ANIMAL PATHOLOGY, MORPHOLOGY, PHYSIOLOGY, PHARMACOLOGY AND TOXICOLOGY

ПАТОЛОГИЯ ЖИВОТНЫХ, МОРФОЛОГИЯ, ФИЗИОЛОГИЯ, ФАРМАКОЛОГИЯ И ТОКСИКОЛОГИЯ

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Main Indices of Laboratory Rabbit Cardiovascular System

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Abstract

Introduction. Rabbits, ferrets, dogs, miniature pigs and monkeys are considered to be the preferable test systems for assessing the efficacy of the developed medicinal products for the cardiovascular system. The heart rate and distribution of cardiac ion channels in the heart of these species is similar to that in the human heart. The present work focuses on rabbits as they are one of the most widely used species in preclinical research, however, the results of measurements carried out on a sufficient sample of intact animals can hardly be found in the open sources. Thus, the aim of the study is to determine the features of the electrocardiogram and to establish the reference intervals of the key cardiovascular indices as well as of the blood pressure in the sexually mature laboratory rabbits of different breeds, ages and sexes, and to compare the obtained data with that in the literature sources.

Materials and Methods. The study was conducted at JSC "Research-and-Manufacturing Company "Home of Pharmacy" (Leningrad Region) in the period from 2019 to 2024. 597 electrocardiograms and 863 values of systolic and diastolic blood pressure in rabbits of various breeds and sexes aged 4 to 8 months were analysed and reference intervals for them were calculated. To minimise possible variability of parameters caused by stress and motor activity of animals, they were anesthetized during physiological studies with a drug containing tiletamine and zolazepam (5 mg/kg) in combination with xylazine hydrochloride (1–2 mg/kg) administered intramuscularly or intravenously. The data were retrieved by recording the background values in all rabbits in the experiment (before administering the studied medicinal products), as well as in rabbits in the control and intact groups. Reference intervals were calculated using a nonparametric (number of values more than 120) or robust (number of values less than 120) methods.

Results. When studying the electrocardiograms of rabbits, the highest variability was noted in the P wave. Also, the absence of one of the Q, S, T waves in one or two leads and absence of S-T and T-P intervals were frequently observed. When comparing rabbit breeds and body weight ranges, no significant differences were found in the calculated reference intervals of the indices assessed. When comparing to the literature sources, the electrocardiogram parameters mainly matched the obtained reference intervals, except for the QRS interval. The obtained intervals of blood pressure indices in the state of anaesthesia were significantly lower than the values presented in the literature for the awaken animals.

Discussion and Conclusion. The calculated reference intervals of the most of electrocardiogram parameters in different rabbit breeds are comparable to the data available in literature and do not significantly vary in relation to age, weight and sex. The obtained reference intervals and the described features of the electrocardiogram of rabbits can be used in the analysis and interpretation of data received during preclinical research.

Keywords: reference intervals, rabbits, pharmacological safety, blood pressure (BP), electrocardiogram (ECG), cardiovascular system (CVS)

Declaration of Compliance with the Principles of the European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes: the authors declare that all research was conducted in compliance with the principles of Good Laboratory Practice.

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Оригинальное эмпирическое исследование

Основные показатели функционирования сердечно-сосудистой системы лабораторных кроликов

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Аннотация

Введение. Предпочтительными тест-системами в ходе оценки влияния разрабатываемых лекарственных препаратов на сердечно-сосудистую систему являются кролики, хорьки, собаки, карликовые свиньи и обезьяны. Сердце данных видов имеет сходство с сердцем человека в частоте сердечных сокращений и распределении сердечных ионных каналов. Данная работа сфокусирована на кроликах как одном из наиболее широко задействованных в доклинических исследованиях виде, при этом в открытых источниках практически не встречаются результаты измерений на достаточной выборке интактных животных. Таким образом, целью исследования было определение особенностей электрокардиограммы и референтных интервалов основных показателей сердечно-сосудистой системы и артериального давления у половозрелых лабораторных кроликов разных пород, возраста и пола, и сравнение полученных данных с литературными источниками.

Материалы и методы. Исследование проведено в АО «НПО «ДОМ ФАРМАЦИИ» (Ленинградская область) в период с 2019 по 2024 гг. Проанализированы 597 электрокардиограмм и 863 значения систолического и диастолического артериального давления кроликов различных пород и пола в возрасте от 4 до 8 месяцев и рассчитаны их референтные интервалы. Для нивелирования возможной вариативности параметров, обусловленной стрессом и двигательной активностью животных, при проведении физиологических исследований применяли анестезию: внутримышечно или внутривенно препарат, содержащий тилетамин и золазепам (5 мг/кг), в комбинации с ксилазина гидрохлоридом (1–2 мг/кг). Данные получены при регистрации фоновых значений у всех кроликов в эксперименте (до введения исследуемых препаратов), а также у кроликов, находившихся в контрольных и интактных группах. Расчет референтных интервалов проводился непараметрическим (количество значений больше 120) или робастным методом (количество значений менее 120).

Результаты исследования. При изучении электрокардиограммы кроликов наибольшая вариативность отмечена у зубца P, также часто наблюдали отсутствие одного из зубцов Q, S, T в одном или двух отведениях и интервалов S-T и T-P. Значительных различий, рассчитанных референтных интервалов по оцениваемым показателям при сравнении между породами и диапазонами массы тела кроликов, не обнаружено. При сравнении с литературными источниками параметры электрокардиограммы преимущественно попадают в полученные референтные интервалы, за исключением интервала QRS. Полученные интервалы показателей артериального давления в состоянии наркотизации значительно ниже представленных в литературе значений у животных в сознании.

Обсуждение и заключение. Рассчитанные референтные интервалы большинства параметров электрокардиограммы кроликов различных пород сопоставимы с данными литературы и не имеют значительных колебаний в зависимости от возраста, массы и пола. Полученные референтные интервалы и описанные особенности электрокардиограммы кроликов могут быть использованы при анализе и интерпретации данных, полученных в доклинических исследованиях.

Ключевые слова: референтные интервалы, кролики, фармакологическая безопасность, артериальное давление (АД), электрокардиограмма (ЭКГ), сердечно-сосудистая система (ССС)

Декларация о соблюдении принципов Европейской конвенции о защите позвоночных животных, используемых для экспериментов и других научных целей: авторы заявляют, что все проведенные исследования соответствовали принципам конвенции и правилам надлежащей лабораторной практики.

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Introduction. Electrophysiological studies are an important tool for assessment of cardiovascular system (CVS) functioning. These studies are an integral part of research on the pharmacological safety of new medicinal products, thus, help to evaluate the pharmacological efficacy of potential therapeutic agents. The animal species most commonly used in experimental cardiac electrophysiology are mice, guinea pigs, rats, miniature pigs, ferrets, rabbits, dogs, and monkeys. The electrocardiograms (ECG) of mice and rats demonstrate significant differences from humans', including differences in the process of cardiac impulse generation, therefore, the mechanisms of arrhythmia may differ from those in humans. Moreover, the small size of rodent's heart complicates surgical interventions on this organ and prevents its use for testing cardiac devices such as valve prostheses or pacemakers [1]. The cardiac ion channel distribution in rabbits, ferrets, dogs and miniature pigs is similar to that in human heart, therefore, these animals proved to be suitable for studying ventricular repolarization or pro- and antiarrhythmic effects of medicinal products[3] [2, 3]. Moreover, the heart size and similar to human processes of cardiac impulse generation and lipoprotein metabolism in laboratory rabbits have led to their widespread use as test systems for studying human cardiovascular diseases [4–6]. Currently, laboratory rabbits are often used to study genetic cardiomyopathies in humans and long QT syndrome [7], as well as the mechanisms of cardiac conduction disorders and arrhythmias [1, 8].

It should be noted that one of the necessary approaches to studying the CVS is the ability of a medicinal product to slow ventricular repolarization (prolong the QT interval)[4]. In the past it was found that some medicinal products could cause severe life-threatening arrhythmias (such as torsades de pointes), which can be fatal. Such properties were, for example, found in cizapride and terfenadine, which were withdrawn from the market for this reason. The effect of medicinal products on ventricular repolarization and arrhythmogenic risk is actively evaluated at the preclinical and clinical stages of medicinal product development[5].

Most often, CVS indices are determined in the frame of establishing the pharmacological safety profile, when the laboratory rabbits are used as second animal species (non-rodents)[6] [9]. In the public domain, one can find mean values or intervals of ECG parameters, including heart rate (HR) and blood pressure (BP), obtained from a small number of rabbits in the control group, as well as from domestic rabbits. However, in open sources there are practically no summarised data on reference values of CVS indices for different breeds of rabbits, and ECG changes possible to encounter in healthy rabbits are also extremely poorly represented.

*The aim of the research i*s to determine the ECG features and reference intervals for the main CVS indices (ECG and BP) in mature laboratory rabbits of different breeds, ages and sexes, and then compare the obtained data with literature sources.

Materials and Methods. All studies were conducted at JSC "Research-and-Manufacturing Company "Home of Pharmacy" (Leningrad Region) in the period from 2019 to 2024 in compliance with the principles of the European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes[7], and rules of Good Laboratory Practice[8]. The effect of the medicinal products on the cardiovascular system was studied by assessing the blood pressure, heart rate, and electrocardiogram; additionally, *in vivo*, *in vitro*, and/or *ex vivo* obtained data were analysed, including the methods for assessing repolariza-

[3] On the Guidelines for the Study of Pharmacological Safety of the Medicinal Products for Medical Use. Recommendation of the Board of the Eurasian Economic Commission No. 18 of October 27, 2020. (In Russ.) URL: https://docs.eaeunion.org/upload/iblock/7f5/a2kjnu4hopvymlaefwp0caw97k3nv2us/err_30102020_18_doc.pdf (accessed: 02.06.2025).

[4] S7B Non-Clinical Evaluation of the Potential for Delayed Ventricular Repolarization (QT Interval Prolongation) by Human Pharmaceuticals. Guidance for Industry. U.S. Department of Health and Human Services Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER). ICH; 2005. URL: https://www.fda.gov/media/72043/download (accessed: 02.06.2025).

[5] On the Guidelines for the Study of Pharmacological Safety of the Medicinal Products for Medical Use. Recommendation of the Board of the Eurasian Economic Commission No. 18 of October 27, 2020. (In Russ.). URL: https://docs.eaeunion.org/upload/iblock/7f5/a2kjnu4hopvymlaefwp0caw97k3nv2us/err_30102020_18_doc.pdf (accessed: 02.06.2025).

[6] On Approval of the Guidelines for Preclinical Safety Studies for the Purpose of Conducting Clinical Trials and Drug Registration. The Decision of the Board of the Eurasian Economic Commission No. 202 of November 26, 2019. (In Russ.). URL: https://docs.eaeunion.org/upload/iblock/072/nzmd6i2fwbj90ndkm4riswwcz9ecgsa2/clcd_29112019_202_doc.pdf (accessed: 02.06.2025).

[7] European Convention for the Protection of Vertebrate Animals used for Experimental and Other Scientific Purposes. ETS No.123. Strasbourg: Council of Europe; 1986. URL: https://clck.ru/3MeTdd (accessed: 02.06.2025).

[8] On Guidelines for Working with Laboratory (Experimental) Animals when Conducting Preclinical (Non-Clinical) Studies. Recommendations of the Board of the Eurasian Economic Commission No. 33 November 14, 2023. (In Russ.) URL: https://docs.eaeunion.org/upload/iblock/46d/ccxcn6996c79u3xvgecp05qhx5g5e692/err_20112023_33_doc.pdf (accessed: 02.06.2025).

tion and conduction disorders in the myocardium[9,10,11,12,13,14]. Data for calculating reference intervals for BP and ECG parameters were obtained by recording the background values in all rabbits in the experiment (before administering the studied medicinal products), as well as in rabbits in the control and intact groups.

Regulatory documents for conducting preclinical studies describe the main set of pharmacological safety studies aimed at investigating the effect of the tested agent on the vital functions of a human body (cardiovascular, central nervous and respiratory systems)[15,16,17,18,19]. These studies are conducted prior to clinical development in compliance with the principles stipulated in the S7A and S7B Guidelines of ICH[20,21]. If necessary, additional and subsequent safety pharmacological studies may be conducted in the later stages of clinical development[15].

Thereby, additional studies on the cardiovascular system are aimed at deeper understanding of the obtained results of the vital functions, e.g.: measurement of cardiac output, ventricular contractility, vascular resistance[22,23,24]. To assess additional parameters, echocardiography is normally used as a clarifying examination [10, 11].

In all the experiments, rabbits from the nurseries, with the necessary veterinary documentation, were used of the Soviet Chinchilla, White Giant, and New Zealand breeds aged 4 to 8 months. The animals were kept in the equally standard conditions: air temperature 15–22°C, relative humidity > 45%, 12-hour daylight. Non-pregnant and nulliparous females were used. The rabbits were kept individually or in pairs (same sex) in standard plastic cages with wood bedding, or in groups of no more than 5 specimens of the same sex in isolated boxes with a removable panel floor. The floor area of the cage per animal complied with the Guide for the Care and Use of Laboratory Animals[25].

[9] S7A Safety Pharmacology Studies for Human Pharmaceuticals. Guidance for Industry U.S. Department of Health and Human Services Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER). ICH; 2001. URL: https://www.fda.gov/media/72033/download (accessed: 02.06.2025) [GOST R 56700–2015. Medicines for Medical Applications. Safety Pharmacology Studies for Human Pharmaceuticals (In Russ.). URL: https://files.stroyinf.ru/Data2/1/4293758/4293758370.pdf (accessed: 02.06.2025).

[10] GOST R 56701–2015. Medicines for medical applications. Guidance on nonclinical safety studies for the conduct of human clinical trials and marketing authorization for pharmaceuticals. (In Russ.). URL: https://clck.ru/3MeU4u (accessed: 02.06.2025).

[11] S7B Non-Clinical Evaluation of the Potential for Delayed Ventricular Repolarization (QT Interval Prolongation) by Human Pharmaceuticals. Guidance for Industry. U.S. Department of Health and Human Services Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER). ICH; 2005. URL: https://www.fda.gov/media/72043/download (accessed: 02.06.2025).

[12] On the Guidelines for the Study of Pharmacological Safety of the Medicinal Products for Medical Use. Recommendation of the Board of the Eurasian Economic Commission No. 18 of October 27, 2020. (In Russ.). URL: https://docs.eaeunion.org/upload/iblock/7f5/a2kjnu4hopvymlaefwp0caw97k3nv2us/err_30102020_18_doc.pdf (accessed: 02.06.2025).

[13] On Approval of the Guidelines for Preclinical Safety Studies for the Purpose of Conducting Clinical Trials and Drug Registration. The Decision of the Board of the Eurasian Economic Commission No. 202 of November 26, 2019. (In Russ.). URL: https://docs.eaeunion.org/upload/iblock/072/nzmd6i2fwbj90ndkm4riswwcz9ecgsa2/clcd_29112019_202_doc.pdf (accessed: 02.06.2025).

[14] On Rules for Registration and Examination of Medicinal Products for Medical Use. Decision of the Board of the Eurasian Economic Commission No. 78 of November 3, 2016. (as amended on May 29, 2024). (In Russ.) URL: https://docs.eaeunion.org/upload/iblock/cf0/9pi8f6zal9za9xhhcz1lt5aq6nxd7gvi/cncd_21112016_78_doc.pdf (accessed: 02.06.2025).

[15] GOST R 56701–2015. Medicines for medical applications. Guidance on nonclinical safety studies for the conduct of human clinical trials and marketing authorization for pharmaceuticals. (In Russ.). URL: https://clck.ru/3MeU4u (accessed: 02.06.2025).

[16]On the Guidelines for the Study of Pharmacological Safety of the Medicinal Products for Medical Use. Recommendation of the Board of the Eurasian Economic Commission No. 18 of October 27, 2020. (In Russ.). URL: https://docs.eaeunion.org/upload/iblock/7f5/a2kjnu4hopvymlaefwp0caw97k3nv2us/err_30102020_18_doc.pdf (accessed: 02.06.2025).

[17] On Approval of the Guidelines for Preclinical Safety Studies for the Purpose of Conducting Clinical Trials and Drug Registration. The Decision of the Board of the Eurasian Economic Commission No. 202 of November 26, 2019. (In Russ.). URL: https://docs.eaeunion.org/upload/iblock/072/nzmd6i2fwbj90ndkm4riswwcz9ecgsa2/clcd_29112019_202_doc.pdf (accessed: 02.06.2025).

[18] On Circulation of Medicines. Federal Law of Russian Federation No. 61-FZ of April 12, 2019 (edition of April 1, 2024) (In Russ.). URL: https://roszdravnadzor.gov.ru/i/upload/images/2025/4/7/1744053375.88887-1-3771747.pdf?ysclid=mc34cwsi54623589355 (accessed: 02.06.2025).

[19] On Guidelines for Working with Laboratory (Experimental) Animals when Conducting Preclinical (Non-Clinical) Studies. Recommendations of the Board of the Eurasian Economic Commission No. 33 November 14, 2023. (In Russ.). URL: https://docs.eaeunion.org/upload/iblock/46d/ccxcn6996c79u3xvgecp05qhx5g5e692/err_20112023_33_doc.pdf (accessed: 02.06.2025).

[20] S7A Safety Pharmacology Studies for Human Pharmaceuticals. Guidance for Industry. U.S. Department of Health and Human Services Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER). ICH; 2001. URL: https://www.fda.gov/media/72033/download (accessed: 02.06.2025) [GOST R 56700–2015. Medicines for Medical Applications. Safety Pharmacology Studies for Human Pharmaceuticals (In Russ.). URL: https://files.stroyinf.ru/Data2/1/4293758/4293758370.pdf (accessed: 2.06.2025)]

[21] S7B Non-Clinical Evaluation of the Potential for Delayed Ventricular Repolarization (QT Interval Prolongation) by Human Pharmaceuticals. Guidance for Industry. U.S. Department of Health and Human Services Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER). ICH; 2005. URL: https://www.fda.gov/media/72043/download (accessed: 02.06.2025).

[22] S7A Safety Pharmacology Studies for Human Pharmaceuticals. Guidance for Industry. U.S. Department of Health and Human Services Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER). ICH; 2001. URL: https://www.fda.gov/media/72033/download [GOST R 56700–2015. Medicines for Medical Applications. Safety Pharmacology Studies for Human Pharmaceuticals (In Russ.). URL: https://files.stroyinf.ru/Data2/1/4293758/4293758370.pdf (accessed: 02.06.2025).

[23] GOST R 56701–2015. Medicines for medical applications. Guidance on nonclinical safety studies for the conduct of human clinical trials and marketing authorization for pharmaceuticals. (In Russ.) URL: https://clck.ru/3MeU4u (accessed: 02.06.2025).

[24]On the Guidelines for the Study of Pharmacological Safety of the Medicinal Products for Medical Use. Recommendation of the Board of the Eurasian Economic Commission No. 18 of October 27, 2020. (In Russ.). URL: https://docs.eaeunion.org/upload/iblock/7f5/a2kjnu4hopvymlaefwp0caw97k3nv2us/err_30102020_18_doc.pdf (accessed: 02.06.2025).

[25] *Guide for the Care and Use of Laboratory Animals. Eight Edition. Translation to Russian.* Belozerceva IV, Blinov DV, Krasilshikova MS (Eds.). Moscow: IRBIS; 2017. 336 p. (In Russ.). URL: https://bioethics.msu.ru/knowledge/standarts/Guide_book_short.pdf (accessed: 02.06.2025).

Access to water was not restricted throughout the duration of each experiment. Animals were fed twice a day, in the morning and in the evening, in conformity with the Directive 2010/63/EU[26] и and the Guide for the Care and Use of Laboratory Animals[27]. The compound feed for rodents prepared in accordance with GOST 34566–2019[28] requirements was used as the feed.

Although it is preferable to conduct physiological studies in the awaken animals, the use of anesthesia is acceptable to minimise possible variability of parameters caused by stress and motor activity of animals[29]. In literature sources the use of anesthetics such as tiletamine/zolazepam in combination with xylazine in rabbits is reported to have relatively minor side effects with anesthesia deep enough for the study [12–14]. Animals were anesthetized with a drug containing tiletamine and zolazepam in combination with xylazine hydrochloride 5 mg/kg and 1–2 mg/kg, respectively, administered intramuscularly or intravenously.

The blood pressure and ECG were recorded at different time intervals during a day in anesthetized animals in the supine position. After confirming the absence of reflexes in the animal, the ECG was recorded using a computerized veterinary electrocardiograph “Poli-Spektr-8/E” (“Neurosoft” LLC, Russia). The ECG was recorded for 1 minute in three standard and six chest leads. The following parameters were assessed within the ECG analysis: heart rate (HR, beats/min), RR (ms), P (ms), PQ (ms), QRS (ms), QT (ms), and the amplitude of the R- and T-waves (mV). The duration of the intervals and the P-wave were assessed in three standard leads (I, II, and III), as the most frequently used and visualized in the assessment of CVS pathologies [15, 16], the amplitude of the waves was measured in lead II as a mean one. Duration of the intervals in the majority of cases coincided in the two leads; with rare exceptions. When the duration was different, the measurement was carried out in the lead with the longest duration (usually in lead II).

After electrocardiography, the animals’ blood pressure, including systolic and diastolic values, was measured non-invasively using a cuff and a Zoomed BPM-2 veterinary pressure monitor (“ZOOMED” LLC, Russia). The cuff was placed on the right or left thoracic limb, the measurement was taken three times with an interval of 1 to 3 minutes between each, then the mean value of the SBP and DBP readings was calculated. Incorrect outlier values of the device (change in numbers by more than 20 units relative to previously measured values) were not taken into account and immediately re-registered.

The values of the measured BP and ECG in the form of the lower and upper limits of the reference interval were presented in the tables separately for males and females for each of the breeds studied, as well as by body weight ranges, regardless of breed.

Statistical analysis of reference intervals was performed using the licensed software *Microsoft Excel* and free software *Reference Value Advisor v2.1* (*National Veterinary School*, Toulouse, France), compliant with the CLSI Guideline [30] for robust calculation method. To identify differences resulting from comparing data from different sexes, breeds, and body weight ranges by means of a paired T-test, the licensed software *Statistica 10.0* (*StatSoft*, USA) was used.

The currently approved CLSI Guideline on Defining, Establishing, and Verifying Reference Intervals in the Clinical Laboratory recommends to use a nonparametric method for defining intervals in the sample sizes not less than 120 values and a robust method in the sample sizes between 40 and 120 values. As follows from the data in the literature, the parametric approach is also one of the most commonly used approaches, however, this method is overlooked in the CLSI Guideline despite its potential to demonstrate the best performance for normally distributed data [17]. The parametric method is considered unstable when analysing less than 150 values [18] and is reported in the literature as used, when there are more than 200 values.

Calculation of reference intervals for ECG parameters and blood pressure readings was conducted, depending on the number of animals, by a robust method (number of values less than 120), whereas compliance with the normal distribution law was determined according to Anderson-Darling test, and in the case of abnormal distribution, the Box-Cox transformation was used; otherwise (number of values more than 120), calculation was conducted by a nonparametric method.

Moreover, according to the CLSI Guideline[31], it is necessary to exclude from the data array the statistical outliers that lie outside the interval (Q1–1.5×IQR) – (Q3+1.5×IQR), where Q1 and Q3 are the limits of the 1st and 3rd quartiles;

[26] *Directive 2010/63/EU of the European Parliament and of the Council of September 22, 2010. On the Protection of Animals Used for Scientific Purposes. Translation to Russian.* Krasilshchikova MS, Belozertseva IV (Eds.). St. Petersburg; 2012. 48 p. URL: https://ruslasa.ru/wp-content/uploads/2017/06/Directive_201063_rus.pdf (accessed: 02.06.2025).

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IQR is the interquartile interval [17, 19]. The proportion of detected outliers was determined using Tukey's method.

Research Results. The electrocardiogram of a rabbit has specific features that should be taken into account when assessing the cardiac function, such as the degree of expression of the waves [20]. Therefore, during the analysis, the specific features of ECGs of rabbits, not typical for humans, were recorded and presented in Table 1, which shows the percentage of changes relative to all the animals studied (597 electrocardiograms — 308 males and 289 females). It should be noted that during the analysis there were found the ECG recordings with the isoelectric line practically untrackable due to interference, represented as repeating positive and negative waves, which made measurement of the wave amplitude impossible, and measurement of the duration of the intervals — difficult.

Table 1

ECG features of male and female rabbits, % of the total number of studied animals (n=597)

Index	Features
Males, n=308	
P-wave	42% peaked in leads I and II 11% slight shift in leads I and II 10% absent (3.5% in leads I and II, 6.5% in lead III) 4% bifid(notched) in lead II 3% poly-phasic in lead II 3% negative in lead III
Q-wave	24% absent (12% in lead II, 6% in lead III, 1% in lead I, and 5% in three leads) 15% amplitude greater than S-wave amplitude in lead II
R-wave	2% poly-phasic in lead II 1% bifid (notched) in lead II
S-wave	33% amplitude greater than Q-wave amplitude in lead II 22% absent (15% in three leads, 7% in lead II, 5% in lead I) 2% poly-phasic in lead II 2% positive J-wave present
T-wave	10% negative (7% in lead III, 3% in lead I) 5% absent in lead III
ST interval	2% absent in three leads
TP interval	9% absent or nearly absent in three leads (mainly at heart rate greater than 250 bpm)
Females, n=289	
P-wave	40% peaked in leads I and II 27% negative in lead III 11% slight shift in leads I and II 10% absent (3.5% in leads I and II, 6.5% in lead III) 4% poly-phasic in lead II 3% bifid (notched) in lead II
Q-wave	29% absent (11% in lead III, 9% in lead II, 2% in lead I, and 7% in three leads) 10% amplitude greater than S-wave amplitude in lead II
R-wave	1% poly-phasic in lead II 3% bifid (notched) in lead II
S-wave	31% absent (15% in lead I, 6% in lead III, 1% in lead II, and 9% in three leads) 29% amplitude greater than Q-wave amplitude in lead II 3% positive J-wave present
T-wave	21% negative (20% in lead III, 1% in lead I) 7% absent in lead III
ST interval	2% absent in three leads
TP interval	10% absent or nearly absent in three leads (mainly at heart rate greater than 250 bpm)

Also, in males and females, there were observed cases of strong dependence of the Q- and S-wave amplitude on the lead — the wave could be practically absent in one lead and exceed the values of the R-wave amplitude in another one (to negative values). In males, this phenomenon was registered in 3% of ECG recordings with S-wave and in 5.5% — with a Q-wave; in females — in 1.4% of ECG recordings with S-wave and in 1.7% — with a Q-wave. Due to the absence of a Q-wave in ECG recording, the PQ interval is generally replaced by the PR interval [21, 22].

The amplitude of the QRS complex in the leads depends on the projection of the electrical axis of the heart, this measurement was not carried out in rabbits due to the anatomical features of the heart and the ECG image, the difficulty of interpretation, as well as the lack of data in the literature on the correct body position for this analysis. However, during the analysis, the amplitude of the R-wave was measured and the correlation of the height of the R-wave in each of the three leads was determined. In 54% of the recordings in males and in 51% in females, the R-wave had the highest amplitude in lead I and an equivalent negative amplitude in lead III, consequently, in lead II the amplitude was almost the same as in lead I or lower, but remained positive. In 22% of cases in males and in 26% of cases in females, the R-wave amplitude in lead II was higher than in leads I and III. In 14% of the recordings in males and in 16% in females, the R-wave amplitude in lead III exceeded that in lead II, which, in turn, exceeded the amplitude in lead I. In the remaining ECG recordings (9% in males and 7% in females), measurements were not performed due to the difficulties in correct assessment of the R-wave amplitude.

Reference intervals for ECG parameters and blood pressure readings are presented separately for males and females for each rabbit breed in Tables 2–4. The duration of ECG intervals was calculated from the rise/depression relative to the isoelectric line of the wave indicated first in the interval (e.g. the Q-wave in the QT interval) until the return of the impulse to the isoelectric line (including in the case of its depression) after the wave indicated last in the interval (e.g. the T-wave in the QT interval) or at the top of the J-wave, if any. As observed earlier, the greatest number of features and the percentage of their occurrence were found in the P- and S-waves, as well as in the Q-wave (Table 1). Therefore, the amplitudes of these waves were not measured to avoid presenting incorrect data. The amplitude of the R-wave was measured relative to the segment of the electrical line located before the QRS complex (Q-wave), the amplitude of the T-wave was measured relative to the segment recorded immediately after the measured T-wave.

Table 2

Reference intervals for ECG parameters and Blood Pressure readings for Soviet Chinchilla rabbit breed (nonparametric method of calculation)

Index	*Males*	*Females*
ECG parameters		
Heart Rate, bpm	151–282 (n=134)	156–269 (n=151)
RR, ms	213–389 (n=133)	221–364 (n=148)
P, ms	29–45 (n=131)	33–45 (n=147)
PQ, ms	53–78 (n=131)	58–84 (n=150)
QRS, ms	38–50 (n=132)	36–50 (n=151)
QT, ms	126–177 (n=131)	133–179 (n=152)
R-wave, mV	0,032–0,394 (n=129)	0,057–0,441 (n=144)
T-wave, mV	0,022–0,166 (n=128)	0,033–0,206 (n=147)
Blood Pressure readings		
Systolic	69–144 (n=166)	66–133 (n=166)
Diastolic	33–88 (n=166)	33–84 (n=167)

Note: here and in Tables 3–5: n is the number of values after excluding outliers from the sample.

Table 3

Reference intervals for ECG parameters and Blood Pressure readings for New Zealand rabbit breed (robust method of calculation)

Index	*Males*	*Females*
ECG parameters		
Heart Rate, bpm	147–266 (n=76)	164–257 (n=71)
RR, ms	208–379 (n=76)	223–346 (n=70)
P, ms	28–51* (n=76)	29–47 (n=73)
PQ, ms	53–91 (n=76)	55–87 (n=73)
QRS, ms	41–53 (n=75)	40–54 (n=71)
QT, ms	135–180 (n=68)	132–179 (n=73)
R-wave, mV	0,010–0,294 (n=70)	0,0–0,411* (n=70)
T-wave, mV	0,016–0,216 (n=75)	0,012–0,222 (n=71)
Blood Pressure readings		
Systolic	70–136 (n=134)	69–130 (n=133)
Diastolic	34–84 (n=135)	31–75 (n=136)

Note: here and in Tables 4, 5: * — values calculated using the Box–Cox transformation.

Table 4

Reference intervals for ECG parameters and Blood Pressure readings for White Giant rabbit breed (robust method of calculation)

Index	*Males*	*Females*
ECG parameters		
Heart Rate, bpm	148–255 (n=95)	142–269 (n=64)
RR, ms	215–377 (n=96)	205–385 (n=64)
P, ms	32–47 (n=97)	30–49 (n=63)
PQ, ms	58–86 (n=98)	57–91* (n=64)
QRS, ms	40–57* (n=95)	40–59 (n=64)
QT, ms	128–169 (n=95)	133–172 (n=63)
R-wave, mV	0,024–0,432* (n=93)	0,023–0,420* (n=60)
T-wave, mV	0,021–0,248 (n=96)	0,036–0,310* (n=64)
Blood Pressure readings		
Systolic	70–147** (n=165)	59–139 (n=90)
Diastolic	35–92** (n=166)	25–75 (n=89)

Note: here and in Table 5: ** — calculation was performed using a nonparametric method (n>120).

When analysing the calculated reference values for three rabbit breeds, the absence of significant differences between the breeds can be found with regard to the heart rate, interval duration, and blood pressure values.

One of the important criteria potentially capable of influencing the ECG parameters, along with breed, age, and sex [23], is the size of animals [24], which, among other factors, depends on the breed and age. Therefore, it was

decided to compare and calculate reference intervals for the ranges of weights of male and female rabbits, regardless of breed. Such a calculation can potentially be applied to other rabbit breeds in the corresponding weight ange. When comparing ECG parameters using a paired T-test, differences were revealed for most of the measured ECG intervals between animals weighing under 3.5 kg and over 3.5 kg.

The reference intervals for ECG parameters, calculated separately for males and females of each weight range, are presented in Table 5.

Table 5

Reference intervals for ECG parameters in rabbits with regard to body weight (robust method of calculation)

Index	*Males weighing 2.0–3.5 kg***	*Males weighing 3.5–5.8 kg*	*Females weighing 1.8–3.5 kg***	*Females weighing 3.5–6.0 kg*
Heart Rate, bpm	149–281 (n=206)	152–273 (n=102)	163–267 (n=174)	146–267 (n=114)
RR, ms	213–402 (n=206)	216–384* (n=102)	222–358 (n=172)	211–370 (n=110)
P, ms	29–46 (n=206)	29–50 (n=102)	31–46 (n=172)	30–49* (n=114)
PQ, ms	54–82 (n=203)	56–89 (n=102)	57–83 (n=172)	59–89* (n=114)
QRS, ms	39–53 (n=197)	41–53 (n=97)	36–53 (n=174)	39–56 (n=113)
QT, ms	125–178 (n=202)	132–176 (n=95)	132–178 (n=175)	131–175 (n=113)
R-wave, mV	0,035–0,396 (n=194)	0,010–0,329 (n=99)	0,035–0,451 (n=161)	0,010–0,396* (n=109)
T-wave, mV	0,027–0,236 (n=197)	0,020–0,214 (n=101)	0,032–0,227 (n=163)	0,022–0,219 (n=109)

When comparing the HR data available in the literature, they turned to be within the range of the obtained reference intervals for the corresponding breed (216±18 bpm, M±SD [15]) or weight (264±33.9 bpm, M±SD [21] 261±13 bpm, M±SD [22], 260±1.8, M±SD [24]). Also, the calculated interval encompassed all the values presented in an article, in which the result of measuring the HR of each of the 90 rabbits was expressed as a percentage relative to the sample [25]. At the same time, when comparing the data of another study conducted on immature rabbits (2–2.5 months), HR proved to be above the reference intervals (240–300 bpm) [20].

In one of the literature sources, a calculation of mean values and reference intervals for a sample of 46 healthy domestic rabbits of different sexes was provided. The mean values of the ECG parameters, including the amplitudes of the R- and T-waves, corresponded to the body-weight-range-intervals, however, the reference intervals provided in the literature source were only partially comparable with the intervals calculated in the present article: the lower limit of almost all parameters was outside the reference values (of this article) [21]. The differences in the intervals might be due to the relatively small sample (46) studied in the literature source (this assumption could be confirmed by the fact that in that article the minimum and maximum values in animals' ECG practically coincided with the reference intervals calculated in it). Whereas, when comparing with the ECG parameters provided in the next literature source that presented a summary of the parameters based on the review of several articles [24], it could be said that P-intervals (0.03–0.04 s), PQ (0.057 s; 0.070 s) and QT (0.132 s; 0.140 s; 0.150 s) coincided with the reference intervals, the QRS interval was either at the lower limit of the interval (0.040 s) or went beyond it (0.031 s). The height of the R-wave in lead II was also within the reference intervals (0.07–0.25 mV and 0.10–0.15 mV). The duration of P (0.03–0.04 s), PQ (0.07–0.08 s), QT (0.13–0.15 s) in immature rabbits was also within the calculated ranges, whereas the QRS interval values were at the lower limit of the references (0.03–0.04 s) [20]. In the paper, which presented the ECG of a rabbit of New Zealand breed, recorded continuously for 24 hours, most of the HR and QT duration values were within the reference intervals, the presented QRS interval values were near the lower limit of the reference intervals [26]. In another study, the QRS and QT interval values were significantly higher than the results obtained in this work for New Zealand rabbits, while the amplitude of the R- and T-waves fell within the calculated reference values, as well as the blood pressure values [27].

In a study on domestic rabbits, the QRS interval was within the calculated reference intervals, while the heart rate values were significantly lower, and the QT interval values, proportionally, were significantly higher than the results obtained in this work for the corresponding weight [28]. These features could result both from the characteristics of domestic rabbits and the drugs used for anesthesia.

When comparing the obtained intervals of SBP and DBP with the values presented in the literature, it was found that the readings were significantly higher, if measured in awaken animals [29] than in anesthetized animals, therefore literature data were higher than the calculated intervals. This could be explained by the mental condition of an animal at the time of measurement. All mean values indicated in the source presenting the review of data summarised from many papers were within the limits of the reference intervals [24]. In another source, where a number of animals with the certain values of SBP were presented [25], it was observed that 92% of rabbits fell within the reference intervals, the remaining values were slightly higher.

The proportion of detected outliers for the studied indices for each sex and breed relative to the data array is presented in Tables 6–8. Table 9 presents the proportion of outliers separately for males and females of each weight range.

Table 6

Proportion of statistical outliers in the analysis of ECG parameters and Blood Pressure readings for Soviet Chinchilla rabbit breed

ECG parameters	*Males, n=134*	*Females, n=152*
Heart Rate, bpm	0,0%	0,7%
RR, ms	0,7%	2,6%
P, ms	2,2%	3,3%
PQ, ms	2,2%	1,3%
QRS, ms	1,5%	0,7%
QT, ms	2,2%	0,0%
R-wave, mV	0,8%	1,4%
T-wave, mV	1,5%	2,6%
Blood Pressure readings	*Males, n=166*	*Females, n=167*
Systolic	0,0%	0,6%
Diastolic	0,0%	0,0%

Table 7

Proportion of statistical outliers in the analysis of ECG parameters and Blood Pressure indicators for New Zealand rabbit breed

ECG parameters	*Males, n=76*	*Females, n=73*
Heart Rate, bpm	0,0%	2,7%
RR, ms	0,0%	4,1%
P, ms	0,0%	0,0%
PQ, ms	0,0%	0,0%
QRS, ms	1,3%	2,7%
QT, ms	10,5%	0,0%
R-wave, mV	1,4%	0,0%
T-wave, mV	0,0%	0,0%
Blood Pressure readings	*Males, n=136*	*Females, n=136*
Systolic	1,5%	2,2%
Diastolic	0,7%	0,0%

Table 8

Proportion of statistical outliers in the analysis of ECG parameters and Blood Pressure *readings* for White Giant rabbit breed

ECG parameters	*Males, n=98*	*Females, n=64*
Heart Rate, bpm	3,1%	0,0%
RR, ms	2,0%	0,0%
P, ms	1,0%	1,6%
PQ, ms	0,0%	0,0%
QRS, ms	3,1%	0,0%
QT, ms	3,1%	1,6%
R-wave, mV	1,1%	0,0%
T-wave, mV	1,0%	0,0%
Blood Pressure readings	*Males, n=166*	*Females, n=92*
Systolic	0,6%	2,2%
Diastolic	0,0%	3,3%

Table 9

Proportion of statistical outliers in the analysis of ECG parameters in rabbits

Index	*Males weighing 2.0–3.5 kg*	*Males weighing 3.5–5.8 kg*	*Females weighing 1.8–3.5 kg*	*Females weighing 3.5–6.0 kg*
Heart Rate, bpm	0,0%	0,0%	0,6%	0,0%
RR, ms	0,0%	0,0%	1,7%	3,5%
P, ms	0,0%	0,0%	1,7%	0,0%
PQ, ms	1,5%	0,0%	1,7%	0,0%
QRS, ms	4,4%	4,9%	0,6%	0,9%
QT, ms	1,9%	6,9%	0,0%	0,9%
R-wave, mV	0,5%	1,0%	1,8%	0,0%
T-wave, mV	2,0%	0,0%	3,0%	3,5%

The greatest number of outliers were observed in males of the New Zealand rabbit breed for the QT interval (10.5%), while outliers for other ECG parameters and blood pressure readings in this and other breeds did not exceed 4.1% in females and 3.1% in males.

The greatest number of outliers were observed in males weighing 3.5–5.8 kg for the QRS (4.9%) and QT (6.9%) intervals. In males weighing 2.0–3.5 kg, the outliers did not exceed 4.4%, in females weighing 2.0–3.5 kg — 3.0%, in females weighing 3.5–5.8 kg — 3.5%.

Discussion and Conclusion. The described features of the ECG of rabbits can have a significant impact on the interpretation of data and correcting the results that are being obtained. For example, the absence of the Q-wave in the QRS complex was reported in the literature sources. However, apart from the images of ECG recordings, a more detailed description of the ECG image features in rabbits was practically unavailable in the literature.

The ranges of the reference intervals for the ECG parameters and blood pressure readings practically do not differ when analysed in different rabbit breeds, different weights and sexes. Nevertheless, the data were presented depending on the sex, breed and weight of the rabbits to optimize the process of analysing the results.

The established reference intervals for the ECG parameters coincide with some of the values presented in the literature, the most variable are the QRS interval and the amplitudes of the R- and T-waves, which may be induced by the quality of the recording and interpretation of the results by a certain researcher. The results of HR, SBP and DBP measurements mostly coincide with the data found in the literature, with the exception of the source in which the measurement of BP was performed on awaken animals, which significantly increased the range of values.

The obtained reference intervals and the described features of the rabbit electrocardiogram can be used in the analysis and interpretation of data received during preclinical studies.

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