Original article

Effect of short-term rapid ventricular pacing followed by pacing interruption on arterial blood pressure in healthy pigs and pigs with tachycardiomyopathy

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Abstract

Ventricular tachycardia may lead to haemodynamic deterioration and, in the case of long term persistence, is associated with the development of tachycardiomyopathy. The effect of ventricular tachycardia on haemodynamics in individuals with tachycardiomyopathy, but being in sinus rhythm has not been studied. Rapid ventricular pacing is a model of ventricular tachycardia. The aim of this study was to determine the effect of rapid ventricular pacing on blood pressure in healthy animals and those with tachycardiomyopathy. A total of 66 animals were studied: 32 in the control group and 34 in the study group. The results of two groups of examinations were compared: the first performed in healthy animals (133 examinations) and the second performed in animals paced for at least one month (77 examinations). Blood pressure measurements were taken during chronic pacing

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– 20 min after onset of general anaesthesia, in baseline conditions (20 min after pacing cessation or 20 min after onset of general anaesthesia in healthy animals) and immediately after short-term rapid pacing. In baseline conditions significantly higher systolic and diastolic blood pressure was found in healthy animals than in those with tachycardiomyopathy. During an event of rapid ventricular pacing, a significant decrease in systolic and diastolic blood pressure was found in both groups of animals. In the group of chronically paced animals the blood pressure was lower just after restarting ventricular pacing than during chronic pacing. Cardiovascular adaptation to ventricular tachycardia develops with the length of its duration. Relapse of ventricular tachycardia leads to a blood pressure decrease more pronounced than during chronic ventricular pacing.

Introduction

Ventricular tachycardia is a potentially lethal arrhythmia, especially when it occurs in patients with structural heart failure or when the ventricular rate is fast and exceeds 200/min. A chronic accelerated ventricular rate, experimentally induced by rapid stimulation, results in heart muscle impairment known as tachycardiomiopathy (Coleman et al. 1971, Packer et al.1986, Pasławska et al. 2011). Ventricular tachycardia activates compensatory mechanisms aimed at retaining blood pressure at a level ensuring maintenance of homeostasis. Clinical symptoms of hypotension related to ventricular tachycardia include dizziness, presyncope or fainting. A higher ventricular rate is associated with an elevated risk of more serious events (Morady et al. 1985). In patients with a chronic atrioventricular block or sinus bradycardia, cessation of transient ventricular pacing can lead to more serious haemodynamic disturbances than before ventricular pacing. However, it is not known whether arrhythmia cessation and its relapse after a short period of time, in a patient with persistent ventricular tachycardia, may or may not result in haemodynamic collapse.

The aim of this study was to determine the effect of ventricular tachycardia on blood pressure in healthy animals compared with those with tachycardiomyopathy.

Materials and Methods

The study design was previously described (Pasławska et al. 2011). Briefly, pigs of the Polish Landrace breed had a pacemaker implanted, and after 2 weeks of adaptation, it was activated and yielded a stimulation of 170 bpm. During check-ups, the anesthetised animals were weighed, and the pacemaker was deactivated to perform control examinations, including echocardiography, electrocardiography, electrophysiological tests and blood pressure measurements using the oscillometric method and a Medtronic Lifepak monitor. A blood pressure cuff was put on the animals' shank, and blood pressure measurements were taken every 2 minutes. We analysed the arterial blood pressure during 3 periods: period 1 – during chronic pacing at least 20 minutes after the onset of anaesthesia (measured only in chronically stimulated animals), period 2 – 20 minutes after stimulation cessation or in animals not paced at least 20 minutes after the beginning of anaesthesia, period 3 – during pacing at 170 bpm in both groups (restarting pacing in previously paced animals or short lasting pacing in healthy animals.

210 procedures were performed in 66 pigs. The control group consisted of 32 animals (these were control animals from 2 different studies), and the study group comprised 34 animals. Baseline conditions were defined as a period after at least 20 min after the onset of general anaesthesia and in the study group 20 min after pacing cessation. Blood pressure measurements were always made by the same team of researchers and using the same equipment. Measurements of blood pressure during short-term pacing in animals not previously paced were taken in the control group (animals with an implanted, but inactive pacemaker) and in the study group before the beginning of permanent pacing. A total of 210 procedures involved 133 procedures in pigs without previous stimulation and 77 procedures in previously chronically paced animals for at least one month. Blood pressure measurements during short-term pacing were taken in 32 examinations in healthy animals and in 49 examinations in previously chronically paced animals. Blood pressure during chronic pacing was taken in 30 examinations (that examination was included in the study protocol later so some animals had not had that measurement
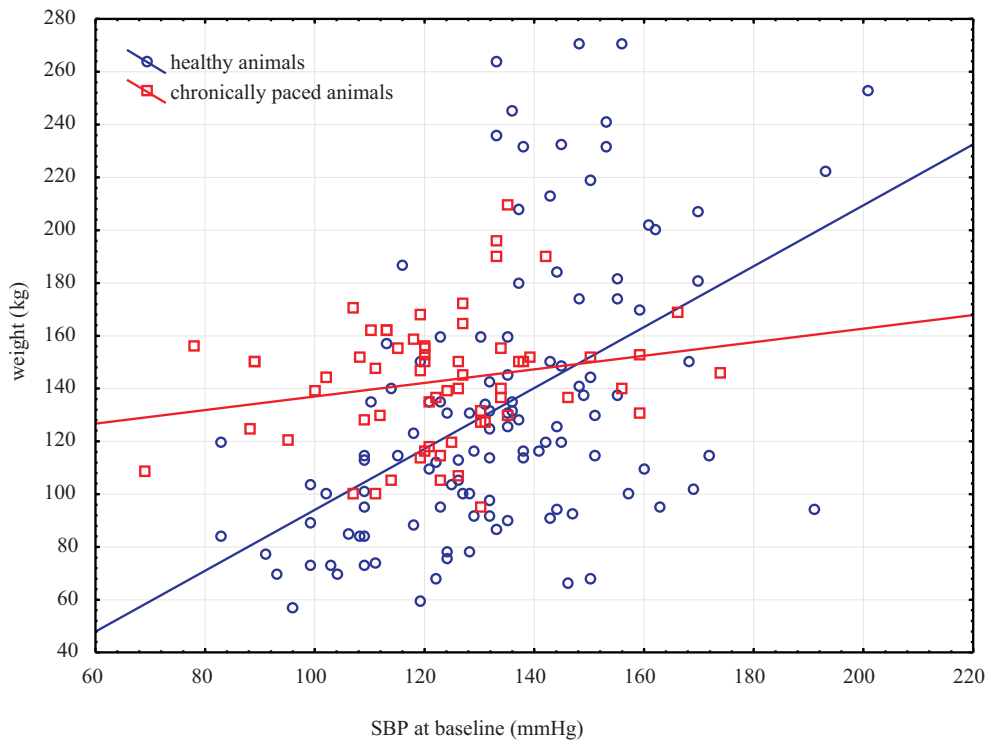
Fig. 1. Correlation between systolic blood pressure (SBP) and body weight in healthy animals and in chronically paced animals.

taken). In two of the latter examinations the baseline blood pressure was not taken.

The study was approved by the Ethics Committee.

Statistical analysis

The statistical analysis was performed using Statistica for Windows, version 8.0, StatSoft, Poland. Data from the experimental groups was analysed by means of Student's t-test or the Mann-Whitney U-test, depending on their distribution. Correlations were tested by Spearman's test and multivariate multiple regression. P level below 0.05 was considered significant.

Results

Clinical Parameters

The group of healthy animals in which the blood pressure measurements were taken (32 animals in the control group and 22 animals in the test group prior to the beginning of chronic stimulation) involved 28 females and 26 males. The group of chronically paced animals in which the blood pressure values were taken consisted of 7 females and 27 males.

Figure 1 presents the relationship between body weight and systolic blood pressure in chronically paced and healthy animals.

The Spearman correlation coefficient between body weight and systolic blood pressure in healthy animals was 0.51 ($p<0.001$) whereas in chronically paced animals it was 0.15 ($p=0.22$).

Arterial blood pressure in baseline conditions

Arterial blood pressure values in baseline conditions in healthy animals and in animals chronically stimulated for at least 1 month are shown in Table 1. Significantly higher systolic and diastolic blood pressure values were observed in healthy animals.

Arterial blood pressure during short-term pacing

Arterial blood pressure values during short-term pacing are shown in Table 2. A significant decrease in systolic and diastolic blood pressure was found in both groups of animals. Table 3 shows the blood pressure during chronic pacing compared to values measured after cessation of pacing and short-term pacing. The lowest blood pressure values were

Table 1. Blood pressure and body weight at examination in baseline conditions.

	Healthy animals	Chronically paced animals	P
Number of examinations (n)	133	77	
SBP (mmHg)	135.8 ± 22.0	121.9 ± 18.8	<0.001
DBP (mmHg)	82.4 ± 18.5	75.3 ± 16.7	0.006
HR (bpm)	78.5 ± 15.4	81.6 ± 16.1	0.18
Body weight at examination (kg)	144.8 ± 60.1	145.3 ± 25.8	0.94

SBP – systolic blood pressure, DBP – diastolic blood pressure

Table 2. Blood pressure in control group and study group in baseline conditions and during short-term pacing.

	Healthy animals	Chronically paced animals	P
Number of examinations (n)	32	49	
SBP baseline (mmHg)	115.6 ± 16.7	120.0 ± 19.7	0.300
DBP baseline (mmHg)	67.4 ± 16.5	74.4 ± 18.1	0.078
SBP short-term pacing (mmHg)	83.9 ± 18.8*	95.9 ± 20.7*	0.010
DBP short-term pacing (mmHg)	42.4 ± 17.0*	55.9 ± 18.3*	0.001
Body weight	99.1 ± 24.8	145.8 ± 28.3	<0.001

* – p<0.001 vs baseline
SBP – systolic blood pressure, DBP – diastolic blood pressure; HR- heart rate

Table 3. Blood pressure at baseline, during chronic pacing and during short-term pacing in the study group.

	Number of examinations (n)	mean ± SD
SBP baseline (mmHg)	30	124.1 ± 20.1
DBP baseline (mmHg)	28	75.7 ± 19.0
HR baseline (bpm)	28	84.4 ± 19.6
Weight (kg)	30	148.5 ± 32.2
SBP chronic pacing (mmHg)	30	110.3 ± 18.6*
DBP chronic pacing (mmHg)	30	65.6 ± 16.4*
SBP short-term pacing (mmHg)	30	100.6 ± 20.9[#,*]
DBP short-term pacing (mmHg)	30	57.5 ± 19.6[#,*]

SBP – systolic blood pressure, DBP – diastolic blood pressure; HR – heart rate
* – p<0.001 vs chronic pacing
# – p<0.001 vs baseline

observed after restarting ventricular pacing, and were significantly lower than those in the other analysed periods.

Multivariate analyses

Table 4 shows the results of multivariate multiple regression analysis of the relationship between systolic blood pressure during short-term pacing as the dependent variable, and the weight, gender and systolic blood pressure in the baseline condition. In multiple regression analysis it was found that the systolic blood pressure during short-term pacing was related to the body weight and systolic blood pressure in the baseline condition, but was not related to pacing duration and gender (p<0.001).

Table 4. Multiple regression of the dependent variable, systolic blood pressure, during the short-term pacing.

	B	Standard error b	BETA	Standard error beta	F	p
Weight	0.410	0.115	0.24	0.07	3.57	0.001
SBP baseline	0.511	0.086	0.57	0.10	5.92	**0.001**

SBP systolic blood pressure
BETA – standardized regression coefficients
B – raw regression coefficients

Discussion

This paper presents the results of a study involving the animal tachycardiomyopathy model used for haemodynamics assessment during chronic rapid ventricular pacing, a short period of sinus rhythm restoration and return to ventricular pacing. Tachycardia, which can be induced experimentally by rapid ventricular pacing, increases the risk of acute heart failure, and its chronic form leads to a number of changes in the circulatory system known as tachycardiomyopathy. Haemodynamic consequences of ventricular tachycardia involve reduced arterial blood pressure and elevated filling pressure, which are unique stimuli for the brain stem (Taneja et al. 2002) to activate mechanisms to maintain homeostasis. Short-term cardiovascular system adaptation to tachycardia is based on the activation of the sympathetic nervous system and alpha-adrenergic mediated vasoconstriction as well as beta-adrenergic mediated increased contractility and relaxation. Chronic rapid heart rate results in structural damage to the heart muscle and can affect the effectiveness of adaptation processes to ventricular tachycardia.

The study revealed that the blood pressure values measured in a short period after cessation of pacing are significantly lower in the study group than in the control animals. Lower blood pressure in those animals with heart failure related to tachycardiomyopathy is consistent with previously published large studies in humans. Lower systolic blood pressure indicates more serious damage to the heart muscle and is associated with increased mortality, as demonstrated in the observation of a large group of 48 612 patients in the OPTIMIZE-HF study (Abraham et al 2008). Studies conducted by other authors in smaller groups of patients showed no significant differences in the blood pressure under baseline conditions between patients with normal and reduced ejection fraction (Kolettis et al 2003). The differences between these studies may be explained by different heart failure pathogenesis in our study group and the works of other authors. Arterial hypertension and its complications are the leading causes of heart failure in humans, while in this study, heart failure was induced by excessive tachycardia. Reduced blood pressure in patients with previous arterial hypertension may be represented by blood pressure decrease to the level observed in healthy subjects.

The Spearman correlation coefficient between body weight and systolic blood pressure was positive in healthy animals, whereas there was no statistically significant correlation in chronically paced animals. This observation confirms the occurrence of reduced blood pressure in chronically paced animals.

Ventricular tachycardia induces significant haemodynamic disorders, but the associated blood pressure fluctuations are not fully predictable; there is a full range of possibilities: from a small drop in blood pressure to collapse and even death (Steinbach et al. 1994). In the present study, the induced ventricular tachycardia resulted in reduced blood pressure in both the study and the control group. This observation is consistent with the results of other authors (Kolettsi et al. 2003). Left ventricular systolic function is an important factor affecting blood pressure during ventricular tachycardia (Hamer et al.1984). The reason for the drop in blood pressure may be different for a healthy and a damaged heart. In the first case, a major role of diastolic dysfunction is indicated, and in the second, left ventricular contraction asynchrony may play the main role (Tanaja el al. 2002).

Ventricular tachycardia in humans is an indication for immediate treatment, and thus systematic studies of blood pressure changes during ventricular tachycardia recurrence, relatively quickly after its interruption, are impossible. The main conclusion of the study is that during prolonged high frequency ventricular pacing, the adaptive mechanisms maintain a higher blood pressure than immediately after the beginning of ventricular pacing, while the blood pressure is not significantly different following the cessation of long-term and short-term pacing.

The results obtained are consistent with the ob-

servation that the onset of tachycardia may lead to a drop in blood pressure, which then gradually increases as tachycardia persists (Feldman et al.1988, Smith et al. 1991).

Blood pressure values depend on the peripheral resistance and the stroke volume. In the period of pacing cessation, the increase in blood pressure depends on the extension of the diastole. The lower systolic and diastolic blood pressure noted immediately after the beginning of pacing suggest that blood pressure is affected not only by purely mechanical parameters associated with reduced diastolic period, but also with an autonomic nervous system imbalance. Previous studies have shown that permanent pacing leads to reduced beta-receptor density and a weakening of the reactions mediated by these receptors (Burchell et al. 1992, Wolff et al. 1992). In a resting condition and at a low cardiac workload, the heart correctly responds to β-adrenergic stimulation, but the response is insufficient when the cardiac workload increases (Francis 1987). Chronic tachycardia also leads to remodelling of ion channels, mainly K^+ and Ca^{2+}, which are responsible for the proper transfer of excitation to the ventricular muscle (Nabauer and Kaab 1998, Tomaselli and Marban 1999, Tsuji et al. 2000).

Ventricular tachycardia activates a complex reflex response, involving reflexes from the cardiac mechanoreceptors, reflexes caused by ischemia, such as during brain or kidney ischemia, decompressed arterial baroreceptors and stimulated cardiac and pulmonary baroreceptors (Landolina el al. 1997). The studies published so far have shown that the greater sensitivity of baroreceptor reflexes is associated with better tolerance of ventricular tachycardia (Hamdan et al 1999). Poor ventricular tachycardia tolerance may be related to inadequate stimulation of the sympathetic nervous system.

Blood pressure stabilisation during long-term ventricular tachycardia may activate other systems than the sympathetic nervous system (tachycardia interruption may diminish this activation), and return of tachycardia may result in more serious haemodynamic disturbances than the initial ones, as chronic heart failure involves impairment of the baroreceptors.

Hamer et al. (1984) conducted a human-based study in an electrophysiological laboratory and showed that syncope during electrically induced ventricular tachycardia did not depend on the ejection fraction or reduced cardiac output during sinus rhythm, but depended only on the heart rate: no loss of consciousness was observed at a rate of < 200/min. and all patients fainted at a rate of > 230/min. Kolettis et al. (2003) reported that patients with an injured

left ventricle had lower blood pressure during ventricular tachycardia than patients with preserved left ventricular function.

The degree of left ventricular function impairment usually depends on stimulation duration and its rate (Packer et al 1986). It should be noted that the progression of the disease and its clinical manifestation are also affected by comorbidities, age and the presence of arrhythmias (Fenelon et al. 1996). These factors were not present in our experiment.

Limitations

The main limitations of the study are significant differences in the weight of chronically paced and healthy animals. It is well known that blood pressure increases with animal weight. The body mass of chronically paced animals was significantly greater than the body mass of healthy ones, which could affect the results obtained. However, the multivariate analyses confirmed the relevance of chronic stimulation to blood pressure during pacing.

Conclusions

Rapid ventricular pacing results in a drop in blood pressure in both healthy animals and in chronically paced ones after short-term pacing cessation. Blood pressure during long-term pacing is higher than immediately after pacing restoration following a short period of sinus rhythm. Cardiovascular adaptation to ventricular tachycardia is different at its early and late stage of heart failure.

Acknowledgements

References

Abraham WT, Fonarow GC, Albert NM, Stough WG, Gheorghiade M, Greenberg BH, O'Connor CM, Sun JL, Yancy CW, Young JB, OPTIMIZE-HF Investigators and Coordinators (**2008**) Predictors of in-hospital mortality in patients hospitalized for heart failure: in-

sights from the Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure (OPTIMIZE-HF). J Am Coll Cardiol 52: 347-356.

Burchell SA, Spinale FG, Crawford FA, Zile MR. (**1992**) Effects of chronic tachycardia-induced cardiomyopathy on the beta adrenergic receptor system. J Thorac Cardiovasc Surg 104: 1006-1012.

Calo L, Sciarra L, Scioli R, Lamberti F, Loricchio ML, Pandozi C, Santini M. (**2005**) Recovery of cardiac function after ablation of atrial tachycardia arising from the tricuspid annulus. Ital Heart J 6: 652-657.

Coleman HN 3rd, Taylor RR, Pool PE, Whipple GH, Covell JW, Ross J Jr, Braunwald E (**1971**) Congestive heart failure following chronic tachycardia. Am Heart J 81: 790-798.

Feldman T, Carroll JD, Munkenbeck F, Alibali P, Feldman M, Coggins DL, Gray KR, Bump T (**1988**) Hemodynamic recovery during simulated ventricular tachycardia: role of adrenergic receptor activation. Am Heart J 115: 576-587.

Fenelon G, Wijns W, Andries E, Brugada P (**1996**) Tachycardiomyopathy: mechanisms and clinical implications. Pacing Clin Electrophysiol 19: 95-106.

Francis GS (**1987**) Hemodynamic and neurohumoral responses to dynamic exercise: normal subjects versus patients with heart disease. Circulation 76: VI11-17.

Hamdan MH, Joglar JA, Page RL, Zagrodzky JD, Sheehan CJ, Wasmund SL, Smith ML (**1999**) Baroreflex gain predicts blood pressure recovery during simulated ventricular tachycardia in humans. Circulation 100: 381-386.

Hamer AW, Rubin SA, Peter T, Mandel WJ (**1984**) Factors that predict syncope during ventricular tachycardia in patients. Am Heart J 107: 997-1005.

Juneja R, Shah S, Naik N, Kothari SS, Saxena A, Talwar KK (**2002**) Management of cardiomyopathy resulting from incessant supraventricular tachycardia in infants and children. India Heart J 54: 176-180.

Kolettis TM, Psarros E, Kyriakides ZS, Katsouras CS, Michalis LK, Sideris DA (**2003**) Haemodynamic and catecholamine response to simulated ventricular tachycardia in man: effect of baseline left ventricular function. Heart 89: 306-310.

Landolina M, Mantica M, Pessano P, Manfredini R, Foresti A, Schwartz PJ, De Ferrari GM (**1997**) Impaired baroreflex sensitivity is correlated with hemodynamic deterioration of sustained ventricular tachycardia. J Am Coll Cardiol 29: 568-575.

Mafirad M, Blaauw Y, van Opstal JM, Crijns HJ (**2012**) Haemodynamic bradycardia in tachycardiomyopathy. Neth Heart J 20: 184-185.

Morady F, Shen EN, Bhandari A, Schwartz AB, Scheinman MM (**1985**) Clinical symptoms in patients with sustained ventricular tachycardia. West J Med 142: 341-344.

Nabauer M, Kaab S (**1998**) Potassium channel down-regulation in heart failure. Cardiovasc Res 37: 324-334.

Nakazato Y (**2002**) Tachycardiomyopathy. Indian Pacing Electrophysiol J 2: 104-13

Packer DL, Bardy GH, Worley SJ, Smith MS, Cobb FR, Coleman RE, Gallagher JJ, German LD (**1986**) Tachycardia-induced cardiomyopathy: a reversible form of left ventricular dysfunction. Am J Cardiol 57: 563-570.

Pasławska U, Gajek J, Kiczak L, Noszczyk-Nowak A, Skrzypczak P, Bania J, Tomaszek A, Zacharski M, Sambor I, Dzięgiel P, Zyśko D, Banasiak W, Jankowska EA, Ponikowski P (**2011**) Development of porcine model of chronic tachycardia-induced cardiomyopathy. Int J Cardiol 153: 36-41.

Salemi VM, Arteaga E, Mady C (**2005**) Recovery of systolic and diastolic function after ablation of incessant supraventricular tachycardia. Eur J Heart Fail 7:1177-1179.

Steinbach KK, Merl O, Frohner K, Hief C, Nurnberg M, Kaltenbrunner W, Podczeck A, Wessely E (**1994**) Hemodynamics during ventricular tachyarrhythmias. Am Heart J 127: 1102-1106.

Taneja T, Kadish AH, Parker MA, Goldberger JJ (**2002**) Acute blood pressure effects at the onset of supraventricular and ventricular tachycardia. Am J Cardiol 90: 1294-1299.

Tomaselli GF, Marban E (**1999**) Electrophysiological remodeling in hypertrophy and heart failure. Cardiovasc Res 42: 270-283.

Tsuji Y, Opthof T, Kamiya K, Yasui K, Liu W, Lu Z, Kodama I (**2000**) Pacing-induced heart failure causes a reduction of delayed rectifier potassium currents along with decreases in calcium and transient outward currents in rabbit ventricle. Cardiovasc Res 48: 300-309.

Walker NL, Cobbe SM, Birnie DH (**2004**) Tachycardiomyopathy: a diagnosis not to be missed. Heart 90: e7.

Wolff MR, de Tombe PP, Harasawa Y, Burkhoff D, Bier S, Hunter WC, Gerstenblith G, Kass DA (**1992**) Alterations in left ventricular mechanics, energetics and contractile reserve in experimental heart failure. Circ Res 70: 516-529.