Bull Vet Inst Pulawy 52, 305-311, 2008

PRELIMINARY OBSERVATIONS OF THE EFFECT OF SHORT TIME EXPERIMENTAL VENTRICULAR TACHYCARDIA ON GLUCOSE AND INSULIN LEVELS IN PIGS. A PRELIMINARY COMMUNICATION

AGNIESZKA NOSZCZYK-NOWAK, PIOTR SKRZYPCZAK[1], JACEK GAJEK[2], URSZULA PASŁAWSKA, DOROTA ZYŚKO[3], AND JÓZEF NICPOŃ

Department of Internal and Parasitic Diseases with Clinic for Horses, Dogs and Cats,
[1]Department and Clinic of Veterinary Surgery,
Wrocław University of Environmental and Life Sciences, 50-366 Wrocław, Poland
[2]Department of Cardiology, [3]Departament of First-aid Service,
Medical University of Wroclaw, 50-367 Wrocław, Poland
agnieszkann@poczta.onet.pl

Received for publication February 22, 2008

Abstract

The aim of the research was to determine whether short-time heart muscle ischemia caused by fast ventricular pacing rate (ventricular tachycardia) provokes insulin and glucose blood level alterations and if so, how long those changes last after return to the physiological heart rate and restoration of proper heart muscle perfusion as well. It was stated that short-lasting tachycardia provoked by fast, forced ventricle rate, with no damage on the cardiac muscle resulted in significant fall of the glucose and insulin blood levels. The glucose returned to its initial level several minutes after heart rate normalisation; however, the insulin drop maintained for more than 10 min.

Key words: pig, tachycardia, glucose, insulin.

Heart failure is the most common disease in men above 45 years of age, often diagnosed in animals as well, especially in dogs (1, 11, 12) with a 10% prevalence. The first adaptive mechanism of heart failure is an increase in heart rate (tachycardia) (3). A common finding in many clinical trials is a negative correlation between the heart rate and life time duration, with no regard to the kind of heart disease (9, 10).

Increasing heart rate shortens the time of diastole and reduces the coronary flow, which impairs cardiomyocyte oxygen supply causing metabolic alterations in the heart tissue. Under condition of physiological heart muscle blood supply, 95% of ATP is derived from oxygenic phosphorylation; meanwhile the remaining 5% of ATP comes from anaerobic glycolysis. The free fatty acids, lactic acid, and products of incomplete fatty metabolism, like ketones, are the main energy source under regular condition of the heart muscle's oxygen supply. It is because of their high-energy value and oxygen abundance in the healthy heart, which need large quantities of oxygen for further metabolism of those substances. It has been proved, that an increase in glycolysis is accompanied by a decrease in oxygenic pathways during ischaemia (4, 14). Afterwards, the intensification of glucose uptake occurs followed by its displacement into the cardiomyocyte with help of the GLUT 4 glucose transporter. Glucose uptake is stimulated by insulin, which also inhibits lipolysis and reduces the level of β-oxidation substrates as well. It redirects the heart muscle's metabolism to anaerobic routes possessing energy for systole. High insulin concentration was observed in patients with severe heart failure where the anaerobic processes become the long-term energy source for cardiomyocytes (15, 17). In this state however, the insulinaemia can be connected to the sign of insulin resistance, related to sympathetic activation and systolic output failure.

There are no studies on the effect of short-time ischaemia caused by tachycardia on the glucose and insulin concentration and metabolism alterations in cardiomyocyte and possible reversion of the mentioned process.

The aim of the study was an evaluation into whether the fast ventricle pacing rate (ventricle tachycardia equivalent), which may induce cardiac ischaemia, can change insulin and glucose levels in the peripheral blood, and if so, how long can those changes remain after the normal rhythm restoration and a proper heart muscle perfusion as well.

Material and Methods

The research was conducted on 5 pigs of a Polish Large White breed. Insulin and glucose levels were evaluated before beginning of ventricle pacing after 24 h of starvation diet (deprive of feed), and then 1, 5, 10, and 15 min after the onset of pacing with 150 bpm rate, and 5, 10, 15, 30, and 60 min after the end of the stimulation (Figs 1 and 2, Table 1). The heart pacing was conducted under ketamine and pentobarbital intravenous anaesthesia proceeded by azaperone premedication, at the dosage of 10 mg/kg, 8-10 mg/kg, and 2 mg/kg, respectively, continued by supporting dosage of pentobarbital according to the effect. The stimulation was driven with use of J&J 4 pole intracardiac electrode with constant distance between electrode rings and equal bend connected to the external Biotronik UHS 20 pacemaker. The electrode was placed by the use of a modified Seldinger's method in the right ventricle through a catheter located in the *vena cava* (10). The electrode was positioned by the use of X-ray imaging (Fig. 2). In all the pigs, insulin and glucose levels were evaluated during physiological heart rate 60-80 bpm (before ventricle pacing). Blood was collected every 5 min from the femoral vein. Glucose level was evaluated by using a glucometer in the laboratory of the Department of Internal and Parasitic Diseases, and insulin concentration was measured on Abbot Axe analyser in the Analytical Laboratory of Cardiology Clinic, Medical University of Wrocław. Right parasternal long- and short-axis two dimensional echocardiography was performed to determine left atrium and ventricle diameters during the stimulation. Blood pressure was measured by using a cuff manometer placed on the radial artery.

The results were statistically analysed by using variable dependent ANOVA calculation. The statistical significance level was accepted for $P \leq 0.05$.

Results

Decreased glucose level was affirmed as early as during the first minute of pacing at a rate of 150 bpm, and after 10 min of stimulation, the level was significantly lower compared to the values before the procedure (Fig. 3). Already 5 min after the stimulation ended, glucose concentration did not differ significantly from the values measured before pacing (Fig. 4). The lowest glucose concentration was observed at the 15th min of the stimulation and furthermore in 2 pigs the level dropped below reference values (16).

Insulin level decreased significantly after 5 min of ventricular pacing (Fig. 5) reaching the lowest level at the 5th min after the stimulation ended (Fig. 6). Significantly lower concentration of insulin maintained for 30 min after ventricular stimulation, until the end of observation in another words (Fig. 1). Short-time tachycardia did not cause atrial enlargement and hypertension in the investigated pigs.

Table 1
Glucose and insulin levels before pacing with 150 bpm rate, then after 1, 5, 10, and 15 min after onset of heart stimulation and 5, 10, 15, and 30 min after pacing

	No.	Before pacing	1 min of pacing	5 min of pacing	10 min of pacing	15 min of pacing	5 min after pacing	10 min after pacing	15 min after pacing	30 min after pacing
Glucose mmol/l	1	4.4	3.6	3.5	2.6	2.7	4.0	4.4	5.2	4.5
	2	3.1	2.9	2.8	2.1	1.7	4.8	6.7	5.6	5.7
	3	5.6	3.8	2.8	1.6	1.9	1.6	1.2	2.2	3.4
	4	5.2	4.3	4.6	3.7	2.8	3.6	3.8	4.0	4.2
	5	3.8	4.1	4.3	3.6	4.6	5.8	5.2	9.2	5.3
Mean±SD		**4.425±1.17**	**3.75±0.62**	**3.6±0.99**	**2.7250±1.1**	**2.7±1.32**	**3.9±1.82**	**4.275±2.41**	**5.25±2.97**	**4.625±1.06**
Insulin mUI/l	1	18.8	14.9	14.1	12.8	12.4	7.3	8.6	7.8	8.6
	2	8.3	5.2	3.5	3.2	4.4	4.2	4.4	5.6	6.8
	3	21.9	17.2	9.2	5.7	2.2	3.1	4.3	4.8	8.1
	4	6.2	7.9	5.7	5.7	2.8	4.3	3.7	6.1	6.3
	5	12.5	9.5	8.1	6.6	5.4	5.9	5.2	6.0	7.4
Mean ±SD		**13.55±8.05**	**10.95±5.98**	**8.1±4.93**	**6.825±4.14**	**5.45±4.72**	**4.975±2.28**	**5.25±2.25**	**6.07±1.26**	**7.45±1.64**

* statistically significant values

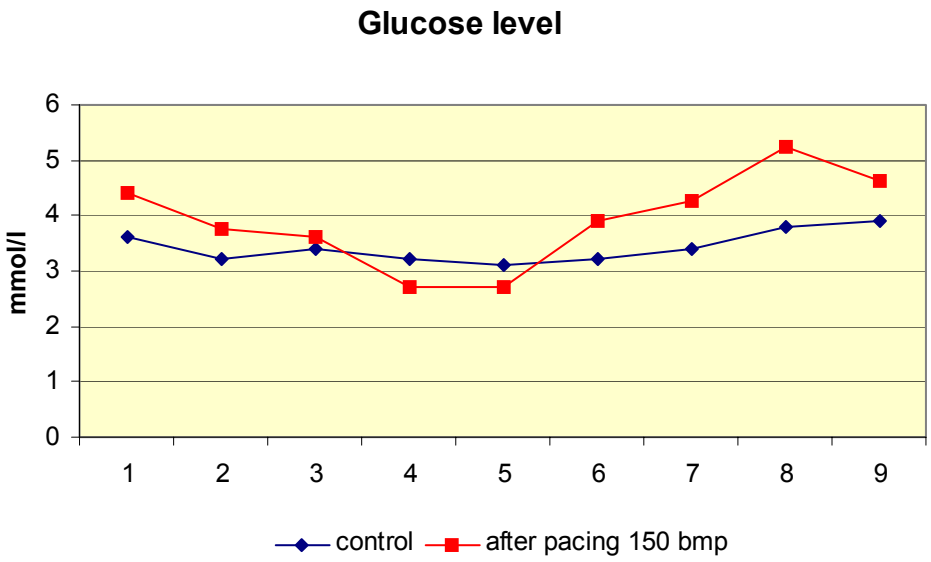


Fig. 1. Glucose level measurement during control and 150 bpm pacing rate.

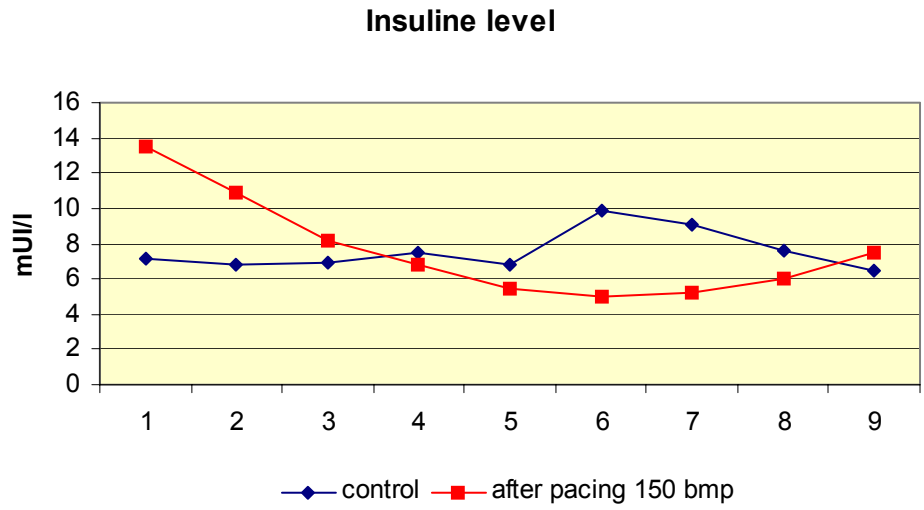
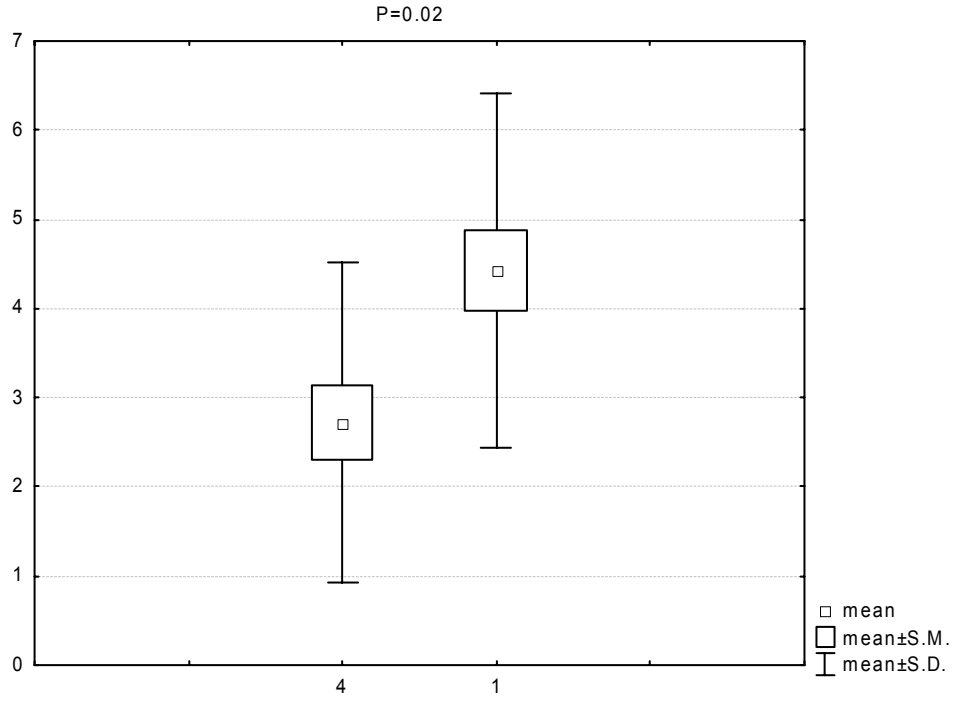
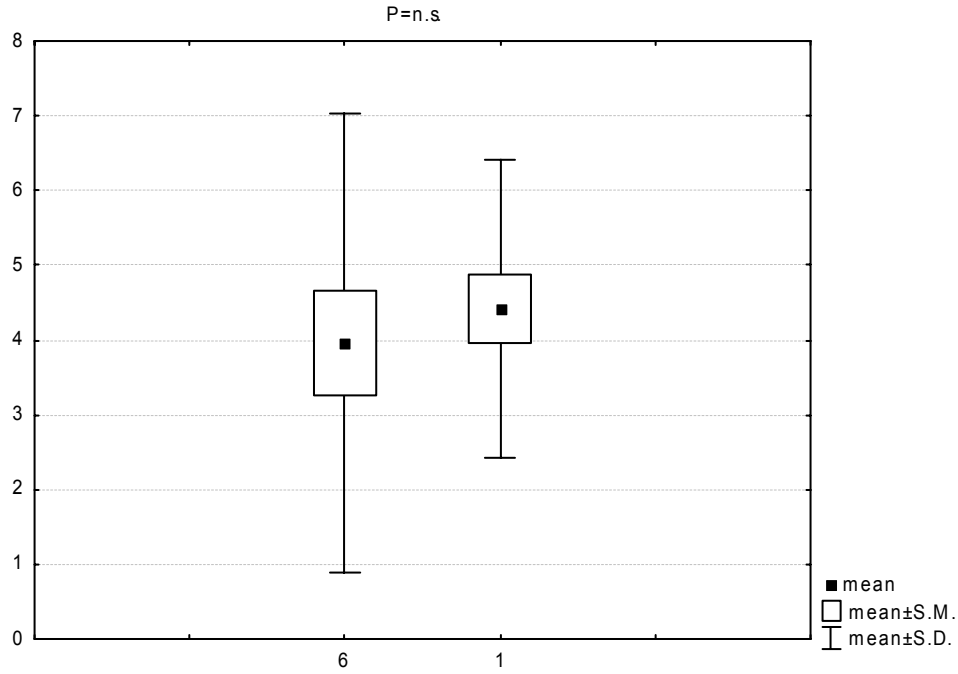


Fig. 2. Insulin level measurement during control and 150 bpm pacing rate.



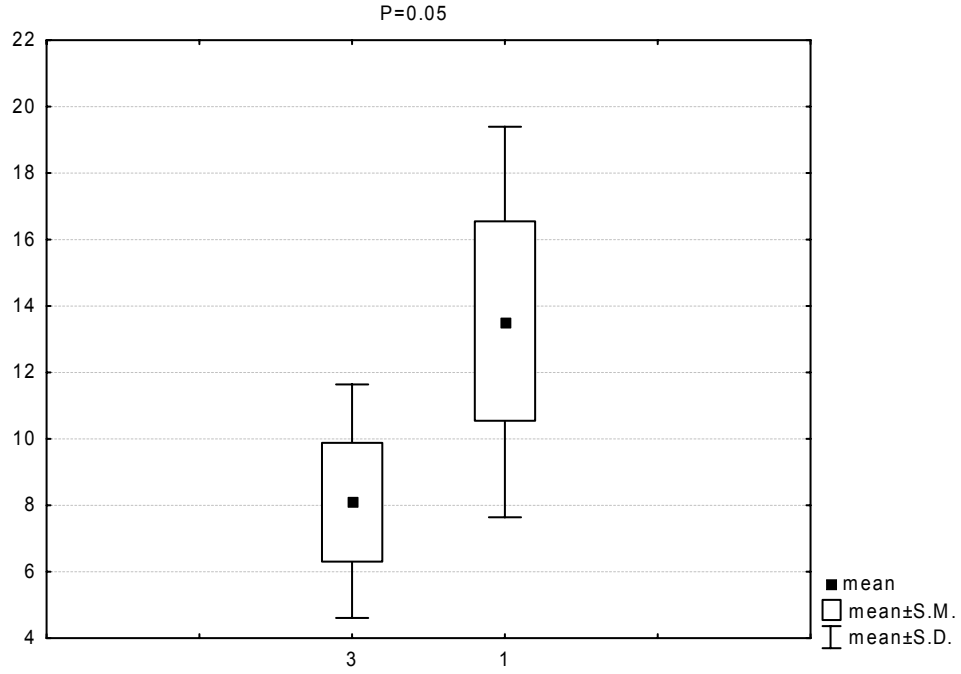
4 – glucose level 10 min after 150 bpm pacing
1 – glucose level before pacing

Fig. 3. Glucose level differences before and 10 min after 150 bpm pacing.



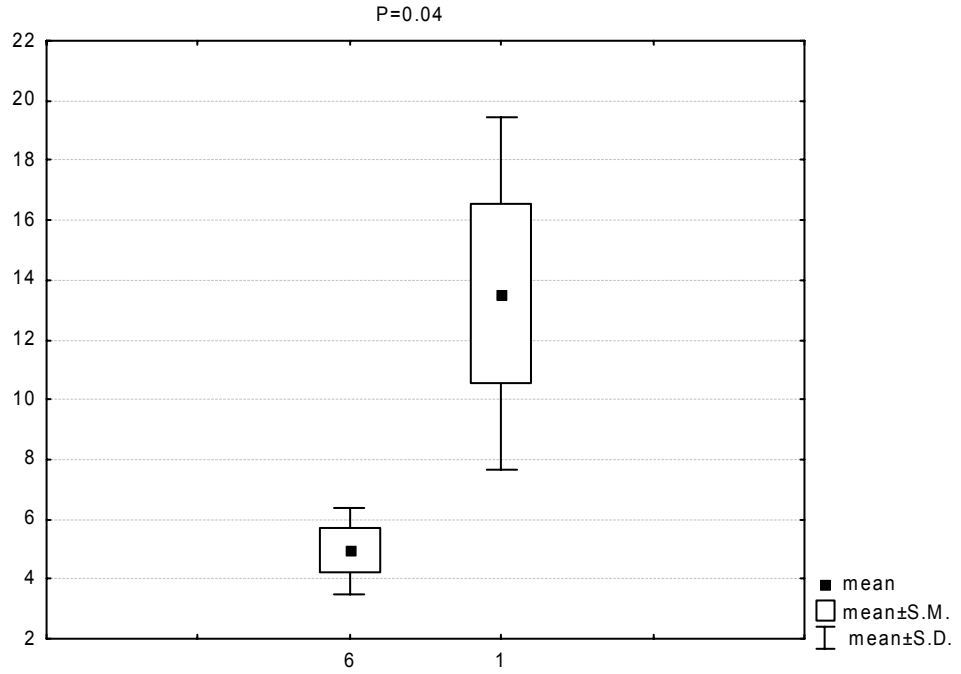
6 – glucose level 5 min after the end of heart stimulation
1 – glucose level before pacing

Fig. 4. Glucose level differences before stimulation and 5 min after the end of 150 bpm pacing.



1 – insulin level before pacing
3 – insulin level 5 min after heart stimulation with 150 bpm

Fig. 5. Insulin level differences before stimulation and 5 min after 150 bpm pacing



1 – insulin level before pacing
6 – insulin level 5 min after the end of heart stimulation

Fig. 6. Insulin level differences before stimulation and 5 min after the end of 150 bpm pacing.

Discussion

The obtained results may argue that there is an increase in glucose uptake by the heart muscle cells during tachycardia, which may lead to a significant hypoglycaemia, especially in persistent arrhythmias. The increase in glucose uptake is correlated with the insulin-dependent dislocation of glucose transporter GLUT-4 into the sarcolemma. A similar mechanism was observed in rats' heart during stress and ischaemia (18). Our experimental model presumed that anaesthesia resulting in metabolism reduction will significantly eliminate muscle and liver influence as two fundamental factors in glucose metabolism.

The adrenergic activation is the most common reason for tachycardia occurrence under physiological conditions. Based on the present study, it may be ascertained that doubling of a normal heart rate causes a considerable increase in energy consumption leading to significant glucose reduction. Insulin level decline was stated simultaneously, which may affirm that the accelerated heart rate alone is not an insulin resistance releasing factor. The source of high insulin levels are probably metabolic disorders, which are in turn induced by tissue hypoperfusion and adrenergic activity. As it results from the experiment, a short-time tachycardia is not correlated with insulin level increase, and is probably not related to the effect of insulin resistance. Even if there is intensified insulin release under catecholamine influence in healthy animals, this substance is rapidly metabolised in the liver so that the blood level of the insulin remains constant (7). It seems however, that the most probable explanation of any insulin level increase is a short duration of ischaemia and lack of significant haemodynamic alterations. Insulin is considered as an important component of a complex compensatory mechanism, having to support hypertension maintenance and to counteract hypotensive influence of ANP (13). Short-time tachycardia did not cause atrial enlargement and hypertension in the investigated pigs. However, these phenomena are responsible for the ANP release. The results of earlier studies suggest that cytokines (like TNF-α) take part in the development of insulin resistance but their level increases significantly only after longer lasting heart failure (6).

Glucose concentration already 5 min after the stimulation ended did not differ significantly from the concentration before pacing; this means that elimination of the arrhythmia not only improves patient's condition through a circulation and the normalisation of the brain's oxygen supply, but also restores normoglycaemia. Marked hypoglycaemia is seen in healthy animals with paroxysmal tachycardia events, but it recovers shortly after regular rhythm restoration. Reduced insulin level maintained to the end of observation. It seems therefore that the phenomenon of insulin level increase and insulin resistance is the expression of advanced but particularly chronic heart diseases. In paroxysmal tachyarrhythmia in animals without organic heart disease and serious metabolic disorders the complicating factor is only a marked fall of the glucose blood concentration.

A potential mechanism responsible for the described glucose and insulin alterations in the presented experiment is a lack of the possibility of cardiac output adaptation and a flow distribution as a result. Cardiac output is precisely regulated by the organism's metabolic demand, mainly resulting from the influence of the autonomic nervous system and resistance alterations in arterioles sensitive to metabolic changes (acidosis) (3, 8, 16). In case of cardiac output increase (in our experiment only by ventricular pacing) by about 60-80% of the resting values, fast blood redistribution must be considered. In relation to many adverse consequences of inappropriate blood flow increase, the most probable mechanism of blood overflow management is an increase in the muscle and/or skin flow. Muscle vessels are particularly voluminous, and, with regard to the results of our experiment, they may be responsible for the glucose and insulin level decrease as well.

Short-lasting tachycardia provoked by fast, forced ventricle rate, with no damage on the cardiac muscle, results in a significant fall of the glucose and insulin blood level. Glucose returns to its initial level several minutes after heart rate normalisation; however, insulin drop maintains for more than 10 min.

With regard to the small animal group, the research is treated as a preliminary communication. We do not know exactly an impact of the used anaesthesia and possible activation of other metabolic pathways involving substances resulting in similar to insulin cell effect (which may lower the insulin level). The blood redistribution in the condition of metabolically unjustified cardiac output increase will be further investigated.

References

1. Braunwald E., Zipes D., Libby P.: Heart Disease. Ed. W.B. Saunders Co., 2001 New York pp. 659-774, 815-889, 2151-2171.
2. Coven D.L., Hu X., Cong L., Bergeron R.: Convergence and divergence of the signaling pathways for insulin and phosphatidylinositolglycans. Mol Med 1998, **4**, 299-323.
3. Delp M.D., O'Leary D.S.: Integrative control of the skeletal muscle microcirculation in the maintenance of arterial pressure during exercise. J Appl Physiol 2004, **97**, 1112-1118.
4. Fenelon G., Wijns W., Andries E.: Tachycardiomyopathy: mechanisms and clinical implications. Pacing Clin Electrophysiol 1996, **19**, 95-106.
5. Gertz E.W., Wisneski J.A., Stanley W.C., Neese R.A.: Myocardial substrate utilization during exercise in human. J Clin Invest 1988, **82**, 2017-2025.
6. Heim K.E., Morrell J.S., Ronan A.M., Tagliaferro A.R.: Effects of ketamine-xylazine and isoflurane on insulin sensitivity in dehydroepiandrosterone sulfate-treated minipigs (*Sus scrofa domestica*). Comp Med 2002, **52**, 233-237.
7. Hotamisligil G.S., Arner P., Caro J.F., Atkinson R.L., Spiegelman B.M.: Increased adipose tissue expression of

tumor necrosis factor-alpha in human obesity and insulin resistance. J Clin Invest 1995, **95**, 2409-2415.
8. Hughson R.L., Tschakovsky M.E.: Cardiovascular dynamics at the onset of exercise. Med Sci Sports Exerc 1999, **31**, 1005-1010.
9. Kim S.P., Ellmerer M., Kirkman E.L., Bergman R.N.: Beta-cell "rest" accompanies reduced first-pass hepatic insulin extraction in the insulin-resistant, fat-fed canine model. Am J Physiol 2007, **292**, E1581-E1589.
10. Noszczyk-Nowak A., Pasławska U., Skrzypczak P., Gajek J., Zyśko D.: The own modification of the Selinger's method of introducing a catheter to the cervical internal vein. Magazyn Wet 2006, **6**, 44-46.
11. Palatini P., Casiglia E., Pauletto P., Staessen J., Kaciroti N.: Relationship of tachycardia with high blood pressure and metabolic abnormalities. A study with mixture analysis in three populations. Hypertension 1997, **30**, 1267-1273.
12. Palatini P.: High heart rate a risk factor for cardiovascular heath in elderly men. Arch Intern Med 1999, **159**, 585-592.
13. Pasławska U., Noszczyk-Nowak A., Glińska K., Kubiak K., Jankowski M., Nicpoń J.: Concentration of catecholamines in dogs with cardiac insufficiency and mitral endocardiosis. НАУКОВИЙ ВІСНИК Lviv, 2006, pp. 257-267.
14. Pasławska U., Noszczyk-Nowak A., Okręglicka E., Nicpoń J.: The analysis of arrhythmias in dogs diagnosed in the years 1996-2001 in the Clinic of Horses, Dogs and Cats Diseases at the Faculty of Veterinary Medicine of the Agricultural University of Wroclaw. Medycyna Wet 2004, **60**, 1191-1195.
15. Sarafidis P.A., Bakris G.L.: The antinatriuretic effects of insulin: an unappreciated mechanism for hypertension associated with insulin resistance? Am J Nephrol 2007, **27**, 44-54.
16. Schremmer B., Dhainaut J.F.: Regulation of myocardial oxygen delivery. Intensive Care Med 1990, **16**, 157-163.
17. Stanley W.C., Lopaschuk G.D., Hall J.L., McCormack J.G.: Regulation of myocardial carbohydrate metabolism under normal and ischemic condition. Cardiovasc Res 1997, **33**, 243-257.
18. Stanley W.C., Recchia F.A., Lopaschuk G.D.: Myocardial substrate metabolism in the normal and failing heart. Physiol Rev 2005, **85**, 1093-1129.
19. Winnicka A.: The referential values of basic laboratory examinations in veterinary medicine. Ed. SGGW, Warszawa, 1997, p. 108.
20. Wisnecki J.A., Gertz E.W., Neese R.A., Gruenke L.D., Morris D.L., Craig J.C.: Metabolic fate of extracted glucose in normal human myocardium. J Clin Invest 1987, **79**, 359-366.