Electrocardiography in rats: a comparison to human.

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Short title: ECG in rats.

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Summary:

Electrocardiography (ECG) in rats is a widely applied experimental method in basic cardiovascular research. The technique of ECG recordings is simple; however, the interpretation of electrocardiographic parameters is challenging. This is because the analysis may be biased by experimental settings, such as the type of anaesthesia, the strain or age of animals. Here, we aimed to review electrocardiographic parameters in rats, their normal range, as well as the effect of experimental settings on the parameters variation. Furthermore, differences and similarities between rat and human ECG are discussed in the context of translational cardiovascular research.

Keywords:

Rats; Cardiovascular system; Cardiac Electrophysiology; QT interval, QRS

Introduction

Electrocardiography (ECG) in humans has been introduced in 1903 by Willem Einthoven. Since then, it has become one of the most widespread diagnostic tools in clinical medicine. ECG recording reflects the electrical activity of the heart and may provide important insights into functional and structural characteristics of the myocardium. The physiological and pathological criteria of ECG recordings have been thoroughly described in multiple handbooks and research papers (Hall *et al.* 2011, Wagner *et al.* 2009).

Despite some differences, such as the lack of Q wave in most leads, (Driscoll 1981, Farraj *et al.* 2011) there are essential similarities between rat and human ECG (Sambhi and White 1960), (Fig. 1). Therefore, ECG in rats has been exploited in basic cardiovascular research dealing with the heart's performance under physiological conditions and in animal models of cardiovascular diseases.

Although the technique of ECG recordings is rather simple, the interpretation of the acquired data is challenging. First, in contrast to humans, the criteria of reference ECG parameters in rats have not been established. Second, there are significant differences in ECG parameters between the experimental studies in rats. The latter seems to result from different experimental settings, such as the age and strain of animals and the type of anaesthesia used (Table 1, 2).

Here, we aimed to review electrocardiographic parameters in rats, their range, as well as the effect of experimental settings on the parameters variation. The review is confined to Sprague Dawley (SD) and Wistar rats, as these are the two strains most commonly used in cardiovascular experiments.

Major ECG techniques

There are several invasive and non-invasive techniques that allow 1 to 12 channel ECG recordings in laboratory animals. Most studies use a limb lead II that is sufficient for the general analysis of ECG parameters in rodents (Farraj *et al.* 2011, Buschmann *et al.* 1980), whereas precordial leads are used to localize pathological processes such as myocardial ischemia (Krenek *et al.* 2009).

Invasive methods

Surface ECG recording is the most commonly used technique in anesthetised rats. To obtain a limb leads recording, the electrodes are placed under the skin of left and right forepaws and the tail. Additionally, unipolar leads can be positioned anteriorly at the midsternum (Normann *et al.* 1961). Advantages of this method include its simplicity, high quality of collected data and repeatability, while its main drawback is that measurements may be confounded by anaesthetics.

An ECG recording technique that escapes the effect of anaesthesia is telemetry. Telemetry transmitters are implanted subcutaneously in the interscapular region or in the abdominal cavity, whereas electrodes connected to the transmitters are placed subcutaneously on the dorsal surface of the xiphoid process and anterior mediastinum. Data from transmitters are gathered wirelessly by a receiver positioned outside the rat cage (Sgoifo *et al.* 1998). This enables measurements in freely moving rats for several weeks. The method provides data that are free of anaesthesia and stress-induced artefacts (Braga *et al.* 2011). However, the quality of the recordings may be compromised by movement of animals, displacement of the electrodes or inflammation at the site of electrode implantation.

An *in vitro* method for recording the electric activity from the isolated heart is the method introduced by the Langendorff in 1898. The heart is extracted form terminally anesthetized rat and placed into a perfusion apparatus. The heart is perfused with a perfusion fluid under physiological pressures, keeping the electromechanical work of the myocardium, functions of the valves and coronary blood flow. Advantages of this technique include a precise recording of the origin and amplitude of electrical events as well as possibility of concomitant evaluation of the coronary blood flow and contractility of

the myocardium. The advantages, however, are limited by the fact that the isolated heart is separated from physiological effects of humoral and nervous control (Skrzypiec-Spring 2007, Döring 1989).

The effect of anaesthesia on ECG

The choice of anaesthesia may significantly affect the results of experiments, as anaesthetics differ in their effects on cardiomyocytes and conducting system of the heart. For example, it has been found that inhalation anaesthetics may have an arrhythmogenic potential. Halotane, isoflurane, and enflurane have been shown to block Ca^{2+} channels and Na^{+}/Ca^{2+} exchange in cardiomyocytes (Mayo and Jamali 1999). Cardiotoxic effects have also been reported after parenteral anaesthesia. Urethane anesthetised rats show a significant depression of HR, whereas the effect is not observed in rats treated with pentobarbital and thiopental. Pentobarbital, however, was found to evoke ventricular arrhythmias. In contrast, thiopental was found to possess antiarrhythmic activity (Zorniak et al. 2010). Ketamine, another commonly used anaesthetic drug, apart from its anti-NMDA activity, interacts with cardiac voltage-sensitive Ca^{2+} channels that may also significantly affect the electrical activity of cardiomyocytes (Hirota and Lambert 1996, Baum and Tecson 1991), (Table 2).

Non invasive systems

An example of a non-invasive method of ECG recordings is dressing rats in a cotton jacket with two electrodes attached to its inner surface. Before wearing the coat, rats' skin must be shaved in anterior thoracic region. Measurements are performed in conscious rats placed in plastic restrainers (Pereira-Junior *et al.* 2010). Advantages of this technique include non-invasiveness, measurements in conscious animals and a significantly lower cost in comparison to telemetry. Nevertheless, restraint-stress and difficulties with placing the electrodes in the same position in different rats are significant limitations of the method.

Another method is a non-invasive ECG recording in conscious rats placed in a restrainer also referred as a tunnel. In this technique paws of the rat are placed on ECG sensors embedded in the tunnel floor.

After short adaptation period up to 6 lead ECG, lasting 30-60 minutes, can be obtained (Mongue-Din *et al.* 2007).

Electrocardiographic parameters

An action potential in the heart is generated in sinoatrial node and subsequently conducted through atrioventricular node, His bundle, His bundle branches and Purkinje fibres, finally reaching ventricular cardiomyocytes. A typical ECG tracing mirrors the repeating cycle of three major electrical events, including atrial depolarization (P wave), ventricular depolarization (QRS complex) and ventricular repolarization (T wave), (Fig. 1).

Heart Rate and RR interval

Heart rate (HR) represents the number of heart contractions over a specific period of time, most commonly 1 min (beats per minute, bpm). RR interval is the time between the consecutive R wave peaks. Under physiological conditions, HR can be calculated from RR interval according to the following formula: HR = 60/(R-R interval in seconds). In humans HR can also be calculated by measuring the time between the consecutive Q waves, while in rats HR is calculated using RR intervals only. This is because rat ECG lacks the Q wave in most leads and/or the Q wave may be difficult to locate, especially in noisy and low amplitude ECG.

Mammals have a wide distribution of resting RR interval. For an adult human, resting RR interval ranges from 0.6-1 s (HR ≈ 60 – 100 bpm) (Hall et al. 2011), whereas for matured rats RR interval is 118-251 ms (HR ≈ 239 - 508), (Table 1). In rats HR depends on age, and it has been found to increase during the first 4 weeks after the birth (Malfatto *et al.* 1990, Dickhout and Lee 1998). In newborn restrained Wistar rats, HR is 298-306 bpm and then reaches steady values of 429-473 bpm just before puberty (Malfatto *et al.* 1990). Therefore, in contrast to humans, there seems to be no clear negative correlation between HR and aging before puberty in rats. On the other hand, a decrease in HR with aging was found in postpubertal Wistar rats using chronic telemetry recording (Sgoifo *et al.* 1998).

HR seems to be strongly affected by the type of anaesthesia used. In SD rats anaesthetised with ketamine and xylazine mixture, light ether, urethane and pentobarbital heart rate was found to be 239-272 bpm (Regan *et al.* 2005, Regan *et al.* 2007), 340-508 bpm (Normann *et al.* 1961), 417-451 bpm (Lin *et al.* 1997), and 387-446 bpm (Sugiyama *et al.* 2005), respectively. HR in Wistar rats was reported as 242-336 bpm under ketamine and xylazine anaesthesia (Miranda *et al.* 2007), 290-378 bpm under light ether anaesthesia (Fraser *et al.* 1967), 357-452 bpm under urethane anesthesia (Buschmann *et al.* 1980), and 334-349 in rats anesthetised with pentobarbital (Ahmad *et al.* 2015).

The P wave

In ECG recording, the P wave reflects depolarization of the atria. In both humans and rats, physiological sinus rhythm is characterized by a positive deflection of the P wave in limb lead II, a negative deflection of the P wave in lead aVR, and the presence of QRS complex after every P wave. The lack of the P wave or its altered shape is present in various cardiac arrhythmias, the most common of which is atrial fibrillation.

Similarly to humans, atrial fibrillation in rats is characterized by the lack of the P wave (Haugan *et al.* 2004, Nattel *et al.* 2005). Although in humans the analysis of the length and shape of the P wave brings clinically important insights, in rats there is not enough experimental data to conclude form alterations in the P wave shape and length. However, Milliez and collaborators reported that the prolongation of the P wave may be associated with increased susceptibility to supraventricular arrhythmias in Wistar rats after myocardial infarction (Milliez *et al.* 2005).

PR interval

The PR interval, also referred to as the PQ interval as Q wave is not always present, reflects the propagation of depolarization from atria to the heart ventricles (Hoffman *et al.* 1960, Beinfield and Lehr 1968). The PR interval is determined by measuring the time from the beginning of the P wave until the beginning of the QRS or RS complex. The analysis of the length of PR interval is crucial in the diagnosis of atrioventricular blocks.

The PR interval in SD rats ranges from 38 to 70 ms and its length seems to be significantly affected by the type of anaesthesia. Namely, the PR interval was reported to be 38-44 ms in pentobarbital anesthesia (Sugiyama *et al.* 2005), 48-70 ms in light ether anaesthesia (Normann *et al.* 1961), 48-56 ms in urethane anaesthesia (Lin *et al.* 1997), 56-66 ms in ketamine combined with xylazine anaesthesia (Regan *et al.* 2005, Regan *et al.* 2007), and 52 - 60 ms in isoflurane anaesthesia (Hamdy and Brocks 2009).

In Wistar rats, PR interval was found to be 39 to 78 ms, and its length also varied dependent on the type of anaesthesia. Rats anesthetized with a mixture of ketamine and xylazine had the shortest duration of the parameter (39-57 ms) (Miranda *et al.* 2007). A longer PR interval was reported in rats under urethane (49-58 ms) (Buschmann *et al.* 1980) and ether anaesthesia (52-78 ms) (Fraser *et al.* 1967).

QRS complex

QRS complex is located between Q and S waves. Its duration shows the time of propagation of depolarization through the ventricles. The analysis of the length of QRS complexes provides important data on electrical activity of the heart. QRS narrowing can be seen in supraventricular arrhythmias, whereas wide QRS complexes reflect ventricular rhythms as well as disturbances of intraventricular conduction that can be seen in right and left bundle branch blocks, heart failure and myocardial ischemia. Wide QRS complexes were found after treating rats with several drugs, for example doxorubicin (Kelishomi *et al.* 2008), disopyramide (Król *et al.* 2015), and azithromycin (Atli *et al.* 2015).

Since Q wave is usually not detectable in rats, RS or Rs complexes are evaluated in rat ECG. Duration of RS complexes in SD rats under a light ether anaesthesia is 11.3-16.1 ms (Kelishomi *et al.* 2008), 12-15.7 ms in rats anesthetized with ketamine and xylazine (Regan *et al.* 2005), 20-22 ms in rats undergoing pentobarbital anaesthesia (Sugiyama *et al.* 2005), and 18.5-21.5 in rats under urethane anaesthesia (Badole *et al.* 2014).

QRS length in Wistar rats was found to be 14-16 ms (Buschmann *et al.*1980), 17-25 ms (Miranda *et al.* 2007), 18-19.6 ms (Ahmad *et al.* 2015), and 18-28 ms (Fraser *et al.* 1967) in rats anaesthetized with urethane, ketamine combined with xylazine, pentobarbital and ether, respectively.

ST segment

ST segment represents the time when the ventricles are depolarized and is defined as the time from the end of QRS complex to the beginning of T wave. It is isoelectric and lasts approximately 80 to 120 ms in humans. The evaluation of the parameter is essential in the diagnosis of myocardial ischemia and myocardial infarction. Therefore, in humans the criteria of significant changes, i.e. a depression or elevation of ST segment, have been thoroughly described (Wagner *et al.* 2009). Alteration of ST segment may also occur in other conditions such as channelopathies e.g. Brugada syndrome, intraventricular conduction blocks, water-electrolyte balance disturbances and others.

Studies in rats showed significant changes in ST segment in myocardial infarction (Chrastina *et al.* 2014) and in myocardial ischemia (Speechly-Dick *et al.* 1994), however, clear criteria of significant changes in ST segment have not been established. Some researchers evaluated the duration of ST in rats. In SD rats undergoing light ether anaesthesia the duration of ST segment was reported to be 12.3-18.1 ms (Kelishomi *et al.* 2008), while in Wistar rats anaesthetized with ether it was 9.58-14.8 ms (Dragojevic-Simic *et al.* 2004). However, the length of ST segment is of limited importance for ECG analysis. First, it is difficult to detect ST segment in rat ECG as the T wave often rises in continuity with the S wave (Sambhi and White 1960, Jensen *et al.* 1984) (Fig. 1). Second, the prolongation of ST segment lengthens QT (RT) intervals. Therefore, it is more convenient to analyse the two latter parameters rather than ST segment.

T wave

T wave reflects repolarization of the ventricles. The T wave has a positive deflection in the majority of leads including limb lead II. In humans, high voltage/peaking of T wave may be found in hyperkalaemia, in early phases of acute myocardial infarction and in patients with Long QT

Syndrome. A decreased amplitude of the T wave may be present in hypokalaemia, whereas a negative deflection of the T-wave may result from myocardial infarction and pulmonary embolism.

Rat ECG shows the upright T wave in limb lead II. Inversion of the parameter in rat ECG was reported after injection of isoproterenol and myocardial infarction (Hill *et al.* 1960). Hypokalaemia in rats was found to produce prolongation and decrease in voltage of T wave (Akita *et al.* 1998).

QT interval

QT interval describes the time from the Q wave to the end of the T wave. In rats, this parameter is usually measured from the onset of Rs complex to the end of T wave, due to difficulties with detecting Q waves. QT interval represents the time of depolarization and repolarization of ventricular cardiomyocytes. Pathological duration of this parameter indicates disturbances in electrical activity of the heart due to an intrinsic heart disease or toxic effects of exogenous compounds. For example, QT interval may be prolonged by hypokalaemia, ischemia, myocardial infarction, channelopathies, including Long QT syndrome. Finally, multiple drugs may produce prolongation of QT interval leading to ventricular tachyarrhythmia, including torsade de pointes. Therefore, the prolonged QT interval is considered to be a useful indicator of drug cardiotoxicity (Hanada *et al.* 1999, Roden *et al.* 2004). Interestingly, sex-related differences have been observed in susceptibility to drug-induced arrhythmias in both humans and laboratory animals (Makkar *et al.* 1993, Liu *et al.* 1999).

A number of studies have shown that cardiotoxic drugs prolong QT interval in rodents, and ECG recording in rats has been used as a screening tool in cardiotoxicity studies (Hanada *et al.* 1999, Ohtani *et al.* 1996, Król *et al.* 2015). However, it needs to be stressed that the translation of the results of those studies to humans has limitations. This is because rats' hearts do not express the human Ether-à-go-go-Related Gene (hERG), whereas drugs cardiotoxicity is strongly associated with blocking of hERG-related potassium channels (De Bruin et al. 2005). However, the rats' hearts express a variant of Ether-à-go-go-Related Gene (rat ERG, also known as Kcnh2) (Matus *et al.* 2015), which may play a role in drug induced cardiotoxicity, but further research is needed to support this notion.

A prolonged QT interval in rats has also been found in hypokalaemia (Akita *et al.* 1998) and myocardial infarction (Mackiewicz *et al.* 2014). Furthermore, as with other ECG parameters, QT length seems to be affected by the type of anaesthesia. In SD rats it was found to be 50-70 ms (mean 53.6 ms) under light ether anaesthesia (Normann *et al.* 1961), 60.6-62.5 ms under urethane anaesthesia (Hanada *et al.* 1999), 63-74 ms under pentobarbital (Sugiyama *et al.* 2005), and 64.1-75.9 ms under isoflurane anaesthesia (Hamdy and Brocks 2009).

In conscious Wistar rats QT length in telemetric recording was reported to be 69-71 ms (Baillard *et al.* 2000), 57-75 ms in rats under ether anaesthesia (Fraser *et al.* 1967), 69-76 ms in rats under pentobarbital anaesthesia (Ahmad *et al.* 2015), and 75-95 ms in rats under ketamine and xylazine anaesthesia (Miranda *et al.* 2007).

Corrected QT interval

It is well-established that the length of QT interval in humans depends on HR. In general, an increase in HR shortens QT as the ratio of the lengths of systole and diastole increases. Therefore, a corrected QT interval (QTc) that takes into account changes in HR is often used as a more objective parameter of depolarization and repolarization of ventricles (Funck-Brentano and Jaillon 1993, Ahnve 1985).

Although in rats HR is about 5-6 times higher than in humans, there is no consensus on whether there is a need to adjust QT to HR (Hayes *et al.* 1994, Kmecova and Klimas 2010). The majority of rat studies use one of several formulas to calculate QTc (Hamdy and Brocks 2009, Baillard *et al.* 2000).

One of the adjustments of QT to HR is the Bazett's formula, which was presented in 1920 after the analysis of ECG changes associated with exercises. The formula is based on dividing QT interval by the square root of RR-interval, ($\frac{QT}{\sqrt{RR}}$), (Bazett 1920). Due to its simplicity, it is a very useful tool in both at the bedside and experimental research. However, it seems inappropriate for HR exceeding 100 bpm (Molnar *et al.* 1996). In Wistar rats, QTc calculated according to Bazett's formula was reported to be 133-173 ms in ether-anaesthetized rats (Fraser *et al.* 1967), and 152-156 ms in telemetry recordings in conscious rats (Baillard *et al.* 2000).

Another method for calculating the QTc is Fridericia's formula, which is as follows: QT interval divided by cube-root of RR-interval, ($\frac{QT}{\sqrt[3]{RR}}$). Some researchers suggest that equation may be the preferable way of correcting the QT (Schwartz and Wolf 1978). QTc interval calculated by Fridericia's formula in isoflurane anaesthetized Sprague-Dawley rats was found to be 119-141 ms (Funck-Brentano and Jaillon 1993).

The profound analysis of correlation between QTc and QT, dependent on HR, was performed by Kmecova and Klimas. Their research suggest that QTc interval should be calculated according to adjusted Bazett's formula, namely QTc = $\frac{QT}{\sqrt{\frac{RR}{f}}}$, where f is the normalization factor according to the basal RR duration in rats, that is 150ms (Kmecova and Klimas 2010).

Conclusions

Rat electrocardiography is an important investigational tool in experimental cardiology. However, the interpretation of electrocardiographic parameters is problematic. In contrast to human studies, the criteria to distinguish significant from insignificant changes in ECG parameters in rats have not been established. This is due to a relatively small number of experimental studies, as well as significant variations in electrocardiographic parameters between the studies. The latter is likely caused by differences in rat strains and anaesthetics used. Therefore, there is a need for more studies, preferably employing measurements in conscious rats. In the meanwhile, the interpretation of ECG in rats should always take into account the effect of experimental settings, especially anaesthesia and the strain of rats.

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Table 1. Comparison of ECG parameters between Sprague-Dawley and Wistar rats.

	HR (bpm)	PR (ms)	QRS (ms)	QT (ms)	QTc (ms)	ST (ms)
Sprague-Dawley	239 – 508	38 – 70	12 – 22	50 – 75.9	119 – 141[1]	12.3 – 18.1
Wistar	242 – 452	39 – 78	14 – 28	57 – 95	133 – 173[2]	9.5 – 14.8

Heart rate in beats per minute (bpm), other parameters in milliseconds (ms). [1] – QTc calculated by Fridericia formula, [2] - QTc calculated by Bazett's formula.

Table 2. The effect of anaesthetics on ECG parameters in Sprague-Dawley and Wistar rats.

Strain/anaesthetics	HR (bpm)	PR (ms)	QRS (ms)	QT (ms)
Sprague-Dawley				
light ether	340 – 508	48 – 70	11.3 – 16.1	50 – 70
ketamine and xylazine	239 – 272	56 – 66	12 – 15.7	–
urethane	417 – 451	48 – 56	18.5 – 21.5	60.6 – 62.5
pentobarbital	387 – 446	38 – 44	20 – 22	63 – 74
Wistar				
light ether	290 – 378	52 – 78	18 – 28	57 – 75
ketamine and xylazine	242 – 336	39 – 57	17 – 25	75 – 95
urethane	357 – 452	49 – 58	14 – 16	–
pentobarbital	334 – 349	–	18 – 19.6	69 – 76

Heart rate in beats per minute (bpm), other parameters in milliseconds (ms).

Fig. 1. Original recording of human (a) and Wistar rat (b) ECG, II limb lead. RR interval in humans in seconds, in rats in milliseconds. Q waves and ST segments in rats are difficult to detect.