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Relation of Ventricular Fibrillation Threshold to Heart Rate during Normal Ventilation and Hypoventilation in Female Wistar Rats: A Chronophysiological Study

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Summary

The aim of our study was to verify the relationship between heart rate (HR) and ventricular fibrillation threshold (VFT) during different types of ventilation in female Wistar rats from the circadian point of view. The experiments were performed under pentobarbital anesthesia (40 mg/kg i.p., adaptation to a light-dark cycle 12:12 h, open chest experiments) and the obtained results were averaged independently of the seasons. The VFT measurements were performed during normal ventilation (17 animals) and hypoventilation (10 animals). The HR was recorded immediately before the rise of ventricular arrhythmias. Results are expressed as arithmetic means ± S.D. and differences are considered significant when $p<0.05$. The basic periodic characteristics were calculated using single and population mean cosinor tests. The results from our experiments have demonstrate that 1) the VFT and HR respond identically to hypoventilation by a decrease in the light and also in the dark phases, and 2) hypoventilation changes the 24-h course of the VFT without a change in the 24-h rhythm of the HR. It is concluded that the HR and VFT behave as two independent functional systems without apparent significant circadian dependence during both types of ventilation.

Key words

Rat • Circadian • Ventricular fibrillation threshold • Heart rate • Hypoventilation

Introduction

The vulnerability of the heart to ventricular arrhythmias is influenced by many factors concerning the internal and external environment. At present, it is supposed that the existence of circadian variations in cardiovascular reactivity is due to the temporal organization of the autonomous nervous system. On the basis of the assumption (Cinca *et al.* 1986) that the sympathetic-parasympathetic system exhibits the daily rhythmicity under basal resting conditions, it is possible to conclude that the electrophysiological properties of the heart may also show parallel circadian variability. A circadian rhythm of several parameters of the autonomous nervous system were clearly demonstrated including higher sympathetic activity in rats during the active period (Bennessiano *et al.* 1983, Witte and Lemmer 1988, Lemmer and Witte 1989, Henry *et al.* 1990, Lemmer *et al.* 1992). Circadian variability of the electrical stability of the heart was also demonstrated in

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rats (Otsuka and Watanabe 1990, Švorc *et al.* 1994) with a positive correlation between sympathetic tone and electrical stability of the heart. Nevertheless, a number of authors (Han *et al.* 1964, Kolman *et al.* 1975, Corr *et al.* 1986, Billman 1990, Morillo *et al.* 1996) have refered to the negative correlation between the sympathetic-parasympathetic nervous system and the electrical stability of the heart, mainly in larger laboratory animals. Increased sympathetic activity, associated with higher heart rate, diminished cardiac electrical stability, whereas parasympathetic activation appeared to protect against arrhythmia formation. It seems that the relation between heart rate as one of parameters of the autonomous nervous system and the electrical stability of the heart in rats is less important.

Similarly, hypoxia, as one of the results of the disorders of normal ventilation or of the diseases of the respiratory system, belongs among factors influencing the electrical stability of the heart. Although hypoventilation-induced respiratory acidosis did not influence the heart vulnerability threshold in dogs (Gerst *et al.* 1966), this threshold was enhanced when hypoxia was superimposed (Rogers *et al.* 1973). The duration of the vulnerable period was considerably prolonged during hypoventilation-induced hypoxia (Kujaník *et al.* 1984), but the ventricular fibrillation threshold was lowered during mild hypoxia and acidosis and increased during extreme hypoxia and acidosis (Kujaník *et al.* 1985). Although the experiments were not performed during the 24-h period, it is apparent that hypoxia decreases the electrical stability of the heart tending to induce ventricular fibrillations. This negative influence was also discovered to depend on the circadian rhythm. The hourly distribution of the apnea index was coincided with the highest peak of the 24-h chronogram of bradyarrhythmias incidence in rats (Otsuka and Watanabe 1990). The unambiguously significant hypoventilation-induced drop of the ventricular fibrillation threshold was found in the course of the whole 24-h period (Švorc *et al.* 1997, 1998).

If the changes in the electrical stability of the heart are conditioned by changes in the autonomous nervous system tone (for example the heart rate), the question remains whether this relation will also be preserved or changed during hypoventilation. Furthermore, the effect of hypoxia on the followed parameters during the dark (active phase) and light (sleep phase) phase of the day is another open question. Therefore, the aim of our study in female Wistar rats was to evaluate the relationship between the electrical stability of the heart, measured by the ventricular fibrillation threshold, and the heart rate during normal ventilation and hypoventilation on the circadian dependence.

Material and Methods

The experiments were performed in the course of a whole year, and the obtained results were averaged independently of the seasons. Female Wistar rats (weighing 315±15 g, 3-4 months old) were used for the experiments. The rats were kept in a light- and climate-controlled room (temperature 24 °C, intensity of the artificial illumination 80 Lux in cages, relative humidity from 40 % to 60 %, 3 animals per cage) for 4 weeks and were allowed access to food and water *ad libitum*. The animals were exposed to a daily light-dark cycle of 12 h : 12 h, with the dark period from 18:00 h to 06:00 h. The experiments were performed in anaesthetized rats (pentobarbital, SPOFA, Prague, 40 mg/kg i.p.) at 3-hour intervals during a 24-h period.

The 24-h rhythms of ventricular fibrillation threshold and the heart rate were followed in two independent experimental groups. The first experimental group (control group, 17 animals at each interval of the measurement) was artificially ventilated with room air (respiratory rate 40 strokes/min, tidal volume 1 ml/100 g of body weight, the parameters of acid-base balance pO_2 = 12.7±3.1 kPa, pCO_2 = 2.9±0.5 kPa, pH = 7.51±0.05). The second experimental group (hypo-ventilatory group) comprised 10 animals at each interval of the measurement, with the following parameters of artificial ventilation: (respiratory rate 20 strokes/min and tidal volume 0.5 ml/100 g of body weight and the parameters of the acid-base balance pO_2 = 9.3±3.7 kPa, pCO_2 = 6.6±1.3 kPa, pH = 7.04±0.03. Artificial respiration was maintained through a tracheal cannula connected to a respirator. The values of acid-base balance were monitored by the ASTRUP method in the blood of the femoral artery during both types of ventilation as control of breathing.

The cardiac stimulation was performed after a thoracotomy directly in the open chest preparation and was triggered by the initial pulse of the R wave. The stimulating electrodes (diameter 1 mm, 5 mm distance between electrodes) were placed at the border between the right atrium and right ventricle. The hearts were stimulated with rectangular pulses at a frequency 30 Hz, 10 ms impulse length, and the duration of the stimulation was 400 ms. The current intensity was increased progressively in steps of 0.5 mA until the ventricular fibrillation threshold was attained. The ventricular fibrillation threshold was estimated after 5, 10, 15 and 20 min of the single types of ventilation and at each interval of the measurement. The measurement of the heart rate was performed immediately (as the mean value of the last 4 cycles) before the onset of ventricular fibrillations.

Data are presented as arithmetic means ± S.D. The differences between single groups are considered significant when $p<0.05$. The basic periodic characteristics (acrophase, mesor and amplitude) were calculated using the single and population mean cosinor tests. The acrophase presents the peak of the regression sinus curve in temporal or angular expression, mesor is the average value of the oscillating parameter, amplitude corresponds to one half of difference between the maximal and minimal duration value of one cycle. We evaluated the courses and relation of these rhythms, not the significance of the changes at single intervals of the measurements.

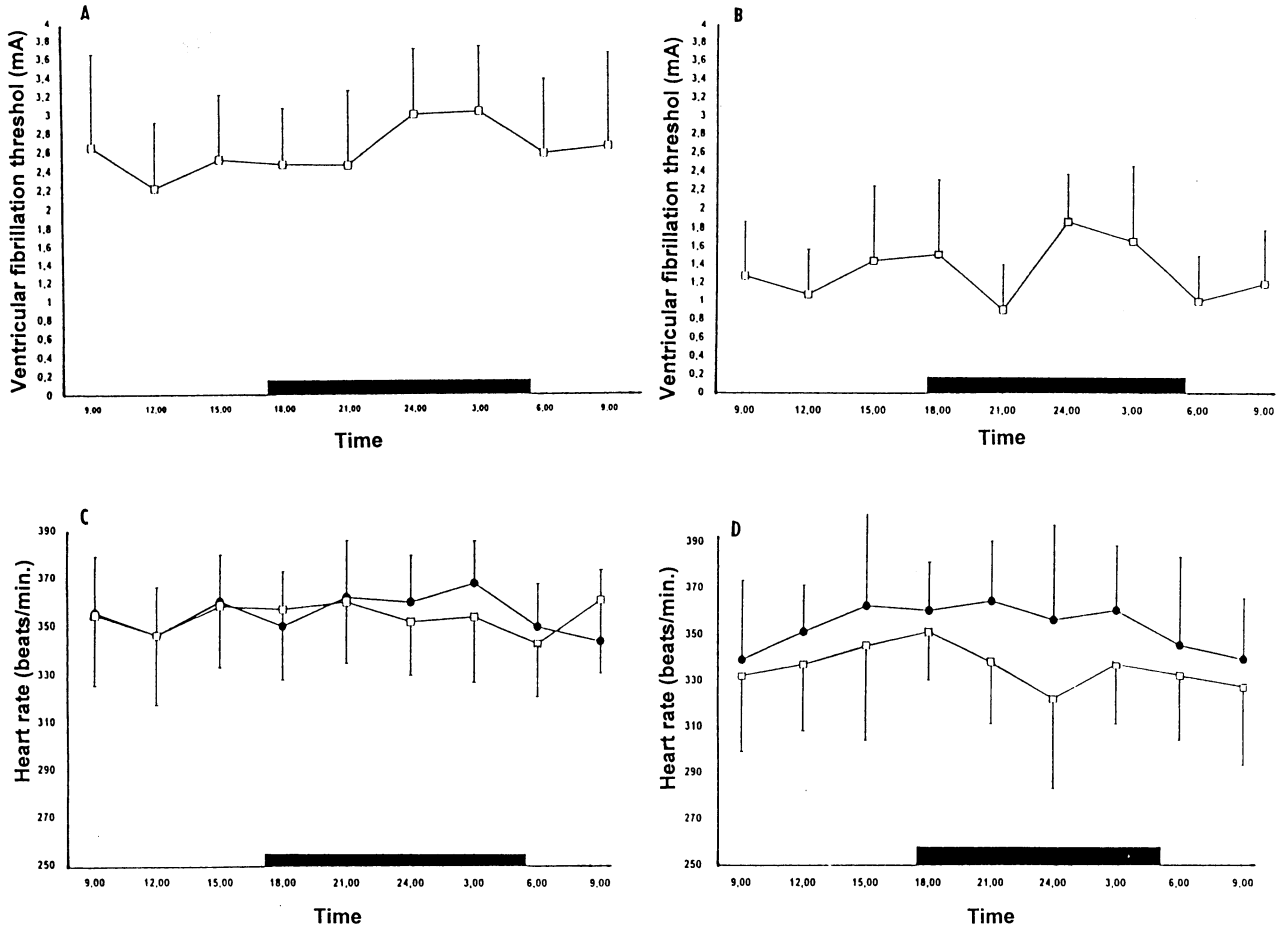

Fig. 1. *24-h rhythms of VFT, INI-HR (filled circles) and EXP-HR (empty squares) during normal ventilation (A and C) and hypoventilation (B and D). The individual values are presented as arithmetic means ± S.D. from each interval of the measurement. The INI-HR is recorded before surgical interventions and EXP-HR is recorded immediately before the rise of ventricular arrhythmias under pentobarbital anesthesia. The dark bar indicates the dark phase of the day.*

Results

The 24-h rhythms of the VFT, the initial HR recorded before the surgical interventions (INI-HR), and the HR measured immediately before the rise of the ventricular arrhythmias (EXP-HR), are showed in Figs 1A, 1B, 1C and 1D during 20 min artificial normal ventilation (control group) and hypoventilation (hypoventilatory group). During normal ventilation, the rhythm of the VFT followed a significant ($p<0.05$) circadian course. During a 24-h period, no significant changes in the INI-HR values were discovered. They fluctuated from interval to interval of the measurement (Fig. 1B – full circles), probably as a result of the effect of pentobarbital. The average INI-HR value from the whole dark phase (360±22 beats/min) was not significantly higher than the INI-HR value from the light phase (351±22 beats/min The 24-h course of the EXP-HR was similar in character

as in the control group, without circadian significance (Fig. 1B – open squares). On more detailed analysis of the VFT and the EXP-HR rhythms, from interval to interval of the measurement, EXP-HR decreases or increases were followed by the same VFT changes, except at 24:00 h. The small percentual EXP-HR changes were accompanied by relatively higher percentual VFT changes. Although the average percentual change of the EXP-HR was higher during the light phase (3.53 %) than during the dark one (0.98 %), approximately equal changes of the VFT were detected in both phases (light: 8.14 % vs. dark: 8.9 %) (Table 1).

Table 1. The average percentual changes of the VFT and the EXP-HR during normal ventilation and hypoventilation. The arrows ↓ or ↑ indicate the percentual decrease or increase of the followed parameter in comparison with the previous value (the value at 12:00 h means the decrease against the value at 09:00 h, the value at 15:00 h is the increase against the value at 12:00 h). Dark bar indicates the dark phase of the day.

	Normoventilation		Hypoventilation	
	VFT	**EXP-HR**	**VFT**	**EXP-HR**
09:00	–	–	–	–
12:00	↓ 4.18 %	↓ 2.26 %	↓ 14.84 %	↑ 1.51 %
15:00	↑ 5.68 %	↑ 3.47 %	↑ 36.78 %	↑ 2.37 %
18:00	↓ 5.78 %	↓ 0.28 %	↑ 1.35 %	↑ 1.74 %
21:00	↑ 11.84 %	↑ 0.84 %	↓ 38.67 %	↓ 3.70 %
24:00	↑ 17.65 %	↓ 2.22 %	↑ 105.43 %	↓ 4.73 %
03:00	↑ 0.33 %	↑ 0.57 %	↓ 15.34 %	↑ 4.66 %
06:00	↓ 18.60 %	↓ 3.11 %	↓ 34.38 %	↓ 1.48 %
09:00	↑ 4.08 %	↑ 5.25 %	↑ 12.38 %	↓ 1.51 %

Hypoventilation changed the 24-h course of the VFT to a more marked biphasic course (Fig. 1C). The 24-h rhythm of the INI-HR from the hypoventilatory group (Fig. 1D – full circles) had a similar character and significance in comparison with the control group. The EXP-HR was decreased at each interval during the whole period followed (Fig. 1D – open squares) against the INI-HR. The EXP-HR values increased gradually and peaked at 18:00 h (onset of the dark period) with a subsequent non-significant decreasing tendency until the end of the day. The nadir of the 24-h rhythms of the EXP-HR (at 24:00 h) corresponded with the peak of the VFT values (Fig. 1C, 1D). The acrophases of the EXP-HR rhythms were significantly shifted, not only during normal ventilation, but also under hypoventilatory conditions against the acrophases of the VFT - control group EXP-HR –47° (03:08 h) vs. VFT –338° (22:31 h) and hypoventilatory group EXP-HR (08:32 h) vs. VFT –348° (23:12h). A similar shift was also found between (the control group –47° (03:08 h) and –128° (08:32 h) hypoventilatory group. The mesors of the VFT and the EXP-HR rhythms were decreased (1.33 mA in hypoventilatory group vs. 2.59 mA in control group; 336 beats/min in hypoventilatory group vs. 352 beats/min in control group) during hypoventilation. Hypoventilation decreased the amplitude of the VFT rhythm (0.14 mA in hypoventilatory group vs. 0.33 mA in control group), but it was increased for the EXP-HR rhythm (7 beats/min in hypoventilatory group vs. 4 beats/min in control group). The average percentual changes of both parameters were markedly higher against the control group (light: EXP-HR 1.72 % vs. VFT 24.35 %; dark: EXP-HR 3.71 % vs. VFT 40.20 %) (Table 1).

The analysis of the VFT and the EXP-HR changes after 5, 10, 15 and 20 min of normal ventilation and hypoventilation showed that the duration of individual types of ventilation did not influence substantially the values of both parameters. The investigated parameters were relatively well stabilized to initial values after 20 min of the ventilation in both phases of the day. A significant difference was detected for the EXP-HR during the dark phase ($p<0.05$) (343±29 beats/min at 5 min vs. 330±25 beats/min at 20 min) (Table 1, Fig. 2B) and for the VFT ($p<0.05$) during the light phase (1.35±0.6 mA at 5 min vs. 1.09±0.5 mA at 20 min) only in the hypoventilatory group (Table 2, Fig. 2A).

Table 2. Average values of the ventricular fibrillation threshold and the heart rate after 5, 10, 15 and 20 min of the normal artificial ventilation (VFT-NV, EXP-HR-NV) and hypoventilation (VFT-HV, EXP-HR-HV). The values are arithmetic means ± S.D. from all intervals of the measurement in the light and dark phases of the day.

	5 min	10 min	15 min	20 min
Light phase				
VFT-NV	2.46±0.9	2.37±0.9	2.33±0.7	2.38±0.9
VFT-HV	1.35±0.6***	1.22±0.6	1.16±0.7	1.09±0.5♦
EXP-HR-NV	355±29	351±30	348±31	350±27
EXP-HR-HV	331±37**	339±33	336±28	333±30
Dark phase				
VFT-NV	2.67±0.8	2.61±0.9	2.66±0.8	2.70±0.9
VFT-HV	1.61±0.8***	1.55± 0.8	1.37±0.7	1.32±0.7
EXP-HR-NV	358±30	355±24	353±26	356±26
EXP-HR-HV	343±29*	343±36	337±26	330±25♦

**** $p<0.001$; ** $p<0.005$; * $p<0.05$ statistical difference between the last value (20 min of normal ventilation) vs. the first value (5 min hypoventilation) ♦ $p<0.05$ statistical difference between the single minutes of ventilation (10, 15 and 20 min) vs. 5 min of ventilation in the same group.*

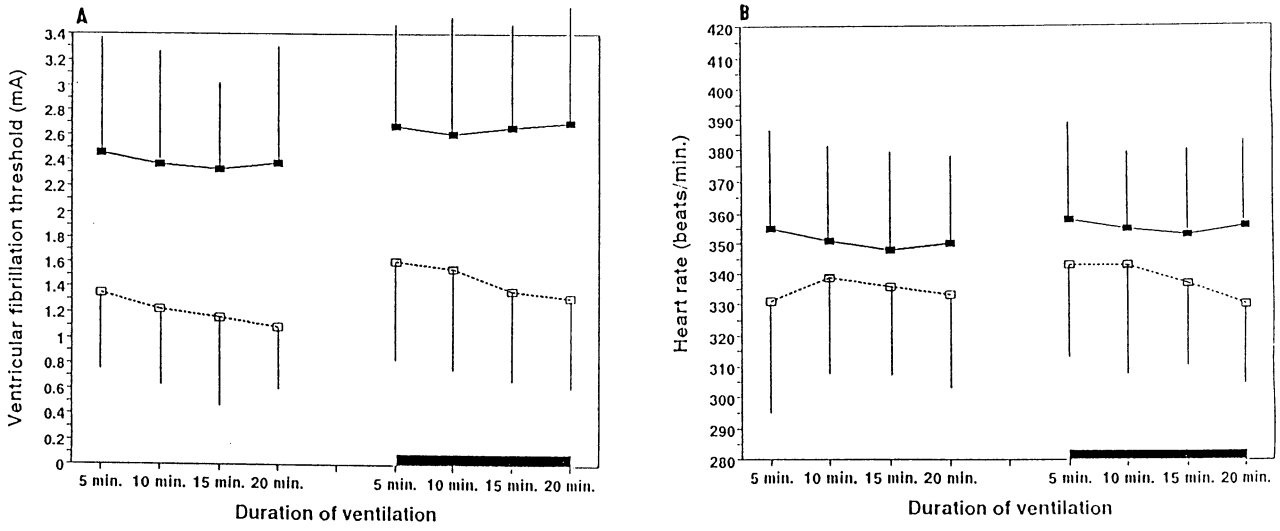

Fig. 2. *Effect of the duration of ventilation during light and dark phases on the VFT (A) and the EXP-HR (B) during normal ventilation (filled squares) and hypoventilation (empty squares) in individual minutes of ventilation. The data are presented as arithmetic means ± S.D. from all measurements of the light and dark phases. The dark bar indicates the dark phase of the day.*

Already 5-min hypoventilation significantly ($p<0.001$) decreased both parameters in the comparison with the control group in both light phases. The EXP-HR significantly decreased (light phase: 350±27 vs. 331±37 beats/min, $p<0.005$; dark phase: 356±26 vs. 343±29 beats/min, $p<0.05$) in comparison with the 20 min value

of normal ventilation. The EXP-HR behavior during the dark and the light phases was similar, with a small increase within 10 min and a subsequent decrease (Table 2, Fig. 2B). The reduction of VFT was highly significant (light phase: 2.38±0.9 mA vs. 1.35±0.6 mA, $p<0.001$; dark phase: 2.70±0.5 mA vs. 1.61±0.8 mA, $p<0.001$) (Table 2, Fig. 2A). The VFT values during 20 min hypoventilation had a decreasing tendency in both phases.

From our previous results (Švorc *et al.* 1997), the mean value of the VFT averaged from all values of the dark phase (from 18:00 h to 06:00 h; $n = 332$) was significantly higher ($p<0.005$) than of the light phase (from 06:00h to 18:00h; $n = 423$), not only during normal ventilation, but also during hypoventilation ($p<0.001$), which did not apply to the EXP-HR. The HR difference between the light and dark phase was minimal during both ventilatory types (352±28 vs. 354±30 beats/min in control group; 335±29 vs. 334± 32 beats/min in hypoventilatory group).

Discussion

The aim of our study was to verify the assertion that circadian variations of cardiovascular system reactivity are caused by the temporal organization of the autonomous nervous system under normal ventilatory conditions and to evaluate the relation between these systems during hypoventilation in female Wistar rats. For this reason, we followed the relationship between one parameter of electrical stability of the heart, namely the ventricular fibrillation threshold (VFT), and an index of the autonomous nervous system activity, i.e. the heart rate (HR).

The initial HR, measured before the surgical interventions, did not exhibit an expressively significant 24-h rhythm, described by several authors in the conscious rats (Benessiano *et al.* 1983, Henry *et al.* 1990, Mattes and Lemmer 1991). The relative similar time course in both groups can be a result of the pentobarbital effect, or the sensitivity of animals to this anesthetic agent, during the 24-h period. It is interesting that pentobarbital probably does not influence the VFT rhythm. This fact is supported by the hypothesis about two independent circadian pacemakers controlling not only the various cardiovascular system functions (Davies *et al.* 1984, Portaluppi *et al.* 1991) but also processes within the heart (DeLeonardis *et al.* 1983).

On the basis of our previous results (Švorc *et al.* 1994) and those of Otsuka and Watanabe (1990), it is possible to conclude that rat hearts are probably most stable against ventricular arrhythmias at the time when the tone of the sympathetic nervous system is increased (Benessiano *et al.* 1983, Lemmer 1985, Witte and Lemmer 1988, Lemmer and Witte 1989, Henry *et al.* 1990, Lemmer *et al.* 1995, Witte and Lemmer 1995). This would mean that increasing sympathetic tone raises the VFT in rats. Similarly, the incidence of bradyarrhythmias was decreased after left or right vagotomy (Otsuka and Watanabe 1990) and vagal tone increased by the administration of carbachol prevented ventricular fibrillation (Billman 1990). The fact that no ventricular arrhythmias were evoked at HR above 400 beats/min (unpublished results) can indirectly confirm the protective effect of increased sympathetic tone against the genesis of arrhythmias under normal ventilatory conditions. From the circadian point of view, a positive correlation was found at each interval of the 24-h period. The decreases or increases of EXP-HR were accompanied by similar but non-significant changes of the VFT. Especially during the dark phase, the minimal HR changes were associated with more expressive VFT changes. It is interesting that 24-h rhythms of VFT and HR showed independent courses with a significant shift in their acrophases.

The results of the hypoventilatory experiments confirm the results of other authors, who followed the effects of ischemia or hypoxia on the incidence of ventricular arrhythmias and on HR behavior. The higher incidence of arrhythmias or the increased myocardial vulnerability to arrhythmias were obvious, but with more or less different HR behavior. Curtis *et al.* (1985) did not find any correlation between the HR and the incidence of arrhythmias in rats during myocardial ischemia after coronary occlusion. An analogous independence was demonstrated in the work of Kujaník *et al.* (1984, 1985) who reported that the VFT was decreased during mild hypoxia, increased during serious hypoxia and the duration of the vulnerable period was prolonged by hypoventilation-induced hypoxia independently of the HR changes. A-H and H-V intervals (time intervals characterizing the conductance of the action potential in the atrio-ventricular region) were prolonged without apparent changes in the HR during hypoxic interventions in multicellular rabbit A-V preparations and single guinea pig ventricular myocytes (Sawanobori *et al.* 1995). Similar corresponding drop in the HR and the VFT was

also demonstrated by Thandroyen (1982) in the isolated perfused rat heart. The significant bradycardia occurred at the beginning of ischemia with the increased incidence of ventricular arrhythmias at the end of the ischemic period (Perchenet and Kreher 1995, Feng *et al.* 1996) or at the end of a coronary artery ligation period (Winslow *et al.* 1983). On the other hand, Lepran *et al.* (1996) showed a moderate tachycardia in conscious rats during the first 15 min of coronary occlusion. The same increase in HR was detected in our hypoventilatory experimental group after 10 min, probably as a reaction to the hypoxic conditions. The high incidence of ventricular tachycardia or fibrillations was also found during hypoxia in isolated rat hearts (Dai 1989, DuToit and Opie 1994). However, Froldi *et al.* (1994) reported that the HR was not changed after 30 min of hypoxia in isolated rat atria. Botting *et al.* (1983) minimized the importance of beta-adrenoceptor stimulation in the genesis of arrhythmias after coronary occlusion in rats. They assume that an adequately functioning sympathetic system is, to some extent, protective in this experimental model.

However, it is not clear whether the experiments of these authors were performed after synchronization of the animals to a constant light-dark cycle or in which phase they were performed. Most probably, the experiments were performed in the light phase of the day, i.e. during the sleep period of the rat. Our interest was therefore concentrated on the question whether hypoventilation will also have the same effect on the followed relation in the dark phase. The results from our experiments have demonstrated that 1) the VFT and HR respond coincidentally to hypoventilation by the decrease in both phases, 2) the 24-h course of VFT was slightly changed and became biphasic without a corresponding change in the 24-h rhythm of HR, and 3) positive but also negative correlations were found at individual single intervals of the measurements in light and dark phases.

It is concluded that the HR probably influences the VFT with a more expressive effect during the active (dark) phase of the rat day under normal ventilatory conditions. Hypoventilation decreases both parameters not only in the light phase of the regime day but also in the dark phase. It changes their 24-h rhythms without apparent dependence in their course and acrophases. The shifts of acrophases probably result from the different rat reactivity on the surgical interventions (tracheotomy, thoracotomy) or as a reaction on the pentobarbital anesthesia. From the circadian point of view, there are probably two independent systems without apparent functional dependence during both types of ventilation.

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