

Electrocardiography in Two Models of Isoproterenol-Induced Left Ventricular Remodeling

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Summary

We studied the ability of the ECG to detect pathological changes in isoproterenol-induced remodeling of rat heart. Myocardial hypertrophy in rats was induced by repeated injections of isoproterenol (5 mg/kg s.c. 7 days, Iso5, n=7). Single overdose of isoproterenol (150 mg/kg s.c., Iso150, n=7) evoked myocardial infarction followed with ventricular remodeling. The electrocardiograms were recorded in anesthetized animals (thiopental 45 mg/kg i.p.) and myocardial contractile performance was analyzed in isolated hearts perfused according to Langendorff. The hypertrophic hearts were characterized by increased heart and left ventricular (LV) weight as well as by thicker LV free wall and interventricular septum. Mean values of LV contraction did not significantly differ from controls. Longer QT interval, QRS complex, negative Q and S waves, higher R amplitude were typical characteristics for Iso5 rats. Iso150 animals showed tendency to decreased systolic blood pressure and heart frequency. Decrease in the thickness of LV compared to Iso5 as well as impaired LV function were related to the dilated left ventricle. Iso150 ECG showed longer QRS and QT, deepened negativity of S wave and mild decrease of R_{II} compared to Iso5. Voltage criteria showed that Sokolow-Lyon index is a good predictor of left ventricular hypertrophy in isoproterenol-induced cardiac remodeling without systemic hypertension.

Key words

Electrocardiography • Isoproterenol • Ventricular remodeling • Rat

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Introduction

Cardiac hypertrophy is a general term signifying an increased workload and is characterized with an increase in cardiac mass in response to applied stimulus (Akazawa and Komuro 2003). Prolongation of this process leads to congestive heart failure (HF) defined as a progressive syndrome that appears as the final phase of most cardiac diseases (Armoundas *et al.* 2001). Myocardial infarction (MI) is manifested with the impaired systolic and diastolic function, ventricular dilatation and ultimately with congestive HF (Bénitah *et al.* 2002).

There is enough evidence today to suggest that sympathoadrenal system besides hemodynamic alternations actively participate in the development of myocardial hypertrophy and human heart failure (Šimko 1996, 2007). Rona *et al.* (1959a) and showed that subcutaneous injections of the synthetic beta-adrenoceptor agonist isoproterenol (Iso) produced infarct-like lesions of the myocardium in the rat similar to those described in association with pheochromocytoma. Teerlink *et al.* (1994) demonstrated that administration of Iso induced diffuse myocardial necrosis and finally resulted in progressive left ventricular enlargement (LV). Taken together, morphological alterations following Iso application have been substantially characterized.

Electrocardiographic diagnostics of left ventricular hypertrophy (LVH) is based on longer QRS and QT interval duration, respectively, and changes in T wave morphology (Yan and Antzelevitch 1998, Gima and Rudy 2002, Kohútová *et al.* 2006, Kráľová *et al.* 2007). ECG changes suggested for experimental IM are the following: pathological Q waves, lengthening of the QRS

complex, and QRS abnormality, P wave enlargement, increased PR interval, increased QT interval, increase in the amplitude of the R wave in all precordial leads (Andrade *et al.* 1978).

Several voltage criteria could characterized LVH, however they possessed high specificities but low sensitivities (Norman and Levy 1995). Widely used are Sokolow-Lyon index and Cornell voltage. Clinical trials had demonstrated that these indexes are altered during chronic hypertrophy and are reversible under therapy (Baillard *et al.* 2000, Okin *et al.* 2003, 2004, Oikarinen *et al.* 2003, 2004).

Thus the objectives of the present study are: i) to determine the effects of different dosages of isoprenaline on cardiac dimensions and function, ii) to characterize the ECG variables in isoproterenol induced myocardial remodeling, iii) to correlate ECG changes with pathological cardiac parameters.

Methods

Animals

In order to determine the most efficacious dosage inducing significant myocardial damage along with an acceptable survival rate, 2 different dosages of isoproterenol (Fluka, Steinheim, Germany) were tested. Left ventricular hypertrophy was evoked by repeated administration of isoproterenol low dosages (Mészáros and Pásztor 1995, Mészáros *et al.* 2001, Křenek *et al.* 2006). The optimal dosage to achieve development of heart failure following the isoproterenol administration was well described by Grimm *et al.* (1998).

Two-three months old male Wistar rats (weighting 240-310 g) were obtained from breeding station Dobrá Voda (SR). Animals from control group (n=5) were pretreated with subcutaneous (s.c.) injection of vehicle (0.05 % ascorbic acid solved in 0.9 % NaCl Centralem, Bratislava, Slovak Republic, for solution stabilization). Rats were pretreated with isoproterenol daily at a dose 5 mg/kg s.c. for 7 days (Iso5, n=7) or at a single dose 150 mg/kg s.c. (Iso 150, n=7).

All care was in accordance with the Guide for the Care and Use of Laboratory Animals in the Statute book Z.z. SR No. 289/2003 and experiments were realized with the approval of the Ethics Committee of the Faculty of Pharmacy CU and by State veterinary and food management SR protocol No. Ro-2222/06-221.

Blood pressure measurement

The mean arterial blood pressure was measured in

awaked animals by the non-invasive blood pressure module (NIBP Controller, ADInstruments, Spechbach, Germany) connected through the manometer and Powerlab 8/30 module (ADInstruments, Spechbach, Germany) to the computer (PS Tronic, Bratislava, Slovak republic).

For every data point, five measurements were performed and mean values were calculated. The data analyses were realized by software Chart 5 pro Windows (ADInstruments, Spechbach, Germany).

Electrocardiograms and assessment

The 12-leads ECG was recorded in anesthetized animals (45 mg/kg, 5 % solution i.p.) thiopental, Biochemie GmbH, Kundl, Austria). The rat was fixed on pad in position on back and 12-leads ECG was recorded by ECG module (SEIVA EKG PRAKTIK, Prague, Czech Republic) and stored by DELL Latitude CP (Dell Bratislava, Slovak Republic). The tracings were analyzed by Seiva Veterinary Praktik software (SEIVA, Prague, Czech Republic).

Hemodynamic study

After ECG monitoring the hearts were excised from anesthetized animals according to the following steps. The abdominal cavity was opened and rats were heparinized (500 IU, Heparin inj. 5000 I.U., Léčiva, Prague, Czech Republic) into vena cava inferior. After chest opening heart was separated and rapidly immersed into the cold (4 °C) Krebs-Henseleit (K-H) solution where cannula was inserted into the aorta and fixed with a silk ligature. Hearts were placed in an organ chamber in Langendorff apparatus and retrogradely perfused with K-H solution at constant pressure mode (90-100 cm H₂O). K-H solution containing (in mM) NaCl 118.0; KCl 4.70; MgSO₄ 1.66; KH₂PO₄ 1.18; CaCl₂ 2.00; NaHCO₃ 15.00; glucose 11.00 (all chemicals are from Centralem, Bratislava, Slovak Republic) and saturated with 95 % oxygen and 5 % carbon dioxide (pH 7.35-7.4, temperature 36.5-37°C). Ventricular pressure was measured by means of a water-filled balloon inserted into the LV cavity through a left atrial incision. A balloon volume was adjusted to yield 9-10 mm Hg of LV end-diastolic pressure. LV pressure was continuously monitored by electromanometer (LDP186 Tesla, Valašské Meziříčí, Czech Republic) and recorded by Powerlab 8/30. LV developed pressure as a measure of cardiac contractility was calculated as a difference between LV systolic and diastolic pressures.

At the end of experiment the heart was placed into cold K-H solution for few minutes to stop beating. The

Table 1. Selected parameters and hemodynamic findings in control and Iso groups.

Parameters	Control n = 5	Iso 5 n = 7	Iso 150 n = 7
sBP (mm Hg)	125 ± 13	121 ± 13	114 ± 3
HR (beat/min)	348 ± 55	338 ± 64	277 ± 30
Body weight (g)	306 ± 7	271 ± 11 [#]	253 ± 17 ⁺
HW/BW (mg/g)	3.92 ± 0.14	4.44 ± 0.80 [*]	4.77 ± 0.45 [#]
LVW (g)	0.72 ± 0.08	1.00 ± 0.05 [*]	0.73 ± 0.19 [#]
LVW/BW (mg/g)	2.35 ± 0.26	2.62 ± 0.64 [*]	4.00 ± 0.40 [#]
LVWT (mm)	3.24 ± 0.21	4.14 ± 0.52 [*]	3.52 ± 0.35
Septum (mm)	2.56 ± 0.27	3.14 ± 0.28 [*]	3.04 ± 0.31 ⁺
LVP _d (mm Hg)	5.64 ± 2.66	6.19 ± 1.60	7.82 ± 1.39 ⁺
LVP _{s-d} (mm Hg)	98.87 ± 32.04	86.97 ± 11.51	38.50 ± 23.75 ^{+#}

Iso – isoproterenol, sBP = systolic blood pressure, HR = heart rate, HW/BW = heart weight/body weight, LV = left ventricle, LVW = left ventricular weight, LVW/BW = left ventricular weight/body weight, LVWT = left ventricular wall thickness, LVP_d = diastolic left ventricular pressure, LVP_{s-d} = systolic-diastolic difference of left ventricular pressure. Data are expressed as mean ± S.D. *p < 0.05 control vs Iso 5, ⁺p < 0.05 control vs Iso 150, [#]p < 0.05 Iso 5 vs Iso 150.

hypertrophy was estimated by measuring blotted wet heart (HW) and left ventricle weight (LVW), and calculating HW or LVW-to-body weight (BW) ratio. The thickness of interventricular septum and left ventricular free wall was measured.

Statistics

Statistical analysis was performed with Excel version 5.0 and OriginPro version 5. All values are expressed as mean ± S.D. Statistical comparison between the control and Iso groups were analyzed using one way ANOVA and Spearman test at level p ≤ 0.05 that was considered as a statistically significant.

Results

Seven days lasting repeated administration of 5 mg/kg isoproterenol (Iso 5) demonstrated compensated, moderate left ventricular hypertrophy without heart failure. Rats that received once isoproterenol dosage of 150 mg/kg (Iso 150) showed marked cardiac enlargement and visible apical or disseminated ventricular ischemic lesions. Dosages of 5 mg/kg and 150 mg/kg resulted in death rates of 46 % and 55 %, respectively, within the premedication period. Surviving animals were used for the experiments 24 h after the last application of 5 mg/kg isoproterenol or 14 days after administration of single overdose.

Systolic blood pressure and heart rate did not significantly changed between the groups, however smaller

decrease was seen in Iso 150 (Table 1). Left ventricular pressure was measured in isolated perfused hearts. As compared with vehicle left ventricular diastolic pressure (LVP_d) was increased in Iso groups (Table 1). Significant increase in LVP_d together with significant reduction in left ventricular developed pressure (LVP_{s-d}) in Iso 150 group indicated deterioration of left ventricular mechanical function compared with both control and Iso 5 group.

Body weight was significantly reduced in both Iso groups (Table 1) as compared to control rats. Heart weight/body weight ratio as well as LV weight/body weight index were increased in Iso 5 group and augmented in Iso 150 rats. Significantly increased thickness of interventricular septum and LV free wall was found in Iso 5 group in comparison with control or Iso 150 group.

The standard and precordial leads were recorded for each animal during deep anesthesia. Significant changes in the ECG configuration (Table 2) in the rats with cardiac hypertrophy (Iso 5) were as follows: increased amplitude of P wave for about 50 % in the I. standard lead compared to Iso 150 and nonsignificant prolongation of PQ interval and QRS complex increased amplitude of R in the I limb lead, longer QT interval, presence of negative Q and S waves in the I and II standard limb leads, flattening and lengthening of T wave for about 53 % and inversion in 25 % of rats compared to control rats. In Iso 5 group the significantly higher amplitude of R was found in precordial leads V4-V5 (105, 68 a 90 %, respectively) as well as the augmented negativity (about 41 %) of S in V1 and

Table 2. Electrocardiographic parameters at baseline and after Iso pretreatment.

Parameters	Control n = 5	Iso 5 n = 7	Iso 150 n = 7
R-R (ms)	14.67 ± 0.86	20.65 ± 1.94 ^{*#}	15.20 ± 0.50
R _{II} amplitude (mV)	0.79 ± 0.15	0.78 ± 0.18	0.64 ± 0.19
R _I amplitude (mV)	0.52 ± 0.12	0.82 ± 0.19 ^{*#}	0.62 ± 0.10
QRS duration (ms)	15.13 ± 1.51	16.54 ± 1.00	18.57 ± 2.50 [#]
QT interval (ms)	55.00 ± 8.82	67.62 ± 2.23	58.33 ± 0.83
Q _{II} amplitude (mV)	-0.60 ± 0.20	-2.29 ± 1.49 ^{*#}	-0.78 ± 0.43
Q _I amplitude (mV)	-0.52 ± 0.10	-1.00 ± 0.58 [#]	-0.88 ± 0.38 ⁺
S _{II} amplitude (mV)	-0.03 ± 0.01	-0.11 ± 0.07 [*]	-5.03 ± 0.25 ^{+ #}
S _I amplitude (mV)	-0.03 ± 0.01	-0.05 ± 0.03	-1.25 ± 0.47 ^{+ #}
Sokolow-Lyon R _I +S _{III} (mV)	0.77 ± 0.24	1.20 ± 0.17 [*]	1.16 ± 0.15 ⁺
Sokolow-Lyon R _{V6} +S _{V1} (mV)	0.67 ± 0.18	2.09 ± 0.48 ^{*#}	1.11 ± 0.55 ⁺
Cornell R _{aVL} +S _{V3} (mV)	0.49 ± 0.14	0.74 ± 0.13 [*]	0.80 ± 0.26 ⁺

Iso – isoproterenol. Data are given as mean ± S.D. *p<0.05 control vs Iso 5, ⁺p<0.05 control vs Iso 150, [#]p<0.05 Iso 5 vs Iso 150.

negative T wave in V3–V6 in 3 rats compared to control group. ST depression could be related to subendocardial ischemia and necrosis.

The Iso overdose (Table 2) induced longer duration of QRS complex, lower R amplitude and surprisingly smaller Q but deeper S waves in both I and II standard leads in contrast to Iso 5. ST segment depression was found in 86 % and T wave inversion in 28 % of rats. The QT interval was the longest in Iso 5 group compared to other groups. Both pretreatments with Iso modified the average RR interval.

Compared to control rats in Iso 150 precordial leads showed the 33 % increase of R in V4, but 16 % decrease in V5 and 32 % in V6, together with 65 % raise in S negativity in V1 and elevation of ST segment mostly in V2, V3 leads. Elevation of ST segment indicated subepicardial ischemia in the apex and in the lateral left ventricular wall.

In clinical trials voltage criteria present an alternative eligibility for identifying ventricular hypertrophy. Both Iso groups showed higher Sokolow-Lyon indexes calculated either from standard or precordial leads and Cornell voltage than the baseline voltage criteria found in control group (Table 2). Sokolow-Lyon index calculated from the amplitudes in precordial leads was 1.6-fold higher in Iso 150, and even more than three times higher in Iso 5 compared to control showing intensive hypertrophy induced by repeated administration of low Iso dosages.

Discussion

The present study provides further evidence about isoproterenol-induced remodeling of myocardium. Relatively short time period of administration of repeated low doses of isoproterenol induced cardiac hypertrophy. This phenomenon was described in past century and later confirmed with many authors (Mészáros and Pásztor 1995, Baillard *et al.* 2000, Mészáros *et al.* 2001, Sia *et al.* 2002, Křenek *et al.* 2006). It was suggested that observed myocardial changes could be induced as direct response of the elevated level of circulating isoproterenol at the time of experiments (Mészáros *et al.* 2001).

Synthetic β-adrenoceptor agonist isoproterenol leads to development of cardiac hypertrophy without increased blood pressure as a consequence of increased heart work. (Ozaki *et al.* 2002, Kaye and Esler 2005). The massive decrease of peripheral resistance and vasodilatation lead to diastolic and systolic pressure decrease, despite positive inotropic and chronotropic effect on the heart. Leenen *et al.* (2000) found out that the increased activity of the circulatory renin-angiotensin system appears to blunt the hypotensive effects of isoproterenol.

The microscopic characteristics of Iso-induced cardiomyopathy are focal or confluent myocardial lesions (Rona *et al.* 1959a,b). Goldspink *et al.* (2004) applied isoproterenol in single dose (5 mg/kg) and found out the disseminated necrosis in the heart. Kahn *et al.* (1969)

applied Iso (85 mg/kg, 2 days) to rats and detected extensive necrosis in endocardium. Cardiomyocyte loss is the initial insult that triggers the development of heart failure. Jalil *et al.* (1989) reported expanded myocardial fibrosis after high doses of isoproterenol, which may have a significant impact on both systolic and diastolic function of the heart. In our experiments LV function and myocardial contractility were slightly affected with hypertrophy, but significant deterioration of contractile ability was found after high dose of isoproterenol.

Single injection of Iso overdose induces development of LV dilatation and hypertrophy (Grimm *et al.* 1998) usually found in mild heart failure. Loss of ventricular power in Iso 150 means loss efficient emptying of the ventricle causing a diastolic pressure increase within the ventricle. This causes the remaining viable myocytes stretching and thinning the myocardium, ultimately causing dilatation of ventricle. In order to maintain contractility, the myocytes increase the width, and so increase the thickness of the myocardial wall.

The Iso overdose (Iso 150) induced longer duration of QRS complex, lower R amplitude and smaller Q but deeper S waves in both I and II standard leads in contrast to Iso 5. ST segment depression and T wave inversion was found in rats, too. Some studies analyzed QRS voltage in hypertrophic hearts. Yamori *et al.* (1976) published increased QRS amplitude in SHR as compared to normotensive Wistar-Kyoto strain. In contrast Bachárová *et al.* (2005) presented decreased values of QRS. The explanation for the results is in use of orthogonal vectorcardiography analyzing maximal spatial vector of QRS.

In control rats the amplitude of R is taller in II.limb lead than in I. lead indicating normal position of the heart in the chest cavity. In Iso 5 the increased R amplitude was seen in the first standard lead outlined horizontal position of hypertrophic heart. Even increased thickness of interventricular septum in hypertrophic hearts probably corresponded to deep Q waves found in Iso 5 in standard leads.

In hypertensive patients with ECG LVH, increase in LV mass was associated with prolonged QRS and QT interval durations (Dritsas *et al.* 1992, Baillard *et*

al. 2000, Oikarinen *et al.* 2003). Lengthening of the QRS complex is related to the diffuse myocardial damage where myocardium is replaced by fibrosis (Mazzoleni *et al.* 1975). The QT interval is also prolonged and correlates with the LV mass as assessed by 2D echocardiography in hypertrophic cardiomyopathy in humans (Galiner *et al.* 1997). QT interval assumes for both ventricular depolarization and repolarization. Mild prolongation of QT and QRS in Iso 150 could indicate slowing in ventricular conduction. However, longer QT without intense QRS prolongation could suggest changes preferentially in ventricular repolarization in Iso 5.

Some clinical trials (Okin *et al.* 2003, 2004, Oikarinen *et al.* 2003, 2004) enrolled hypertensive patients with ECG LVH by voltage criteria. Denarie *et al.* (1998) showed low performance of Sokolow-Lyon index for estimating increased LVM, but Alfakih *et al.* (2004) demonstrated that Sokolow-Lyon index and Cornell voltage were comparable in identification of LVH. Our results demonstrated that calculated voltage criteria were higher for both Iso groups compared to control indicating the presence of myocardial hypertrophy and/or myocardial ischemia. Only Sokolow-Lyon index from precordial leads showed significant difference between Iso 5 and Iso 150 group and probably indicate significant association with myocardial hypertrophy. These data filled in the missing information about clinically used voltage criteria in animal experiments with isoproterenol.

Conflict of Interest

There is no conflict of interest.

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