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Effect of xylazine, medetomidine and dexmedetomidine on cardiac conduction in pigs[1) 2)]

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Summary

The majority of anaesthetics used in studies regarding heart arrhythmias may affect the cardiac conduction system, thus influencing the results. In veterinary medicine, xylazine, medetomidine and dexmedetomidine are commonly used for premedication in laboratory and companion animals. To date, there have been no studies assessing the effect of these substances on the cardiac conduction system. The aim of this study was to assess the effect of xylazine, medetomidine and dexmedetomidine on the parameters of the cardiac conduction system in pigs. The study was carried out on 18 Great White Polish male pigs weighing from 21 to 40 kg. The animals were divided into three equal groups. The animals from the first group received xylazine at a dose of 2 mg/kg i.v.; those from the second group received medetomidine at 40 mcg/kg i.v.; and those from the third group received dexmedetomidine at 10 mcg/kg i.v. The electrophysiological activity of the heart was analysed using an invasive electrophysiological study (EPS). During the EPS, a decrease in the heart rate after substance administration was observed in all animals, but there were no statistically significant differences in the cardiac conduction parameters. A pro-arrhythmic effect of xylazine was observed, but no statistically significant changes in the EPS parameters were noted. Our results indicate that medetomidine and dexmedetomidine may be used as standard premedication drugs in electrophysiological studies in pigs. Their use may facilitate animal preparation procedures without affecting study results.

Keywords: xylazine, medetomidine, dexmedetomidine, EPS, pigs

Pigs are widely used as models to study the cardiovascular, gastrointestinal, reproductive, excretory and integumentary systems (1, 2, 6, 9, 20, 21, 28). Pigs are also used as models in immunology, transplantology, gene therapy, toxicology, neurology, oncology and regenerative medicine (4, 7, 11, 13, 35). Pig models are considered valuable because of their physiological and anatomical similarities to humans. They became increasingly popular in cardiac surgery and were used as heart transplantation models in Poland in the late 1990s. The majority of studies require the animal to be immobilised or fully anesthetised. Most of anaesthetics affect and change the physiology of the body systems, particularly the circulatory system (21, 22, 29, 30). This effect is particularly significant in cardiac arrhythmia studies. Hence, new anaesthetics are constantly sought, and the effects of the available anaesthetic drugs are being widely studied. The most common drugs used to anesthetise pigs include midazolam, azaperon, fentanyl, droperidol, ketamine and barbiturates (5, 19, 36). Alpha-2 adrenergic agonists, which are commonly used in companion animals, are rarely used in laboratory animals prior to cardiovascular procedures, because they reduce the blood pressure and heart rate. To date, there have been no studies assessing the precise impact of the anaesthetics used in pigs on the specific parts of the cardiac conduction system.

Xylazine, medetomidine and dexmedetomidine, alpha-2 adrenergic receptor agonists that have an

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imidazole ring in their structure, are widely used for premedication, alone or in combination with other drugs. They have sympatholytic, sedative, hypnotic, analgesic and slight muscle relaxing properties. Studies have shown that there are at least five different effector mechanisms triggered by the activation of alpha-2 adrenergic receptors, including inhibition of adenylate cyclase, the acceleration of the sodium and hydrogen ion exchange across cell membranes, the activation of potassium ion channels, the inhibition of voltage-operated calcium ion channels and modulation of the activity of phospholipase C in cell membranes. Alpha-2 mimetics can also be classified from a practical point of view, on the basis of their effect on alpha-1 and alpha-2 receptors. The alpha-2:alpha-1 receptor selectivity amounts to 160 : 1 for xylazine and 1620 : 1 for medetomidine and dexmedetomidine (26). Xylazine is the least selective of the three drugs, but is popularly used in veterinary medicine. Dexmedetomidine is the newest of these drugs and is an active enantiomer isolated from a racemised mixture of medetomidine. It is more active and gives longer-lasting analgesia at the same dose as medetomidine.

The aim of the study was to assess the effect of xylazine, medetomidine and dexmedetomidine on the successive parts of the cardiac conduction system in pigs.

Material and methods

The study was carried out on 18 Great White Polish male pigs weighing from 21 to 40 kg. The animals were divided into three groups, each containing six pigs. The animals from the first group received xylazine at a dose of 2 mg/kg i.v.; pigs from the second group received medetomidine at 40 mcg/kg i.v.; and those from the third group received dexmedetomidine at 10 mcg/kg i.v. (8, 25, 32). The clinical status of the animals was assessed on the basis of a complete blood cell count and biochemical analysis (ALT, AST, urea, creatinine, Na^+, K^+, Mg^{2+}, Cl^-, glucose, CRP) and an electrocardiography examination, in which the heart rate, sinus rhythm, presence of arrhythmias and basic ECG parameters (P wave, T wave, QRT complex, PQ, QT and QTc interval) were assessed. The electrophysiological properties of the heart were measured via an invasive electrophysiological study carried out with a BARD Electrophysiology LABSYSTEM PRO system. Four-pole electrodes with different curvature values, including a BARD Electrophysiology Cournand Curve and Josephson Curve, were used. All the electrodes were size 6F. The procedure was carried out under inhaled general anaesthesia using 1.5-2% Vol isoflurane, after premedication with midazolam at 30 mg/m^2 and induction of sleep with propofol (2 mcg/kg/min). The anesthetized animals were placed in dorsal recumbency, and the Seldinger method was used to place a catheter in the right and left external jugular veins and the left femoral vein (3). Two or three electrodes were inserted into the right atrium, coronary sinus, bundle of His and right ventricle through vascular sheaths under fluoroscopy and intracardiac potential guidance. The first (passive) part of the study consisted of the registration of intracardiac potentials from the right atrium, coronary sinus, bundle of His and right ventricle during the sinus rhythm. In the second, dynamic part of the study, selected regions of the heart were stimulated. The electrophysiological study was carried out at two time points: prior to and 15 minutes after intravenous administration of the anaesthetics. Basic conduction parameters during a normal rhythm and during the programmed stimulation according to the previously described protocol were recorded in the EPS. All the parameters were recorded in milliseconds (ms). At the end of the study, the animals were euthanised.

The following parameters were recorded in the first part of the study: the HRA-LA (interatrial conduction time) from the high right atrium electrodes and coronary sinus; the AH interval (interval between the right atrium and the bundle of His) and the HV (interval between the area of the bundle of His and the ventricle) recorded from the electrodes in the right ventricle and the area of the bundle of His. The HRA--LA, which was the interatrial conduction time, was measured from the start of the impulse at the top of the atrium to the left atrium registered at the distal part of the coronary sinus. The AH was measured from the atrial deflection to the His bundle deflection. The HV was measured from the His bundle deflection to the earliest ventricular activation visible in the intracardiac electrocardiogram.

The following stimulation protocols were carried out during the dynamic phase:

- gradual atrial stimulation with a shortening cycle length to determine the Wenckebach point. The Wenckebach point is the lowest atrial stimulation frequency at which there is an AV delay, causing a Wenckebach block,
- continuous 30-second atrial stimulation using a 400 ms cycle in order to determine the sinus node recovery time (SNRT). The time from the last induced atrial stimulation to the resuming of the sinus rhythm atrial stimulation was recorded. In addition, the corrected sinus node recovery time (CSNRT), which was the sinus node recovery time minus the sinus cycle length, was recorded,
- a programmed atrial and ventricular stimulation with an additional impulse of a gradually shortening feedback in order to determine the atrial effective refractory period (AERP), the atrioventricular nodal effective refractory period (AVNERP) and the ventricular effective refractory period (VERP). The atrial effective refractory period is the longest interval between the last paced beat (S1-S1) and premature beats (S2), which does not cause premature atrial depolarization. The atrioventricular nodal effective refractory period is the longest interval between S1-S2, during which the stimulation is not conducted from the atrium to the ventricles. VERP is the longest S1-S2 interval, after which there is contraction of the ventricles. The refractory period was measured during the normal rhythm as well as induced heart rates of 130 beats/min (460 ms cycle), 150 beats/min (400 ms cycle) and 180 beats/min (330 ms cycle), in an 8+1 system (8 stimulated impulses and 1 impulse with a shortened cycle),
- a short-term continuous stimulation, lasting 400 ms and originating in the atrium, was recorded in order to determine interatrial conduction during an imposed rhythm (HRA-LA 150/min); another stimulation originating in the

coronary sinus was recorded in order to assess interatrial conduction during an imposed rhythm (LA-HRA 150/min).

Statistical analyses were carried out using version 12.0 PL of Statistica. The differences between the groups for related and unrelated parametric data with a normal distribution were assessed using Student's t-test. Non-parametric data or data with a non-normal distribution were assessed using Friedman's ANOVA and the Kendall coefficient for multiple related variable groups or Kruskal-Wallis ANOVA for multiple variable unrelated groups. The correlations were analysed using Spearman R test. Statistical significance was set at $p \leq 0.05$.

The study was approved by the Second Local Ethics Committee for Experiments on Animals, permit no 8/2015 from 18.02.2015.

Results and discussion

The results of the complete blood count and blood biochemical analysis were within reference ranges (18). In all the animals, the resting EKG did not reveal any abnormalities. All the animals had a lower heart rate in the course of the EPS following the administration of alpha-2-adrenergic receptors. After administering xylazine, the mean heart rate decreased from 97 (SD ± 12) bmp to 78 (SD ± 5) bmp. It decreased from 117 (SD ± 13) bmp to 86 (SD ± 8) bmp following the administration of medetomidine and from 133 (SD ± 18) bmp to 94 (SD ± 4) bmp after administering dexmedetomidine. There were no statistically significant differences in the cardiac conduction parameters in group I. In groups II and III, there were statistically significant differences in the effective refractory period (ERPV 130) of the right ventricle at an induced rhythm of 130/min. The values of the parameters in the groups are presented in Tables 1-3. In the group of animals receiving medetomidine, the mean refractory period of the ventricles at an induced rhythm of 130/min increased from 198 ms (SD ± 21) to 228 ms (SD ± 18). In the group receiving dexmedetomidine, this period increased from 203 ms (SD ± 18) to 218 ms (SD ± 19). In addition, an arrhythmogenic effect of the substances was observed. In group I, four pigs developed arrhythmias following xylazine administration, atrial flutter was observed in three of them (Fig. 1) and supraventricular tachycardia in one pig. In one pig from group I, the atrial flutter prevented the identification of the atrial effective refractory period and the atrioventricular effective refractory period under induced rhythms of 130/min and 150/min. Atrial flutter was also observed in two pigs in group II receiving medetomidine and in one pig in group III receiving dexmedetomidine.

No statistically significant differences in the cardiac conduction parameters following the administration of the three substances were found despite their substantial effects on the heart rate. The results may be affected by the other substances used in the anaesthesia of pigs, including isoflurane, midazolam and propofol. Previous studies have shown that inhalation

Tab. 1. Values of the electrophysiological parameters in the pigs before and after administration of xylazine (milliseconds)

Parameter	Pig 1		Pig 2		Pig 3		Pig 4		Pig 5		Pig 6		Mean value (± SD)	
	Before	After	Before	After	Before	After	Before	After	Before	After	Before	After	Before	After
HV	31	34	40	24	35	34	41	60	34	30	43	82	37 ± 4.7	44 ± 22.3
HRA-LA	42	38	48	50	70	72	60	66	82	66	38	82	57 ± 17.1	62 ± 15.8
HRA-LA 150	56	76	72	94	70	96	82	72	100	106	88	76	78 ± 15.1	87 ± 13.8
LA-HRA 150	156	212	72	78	72	96	80	72	100	110	88	49	95 ± 31.9	103 ± 57.4
AV Wenckebach	200	190	200	210	200	230	200	240	200	220	200	200	200 ± 0	215 ± 18.7
SNRT	716	1018	750	882	914	786	648	788	948	1068	638	816	769 ± 132.7	893 ± 122.3
CSNRT	94	154	72	108	122	114	80	66	112	184	68	94	91 ± 22.0	120 ± 42.5
VERP 130	230	180	240	240	240	260	220	230	220	230	270	300	237 ± 18.6	240 ± 39.5
VERP 150	230	170	220	230	190	240	220	220	200	240	270	310	222 ± 27.9	235 ± 45.1
VERP 180	160	160	190	190	190	210	190	210	180	240	230	340	190 ± 22.8	225 ± 62.2
AERP 130	110	140	120	150	140	*	140	160	150	130	130	150	132 ± 14.7	146 ± 11.4
AERP 150	110	130	110	140	130	*	130	160	140	120	140	140	127 ± 13.7	138 ± 14.8
AVNERP 130	250	250	280	150	310	*	250	290	290	310	290	300	278 ± 24.0	260 ± 65.6
AVNERP 150	250	230	270	280	280	*	270	270	300	280	290	270	277 ± 17.5	266 ± 20.7
HR	98	78	94	71	83	80	88	85	104	80	118	74	97 ± 12.4	78 ± 4.9

Explanations: HV – interval between His bundle electrogram and ventricular electrogram; SNRT – sinus node recovery time; CSNRT – corrected sinus node recovery time; HRA-LA – conduction time between high right atrium and left atrium; HRA-LA 150 – conduction time between high right atrium and left atrium on a pacemaker set at 150/min; LA-HRA 150 – retrograde conduction time from left atrium to high right atrium at an externally induced heart rate of 150/min; AV Wenckebach – the lowest atrial stimulation frequency at which there is an AV delay, in a 1 : 1 ratio; AERP 130, 150 – atrial effective refractory period during an externally induced heart rate of 130/min and 150/min; AVNERP 130, 150 – atrioventricular node effective refractory period during an externally induced heart rate of 130/min and 150/min; VERP 130/min, 150/min, 180/min – ventricular effective refractory period on a pacemaker set at 130/min, 150/min, 180/min; * not recorded; SD – standard deviation

Tab. 2. Values of the electrophysiological parameters in the pigs before and after administration of medemtonidine (milliseconds)

Parameter	Pig 1		Pig 2		Pig 3		Pig 4		Pig 5		Pig 6		Mean value (± SD)	
	Before	After	Before	After	Before	After	Before	After	Before	After	Before	After	Before	After
AH	81	96	78	83	72	75	67	78	72	66	67	71	73 ± 5.7	78 ± 18.3
HV	40	55	44	44	27	37	45	41	46	45	51	47	42 ± 8.2	45 ± 6.1
HRA-LA	50	54	54	64	42	46	60	58	40	50	54	54	50 ± 7.7	54 ± 6.2
HRA-LA 150	86	104	78	100	80	76	90	72	76	74	60	72	78 ± 10.1	84 ± 14.8
LA-HRA 150	104	108	70	96	82	84	90	80	72	74	134	70	92 ± 24.1	85 ± 14.3
AV Wenckebach	240	230	180	180	180	200	190	180	190	190	200	200	197 ± 22.5	197 ± 18.6
SNRT	782	768	772	838	818	970	840	886	770	744	890	808	812 ± 47.3	836 ± 82.9
CSNRT	94	76	104	130	198	200	182	144	54	58	212	76	141 ± 65.0	114 ± 54.0
VERP 130	230	260	180	210	210	230	200	240	190	220	180	210	198 ± 19.4	228 ± 19.4
VERP 150	210	240	170	200	200	160	190	210	180	200	180	200	188 ± 14.7	201 ± 25.6
VERP 180	180	220	170	180	180	160	190	210	180	190	170	190	178 ± 7.5	192 ± 21.4
AERP 130	140	130	110	130	110	100	130	130	130	130	130	130	125 ± 12.2	125 ± 12.2
AERP 150	130	130	110	120	110	100	120	130	130	120	130	130	122 ± 9.8	122 ± 11.7
AVNERP 130	320	280	230	230	240	230	270	270	280	290	200	250	257 ± 42.3	258 ± 25.6
AVNERP 150	290	290	210	210	230	230	240	250	270	270	270	260	252 ± 29.9	252 ± 28.6
HR	104	74	120	90	130	80	126	88	98	90	128	97	118 ± 13.5	87 ± 8.2

Explanations: AH – interval between atrial electrogram and His bundle electrogram; HV – interval between His bundle electrogram and ventricular electrogram; SNRT – sinus node recovery time; CSNRT – corrected sinus node recovery time; HRA-LA – conduction time between high right atrium and left atrium; HRA-LA 150 – conduction time between high right atrium and left atrium on a pacemaker set at 150/min; LA-HRA 150 – retrograde conduction time from left atrium to high right atrium at an externally induced heart rate of 150/min; AV Wenckebach – the lowest atrial stimulation frequency at which there is an AV delay, in a 1 : 1 ratio; AERP 130, 150 – atrial effective refractory period during an externally induced heart rate of 130/min and 150/min; AVNERP 130, 150 – atrioventricular node effective refractory period during an externally induced heart rate of 130/min and 150/min; VERP 130/min, 150/min, 180/min – ventricular effective refractory period during an externally induced heart rate of 130/min, 150/min, 180/min; SD – standard deviation

Tab. 3. Values of the electrophysiological parameters in the pigs before and after administration of dexmedemtonidine (milliseconds)

Parameter	Pig 1		Pig 2		Pig 3		Pig 4		Pig 5		Pig 6		Mean value (± SD)	
	Before	After	Before	After	Before	After	Before	After	Before	After	Before	After	Before	After
AH	77	80	65	64	59	66	60	61	89	85	57	63	68 ± 12.6	70 ± 10.1
HV	41	46	43	40	43	53	47	41	43	46	31	30	41 ± 5.4	43 ± 7.7
HRA-LA	66	60	28	34	52	50	34	32	38	34	46	28	44 ± 13.7	40 ± 12.5
HRA-LA 150	82	92	84	60	110	118	54	64	68	64	76	98	79 ± 18.7	83 ± 23.6
LA-HRA 150	70	80	94	66	106	112	52	74	68	56	70	96	76 ± 19.7	81 ± 20.4
AV Wenckebach	220	220	190	180	200	220	190	240	190	190	200	200	198 ± 11.7	208 ± 22.3
SNRT	498	898	742	682	720	784	442	740	1030	814	672	792	684 ± 208.6	785 ± 72.5
CSNRT	70	188	124	94	108	120	36	124	280	182	100	130	120 ± 84.5	140 ± 37.2
VERP 130	200	210	200	210	240	250	210	230	190	210	180	200	203 ± 20.7	218 ± 18.3
VERP 150	190	200	180	180	230	230	210	230	200	200	170	190	197 ± 21.6	205 ± 20.7
VERP 180	180	190	180	170	210	200	190	200	170	180	160	180	182 ± 17.2	187 ± 12.1
AERP 130	110	120	110	140	170	210	110	120	130	120	120	130	125 ± 23.4	140 ± 35.2
AERP 150	120	110	110	140	160	180	110	110	120	110	120	130	123 ± 18.6	130 ± 27.6
AVNERP 130	290	290	290	300	300	250	270	280	280	280	230	260	277 ± 25.0	277 ± 18.6
AVNERP 150	270	280	280	230	280	270	260	260	270	270	240	250	267 ± 15.1	260 ± 17.9
HR	150	90	119	100	128	90	113	95	130	95	160	96	133 ± 18.1	94 ± 3.8

Explanations: AH – the interval between the atrial stimulation and the bundle of His; HV – interval between the bundle of His and the ventricular stimulation; SNRT – sinus nodal reentrant tachycardia; CSNRT – corrected sinus node recovery time; HRA-LA – activation from the high right atrium to the left atrium; HRA-LA 150 – interventricular stimulation at 150/min; LA-HRA 150 – reverse interatrial conduction time at am induced heart rate of 150/min, from the left atrium to the high right atrium; AV Wenckebach – the lowest atrial stimulation frequency at which there is an AV delay, in a 1 : 1 ratio; AERP 130, 150 – atrial effective refractory period during an externally induced heart rate of 130/min and 150/min; AVNERP 130, 150 – atrioventricular node effective refractory period externally induced heart rate of 130/min and 150/min; VERP 130/min, 150/min, 180/min – ventricular effective refractory period during an externally induced heart rate of 130/min, 150/min, 180/min; SD – standard deviation

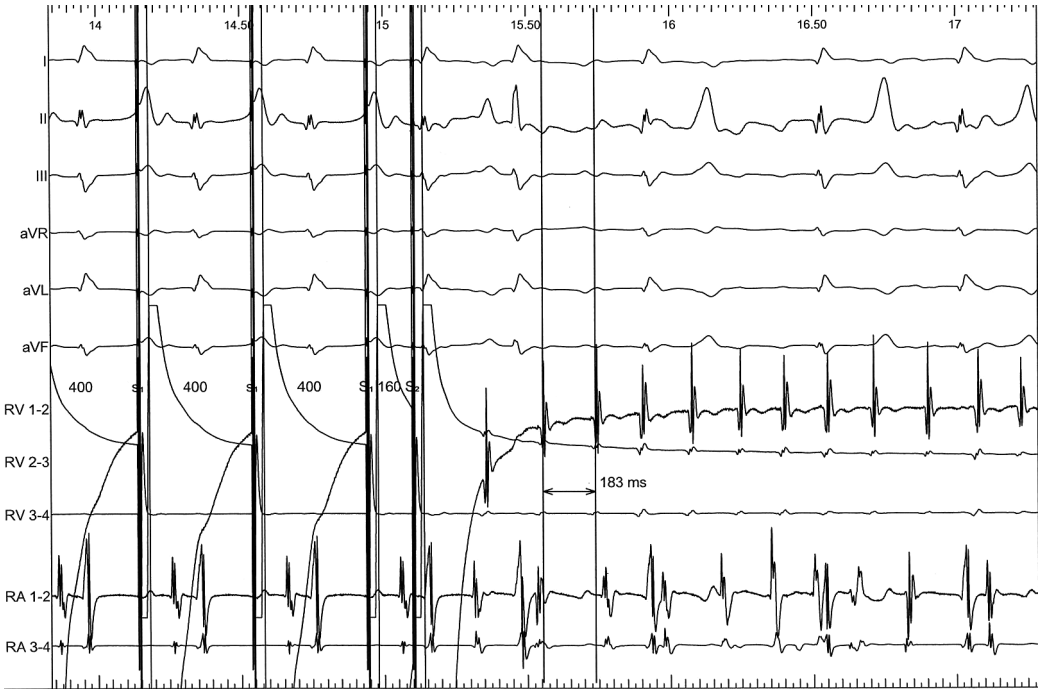

Fig. 1. Atrial flutter with an atrial cycle of 183 ms triggered during the gradual atrial pacing protocol with a shortened cycle in pig number 5 after the administration of xylazine (sweep speed 67 mm/s)

anaesthetics, including isoflurane, protect the myocardium from ischemia. This mechanism of action is not fully understood, but it is believed that the relaxation of the coronary artery vascular smooth muscle and a decreased oxygen demand of the myocardium play an important role in the process (12, 30). No significant changes in cardiac conduction are likely to be caused by the cardioprotective effect of isoflurane. On the other hand, it has been shown that inhalational anaesthetics may sensitize the heart to catecholamines and thereby cause premature ventricular contraction (23). However, we did not observe ventricular arrhythmias. All the recorded arrhythmias were atrial, suggesting that they were caused by the alpha-2 agonists. The hemodynamic and electrical effects of midazolam and propofol on the circulation are low (29).

A reduction in the heart rate was observed following the administration of the three substances, which is a known effect, already described in the literature. The main adverse effects of the alpha-2 adrenergic receptors on the cardiovascular system include a decrease in the cardiac output, an increase in systemic vascular resistance, bradycardia and bradyarrythmias, including first- and second-degree atrioventricular blocks (10, 14, 24, 33). The three drugs cause a reduction in the sympathetic tone and an increase in systemic vascular resistance, leading to bradycardia. Alpha-2 agonists reduce the release of noradrenaline in the OUN, inhibiting sympathetic activity. The desired effect of this mechanism is sedation, but it also reduces the heart rate. Alpha-2 agonists act on the peripheral receptors by significantly increasing systemic vascular resistance and causing an increase in blood pressure, which in turn triggers the baroreceptor reflex, leading to bradycardia. The lack of significant differences in the values of the electrophysiological parameters may be explained by the fact that, in general, pigs demonstrate a low response to alpha-2 adrenergic receptor agonists, particularly to xylazine (8, 31). The available literature suggests that, despite its weak anaesthetic effect, xylazine has the previously described cardiovascular effects (8). The intensity and duration of systemic vascular resistance is dose- and route-dependent and is also affected by substance selectivity. At lower doses, the main effect is a block of the sympathetic autonomic nervous system via alpha-2 receptors, causing a decrease in blood pressure. At higher doses, there is an increase in arterial blood pressure and a decrease in the heart rate, caused by the stimulation of alpha-2B isoreceptors in the capillary smooth muscles (24). The initial increase in arterial blood pressure is greater following intravenous drug administration compared to intramuscular administration (34). Three different substances with varying alpha-2 selectivity compared to the alpha-1 selectivity were analysed at a single dose. Dexmedetomidine was the most selective, although it caused the largest decreases in the heart rate. The initial heart rate was also the highest in that group, which may have affected the differences in the heart rate before and after drug administration. The only parameter that differed significantly among the groups was the change in the refractory period in the right ventricle at an induced heart rate of 130/min. These differences may have been caused by different electrode placements in the right ventricle during the first and second examinations. We did not find an explanation for the change in this single parameter in the available literature. The absence of changes in the remaining cardiac conduction parameters may be explained by the fact that the bradycardia we observed was caused by stimulation of the autonomic nervous system and systemic vascular resistance, not by changes in cardiac conduction. Despite the absence of statistically significant differences in the EPS parameters, we found a proarrhythmic activity of the drugs, particularly xylazine. The most common arrhythmias caused by alpha-2 agonists described in veterinary literature include bradyarrhythmias, such as first- and second-degree atrioventricular blocks and sinus arrhythmias (15, 27). Third-degree atrioven-

tricular block and cardiac arrest are rarely noted (17). We did not note such arrhythmias in our study. Those arrhythmias were triggered during the atrial stimulation protocol after administering the substances. The arrhythmias occurred most commonly in the pigs that received xylazine and were the least common in the group that received dexmedetomidine (one pig). Hence, xylazine seems to be the most arrhythmogenic of the three substances, which is in accordance with literature reports, stating that arrhythmogenicity decreases with an increased selectivity of alpha-2 agonists (16).

The results of this study indicate that medetomidine and dexmedetomidine may be added to the standard anaesthetic drugs used during electrophysiological studies in pigs. The use of these substances may facilitate animal preparation for electrophysiological procedures, while minimally affecting the results.

In order to draw clear conclusions, the arrhythmogenic potential of the three drugs needs to be studied on a larger group of animals. The study was carried out using only single-dose intravenous administration of the alpha-2 agonists. Hence, these factors should also be considered in future studies.

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