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Bainbridge reflex in rats with post-myocardial infarction heart failure – mathematical considerations**

Odruch Bainbridge'a u szczurów z pozawałową niewydolnością serca – rozważania matematyczne

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Sowa kluczowe

pętla ciśnienie-objętość, zawał mięśnia sercowego, odruch Bainbridge'a, korelacje wzajemne

Conflict of interest

Konflikt interesów

None

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Summary

Introduction. Bainbridge reflex, referring to an increase in heart rate (HR) secondary to an increase in central blood volume, is a very important cardiovascular reflex for adjusting hemodynamic performance of the heart to the preload. Its efficiency in heart failure is unknown.

Aim. To characterize the Bainbridge reflex in the post-myocardial infarction (MI) heart failure in the rat model.

Material and methods. Rats were subjected to induction of large non-reperfused MI or sham operation and were followed-up for 8 weeks after the surgery. The left ventricle pressure-volume (PV) loops were recorded to obtain multiple parameters characterizing LV systolic and diastolic performance and preload and afterload, under baseline conditions and following rapid saline infusion to increase the preload.

Results. Increase of HR in response to increased preload was higher in post-MI than in sham operated rats (80 ± 20 vs. 31 ± 10 bpm, respectively). To gain further insight into the Bainbridge reflex, we performed cross correlations between multiple hemodynamic parameters and HR. During the preload increase strength of cross correlations for HR was poorer in post-MI heart failure rats than in sham operated control animals, indicating that overall reflex control of the cardiovascular system may be impaired in this condition.

Conclusions. The Bainbridge reflex is preserved and even exaggerated in the post-MI heart failure in the rat.

Streszczenie

Wstęp. Odruch Bainbridge'a oznacza wzrost częstotliwości rytmu serca w odpowiedzi na zwiększone obciążenie wstępne. Jego aktywność w niewydolności serca jest nieznana.

Cel pracy. Scharakteryzowanie odruchu Bainbridge'a w pozawałowej niewydolności serca u szczura.

Materiał i metody. U szczurów indukowano rozległy, niereperfundowany zawał mięśnia sercowego (MI) lub wykonywano operację pozorowaną (Sham). Zwierzęta obserwowano przez 8 tygodni po operacji, a następnie cewnikowano lewą komorę serca z rejestracją pętli ciśnienie-objętość w celu pomiaru ciśnienia skurczowego i rozkurczowego oraz pomiaru parametrów charakteryzujących obciążenie wstępne i następcze w warunkach podstawowych i po podaniu szybkiego wlewu soli fizjologicznej w celu zwiększenia obciążenia wstępnego.

Wyniki. Wzrost częstotliwości rytmu serca w odpowiedzi na zwiększone obciążenie wstępne był większy u szczurów z niewydolnością serca (odpowiednio 80 ± 20 wobec 31 ± 10 uderzeń na minutę). Korelacje wzajemne licznych parametrów hemodynamicznych z częstotliwością rytmu serca w okresie zwiększenia obciążenia wstępnego wykazywały niższe współczynniki korelacji w grupie z niewydolnością serca niż u zwierząt kontrolnych.

Wnioski. Odruch Bainbridge'a jest zachowany, a nawet nasilony w pozawałowej niewydolności serca u szczura.

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INTRODUCTION

The cardiac cycle involves five major stages. The first stage, “diastole”, begins when the atrioventricular valves (the mitral valve and tricuspid valve) open to allow free inflow of blood, and both atria and ventricle relax. During this stage, the blood inflows from the superior and inferior vena cavae to the right atrium and right ventricle and from the pulmonary veins to the left atrium and left ventricle. The healthy myocardium is progressively stretched by the inflowing blood and diastolic pressures rise.

The second stage, named “atrial systole,” follows when the atrium contracts and pumps additional volume of blood into the ventricles, causing additional increase of ventricular diastolic pressures. This is an important stage of the cardiac cycle, since the strength of ventricular contraction relates directly to end-diastolic ventricular filling, and more particular to the end-diastolic length of the sarcomeres of ventricular myocytes. The third stage, “isovolumic contraction” is when the ventricles begin to contract, the atrioventricular valves close, semilunar valves continue to be closed, and there is no change in volume. The fourth stage, “ventricular ejection,” is when the semilunar valves open and ventricles are ejecting blood. This phase is termed ejection phase. The fifth stage, “isovolumic relaxation” begins when ventricles start to relax, the ventricular pressures decrease, and eventually when ventricular pressure drops below the pressure in respective arteries (aorta and pulmonary artery), the semilunar valves close. When the ventricular pressure drops below the atrial pressure, atrioventricular valves open and the cycle begins again. Recently the simultaneous measurement of LV pressure and volume (so called pressure-volume loops) has become a state-of-the-art approach to assess in detail global cardiac function and cardiac cycle *in vivo* (1, 2).

Cardiac function is regulated by a number of cardiovascular reflexes. These include arterial baroreceptor reflex, Bezold-Jarisch reflex and Bainbridge reflex. While the first two of these reflexes are relatively well known, the latter has not been examined in detail. The Bainbridge reflex refers to the increase in heart rate secondary to an increase in central blood volume (3). Francis A. Bainbridge and collaborators demonstrated that an infusion of saline into the jugular vein of the anesthetized dog produced tachycardia (4). Subsequently they showed that the tachycardia was reflex in origin, with the vagus nerves constituting the afferent limb and a withdrawal of vagal tone the primary efferent limb (5). The mechanoreceptors that elicit the reflex are located at the junction of the right atrium and caval veins or at the junctions of the pulmonary veins and the left atrium. The Bainbridge reflex and the baroreceptor reflex act antagonistically to control the heart rate. It was shown convincingly that the Bainbridge reflex was present in primates, including humans, but that the reflex was much less prominent than in the dog.

Myocardial infarction (MI) was shown to affect cardiovascular reflexes. Arterial baroreceptor sensitivity is impaired after MI both in humans (6) and in rats (7). However, Bainbridge reflex has not been investigated in this setting. Thus the aim of our study was to analyze

reflex regulation of the cardiovascular system with particular emphasis on Bainbridge reflex in the model of post-myocardial infarction rat.

MATERIAL AND METHODS

This examination conformed to the National Institutes of Health *Guide for the Care and Use of Laboratory Animals* (NIH Pub. No. 85-23, Revised 1996) and was performed with the approval of the local Ethics Committee for Animal Use.

Study design

For the purpose of the study, 23 male Wistar-Kyoto rats (280-330 g) were used in, where 14 underwent induction of non-reperfused myocardial infarction and 9 underwent sham operation. MI was induced as described previously (8). Briefly, the rats were anaesthetized with ketamine HCl (100 mg/kg body weight, i.p.) and xylazine (5 mg/kg body weight, i.p.), and left thoracotomy was performed. The heart was externalized and a suture (5-0 silk) was placed around the proximal left coronary artery and tightly tied. The heart was internalized, the chest was closed, and pneumothorax was reduced. The sham operated rats were subjected to the same protocol except that the snare was not tied.

Eight weeks after MI induction/sham procedure, the rats underwent echocardiographic imaging and recording of pressure-volume (PV) loops.

Echocardiography

Echocardiography was performed using MyLab25 (Esao, Italy) with 13 MHz linear array transducer under light anaesthesia (ketamine HCl and xylazine, 75 and 3.5 mg/kg body weight, i.p.), as reported previously (9).

Pressure-volume loops recording

To record PV loops, rats were anesthetized with ketamine HCl (100 mg/kg body weight, i.p.) and xylazine (5 mg/kg body weight, i.p.). The animals were placed on a heating pad, tracheotomized and connected to an animal respirator (respiratory rate 60/min, tidal volume 4 ml). The upper abdominal cavity was opened and through cutting of the diaphragm, the heart was exposed. The left ventricular apex was punctured with a 25G needle and a microtip P-V catheter (SPR-838, Millar Instruments; Houston, TX) was inserted into the LV. Its position was established based on pressure and volume signals. After stabilization for 5 minutes, the signals were continuously recorded at sampling rate of 1000/s using an ARIA P-V conductance system (Millar Instruments) coupled to a PowerLab/4SP A/D converter (AD Instruments; Mountain View, CA) and a personal computer. Cardiovascular parameters: HR, maximal LV systolic pressure (LVSP), LV end-diastolic pressure (LVEDP), maximal slope of systolic pressure increment (+dP/dt) and diastolic pressure decrement (−dP/dt), time constant of LV pressure decay (τ), ejection fraction (EF), end-diastolic volume (LVEDV), end-systolic volume (LVESV), stroke volume (SV), cardiac output (CO) were computed

using a cardiac P-V analysis program (PVAN3.2, Millar Instruments). The presented parameters were averaged from at least 10 consecutive stable beats.

Preload was increased using a bolus of warm physiological saline (12 ml/kg b.wt.), given to the femoral vein through a catheter over approximately 20 seconds.

Thus, the study protocol involved recording of PV loops in the following three stages: (I) baseline, (II) after preload increase and (III) normalization.

Mathematical evaluation: cross correlation as a method of analysis of PV loops

Cross correlation is a measure demonstrating interrelations between two variables (10) that characterize a specific process. Time series are analyzed by demonstrating relations between them. In such context, time shift (τ) can be used, corresponding to a delay. Cross correlation ranges from -1 to 1. The sign of relation indicates direction of cross correlation. If values are close to zero, there is simply no cross correlation. In this paper we calculated and investigated correlations of the following hemodynamic parameters with heart rate: CO, LVESV, LVESP, LVEDV, LVEDP.

The following formula was used to calculate cross correlations:

$$\rho_{XY}(\tau) = \frac{E[(X_t - \mu_x)(Y_{t+\tau} - \mu_y)]}{\sigma_x \sigma_y} \quad (4.3)$$

where:

$E[]$ – an expected value,

$X_t, Y_{t+\tau}$ – compared time series shifted by τ one to another

μ_x, μ_y – average values of time series

σ_x, σ_y – a standard deviation of time series

Analyzed values of cross correlations are for zero time shift. Justification for such selection of time shift is short time series obtained in the study and the assumed interrelation between pressure and volume in a given cardiac cycle.

RESULTS

Table 1 shows that post-MI rats had markedly reduced LV ejection fraction, stroke volume and cardiac output, as well as LV contractility and increased LV end-diastolic pressure. This was accompanied by lower resting heart rate. This indicates typical chronic systolic heart failure.

Rapid infusion of saline resulted in increased preload (reflected by increased LV end-diastolic volume and pressure), leading to increased stroke volume and LV end systolic pressure, though the increase of LV end diastolic volume and LV end systolic pressure was smaller in post-MI rats, the former probably due to baseline LV dilation and elevation of LV end diastolic pressure, the latter due to impaired contractility (tab. 2). Increase of heart rate (HR) caused by rapid infusion of saline, a marker of Bainbridge reflex (fig. 1), was higher in post-MI rats than in sham operated rats, but due to

Tab. 1. Hemodynamic parameters in sham operated and post-myocardial infarction (MI) rats 8 weeks after the procedure

	Sham operated (n = 9)	MI (n = 6)
Body weight, g	331 ± 18	342 ± 21
Infarct size, % left ventricle	0	42 ± 4*
Heart rate, beats/min	392 ± 27	342 ± 36*
LVEF, %	58 ± 4	15 ± 3*
SV, μ l	121 ± 13	55 ± 10*
CO, ml/min	48.8 ± 3.7	20.4 ± 2.6*
LVESP, mmHg	119 ± 13	87 ± 9*
LVEDP, mmHg	5 ± 1	18 ± 3*
LVEDV, μ l	210 ± 16	463 ± 36*
dP/dt _{max} , mmHg/s	7935 ± 1240	3722 ± 483*
dP/dt _{min} , mmHg/s	5304 ± 1012	2801 ± 404*

*p < 0.05 vs. sham operated rats. CO, cardiac output; LVEDP, left ventricular end diastolic pressure; LVEDV, left ventricular end diastolic volume; LVESP, left ventricular end systolic pressure; LVEF, left ventricular ejection fraction; SV, stroke volume.

lower resting HR in the post-MI rats, maximum HR value during the saline challenge was almost identical in both groups (424 ± 22 bpm and 419 ± 35, sham operated and post-MI rats, respectively) (tab. 2).

Tab. 2. Hemodynamic reaction to rapid increase of preload (saline infusion) in sham operated and post-myocardial infarction (MI) rats 8 weeks after the procedure

	Sham operated (n = 9)	MI (n = 6)
Δ HR, bpm	+31 ± 10#	+80 ± 20#*
Δ LVEDP, mmHg	+6.5 ± 2.0#	+6.0 ± 2.3#
Δ LVESP, mmHg	+28 ± 5#	+10 ± 2#*
Δ LVEDV, μ l	+120 ± 15#	+73 ± 10#*
Δ LVESV, μ l	+78 ± 10#	+60 ± 10#

*p < 0.05 vs. sham operated rats; #p < 0.05 vs. baseline (stage I) value. CO, cardiac output; LVEDP, left ventricular end diastolic pressure; LVEDV, left ventricular end diastolic volume; LVESP, left ventricular end systolic pressure; LVEF, left ventricular ejection fraction; SV, stroke volume.

Cross correlations were calculated for each stage of the protocol for sham operated and post-MI rats. For the assessment of cross correlation between heart rate and hemodynamic parameters, number of cases in which cross correlation was higher than 0.3 and lower than -0.3 was shown in bold (tab. 3-8). Mean referred to a mean value of module of cross correlation. Table 3 indicates that cardiac output (CO) exhibited the highest correlation with HR in stage I. In stage II LV end systolic and diastolic pressures and volumes exhibited the highest cross correlation coefficients, which could be interpreted as high correlation of hemodynamic parameters with HR, providing normal reaction of the myocardium to preload (tab. 4). Table 5 indicates that CO exhibited the highest correlation with HR in stage III as in stage I, while the correlation of other parameters (LVEDV, LVEDP, and SV) with HR was negative.

LV end diastolic pressure exhibited the highest correlation with HR in stage I in post-MI rats (tab. 6).

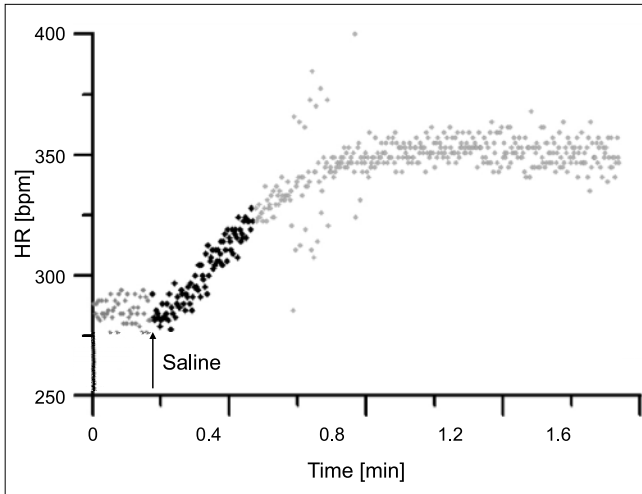


Fig. 1. Increase of heart rate (HR) caused by rapid infusion of saline in representative rat 8 weeks after myocardial infarction

As shown in Table 7 LV, end diastolic and systolic volumes exhibited the highest correlation with HR in stage II in post-MI rats, while LV end systolic and diastolic pressures exhibited poorer correlation with HR than sham operated rats (tab. 4). LV end diastolic volume exhibited the highest correlation with HR in stage III in post-MI rats (tab. 8).

DISCUSSION

For the first time we show that Bainbridge reflex is preserved or even exaggerated in the post-myocardial infarction systolic heart failure in the rat model.

The probable role of the Bainbridge reflex is to the increase heart rate as a response to increased pre-load and as a results to increase pumping ability of the heart (3). The reflex is elicited by the stretch receptors located at the junction of the right atrium and caval veins and at the junctions of the pulmonary veins and

Tab. 3. Cross correlation values for stage I for sham operated rats

Parameter	No. 1	No. 2	No. 3	No. 4	No. 5	No. 6	No. 7	No. 8	No. 9	Mean	Number
CO, HR	0.27	0.06	0.31	0.12	0.33	0.67	0.09	-0.33	0.41	0.29	5
LVESV, HR	0.01	0.05	0.31	-0.04	0.01	-0.65	-0.02	-0.29	-0.07	0.16	2
LVESP, HR	-0.04	0.10	0.13	0.03	-0.01	-0.09	-0.14	0.36	-0.07	0.11	1
LVEDV, HR	-0.02	-0.01	0.00	-0.13	-0.02	-0.52	-0.06	-0.51	0.07	0.15	2
LVEDP, HR	-0.10	-0.06	0.01	-0.08	0.00	0.56	-0.16	0.43	-0.11	0.17	2
HW, HR	0.04	-0.01	-0.12	0.07	-0.04	-0.58	0.11	-0.32	0.22	0.17	2
SV, HR	-0.02	-0.04	-0.15	0.01	-0.03	0.58	-0.01	-0.41	-0.03	0.14	2

CO, cardiac output; HR, heart rate; LVEDP, left ventricular end diastolic pressure; LVEDV, left ventricular end diastolic volume; LVESP, left ventricular end systolic pressure; LVEF, left ventricular ejection fraction; SV, stroke volume.

Tab. 4. Cross correlation values for stage II for sham operated rats

Parameter	No. 1	No. 2	No. 3	No. 4	No. 5	No. 6	No. 7	No. 8	No. 9	Mean	Number
CO, HR	0.16	0.11	0.52	-0.07	-0.75	0.31	-0.19	0.50	0.09	0.30	4
LVESV, HR	0.61	0.79	0.27	0.55	0.91	-0.67	0.80	-0.72	0.09	0.60	7
LVESP, HR	0.57	0.64	0.08	0.53	0.92	0.35	0.76	-0.72	0.15	0.53	7
LVEDV, HR	0.44	0.75	-0.04	0.50	0.87	-0.61	0.79	-0.56	0.15	0.52	7
LVEDP, HR	0.45	0.73	-0.09	0.44	0.86	-0.16	0.87	-0.60	-0.01	0.47	6
HW, HR	0.34	0.28	-0.47	-0.33	-0.27	-0.24	-0.14	-0.06	0.07	0.24	3
SV,HR	-0.44	-0.08	-0.43	-0.47	-0.86	0.09	-0.37	0.40	-0.02	0.35	6

Tab. 5. Cross correlation values for stage III for sham operated rats

Parameter	No. 1	No. 2	No. 3	No. 4	No. 5	No. 6	No. 7	No. 8	No. 9	Mean	Number
CO, HR	-0.37	0.15	0.72	-0.04	0.66	0.42	0.36	0.41	-0.35	0.39	7
LVESV, HR	-0.50	-0.03	0.28	0.22	-0.57	0.27	-0.27	-0.59	0.47	0.36	4
LVESP, HR	-0.07	0.04	0.12	0.41	-0.60	0.24	-0.18	0.00	0.42	0.23	4
LVEDV, HR	-0.53	-0.02	-0.17	0.10	-0.51	0.11	-0.31	-0.42	0.32	0.28	5
LVEDP, HR	-0.02	0.12	-0.05	-0.02	-0.04	-0.04	-0.11	-0.28	0.12	0.09	0
HW, HR	-0.48	-0.04	-0.59	0.10	-0.39	0.23	0.04	0.16	-0.42	0.27	4
SV, HR	-0.47	0.00	-0.56	-0.30	0.44	-0.18	0.17	0.24	-0.43	0.31	5

Tab. 6. Cross correlation values for stage I for post-MI rats

Parameter	No. 10	No. 11	No. 12	No. 13	No. 14	No. 15	Mean	Number
CO, HR	0.26	-0.04	0.08	-0.17	0.14	0.28	0.16	0
LVESV, HR	-0.03	0.02	-0.01	0.34	-0.15	-0.10	0.11	1
LVESP, HR	-0.04	0.04	0.04	0.19	0.34	0.18	0.14	1
LVEDV, HR	-0.05	-0.32	0.05	-0.01	-0.11	-0.21	0.13	1
LVEDP, HR	-0.30	-0.29	-0.12	-0.07	-0.12	-0.36	0.21	2
HW, HR	0.12	0.00	0.02	-0.31	0.32	-0.14	0.15	2
SV, HR	-0.03	-0.22	0.04	-0.31	0.09	-0.20	0.15	1

Tab. 7. Cross correlation values for stage II for post-MI rats

Parameter	No. 10	No. 11	No. 12	No. 13	No. 14	No. 15	Mean	Number
CO, HR	0.29	0.13	0.72	-0.61	0.06	0.05	0.31	2
LVESV, HR	0.62	-0.19	0.36	0.88	0.74	0.37	0.53	5
LVESP, HR	0.28	-0.10	-0.34	0.87	0.70	-0.05	0.39	3
LVEDV, HR	0.55	-0.27	0.35	0.68	0.69	0.33	0.48	5
LVEDP, HR	0.33	0.04	0.02	0.41	0.11	0.25	0.19	2
HW, HR	-0.46	-0.30	0.14	-0.35	-0.41	-0.43	0.35	5
SV, HR	-0.32	-0.18	0.25	-0.84	-0.53	-0.19	0.39	3

Tab. 8. Cross correlation values for stage III for post-MI rats

Parameter	No. 10	No. 11	No. 12	No. 13	No. 14	No. 15	Mean	Number
CO, HR	0.62	-0.07	0.76	-0.20	0.01	0.23	0.32	2
LVESV, HR	0.11	-0.12	0.27	-0.51	0.61	0.45	0.34	3
LVESP, HR	0.18	-0.10	-0.03	-0.25	0.16	0.18	0.15	0
LVEDV, HR	0.26	-0.30	0.31	-0.64	0.43	0.41	0.39	5
LVEDP, HR	0.03	-0.16	0.26	0.03	0.51	-0.06	0.18	1
HW, HR	0.19	-0.47	0.20	-0.62	-0.64	-0.03	0.36	3
SV, HR	0.32	-0.43	0.32	-0.30	-0.38	0.11	0.31	5

the left atrium. Since heart failure is accompanied by marked dilation of both atria and remodeling of atrial ion channels and receptors (11) and elevated left ventricular end diastolic pressure and atrial pressure limit further increase of atrial pressure and distension, we hypothesized that Bainbridge reflex may be impaired in heart failure. However, this was not the case and the HR increase in response to increased preload was even higher in post-MI heart failure rats. There could be several explanations of this unexpected finding. First, baseline HR was lower in heart failure rats, so the maximum achievable HR was higher in this group. Second, the Bainbridge reflex and the arterial baroreceptor reflex act antagonistically to control heart rate (5) and the arterial baroreceptor reflex was found to be impaired in heart failure (6, 7) so this exaggerated Bainbridge reflex could be due to reduction of the opposing mechanism rather than increased sensitivity of the Bainbridge reflex itself. And third, the Bainbridge reflex itself may indeed be exaggerated in heart failure. We were unable to differentiate between these possibilities.

To gain further insight into the Bainbridge reflex, we performed cross correlations between multiple hemodynamic parameters and HR at baseline, following preload increase and in the stabilization period. Indeed, these parameters exhibited the highest correlation strength during the saline challenge, providing validation of assumptions underlying the model. During the preload increase strength of cross correlations for HR was poorer in post-MI heart failure rats than in sham operated control animals, indicating that overall reflex control of the cardiovascular system may be impaired in this condition. Unfortunately, this technique was unable to indicate the site of disturbance, i.e. other reflexes besides the Bainbridge reflex, such as arterial baroreflex or Bezold-Jarisch reflex could contribute or be responsible for this effect.

Although further studies are needed to obtain more complete information, we obtained data indicating that the Bainbridge reflex, a very important cardiovascular reflex for adjusting hemodynamic performance of the heart to preload, is preserved in the post-MI heart failure in the rat model.

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