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Prediction of the degree of the right heart chambers overload in patients with acute massive pulmonary embolism based on the results of MSCT diagnostics

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The study group included 147 patients at the stage of preparation for emergency surgical treatment of acute massive PE in the period from March 2012 to December 2019 inclusive. As CT indicators of overload of the right chambers of the heart, the usual CT indicators that do not require the use of expert – class computed tomographs were taken – they were the superior vena cava, inferior vena cava, unpaired vein; reflux of the contrast drug into the inferior vena cava; reflux of the contrast drug into the hepatic veins. In the course of the study, a comparative analysis of the average pressure in the pulmonary artery with the above CT indicators was performed. The most stable statistical relationship with the indicators of mean pressure in the pulmonary artery was demonstrated by CT parameters – the diameter of the unpaired vein and the reflux of the contrast agent into the hepatic veins. Based on the results of the work, a method for calculating the actual values of the average pressure in the pulmonary artery based on the CT parameter of the diameter of the unpaired vein is proposed.

Keywords: multispiral computed tomography, pulmonary embolism, pulmonary artery pressure, pulmonary hypertension, thrombembolectomy, thrombectomy, angiopulmonography, unpaired vein, overload of the right chambers of the heart

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Informed consent. "Informed consent was obtained from all individual participants included in the study."

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Introduction

The acute massive form of pulmonary embolism (PE) remains one of the most difficult problems of emergency radiodiagnosis, cardiovascular surgery, and cardiology due to the fulminant course and high risk of mortality in the first hours of the disease. The relevance of the topic is also determined by the increasing demand for surgical methods in the treatment of an acute massive form of pulmonary embolism.

To date, CT diagnostics has almost completely replaced other radiation methods for emergency diagnosis of pulmonary embolism, becoming not only the first but often the only method of radiation diagnosis of a life-threatening massive form of PE [1–5], based on which patients are selected for emergency surgery.

Modern tasks of emergency CT diagnostics are the assessment of not only direct angiographic signs of PE but also the analysis of the degree of right ventricular heart failure, which justifies a fundamentally new approach to risk stratification in the surgical treatment of PE based on the results of X-ray computed tomography [6–8].

Successful surgical treatment of massive PE is superior to the results of conservative therapy in several parameters, providing both a rapid clinical recovery of the patient and a low percentage of recurrence of the disease in the future. Only such a one-time objective assessment of angiographic massiveness and the degree of overload of the right heart chambers can determine the true severity, life-threatening thromboembolic lesion, the possibility and necessity of emergency surgical treatment of pulmonary embolism [1, 8–11].

In 1936, Feinberg and Wiggers hypothesized that “circulatory failure after obstruction of the pulmonary artery had no other cause than the dysfunction of the right ventricle” [12]. Since specifically the rate of increase of right ventricular failure in acute massive occlusion of the arterial pulmonary system determines the mortality of PE [5, 12–16]

For a long time, transthoracic echocardiography (echo) has been the traditional and only non-invasive method for the quantitative determination of pulmonary artery pressure [13, 17, 18]. The visualization capabilities of echo are undeniable in the case of the left chambers and remain insufficient about the right heart. Many authors have noted both operator dependence and high subjectivity in the interpretation of the results obtained when calculating the pressure in the pulmonary artery by echocardiography [11, 16, 18, 19]. At the same time, the pressure in the pulmonary artery, as the main indicator of the degree of right heart chambers overload is considered by most clinicians as a criterion for choosing a surgical treatment method in the case of acute massive PE [7–9, 11, 13, 19, 20].

Therefore, the search for universal objective radiation methods of emergency diagnostics in cardiology continues [1, 3, 6, 7, 9, 13, 14, 18]. Taking this into account, it was relevant for our work to study the possibility of predicting pressure in the pulmonary artery based on universal CT predictors at the stage of selecting patients with active massive PE for urgent surgical treatment.

So, the aim of the current study was to study the correlation between pulmonary artery pressure and MSCT parameters obtained during contrast-enhanced MSCT angiography in patients with acute massive PE.

Materials and methods

The study was conducted by the Declaration of Helsinki (2013). Informed consent was obtained from each patient. The study was conducted from March 2012 to December 2019. The study group included patients with acute massive PE in preparation for emergency surgical treatment. Clinical and laboratory examinations, MSCT-angiopulmonography, transthoracic echocardiography were performed.

Current work considers the surgical approach to the treatment of acute massive pulmonary embolism. At the stage of preparation for surgery, clinical and laboratory examinations, CT angiopulmonography, transthoracic echocardiography (ECHO-CG) were urgently performed.

CT angiopulmonography was performed on a Toshiba Aqullion CXL computed tomography scanner with image post-processing done using a Vitrea visualization system. All patients included in the study initially had a severe angiographic variant pulmonary arterial bed obstruction with a proximal level of obstruction at the level of the pulmonary artery trunk and/or of the main branches of the pulmonary artery. Two types of reflux were considered as CT indicators of the right chambers overload: “case-reflux 1” (contrast reflux in the supradiaphragmatic segment of the inferior vena cava) and “case-reflux 2” (contrast reflux into the hepatic veins); diameters of hollow and unpaired veins were also examined. The diameter of the azygos vein was measured at the level of drainage into the superior vena cava; superior vena cava (SVC) – 2 cm above the cavoatrial junction; inferior vena cava (IVC) – 1 cm below the inferior cavoatrial junction.

Echocardiographic examination was carried out on ultrasound diagnostic systems “VIVID 3”, “VIVID 7” by GE (USA) with a 3.5 MHz transducer. Transthoracic echocardiography in 2D and M-mode was used with the technique of pulsed and continuous-wave Doppler studies and color mapping. The main aim of echocardiography was to determine the pressure in the pulmonary artery (pressure calculated from the time of flow acceleration in the outflow tract of the right ventricle (RVE)) – as the main and traditional ultrasound indicator of right chambers overload.

The method of treatment in all cases was surgical – thromboembolectomy from the pulmonary artery under cardiopulmonary bypass (n = 147). The following surgical techniques were used: thromboembolectomy from the pulmonary artery under cardiopulmonary bypass (n = 123); thromboembolectomy supplemented by endarterectomy from the pulmonary artery under cardiopulmonary bypass (n = 24).

Analysis of the relationship between pressure in the pulmonary artery and selected MSCT parameters was carried out by constructing linear regression models. The relationship between pressure in the pulmonary artery and the presence of reflux in the inferior vena cava and hepatic veins was analyzed by comparing the mean pressure in the groups with and without reflux, which was carried out using Welch's t-test.

Results

The study included 147 patients who, for health reasons, urgently underwent surgical treatment of acute massive pulmonary embolism under cardiopulmonary bypass.

The duration of acute massive PE before surgery ranged from 1 to 19 days (average 6.5 days). The age of the patients ranged from 24 to 79 years (average 54.2 years) (Fig. 1a, b).

The largest number of patients was in the age range of 44–60 years (middle-aged, n = 45) and 60–75 years (senior, n = 41); the smallest in the age range of 75–90 years (elderly, n = 4); young patients 18–44 years old – n = 24 (Fig. 1a, b). The ratio of men (n = 75, 51.1%) and women (n = 72, 48.9%) included in the study was comparable.

Indicators of calculated pressure in the pulmonary artery according to the echocardiography method are graphically presented in Fig. 2a, b.

The relationship between the diameter of vena cava, azygos vein, and pressure in the pulmonary

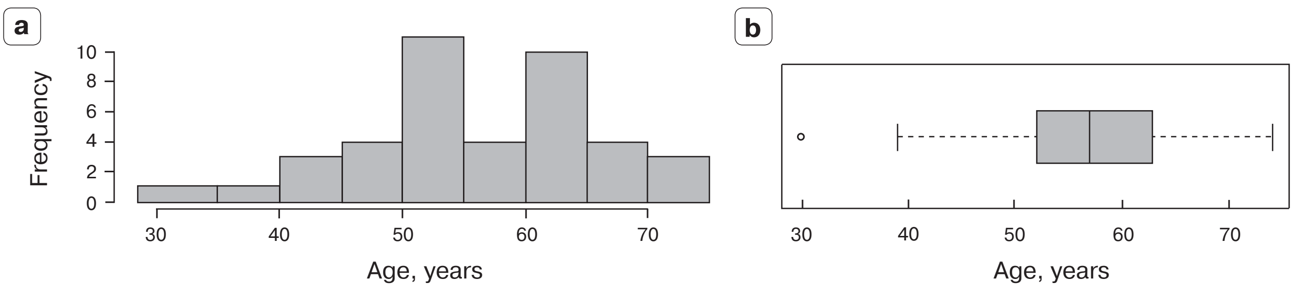

Fig. 1. Distribution histogram (**a**) and range diagram (**b**) of the age of patients with acute massive PE at the preoperative phase (n = 147).

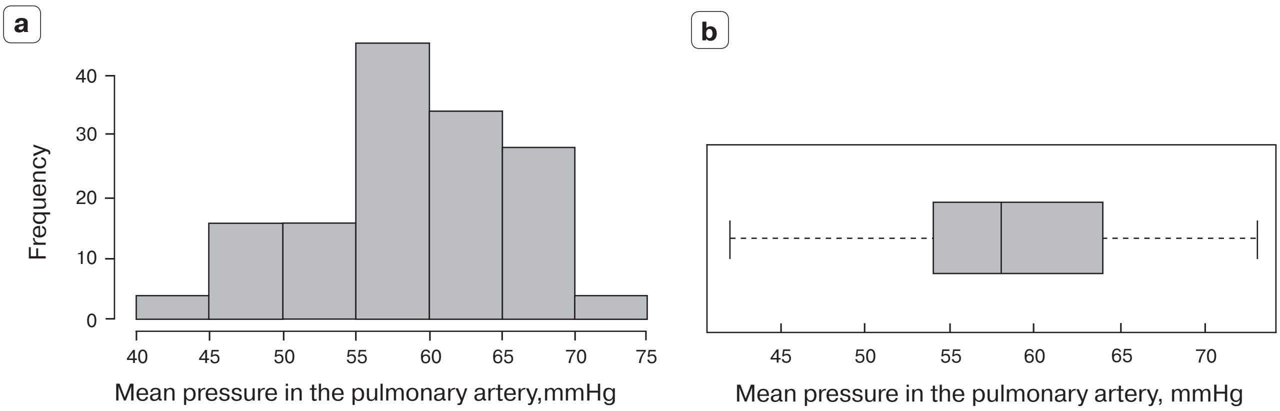

Fig. 2. Distribution histogram (**a**) and range diagram (**б**) of mean pressure in the pulmonary artery (mmHg) in patients with acute massive PE at the preoperative phase.

artery was carried out by constructing linear regression models of dependence. In the current model of analysis, the diameter of the veins is taken as an independent variable, and pressure in the pulmonary artery became the dependent variable (Fig. 3, 4). On the curve, the logistic model of dependence does not demonstrate the likelihood of an increase in the diameter of the superior vena cava in response to an increase in mean pulmonary artery pressure, the dependence is not confirmed ($F_{1,\ 145}$ = 0.129; p = 0.72).

The logistic model of the pressure in the pulmonary artery dependence on the diameter of the inferior vena cava also does not demonstrate the likelihood of an increase in diameter of the inferior vena cava in response to an increase in the mean pressure in the pulmonary artery ($F_{1,\ 145}$ = 0.287; p = 0.59) (Fig. 4).

Figure 5 shows a straight line of regression dependence of pressure in the pulmonary artery on the diameter of the azygos vein. A correspondence was obtained – with an increase in the diameter of the azygos vein, the mean pressure in the pulmonary artery increases proportionately, the solid line reflects the regression line (equation (1)), the dotted lines reflect the position of the 95% confidence interval for predicting the mean pressure in the pulmonary artery in new patients ($F_{1,\ 145}$ = 297.1; p < 0.001).

Statistical analysis of the regression model revealed a statistically significant relationship between the diameter of the azygos vein and the mean pulmonary artery pressure (p < 0.001).

According to the regression equation, when the diameter of the azygos vein changes by 1 mm, the expected pressure increases by 3.827 mmHg. The variability of the CT parameter (diameter of the azygos vein) explains 66.9% of the variability of pressure in the pulmonary vein. The high coefficient of determination (r^2 = 0.669) allows the obtained regression model to be used to predict the mean pressure in the pulmonary artery. The forecast can be obtained in the form of a point or interval estimate. The expected pulmonary artery pressure (point estimate) can be obtained by substituting the diameter of the azygos vein in equation (1).

$$P = 8.248 + 3.827 \cdot d, \qquad (1)$$

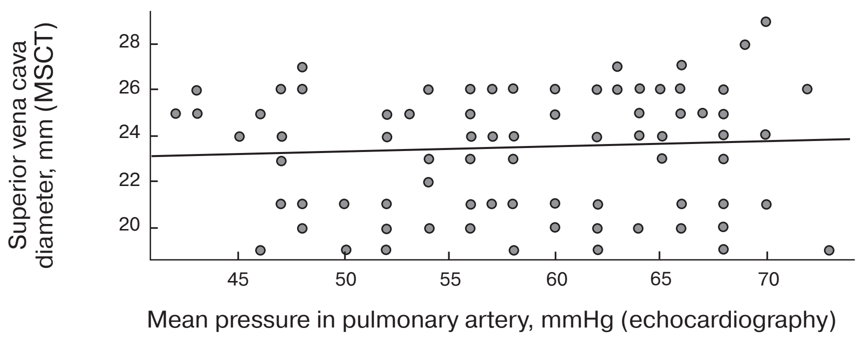

Fig. 3. Dependence of the mean pressure in the pulmonary artery on the diameter of the superior vena cava. The abscissa shows the pressure in the pulmonary artery, and the ordinate shows the diameter of the superior vena cava.

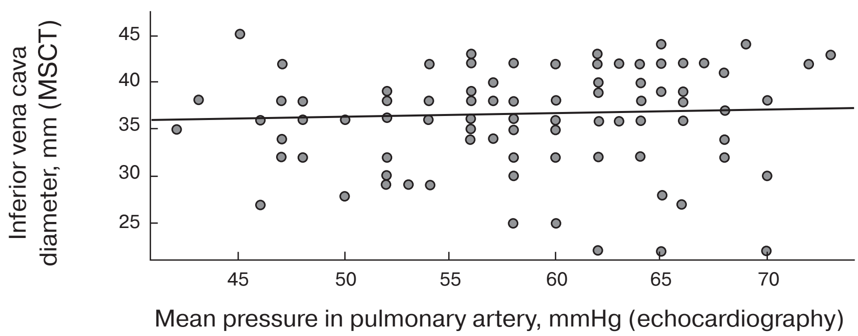

Fig. 4. Dependence of mean pressure in the pulmonary artery on the diameter of the inferior vena cava. The abscissa shows the pressure in the pulmonary artery, and the ordinate shows the diameter of the inferior vena cava.

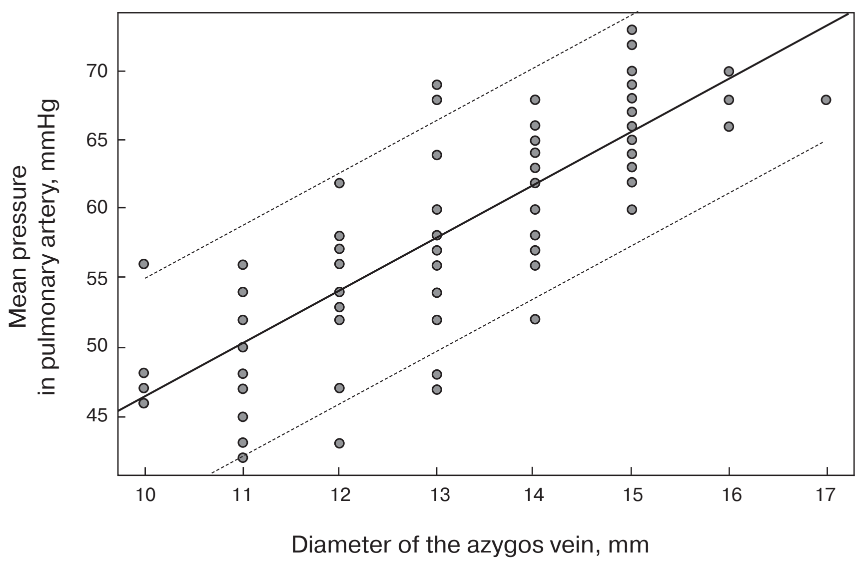

Fig. 5. Dependence of the average pressure in the pulmonary artery on the diameter of the azygos vein. The abscissa shows the diameter of the azygos vein, the ordinate shows the pressure in the pulmonary artery.

where P is the average pressure in the pulmonary artery, d is the diameter of the azygos vein at the level of drainage into the superior vena cava.

So, for example, if the diameter of the azygos vein is 10 mm, the expected pressure in the pulmonary artery will be 8.248 + 3.827 10 = 46.518 mmHg.

To construct the confidence interval, it is necessary to calculate the standard error of forecast sp:

$$s_p = s_\varepsilon \sqrt{1 + \frac{1}{n} + \frac{(d - \bar{d})^2}{S_d^2 (n-1)}}, \qquad (2)$$

where s_ε is the residual standard deviation (4.167), n is the sample size (147 patients), $\bar{d}$ is the average diameter of the azygos vein in the analyzed data set (13.326, S_d^2 is the variance of the diameter of the azygos vein in the analyzed data set (2.413), d is the value of the diameter of the azygos vein in the patient for whom the prognosis is made.

The confidence interval is based on the formula:

$$\hat{P} \pm s_p \cdot t_{1-\frac{\alpha}{2}, df}, \qquad (3)$$

where $\hat{P}$ is a point estimate of the pressure in the pulmonary artery, calculated by equation (1), s_p is the standard error of forecast calculated by equation (2), $t_{1-\frac{\alpha}{2}, df}$ is the quantile of the Student's t-distribution with df = n – 2 degrees of freedom, 1 – α – confidence probability. To calculate the 95% confidence interval, you need a quantile of the level $1 - \frac{0.0_5}{2} = 0.97_5$ 2 of the Student's distribution with 145 degrees of freedom: $t_{0.975, 14_5} = 1.97_6$.

So, substituting specific values in formulas (1), (2) and (3), you can get the following expression for the 95% confidence interval:

$$(8.248 + 3.82_7 \cdot d) \pm 4.16_7 \cdot \sqrt{1 + \frac{1}{14_7} + \frac{(d - 13.32_6)^2}{2.413 \cdot 14_6}} \cdot 1.976 = \\ = (8.248 + 3.82_7) \pm 8.23_4 \cdot \sqrt{1.007 + \frac{(d - 13.32_6)^2}{352.29_8}} \qquad (4)$$

As an example, let us use formula (4) to calculate the 95% confidence interval for predicting pulmonary artery pressure in a patient with an azygos vein diameter of 17 mm:

$$(8.248 + 3.827 \cdot 1_7) \pm 8.23_4 \cdot \sqrt{1.007 + \frac{(1_7 - 13.32_6)^2}{352.29_8}} = \\ = 73.307 \pm 8.419$$

Thus, with a probability of 95%, the value of pressure in the pulmonary artery in a patient with an azygos vein diameter of 17 mm will fall in the range (64.888, 81.726).

The concept of “case-reflux” of contrast agent was defined by us as an additional CT parameter of an increase in the mean pressure in the pulmonary artery. Reflux contrast to the inferior vena cava (or “case-reflux 1”) was visualized in 64 patients; reflux contrast in the hepatic veins (or “case-reflux 2”) – in 41 patients. A series of pairwise comparisons of the groups with reflux of the contrast agent with the group without re-

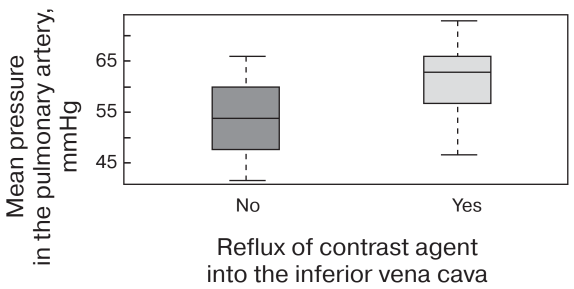

Fig. 6. Diagrams of the mean pressure range in the pulmonary artery from cases of reflux of contrast agent into the inferior vena cava ("case-reflux 1").

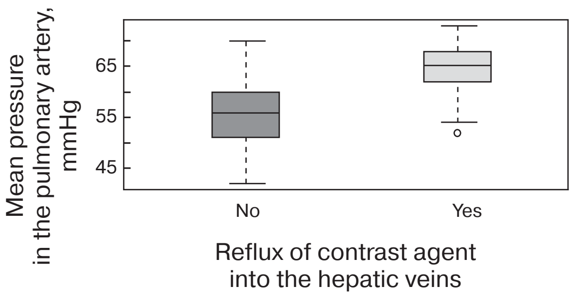

Fig. 7. Diagrams of the mean pressure range in the pulmonary artery from cases of reflux of contrast agent into the hepatic veins ("case-reflux 2").

flux (group 0) was performed to analyze the dependence of the mean pressure in the pulmonary artery on the presence of cases of reflux of contrast agent. A parametric method was used, the Student's test as adapted by Welch.

It was determined that the pressure in the pulmonary artery increases with an increase in the number of "case-reflux 1", Student's test confirmed statistically significant differences ($t = -2.18$, $p < 0.05$). The independent explanatory variable (reflux of contrast agent into the inferior vena cava) was determined at an average pressure in the pulmonary artery of at least 57 mmHg. The coefficient of variation of the random variable showed that with an average pressure in the pulmonary artery (mean PAP) of 57 mmHg reflux of the contrast agent into the inferior vena cava ("case-reflux 1") was recorded in 25% of cases; with an average pressure in the pulmonary artery (mean PAP) of 66 mmHg – in 75% of cases; with an average pressure in the pulmonary artery (mean PAP) of 63 mmHg – in half of the cases (Fig. 6).

It was determined that the pressure in the pulmonary artery increases with an increase in the number of "case-reflux 2", Student's test confirmed statistically significant differences ($t = -3.753$, $p < 0.05$). In the presence of reflux of contrast agent into the hepatic veins ("case-reflux 2"), the average pressure in the pulmonary artery in the group was a.2 ± 4.95 mmHg. In the absence of reflux of the contrast agent into the hepatic veins, the mean pressure in the pulmonary artery was 55.7 ± 6.61 mmHg. The independent variable of contrast agent reflux into the hepatic veins ("case-reflux 2") was determined in all patients with a mean pulmonary artery pressure equal to or greater than 65 mmHg. (Fig. 7).

Discussion

Until now, quick objective assessment of the degree of right ventricular failure has been an unresolved issue in emergency cardiac surgery. Risk stratification in "real-time" is most relevant specifically for acute massive PE, when obstruction of the arterial pulmonary bed by thromboembolic exceeds 50% with a sharp and often uncontrolled progression of right ventricular failure, where the time factor is of paramount importance for determining treatment tactics [1, 10, 13, 19–21].

Precisely this category of patients needs a quick comprehensive objective diagnosis, based on the results of which a decision of the possibility and prognosis of surgical treatment of PE is made. The main method for PE diagnosing is the method of X-ray computed tomography, the modern tasks of which are not only the assessment of direct angiographic signs of PE but also the analysis of the degree of overload of the right chambers of the heart. Additional use of other methods of radiation diagnostics, such as scintigraphy, MRI and PET-CT often is not possible due to the severity of the patients' clinical condition. This category of patients usually has the maximum severity and a very high risk of death according to all known cardiological scales. It becomes necessary to search for CT parameters that allow assessing the dynamic dysfunction of the right ventricle with the possibility of simultaneous pulmonary artery pressure assessment [1, 10, 11, 22–26]. This became fundamental to our study.

Expansion of the CT protocol of examination of patients with acute massive PE by including static dimensional indicators of the right heart chambers, which has been proposed by foreign authors, finds its justification from the standpoint of fundamental medicine, but the specificity of these indicators for the analysis of the degree of overload of the right heart chambers is too small [1, 14, 17, 21]. It is becoming more important to determine the CT parameters that make it possible to assess the dynamic dysfunction of the right ventricle with the possibility of actually assessing the pressure in the pulmonary artery instead of indirect manifestations of overload of the right chambers (an increase in the transverse dimensions of the right atrium, right ventricle, trunk and branches of the pulmonary artery, the degree of displacement of the interventricular septum) [1, 11, 22–27], which became fundamental in our work.

From an etiopathogenetic point of view, an increase in resistance of pulmonary veins and mediastinal veins system is a unified process that occurs in response to pulmonary embolism. An increase in pressure in the right atrium leads to expansion of dependent veins – azygos, superior and inferior vena cava. The relevance of comparing the size of vena cava and azygos vein with the pressure in the pulmonary artery has been noted by several authors, however, completed studies have not been conducted to date [1, 5, 10, 11, 15, 24–27].

Statistical analysis in our study confirmed a direct relationship between the diameter of the azygos vein and the pressure in the pulmonary artery ($p < 0.001$). According to the regression equation, when the diameter of the azygos vein changes by 1 mm, the expected pressure increases by 3.827 mmHg. The high coefficient of determination ($r^2 = 0.669$) allows the obtained regression model to be used not only for prognosis but also for obtaining actual values of pressure in the pulmonary artery by CT, which is a new pioneering trend in modern radiation diagnostics.

In the comparison groups by CT parameters (the diameter of the superior and inferior vena cava), the relationship was not found to be statistically significant in the course of our work ($p > 0.05$), therefore, the isolated use of the results have limited practical value.

An additional factor confirming the hemodynamic significance of overload of the right heart chambers was the reflux of contrast agents into the inferior vena cava and hepatic veins. Contrast reflux in the inferior vena cava and hepatic veins, the so-called “retrograde opacification”, is considered by several researchers [8, 23–25] as one of the indicators of overload of the right chambers of the heart. The studies presented in the literature confirm the effect of this parameter on the 30-day survival rate of patients, reporting that reflux of the contrast agent in the IVC and hepatic veins are more common in the group of lethal outcomes of acute massive PE, but a quantitative comparison of the case-reflux CT parameter with the actual pulmonary artery pressure was not reported [8, 10, 17, 24, 28, 29].

Our study allows us to state that both types of reflux are statistically associated with indicators of pressure in the pulmonary artery ($p < 0.05$), of which the most prognostically stable CT parameter of the overload of the right heart chambers was the reflux of contrast agent into the hepatic veins: its presence indicated pressure in the pulmonary artery of more than 65 mmHg. However, the practical application of this CT parameter may have technical limitations. According to several authors [8, 28], the specificity of the CT-parameter “case-reflux” may depend on the rate of administration of a contrast agent during CT-angiopulmonography, having the lowest numbers at a high rate of administration of contrast agent at the time of the procedure. However, even with a contrast agent injection rate of more than 3 ml/s, the specificity of the parameter in assessing right ventricular failure approaches 70%, and the sensitivity exceeds 80% [8, 27], which allows us to consider the CT parameter – reflux of a contrast agent into the hepatic veins – in practical medicine as an alternative CT predictor of an increase in pressure in the pulmonary artery, in the case of correct performance of CT-angiopulmonography.

Of course, the CT method should not be the first method of choice for isolated assessment of the right heart chambers due to the concomitant negative effect of using an iodine-containing contrast agent and radiation exposure. However, in the case of pulmonary thromboembolism, when CT is already the method of choice, the expansion of postprocessing analysis of the obtained CT results can and should provide additional information in assessing the overload of the right heart chambers, which will further unify the CT method for emergency diagnosis of life-threatening cardiovascular conditions.

Conclusions

The current study describes the analysis of CT angiography parameters, which have not been considered previously, such as the diameter of the azygos vein, reflux of the contrast agent into the hepatic veins; and this makes it possible to calculate the actual values of the mean pressure in the pulmonary artery for an objective assessment of the overload of the right heart chambers. Such diagnostic algorithm extension changes the view on the possibilities of emergency CT diagnostics of a life-threatening cardiovascular disease - acute massive pulmonary embolism.

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Declarations of interest: none

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Notifications of Ethical Adherence: The study was conducted in accordance with the Declaration of Helsinki

(2013). Informed consent was obtained from each patient which was approved by the Hospital Ethical Committee

Authors' participation

Sukhova M.B. – concept and design of the study, conducting research, analysis and interpretation of the obtained data, collection and analysis of data, writing text.

Trofimova T.N. – concept and design of the study, analysis and interpretation of the obtained data, approval of the final version of the article.

Yakimov V.N. – analysis and interpretation of the obtained data, collection and analysis of data, statistical analysis, participation in scientific design.

Vedunova M.V. – analysis and interpretation of the obtained data, participation in scientific design.

Kryukova E.V. – text preparation and editing, participation in scientific design.

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