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Clinical significance of homoarginine level in patients with ascending aortic aneurysm and aortic stenosis

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Abstract

Objective. To assess homoarginine (hArg) level in patients with ascending aortic aneurysm and aortic stenosis. **Design and methods.** The study included 26 patients with ascending aortic aneurysm and 19 patients with aortic stenosis. The comparison group consisted of 30 healthy donors. Plasma levels of hArg, asymmetric dimethylarginine (ADMA), and the parameters of mitochondrial dysfunction (pyruvic acid, PGC-1a protein, lactic acid, cytochrome C) were determined. **Results.** Patients with ascending aortic aneurysm and aortic stenosis demonstrated a decrease in the level of serum hArg ($p = 0,002$), most pronounced in the group with ascending aortic aneurysm, an increase in ADMA and markers of mitochondrial dysfunction-lactic acid, PGC-1a protein. There was no relation between hArg level and well-known metabolic markers of mitochondrial (lactic and pyruvic acids) and endothelial dysfunction (ADMA). The following factors contributed to the lowering of hArg levels: an increased body mass index ($rs = –0,34$, $p = 0,02$), impaired glucose tolerance ($p = 0,006$), and myocardial infarction ($p = 0,09$). In a subgroup of patients with a tricuspid aortic valve and ascending aortic aneurysm, an inverse relationship was found between hArg level and descending thoracic aortic diameter ($rs = –0,5$, $p < 0,05$). **Conclusion.** The decreased level of hArg is a marker of mitochondrial and endothelial dysfunction in patients with ascending aortic aneurysm and aortic stenosis, especially in patients with myocardial infarction, obesity and diabetes mellitus.

Key words: aortic aneurysm, aortic stenosis, homoarginine

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Клиническое значение исследования гомоаргинина у пациентов с аневризмой восходящего отдела аорты и аортальным стенозом

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Резюме

Цель исследования — оценить уровень гомоаргинина (гАрг) у лиц с аневризмой восходящего отдела аорты и аортальным стенозом. **Материалы и методы.** В исследование включены 26 пациентов с аневризмой восходящей аорты и 19 больных с аортальным стенозом. Группу сравнения составили 30 здоровых доноров. В сыворотке крови определены уровни гАрг, асимметричного диметиларгинина (АДМА), а также показателей митохондриальной дисфункции: пировиноградной кислоты, белка PGC-1a, молочной кислоты, цитохрома С. **Результаты.** У больных с аневризмой аорты и аортальным стенозом выявлено снижение уровня сывороточного гАрг ($p < 0,0001$), наиболее выраженное в группе с аневризмой восходящей аорты, а также повышение уровня АДМА и маркеров митохондриальной дисфункции — молочной кислоты, белка PGC-1a. Не обнаружено связи уровня гАрг с известными метаболическими маркерами митохондриальной (молочная и пировиноградная кислоты) и эндотелиальной дисфункции (АДМА). С уровнем гАрг значимо коррелировали: повышенный индекс массы тела ($r_s = –0,34$; $p = 0,02$), нарушение метаболизма глюкозы ($p = 0,006$) и перенесенный инфаркт миокарда ($p = 0,09$). В подгруппе больных с трехстворчатым аортальным клапаном и аневризмой восходящего отдела аорты выявлена обратная связь между уровнем гАрг и диаметром нисходящей грудной аорты ($r_s = –0,5$; $p < 0,05$). **Заключение.** Для больных с аневризмой восходящего отдела аорты и аортальным стенозом характерно снижение уровня гАрг. С учетом проведенных ранее эпидемиологических исследований гАрг может рассматриваться как потенциальный маркер митохондриальной и эндотелиальной дисфункции. Наиболее выраженные изменения данного показателя отмечены у больных, перенесших инфаркт миокарда, имеющих избыточную массу тела или сахарный диабет.

Ключевые слова: аневризма аорты, аортальный стеноз, гомоаргинин

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Introduction

The most common variants of the left ventricular outflow tract defects are aortic stenosis and ascending aortic aneurysm.

According to autopsy data, 1% of the Russian population has a dilatation of the ascending aorta, which is the most dangerous localization due to its proximal localisation. According to the results of epidemiological studies, aortic stenosis is the most common acquired heart defect. It is detected in 26% of the population older than 65 years [1].

Due to the fact that timely surgical treatment plays an important role in the outcome of both diseases, an early detection of them is an extremely important task. Despite the multiple studies, no specific biomarkers for left ventricular outflow tract defects have been identified so far [2]. Most of the currently known biomarkers are used mainly to assess the prognosis of the disease, as in the case of determining the severity of aortic stenosis by natriuretic peptide level[3].

Nitric oxide (NO) plays an important role in regulating the vascular wall homeostasis. It was shown that patients with an aneurysm of the ascending aorta have abnormalities of the endothelial function [4]. However, the causes and mechanisms of endothelial dysfunction in patients with ascending aortic aneurysm and those with aortic stenosis are not fully disclosed. In connection with the fact that the main source of nitric oxide is arginine (Arg), the main interest is the study of the metabolism of arginine and its derivatives. Therefore, a number of studies have been devoted to assessing the level of asymmetric dimethylarginine (ADMA), a competitive inhibitor of NO-synthase [5,6]. At the same time, the data on the change in the level of ADMA in patients with pathology of the aorta and aortic valve are contradictory. Thus, some authors claim that ADMA level is higher in patients with aortic stenosis than in patients with ascending aortic aneurysm [6], others show an increase in ADMA only in patients with ascending aortic aneurysm [5].

Homoarginine (hArg) is an Arg homologue, differing from it by an additional methylene group. For many years the level of hArg was used only as an internal standard in the calculation of the concentrations of other arginine derivatives. It was believed that garg has no clinical significance. The situation changed dramatically in 2008, when for the first time there was described an increase in hArg during pregnancy [7]. From that moment, interest in studying the physiological role and metabolism of hArg sharply increased.

In particular, recent studies have discovered an association between low hArg levels and high risk of cardiovascular events, as well as a higher mortality among patients in a cohort with a low level of hArg [8,9,10,11]. The results of experimental studies on reduction of ischemic stroke zone with administration of exogenous hArg [11] demonstrate, that the given Arg homologue should be considered not only as a prognostic marker, but also as a potential therapeutic agent.

The mechanism underlying these relationships remains unclear. Generally, a high level of hArg is associated with an improvement in endothelial function due to activation of the NO synthesis pathways. On the one hand, hArg is a substratum of NO-synthases; on the other hand, hArg, being a product of modification of Lysine, retains the ability of Lysine to inhibit arginase, thereby increasing the Arg concentration and its availability for NO synthesis in cells. However, the absence of a pronounced association between Arg concentration and mortality rate suggests that the effects of hArg are not limited to those with Arg metabolism [8].

The level of hArg, whose physiological role is associated with both modulation of endothelial function and energy metabolism in tissues, can be considered an important integral metabolic indicator reflecting the progression of mitochondrial and endothelial dysfunctions. The study of hArg as a new biomarker of endothelial and mytochondrial dysfunction is extremely important for understanding the biochemical processes accompanying the formation of ascending aorta and aortic valve pathology.

Material and methods of research

Collection of clinical material was conducted from 2012 to 2014 on the basis of North-West Medical Research centre named after V.A. Almazov. The protocol of the study in accordance with the principles of Helsinki Declaration was approved by the Ethical Committee of North-West Medical Research centre named after V.A. Almazov. Written informed consent to the anonymous use of the results was obtained from all persons participating in the study.

The study included 26 patients with ascending aotric aneurysm and 19 patients with aortic stenosis, an age distribution of 60 (52–64) years. The comparison group consisted of 30 healthy donors (11 men and 19 women) aged 30 to 61 years.

Table 1

CHARACTERISTICS OF THE SELECTED SUBJECTS

	Ascending aortic aneurysm M ± σ N = 26	**Aortic stenosis M ± σ N = 19**
Age (years)	55 ± 2	63 ± 2
BMI (kg/m²)	28.5 ± 0.8	28.7 ± 1.9
Men, n (%)	17 (65%)	10 (52%)
Smokers, n (%)	14 (53%)	9 (47%)
Glucose intolerance, n (%)	4 (15%)	3 (16%)
Waist (mm)	94 ± 3	101 ± 3
Metabolic syndrome (%)	44%	48%
Hypertension, n (%)	21 (81%)	15 (79%)
Office systolic BP (mm Hg)	127 ± 3	132 ± 4
Office diastolic BP (mm Hg)	81 ± 3	80 ± 3
Creatinine (μmol/l)	78 ± 3	76 ± 5
Glucose (mmol/l)	5.3 ± 0.1	5.6 ± 0.4
Total Cholesterol (mmol/l)	4.9 ± 0.2	5.9 ± 0.5
C-reactive protein (mg/l)	4.1 ± 0.8	1.8 ± 0.6
Maximal aortic diameter (mm)	47.0 ± 1.3*	35.8 ± 0.7
Mean aortic gradient (mmHg)	–	87 ± 9*
Peak aortic gradient (mmHg)	12 ± 2	50 ± 7
AVA (cm²)	–	0.82 ± 0.03
LVMI (g/m²)	136 ± 9	164 ± 12**
LV geometry Concentric LVH, n (%) Eccenrtic LVH, n (%) Normal LV geometry, n (%)	 13 (50%) 12 (46%) 1 (4%)	 15 (79%)* 4 (21%)* 0
Beta-blockers, n (%)	18 (69%)	14 (75%)
Angiotensin-converting enzyme inhibitors, n (%)	12 (46%)	10 (53%)
Angiotensin II receotor blockers, n (%)	4 (15%)	4 (21%)
Calcium Channel blockers, n (%)	3 (12%)	2 (11%)
Diuretics, n (%)	8 (31%)	10 (53%)*
Statins, n (%)	8 (31%)	7 (37%)

Note: AVA — aortic valve area; BMI — body mass index; BP — blood pressure; LV — left ventricular; LVMI — left ventricular myocard index; LVH — left ventricular hypertrophy; * — Significant $p < 0.05$; ** — $p = 0.07$.

All patients underwent echocardiography using a standard protocol on a Vivid 7.0 (GE, USA). The severity of aortic stenosis was assessed by magnitude of the blood flow velocity on the aortic valve, aortic valve area and mean aortic gradient. The study included patients with a flow rate at the valve ≥ 4 m/s, mean aortic gradient> 40mmHg and aortic valve area < 1cm². The aortic root in patients with ascending aortic aneurysm was visualized using multispiral contrast-enhancet computer tomography (Siemens Somatom Definition 128). The inclusion criteria was aortic dilatation ≥ 4.5 cm. Exclusion criteria included connective-tissue syndromes, inflammatory diseases of the aorta and aortic valve,

Table 2

MARKERS OF ENDOTHELIAL AND MITOCHONDRIAL FUNCTION IN PATIENTS WITH LEFT VENTRICULAR OUTFLOW TRACT DEFECTS

Показатель	Patient [1]	Reference [2]
Lactic acid, μmol/l	1.1 (0.9–1.6)*	0.5–1.0 [12]
Piruvic acid, μmol/l	59 (41–95)	15–100 [12]
TML, μmol/l	0.29 (0.24–0.39)*	0.34–0.67 [13]
PGC1a, ng/l	132 (99–173)*	< 80 [12]
ADMA, μmol/l	0.46 (0.42–0.53)*	0.13–0.39 [13]
SDMA, μmol/l	0.46 (0.39–0.53)*	0.24–0.36 [13]

Note: ADMA — asymmetric dimethylarginin; SDMA — symmetric dimethylarginin; PGC1a — peroxisome proliferator! activated receptor gamma coactivator- 1 alpha, TML — trimethyllysine; * — Significant $p < 0.001$.

[1] Data presented as mean ± standard deviation and median (Q25:Q75).

[2] According to own data (see links) .

Reference is presented as range of concentration between 10 and 90 percentiles in healthy individuals.

posttraumatic aortic aneurysm, and decompensation of internal diseases. Another criterion for exclusion from the study was the presence of diseases of the kidneys, liver, and endocrine patholigy (except for type 2 diabetes mellitus). Half of the patients (n = 33) had arterial hypertension, and 24 patients had initial clinical manifestations of heart failure, corresponding to II class according to classification of New York Heart Association (NYHA class II).

The materials of study was plasma samples of blood taken from cubital vein in the morning on an empty stomach into vacuum containers with sodium citrate or EDTA as anticoagulants. The separation of blood elements was carried out within no more than 20 minutes from the moment of taking blood. Plasma samples were stored at –80 °C until analysis.

Laboratory studies were carried out in the Department of Biochemistry of the Pavlov First Saint Petersburg State Medical University.

Determination of homoarginine level

Homoarginine level was determined as part of blood plasma encoded amino acids spectrum by reversed-phase HPLC analysis [12] using orthophthalaldehyde for pre-columnar derivatization and a Zorbax Eclipse AAA C 18 column (150 x 4.6 mm, 3.5 μm) in a modification supported by RF patent (Positive decision of January 10, 2017 № 2015152677 / 15 (081202)). Amino acid concentrations were calculated using norvaline as an internal standard.

Determination of other metabolites

The concentration of lactic acid in the blood plasma was determined colorimetrically with lactoxidase test according to the set of Vital Development Corporation (Russia).

The concentration of pyruvic acid was determined in the protein-free plasma ultrafiltrate using lactate dehydrogenase, as described previously[12].

The proteins level was determined using commercial reagent kits for enzyme-linked immunosorbent assays: PGC 1a (1 alpha co-activator of the gamma receptor activating peroxisome proliferation; Uscn Life Science Inc., PRC); cytochrome C (Bender MedSystems GmbH, Austria).

The concentration of methylated basic amino acids derivatives; Asymmetric and symmetrical dimethylarginines (ADMA, SDMA) as well as trimethyllysine — was determined by HPLC after solid-phase extraction with subsequent derivatization of ortho-phthalaldehyde [13].

Statistics

All statistical analyses were performed using the SAS 9.3 software package. The data are presented as median and quartiles (Me (Q25-Q75). Nonparametric Mann-Whitney criterion was used to estimate intergroup differences. Correlation analysis was carried out using the Spearman criterion.The critical level of null statistical hypothesis reliability was assumed to be 0.05.

Results

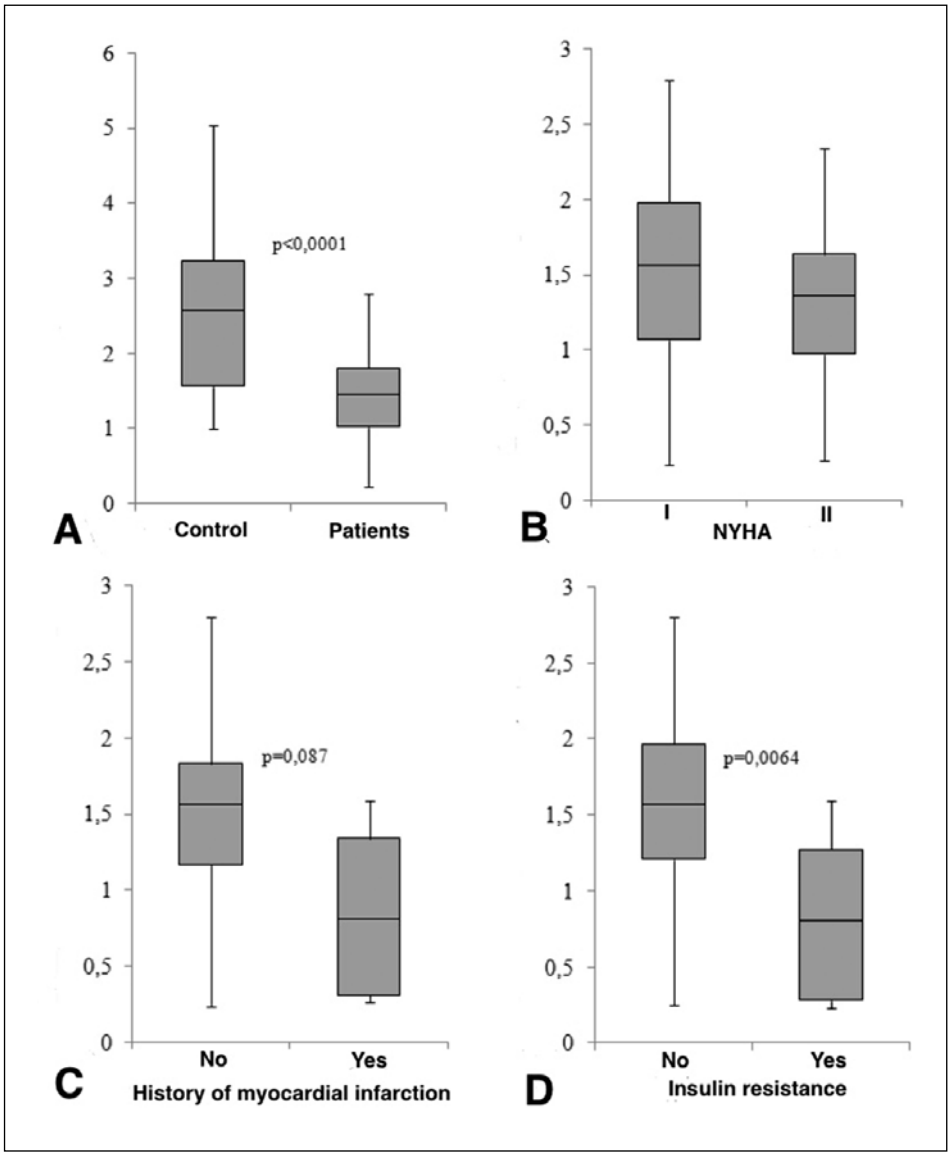
The patients exhibited only minimal deviations in routine laboratory markers (Table 1). Patients in both groups had metabolic signs of mitochondrial dysfunction (Table 2), including increased levels of lactic acid, PGC 1a protein, decreased trimethyllysine concentration and detection of cytochrome C protein in the blood (data not shown). There also have been found increased concentration of ADMA, which is marker of endothelial dysfunction. The values of these parameters in subgroups with ascending aortic aneurysm and aortic stenosis were comparable.

In both groups, regardless of diagnosis, a reduction in hArg was observed (Fig. A). However, the lowest hArg level was found in patients with ascending aortic aneurysm — 1.23 (0.71–1.56) μmol / L compared to 1.66 (1.56–2.00) μmol / L in patients with aortic stenosis (p = 0.002). Initial signs of heart failure was not accompanied by an additional significant decrease in hArg level (Fig. B). The tendency to decrease in hArg level relative to the remaining patients was found in people who underwent myocardial infarction (Fig. B).

Patients with impaired glucose metabolism (type 2 diabetes mellitus or impaired glucose tolerance) had lowest level of hArg (Fig. D). In three patients who had combination of myocardial infarction and impaired glucose toleranse, the level of hArg was 0.26, 0.31 and 1.59 μmol / L.

It is important that in the examined patients the association of decreased hArg level with increased body mass index (rs = –0.34, p = 0.02) was revealed.

Figures. Homoarginine concentration in patients compared control group (A) and in different clinical state (B,C,D), μmol/l



There were no correlations between hArg level and the well known metabolic markers of mitochondrial (lactic and pyruvic acids) and endothelial dysfunction (ADMA), as well as with routine biochemical markers.

Homoarginine level was correlated only with the concentration of trimethyllysine (rs = 0.38, p = 0.009), the value of which was studied by us previously [13]. In a subgroup with ascending aortic aneurysm aneurysm and tricuspid aortic valve, an inverse correlation was established between the level of hArg and descending aortic diameter (rs = –0.5, p < 0.05).

Discussion

The association of hArg with risk of vascular complications is usually associated with possible participation of this amino acid in NO metabolism. Nevertheless, as a substrate for NO synthase, hArg is much less effective than Arg [7], and its inhibitory effect on arginase is weak. According to the experimental studies using mouse lines [11], as well as the results of the study on biosynthesis of hArg in man [14], the level of this amino acid in blood is mainly determined by activity of glycine aminotransferase (AGAT). AGAT is enzyme of biosynthetic pathway of creatine-arginine. Expression of the AGAT gene in humans is found in many tissues, but it is highest in the kidney [15]. It was shown that hArg level in blood plasma is associated with genetic variants of AGAT in humans [14], the frequency of which varies in different ethnic groups. Considering hArg as a by-product of creatine biosynthesis, it can be concluded that its level reflects the intensity of energy metabolism in tissues. In this connection, it is important to note that we did not find associations between hArg level and parameters associated with mitochondrial function (lactic acid, pyruvic acid, PGC 1a, cytochrome C). On the other hand, there is no decrease in hArg in individuals with initial signs of heart failure. There also were not revealed correlations with ADMA and SDMA levels, which is in accordance with the modern concept of the specific diagnostic and prognostic significance of hArg [8, 11]. The results indicate that hArg should be considered as an independent marker of metabolic changes.

Experimental data on ischemic brain injury zone reduction due to injection of exogenous hArg [11] indicate that this derivative of Arg is not simply a by-product of the way of creatine formation, but probably has its own metabolic significance.

The observed decrease in hArg concentration in studied patients with the ascending aortaic and aortic valve pathology is consistent with data from other studies in cohorts of individuals at high risk of cardiovascular complications [8–11]. A large-scale study of individuals with coronary heart disease (n = 3305, LURIC study) showed that among patients with hArg level below 1.85 μmol / L, mortality from cardiovascular diseases is 4 times higher than among those with hArg level more than 3.1 μmol / l [9]. For the group of patients with high risk of death who have type 2 diabetes and who are on hemodialysis (n = 1244, 4D study), lower values of the hArg level were demonstrated in comparison with the LURIC study — 1,2 ± 0,5 and 2,6 ± 1.1 μmol / l, respectively [8,9]. According to the results of the present study, in patients with a history of myocardial infarction and in patients with diabetes mellitus, the lowest values of the hArg level were also found. There was also decreased hArg level associated with increased body mass index. Together, these data support the association of components of metabolic syndrome with low hArg level.

Mitochondrial dysfunction itself reflects the state of metabolic processes in tissues and is more common in patients with atherosclerosis and metabolic syndrome. This fact is especially interesting in the context of studied pathology, since it is known that atherosclerosis, as the cause of ascending aortic aneurysm formation was virtually rejected. In addition, there is evidence of low risk of ischemic disease and heart attacks in individuals with ascending aortic aneurysms[16]. In the present work, a correlation was found between decreased hArg level and diameter of descending thoracic aorta. However, this association was demonstrated only in patients with ascending aortic aneurysm having a tricuspid aortic valve. It might be explained by atherosclerosis that underlies the dilatation of the descending thoracic aorta, along with specific changes in the brachiocephalic, coronary arteries and abdominal aorta. Thus, it is possible that metabolic abnormalities occurring in persons with ascending aortic aneurysm and tricuspid aortic valve are reflected in formation of dilatation descending thoracic aorta. On the contrary, the ascending aortic diameter was not associated with hArg level, which is in agreement with modern concepts of a more complex pathogenesis of ascending aortic aneurysm [16].

Attention is also drawn to the fact that in persons with ascending aortic aneurysm, hArg was

much lower than in patients with aortic stenosis. It is contrary to the theory about greater significance of atherosclerosis and metabolic syndrome in development of aortic stenosis in comparison with ascending aortic aneurysm.

It is important to note that hArg is a marker of endothelial and mitochondrial dysfunctions. One of the pathogenetic processes that bind metabolic disorders with mitochondrial and endothelial dysfunction is altered mitochondrial division. In particular, it has been shown that in the case of hyperglycemia, active oxygen forms are formed in the aortic wall, which alter the process of mitochondrial fission, which leads to disruption of NO-synthase. The main argument is the improvement of NO-synthase activity in suppressing mitochondrial division [17]. It might be explain by evidance, that altered fusion / division of mitochondria directly affects the processes of apoptosis and autophagy. Due to the fact that an increased number of smooth muscle cell apoptosis is described in aortic tissues in patients with ascending aortic aneurysm, this mechanism can explain the formation of ascending aortic dilatation in patients with diabetes mellitus without severe atherosclerotic vascular wall lesion.

In conclusion, it should be emphasized that, according to the data obtained in the present study, a decreased hArg level is an indicator of mitochondrial and endothelial dysfunction in ascending aortic aneurysm and aortic stenosis. However, as in case of ADMA level, it is too early to talk about cause-effect relationships, since there is too little known about metabolism of arginine derivatives. Given that in this work the small cohort is the main limiting factor, further study of Arg derivatives in large-scale studies will help to determine their diagnostic role in ascending aortic aneurysms and aortic stenosis.

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Conflict of interest

The study is supported by the grant of the Russian Scientific Foundation, project # 17–75–30052 "The development of the personalized treatment of patients with obesity and type 2 diabetes mellitus in order to reduce cardiovascular risk".

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