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Normal Values for Heart Electrophysiology Parameters of Healthy Swine Determined on Electrophysiology Study*

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A – research concept and design; **B** – collection and/or assembly of data; **C** – data analysis and interpretation; **D** – writing the article; **E** – critical revision of the article; **F** – final approval of article

Abstract

Background. Swine are a well-recognized animal model for human cardiovascular diseases. Despite the widespread use of porcine model in experimental electrophysiology, still no reference values for intracardiac electrical activity and conduction parameters determined during an invasive electrophysiology study (EPS) have been developed in this species thus far.
Objectives. The aim of the study was to develop a set of normal values for intracardiac electrical activity and conduction parameters determined during an invasive EPS of swine.
Material and Methods. The study included 36 healthy domestic swine (24–40 kg body weight). EPS was performed under a general anesthesia with midazolam, propofol and isoflurane. The reference values for intracardiac electrical activity and conduction parameters were calculated as arithmetic means ± 2 standard deviations.
Results. The reference values were determined for AH, HV and PA intervals, interatrial conduction time at its own and imposed rhythm, sinus node recovery time (SNRT), corrected sinus node recovery time (CSNRT), anterograde and retrograde Wenckebach points, atrial, atrioventricular node and ventricular refractory periods. No significant correlations were found between body weight and heart rate of the examined pigs and their electrophysiological parameters.
Conclusions. The hereby presented reference values can be helpful in comparing the results of various studies, as well as in more accurately estimating the values of electrophysiological parameters that can be expected in a given experiment (**Adv Clin Exp Med 2016, 25, 6, 1249–1254**).

Key words: heart, reference values, swine, electrophysiology study.

Swine are a well-recognized animal model for human cardiovascular diseases [1–4]. Porcine models have been increasingly used in human cardiovascular research due to similarities in the heart size, diameters of coronary arteries, susceptibility to coronary atherosclerosis, coronary stent-related restenosis, infarct development and post-infarction remodeling in these two species, and owing

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to the predisposition of swine to sudden cardiac death (SCD) [1, 4]. To this date, normal values for electrocardiographic (ECG) parameters were published for brown hares [5], dogs [6], cats [7], and swine [8], and the reference values for echocardiographic parameters were established for dogs [9], cattle [10], ferrets [11], sheep [12], monkeys [13], Syrian hamsters [14], mice [15], rats [16], and swine [8]. However, despite the widespread use of porcine models in experimental electrophysiology, still no reference values for intracardiac electrical activity and conduction parameters determined during an invasive electrophysiology study (EPS) have been developed in this species thus far.

The aim of this study was to develop a set of normal values for intracardiac electrical activity and conduction parameters determined during an invasive EPS of swine, performed under a general anesthesia.

Material and Methods

The study included 36 healthy domestic swine (*Sus domesticus*) with body weights (b.w.) between 24 kg and 40 kg. All animals were acclimated for 2 weeks before any measurements were taken. They were singly housed in pens at a room temperature of 18–20°C and relative humidity of 60–75%. The pens were cleaned twice a day. The swine were fed a diet (90.44% dry weight) containing 14.7% of protein, 3.1% of fat, 4.7% of crude protein, 6.06% of ash, 0.5% of salt (NaCl), 1.05% of calcium, 0.77% of phosphorus, 0.62% of lysine, 0.24% of methionine, 0.3% of cysteine, 0.48% of threonine, 0.183% of tryptophan, vitamin A (13 243 IU/kg), vitamin D3 (2 000 IU/kg), vitamin E (81.65 mg/kg), vitamin B1 (4.11 mg/kg), vitamin B2 (7.16 mg/kg), niacin (vitamin B3, 50.22 mg/kg), vitamin B5 (24.29 mg/kg), vitamin B6 (6.11 mg/kg) and vitamin B12 (36 μg/kg), and had unlimited access to water. EPS was preceded by determining a complete blood count, alanine aminotransferase (ALT) and aspartate aminotransferase (AST) activities, concentrations of urea, creatinine, glucose, magnesium (Mg2+), sodium (Na+), chloride (Cl–), potassium (K+), calcium (Ca2+), as well as by an electrocardiographic and echocardiographic examination.

EPS was performed under a general anesthesia. The animals were premedicated with midazolam (30 mg/m^2 intravenously), and then general anesthesia was induced with propofol (2 μg/kg/min intravenously) and maintained with inhalation isoflurane (2–3 Vol. %). After the inducing anesthesia and placing the swine in a supine position, the right and left external jugular veins and the femoral vein were accessed by means of the Seldinger technique. Once anesthetized, the vital signs of each pig, namely tongue pulse oximetry, non-invasive blood pressure, respiration rate and body temperature, were monitored by a LIFEPAK® 12 multiparameter monitor (Physio-Control, Inc., Redmond, USA).

Echocardiographic measurements were taken by the same researcher over at least 3 consecutive cardiac cycles with the examined pig in the left lateral recumbent position, using Aloka 4000+ echocardiograph (Aloka Company, Japan) with a 3.5-MHz transducer, in line with the guidelines of the American Society for Echocardiography. The following cardiac dimensions were determined from the echocardiograms. The relative left atrial size was estimated from the left atrial (LA)-to-aortic root (Ao) diameter ratio (LA/Ao). This measurement was taken from the images that were collected from a right short-axis view at the base of the heart. The probe was placed in the right third intercostal space above the sternum. The end-diastolic and end-systolic thickness of the interventricular septum (IVSd and IVSs) and left ventricular posterior wall thickness (LVPd and LVPs) were measured from the images collected from a right long-axis four-chamber view (after moving the probe caudally and rotating it 90°). Estimates of left ventricular systolic function were obtained from the index of circumferential myocardial contraction (EF) and fractional shortening (FS), using the Teicholz formula: (LVIDd – LVIDs/LVIDd) × 100), where LVIDd and LVIDs are left ventricular internal dimensions at end-diastole and end-systole, respectively.

Subsequently, the self-adhesive electrodes were placed to obtain standard ECG records. The 6F quadripolar electrode catheters with various curvatures, Cournand Curve and Josephson Curve, were used. Under fluoroscopic guidance and intracardiac potential control, 4 catheters were inserted *via* vascular sheaths to the high right atrium, coronary sinus, the His bundle area and apex of right ventricle. Electrical potentials from the main leads of standard ECG (I, II, III, aVR, aVL, aVF) were recorded during EPS, along with intracardiac potentials from the intracardiac electrode catheters. The study comprised a passive stage, during which the intracardiac potentials form the right atrium, coronary sinus, the His bundle area and right ventricle were recorded at its own rhythm of the patient, and a dynamic stage, i.e., stimulation of the selected cardiac regions.

The following parameters were determined during the passive stage: interatrial conduction time (HRA-LA) from the electrode catheters placed in the right atrium and coronary sinus, intraatrial conduction time (PA), interval between the right atrium and His bundle (AH) and the interval be-

tween the His bundle area and ventricle (HV) from the catheters inserted into the right atrium and His bundle area. HRA-LA was defined as the conduction time from the high right atrium to the distal coronary sinus. PA interval was determined as the interval between the onset of the P wave recorded from lead II of the standard electrocardiogram and the intrinsic deflection of the atrial electrogram on the His bundle recording catheter. AH interval was measured as the interval between the intrinsic deflection of the atrial electrogram and the earliest onset of the His potential, and HV interval as the interval between the intrinsic deflection of the His potential and the earliest onset of ventricular activation on the intracardiac electrogram.

The following pacing protocols were used during the dynamic stage of the EPS atrial and ventricular pacing.

1. Atrial pacing at progressively shorter cycle length, to determine the anterograde (AV) Wenckebach point, along with the ventricular pacing with retrograde conduction, in order to identify the retrograde (VA) Wenckebach point. The AV Wenckebach point was defined as the lowest atrial pacing rate at which atrioventricular block was observed, usually in the form of Wenckebach periodicity. The VA Wenckebach point was defined as the ventricular pacing rate at which the loss of 1 : 1 ventriculoatrial conduction occurred.

2. Continuous 30-s atrial pacing at a 400-ms cycle length in order to determine sinus node recovery time (SNRT) defined as the interval between the delivery of last atrial stimulus and the first spontaneous atrial depolarization. Additionally, the corrected sinus node recovery time (CSNRT) was determined as the difference between SNRT and regular spontaneous cycle length.

3. Programmed atrial and ventricular pacing with a single premature impulse at progressively shorter coupling interval were performed in order to determine atrial effective refractory period (AERP), atrioventricular nodal effective refractory period (AVNERP) and ventricular effective refractory period (VERP). AERP was defined as the longest coupling interval (S1–S1) of the premature atrial stimulus (S2) that did not result in a premature atrial depolarization. AVNERP was determined as the longest S1–S2 interval that did not result in a His bundle depolarization. VERP was defined as the longest S1–S2 interval that did not result in ventricular capture. The refractory periods were determined at its own rhythm and at imposed rhythms of 130 beats per min (bpm) (460-ms cycle length), 150 bpm (400-ms cycle length), and additionally at 180 bpm (330-ms cycle length) for the purpose of VERP determination, in an 8 + 1 system, i.e. with 8 impulses at an imposed rhythm and a single premature impulse at progressively shorter coupling interval.

4. Short-term continuous atrial pacing at 400 ms to determine the interatrial conduction time at imposed rhythm of 150 bpm (HRA-LA 150 bpm), along with the short-term coronary sinus pacing to examine the retrograde interatrial conduction time at imposed rhythm of 150 bpm (LA-HRA 150 bpm). For the purposes of the present article, it is assumed that the stimulation and activation of CS results in the stimulation of the left atrial muscle fibers of different locations as shown in the work by Chauvin et al. and as confirmed by clinical experience [17].

The results were expressed in milliseconds (ms). Their statistical characteristics are presented as arithmetic means, standard deviations (SD), min and max values. The reference values for intracardiac electrical activity and conduction parameters were calculated as arithmetic means ± 2 standard deviations (SD) [18]. Spearman's rank correlation coefficients (R) were used to study relationships between the pairs of analyzed parameters. The correlations were considered significant at $p \leq 0.05$. All statistical analyses were conducted with STATISTICA 10 package (StatSoft, Inc., Tulsa, USA).

The protocol of the study was approved by the 2nd Local Bioethics Committee in Wrocław (decisions no. 97/2014 of September 17, 2012 and number 119/2014 of December 17, 2014).

Results

All blood parameters, ECG and echocardiographic indices were within their reference ranges [8], both at the baseline and under anesthesia for the EPS. The reference values for intracardiac electrical activity and conduction parameters, determined in 36 healthy domestic swine, are presented in Table 1. No retrograde conduction between the ventricles and atria was observed.

Programmed atrial pacing with a premature impulse at progressively shorter coupling interval induced a short-term paroxysm of atrial fibrillation in four pigs. This form of arrhythmia was observed during the pacing with a premature impulse S2 at a coupling interval < 120 ms. The duration of the longest documented episode of atrial fibrillation/flutter was 4.6 s. All the episodes of arrhythmia resolved spontaneously. No other arrhythmias were recorded.

No significant correlations were found between body weight of the examined pigs and their electrophysiological parameters. Also, the heart rate (HR) of the pigs did not correlate significantly with their AH, HV, HRA-LA, SNRT, CSNRT, AERP, AVNERP and VERP values.

Table 1. Reference values for swine electrophysiological parameters (rounded to the nearest 5 ms)

Parameter	Mean	SD	Min	Max	Reference value
HR (bpm)	108.64	17.9	70	140	
A-A (ms)	616.39	117.03	352	896	
V-V (ms)	617.94	115.2	354	875	
PA (ms)	13.5	6.36	9	18	≤ 25
AH (ms)	73.44	12.99	46	106	45–100
HV (ms)	41.36	9.58	28	71	20–60
SNRT (ms)	660.42	142.25	440	1026	375–945
CSNRT (ms)	88.62	37.01	24	154	15–160
HRA-LA (ms)	43.38	10.07	24	66	25–65
HRA-LA 150 (ms)	71.05	16.27	36	112	40–105
LA-HRA 150 (ms)	67.02	15.34	42	104	35–100
AV Wenckebach (ms)	< 200		< 200	240	< 200
AERP (ms)	110.32	16.22	80	150	75–140
AERP 130 (ms)	122.72	17.01	90	170	85–160
AERP 150 (ms)	125.62	17.94	90	180	85–160
AVNERP (ms)	213.14	44.71	100	290	125–300
AVNERP 130 (ms)	226.28	39.11	100	290	145–315
AVNERP 150 (ms)	223.42	40.28	100	270	140–305
VERP (ms)	183.15	29.77	100	260	125–240
VERP 130 (ms)	190.93	31.35	110	260	125–255
VERP 150 (ms)	184.44	29.61	110	280	125–245
VERP 180 (ms)	172.06	30.03	110	280	110–235

HR – heart rate; A-A – interval between the onset of the P-wave; V-V – interval between the onset of the R- wave; PA – interval between the onset of the P-wave and the intrinsic deflection of the atrial electrogram on the bundle recording catheter; AH – interval between the intrinsic deflection of the atrial electrogram and the earliest onset of the His potential; HV – interval between the His bundle area and ventricle; SNRT – sinus node recovery time; CSNRT – corrected sinus node recovery time; HRA-LA – interatrial conduction time from the high right atrium to the distal coronary sinus; HRA-LA 150 – interatrial conduction time at an imposed rhythm of 150 beats per min (bpm); LA-HRA 150 – retrograde interatrial conduction time from the distal coronary sinus to the high right atrium at an imposed rhythm of 150 bpm; AV Wenckebach – ventricular pacing rate at which the loss of 1 : 1 atrioventricular conduction occurred; AERP – atrial effective refractory period at an own rhythm; AERP 130; 150 – atrial effective refractory period at an imposed rhythm of 130 bpm and 150 bpm; AVNERP – atrioventricular nodal effective refractory period at an own rhythm; AVNERP 130; 150 – atrioventricular nodal effective refractory period at an imposed rhythm of 130 bpm and 150 bpm; VERP – ventricular effective refractory period at an own rhythm; VERP 130, 150, 180 – ventricular nodal effective refractory period at an imposed rhythm of 130 bpm, 150 bpm and 180 bpm.

Discussion

Swine are a common model for electrophysiology studies of arrhythmia [19, 20] or potential anti-arrhythmic effects of novel therapeutic agents [21–23]. However, due to differences in EPS protocols and anesthesia models, direct comparison of the results published by various researchers is challenging. We proposed a model of anesthesia which exerted only a marginal effect on the electrical conduction system of the heart and seems suitable for most experiments involving swine. Our protocol of anesthesia included midazolam, propofol and isoflurane. Propofol modulates the intracardiac conduction in a dose-dependent manner. At higher concentrations, this agent may block the sinoatrial node function and His-Purkinje system conduction [24]. Administered at a dose similar

to that used in our study, midazolam exerts only a slight effect on the conduction parameters [25]. Only few studies with complete EPS protocols have been published thus far, and, owing to the different models of anesthesia used in these experiments, their results are hardly comparable. The fact that the body weight of pigs undergoes substantial changes with their age makes development of the reference values even more challenging.

Zaballos et al. [22] analyzed electrophysiological parameters of the heart in 18 pigs with body weights between 16 kg and 60 kg, anesthetized with ketamine (20 mg/kg b.w. intramuscularly) and propofol (4.5 mg/kg intravenously for premedication and then 13 mg/kg/h intravenously). Only HR, basic cycle length and AH during sinus rhythm were similar as the respective parameters determined in our study. The remaining parameters reported by these authors, i.e., SNRT, CSNRT, HV, AV Wenckebach, AERP, AVNERP and VERP during sinus rhythm differed considerably from those recorded in our experiment. Also AERP, AVNERP and VERP values at paced cycle length of 600 ms and 400 ms were different despite similar SD values [21].

AERP and VERP values determined in our study differ only slightly from the results published previously by Carvas et al. [26] and Kumar et al. [21]. Unfortunately, these authors did not determine the remaining intracardiac electrical activity and conduction parameters, since the principal aim of their research was to analyze the effects of ranolazine on atrial refractory period and atrial fibrillation in the intact porcine heart. Moreover, our results differ from those published by Noszczyk-Nowak [27] who used a different protocol of anesthesia (azaperone 2 mg/kg intramuscularly, ketamine 10 mg/kg intramuscularly, pentobarbital 8–10 mg/kg intravenously) during the EPS of swine. This implies that the type of anesthesia used exerts a considerable effect on the EPS outcome, which likely constitutes the reason behind the discrepancies in the results published by various researchers. This, in turn, justifies the development of separate sets of reference values for the most commonly used anesthesia protocols; this will allow us to reduce the number of control animals participating in experimental studies which is consistent with both national and EU legislation.

Limitations

This study included solely juvenile pigs. The effect of age on provoked arrhythmias, such as atrial fibrillation/flutter, has not been evaluated thus far. A lack of sinus node parameters after autonomic blockade and the measurement HRA-LA and LA-HRA was performed only during pacing at 130.

The presented reference values for basic intracardiac electrical activity and conduction parameters can be helpful in comparing the results of various studies as well as in more accurate estimations of the values of electrophysiological parameters that can be expected in a given experiment.

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