J Anesth (1997) 11:22–26

Journal of
Anesthesia

Parasympathetic nervous activity after administration of atropine and neostigmine using heart rate spectral analysis

KEN-ICHI IWASAKI[1,2], HAJIME SUZUKI[1], SHIGERU SAEKI[1], KIYOSHI MASE[1], SETSURO OGAWA[1], KANAME HIRAYANAGI[2], and KAZUYOSHI YAJIMA[2]

[1] Department of Anesthesiology, Surugadai Nihon University Hospital, 1-8-13 Kanda-Surugadai, Chiyoda-ku, Tokyo 101, Japan
[2] Department of Hygiene, Nihon University School of Medicine, 30-1 Ohyaguchi-Kamimachi, Itabashi-ku, Tokyo 173, Japan

Abstract: Recently, heart rate spectral analysis has become recognized as a powerful tool for quantitatively evaluating autonomic nervous system activity. The purpose of this study was to analyze parasympathetic nervous activity by heart rate spectral analysis after administration of atropine and neostigmine for reversal of residual neuromuscular blockade. For our study, 36 female patients (26–37 years of age), ASA physical status (PS) I, who were scheduled for laparoscopic examination, were randomly allocated to one of the following four groups: In group A (1:1), 9 patients received 1.0mg atropine followed 4min later by 1.0mg neostigmine. In group B (1:2), 9 patients received 0.5mg atropine followed 4min later by 1.0mg neostigmine. In group C (1:2.5), 9 patients received 1.0mg atropine followed 4min later by 2.5mg neostigmine. In group D (1:2mix), 9 patients received a mixed solution of atropine 0.5mg and neostigmine 1.0mg. After finishing the laparoscopic examination, additional anesthesia was maintained with 70% nitrous oxide, 30% oxygen, and 0.5% isoflurane. The control data were obtained 10min after finishing the laparoscopic examination. After that, the data on atropine were obtained between 2 and 4min after administration of atropine, and the data on neostigmine were obtained between 5 and 7min after administration of neostigmine. We selected power spectral density of the high-frequency component (HF-p) in heart rate spectral analysis as an index to assess parasympathetic activity. In groups A, B, and C, the HF-p decreased after administration of atropine. In groups B and C, the HF-p increased after administration of neostigmine as compared to the control. In group A, the HF-p increased after neostigmine but did not differ from the control. The difference between groups D and B was not statistically significant. From the results of this study, we concluded that the muscarinic effect of neostigmine could not be sufficiently blocked by atropine at $^1/_2$ dosages of neostigmine, but could be sufficiently blocked by atropine at equivalent dosages of neostigmine, under light isoflurane anesthesia.

Address correspondence to: K. Iwasaki
Received for publication on January 18, 1995; accepted on August 5, 1996

Key words: Heart rate spectral analysis, Reversal of residual neuromuscular blockade, Parasympathetic nervous system, Atropine, Neostigmine

Introduction

Neostigmine is administered for the reversal of residual neuromuscular blockade during anesthesia, and atropine is used to antagonize the muscarinic effects. However, the use of these two agents sometimes results in bradycardia, which is caused by an increase in parasympathetic activity and a decrease in sympathetic activity. Many investigators have studied the influence of atropine and neostigmine on heart rates and recovery from neuromuscular blockade in anesthetized patients [1–6]. However, each study has recommended different ratios of atropine and neostigmine doses (1:1–0.3:2.5), and there is no consensus about the ideal doses of atropine and neostigmine [1–6]. Moreover, Naguib and Gomaa suggested that in order to prevent late reductions in heart rates, the appropriate dose of atropine, when used with neostigmine, should be larger than that commonly used [1].

Recently, heart rate spectral analysis has become recognized as a powerful tool for quantitatively evaluating parasympathetic and sympathetic activity separately in awake and anesthetized humans [7–11]. It has been reported that the low-frequency component (LF-p) is mediated jointly by the sympathetic and parasympathetic nervous systems, whereas the high-frequency component (HF-p) is selectively mediated by the parasympathetic nervous system [7–11]. The purpose of this study was to assess parasympathetic nervous activity after administration of both atropine and neostigmine using heart rate spectral analysis.

Methods

Approval of the Ethics Committee at Surugadai Nihon University Hospital was obtained. Informed consent for the study was obtained from 36 female patients (26–37 years of age), ASA PS I, who were scheduled for laparoscopic examination.

All patients were premedicated with hydroxyzine 50 mg i.m. 45 min before the induction of anesthesia. On arrival to the operating room, ECG leads, pulse oximetry, and intravenous cannulae were placed. Anesthesia was induced with thiamylal 5 mg·kg^{-1}, and suxamethonium 1 mg·kg^{-1} was given to facilitate orotracheal intubation. Anesthesia was maintained with 1%–2% isoflurane and 70% nitrous oxide in oxygen, with intermittent administration of vecuronium bromide 0.08 mg·kg^{-1}. Breathing of the patients was controlled mechanically with 10–12 ml·kg^{-1} tidal volume and 10 breaths·min^{-1} (0.17 Hz) to maintain end-tidal carbon dioxide pressure ($ETco_2$) at between 30 and 40 mmHg. After finishing the laparoscopic examination, additional anesthesia was maintained with 70% nitrous oxide, 30% oxygen, and 0.5% isoflurane. Within 10 min, the end-tidal isoflurane concentration had stabilized at 0.5%, and the patients' heart rates had stabilized at the fasting level (62–89 · min^{-1}).

The electrocardiogram (ECG), obtained from the third lead of a standard ECG instrument, was analyzed with an R-R analyzer (TM-55, Cerx, Tokyo, Japan) which allows direct computation of the R-R interval (ms). The analyzed R-R intervals (beat-to-beat mode) were sent to a microcomputer PC9801N (NEC, Tokyo, Japan) through an RS-232C line and were recorded on floppy disks. The mean heart rates (m-HR) were calculated from mean R-R intervals during 128 s. The R-R intervals (beat-to-beat mode) were changed to a time series data of 256 points every half second by the Spline interpolation method. Spectrum of R-R intervals were obtained by applying the fast Fourier transform (FFT) to the time series data and the Hanning window processing [12]. Power spectral density of the high-frequency component (HF-p) and low-frequency component (LF-p) were used to assess sympathetic and parasympathetic activity. In this study, we selected HF-p as an index to assess parasympathetic activity. The high-frequency component was centered at the frequency of respiration. We fixed the respiration rate at 10 · min^{-1} (0.17 Hz), and as a result the high-frequency component had a peak at 0.17 Hz. Therefore, we defined high frequency as 0.141–0.25 Hz and low frequency as 0.04–0.14 Hz.

The 36 patients were randomly allocated to one of the following four groups: In group A (1:1), atropine 1.0 mg (16–20 μg·kg^{-1}) was followed 4 min later by neostigmine 1.0 mg (16–20 μg·kg^{-1}) (9 patients). In group B (1:2), atropine 0.5 mg (9–11 μg·kg^{-1}) was followed 4 min later by neostigmine 1.0 mg (18–22 μg·kg) (9 patients). In group C (1:2.5), atropine 1.0 mg (18–21 μg·kg^{-1}) was followed 4 min later by neostigmine 2.5 mg (45–53 μg·kg^{-1}) (9 patients). In group D (1:2 mix), a mixed solution of atropine 0.5 mg (9–10 μg·kg^{-1}) and neostigmine 1.0 mg (18–22 μg·kg^{-1}) was injected (9 patients). Each drug was injected intravenously over a period of 30 s.

The R-R intervals data were measured for 128 s from the ECG, before administration of atropine or the mixed solution of atropine and neostigmine as controls, between 2 and 4 min after administration of atropine, and between 5 and 7 min after administration of neostigmine.

In all group C patients, additional atropine was administrated 6 min after the neostigmine administration because of extreme bradycardia (HR $\leq$ 52), and data during 5–7 min following neostigmine administration could not be obtained in this group. Therefore, we used the data during 3–5 min following neostigmine administration instead. In group D, the R-R intervals data were obtained between 5 and 7 min after administration of the mixed solution.

Statistical analysis of the data was performed with the Friedmann test in groups A, B, and C. Significance of difference was calculated using Dunnett's test (two-tailed; $P < 0.01$ vs control). The difference between groups was evaluated by the unpaired Wilcoxon test (two-tailed; $P < 0.01$) on mean percent changes.

Results

The background data on physical status in the four groups were not significantly different. (Table 1). There were no ectopic beats and no other artefacts on the ECG. Spectra of R-R intervals such as those shown in Fig. 1 were obtained.

The mean values of each index in the four groups are summarized in Table 2. HF-p decreased significantly ($P < 0.01$) after atropine administration in groups A, B, and C. The HF-p increased after administration of neostigmine as compared to the control levels in groups B and C ($P < 0.01$), while no significant difference could be found in group A (Table 2). Percent changes in HF-p are presented in Fig. 2. After neostigmine administration, there was a significant difference both between groups A and B, and between groups A and C ($P < 0.01$).

LF-p decreased significantly ($P < 0.01$) after atropine administration in groups A, B, and C. The LF-p increased after administration of neostigmine as compared to the control levels in groups B and C ($P < 0.01$), while no significant difference could be found in group A (Table 2).

Table 1. Physical status of the four groups

Group	A	B	C	D
Age (years)	31.9 ± 3.1	30.6 ± 3.7	31.7 ± 4.0	30.4 ± 2.7
Weight (kg)	54.0 ± 3.6	51.8 ± 3.7	52.9 ± 3.3	48.2 ± 2.3
Height (cm)	159 ± 6.3	158 ± 7.5	158 ± 5.0	155 ± 4.5

Values are mean ± SD.

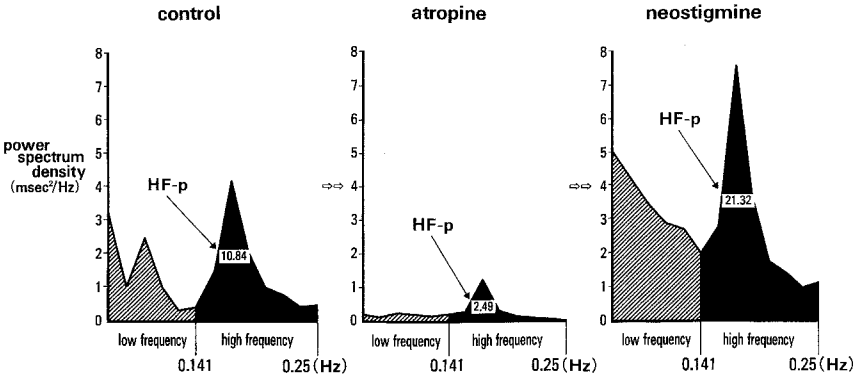

Fig. 1. Power spectrum from a subject in group B. *Control*, power spectrum obtained as control; *atropine*, power spectrum obtained after atropine administration; *neostigmine*, power spectrum obtained after neostigmine administration. *HF-p*, high-frequency component

Table 2. Mean value of each index in the four groups

Index	Group	Control	Atropine	Neostigmine
HF-p (ms^2)	A	9.1 ± 3.4	3.6 ± 2.2*	10.8 ± 3.3
	B	8.2 ± 2.5	3.1 ± 2.5*	16.7 ± 4.0*
	C	8.4 ± 3.3	3.0 ± 2.0*	21.6 ± 3.6*
	D	9.7 ± 4.0		14.1 ± 4.5*
LF-p (ms^2)	A	11.0 ± 4.0	1.7 ± 0.5*	14.6 ± 5.5
	B	9.4 ± 4.5	4.1 ± 5.5*	24.4 ± 8.7*
	C	8.7 ± 4.2	3.0 ± 1.2*	21.3 ± 6.0*
	D	10.2 ± 4.4		19.5 ± 8.1*
m-HR (bpm)	A	74.0 ± 8.2	102.9 ± 10.1*	76.2 ± 5.6
	B	78.1 ± 8.3	102.2 ± 9.4*	68.2 ± 8.2
	C	76.1 ± 8.1	101.7 ± 9.2*	57.5 ± 3.6*
	D	75.7 ± 12.7		68.6 ± 8.8

Values are mean ± SD.
* $P < 0.01$ compared with controls.
HF-p, power spectral density of the high frequency component in heart rate spectral analysis; LF-p, power spectral density of the low frequency component; m-HR, mean heart rate.
In group C, the mean value is given of each index between 3 and 5 min after neostigmine administration.

The mean values of m-HR in all groups significantly increased after atropine administration to almost similar levels, and then decreased after neostigmine administration. In group A, the mean values of m-HR after neostigmine administration recovered to near control levels. In group C, the mean values of m-HR after neostigmine administration significantly decreased when compared with control levels ($P < 0.01$) (Table 2). Percent changes in m-HR are presented in Fig. 3. Again, there was a significant difference ($P < 0.01$) between groups A and B, and also between groups A and C, after neostigmine administration.

No statistical difference could be detected in the mean values of these indices between groups B and D which were given the same dosages of atropine and neostigmine (Fig. 4 and Fig. 5).

Discussion

Many investigators have studied the effect of atropine and neostigmine on heart rate with regard to the optimal modes and time of administration of these agents. However, there is no consensus about the ideal doses of atropine and neostigmine.

Most anesthesiologists are using a combined injection with a ratio of 1:2 or 1:2.5 of atropine to neostigmine [2–5]. However, patients managed by these regimens

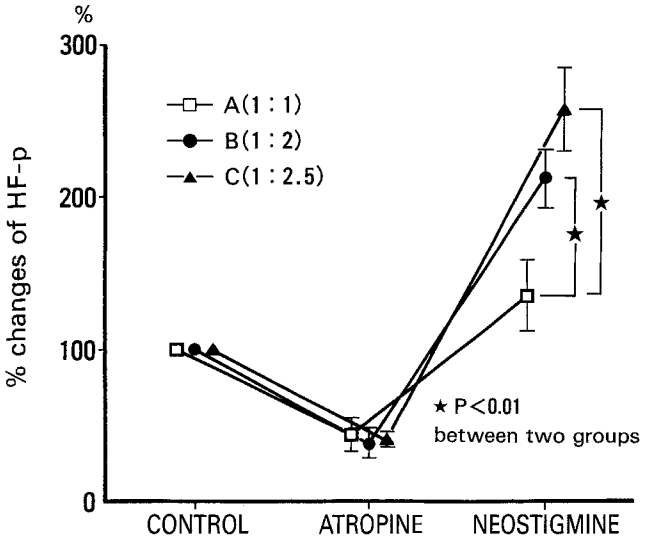

Fig. 2. Percent changes in power of the high-frequency component (*HF-p*) in groups A, B, and C (mean ± SD). *Atropine*, 2–4 min after administration of atropine; *neostigmine*, 5–7 min after administration of neostigmine. $*P < 0.01$ between two groups

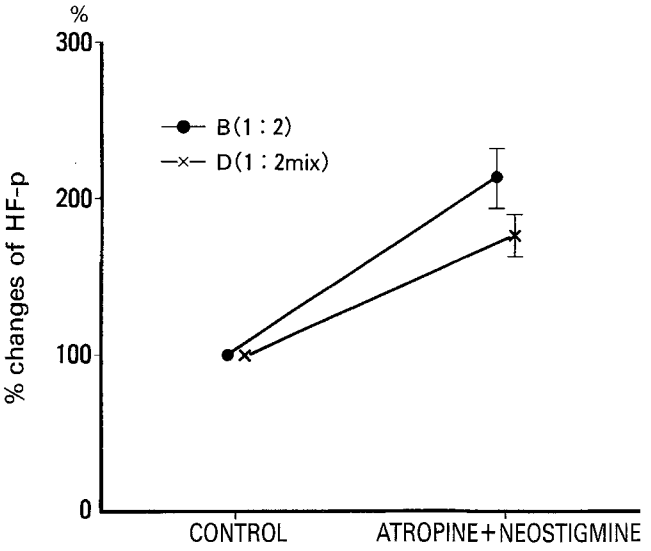

Fig. 4. Percent changes in power of the high-frequency component (*HF-p*) in groups B and D (mean ± SD). *Atropine + neostigmine*, in group B, 5–7 min after administration of neostigmine. In group D, 5–7 min after administration of the mixed solution

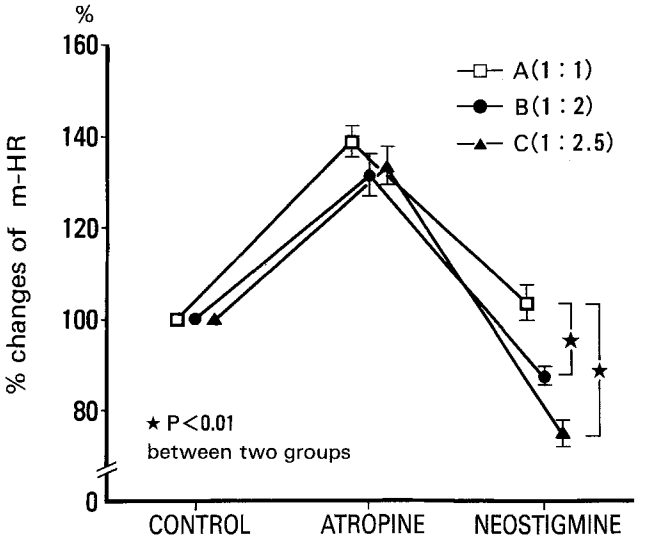

Fig. 3. Percent changes in mean heart rate (*m-HR*) in groups A, B, and C (mean ± SD). *Atropine*, 2–4 min after administration of atropine; *neostigmine*, 5–7 min after administration of neostigmine. $*P < 0.01$ between two groups

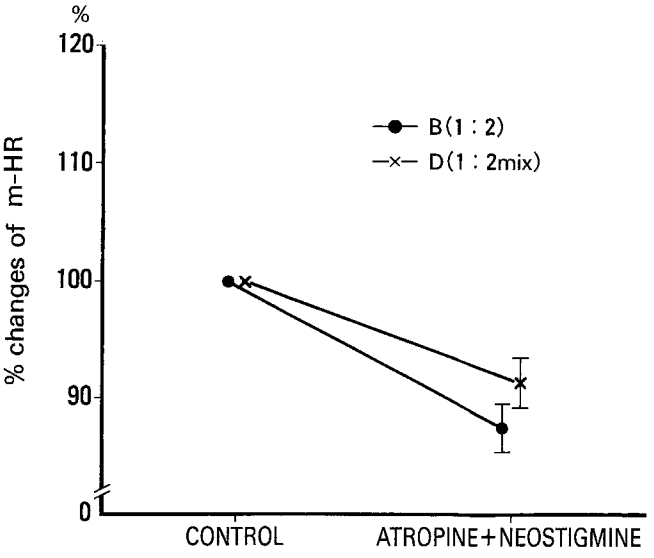

Fig. 5. Percent changes in mean heart rate (*m-HR*) in groups B and D (mean ± SD). *Atropine + neostigmine*, in group B, 5–7 min after administration of neostigmine. In group D, 5–7 min after administration of the mixed solution

frequently demonstrate increased salivation or bradycardia after injection of these drugs. Moreover, Naguib and Gomaa suggested that in order to prevent late reductions in heart rates, the appropriate doses of atropine when used with neostigmine should be larger than those used clinically by most anesthesiologists [1]. In this study, we chose ratios of 1:1, 1:2, and 1:2.5 of atropine and neostigmine and assessed parasympathetic nervous activity under 0.5% isoflurane anesthesia.

The parasympathetic effects of these agents have been studied with evaluation of changes in heart rate [1–5]. These studies were conducted under various conditions of anesthesia. However, heart rate is known to be controlled by both the sympathetic and parasympathetic nervous systems, and it fluctuates widely due to many influencing factors. Recently, heart rate spectral analysis has become recognized as a powerful tool for quantitatively evaluating parasympathetic and sympathetic activity separately [7–11]. The power spectrum of

R-R intervals such as that shown in Fig. 1 was constructed from two main low- and high-frequency components. It has been reported that the low-frequency component is mediated jointly by sympathetic and parasympathetic activity, and the high-frequency component is mediated selectively by parasympathetic activity [7–9]. We assessed parasympathetic nervous activity after the administration of atropine and neostigmine by the HF-p of heart rate spectral analysis.

In this study, anesthesia was maintained with 0.5% isoflurane. The potential effects of isoflurane on heart rate spectral analysis need to be considered as well. Isoflurane decreased the LF-p and the HF-p in a concentration-dependent manner [11]. Light isoflurane anesthesia seems to modify our results as compared to the awake state. However, the end-tidal isoflurane concentration stabilized at 0.5%. The influence of isoflurane on autonomic nerve system activity did not change during this study.

The results of this study show that the muscarinic effect of neostigmine could not be sufficiently blocked by atropine at $^1/_2$ dosages of neostigmine, and that equivalent dosages of atropine and neostigmine demonstrated lesser degrees of change in the parameters.

The changes in the indices were slightly smaller in group D (in which atropine and neostigmine were administrated as a mixed solution), than in group B (in which atropine preceded the administration of neostigmine), but the difference was not statistically significant. Findings that the onset and the maximum effect of atropine are more rapid than those of neostigmine were observed by Rosner et al. as changes in heart rate [5]. The small difference in the results between groups B and D may be caused by the different onset and duration of the two drugs.

There have been conflicting results on heart rates in previous studies [1–5]. Decreases in heart rate during antagonism of d-tubocurarine by neostigmine 2.5 mg with atropine 1.0 mg were of a lesser degree than those in this study [2]. However, the results obtained in Naguib and Gomaa's report and this study were similar [1]. Conceivably, the causes of conflicting results are different neuromuscular blockades, heart rates before administration of these drugs, injection interval, time of administration, and anesthesia. Fogdall and Miller suggested that the decreases in heart rate they observed were partly related to control heart rates [2].

When these drugs were clinically administered to reverse vecuronium-induced neuromuscular blockades, it may have been noted that the decreases in heart rate were of a lesser degree than those in this study. The reason may be that residual neuromuscular blockades are reversed clinically when the patients are awakened from anesthesia or when they are coming out of anesthesia. When sympathetic activity is reduced during general anesthesia as in this study, we must be aware of the possibility of severe bradycardia, and care must be taken to use sufficiently large dosages of atropine. Lange doses of atropine, however, might be responsible for the development of cardiac arrhythmia. Rosner et al. pointed out that prevention of excessive tachycardia is just as important as the avoidance of bradycardia [5].

It is concluded that the muscarinic effect of neostigmine could not be sufficiently blocked by atropine at $^1/_2$ dosages of neostigmine, but could be at equivalent dosages. Accordingly, the combination of atropine and neostigmine at a ratio of 1:1 is recommended during light isoflurane anesthesia using vecuronium.

References

1. Naguib M, Gomaa M (1989) Atropine-neostigmine mixture: a dose-response study. Can J Anaesth 36:412–417
2. Fogdall RP, Miller RD (1973) Antagonism of d-tubocurarine- and pancuronium-induced neuromuscular blockades by pyridostigmine in man. Anesthesiology 39:504–509
3. Usui K, Hashimoto Y, Iwatsuki K (1976) The effects of atropine and neostigmine on heart rate in humans (in Japanese with English abstract). Masui (Jpn J Anesthesiol) 25:386–390
4. Harper KW, Bali IM, Gibson FM, Carlisle R, Black IHC, Grainger DJ, Dundee JW (1984) Reversal of neuromuscular block: heart rate change with slow injection of neostigmine and atropine mixtures. Anesthesia 39:772–775
5. Rosner V, Kepes ER, Foldes FF (1971) The effect of atropine and neostigmine on heart rate and rhythm. Br J Anaesth 43:1066–1074
6. Baurain MJ, Dernovoi BS, d'Hollander AA, Barvais L (1992) The influence of atropine dose on recovery from vecuronium-induced neuromuscular blockade. Anesthesiology 77:17–20
7. Akselrod S, Gordon D, Ubel FA, Shannon DC, Barger AC, Cohen RJ (1981) Power spectrum analysis of heart rate fluctuation: a quantitative probe of beat-to-beat cardiovascular control. Science 213:220–222
8. Pomeranz B, Macaulay RJB, Caudill MA, Kutz I, Adam D, Gordon D, Kilborn KM, Barger AC, Shannon DC, Cohen RJ, Benson H (1985) Assessment of autonomic function in humans by heart rate spectral analysis. Am J Physiol 248:H151–H153
9. Hayano J, Sakakibara Y, Yamada M, Ohte N, Fujinami T, Yokoyama K, Watanabe Y, Takata K (1990) Decreased magnitude of heart rate spectral components in coronary artery disease. Circulation 81:1217–1224
10. Kawamoto M, Tanaka N, Takasaki M (1993) Power spectral analysis of heart rate variability after spinal anaesthesia. Br J Anaesth 71:523–527
11. Kato M, Komatsu T, Kimura T, Sugiyama F, Nakashima K, Shimada Y (1992) Spectral analysis of heart rate variability during isoflurane anesthesia. Anesthesiology 77:669–674
12. Luczak H, Laurig W (1973) An analysis of heart rate variability. Ergonomics 16:85–97