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P-R interval in porcine model of chronic tachycardia-induced cardiomyopathy

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Abstract

The aim of the study was to assess the atrioventricular conduction in the model of porcine pacing induced tachycardiomyopathy. Fifty-one swine were examined: 27 were paced and 24 served as a control group. Every 4 weeks, the animals were anaesthetised for 1 h and an ECG Holter was performed. Thirty minutes after the onset of anaesthesia, P-R and R-R intervals were measured. Each result was assigned to the subgroup according to the animal's weight and the presence or absence of previous pacing. P-R interval was longer in animals after at least 4 weeks of rapid ventricular stimulation than in adjusted group of the animals according to the body mass. Multivariate analysis has showed that longer P-R interval was related to male gender, higher body mass, slower heart rate, and history of previous pacing. Chronic ventricular pacing led to the slowing of atrioventricular conduction. The presence of differences in the duration of R-R intervals between groups was only found in swine weighing 120-139 kg. The R-R interval was shorter in paced animals, whereas PR interval was longer in that group, indicating that PR prolongation is related to electrical or structural remodelling of the cardiac conductive tissue but not increased sympathetic nervous system activity, which is expected to produce corresponding changes in PR and R-R intervals.

Key words: pigs, heart, electrical remodelling, tachycardiomiopathy.

Introduction

P-R interval represents the time since the onset of atrial depolarisation to the onset of ventricular depolarisation. P-R interval's duration depends on the sinoatrial node (SAN), intraatrial, interatrial, atrio-ventrricular node (AVN), and His-Bundle conduction. P-R interval is longer in adults than children and in men than women due to a larger body surface area and heart size, and is prolonged in hypothyroidism (6, 22, 27). P-R interval is also longer in older people due to changes related to ageing (4, 28), in patients with a slower heart rate (19), and in athletes in comparison to sedentary men. Genetic factors also have an influence on the P-R interval duration (9, 10, 16). Bigger animals have a longer P-R interval than the smaller ones (17, 20). Elongation of P-R interval can be obtained by either an increase in vagal activity and/or a decrease in sympathetic activity (11, 14, 25). P-R interval duration may lengthen in a wide range of pathological states: disturbances of water and electrolyte balance, hormonal imbalance, and during antiarrhythmic therapy (5, 12, 25). The other cause of P-R interval prolongation may be electrical remodelling due to rapid rhythms, both spontaneous, and pacing induced.

The electrical remodelling seen during rapid ventricular pacing is revealed as a prolongation of the repolarisation process. However, electrical remodelling

in cardiac automaticity and the conduction system in patients with pacing induced tachycardiomyopathy is less known.

The aim of the study was to assess atrioventricular conduction in a model of porcine pacing induced tachycardiomyopathy.

Material and Methods

Animals and design of experiment. The study was performed on domestic white swine, which were investigated as a model of porcine pacing induced tachycardiomyopathy. The details of the study design have been described elsewhere (21). Only animals weighing at least 100 kg were included in this study. In total, 51 swine were used: 27 were paced and 24 served as a control group.

Every 4 weeks, the animals have been anaesthetised for 1 h and an ECG Holter was performed. There were 56 examinations of animals, which were not chronically paced and 40 examinations of animals, which were paced for at least 4 weeks before the examination. In some animals, the examination was performed again after a set time. Therefore, the number of animals was lower than the number of observations separated by at least one month. The animals were fasted 12 h before the examination. The pigs were premedicated by intramuscular injection of a mixture of medetomidine hydrochloride (Cepetor, CP-Pharma Handelsges) 0.02 mg/kg, midazolam (Midanium 5 mg/mL) 0.1 mg/kg, and ketamine hydrochloride (Bioketan, Vetoquinol Biowet, Poland) 8 mg/kg. Anaesthesia was continued by bolus injection of propofol (Propofol 1% MCT/LCT Fresenius) at a dose of 2 mg/kg.

P-R and R-R intervals were measured 30 min after the beginning of the anaesthesia in all animals. Within both groups, the animals were divided into three subgroups taking into account their body mass at the examination.

Statistical analysis. Quantitative variables were presented as mean and standard deviation and compared with analysis of variance. In cases of significant interactions, *post hoc* intergroup comparisons were performed using the least significant difference test with the Bonferoni correction of P value.

Categorical variables were presented as numbers and percentages, and compared with chi^2 test. The variables between the experimental and control groups were compared. Since only few animals had examinations in all periods, and also taking into account the small number of animals, all examinations were grouped into group 1 and group 2. Results of the examinations performed after chronic pacing were grouped in group 1, and those, which were not preceded by chronic pacing in group 2. This approach has enabled a comparison among the studied time points.

The multivariable linear regression analysis was used to assess the relation between the P-R interval duration and the heart rate, body mass, male gender, and chronic pacing.

Receiver-operator curve (ROC) analysis was used to calculate the best cut-off point of the P-R interval to predict chronic cardiac pacing.

A classification and regression tree (CART) analysis was used to find other than chronic pacing predictors of the P-R interval duration above that cut-off point. $P < 0.05$ was regarded as significant.

Results

A total of 96 measurements were performed. Table 1 shows the number of measurements and the average of the electrocardiographic parameters in animals of different body weight.

In all body weight subgroups, the PR interval was longer in group 1. It was found that PR intervals were longer in paced that in control animals in each subgroup specified according to the body mass. R-R intervals did not differ between groups with the exception of the groups weighing 120-139 kg in which R-R interval was shorter in paced animals.

Table 1. P-R and R-R interval in animals in body weight subgroups

	Group 1 (before examination the animal was paced at least 4 weeks)			Group 2 (before examination the animal was not chronically paced)		
Body weight (kg)	100-119	120-139	Over 139	100-119	120-139	over 139
N	7	10	23	19	14	23
P-R (ms)	188 ± 22*	184 ± 18*	206 ± 31*#	147 ± 18	151 ± 32	167 ± 23$
R-R (ms)	758 ± 116	735 ± 134*	812 ± 148	748 ± 97	850 ± 134	843 ± 131

Intergroup difference between subgroups belonging to the same weight category
* - $P < 0.001$ group 1 *vs* group 2 of the same weight range
Intragroup differences within the same group between different weight category
- $P < 0.01$ *vs* the group of the weight range 120-139 kg
$ - $P < 0.01$ *vs* the group of the weight range 100-119 kg

Table 2. The results of multivariate linear regression analysis

	BETA	St error Beta	b	St error b	P
Male gender	0.33	0.08	22.6	5.3	<0.001
Weight	0.36	0.08	0.4	0.1	<0.001
Chronic pacing	0.64	0.06	43.2	4.3	<0.001
R-R interval	0.30	0.07	0.1	0.0	<0.001

BETA- the standardised regression coefficients
St the error beta- standard error beta
b –the raw regression coefficients
St error b- the standard error of raw regression coefficient

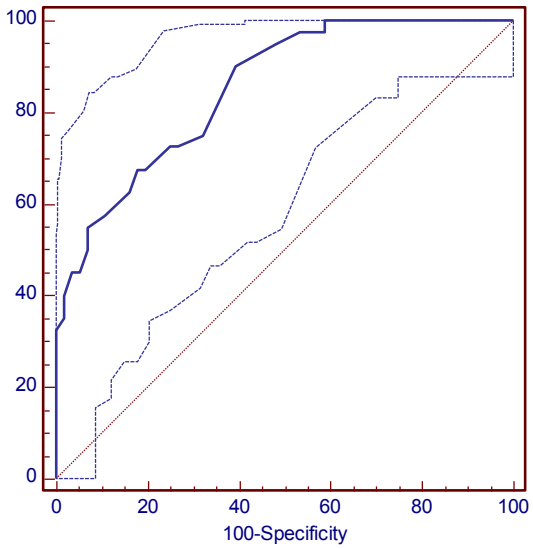


Fig. 1. ROC analysis finding the best cut off value for P-R interval for examinations preceded by and not preceded by chronic pacing

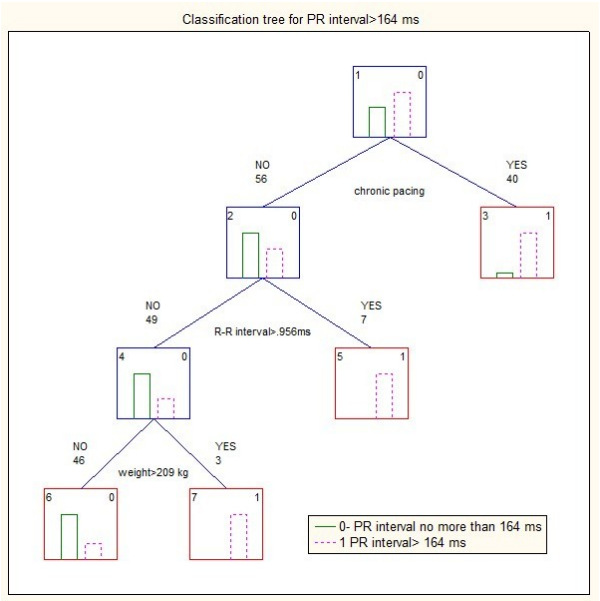


Fig. 2. CART analysis

Multivariable linear regression analysis. The multivariate linear regression analysis revealed that P-R interval duration was related to chronic pacing, higher weight, male gender, and longer R-R interval duration. The results are presented in Table 2.

Receiver -operator curve analysis. The cut off point of the P-R interval duration, which was set to discriminate the animals with and without chronic pacing, was 164 ms with sensitivity 90% and specificity 60.7%.

CART analysis revealed that a longer P-R interval was related to chronic pacing. In control group the longer P-R interval was related to body mass above 209 kg and slower heart rate.

Results of CART analysis are presented in Fig 2. P-R interval longer than 164 ms was related to chronic pacing, as well as a weight over 209 kg or R-R interval longer than 908 ms in the group without chronic pacing. Positive predictive value (PPV) of obtained algorithm was 79% and negative predictive value (NPV) - 94%.

Discussion

The first finding of the study was that P-R interval lengthened after 4 weeks of rapid ventricular stimulation and later slightly increased due to further growth of animals.

The multivariable regression analysis revealed that a longer P-R interval was related to male gender, higher body mass, slower heart rate, and chronic pacing.

The relationship between P-R interval duration and the body mass and gender is corresponding with the data from literature; however, P-R interval elongation due to ventricular pacing merits further evaluation. A heart failure is related to the sympathetic nervous system activation, which is supposed to shorten the P-R interval thus its elongation seems to be related to electrical or structural remodelling. An example of an adrenergic stimulation and consequent acceleration of atrioventricular conduction is P-R interval shortening during the hypoglycaemic clamp, exercise, and tilt testing (2, 13, 32).

The study did not aim at explanation of the causes of PR interval prolongation in paced animals. The future studies should be designed to explain it. It can be

presumed that the observed electrical remodelling may be caused by the retrograde conduction of the electrical activity or deleterious effect of catecholamines, the levels of which are increased in pacing induced heart failure. Stambler *et al.* (26) reported that inducibility of atrial tachyarrhythmias was increased, the atrial refractory period was prolonged, and atrial cells were delayed after depolarisations in animals with rapid ventricular pacing.

An electrical remodelling is defined as the process of the changing cardiac cells' electrical properties. It results in alterations in refractoriness, conductance, or automaticity. The most known form of electrical remodelling is occurring in atrial myocardium during atrial fibrillation, which relies on shortening of action potential, loss of physiological rate adaptation of the action potential, and a decline in conduction velocity (18, 19, 23, 24, 29, 30). However, remodelling may also affect other than atrial cardiac cells (7, 8, 31). Electrical remodelling on the cellular basis is caused by changes in expression of gap junction proteins and ion channel density and function. Birner *et al*. (1) have observed prolongation of PQ intervals in rabbits with experimental tachycardia-induced heart failure. In their study, rapid right ventricular pacing induced atrial dilation and hypertrophy. Atrial remodelling was accompanied by an expressional down regulation of Kv4.3 and KvLQT1. In the study on the effect of experimental heart failure on atrial electrophysiology performed on a dog model, reduction in Ito and IKs was observed (3, 15). This suggests that heart failure may increase atrial action potential duration due to the reduction in repolarising K^+-currents making the atria more susceptible to after depolarisation-related ectopic activity.

Ultrastructural degeneration and alterations in the nervous system may also contribute to the altered electrical properties of the cardiac myocytes, both the specialised cells of the conducting system and working myocardium.

CART analysis is a method belonging to non-parametric multivariate exploratory techniques, which allow to find factors related to the occurrence of the assessed dependent variable, which in the case of this study was PR interval longer than 164 ms. It was found that the most important factor to the dependent variable was previous chronic pacing, whereas slow heart rate and high weight had lower significance. The results of CART analysis were corresponding with the multivariate regression analysis and allowed to assess the relative importance of factors which may influence PR interval duration. A relatively high sensitivity of the assessed model was related to the prolongation of PR interval in almost all paced animals, but modest specificity was related to the fact that some non-paced animals had high weight or slow heart rate, which was related to the longer PR interval.

The growth of animals leads to the concomitant increase in AVN dimensions and PR interval elongation. This phenomenon was observed in both paced or non-paced animals. Similarly, slowing the heart rate, which may be related to the vagal predominance is also related to P-R interval elongation. The demonstrated slowing of the atrioventricular conduction due to previous chronic pacing was independent of changes in body weight or heart rate. The retrograde atrioventricular conduction was not systematically assessed. However, since P-R prolongation was observed in all paced animals, it could be presumed that P-R interval was prolonged in animals either with retrograde conduction or without it.

These findings provide new insight into the electrical remodelling of the atrioventricular conduction system during paced induced ventricular tachycardia. Chronic ventricular pacing leads to the slowing of atrioventricular conduction. The atrioventricular prolongation seems to be related to electrical or structural remodelling of the cardiac conductive tissue.

Limitations. P-R interval was measured from the surface electrocardiogram so the relative contributions of delay at different conduction levels could not be assessed.

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