.0001$ vs models #1 and #3, and not significantly different than model #5). Thus, only data from model #4 are presented.

A second method to assess for differences in diurnal heart rate trends was employed. In order to remove baseline shift in mean heart rate (HR) as a cause of interindivdual differences and examine only diurnal variation differences, each individual patient's hourly average heart rates were first normalized to their own mean 24-hour heart rate by the following method:

Normalized HR at hour t = (60-minute mean HR at hour t − 24-hour mean HR). In this fashion, the magnitude of the interindividual differences in mean 24-hour heart rate were removed and only hourly changes from the individual's mean HR were examined. The 24-hour period was further divided into four 6-hour quarters for analysis.

As needed, paired comparisons were performed with Student's *t*-test. A P value < 0.05 was considered significant.

Results

Patient Population

The study population consisted of 22 patients with a previous diagnosis of inappropriate sinus tachycardia (ages 32.6 ± 9.0 years, all female) and 38 control subjects (ages 37.1 ± 10.7, all female). The IAST group was 100% female, and therefore the control group was chosen to also have exclusively women. The mean HR was 86.0 ± 12.8 bpm in the IAST group and 73.9 ± 8.6 bpm in the control group (P = 0.056). The maximum hourly HR was 117.1 ± 19.9 bpm in the IAST group and 100.9 ± 11.5 bpm in the control group (P = 0.002). The minimum hourly HR was 68.6 ± 13.0 bpm in the IAST group and 64.6 ± 7.4 bpm in the control group (P = 0.2). The intraindividual difference between maximum and minimum HR was 48.5 ± 21.1 bpm in the IAST group and 36.2 ± 8.7 bpm in the control group (P = 0.02). Of the patients with IAST, four were status-post ablation for supraventricular tachycardia. The indications for Holter monitoring in the control group was palpitations (n = 23), presyncope (n = 5), screening (n = 4), chest pain (n = 3), syncope (n = 2), and shortness of breath (n = 1), but no rhythm abnormalities were found related to these complaints. None of the control group subjects met the criteria for IAST.

There were 14 patients with IAST and average daily HR > 80 bpm, and eight with average daily HR ≤ 80 bpm. Of the 38 controls, 18 had average daily HR > 80 bpm. The average age in the four subgroups was 36.9 ± 11.5 years in the control group with average HR ≤ 80 bpm, 37.3 ± 9.9 years in controls with HR > 80 bpm, and in the IAST group the average age was 31.8 ± 8.4 in those with average HR ≤ 80 bpm and 33.1 ± 9.6 years in those with average HR > 80 bpm. There was no significant difference in ages among any of the subgroups (P = 0.44).

The average daily HR in the IAST subgroups was 93.4 ± 8.6 bpm in the group with averages >80 bpm, and 73.1 ± 7.7 bpm for those ≤80 bpm. In the control group, the average daily HR was 86.6 ± 6.9 bpm in the group with averages >80 bpm, and 73.9 ± 4.8 bpm for those ≤80 bpm. The daily average HR was significantly different (P < 0.001) among the four subgroups. When comparing the 24-hour mean heart rates for the patients with mean HR ≤ 80 bpm, there was no significant difference between the IAST group and the controls (73.1 ± 7.7 bpm vs 73.9 ± 4.8 bpm, P = 0.750). However, the 24-hour mean heart rates for the patients with mean HR > 80 bpm was significantly higher in the IAST group compared to controls (93.4 ± 8.6 bpm vs 86.6 ± 6.9 bpm, P = 0.019). While analysis of variance (ANOVA) showed a difference in heart rate range among the four subgroups (P = 0.017), there was no significant difference in those with average HR > 80 bpm in the IAST group compared to controls (50.1 ± 24.5 bpm vs 40.7 ± 7.6 bpm, P = 0.1), nor in those with average HR < 80 bpm (45.5 ± 14.5 bpm vs 38.4 ± 9.4 bpm, P = 0.07).

The average hourly heart rate of all patients in the IAST and control groups is plotted in Figure 1. There is an increased overall heart rate for the IAST group, which appears to be more prominent in the morning hours. Figure 2 shows the hourly heart rate trend of patients in both groups whose total average daily HR was ≤80 bpm. In this IAST subgroup, hourly HR appears similar to controls for the period 8pm–8am. However, in the late AM, the IAST group has an increase in HR not seen in the control subjects. Figure 3 shows the hourly heart rate trend of patients in both groups whose total average HR was >80 bpm. In this IAST subgroup, there appears to be a fixed difference in HR compared to the control group, without hourly change.

Harmonic Regression Analysis

Table I demonstrates the results of the harmonic regression analysis. For all patients, there was significant diurnal variation (significant sine and cosine coefficients) with a significant shift in the IAST patients (IAST coefficient P < 0.048) and significant difference in the diurnal variation in the IAST group (log likelihood −5341.66 and Akaike Information Criterion 10711.32 for this model).

In the patients with a mean HR ≤ 80 bpm, there was also significant diurnal variation. However, the IAST coefficient was not significantly consistent with no difference in 24-hour mean heart rate for the controls and IAST patients. However, there was a difference in the diurnal variation in the IAST group (log likelihood −2396.26 and Akaike Information Criterion 4820.52 for this model). This is consistent with the difference noted in the early morning hours.

In the patients with a mean HR > 80 bpm, there was also significant diurnal variation. In this analysis, the IAST coefficient was significant consistent with a mean difference in 24-hour mean heart rate for the controls and IAST patients. However, the diurnal variation coefficients were not different for the IAST patients compared to controls (log likelihood −2891.46 and Akaike Information Criterion 5810.92 for this model). This is consistent with the shift noted in the curve

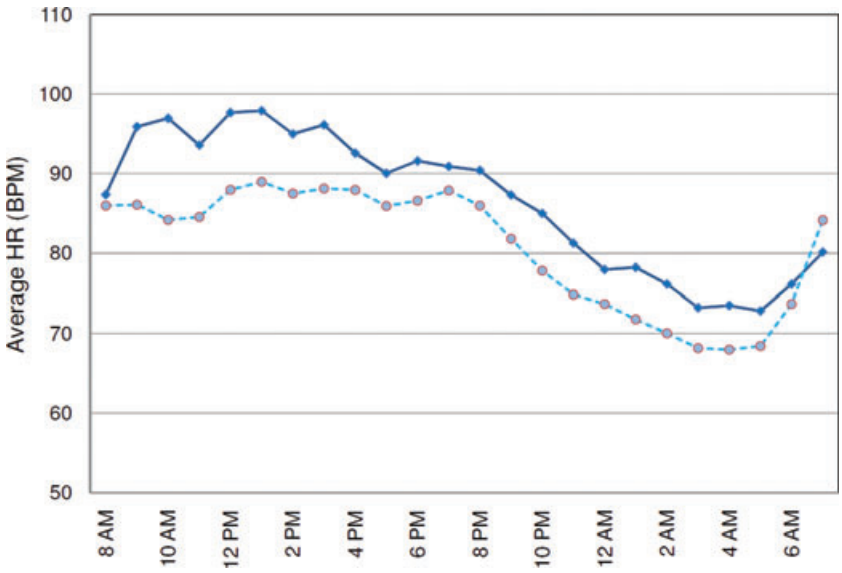

Figure 1. *Average HR trends for all patients over a 24-hour period, by hourly mean HR. Solid lines w/ diamonds = IAST; Dashed lines w/ circles = Controls.*

without any real difference in the actual diurnal variation.

Normalized Heart Rate Analysis

The hourly normalized HR is shown in Figure 4 for patients whose average daily HR was ≤80 bpm, and in Figure 5 for patients whose average daily HR was >80 bpm. Figure 4 demonstrates the prominent late-morning increase in HR in the IAST patients relative to controls with overlap during the other time intervals. Figure 5 shows that the diurnal variation in the IAST patients with HR > 80 bpm is similar to controls. The hourly normalized HR was then averaged for each 6-hour period in the day, into groupings of 8am–1pm, 2pm–7pm, 8pm–1am, and 2am–7am. These results are shown in Table II. The only significant difference was noted in the subgroup of patients with mean

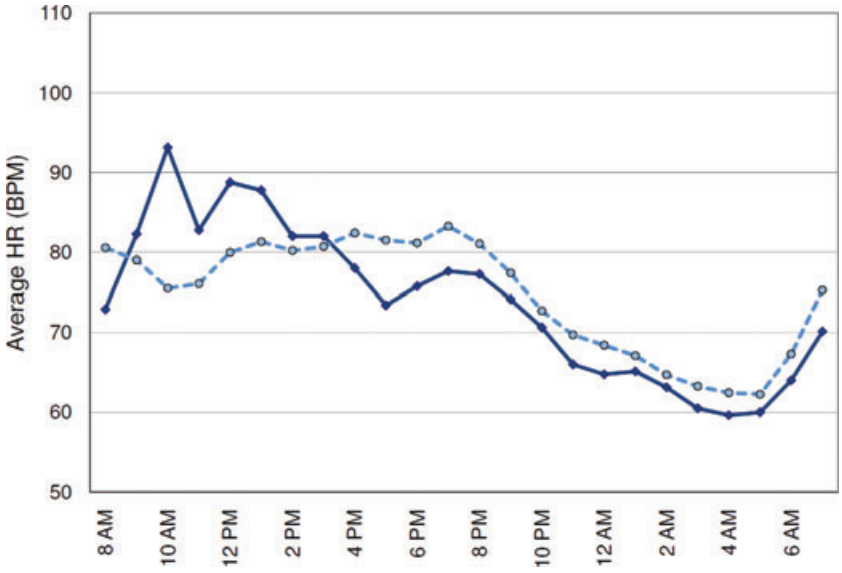

Figure 2. *Average HR trends for patients with mean HR < 80 bpm over a 24-hour period, by hourly mean HR. Solid lines w/ diamonds = IAST, mean HR < 80 bpm; Dashed lines w/ circles = Controls, mean HR < 80 bpm.*

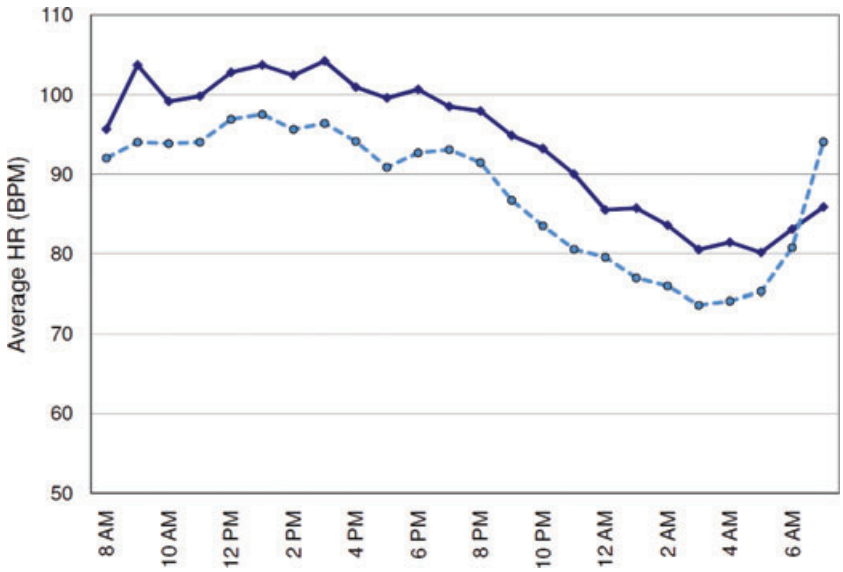

Figure 3. *Average HR trends for patients with mean HR > 80 bpm over a 24-hour period, by hourly mean HR. Solid lines w/ diamonds = IAST, mean HR > 80 bpm; Dashed lines w/ circles = Controls, mean HR > 80 bpm.*

HR < 80 bpm and occurred during the time period between 8am–1pm, 11.5 ± 6.3 bpm in IAST patients versus 4.8 ± 4.5 bpm in controls (P < 0.004). There was no significant difference in normalized heart rates for any of the 6-hour periods for the subgroup of patients whose average daily HR was >80 bpm.

Discussion

IAST is a relatively common disorder[5] whose underlying pathophysiology has not been well characterized. The major finding in this study is that patients with inappropriate sinus tachycardia exhibit two distinct patterns of diurnal variation

Table I.

Results of Harmonic Regression Analysis

$$HR(t) = A + \sum_{i=1}^{2}\left(B_i \sin\left(\frac{2\pi it}{24}\right) + C_i \cos\left(\frac{2\pi it}{24}\right)\right) + IASTx\left(\sum_{i=1}^{2}\left(IB_i \sin\left(\frac{2\pi it}{24}\right) + IC_i \cos\left(\frac{2\pi it}{24}\right)\right)\right)$$

where HR(t) is the heart rate at hour t, and A, B_i, C_i, IAST, IB_i, and IC_i are constants

	All Patients (n = 60)			Patients with Heart Rate ≤ 80 bpm (n = 28)			Patients with Heart Rate > 80 bpm (n = 32)		
Coefficient	**Estimate**	**SE**	**P**	**Estimate**	**SE**	**P**	**Estimate**	**SE**	**P**
A	81.08	1.69	<0.0001	74.68	1.28	<0.0001	87.90	1.83	<0.0001
B_1	−5.96	0.49	<0.0001	−6.62	0.59	<0.0001	−5.20	0.78	<0.0001
B_2	−3.22	0.44	<0.0001	−3.07	0.54	<0.0001	−3.38	0.70	<0.0001
C_1	−7.66	0.43	<0.0001	−6.13	0.53	<0.0001	−9.35	0.67	0.77
C_2	−0.71	0.43	0.0984	−1.17	0.53	0.03	−0.19	0.67	0.77
IAST	5.62	2.79	0.0485	−0.89	2.40	0.71	6.05	2.77	0.04
IB_1	−0.56	0.81	0.49	1.42	1.10	0.20	−2.06	1.17	0.08
IB_2	0.11	0.73	0.88	−0.83	1.01	0.41	0.72	1.05	0.49
IC_1	−1.46	0.71	0.04	−4.50	0.98	<0.001	1.10	1.01	0.28
IC_2	2.98	0.71	<0.0001	4.66	0.98	<0.001	1.76	1.01	0.08

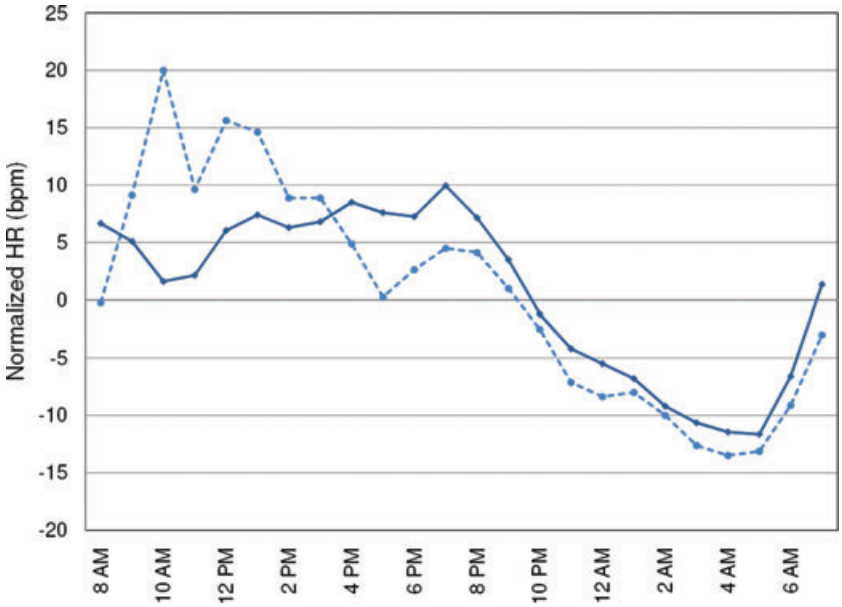

Figure 4. *Normalized HR trends for patients with mean HR < 80 bpm over a 24-hour period, by hourly mean HR. Solid lines w/ diamonds = Controls, mean HR < 80 bpm; Dashed lines w/ circles = IAST, mean HR < 80 bpm.*

in HR, depending on the average mean daily HR. Those with lower, "normal" average daily heart rates (i.e. <80 bpm) have an exaggerated increase in morning heart rates when compared to controls of similar average daily heart rates, but similar heart rates at other times. They may be considered to have paroxysmal IAST. However, those with elevated mean HR and IAST have similar temporal variation in their heart rate response compared to controls. They may be considered to have persistent IAST. These different patterns in diurnal variation likely reflect different underlying

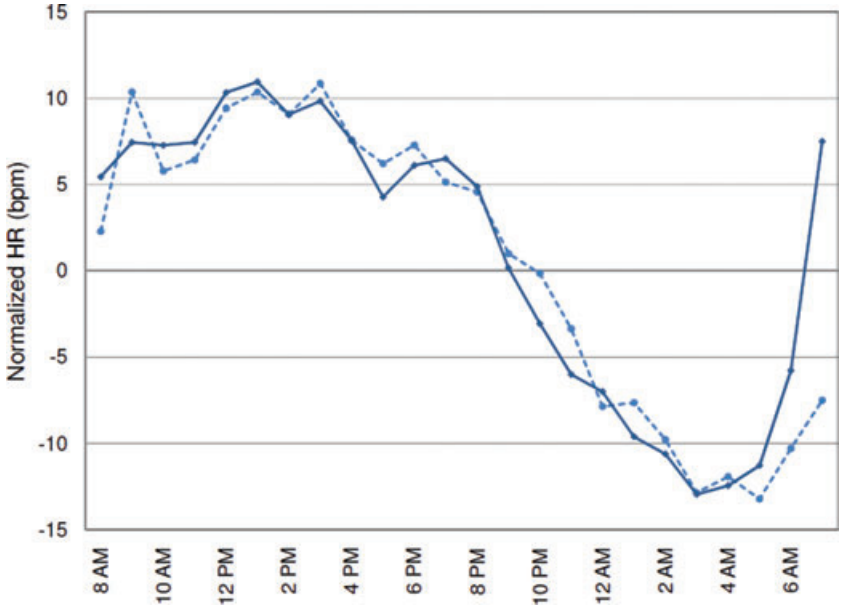

Figure 5. *Normalized HR trends for patients with mean HR > 80 bpm over a 24-hour period, by hourly mean HR. Solid lines w/ diamonds = Controls, mean HR > 80 bpm; Dashed lines w/ circles = IAST, mean HR > 80 bpm.*

Table II.

Quarterly Normalized Mean Heart Rates

		Normalized Mean (BPM)	SD	P Value
8am–1pm	IAST ≤ 80	11.5	6.3	0.004
	Control ≤ 80	4.8	4.5	
2pm–7pm	IAST ≤ 80	5.0	3.2	0.14
	Control ≤ 80	7.6	4.4	
8pm–1am	IAST ≤ 80	−3.5	4.0	0.16
	Control ≤ 80	−1.2	3.7	
2am–7am	IAST ≤ 80	−10.2	4.9	0.18
	Control ≤ 80	−8.0	3.3	
8am–1pm	IAST > 80	7.4	9.7	0.81
	Control > 80	8.2	6.5	
2pm–7pm	IAST > 80	7.7	4.7	0.76
	Control > 80	7.2	3.9	
8pm–1am	IAST > 80	−2.2	8.4	0.59
	Control > 80	−3.4	5.0	
2am–7am	IAST > 80	−10.9	4.0	0.06
	Control > 80	−7.6	5.4	

pathophysiologies and are consistent with abnormalities in intrinsic sinus node function and extrinsic autonomic influences on the sinus node. Better delineation of the underlying physiology could help better tailor therapy for the patient who requires it.

Relationship of Circadian Variation in Heart Rate to Autonomic Tone

In healthy individuals there is a circadian pattern of heart rate and blood pressure with a peak heart rate and blood pressure around 10am, and a gradual decline to a nadir in the morning hours just prior to awakening.[14,15] The rise in blood pressure and heart rate is associated with an increase in cortisol and a doubling of the plasma catecholamines, and alteration in sympathovagal balance.[16] The exact mechanisms for the diurnal variation in heart rate and blood pressure are not clear; they are likely related to both an actual circadian variation and also the response to being upright. The parasympathetic nervous system seems to exhibit a true circadian variation with gradual withdrawal during the daytime.[17] The sympathetic system is activated during the morning hours and is influenced by posture, waking, activity and environmental stress.[18–20]

Altered Autonomic Tone and Circadian Rhythms

Disease states with alterations in autonomic tone can have an effect on circadian rhythms. States associated with sympathoexcitation such as congestive heart failure and autonomic neuropathy retain their diurnal variation in heart rate, though it may be blunted. Patients with congestive heart failure maintain a circadian variation in heart rate despite a sustained imbalance in sympathovagal balance with lack of parasympathetic augmentation during nighttime hours.[21] Diabetics with autonomic neuropathy, despite enhanced sympathetic tone and high resting heart rates, also maintain some degree of circadian variation in heart rates, although blunted.[4,22] Activity and stress can increase daytime heart rates, but the diurnal drop in heart rate is still observed.[20] Low sympathetic states such as daytime reclining are associated with a decreased diurnal variation in heart rate.

Potential Mechanisms for Inappropriate Sinus Tachycardia

The present findings suggest that there are at least two types of IAST. In the patients with elevated mean 24-hour HR, the diurnal variation was no different than the control group. The only difference was a slightly higher 24-hour mean HR. After normalizing the hourly heart rate data by each individual patient's 24-hour mean HR, there was no difference in the IAST patients versus controls. The most likely mechanism for IAST in these patients is therefore an intrinsic abnormality of the sinus node resulting in a higher set-point for the 24-hour mean HR. The extrinsic autonomic function and the response of the sinus node to diurnal variations in autonomic tone are normal. In contrast, in patients in the lower mean 24-hour heart rate group, the IAST patients had a clear exaggerated HR increase in the morning compared to the controls. This pattern was confirmed by normalizing the hourly heart rate data by each individual patient's 24-hour mean HR, as well as by harmonic analysis. This may result from either an exaggerated adrenergic surge (or, less likely, an abnormality in parasympathetic function) in the morning or hypersensitivity of the sinus node to adrenergic stimuli; the latter mechanism may also be associated with a tachyphylaxis response as the elevated HR does not persist throughout the day.

Understanding the mechanistic differences responsible for IAST may have important therapeutic implications. Although the clinical diagnosis of IAST is made by the presence of symptoms and sinus tachycardia, both of these may be present whether the underlying cause is a high set-point for the sinus node or an excessive adrenergic surge or response. It is possible that patients who have a high set-point may respond well to catheter ablation to achieve sinus node modification, while those with autonomic abnormalities would not. Given the mixed long-term

success rates reported for sinus node modification procedures,[23,24] it would be important to evaluate whether this could be related to patient selection.

Prior Studies

Some previous reports on the mechanism of IAST have suggested an intrinsic abnormality of the sinus node; others report abnormal sympathovagal interaction. Morillo et al.[8] found among their seven patients some with normal sympathovagal balance with evidence of a primary sinus node abnormality with high intrinsic heart rates and β-adrenergic hypersensitivity. Patients with inappropriate sinus tachycardia had several normal indices of heart rate variability including a normal low frequency to high frequency ratio at rest and with orthostatic stress. This supports the mechanism of IAST as an abnormal sinus node set point.

In contrast, Castellanos et al.[2] found evidence of reduced heart rate variability. They studied 24-hour heart rate variability and found a decrease in time and frequency domain indices suggestive of reduced parasympathetic tone even when heart rates were normalized to 75 bpm. However, they could not rule out that this was due to a primary increase in sinus rate. In the initial studies by Bauernfeind et al.,[6] they demonstrated abnormal autonomic function in all seven patients who had resting heart rates >100 bpm. They studied seven patients with IAST, and found that six of seven patients had normal intrinsic heart rates and all seven patients had evidence of either a diminished increase in rate with atropine or a marked slowing with propranolol. This suggested to the authors abnormal autonomic control of the sinus node. Other authors found a decrease in heart rate variability and a decrease in parasympathetic tone.[9] In addition, some studies of heart rate variability in patients with inappropriate sinus tachycardia after catheter ablation have noted increased parasympathetic withdrawal, although this finding is not uniform.[7,25,26] More recent data have shown that anti-β1 adrenergic receptor antibodies in IAST patients exert positive chronotropic effects, suggesting an autonomic mechanism for this disease process.[27]

The discrepancy in these reports may be due to the inclusion of distinct populations with different pathophysiologies responsible for the IAST disease; one group with intrinsic sinus node dysfunction—higher average resting heart rates; and another group with dysfunction extrinsic to the sinus node due to abnormal autonomic input and/or response. This is consistent with our findings that patients with low average daily heart rates exhibit increased early morning heart rates, while those patients with higher daily average heart rates have diurnal variation in heart rates similar to controls.

Limitations

The present study explored the diurnal variation in heart rates in patients with IAST and used control patients who had Holter monitors ordered for various complaints. Although the control group was deemed to have no significant cardiac disease by their primary cardiologist and exhibited normal diurnal variation, this was not a preselected group of normal volunteers. Detailed logs of patient activity are not available during the Holter monitoring period; it is conceivable the IAST group was more active than the controls. However, this seems unlikely as heart rate differences are seen throughout the day, including during nighttime hours. More importantly, our analyses and the current findings focus primarily on the diurnal patterns, rather than on actual differences (or lack of differences) in mean heart rate.

Additionally, the groups represent a small number of individuals. Although the study population was initially divided into groups by the median heart rate of 80 bpm, it is not clear that this is the optimal cutpoint to differentiate the groups. However, now that the patterns of diurnal variation have been defined, it may be more appropriate to classify IAST patients based on the actual diurnal heart rate pattern rather than the average 24-hour heart rate.

A portion of the differences in mean 24-hour HR between groups may be attributable to the definitions used either to dichotomize the patients (HR > 80 vs HR < 80), or the definition of IAST itself, rather than true differences (or similarities) between the control and IAST groups. However, the analysis of normalized HR should remove any differences due to mean HR alone, and the dissimilar diurnal patterns between groups shown by harmonic analysis should also be independent of any such bias.

Conclusions

These data suggest two distinct populations of patients who all fall under the diagnostic criteria for IAST. One population has an elevated mean HR with normal diurnal variation; a second population has a lower mean HR but disordered diurnal patterns. IAST can be a frustrating disorder for both patients and physicians. It is likely underdiagnosed due to the documentation of sinus rhythm, albeit at an elevated rate, at the time of symptoms. Attempts to treat IAST with catheter ablation have been disappointing, as many patients with successful procedures resulting in normalization of sinus rates have remained

symptomatic. Further studies evaluating treatment that is tailored to these distinct IAST subpopulations and targeting the possibly different underlying pathophysiologies are necessary to define which treatments are appropriate for the individual patient.

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