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IVABRADINE AND QUALITY OF BIOFEEDBACK IN THE LOOP OF PACED BREATHING UNDER THE CONTROL OF HEART RATE VARIABILITY PARAMETERS IN HEALTHY VOLUNTEERS

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On 15 healthy volunteers aged from 18 to 22 years the effect of ivabradine on the quality of biofeedback in the loop of paced breathing under the control of heart rate variability parameters were estimated. It was found that ivabradine contributes to an earlier onset and more significant optimization of regulatory systems in systematic sessions of biofeedback that allows to expand the indications for its clinical use.

KEY WORDS: ivabradine, heart rate variability, paced breathing, regulation

ІВАБРАДИН ТА ЯКІСТЬ БІОЛОГІЧНОГО ЗВОРОТНЬОГО ЗВ'ЯЗКУ В КОНТУРІ МЕТРОНОМІЗОВАНОГО ДИХАННЯ ПІД КОНТРОЛЕМ ПАРАМЕТРІВ ВАРІАБЕЛЬНОСТІ СЕРЦЕВОГО РИТМУ У ЗДОРОВИХ ДОБРОВОЛЬЦІВ

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На 15 здорових добровольцях у віці від 18 до 22 років оцінили вплив івабрадину на якість біологічного зворотнього зв'язку в контурі метрономізованого дихання під контролем параметрів варіабельності серцевого ритму. У ході дослідження було встановлено, що івабрадін сприяє більш ранньому настанню і більш істотною за ступенем оптимізації регуляторних систем у систематичних сеансах біологічного зворотнього зв'язку, що дозволяє розширити показання до його клінічного використання.

КЛЮЧОВІ СЛОВА: івабрадін, варіабельність серцевого ритму, метрономізоване дихання, регуляція

ИВАБРАДИН И КАЧЕСТВО БИОЛОГИЧЕСКОЙ ОБРАТНОЙ СВЯЗИ В КОНТУРЕ МЕТРОНОМИЗИРОВАННОГО ДЫХАНИЯ ПОД КОНТРОЛЕМ ПАРАМЕТРОВ ВАРИАБЕЛЬНОСТИ СЕРДЕЧНОГО РИТМА У ЗДОРОВЫХ ДОБРОВОЛЬЦЕВ

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На 15 здоровых добровольцах в возрасте от 18 до 22 лет оценили влияние ивабрадина на качество биологической обратной связи в контуре метрономизированного дыхания под контролем параметров вариабельности сердечного ритма. В ходе исследования было установлено, что ивабрадин способствует более раннему наступлению и более существенной по степени оптимизации регуляторных систем в систематических сеансах биологической обратной связи, что позволяет расширить показания к его клиническому использованию.

КЛЮЧЕВЫЕ СЛОВА: ивабрадин, вариабельность сердечного ритма, метрономизированное дыхание, регуляция

Heart rate is one of the most important physiological characteristics of the organism and has predictive significance in health and illness [1]. Its functional range is formed by sympathovagal and neurohumoral balance of regulation [2]. Distress, especially chronic, causes overstrains of regulatory systems of the organism and upsets the balance of the regulation that is reflected, in particular, in the high heart rate at rest [3].

One of the perspective ways is to optimize the balance of regulation during biofeedback sessions [4, 5] in the loop of paced breathing under the control of heart rate variability (HRV) parameters [6–8].

We showed before that systematic biofeedback sessions in healthy volunteers [6, 7] and in patients with arterial hypertension [8] optimizes regulatory systems by restoration sympatovagal and neurohumoral balance of regulation with reproducibility of these results for 3 months [9].

Ivabradine is positioned as a drug that selectively lowers heart rate by specific suppression of the sinus node If-channels [10]. Whereas heart rate is controlled by regulatory systems of the organism, especially by sympathovagal balance, ivabradine effect on heart rate may have an effect on regulatory systems. However, there is no such information in literature.

Considering to this, it is interesting to evaluate the effect of ivabradine on the regulatory systems during biofeedback sessions in the loop of paced breathing with more effective start with free breathing [7].

The study is conducted as a part of research project of V. N. Karazin Kharkiv National University «Development and research of automatic control of heart rate variability», registration No. 0109U000622.

Research objective: to evaluate the effect of ivabradine on the regulatory systems during biofeedback sessions starting with free breathing in the loop of paced breathing.

MATERIALS AND METHODS

The study involved 15 conventionally healthy volunteers aged from 18 to 22 years (average age is 19,53 ± 1,55). Exclusion criteria: pernicious habits, medication taking last 3 months, heart rate less than 60 bpm at rest.

The study is conducted with computer diagnostic complex «CardioLab 2009» («KhAI-Medica») with special module «Biofeedback» that contains programmatically connected aural-visual breathing metronome and algorithm of HRV parameters estimation.

HRV parameters were estimated in slide buffer for 1 minute through dynamic spectral decomposition by fast Fourier transform of R-R intervals sequence of lead I ECG records with 1000 Hz digitization frequency. All calculations were conducted in real-time during 7-minute biofeedback session. Power of low (V, up to 0,05 Hz), medium (L, 0,05–0,15 Hz) and high (H, 0,15–0,40 Hz) HRV parameters were estimated [11], then they were transformed into two-dimensional coordinate space with L/H and V/(L+H) axes, which correspond to power of sympathovagal and neurohumoral balances of regulation.

During biofeedback session, initialization of adaptation algorithm of biofeedback module was conducted in first 2 minutes, when volunteer breathe in his normal rhythm. After that for each following minute exact frequency of paced breathing was set through frequency rearrangement of aural-visual breathing metronome. Adaptation algorithm consists in automatic seeking of such frequency, when current L/H and V/(L+H) values are maximally approximate to optimum zone.

Biofeedback quality estimation was based on optimality (O), sensitivity (S), effectiveness (E) parameters both for whole regulatory system (D) and sympathovagal (L/H) and neurovagal (V/(L+H)) sections of regulatory system, and also on BQI integral index [6] that reflects all qualitative changes of biofeedback process.

In compliance with research objective, volunteers were conducted two series of 7-day biofeedback sessions in loop of paced breathing under HRV control with a 3 months interval between sessions [9]. In second session, biofeedback series were conducted 1 hour after oral intake of 5 mg ivabradine.

Values calculations of O, S, E parameters for D, L/H, V/(L+H) indicators and of BQI index were carried out using MathCAD 15 software program.

Statistical analysis of the results for each volunteer was carried out using Microsoft Excel 2003 software program. Average values (M) and standard deviation (sd) of O, S, E parameters for D, L/H, V/(L+H) indicators of first and last records of each volunteer were put down in spreadsheet.

The differences reliability of each parameter between first and second sessions and in each session was determined by Wilcoxon signed-rank test [12].

RESULTS AND DISCUSSION

O, S, E parameters values for D, L/H, V/(L+H) indicators of 1st and 7th sessions of 1st and 2nd biofeedback series on conventionally healthy volunteers are shown in the table. Biofeedback series with ivabradine led to more rapid approach of examined rates levels to the optimum, while levels of reference values of both series were nearly equal.

Table

O, S, E parameters values for D, L/H, V/(L+H) indicators of 1st and 7th sessions of 1st and 2nd biofeedback series on healthy volunteers

Parameter		Series			
		1		2	
		Session 1	Session 7	Session 1	Session 7
D	O	–5,08 ± 5,42	–1,11 ± 5,31†	–2,93 ± 4,58*	–0,60 ± 4,52*†
	S	0,85 ± 0,31	0,91 ± 0,30†	0,77 ± 0,25*	0,88 ± 0,21*†
	E	0,23 ± 0,22	0,26 ± 0,28†	0,21 ± 0,23*	0,35 ± 0,26*†
L/H	O	–5,88 ± 10,84	–3,84 ± 5,30†	–4,18 ± 6,96*	–3,80 ± 1,48*†
	S	5,08 ± 1,04	6,39 ± 2,28†	5,15 ± 2,99*	8,87 ± 1,76*†
	E	0,78 ± 0,02	0,99 ± 0,40†	0,95 ± 0,09*	1,00 ± 0,01*†
V/(L+H)	O	–1,72 ± 1,08	–1,43 ± 0,90†	–2,65 ± 0,30*	–1,39 ± 1,40*†
	S	1,36 ± 2,14	1,44 ± 2,00†	0,23 ± 0,03*	0,38 ± 2,72*†
	E	0,35 ± 0,37	0,37 ± 0,38†	0,13 ± 0,13*	0,14 ± 0,46*†

Note:
* — P > 0,05 between series;
** — P < 0,01 between series;
† — P > 0,05 in the series against the baseline values;
‡ — P < 0,01 in the series against the baseline values

The figure shows the changes of BQI index level of all subjects of first and second biofeedback series for 7 sessions. Systematic biofeedback sessions in loop of paced breathing under HRV control led to expected approaching of BQI index level to the optimum in both series. Biofeedback series with ivabradine led to more rapid approach of BQI index level to the optimum starting from the second session.

We showed before [9] that biofeedback in loop of paced breathing under HRV control is reproducible for 3 months. This allows to estimate the contribution of ivabradine in optimization of regulatory systems on a single cohort of volunteers by carrying out two series of biofeedback sessions with this interval, adding ivabradine to the sessions of second series.

These results demonstrate the influence of ivabradine on the regulatory systems of the organism, showed by changes of studied biofeedback reflective parameters (O, S, E for D, L/H, V/(L+H), BQI). Biofeedback series with ivabradine led to more rapid and significant optimization of regulatory systems of the organism.

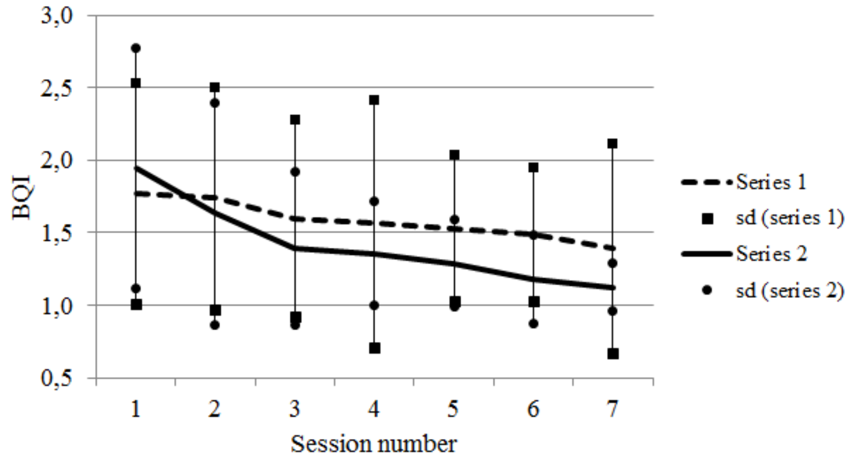

Fig. BQI changes at the first and second biofeedback series in all volunteers

Note:
* — P < 0,01 in the series against the baseline values;
** — P > 0,05 in the series against the baseline values;
† — P > 0,05 on the close sessions of the series;
‡ — P > 0,05 between series on the current session

These changes of the regulatory systems under the influence of ivabradine is a ground for its future pharmacodynamics studies with a perspective expansion of its clinical indications for use.

CONCLUSIONS

Systematic biofeedback sessions in the loop of paced breathing under HRV control optimizes regulatory systems of the organism.

Systematic biofeedback series with ivabradine led to more rapid and significant optimization of regulatory systems of the organism.

Ivabradine effects in biofeedback on regulatory systems of the organism requires a focused study and may become a ground for expansion of its indications for use.

REFERENCES

1. Yabluchansky N. I. Independent predictor of death, disease ... and health [electronic resource] / N. I. Yabluchansky // Access mode : http://www.medicusamicus.com/index.php?action=2x621-3e-9cef-13gx1
2. Magder S. A. The ups and downs of heart rate / S. A. Magder // Crit Care Med. — 2012. — № 40 (1). — P. 239—245.
3. Grippo A. J. Stress, depression and cardiovascular dysregulation: a review of neurobiological mechanisms and the integration of research from preclinical disease models / A. J. Grippo, A. K. Johnson // Stress. — 2009. — № 12 (1). — P. 1—21.
4. Association for Applied Psychophysiology and Biofeedback. What is biofeedback? [electronic resource] // Access mode : http://www.aapb.org/
5. Frank D. L. Biofeedback in medicine: who, when, why and how? / D. L. Frank, L. Khorshid, J. F. Kiffer [et al.] // Ment Health Fam Med. — 2010. — № 7 (2). — P. 85—91.
6. Belal S. A. S. Biofeedback quality in healthy volunteers in paced breathing algorithm starting from the age physiological norm / S. A. S. Belal, K. I. Linskaya, A. L. Kulik // The Journal of V. N. Karazin` Kharkiv National University. Series «Medicine». — № 938. Is. 21. — 2011. — C. 29—37.
7. Belal S. A. S. A comparison of search algorithms for optimal frequency metronomizirovannogo breath at the start from the physiological norm, and a free breathing in healthy volunteers on the basis of quality assessment of biofeedback / S. A. S. Belal, K. I. Linskaya, A. L. Kulik [et al.] // Heart rate variability: Theoretical and practical aspects of the application: V All-Russian. Symp. / Otv. red. R. M. Baevskii, N. I. Shlyk. — Izhevsk Publishing house «Udmurtia University», 2011. — P. 25—30.
8. Kulik A. L. Closed loop biofeedback of heart rate variability and paced breathing efficacy evaluation in patients with arterial hypertension / A. L. Kulik, E. Yu. Shmidt, A. V. Martynenko, N. I. Yabluchansky // The Journal of V. N. Karazin’ Kharkiv National University. Series «Medicine». — 2011. — № 975. Is. 22. — P. 29—37.
9. Belal S.A.S. Biofeedback reproducibility in healthy volunteers in the algorithm paced breathing under control of heart rate variability parameters / [S. A. S. Belal, A. L. Kulik, A. V. Martynenko, N. I. Yabluchansky] // Medicine today and tomorrow. — 2012. — № 2 (55). — P. 44—48.
10. Ferrari R. Selective and specific I(f) inhibition with ivabradine: new perspectives for the treatment of cardiovascular disease / R. Ferrari, C. Ceconi // Expert Rev Cardiovasc Ther. — 2011. — № 9 (8). — P. 959—973.
11. Yabluchansky N. The heart rate variability (HRV) Point: Counterpoint discussion raises a whole range of questions, and our attention has also been attracted by the topic / N. Yabluchansky, A. Kulik, A. Martynenko // J Appl Physiol. — 2007. — № 102. — P. 1715.
12. Lapach S. N. Statistical methods in biomedical studies using Excel / S. N. Lapach, A. V. Tschubenko, P. N. Babich. — K. : Morion, 2000. — 320 p.