General anesthesia and electrocardiographic parameters in *in vivo* experiments involving rats

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Abstract

In *in vivo* cardiovascular or toxicological studies involving rat models, changes in selected electrocardiographic (ECG) parameters are monitored after various interventions to assess the origin and development of heart rhythm disorders. Each ECG parameter has diagnostic significance; as such, commonly evaluated ECG parameters, including heart rate, PR interval, P wave duration, P wave amplitude, QRS complex, QT and QTc interval duration, R wave and T wave amplitude, of rats under various types of general anesthesia were the focus of this study. Studies that performed *in vivo* cardiovascular or toxicological experiments in rats were retrieved from a search of the Web of Science database for articles published mainly between 2000 and 2021. In total, the search retrieved 123 articles. ECG parameters that were reported as baseline or control values were summarized and averages with ranges were calculated. It is important to be cautious when interpreting results and, in discussions addressing the mechanisms underlying a given type of arrhythmia, acknowledge that initial ECG parameters may already be affected to some extent by the general anesthesia as well as by sex and the time of day the experiments were performed.

Key words: ECG parameters, general anesthesia, sex, chronobiology, rat

Introduction

In experimental studies, *in vivo* animal models are often developed to elucidate specific mechanisms or to identify interrelationships between monitored parameters that cannot be observed in human subjects. In cardiovascular or toxicological studies, changes in selected electrocardiographic (ECG) parameters are monitored after various interventions to assess the basis of the origin and development of heart rhythm disorders. Undoubtedly, the results of such studies have been revealing and have had significant scientific impact, contributing to a more detailed knowledge and understanding of the reactions of the cardiovascular system to various stimuli.

However, in *in vivo* experiments, homeostatic regulatory mechanisms are not eliminated; as such, we gain insight to a given event(s) only in the context of all its complexity. Because *in vivo* experiments are usually performed with the subject(s)/animals under general anesthesia, different anesthetics may have varying impact(s) on myocardial electrophysiology. Thus, the extent to which ECG parameters are altered from normal after anesthetic administration can become a problem even before assessing the effect(s) of the intervention itself.

Another issue is that many published methodologies do not describe the synchronization of the animals to the light-dark (LD) cycle. Moreover, even when this synchronization is described, the time of day at which the experiments are performed is not reported. In common practice, experiments are performed during regular work hours (i.e., during the day); therefore, after synchronization of rats, for example, to the LD cycle (12 h: 12 h), these experiments are essentially being performed on "sleeping" animals during their naturally inactive period. The question then becomes, what are the values of ECG parameters during a 24 h period (i.e., spanning the light and dark period) in healthy, sexually mature rats?

Similarly, sex is not typically considered in *in vivo* cardiovascular experiments involving rats, although this type of experimental model animal is commonly used to examine normal and pathological physiology. In the majority of experimental studies, only male rats are used; however, there is another sex (i.e., female) in which differences in the essence of functional systems and response(s) to the same intervention(s) is different from males. The study of sex differences is also a driving force of development and, in many cases, the basis of health and medicine. However, there are opinions that the study of sex differences is ineffectual and does not merit extensive research (Field, 2014)[1]. One of the reasons why both sexes are not used in experiments is the simple fact that males and females are biologically different and these differences increase the range of variability. However, if sex differences are documented and accounted for in experimental studies, they must be respected. Future studies should address these questions and attempt to include females in experiments where possible.

Evaluation of ECG parameters

Studies that performed *in vivo* cardiovascular or toxicological experiments in rats were retrieved from a search of the Web of Science database for articles published mainly between 2000 and 2021. In total, 123 articles were retrieved. ECG parameters that were reported as baseline or control values were summarized and averages with ranges were calculated. Not all ECG parameters were described and evaluated in each study and, in some studies, two to three control values were reported. Some works only described changes in ECG parameters in terms of lengthening and/or shortening, and these changes were directly indicated in graphs without reporting numerical baseline values.

Pentobarbital (28 studies), thiopental (13 studies), ketamine/xylazine (20 studies), isoflurane (6 studies) and urethane (12 studies) anesthesia are most commonly used. There are also works with ether anesthesia (6 article), of which values are not included in the tables, because this type of anesthesia is no longer used. In works, where a another type of anesthesia has been used and there is only one, two studies, so these values are not included in the tables and figures. These are works where phenobarbital (1 study), ketamine/medetomidine (1 study), ketamine/diazepan (2 studies), ketamine/midazolam (1 study), desflurane (1 study) and chloralose (2 studies) anesthesia were used, 5 studies describe some ECG parameters on isolated hearts. Tables 1, 2 and 3 also take into account studies (although only one study), which also point to a possible sex difference, respectively to the effect of light and dark on the monitored parameter. In figures are showed the ranges of the monitored parameter from only at least 3 baseline or control values.

Because each ECG parameter has diagnostic significance, we focused on commonly evaluated ECG parameters, including heart rate (HR), atrial complex (PR interval, P wave duration and P wave amplitude), and ventricular complex (QRS complex, QT and QTc interval duration, R wave and T wave amplitude).

Prognostic significance of changes in HR in arrhythmogenesis

HR is an easily measurable parameter of cardiac activity, and alterations in HR can have a direct effect on the cardiovascular system. Caetano and Alves [2] warned that increased resting HR is an independent predictor of cardiovascular and overall mortality in the general population. Thus, the occurrence of arrhythmias is often associated with baseline HR, which has prognostic significance. In a review article titled “Arrhythmias and heart rate: Mechanisms and significance of a relationship”, Zaza et al. [3] describe, in detail, the mechanisms influencing arrhythmogenesis according to HR; the authors focused on several factors related mainly to electrical stability of the myocardium. HR also reflects autonomic balance, which also affects this factor. The prognostic significance of the relationship between arrhythmias and HR may vary depending on the substrate present in a specific case and should be considered. In rats, electrical stability of the heart has been shown to be greatest at increased HRs in the dark (i.e., active) part of the regimen day, when myocardial vulnerability to ventricular arrhythmias decreases [4].

It has been found that tachycardia may provide greater electrical stability to the myocardium; however, if an abnormal substrate is present, it may trigger an arrhythmia [5]. Severe bradycardia, in turn, can trigger life-threatening arrhythmia, thus predicting its destabilizing effect on repolarization. Zaza et al. [3] remained cautious, arguing that from a mechanistic perspective in assessing the relationship between HR and arrhythmias, the question should be “what is the appropriate sinus rate for autonomic balance?” and not “what is the high (or low) heart rate?” Thus, we can safely assume that baseline HR in *in vivo* cardiovascular studies can significantly affect results obtained during experimentation.

Telemetry studies and HR

If we want to determine reference values for HR, as well as other ECG parameters, logically, the most suitable method is from telemetry studies, in which the rats are not under general anesthesia and ECG data can be recorded continuously throughout the day. Telemetry studies help to reveal very important information about fluctuations in myocardial electrophysiological parameters during the day. Currently, however, relatively few telemetry studies

have analyzed selected ECG parameters in rats under *in vivo* conditions, and have not addressed circadian dependence and/or the dependence on sex.

Sex differences can also be a problem. Nevertheless, several experimental rat studies [6] did not report any sex differences in heart repolarization, or that there is little clear evidence supporting sex differences in ventricular repolarizations *per se*, in which there is only a short estrous cycle lasting only four days [7]. Although no sex differences have been found in the repolarization of isolated ventricular myocytes, it was associated with excitation and contraction [8]. Sex differences were not found in action potential duration at 90% (i.e., APD90) between isolated ventricular myocytes, in external K^+ currents, Ipk and Isus, in internal rectification current IK1, or in ICa [8, 9]. While less information is available from animal models, sex differences in the ionic basis of the effective refractory period in the atria and atrioventricular node may also contribute to sex differences in the incidence of atrial fibrillation and supraventricular tachycardias. Nevertheless, the physiological significance of sex differences has yet to be fully determined; as such, further studies are needed to clarify the basic mechanisms.

Baseline HR analysis from telemetry studies involving non-anesthetized rats, in which a chronobiological approach was applied, indicates that there is a circadian rhythm in HR in rats, with a higher HR during the active (i.e., dark) period of the regimen day, not only in males [10-14] but also in females [12, 15]. If HR exhibits circadian fluctuations, then when exactly HR is evaluated can be problematic.

The question is also whether there are sex differences in single light periods. Telemetry studies have shown that in females, HR values are lower in both light periods (Table 1). The averaged results of baseline HR values indicate that sex differences are exhibited in both the light and dark period of the rat regimen day; however, more experimental studies are needed to confirm this conclusion. In female rats, changes in HR depended on the LD cycle; however, LD differences were modified by the anesthetic used [16, 17]. Although the adaptation of animals to the LD cycle is described in the Methods section, it is not clear whether the reported HRs are average values calculated from the entire 24 h period or the current baseline value from a specific time interval(s) before the intervention itself when the measurements were performed/recorded.

General anesthesia and HR

The question is, what are the reference values for HR in the rat under normal conditions? From the values reported in Table 1, is clear that HR varies depending on the type of general anesthesia, which can be problematic in evaluating changes in HR after an intervention. Other factors, in addition to general anesthesia, that may directly or indirectly affect the initial HR, can be the method used to determine HR, the time of day (or part of the rat regimen day) at which the experiments are performed, or the fact that the majority of ECGs are evaluated only in male rats. As such, there is little to no information regarding HR in females.

Evaluation of HR in telemetry studies involving male rats [18-28] revealed a mean HR of 347 beats/min with a range of 303 to 362 beats/min without accounting for the evaluation methods and the time of day the experiments were performed.

Mean HR under pentobarbital anesthesia [29-48] and thiopental anesthesia [49-55, 28, 56-59] was higher than the mean HR reported in telemetry studies. Unfortunately, there is only one study under pentobarbital anesthesia that takes into account sex and LD cycle dependence. Even for pentobarbital anesthesia, although statistically nonsignificant, there are LD differences. In female Wistar rats, pentobarbital likely only modifies circadian rhythms, but does not disrupt them [17].

Under ketamine/xylazine anesthesia [60-67, 42, 68-74], HR was drastically reduced in males, and reduced values were also recorded in females [75, 16, 76]. In female Wistar rats, LD differences were maintained [16].

Inhalation isoflurane anesthesia [80-83] significantly increased HR, and a mild tachycardic effect was observed under urethane anesthesia [84-91] compared to avarage values from telemetry studies (Table 1, Figure 1). However, these comparisons were made only among male animals and without a description of their adaptation to the LD cycle.

From Table 1 and Figure 1, it is clear that for different types of general anesthesia, baseline or control HR values can differ significantly compared to the mean baseline HR from telemetry studies, which can logically be considered a reference value. There is very little information about HR in females, and virtually no studies accounted for circadian fluctuations.

Prognostic significance of changes in the atrial complex in arrhythmogenesis

The PR (PQ) interval is measured from the beginning of the P wave to the beginning of the QRS complex. This interval reflects the time that electrical impulses pass from the SA node through the AV node. The PR interval provides information about the time required for the transmission of the electrical impulse from the atria through the AV node, His bundle, Tawar's branches, and Purkinje fibers to the start of ventricular muscle depolarization.

Prolonged PQ interval reflects a longer time of transmission of the impulse from the atrium to the ventricles in case of disorders of the AV node of the conductive system. A shortened PQ interval means that the impulse was transmited to the ventricular conductive system earlier than normal; thus, it is likely that it passes around the AV node through abnormal connections of the conductive system. The duration of the PR interval is a crucial marker in the diagnosis of atrioventricular blocks. However, it appears that the PR interval in rats also appears to be dependent on the type of anesthesia, and we have practically no information about sex differences and changes dependent on the LD cycle.

Although mean values of the duration of the PR (PQ) interval were comparable among the different types of anesthesia and did not exhibit significant differences (Table 2, Figure 2). Duration of the PR (PQ) interval from telemetry studies [18, 20-22, 92, 27, 93, 94], isoflurane [80, 95, 96, 82, 83], pentobarbital [97, 29, 98, 99, 100, 31, 101, 33, 34, 37, 40-46], thiopental [51-53, 56, 59], urethane [102, 85, 42, 88. 103, 84] did not differ significantly from one another. A shortened duration of the PR (PQ) interval was found for ketamine/xylazine anesthesia [60, 61, 104-106, 66, 67, 42, 71, 73, 74] comparised to telemetry study.

In female rats, LD differences were eliminated under pentobarbital anesthesia [17], but under ketamine/xylazine anesthesia [16], LD differences were maintained. Interestingly, under pentobarbital anesthesia, there is a nonsignifacant shortening of the PQ interval in the light period and under ketamine/xylazine anesthesia it is the opposite (Table 2). There are also probably sex differences, with a shorter duration in females (Table 2). The problem remains that it is difficult to determine sex differences, as well as differences depending on the cycle of light and dark because there was only one study (Table 2, Figure 2).

The P wave represents depolarization of the atria. Atrial depolarization spreads from the SA node toward the AV node, and from the right to the left atrium. In humans, but also in rats, the physiological sinus rhythm is characterized by the same P wave orientation as the R wave and its occurrence before each QRS complex in all cardiac cycles. P wave duration has been evaluated in Wistar rats, for which prolongation after myocardial infarction may be associated with increased sensitivity to supraventricular arrhythmias [107].

Other parameters used to evaluate the atrial complex include amplitude and polarity (either negative or positive, although it can also be so flat that it is indistinguishable from the isoelectric line). If the P wave is unusually high, it may reflect enlargement of the atria. Typically, an enlarged right atrium exhibits a high, spiked P wave, while an enlarged left atrium is reflected on ECG by a bifidic P wave. The absence of a P wave or its altered shape is present in various cardiac arrhythmias, the most common of which is atrial [108, 109]. Although the analysis of P wave duration and shape in humans provides clinically important information, there is a lack of experimental data from rats to draw conclusions about sex-related changes and circadian rhythm in P wave amplitude and duration [42].

The duration and amplitude of the P wave, despite their important prognostic significance, have only been sporadically evaluated in *in vivo* experiments involving rats. Unfortunately, we have no telemetry study that took into account the P wave amplitude. The highest amplitude was under pentobarbital anesthesia (0.39 mV; range 0.34 – 0.44 mV, n = 2) and a significant reduction was under ketamine/xylazine (0.05 mV; range 0.03 – 0.07 mV, n = 4), isoflurane (0.19 mV; range 0.17 – 0.21 mV, n = 1) and urethane anesthesia (0.077 mV; range 0.074 – 0.080 mV, n = 1). There is an indication, however, that there may be LD differences in the amplitude of the P wave under ketamine/xylazine [16] and pentobarbital [17] anesthesia in female rats. However, to date, this is not statistically demonstrable for other types of anesthesia.

Only one telemetry study evaluated P wave duration (21.51 ms; range 19.84 – 23.18 ms, n = 1), and if it is considered as a reference value, only in males, longer duration was found under ketamine/xylazine anesthesia (26.25 ms; range 24.25 – 28.25 ms, n = 2) and shorter durations were under thiopental (14 ms; range 12.8 – 15.2 ms, n = 1) and pentobarbital anesthesia (16.15 ms; range 15.65 – 16.65 ms, n = 2). A slight prolongation was found under isoflurane (24.1 ms; range 23.1 – 25.1 ms, n = 1 and urethane (22.1 ms; range 18.7 – 25.5 ms, n = 20) anesthesia. The extent to which these values are valid cannot yet be assessed because there is an insufficient number of studies; this problem also affects sex and the LD effect on amplitude and duration of the P wave.

Prognostic significance of changes in the ventricular complex in arrhythmogenesis

Evaluating the parameters of the ventricular complex (QT interval, QTc interval, QRS complex, R and T wave amplitudes) is undoubtedly important because it provides information about the course of depolarization and repolarization of the ventricles. The distance from the beginning of the QRS complex to the end of the T wave is measured. The total length corresponds to the duration of depolarization and repolarization of the ventricular muscle.

The QT interval changes in response to HR; more specifically, as HR increases, the QT interval shortens and vice versa. As such, it can be difficult to compare QT intervals measured at different HRs. Therefore, and to improve the reliability of QT measurements, the QT interval can be corrected for HR using various mathematical formulas, a process often performed automatically by modern ECG recorders. Prolonged QTc is caused by premature action potentials during the late phases of depolarization. This increases the risk for ventricular arrhythmias, including fatal ventricular fibrillation [110]. Higher rates of prolonged QTc are observed in women, older patients, at high systolic blood pressure or HR, and low body height [111]. There are many causes of prolonged QT intervals, and acquired causes are more common than those with genetic causes [112].

In rats, determination of the QT interval is more complicated because the T wave is not clearly separated from the QRS complex. Therefore, it is necessary to develop a method for analyzing repolarization time in non-anesthetized rats. However, the importance of QT interval dispersion is a complex matter involving at least 2 different phenomena—namely, prolongation of the average action potential duration and myocardial heterogenity [23]. Based on evaluation of the QT, as well as the QTc interval in rat experimental models, cardioprotection was also assessed after stimulation of vitamin D receptors and the effect of isoprenaline [39], the effect of doxorubicin [113], and L-glutamine in diabetic rats [114], and saffron on atrial and ventricular conduction velocity [52], or the effect of preconditioning at different doses of noradrenaline on ischemia-induced ventricular arrhythmias. In control rats, induction of ischemia shortened the QTc interval and led to ventricular arrhythmias. Administration of low doses of noradrenaline prevented shortening of the QTc interval during ischemia, but could not significantly reduce the severity and incidence of arrhythmias [35].

The above-mentioned examples confirm the informative value of changes in the duration of the QT interval in evaluating the severity of disorders in the dispersion of ventricular refractory periods and their impact on the onset and development of ventricular arrhythmias. If the values reported in telemetry studies can be accepted as references and ranges [18, 23, 92, 93], under pentobarbital anesthesia [97, 29, 99, 100, 31, 101, 34, 35, 37, 38, 40-42, 44, 46, 47] and thiopental [49- 52, 54, 55, 57], the QT interval was prolonged. The greatest prolongation of the QT interval, compared to the mean value from telemetry studies, was found in ketamine/xylazine anesthesia [60, 106, 67, 42, 69, 71-74, 115], and the shortest in urethane anesthesia [102, 114, 42, 87, 88, 103, 116, 84]. Isoflurane anesthesia had no effect on QT interval duration. All experiments were performed on males without specifying the adaptation of the animals to the LD cycle, and no studies addressed sex differences. Similarly, it was not possible to determine the circadian fluctuation in the duration of the QT interval or dependence on the LD cycle. Similarly, it was not possible to determine circadian fluctuation in the duration of the QT interval or dependence on the LD cycle (Table 3, Figure 3).

In some cases, it is also important to evaluate other parameters related to ventricular electrophysiology. For example, the QRS complex indicates depolarization of the right and left ventricles and the contraction of large ventricular muscles. Any conduction abnormality lasts longer and causes “extended” QRS complexes. The duration, amplitude, and morphology of the QRS complex are useful for the diagnosis of cardiac arrhythmias, conduction abnormalities, ventricular hypertrophy, myocardial infarction, electrolyte disturbances, and other disease states. High-frequency analysis of the QRS complex may be useful for detecting coronary artery disease during a stress test. Evaluation of the amplitude of the R wave, as well as the P wave in experimental work on rats, have also proved to be important. They are informative and changes can help determine the tendency of the myocardium to arrhythmia.

Similar to QT interval duration, there are significant differences in QTc interval, QRS complex duration, R and T wave amplitudes in the dependence on the type of used anesthesia. Substantial prolongation in the duration of the QTc interval was observed in pentobarbital (203.77 ms; range 196.2 – 211.5 ms, n = 7), thiopental (110.23 ms; range 100.5 – 120 ms; n = 7), and ketamine/xylazine anesthesia (143.76 ms; range 138.97 – 148.55 ms, n = 6) and shorter duration under isoflurane (58.32 ms; range 43.68 – 61.48 ms, n = 6) and urethane anesthesia (53.05 ms; range 48.74 – 57.35 ms, n = 9) compared to telemetry studies (87.02 ms; range 81.79 – 92.31 ms, n = 5). Differences in QRS complex duration varied depending on the type of anesthesia used, with the longest duration in telemetry studies (26.08; range 25.68 - 29.52 ms, n = 5). A moderate shorter duration was found under

pentobarbital (25.4 ms; range 23.68 – 27.13, n = 19), thiopental (22.76 ms; rang (21.12 – 24.47 ms, n = 8) and ketamine/xylazine (23.9 ms; range 22.16 – 25.64 ms, n = 12) anesthesia. Significant shortening of the QRS complex was under isoflurane (18.3 ms; 16.75 – 19.85 ms, n = 4) and urethane (18.41ms; 17.39 – 20.5 ms, n = 15) anesthesia. R and T wave amplitude, also varied depending on the type of anesthesia used, but, the found differences are only from males, without specifying the time of the experiments.

No LD differences in QTc interval were found in ketamine/xylazine anesthesia in female Wistar rats, in contrast to QTc interval and QRS complex. Under pentobarbital anesthesia, LD differences in the monitored parameters were eliminated. Similar chronobiological studies have not been performed with other types of anesthesia. As there is only one study on LD differences, and only in female rats, it is not possible to draw general conclusions to assess sex differences either.

Conclusion

In the discussion section of many *in vivo* studies, the results are compared with previously published findings. Changes in ECG parameters are often described, but without accounting for the type of anesthesia used in the experiments. In acute *in vivo* experiments, the time of day the experiments are performed, or the adaptation of the animals to the LD cycle, and sex, are often not accounted for whatsoever. This approach is self-evident and logical because the experiments are mostly performed only on males and during the work day, without acceptance of chronobiological principles.

However, if changes in ECG parameters are considered to be important indicators of arrhythmogenesis, such comparisons may be misleading and must not necesarily indicate a difference in myocardial electrical stability. As such, it is important to be careful in interpreting the results and, in discussing the mechanisms underlying a given type of arrhythmia, acknowledge that the initial ECG parameters may already be affected to some extent by the anesthesia itself. The data reported clearly demonstrate the differences in baseline or control values with different types of anesthesia and whether the baseline or control value is “normal” or already altered by anesthesia should be taken into account. For example, a change in the evaluated ECG parameter after an intervention may not actually indicate a possible electrophysiological substrate for the development of an arrhythmia, it can only be “adjusted to a normal value” because the reference value is not known.

Similarly, sex and the time of day the experiments are perfomred can be a problem because it is not possible to determine sex differences as well as changes during the active and nonactive period of the rat regimen day because there are no studies that have directly addressed this aspect. Telemetry studies that would reveal changes in ECG parameters in circadian dependence, to describe reference values, and possibly also sex differences, could help to facilitate interpretation of the results obtained. However, it is highly speculative to consider the values from the cited telemetry studies as reference values (although the ECG is measured from non-anesthetized rats) because the methodologies do not describe whether the indicated baseline value is the 24 h average or is the current value recorded immediately before the intervention. Most likely, they are baseline values before the experimental intervention and this only applies to male rats, whereas the light (light or dark) period when the experiment was performed is not reported, although the methodologies describe the adaptation of animals to the LD cycle.

If we take into account only the most important prognostic parameters for assessing tendency toward the development of heart rhythm disorders (HR, PR [PQ] and QT interval), then we can conclude that in males, these parameters are affected by general anesthesia. If we accept the data reported in telemetry studies as reference

values—despite the problematic nature of doing so—HR would be out of range for ketamine/xylazine anesthesia (bradycardic effect) and for isoflurane, and borderline for pentobarbital anesthesia (tachycardic effect).

The PQ interval appears to be stable under the mentioned types of anesthesia except for ketamine/xylazine anesthesia. The greatest variability was found for urethane anesthesia.

If we accept QT interval values from telemetry studies as the desired reference values, then QT interval duration (prolongation) is out of range for pentobarbital, ketamine/xylazine anesthesia, with the greatest variability in isoflurane anesthesia. This analysis suggests that ketamine/xylazine anesthesia is not a suitable type of general anesthesia in *in vivo* rat experiments when electrocardiological parameters are evaluated.

In conclusion, when evaluating changes in ECG parameters in rats, possible variations should also be taken into account. The correct assessment of changes, in turn, depends on the knowledge of reference values for sex and the time of day experiments are performed.

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Table 1. Heart rate under individual types of anesthesia according to sex and light cycle (light inactive.) versus dark active.).

Anesthesia	Not specified		Light period		Dark period	
	Female	**Male**	**Female**	**Male**	**Female**	**Male**
Telemetry studies	460 (432–488); n = 1	346 (310–362); n = 16	316 (307–325); n = 2	349 (340–57); n = 5	371 (345–397); n = 2	390 (382–398); n = 5
Pentobarbital	–	374 (359–389); n = 22	346 (315–377); n = 1	–	369 (328–410); n = 1	–
Thiopental	–	349 (332–366); n = 13	–	–	–	–
Ketamine/xylazine	331 (304–257); n = 2	288 (239–293); n = 18	230 (207–253); n = 1	–	276 (247–305); n = 1	–
Isoflurane	–	408 (400–416); n = 5	–	–	–	–
Urethane	–	378 (352–403); n = 14	–	–	–	–

Data presented as average heart rate (beats/min) (range); n, number of baseline or control values from which heart rate was evaluated. –, not specified, the lighted period when the experiments were performed were not described in the methodology.

Table 2. Duration of PR (PQ) interval duration under individual types of anesthesia according to sex and light cycle (light inactive.) versus dark active.)

Anesthesia	Not specified		Light period		Dark period	
	Female	**Male**	**Female**	**Male**	**Female**	**Male**
Telemetric studies	42.23 (41.5–42.96); n = 1	49.26 (47.51–50.88); n = 10	–	–	–	–
Pentobarbital	–	47.53 (45.35–49.71); n = 18	44.16 (36.46–1.86); n = 1)	–	45.3 (40.6–50); n = 1	–
Thiopental	–	48.35 (46.52–50.18); n = 6	–	–	–	–
Ketamine/xylazine	44 (34–54); n = 1	44.77 (41.02–45.42); n = 13	47 (35.7–58.3); n = 1	–	36.5 (30.7–42.3); n = 1	–
Isoflurane	–	48.05 (46.52–49.63); n = 6	–	–	–	–
Urethane	–	48.99 (45.03–52.95); n = 9	–	–	–	–

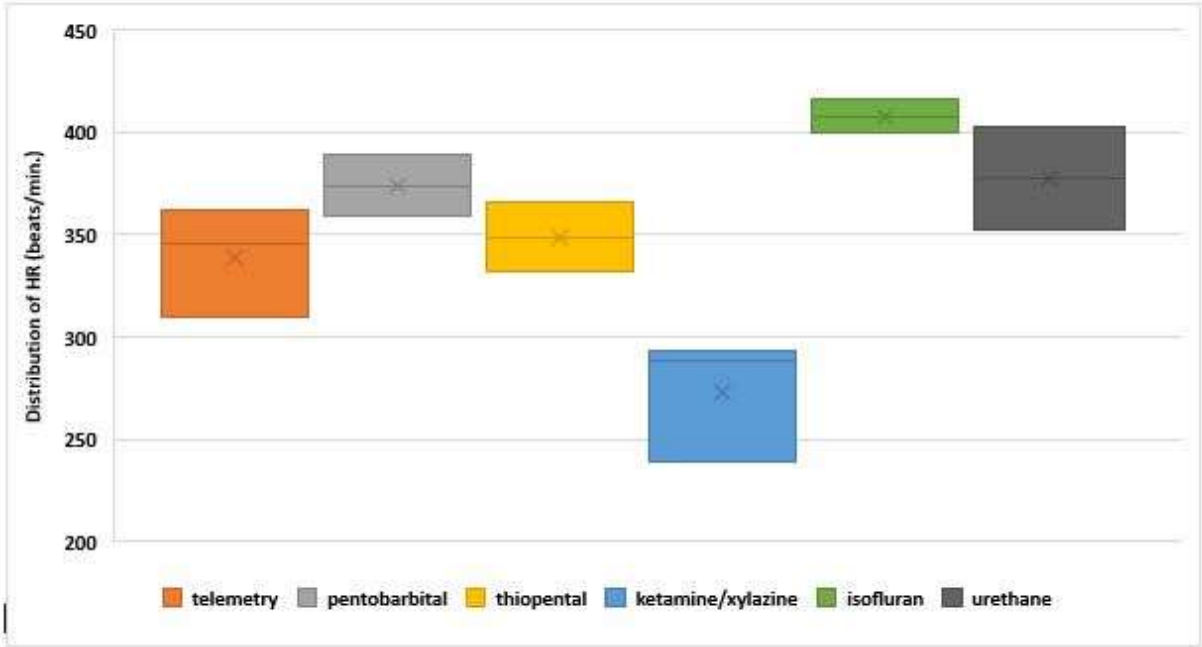
Data presented as average value of PR (PQ) interval duration (ms) (range); n, number of baseline or control values from which heart rate was evaluated. –, not specified, the methodology does not specify the lighted period when the experiments were performed.

Table 3. QT interval duration (ms) under individual types of anesthesia with regard to sex and light cycle (inactive) and dark (active).

	Not specified		Light period		Dark period	
Anesthesia	**Female**	**Male**	**Female**	**Male**	**Female**	**Male**
Telemetry studies	–	58.02 (51.7–64.34); n = 4	–	–	–	–
Pentobarbital	–	68.85 (65.56–69.26); n = 19	73.5 (58.1–8.9); n = 1	–	76.02 (66.36–85.68); n = 1	–
Thiopental	–	64.75 (54.03–67.52); n = 8	–	–	–	–
Ketamine/xylazine	87 (79–95); n = 1	74.97 (70.88–79.23); n = 11	89.9 (73–106.8); n = 1	–	91.7 (82–101.4); n = 1	–
Isoflurane	–	58.32 (43.68–61.48); n = 6	–	–	–	–
Urethane	–	53.05 (48.74–57.35); n = 9	–	–	–	–

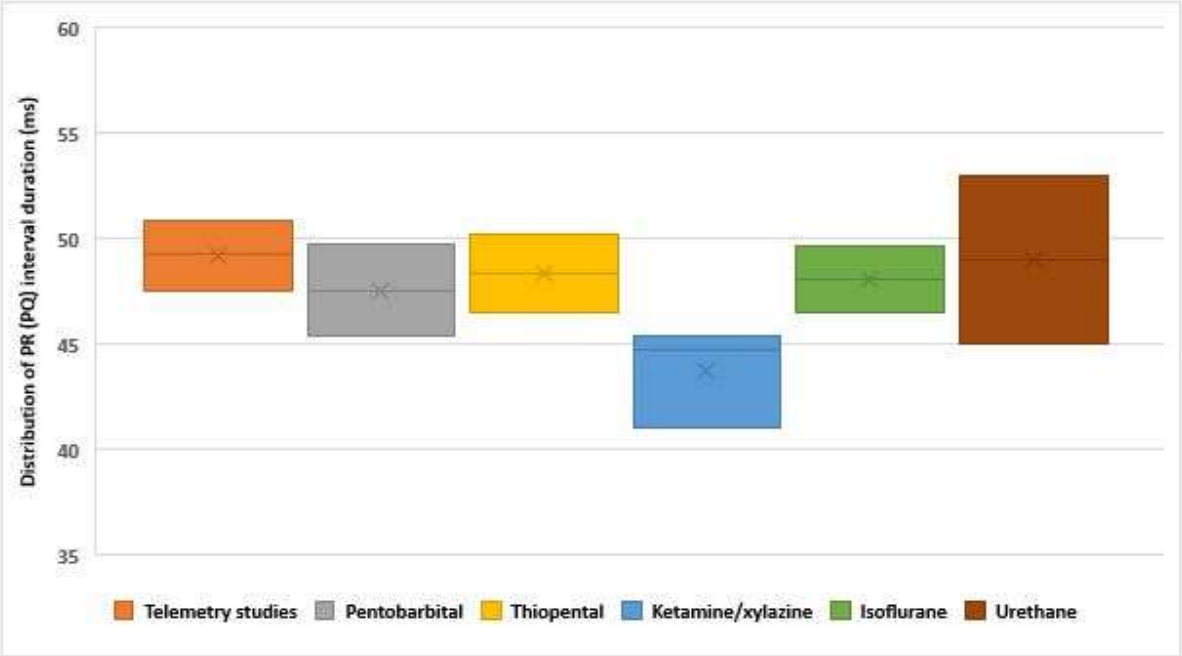
Data presented as average (range); n, number of baseline or control values from which the QT interval was evaluated. Not specified - the methodology does not specify the lighted period when the experiments were performed.

Figure 1. Distribution of average values and ranges of heart rate (HR) from telemetry studies and under different types of general anesthesia in male rats without accounting for the light periods of the rat regimen day when the experiments were performed.



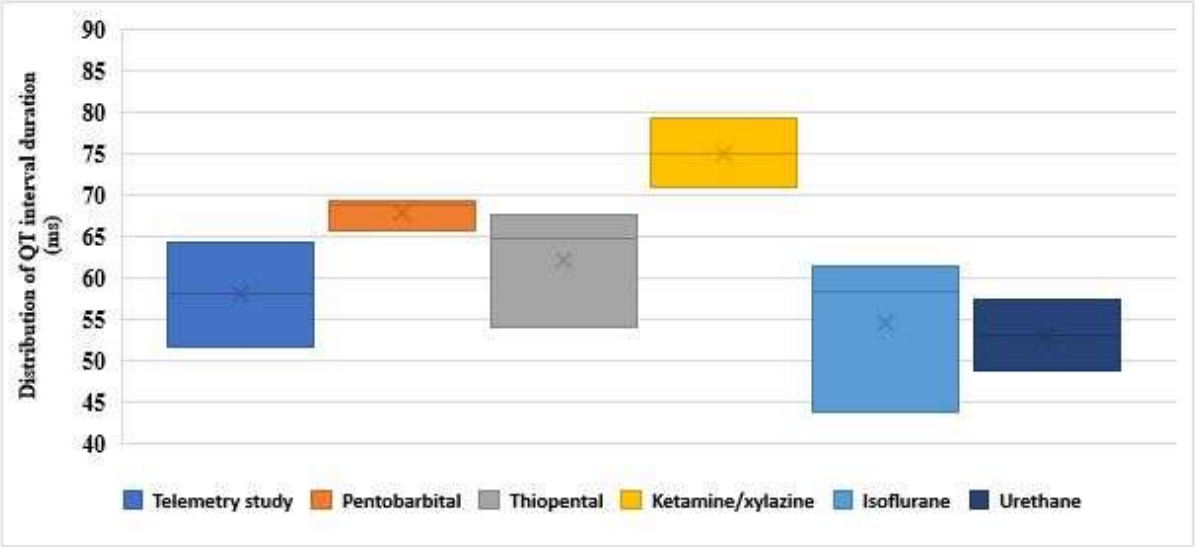
Telemetry studies (n = 16), pentobarbital anesthesia (n = 22), thiopental anesthesia (n = 13), ketamine/xylazine anesthesia (n = 18), isoflurane anesthesia (n = 5), urethane anesthesia (n = 14). n represents the number of baseline or control values from which heart rate was evaluated.

Figure 2. Distribution of ranges of PR(PQ) interval from telemetry studies and under different types of general anesthesia in male rats without accounting for light periods of the rat regimen day when the experiments were performed.



Telemetry studies (n = 10), pentobarbital anesthesia (n = 18), thiopental anesthesia (n = 6), ketamine/xylazine anesthesia (n = 13), isoflurane anesthesia (n = 6), urethane anesthesia (n = 9). (n - number of baseline or control values from which duration of PR (PQ) interval was evaluated).

Figure 3. Distribution of ranges of QT interval from telemetry studies and under different types of general anesthesia in male rats without accounting for light periods of the rat regimen day when the experiments were performed.



Telemetry studies (n = 4), pentobarbital anesthesia (n = 19), thiopental anesthesia (n = 8), ketamine/xylazine anesthesia (n = 11), isoflurane anesthesia (n = 6), urethane anesthesia (n = 9). (n - number of baseline or control values from which duration of QT interval was evaluated).