INTERNAL DISEASES

UDC 616.01

Determination of the most informative indicators of right-ventricular dysfunction in patients with chronic obstructive pulmonary disease

M. A. Kharitonov[1], *V. A. Tarasov*[1], *S. L. Grishaev*[1], *A. E. Filippov*[2], *D. V. Cherkashin*[1], *T. R. Lokshina*[1], *N. A. Varavin*[1]

[1] S. M. Kirov Military Medical Academy,
6, ul. Academika Lebedeva, St. Petersburg, 194044, Russian Federation
[2] St. Petersburg State University,
7–9, Universitetskaya nab., St. Petersburg, 199034, Russian Federation

For citation: Kharitonov M. A., Tarasov V. A., Grishaev S. L., Filippov A. E., Cherkashin D. V., Lokshina T. R., Varavin N. A. Determination of the most informative indicators of right-ventricular dysfunction in patients with chronic obstructive pulmonary disease. *Vestnik of Saint Petersburg University. Medicine*, 2020, vol. 15, issue 2, pp. 115–123. https://doi.org/10.21638/spbu11.2020.203

The aim of the article was the evaluation of structural and functional indicators that reflect the nature of right heart remodeling in patients with chronic obstructive pulmonary disease (COPD) in order to identify the most informative indicators of right ventricular heart dysfunction. The study included 60 patients, who were on inpatient treatment. Patients were divided into two groups: I — study group with COPD (n = 30), and II — control group — patients of comparable age without COPD (n = 30). During hospitalization, all patients underwent ECHO-KG with an emphasis on evaluating the systolic-diastolic parameters of the right ventricle. Criteria for inclusion in the study: age over 50 years, presence of COPD, signed informed consent when reading the terms of the study. Exclusion criteria: history/course of neoplastic or hematological disease, systemic connective tissue diseases, documented ischemic disease, valvular heart disease, interstitial lung disease, bronchial asthma. When comparing echocardiographic indicators of right ventricular (RV) function detected significant decrease of systolic function the RV — TAPSE (16.64 ± 4.0 vs 23.21 ± 2.31; p = 0.043), S’(12.57 ± 1.87 vs. 14.96 ± 1.09; p = 0.026), estimated RV EF (49.27 ± 9.23 vs 66.12 ± 7.42; p = 0.021), EFSRV (55.58 ± 7.16 vs 72.4 ± 13.06; p = 0.01) and higher rates SDLA (49.55 ± 6.0 vs 27.1 ± 5.29; p = 0.023) in the study group 1. Measure of right ventricular arterial pairing TAPSE/SDLA was significantly reduced compared with the control group (0.36 ± 0.05 vs 0.86 ± 0.14; p = 0.01). In the main 1 group of patients with COPD, there was a tendency increase of the myocardial performance index (TEI index) (0.76 ± 0.42 vs 0.59 ± 0.22; p = 0.43), which is probably associated with a violation of the relaxation of the right ventricle. To confirm the presence of diastolic RV dysfunction in patients with COPD (in comparison with the control group) revealed significant changes in the indicators obtained from transtricuspid flow — E/A_{tk} (0.67 ± 0.02 vs 1.5 ± 0.38; $p = 0.016$). The dynamics of the degree of severity of right ventricular dysfunction, estimated using the proposed indicators, may be another additional characteristic of the success of therapy to achieve disease control in patients with COPD.

Keywords: right ventricle of the heart; echocardiography; systolic-diastolic indicators; chronic obstructive pulmonary disease.

Introduction

Left chambers of heart, especially left ventricle of heart (LV), were always in the spotlight of cardiologists attention. The reason of such interest were conditioned of mostly frequent involvement of these heart chambers in pathogenetic circles of cardiac pathology . It is well known, that LV is the main field, involved in case of myocardial infarction development, which is the main reason of high disease level and death rate. Besides, the image of LV was considerably easier to "withdraw" and to estimate. On the other hand, right ventricle of heart (RV) was often called "forgot" or even "poor relation" of the left one, that was related with its insufficient state of knowledge. Recently, due to technical improvement of ultrasonic recording instruments and desire to comprehensively estimate functional opportunities of cardiac muscle, ever-greater interest is directed on right heart parts visualization, especially on RV [1–3]. A lot of program versions were developed to estimate structure and function of LV, otherwise there was no separate program for RV study, that is why for a long time specialists of functional diagnostics in the field of echocardiography (EC) tried to apply to estimate this part of the heart chamber methods similar to thous, which are used to estimate LV [2; 4].

Unquestionable the fact, that recently magnetic resonance imaging is a golden standard for RV estimate, but being easily accessible and relatively inexpensive by costs, EC still remains a standard instrument for RV visualization [3; 5; 6].

RV anatomy. The right and the left heart ventricles considerably differs by many parameters, nevertheless they posses a number of uniting features. Interventricular interaction is expressed in the influence of contractility, post- and overloading of both ventricules, their interdependency during systole and diastole phases in normal condition and in case of myocardial lesion as well [4]. RV consists of three anatomic regions: inflow tract (sinus), vertex and outflow tract. Because RV does not corresponds to conventional symmetrical ellipsoidal form, its volume (RV) defies adequate estimation. RV's cavity is formed, from the medial side, by interventricular septum and free wall, which, in its turn, may be divided in 3 parts — front, side and lower wall. Each of them has 3 segments — basal, middle and apical. Muscle layer of RV is considerably finer than myocardium of LV. At an everage thickness of healthy myocardium constitutes 3–5 mm, excluding trabecule thickness. But in the zone of RV vertex myocardium thickness often slightly exceeds 1 mm. The wall movement is difficult to estimate due to combination radial, longitudinal and circular contractions. It is associated with small mass of RV myocardium, as well as with it abnormal form and with low visualization quality of right heart divisions [3; 7].

Peculiarities of RV functioning. Morphological peculiarities of RV and LV are stipulated by different conditions, in which they are functioning. Due to different myocyte allocation and relatively thin myocardium, mechanics of RV contraction does not repeat the process of LV contraction. The main RV contraction take place in longitudinal direction, beginning from inflow tract, RV vortex, and propagates in direction to outflow tract. RV differently reacts to the changes of pressure and volume. RV in pathological states tolerates overloading by volume quit well, primarily changing its geometry, but not the function. Physiological increase of pre-loading even increases RV ejection. But in case of prolonged and pathological overloading by volume RV ejection decreases. RV considerably more sensitive to post-loading variations and reacts swiftly. Possibilities for adaptation to overload by pressure are less, and this rapidly leads to minute volume decrease [3; 7].

Difficulties of RV estimation. Estimate of RV condition by echocardiogram has the following restrictions:

- nonoptimal visualozation due to its substernal localization;
- impossibility of RV cavity overview as a whole because of its crescentic form and location of inflow and outflow tracts in different planes;
- absence of adequate geometrical echocardiogram model; difficulties in shaping endocardial RV surface due to inadequate visualization and expressed trabecularity;
- regional heterogeneity of RV contraction and relaxation;
- considerable RV dependence on pre- and post-loading, as well as on pressure in left departments of the heart [4; 8; 9].

Actual methods of RV function estimate using echocardiogram. Over many years, as a rule, only qualitative ultrasonic estimates of RV condition were carried out. Qualitative estimation predominantly was characterized by determination of RV anteroposterior size in parasternal position by axis length of LV. For today this index presents rather historical interest, because it was proved, that skew projections of ultrasonic scanning may erroneously increase and decrease RV cavity [4].

Two-dimensional (2D) RV estimate. Ever growing significance acquire quantitative methods of estimation. These measurements include determination of tricuspid annular plane systolic excursion (TAPSE), RV fractional area (FAC), peak systolic motion velocity of tricuspid valve (S') and RV myocardial performance index (Tei index) [10].

TAPSE is measured by means of echocardiogram in M-mode. That index directly measure displacement of tricuspid valve side ring during heart cycle. In 2015 value < 17 mm was designated as lower border of reference values, but this method possesses some restrictions [3].

Functional RV area (FAC) in estimated using the formula: $FAC = (S_{ED} - S_{ES}) / S_{ED} \times 100\,\%$, where S_{ED} — enddiastolic RV area, S_{ES} — endsystolic RV area. FAC index is recommended for quantitative estimation of RV function, thereat lower border of normal condition constitutes 35 %. Determination of FAC is restricted by visualization quality. So, for patients, whose endocardium is not clearly visualized, this method can not be used. Peak systolic motion velocity of tricuspid valve (S'), which is measured by displacement of RV basal free wall tissues during heart cycle, was recognized as accurate and reproducible. Value <9.5 cm was set as a lower border of normal state. Presented method characterizes only smal portion of RV, that is why it can't be used for patients with regional anomalies of the wall motion [3].

Myocardial performance index of RV (Tei index) provides information about systolic and diastolic function of RV. This index is calculated on the base of tissues Doppler velocities estimate or pulse wave velocities from RV: (calculated as a ratio of the sum between the time of isovolumic relaxation and the time of isovolumic contraction to duration of RV ejection). These variable values are measured during the flow and does not require RV visualization. Application of Tei index is restricted for patients with non-regular frequency of heart contractions and with increased pressure in right atrium (RA), because it influence on the time of iso-volumetric relaxation. Increase of this index ascertain at values exceeding 0.43 if using pulse wave Doppler method or at values exceeding 0.54 if using tissue Doppler imaging. Despite the fact that there exists established threshold of exceedance, rate gradation of that exceedance does not exist [2; 3].

When using pulse wave Doppler and tissue Doppler echocardiography it is possible to estimate diastolic function of RV. It is possible to do due to combined estimation of a number of indices (ratio of earlier (E) and later (A) transtricuspidal blood flow velocities (E/A_{TB}), earlier rising of RV base in the mode of tissue Doppler (E') and ratio E/E'_{TB} [11].

It is commonly accepted to divide diastolic RV disfunction on the following types:

— $E/A < 0.8$ customary for diastolic disfunction by the type of late relaxation;
— E/A from 0.8 to 2.1 and $E/E' > 6$ or predominance of diastolic phase of blood flow in hepatic veins — by the type of pseudo-normalization;
— $E/A > 2.1$ and deceleration time of blood flow $(DT) < 120$ msc — by restrictive type (similar to the case of late diastolic antegrade of blood flow in LV [10; 12].

3D methods: Direct measurement of RV volume by means 3D echocardiography enables to provide the most accurate data. That is why 3D visualization most likely will become the best instrument for RV estimation in the future [3; 9].

Innovative and most perspective instrument of complex regional and global RV mechanics is speckle-tracking echocardiography. It was initially developed for LV function estimation, but lately was used for estimation of RV work efficiency. Many investigators showed, that free wall as well as 6-segmental longitudinal deformation of RV, permits to provide stronger correlation with the fraction of RV ejection, that ordinary parameters, and, likely, would more sensitive to detection of RV myocardium disfunction at earlier, subclinical stage [3; 9].

RV investigation includes estimation of pulmonary hypertension severity — calculations of systolic and average pressure in pulmonary artery. It is recommended to estimate systolic pressure in pulmonary artery (SPPA) by velocity of tricuspid regurgitation and by systolic gradient with pressure addition into the right atrium (RA) [4; 5]. That method enables to estimate the value of afterload on RV.

In estimating RV function it is also necessary to account its coupling with pulmonary circuit, i.e. to considerRV indices together with pulmonary artery characteristics — as a united cardiopulmonary system [5; 12]. The most simple and practical echo-cardiography index of RV arterial coupling (RVAC) is a rario TAPSE to SPPA. Tgat index is considered to be valid and independent predictor of patiets mortality with circulatory deficiency, prognostic role of which does not depend on genesis and type of chronic heart failure (CHF) (systolic or diastolic) [8].

It is necessary to stress again that recently for RV function estimate, simultaneous application of at least two methods is recommended due to theirimperfection. The most reproducible parameters are TAPSE and S'. In multiple of investigation their correlation with RV EF and with each other was proved as well as their prognostic role. For example, reduction of specified indices values is associated with high probability of unfavorable outcomes development (death or urgent translantation) in case of CHF with decreased or even preserved RV EF [2; 4].

Considering the foregoing, the results of our own investigation devoted to estimation of RV disfunction in patients with COPD with application of modern cardiography methods.

Purpose of investigation was The estimate of structural-functional indices, reflecting the character of respiratory heart remodeling in patient with chronic obstructive pulmonary disease (COPD) for revealing the most informative indices of right ventricle failure.

Material and methods

Investigation was carried out with 60 patients (Table 1), undergoing inpatient treatment in 1st clinic (therapy of advanced medical education) of Military Medical Academy named after S. M. Kirov in the period from September 2019 till the March 2020. Patients were devided in two groups: I — investigated group of patients with COPD (n=30), and II — control one — patients, comparable by their age without COPD (n=30). Patients with COPD were with different severity (low (n=6), middle (n=12), high (n=9), extrimely high (n=3)), avearage score by mMRC scale — 2.25±0.5, by CAT test — 22±2.9.

Table 1. **Clinical characteristics of examined patients**

Index	Main group	Control group	$p<0.05$
Men/women	30/0	30/8	–
Age (years)	67.37±4.4	61.5±7.7	0.68
BMI (kg/m^2)	25.0±2.33	27.95±6.95	0.47
Charlson comorbidity index (scores)	4.1±2.07	3.1±0.74	0.32
Systolic arterial pressure, mm of Mercury	136.04±16.21	134.58±14.44	0.66
Diastolic arterial pressure, mm of Mercury	82.12±6.67	81.84±7.59	1.0
HR, bpm	76.5±8.45	72.31±7.24	0.097
Total cholesterol, millimole/litre	4.8±1.2	5.01±0.9	0.36
Low density lipoprotein cholesterol, millimole/litre	0.95±0.22	1.23±0.57	0.74
Low density lipoprotein cholesterol, millimole/litre	1.27±0.32	1.36±0.45	0.92
Low density lipoprotein cholesterol, millimole/litre	2.48±1.48	3.05±0.94	0.86
Smoker index (pack of cigarettes/years)	41.4±9.5	14.87±4.8	0.02
mMRC scale (scores)	2.25±0.5	–	–
CAT-test (scores)	22±2.9	–	–
Distance in six-minute walk test (m)	371±11	486±27	0.03
Distance in six-minute walk test required (m)	537.27±40.7	514.13±40.3	0.1

Note: Abbreviations see on page 122.

In course of hospitalization all the patient underwent the following investigations: Echocardiogram with a focus on estimation of RV systolic-diastolic indices — tricuspidal annular plane systolic excursion (TAPSE) in M mode, peak systolic velocity of tricuspidal valve motion (S'), fraction of RV area ejection (FRVAE) was determined by Kaul method (FRVAE = 3.2 × TAPSE), index of RV myocardial performance (Tei index) was estimated in the mode of pulse Doppler scationg by formula (Tei index = (a – b/b = (IVCT + IVRT)/ET), fraction of RV ejection was calculated by the method proposed by Sokolov A. A. et al. [13], maximal SPPA, ratio of systolic tricuspidal annular plane systolic excursion of RV to SPPA (TAPSE/SPPA), ratio of peak velocities of earlier and later diastolic filling of tricuspidal blood flow in pulse-wave mode (PW) of standard echocardiogram (E/A_{TB}), ratio of peak velocity of earlier diastolic filling of tricuspidal blood flow to earlier diastolic rise of RV base (E/E'_{TB}). Obtained results were processed by means of statistical programs "Statistica 10". For comparison of quantitative indices between the groups non-parametrical statistics module was used (non-parametrical U-test Mann-Whitney). Level of statistical significance was accept at error probability < 0.05.

Results and discussions

It is important to reveal in patients with COPD structural-functional heart changes starting from earlier stages of disease. There is no single generally accepted index, ideally characterizing RV, that is why application of the proposed list of echocardiogram methods, to our mind, will enable charecterize fuctional state of RV at the mosty high level of qualiy. By comparising echocardiological indices, reflecting RV function, considerable decreasing of systolic RV function — TAPSE (16.64 ± 4.0 vs 23.21 mm; $p = 0.043$) was detected, as well as high SPPA indices (49.55 ± 6.0 mm of Mercury; $p = 0.023$) in the studied group (group no. 1) (Table 2). Index, characterizing arterial RV coupling — TAPSE/SPPA appeared to be reliably decrease in comparison with control group (0.36 ± 0.05 vs 0.86 ± 0.14; $p = 0{,}01$).

S' index has a reliable tendency for registration in lower values (12.57 ± 1.87 vs 14.96 ± 1.09; $p = 0.026$).

Calculated indices RV FB (49.27 ± 9.23 vs 66.12 ± 7.42; $p = 0.021$) and EFRAA (55.58 ± 7.16 vs 72.4 ± 13.06; $p = 0.01$) in first group of examined patients, also showed reliable decrease in comparison with control group.

Similar results, demonstrating decrease of systolic RV function indices at COPD development, were presented in the works of Zhuk O. A. et al. [14].

In the main (first) group of patients with COPD disease a tendency to myocardial performance index increase of RV was detected (Tei index) (0.76 ± 0.42 vs 0.59 ± 0.22; $p = 0.43$). Higher Tei index, to our mind, was verified due to increase of isovolumetric relaxation period, that is related with decreasing velocity of RV relaxation and slowed pressure decreasing in it, in other words, due to RV relaxation abnormality.

In support to the presence of diastolic disfunction in RV in the group of COPD diseased patients (as compared with control group), considerable changes of indices, obtained in estimate of transtricuspidal flow — ratio of earlier (E) and later (A) velocities of transtricuspidal blood flow (E/A_{TF}) (0.67 ± 0.02 vs 1.5 ± 0.38; $p = 0.016$) were revealed.

Comparable results in diastolic RV function in patients with COPD, were obtained in the works of other authors [11].

Table 2. **Echocardiological indices**

Index	Main group (n = 30)	Control group (n = 30)	p < 0.05
LV			
EF, %	56.84 ± 7.76	64.15 ± 5.53	0.4
E/A тк	1.1 ± 0.33	1.04 ± 0.31	1.0
RV			
Systolic indices			
EFest., %	49.27 ± 9.23	66.12 ± 7.42	0.021
EFRAA, %	55.58 ± 7.16	72.4 ± 13.06	0.01
TAPSE, mm	16.64 ± 4.00	23.21 ± 2.31	0.043
S', cm/s	12.57 ± 1.87	14.96 ± 1.09	0.026
Diastolic indices			
E/A тк	0.67 ± 0.02	1.50 ± 0.38	0.016
E/E' TB	7.84 ± 4.38	5.01 ± 1.53	0.17
Systolic-diastolic index			
Tei index	0.76 ± 0.42	0.59 ± 0.22	0.43
Index of pulmonary hypertension			
SPPA, mm of Mercury	49.55 ± 6.00	27.1 ± 5.29	0.023
Index of RV arterial coupling			
TAPSE/SPPA	0.36 ± 0.05	0.86 ± 0.14	0. 01

It should be noted, that expressivity of diastolic RV function was more considerable than systolic disfunction. Estimated by means of proposed indices dynamics of RV disfunction severity, may, probably be another additional characteristic of ongoing therapy efficiency for attaining control over disease in patients with COPD.

Conclusions

RV systolic-diastolic disfunction detected in patients with COPD of different severity, with prevailing RV diastole obstruction, while mostly informative indices of its verification were:

— tricuspid annular plane systolic excursion;
— systolic velocity peak of transtricuspid valve movement;
— calculated indices of RV fraction ejection;
— ratio of tricuspid annular plane systolic excursion to systolic pressure in pulmonary artery;

— ratio of peak velocities of earlier and later diastolic filling of tricuspidal blood flow in pulse-wave mode.

Relations and activity

The authors declare about the absebce of potential conflict of interests, requiring dicclosure in this paper.

Abbreviations:

BMI — bodymass index
Tei index — index of myocardial performance
LV — left ventricle of heart
RV — right ventricle of heart
RVAC — RV arterial coupling
RA — right atrium
SPPA — systolic pressure in pulmonary artery
TG — triglycerides
$EF_{est.}$ — estimated ejection fraction
EFRAA — ejection fraction of RA area
COPD — chronic obstructive pulmonary disease
HDLPC — high density lipoprotein cholesterol
LDLPC — low density lipoprotein cholesterol
CAT test — COPD assessment test
EC — echocardiography
$E/A_{тк}$ — ratio of earlier (E) to later (A) velocities of transtricuspidal blood flow
$E/E'_{тк}$ — ratio of earlier (E) velocity of transtricuspidal blood flow to earlier diastolic uprising of RV basement in the mode of tissue Doppler imaging
FAC — RV fractional area change
mMRC — the Modified Medical Research Council Dyspnea Scale
S' — systolic velocity peak of transtricuspid valve movement
TAPSE — tricuspid annular plane systolic excursion

References

1. Akramova E. G. The clinical importance of assessment of systolic function of the right ventricle at an echocardiography. *Medical alphabet*, 2017, vol. 1, no. 14, pp. 41–45. (In Russian)
2. Gaifulin R. A., Sumin A. N., Arhipov O. G. Estimation of right ventricular diastolic function in patients with ischemic heart disease in different age groups. *Rational pharmacotherapy in cardiology,* 2016, vol. 12, no. 3, pp. 277–284. (In Russian)
3. Dutta T., Aronow W. S. Echocardiographic evaluation of the right ventricle: Clinical implications. *Clinical Cardiology,* 2017, vol. 40, pp. 542–548. https://doi.org/10.1002/clc.22694.
4. Nartsissova G. P. Role of the right ventricle in cardiovascular pathology. *Circulatory pathology and cardiac surgery,* 2014, vol. 1, pp. 32–36. (In Russian)
5. Kyzymly A. V., Ryzhkov A. V., Simakova M. A., Kozlyonok A. V., Naimushin A. V., Moiseeva O. M. Value of Two Dimensional Echocardiography for Assessment of Disease Severity in Patients With Pulmonary. *Cardiology*, 2016, vol. 1, pp. 25–30. (In Russian)
6. Smolarek D., Gruchala M., Sobiczewski W. Echocardiographic evaluation of right ventricular systolic function: Traditional and innovative approach. *Cardiology Journal,* 2017, vol. 24, no. 5, pp. 563–572. https://doi.org/10.5603/CJ. a2017.0051.
7. Pickure Z., Kalinin A., Lejnieks A., Alekhin M. N. Current Echocardiographic Techniques for Evaluation of the Right Ventricle. *Cardiology,* 2017, vol. 57, no. 9, pp. 54–64. (In Russian)

8. Islamova M. R., Lazarev P. V., Safarova A. F., Kobalava Zh. D. The Value of Right Ventricular Dysfunction and Right Ventricular — Pulmonary Artery Coupling in Chronic Heart Failure: The Role of Echocardiography. *Cardiology: news, opinions, training*, 2018, vol. 6, no. 3, pp. 51–58. (In Russian)
9. Dandel M., Hetzer R. Evaluation of the right ventricle by echocardiography:particularities and major challenges. *Expert Review of Cardiovascular Therapy*, 2018, vol. 16, no. 4, pp. 259–276. https://doi.org/10.1080/14779072.2018.1449646.
10. Neklyudova G. V., Naumenko Zh. K. Echocardiography in the diagnosis of pulmonary hypertension. *Practical pulmonology*, 2015, vol. 2, pp. 48–56. (In Russian)
11. Bart B. Ya., Kulbachevskaya O. M., Dergunova E. N., Vartanyan E. A. Tissue dopplerography and the assessment of right heart structure and function in patients with chronic obstructive pulmonary disease. *Russian journal of cardiology*, 2014, vol. 2, no. 106, pp. 79–83. (In Russian)
12. Cherneva Z. V., Denchev S. V., Cherneva R. V. Echocardiographic predicors of stress induced right ventricular diastolic dysfunction in non-severe chronic obstructive pulmonary disease. *Journal of Cardiology*, 2019, vol. 1, pp. 1–8. https://doi.org/10.1016/j.jjcc.2020.02.009. (In Russian)
13. Pat. RU 2613427, MPK A61B 8/00, Russian Federation, Method for determining the right ventricular ejection fraction A. A. Sokolov, G. I. Martsinkevich, M. V. Zlobina, opubl. 16.03.2017, Byull., vol. 8, pp. 1–8. (In Russian)
14. Zhuk O. A., Holin A. V., Titiva O. N., Kuzubova N. A., Alexandrov A. L., Bondareva E. V., Shumai D. V., Egorova N. V. New approaches to early detection of myocardial dysfunction of the levt and right ventricles to stratify the risk of development of chronic pulmonary heart disease in patients with COPD. *Ural medical journal,* 2017, vol. 147, no. 3, pp. 33–38. (In Russian)

Received: October 14, 2020
Accepted: November 1, 2020

Authors' information:

Mikhail A. Kharitonov — MD, Professor; micjul11@yandex.ru
Victor A. Tarasov — PhD; tarvictor@gmail.ru
Sergei L. Grishaev — MD, Professor; grishaev_med@mail.ru
Alexander E. Filippov — MD, Professor
Dmitriy V. Cherkashin — MD, Professor
Tatyana R. Lokshina — Doctor; loksina8@mail.ru
Nikita A. Varavin — Medical Officer; nikvaravin91@mail.ru