Extrapotentials and allorhythmis as an expression of experimental parasystole

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Key words: heart arrhythmias, parasystole, action potentials of cardiomyocytes.

Summary. The aim of the study was to investigate the dynamics of experimental parasystole taking into consideration the peculiarities of recurrent arrhythmias recorded in clinical settings.

Material and methods. The experiments were conducted on isolated right atria of seven chinchilla rabbits. Parasystolic arrhythmias using periodical one-site electrostimulation were provoked in one atrium, where the sinus node was not affected, and in two atria with the spontaneous low value activity of pacemakers. The parasystolic arrhythmias by the dual-site periodical pacing were provoked in four atria, in which the spontaneous activity had disappeared, while the membrane potential of cardiomyocytes remained at the level of 70 to 80 mV.

Results. The parasystolic arrhythmias of the shape of single extrapotentials were obtained in atria when the periods of excitation impulses were within the limits of 0.9–1.2 s, and the differences between these periods being relatively small (0.04–0.2 s). The increase of these differences resulted the various allorhythmias. In cases of single extrapotentials, the recurrence periods of arrhythmias reached 5.6–29 s; while in cases of allorhythmias they shortened to 2.4–4.8 s.

Conclusion. The parasystoles in isolated atria of rabbits can be induced by two competitive excitation sources. They may manifest themselves through single extrapotentials or allorhythmias, whose form depends on the duration of the periods of excitation impulses, the difference between these durations, as well as on effective refractory periods of atrial cardiomyocytes. The determination and evaluation of the recurrence period of these arrhythmias can serve in any given clinical situation as a supplementary criterion.

Introduction

One of the most common manifestations of heart rhythm disorders is extrasystole. The extrasystoles can periodically arise after various numbers of rhythmic heartbeats. This is the case when allorhythmis (bigeminy, trigeminy, quadrigeminy) are diagnosed in clinical settings. Only the type of bigeminy when the duration of ECG R-R intervals continuously change usually is referred to as a parasystole. Such parasystole is caused by a second automatic rhythm source existing simultaneously with a normal sinus node rhythm. According to the prevailing opinion the parasystole is not a common heart rhythm disorder (1). Recent publications show that parasystole can be obscured by other types of rhythm disorders, thus making it difficult to diagnose in a clinical situation (2, 3). For the above-mentioned reasons, we have designed the experiments for the verification of the hypothesis that the parasystole can be concealed by single extrasystoles or allorhythmis. We also strived to establish possible sources of parasystole in the experiments. However, we did not observe visual differences between parasystoles provoked by using the different excitation sources. The detailed test was not carried out because the appearing of these parasystoles in atria was induced by diverse periods of excitation impulses.

In our previous article we showed that the interaction of two excitation sources in rabbit isolated right atrium have resulted in the change of dynamics of the cardiomyocytes action potentials (AP) periods, which
are similar to the superposition dynamics of two excitation generators (4). Bigeminal rhythm type parasystole with the continuously lengthening duration of AP periods, transforms into intervals of tachycardia, then again into bigeminy, but with the continuously shortening duration of AP periods, which is followed by interval of rhythmical AP with normal contraction frequency (4). This pattern is periodically recurrent. It was established that the duration of the recurrence periods of parasystole ($T_p$) is related to the duration of the periods of excitation stimuli obtained from both excitation sources and to the effective refractory period ($T_{ref}$) of cardiomycocytes. In this article we discuss the dynamic changes in experimental parasystole from single extrapotentials (ExP) to allorhythmias such as bigeminy, trigeminy or quadrigeminy.

**Aim.** The aim of the present study was to investigate the dynamics of experimental parasystole taking into consideration the peculiarities of recurrent arrhythmias recorded in clinical settings, and to search for new criteria for more precise diagnostics of parasystole.

**Material and methods**

The experiments were conducted on isolated right atria of seven chinchilla rabbits. The isolated atria were immediately perfused with Tyrode’s solution at a rate of 2 ml/min and temperature 36.7–37°C. The solution consisted of the following components (mM): NaCl 136.9, KCl 3.0, CaCl$_2$ 2.5, MgCl$_2$ 1.05, NaH$_2$PO$_4$ 1.2, C$_6$H$_{12}$O$_6$ 5.5, NaHCO$_3$ 24.0. During continuous saturation of 95% O$_2$ and 5% CO$_2$, the pH of solution was maintained at 7.2–7.4. The intracellular registration of cardiomycocyte AP 30 min after atrium isolation was initiated. Glass microelectrodes for registration of AP were filled with 3 M KCl and had impedance lower than 5 MΩ. In three atria one-site periodical stimulation was performed; in one atrium – when intact sinus node was not injured, and in two atria – after sinus node isolation when the spontaneous activity of low value pacemakers remained. In four atria, in which the spontaneous activity had disappeared, while the membrane potential remained 70–80 mV, parasystole using dual-site periodical pacing was provoked. PACing impulses were 0.5 V higher than diastolic threshold at the beginning of the experiment. Later on, only the periods of electro-stimuli were changed. The periods of electro-stimuli ($T_1$ and $T_2$) of the two excitations sources were changed. The periods of repetitive cycle of parasystole ($T_p$) and $\Delta T$ (differences between $T_1$ and $T_2$) were measured during the experiments.

The duration of $T_p$ later on was compared with the theoretically calculated duration of period of the parasystolic repetitive cycle ($*T_p$), based on the formula of the interaction between periodic excitation impulses of two generators:

$$*T_p = T_1 \cdot T_2 / [T_1 - T_2]$$  \hspace{1cm} (1)

Where $T_1$ and $T_2$ were known periods of excitation impulses.

The duration of effective refractory period ($T_{ref}$) was determined according to the shortest period between AP in $T_p$.

The experiments were performed in accordance with the requirements of the European Ethics Committee for Laboratory Animal Science. The approval for experiments was issued by Lithuanian Commission of Ethics of Handling of Laboratory Animals at the State Food and Veterinary Agency (No. 0027, February 14, 2001).

**Results**

Single ExP type arrhythmias were induced by various excitation periods of the electro-stimuli in seven right atria. There was no significant difference between the types of parasystole induced by distinct techniques: similar arrhythmias arose as the result of interference of two competitive excitation sources. However, in order to induce parasystole when AP are generated in the atrium itself, the duration of the periods of external stimuli has to be a little longer than that of the periods generated by the atrial pacemaker. When periods of external stimuli were shorter than those of the atrial pacemaker, parasystole was not induced in any of the cases; the rhythm of external stimuli was pressed.

The bigeminal parasystolic rhythm was evoked in case of spontaneous activity of atrium, when the periods of cardiomycocytes AP were 1.35 s and electro-stimuli were given every 1.66 s. Each ExP arisen every other AP, when effective refractory period of AP was terminated. The duration of compensatory pause at ExP to following AP, depended on feeding moment of electro-stimuli and after effective refractory period of AP of the cardiomycocytes. The latency of the ExP appearance was 0.014–0.021 s (Fig. 1, a). The single ExP type parasystole induced together by two excitation sources was the following: periodic electro-stimuli delivered with cycle length of 1.19 s when the spontaneous sinus pacemaker rhythm of 1.06 s period. In such case, at $T_p = 9.6$ s single ExP, which arose with latency of 0.021 s, was registered after each eighth AP. The single ExP type parasystole was also induced by two electropacemakers at rhythm periods 0.9 s and 1.02 s or 1.0 s and 1.2 s. In the latter case, single ExP
was recorded after each fifth AP when the recurrent parasystole period length \( T_p \) was 7.6 s. The responses to stimuli (the rise of AP) appeared after 0.014 s.

When the single ExP type parasystole was induced at electro-stimuli periods 1.4 s and 1.2 s (as shown in Fig. 1, b), seven AP were registered during \( T_p \) in this mode. The parasystole of single ExP type arrhythmia was converted to quadrigeminy with \( T_p = 6 \) s, when the length of the periods of electro-stimuli was prolonged up to 1.5 s (Fig. 1, c). Eight AP were recorded during this \( T_p \). When the period of the delivered electro-stimuli was increased to 1.6 s, the trigeminy (Fig. 1, d) with \( T_p = 4.8 \) s turned into bigeminy. The \( T_p \) of cardiomyocytes was determined according to the shortest AP period of \( T_p \). The significant deviations in \( T_p \) were noticed during one type parasystolic arrhythmia.

The comparison of the duration of \( T_p \) (measured using different excitation periods \( T_1 \) and \( T_2 \)), and the theoretically calculated duration of \( *T_p \) for these \( T_1 \) and \( T_2 \), is shown in Table 1. \( T_p \) values correspond well to the calculated \( *T_p \) values and the maximum difference between its quantity does not exceed 4%. The parasystole of single ExP type arrhythmias was obtained when the periods of excitation sources were within the limits of 0.9–1.2 s, however differences between these periods were relatively small (0.04–0.2 s). After increasing this difference to 0.3–0.35 s, various allorhythmias or couplet type arrhythmias appeared. The recurrence periods of single ExP type parasystole reached 5.6–29 s, but in cases of allorhythmias they amounted only to 2.4–4.8 s.

The type of parasystole was dependent on the differences in time gap between the impulses of excitation sources (\( \Delta T \)). The transition from single ExP to arrhythmias of quadrigeminy, trigeminy and bigeminy types occurred with the increase in \( \Delta T \). In all cases \( T_p \) time shortened as the difference between the cycle length of pacemaker impulses and the cycle length of electro-stimuli increased. Considerable shortening of \( T_p \) was observed when the stimuli period of one excita-
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Fig. 2. Relationship between $T_p$ and $\Delta T$ in the isolated atrium of a rabbit in case of experimental parasystole

$T_1=1.0$ s was maintained. $\Delta T$ was gradually increased by changing the pacing periods of the competitive source. This finding clearly indicates why periodic recurrent parasystolic arrhythmias could be very difficult to diagnose in clinical situation, especially in cases when the duration of $T_p$ is long, while ECG recording time is relatively short.

Fig. 2. Relationship between $T_p$ and $\Delta T$ in the isolated atrium of a rabbit in case of experimental parasystole

We observed that the single extrasystoles in the clinic, in 24-hour Holter monitoring of patient R. M. (diagnosis – extrasystole, due to unknown genesis), also frequently exchange with various types allorhythmias: trigeminy, bigeminy (Fig. 3, a). During Holter monitoring the dynamics of extrasystoles, allorhythmias or couplet type arrhythmias (Fig. 3, b) of this

Fig. 3. 24-hour Holter monitoring of patient R. M.

a – the histograms represent the frequency of all arrhythmias together and couplet, bigeminy and trigeminy arrhythmias separately according to data of patient R. M. during 24-hour Holter monitoring; b – fragment of ECG of this patient, in which the couplet type arrhythmia is seen. Bottom – the durations of R-R intervals (ms).
The experimental couplet type arrhythmia was induced when $T_1$ shortened by only 0.1 s later on when trigeminy type arrhythmia was induced (when $T_1$ = 1.5 s, $T_2$ = 1.2 s and $T_{ref}$ did not exceed 0.4 s). Holter monitoring showed that the beginning of the couplet type arrhythmias is also related with the trigeminy type arrhythmia.

**Discussion**

The diagnosis of parasystole in hospital settings remains a problematic and complex task because other types of arrhythmias frequently mask this disorder. Therefore the search for new methods and criteria for diagnosis of parasystole in clinical situations still continues (5). Often it is difficult to differentiate the parasystole from ordinary extrasystole as shown by S. Kinoshita et al (6). It is well known that the recurrent sinus bigeminy in case of parasystole could be obscured by the paroxysmal tachycardia or even transformed into ventricular fibrillation in some clinical situations (7–10).

It is known that the ectopic pacemaker with the highest frequency of excitation impulses determines the heart rate. These pacemakers can be suppressed by some chemical substances and higher doses of antiarrhythmic drugs (11). The causes of parasystole may also include changes in the extracellular concentration of potassium and other ions in heart tissues, pathological reflexes or delayed impulses from excitation sources, or changes in the effective refractory period of cardiomyocytes. Our experimental data leads to the presumption that parasystole could be a more frequent rhythm disorder than usually diagnosed in clinical settings.

Our previous data shows that the AP dynamics in case of parasystole parallels with the superposition phenomenon of competition impulses generated by two pacemakers with different frequencies (4). The experiments showed that the parasystolic rhythm is dependent on the frequency of the impulses of two excitation sources. One $T_p$ can include the interval of the rhythmical lower frequency AP, followed by the bigeminal AP interval, which passes into the tachycardial AP interval, and the latter again turns into the bigeminal interval (4).

The central nervous system or humoral factors have no influence on the isolated rabbit atrium, thus making it easier to interpret the results of our experiments. In the experimental parasystole model the rhythm periodically becomes stable as one of two pacemakers is blocked because his stimuli get in a refractory stage of cardiomyocytes. Allorhythmias such as single ExP, trigeminy and bigeminy are near arrhythmias that in the presence of slight changes of external factors can turn into each other (Fig. 1, b–d). It is known that $T_p$ is changing and is dependent on various external conditions (12, 13). We established that $T_p$ could be quite long (Fig. 2). The parasystole can be masked by the rhythm disturbances of other type, particularly when the registered ECG is relatively short. The measuring of $T_p$ duration in several recurrent cycles of arrhythmia and the comparison this duration with $T_{ref}$ can be useful for interpretation of the arrhythmias genesis. In any given clinical situation when the recurrent single extrasystoles, allorhythmias or couplet type arrhythmias occur periodically or often, time to time turning from one type into another, it is useful to verify whether it is parasystole or not. Should this be the case, it is necessary to calculate $T_p$ using the dual excitation

**Table.** Dependence of different type experimental parasystolic arrhythmias at different $T_1$ and $T_2$ ($T_{ref} < 0.4$ s)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Cases of the single ExP</th>
<th>Cases of the quadrigeminy</th>
<th>Cases of the trigeminy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>every 24–25 AP</td>
<td>every 7 AP</td>
<td>every 5 AP</td>
</tr>
<tr>
<td>$T_1$</td>
<td>1.12</td>
<td>1.06</td>
<td>0.9</td>
</tr>
<tr>
<td>$T_2$</td>
<td>1.08</td>
<td>1.19</td>
<td>1.02</td>
</tr>
<tr>
<td>$\Delta T$</td>
<td>0.04</td>
<td>0.13</td>
<td>0.12</td>
</tr>
<tr>
<td>$T_p$</td>
<td>29</td>
<td>9.6</td>
<td>7.6</td>
</tr>
<tr>
<td>$*T_p$</td>
<td>30.2</td>
<td>9.7</td>
<td>7.6</td>
</tr>
</tbody>
</table>

$T_p$ – was measured. $*T_p$ – was calculated for its cases. All values are in seconds.
sources competition formula. For that reason the periods of impulses of both excitation sources are measured at the moment when two stimuli match and immediately after this. The evaluation of $T_p$ for this purpose can serve as a supplementary criterion. We propose also as criterion to evaluate the spectrum of R-R intervals on ECG for detection of accessory excitation sources.

We believe that in a clinical situation during the Holter monitoring, the $T_p$ estimation is desirable. Having recorded the frequent changes in types of arrhythmia in the clinical situation, it is advisable to investigate the patient for possible existence of parasystole using Holter monitoring. Besides the mentioned arrhythmia, Holter monitoring can be of importance revealing the frequency of the couplet type arrhythmias (Fig. 3) and their relationship with other arrhythmias.

Nowadays many cardiologists believe that the patient is random reorganisation and immediately after this. The evaluation of $T_s$ can be considered as diverse types of parasystole.

**Conclusions**

The experimental parasystoles in isolated atria of rabbits can be induced by two competitive excitation sources that can be either pacemakers of atrium or external stimuli. These parasystoles may manifest themselves through single ExP or various arrhythmias whose form depends on the values of the periods of excitation impulses, the difference between these values, as well as on effective refractory period of atrium cardiomyocytes.

In cases analogous arrhythmias occur in any given clinical situation, it would be useful to verify whether there is any parasystole or not. For this purpose, the evaluation of the recurrence period of arrhythmias can serve as a supplementary criterion.

**Experiments with extrapotentials and allorhythmias as an expression of experimental parasystole**

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**Raktažodžiai:** širdies aritmijos, parasistolija, kardiomyocitų veikimo potencialai.

**Santrauka. Darbo tikslas.** Eksperimentinių parasistolinių aritmijų dinamikos tyrimas atsižvelgiant į pasikartojančių aritmijų ypatinges bei naujų kriterijų tikslėms parasistolijos diagnozavimui paieška. Eksperimentai atlikti su šinšių veisles triušių izoliuotais dešiniaisiais priešsūriškiais. Parasistolės aritmijos sukeltos stimuliuojant vieno stimuliatoriaus periodiniai impulsais: viename priešsūriškyje su nepažeistu sinusiniu mazgu ir dviejose priešsūriškyse po sinusiniu mazgo atskyrimo išlikus žemesnį lygio ritmo vedlo spontaniškiam aktyvumui, taip pat stimuliuojant dviejų stimuliatorių periodiniai impulsai keturis priešsūriškį, kuriuo ritmo vedlį spontaniškio aktyvumo nebuvo, bet kardiomyocitų membraniniu potencialiu lygis siekė 70–80 mV.

**Rezultatai.** Pavienių extrapotencialių parasistolės aritmijos sukeltos sužadinimo šaltiniai periodams esant 0,9–1,2 sek. ribose ir esant sančykinai nedideliam skirtumui (0,04–0,2 sek.) tarp šių periodų. Aritmijos bei „couplet“ tipo aritmijų atsirasdavo šį skirtumą padidinus iki 0,3–0,35 sek. Pavienių extrapotencialių atvejais aritmijų pasikartojojo periodai siekė 5,6–29 sek., o aritmijų atvejais sutrumpėdavo iki 2,4–4,8 sek.

**Išvados.** Eksperimentinės parasistolės triušio izoliuotame priešsūriškyje gali būti sukeltos dviem konkuruojančiais sužadinimo šaltiniais, kuriais gali būti savi ritmo vedliai arba išoriniai stimuli. Šių parasistolijų priešsūriškio gali rastis pavieniais extrapotencialiais ir aloritmijomis, kurių pavidalas priklauso nuo sužadinimo impulsių periodų reikšmių, skirtumo tarp periodų bei kardiomyocitų efektyvaus refrakterinio periodo. Jei pacientams randama besikartojančios analogiško pavidalo ir dinamikos, bet neaiškios genezės aritmijų, būtų tikslina patikrinti, ar nesama parasistolės. Kaip papildomas kriterijus tam – aritmijų pasikartojojo periodo įvertinimas.

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