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Light-dark dependence of electrocardiographic changes during asphyxia and reoxygenation in a rat model

Research Article

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Abstract: The aim of this study was to evaluate the effect of ventilation on electrocardiographic time intervals as a function of the light-dark (LD) cycle in an in vivo rat model. RR, PQ, QT and QTc intervals were measured in female Wistar rats anaesthetized with both ketamine and xylazine (100 mg/15 mg/kg, i.m., open chest experiments) after adaptation to the LD cycle (12:12h) for 4 weeks. Electrocardiograms (ECG) were recorded before surgical interventions; after tracheotomy, and thoracotomy, and 5 minutes of stabilization with artificial ventilation; 30, 60, 90 and 120 seconds after the onset of apnoea; and after 5, 10, 15, and 20 minutes of artificial reoxygenation. Time intervals in intact animals showed significant LD differences, except in the QT interval. The initial significant ($p<0,001$) LD differences in PQ interval and loss of dependence on LD cycle in the QT interval were preserved during short-term apnoea-induced asphyxia (30-60 sec) In contrast, long-term asphyxia (90-120 sec) eliminated LD dependence in the PQ interval, but significant LD differences were shown in the QT interval. Apnoea completely abolished LD differences in the RR interval. Reoxygenation restored the PQ and QT intervals to the pre-asphyxic LD differences, but with the RR intervals, the LD differences were eliminated. We have concluded that myocardial vulnerability is dependent on the LD cycle and on changes of pulmonary ventilation.

Keywords: *Chronobiology • Asphyxia • ECG • Myocardium • Rat*

1. Introduction

Most physiologic functions, especially those involving the cardiovascular system, show a marked circadian rhythmicity [1,2]. Fluctuations in the dependence on the light-dark (LD) cycle are associated with blood pressure and heart rate [3,4], electrical instability of the heart [5], and the incidence of ventricular dysrrhythmias, ventricular tachycardia, ventricular fibrillation, and sudden cardiac death [6-8].

The onset and development of ventricular arrhythmias, which include certain disorders of pulmonary ventilation [9,10] and cessation of ventilation (apnoeic episodes) [11-13], depend on many factors. Acute systemic asphyxia causes profound electrophysiologic dysfunction in the conductive system of the myocardium, which affects sinus node function, the atrioventricular (AV) node refractory period [14-16], PQ interval [17-19], distribution of refractory periods [19], and changes in heart rate [20,21], as well as the threshold for ventricular arrhythmias [22].

The chronophysiologic aspects of the connection between decreased pulmonary ventilation (hypoventilation) or cessation of ventilation (apnoeic episodes) and the changes of the electrophysiologic myocardial properties are less well documented. Although this dependence has been demonstrated in experimental animal models [22-27], many studies involving the factors responsible for the onset and development of ventricular arrhythmias have focused mainly on the temporally current mechanical and metabolic changes in myocardial cells, often irrespective of the circadian or light-dark dependence. It is known that

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cardiac functions in rats show a marked dependence on the light-dark alterations [2], indicating that the LD cycle belongs among the strongest synchronizers of endogenous rhythms of the rat. There are only sparse reports of experiments describing daytime dependence on the synchronization of the LD cycle in animals. However, whether the vulnerability of the myocardium to ventricular arrhythmias is influenced purely by the decreased pulmonary ventilation-induced systemic asphyxia, by additional factors such as anaesthesia, or by natural factors such as changes in the LD cycle remains to be determined.

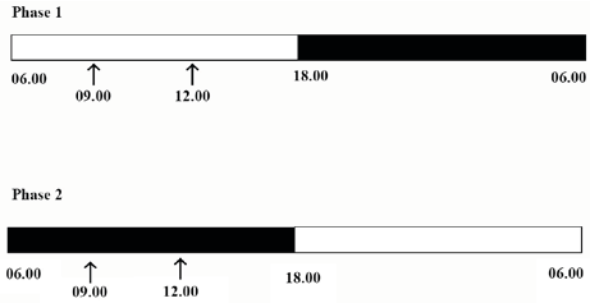
Electrophysiologic properties or an electrophysiologic predisposition to disorders of heart rhythm can be determined directly from the electrocardiographic record. Prolongation of the duration of the PQ interval refers to arrhythmias arising from disorders of impulse conduction (reentry phenomenon). Serious ventricular tachyarrhythmias are usually induced by reentry activity mediated by a mechanism requiring the presence of nonhomogenous conduction or nonhomogenous refractory periods [28]. Abnormalities in repolarization play an important role at the onset and in the development of ventricular arrhythmias, which occur in association with activity of the autonomic nervous system. Asynchrony of the recovery of excitability in the myocardium is an important factor in the genesis of ectopic activity and ventricular fibrillation [29-31]. In this chronobiological study, we focused mainly on the changes of the crucial electrophysiologic myocardial predictors that determine the onset or development of disorders of heart rhythm in conditions of ventilatory systemic asphyxia induced by apnoeic episodes and recovery of ventilation as a function of the LD cycle in the anaesthetized rat model.

2. Material and Methods

2.1. Experimental animals and conditions of adaptation

All experiments were performed on female Wistar rats 3 to 4 months old anaesthetized with both ketamine and xylazine (ketamine/xylazine; ketamine [Narkamon], 100 mg/kg; Prague, Czech Republic, xylazine [Rometar], 15 mg/kg; Prague, Czech Republic, i.m.) after 4 weeks of adaptation to the light–dark cycle (12:12 h) in cages (2 animals/1 cage) in a room with controlled relative humidity (40%) and temperature (24^{0}C). The rats had unrestricted access to food (Larsen's diet) and water at all times. All studies were in conformity with the Guide for the Care and Use of Laboratory Animals published by the US National Institutes of Health (NIH Publication No. 85-23, revised 1996) and were approved by local ethics committe of the Medical Faculty, University P.J.Šafarik in Košice (number of permission 2/05). On completion of the experiments, the animals were euthanized by cardiac administration of a ketamine overdose.

Figure1. Scheme of adaptation to the LD cycle. Light part of the day – empty column, dark part of the day – full column. Arrows indicate the running time of the experiment.



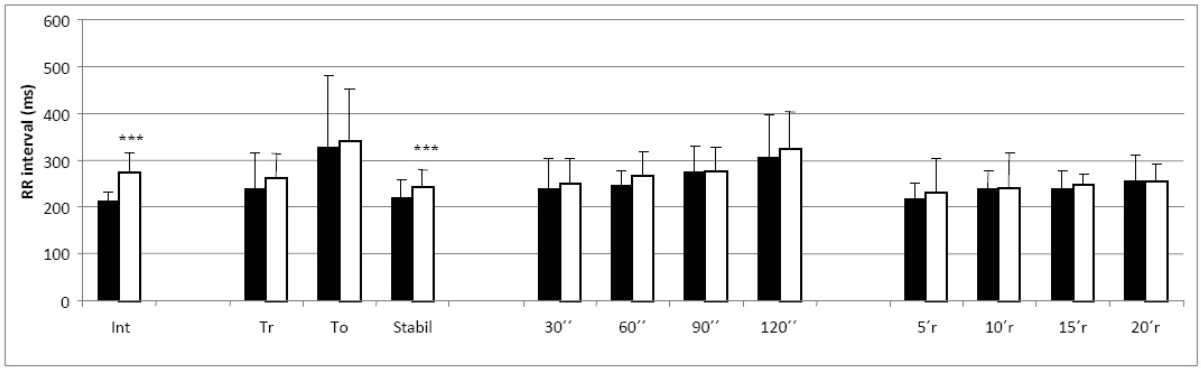
The effect of the light period (the first phase of experiment) was followed by adaptation to the LD cycle (12h L : 12h D) for 4 weeks, with the dark period from 18.00 to 06.00h. The experiments were performed twice in the course of the light period. The first experiment was performed with one animal at 09.00h, and completed by euthanization with ketamine overdose. The second experiment was performed on the second animal at 12.00h and completed in the same manner. The effect of the dark period (the second phase of experiment) was followed by inversion of the LD cycle and after 4 weeks of adaptation by the animals, with the dark part of the day from 06.00 – 18.00h and the time of recording as in the first experiment (Figure 1).

2.2. Experimental protocol

The experiments were performed with two parts of the day in light, in accordance with adaptation of the rats to the LD regimen. For this experiment, a total of 140 rats were allocated (70 representing portion in light, and 70 representing the portion in dark). Of these, 12 allocated for the light portion and 3 for the dark portion were eliminated because of the occurrence of serious cardiac rhythm disorders or death after administration of anaesthetic agent. The remaining 125 were included in the experiment (58 rats representing light, and 67 representing dark).

The experiment was divided into 4 phases: the first phase included intact animals before surgical interventions with the spontaneous breathing; the second phase involved surgical interventions (tracheotomy, thoracotomy) and 5-minute stabilization; the third phase, 2-minute apnoeic episodes; and the fourth phase, 20-minute reoxygenation in both periods of light.

Figure 2. Mean ± SD values of the RR-interval duration in intact animals (Int), after tracheotomy (Tr), thoracotomy (To), 5 minutes after stabilization (Stabil), during each 30 seconds of a 2-minute apnoeic episode, and after 5, 10, 15, and 20 minutes of artificial reoxygenation. Empty and black columns refer to light and dark parts of the day, respectively. The level of significance of differences between the light and dark part of the rat daily regimen is indicated by the symbol (* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$).



2.3. Ventilation techniques

The animals were placed in the supine position on a pre-heated table, and the trachea was exposed at the midcervical level and cannulated by a plastic tube. The tracheal cannula was attached to a volume-rate-regulated artificial ventilator (UGO BASILE, Italy), and the animals were ventilated with room air. The parameters of the initial ventilation and reoxygenation were a respiratory rate of 50 breaths per minutes and tidal volume 1 ml per 100 g of body weight [32,33]. Apnoeic episodes were simulated by switching off the respirator for one 2-minute interval. The chest was opened by a parasternal thoracotomy for the elimination of the mechanisms of breathing under autonomic nervous control.

2.4. Measurement of ECG

Bipolar electrodes were attached to the forelimbs and hind limbs for purposes of ECG recording, which was further analysed by a computer system (ECG Practic Veterinary, Prague, Czech Republic). The time interval values (RR interval, PQ interval, QT interval, and QTc interval) were calculated from two cardiac cycles from one 16-second ECG recording (the first from start and the second from end of recording) in intact animals in the supine position before surgical interventions with spontaneous breathing (light, n=58 rats; dark, n=67 rats); after tracheotomy and thoracotomy and after 5 minutes of stabilization with normal artificial ventilation (light, n=58 rats; dark, n=67 rats); 30, 60, 90, and 120 seconds after an apnoeic episode (light, n=47 rats; dark, n=56 rats); and 5, 10, 15, and 20 minutes after artificial reoxygenation (light, n=15; dark, n=24 rats). The discrepancy in the number of rats was due to increased mortality mainly after phases 3 and 4 of the experiment.

2.5. Statistical analysis

The data are presented as the means ± SD. A non-paired t-test was used for statistical evaluation. Differences of $p < 0.05$ were considered significant. The experiments were performed during the entire year, and the results were averaged independent of seasons.

3. Results

3.1. RR interval

Significant ($p < 0.001$) LD differences for RR-interval duration were found (light, 273 ± 42 ms compared with dark, 213 ± 19 ms) only in the intact ketamine/xylazine anaesthetized animals (spontaneous breathing and before the surgical interventions). The surgical interventions, apnoeic episodes, and reoxygenation eliminated significant light-dark differences with a slightly longer RR interval during the light period of the rat day (Figure 2). Thoracotomy, but not tracheotomy, significantly ($p < 0.001$) increased RR-interval duration compared with intact rats in both periods of light. Significant increases in the RR interval were recorded in the second half of apnoeic episodes (light–apnoeic episode 30 sec, 251 ± 52 ms; 60 sec, 267 ± 51 ms; 90 sec, 278 ± 48 ms; and 120 sec, 325 ± 79 ms: dark–apnoeic episode 30 sec, 240 ± 65 ms; 60 sec, 247 ± 31 ms; 90 sec, 275 ± 55; and 120 sec, 308 ± 89 ms). RR intervals were significantly ($p < 0.001$) shortened after 5 minutes of reoxygenation compared with 120 seconds after an apnoeic episode in both periods of light (light–5 reoxy, 230 ± 72 ms; 120 sec, 325 ± 79 ms: dark–5 reoxy, 219 ± 34 ms; 120 sec, 308 ± 89 ms). The recovered ventilation after 20 minutes rectified the RR-interval duration to the values in intact animals only in the light period (254 ± 36 ms at the end of reoxygenation compared with 273 ± 42 ms in intact animals). In the dark period, the RR interval

Figure 3. Mean ± SD values of the PQ interval duration in intact animals (Int), after tracheotomy (Tr), thoracotomy (To), 5 minutes after stabilization (Stabil), during each 30 seconds of 2-minute apnoeic episodes, and after 5, 10, 15, and 20 minutes of artificial reoxygenation. Empty and black columns refer to light and dark parts of the day, respectively. The level of significance of differences between the light and dark part of the rat daily regimen is indicated by the symbol (* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$).

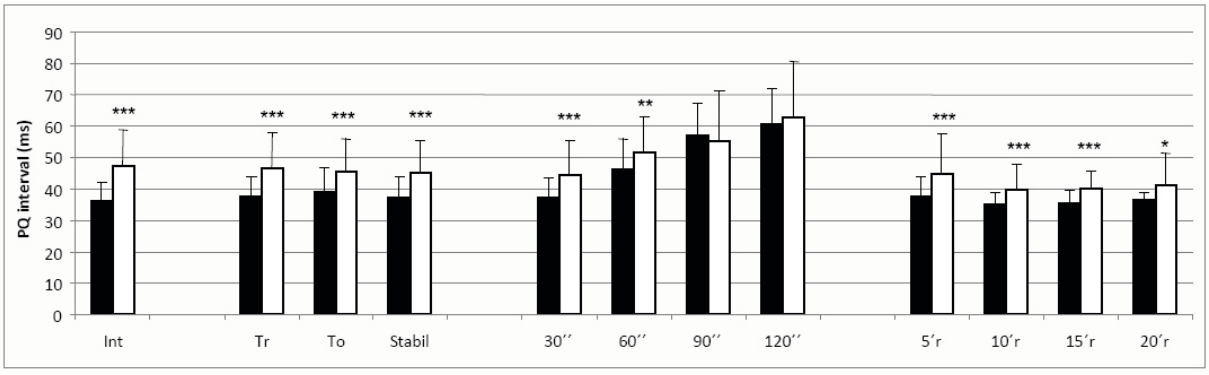
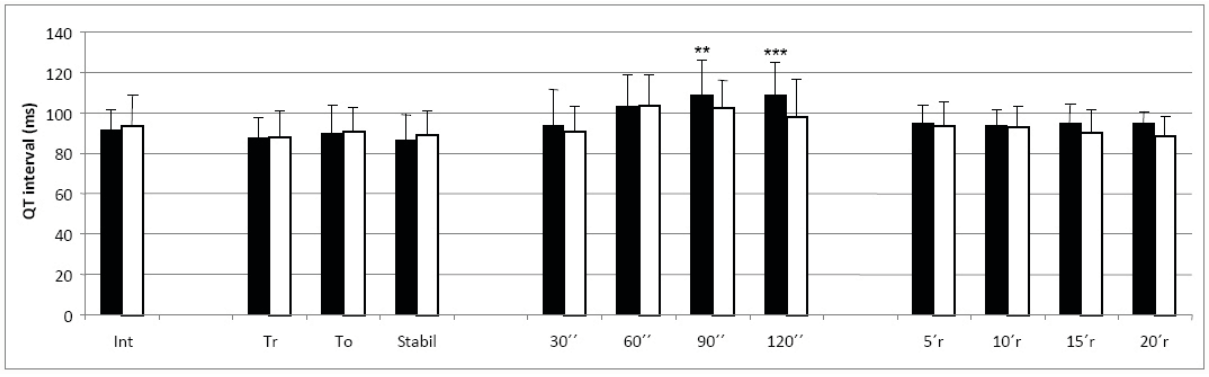


Figure 4. Mean ± SD values of the QT-interval duration in intact animals (Int), after tracheotomy (Tr), thoracotomy (To), 5 minutes after stabilization (Stabil), in each 30 seconds of a 2-minute apnoeic episode, and after 5, 10, 15, and 20 minutes of artificial reoxygenation. Empty and black columns refer to light and dark parts of the day, respectively. The level of significance of differences between the light and dark part of the rat daily regimen is indicated by the symbol (* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$).



was significantly prolonged in contrast to the intact value (255 ± 58 ms compared with 213 ±19 ms).

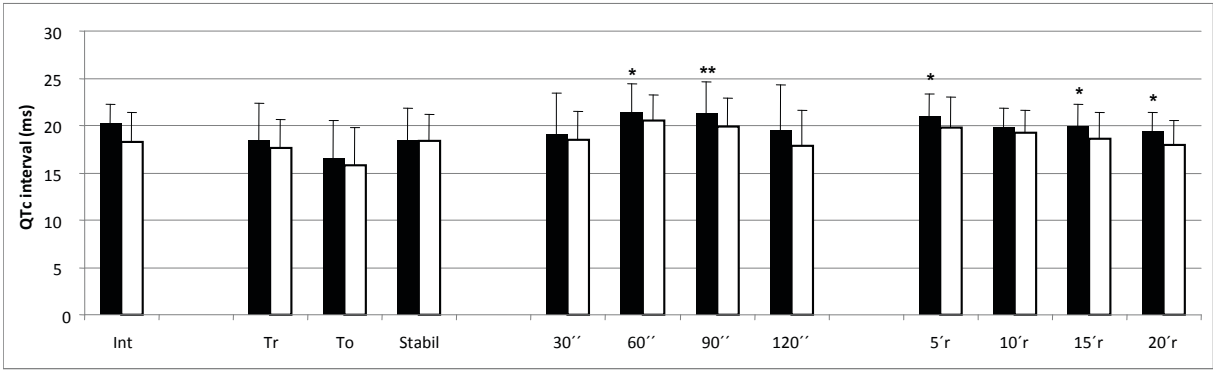
3.2. PQ interval

Significant LD differences in the duration of the PQ interval exist in intact animals anaesthetized with ketamine/xylazine (light, 47.71 ± 11.21 ms compared with dark, 36.47 ± 5.82 ms [Figure 3]). The surgical interventions, as well as the period of stabilization, did not disturb the light-dark dependence on the duration of the PQ interval, with a significant shorter duration ($p < 0.001$) in the dark period of the day in contrast to the light period of the day. Apnoeic episodes prolonged the duration of the PQ interval with significant preservation of the light-dark differences after 30 seconds (light, 44.67 ± 11.0 ms compared with dark, 37.47 ± 5.83 ms; $p < 0.001$) and after 60 seconds (light, 51.35 ± 11.73 ms compared with dark, 46.7 ± 9.14 ms, $p < 0.01$). Apnoeic episodes of 90 seconds and 120 seconds abolished the light-dark differences. Reoxygenation shortened the duration of the PQ interval in both periods of light, restored the PQ-interval duration to the pre-asphyxic level only in the dark period, and significantly restored the light-dark differences ($p < 0.001$).

3.3. QT interval

No significant LD differences in the duration of the QT interval were found in intact animals or in the rats after surgical interventions (Figure 4). Significant LD differences existed 90 seconds after apnoeic episodes (light, 102.58 ± 13.3 ms compared with dark, 108.86 ± 17.38 ms; $p < 0.01$) and 120 seconds (light, 98.13 ± 18.55 ms compared to dark, 108.8 ± 16.43 ms; $p < 0.001$), with a longer duration in the dark period of the day. QT-interval duration was significantly ($p < 0,001$) shortened after 5 minutes of reoxygenation compared to 120 seconds after apnoeic episodes only in the dark period (dark–5 minutes reoxygenation, 94.93 ± 9.1 ms compared with 120 seconds after apnoeic episode, 108.8 ± 16.43 ms: light–5 minutes reoxygenation, 93.25 ± 12.1 ms compared with 120 seconds after apnoeic

Figure 5. Mean ± SD values of the QTc-interval duration in intact animals (Int), after tracheotomy (Tr), thoracotomy (To), 5 minutes after stabilization (Stabil), in each 30 seconds of a 2-minute apnoeic episode, and after 5, 10, 15, and 20 minutes of artificial reoxygenation. Empty and black columns refer to light and dark parts of the day, respectively. The level of significance of differences between the light and dark part of the rat daily regimen is indicated by the symbol (* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$).



episode, 98.13 ± 18.55 ms). Gradual reoxygenation non-significantly shortened the QT-interval duration only in the light period of the day.

3.4. QTc interval

Significant ($p < 0{,}001$) LD differences in the QTc interval were detected in intact animals anaesthetized with ketamine/xylazine (light, 182.31 ± 31.21 ms compared with dark, 202.06 ± 20.93 ms [Figure 5]). The LD differences did not recover with the surgical interventions and period of stabilization. The QTc interval was significantly ($p < 0{,}001$) increased to 60 seconds after the apnoeic episodes, without changes in the 90-second mark and with statistically significant ($p < 0.001$) shortening after 120 seconds in both periods of light. The significant light-dark differences were seen only 60 seconds after an apnoeic episode (light, 204.92 ± 27.57 ms compared with dark, 213.58 ± 30.11 ms; $p < 0.05$) and 90 seconds (light, 199.00 ± 29.9 ms compared with dark, 213.16 ± 32.85 ms, $p < 0.01$) apnoeic. The QTc-interval duration was significantly prolonged after 5 minutes of reoxygenation compared with 120 seconds after an apnoeic episode (light, 198.35 ± 31.71 ms compared with 194.94 ± 49.51 ms, $p < 0.01$; dark 209.58 ± 24.23 ms vs. 195.15 ± 47.49 ms; $p < 0.01$), with gradual shortening to the end of reoxygenation. The statistically significant light-dark differences were found after 5, 15, and 20 minutes of reoxygenation.

4. Discussion

A number of electrophysiologic properties of the cardiac structures are recognized as essential for the triggering and maintenance of arrhythmias and show dependence not only on the time of day [2], but also on the alterations of light and dark parts of the day [5]. Because some ventilatory disorders act arrhythmogenically, the chronophysiologic view on the functional interconnection between disorders of pulmonary ventilation and changes in the electrophysiologic properties of the heart are also important. The main goal of this study was to gain information regarding the chronophysiologic aspects of electrocardiographic changes in time intervals predisposing to arrhythmias during anaesthesia with ketamine/xylazine and after apnoeic episodes induced by asphyxia and subsequent reoxygenation in an *in vivo* rat model.

Absence of reference electrocardiographic values (also current data in the literature) from non-anaesthetized animals associated with light-dark dependence can be a limitation in our study. Complex comparisons are needed for the evaluation not only of the effect of ketamine/xylazine anaesthesia but also of the effects of apnoeic episodes induced by systemic asphyxia and subsequent reoxygenation. Another limitation could be the relatively large dispersion of the measured values. The ECG values showed intra- and interindividual variability, which is a problem, principally with *in vivo* studies. The discrepancy can be explained by the production of spontaneous, unpredictible alterations in the electrophysiologic properties of the heart induced by anaesthesia or by hormonal and homeostatic reflexes in the animals.

Despite these limitations, in intact animals under ketamine/xylazine anaesthesia in our experimental model, such anaesthesia did not perturb the light-dark dependence as seen in the RR interval, in the time of impulse transmission from the atria to the ventricles (PQ interval), and in QTc intervals. Conversely, dispersion of the refractory periods measured by the QT interval did not show a significant light-dark dependence. Surgical interventions (tracheotomy and thoracotomy) eliminated the LD differences in the RR, QT, and QTc intervals, but

not in the PQ interval. This means that the significant LD differences in ECG parameters refer to fact that ketamine/xylazine anaesthesia does not disturb light-dark dependence, but it can modify acrophase, mesor, and amplitude of the circadian rhythms without loss of daily rhythmicity [34,35]. We found that circadian rhythm was present in the rats' heart rate before implantation of the transmitters (for the recording of heart rate) and that non-detection of a daily rhythm after implantation of the transmitters under general anaesthesia was essentially due to surgical aggression; the general anaesthetic agent was responsible only for perturbations of the characteristics of this rhythm. This perturbation could be seen in the QT interval, where light-dark dependence was not detected. The loss of LD dependence of some electrophysiologic parameters after the surgical interventions in our experimental model affirms the assumption that surgery can have a more marked effect on LD dependence than the simple effect of the anaesthetic agent [36].

Mechanisms of the different effects of ketamine/xylazine anaesthesia are still unknown and were not analyzed in detail. However, it is known that ketamine/xylazine anaesthesia decreases heart rate [37-39], which has been associated with systemic asphyxia after the administration of an anaesthetic agent [40]. The speed of the impulse conduction from atria to ventricles (PQ interval) depends on action potential amplitude, reflecting the active role of Na^+ channels [41,42]. Ketamine/xylazine anaesthesia, together with initial systemic asphyxia and surgical interventions, probably does not exert any influence on these channels in the setting of the LD cycle. It seems that the PQ interval is the relatively stable electrophysiologic parameter of the heart, and it is directly influenced by the LD cycle.

Loss of LD differences in the dispersion of the durations of the refractory period (QT interval) can be a result of the effect of the initial asphyxia, which has a disturbing influence on the LD differences in the QT interval. A similar situation was described by Gunes et al. [43] in a clinical study, where the loss of diurnal variation of the dispersion of the refractory periods was also present in patients having heart failure of either ischemic or nonischemic origin that was treated with optimal drug therapy. Although dispersion of duration of the refractory period (QT interval) is the result of the action of more ion currents (Ca^{2+}, Na^+, Cl^- and inward rectifying K^+ current) [42], it depends mainly on intracellular K^+ concentration [44]. This suggests that ketamine/xylazine anaesthesia, together with initial asphyxia, probably influenced mainly the K^+ ion current in the same manner in both periods of light and disturbed the light-dark dependence.

The identical prolongations of the RR, PQ, and QT intervals affirmed the effect of the apnoeic episodes on heart rhythm in both periods of light. Apnoeic episodes, obstructive or central and often in connection with the sleep apnea syndrome, are linked with cardiac arrhythmias [45-50].

What is known about the effects of hypoxia on circadian patterns is still very limited, especially the causative mechanistic sequence of the effects. It appears that the most common effect of prolonged hypoxia is to decrease, and in some cases to abolish, the amplitudes of the daily oscillations, irrespective of the state of arousal or activity level. On the other hand, the evidence shows that hypoxia causes only minimal and transient perturbation of the periodic rhythm. The fact that hypoxia modifies the circadian oscillations of variables as important as body temperature and metabolism leads to the expectation that the daily rhythms of many other functions are perturbed by hypoxia, according to their link to the primary variables [51]. This modification can also probably be seen in our experimental model, where definite loss of the light-dark dependence was not demonstrated in all electrocardiographic parameters.

Short-term asphyxia increases vulnerability to the arrhythmias originating from disorders of impulse production and conduction more in the light (nonactive) period than in the dark (active) one and does not disturb light-dark dependence. Long-term apnoeic episodes are associated with more serious asphyxia and therefore prolong the PQ interval and increase vulnerability to the arrhythmias, but they are probably independent of the light and dark periods of the rats' daily regimen.

The opposite situation is true of the QT interval. Short-term apnoeic episodes increased vulnerability to the arrhythmias originating from dispersion of the refractory period independent of the LD cycle, but long-term apnoeic episodes facilitated the LD differences, with higher dispersion during the dark (active) than light (nonactive) period of the rats' daily regime. Another light-dark difference was seen at the end of asphyxic period. The QT-interval duration was only slilghtly decreased during the light (nonactive) period, but not during the dark (active) one. The QTc interval did not show any regular changes or tendency relating to the independence of the QT-interval changes on heart rate.

These changes may be caused by changes in ion channel sensitivities associated with the duration and gravity of asphyxia. Hypoxia exacerbated the atrioventricular conduction by reducing the slow inward Na^+ current and by rectifying the K^+ current; it depressed automaticity by increasing the outward K^+ current and in to a certain degree by reducing the slow inward Na^+ current in the isolated rabbit AV node [52]. Sinus,

AH, and HV intervals are gradually prolonged with the duration of the hypoxia. These effects are attributed to the K^+_{ATP} channel [53], which is probably activated by the endogenous adenosine released from the hypoxic myocardium [54,55]. Our results suggested that those changes can also be modified by the LD cycle.

Similarly, contrary conclusions have been drawn about the effect of reoxygenation on changes in the electrophysiologic myocardial properties. Our results affirmed the opinion of some authors about the antiarrhythmogenic effect of reoxygenation [56,57]. However, some reports describe serious injury to the heart by the reoxygenation [58,59].

Reoxygenation returned all parameters to pre-asphyxic values, with preservation of the light-dark differences observed in intact animals, except in RR intervals, where the light-dark differences were eliminated. It is interesting that the average values of the QT interval were slightly and nonsignicantly longer in the dark period after reoxygenation compared to the values in the light period, whereas the opposite tendency was observed in the intact animals and after stabilization. These slight differences probably do not have any biological significance because they may be a result of the relatively large variation in dispersion of the refractory periods, which corresponds with our second limitation [60].

Mechanisms responsible for the changes we have described are probably multifactorial, and at present, more detailed analyses of conditions *in vivo* regarding dependence on the LD cycle have not been conducted. We suppose a direct influence of ketamine/xylazine anaesthesia on myocardial cells resulting in a changed sensitivity to asphyxia and its associated processes. Despite various opinions and conclusions about the effect of asphyxia and recovery of pulmonary ventilation on electrophysiological myocardial properties, the importance of our results lies in the finding that myocardial vulnerability to the development of arrhythmias was dependent on the LD cycle not only in the intact ketamine/xylazine anaesthetized animals, but also in the animals after changes in pulmonary ventilation.

It is evident from this experimental rat model that the electrophysiologic parameters predisposing the animals to cardiac arrhythmias were changed not only by apnoeic episodes but also by their dependence on the LD cycle; also, the vulnerability of the heart to ventricular arrhythmias associated with apnoeic episodes is different at various times of day, an occurrence that carries the highest probability in humans. The question remains of the impact of apnoeic episodes on patients with sleep apnea syndrome during shiftwork or after a transition through time zones, when internal rhythms are desynchronized from environmental rhythmicities.

Acknowledgements

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