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PREDICTIVE VALUE OF NON-INVASIVE COMMON CAROTID ARTERY ELASTICITY IN HEART RECIPIENTS

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Objective: to study the predictive value of the local noninvasive elasticity index of the common carotid artery (CCA) wall in heart transplant recipients**. Materials and methods.** The study included 101 heart recipients. All study subjects underwent ultrasound examination of carotid arteries with assessment of the damping function of arteries and measurement of local and regional indicators of elastic properties of the CCA. The vascular wall elasticity index (iCOMPL) of the CCA was calculated according to the formula using the CCA diameters in systole and diastole and measurements of systolic and diastolic blood pressure. All-cause death, heart retransplantation, and clinically significant heart transplant coronary artery disease were evaluated as combined endpoints (adverse outcomes). **Results.** In heart recipients without morphological and immunohistochemical signs of heart graft rejection, detection of relatively low iCOMPL of CCA is a predictor of earlier development of adverse events ($p = 0.03$). Conclusion. iCOMPL of the CCA is a noninvasive and easily reproducible predictor of adverse outcomes in the long-term period after heart transplantation and can be used in clinical practice for the purpose of risk stratification in heart recipients.

Keywords: vascular wall elasticity, common carotid artery, heart transplantation, recipients.

INTRODUCTION

The issue of improving long-term prognosis and achieving active longevity in heart recipients are currently coming to the forefront and will actually dictate how the discipline of transplant cardiology develops going forward. Heart transplantation (HT) is still the gold standard for treating end-stage heart failure; the number of HT centers in the Russian Federation has increased, the number of HT operations has risen, medical care technologies have improved, and perioperative and in-hospital mortality has decreased tenfold, and rehabilitation programs have been developing. All these factors have led to a multiple increase in the number of heart recipients [1, 2]. At the same time, the success attained is largely attributable to the reduced rate of postoperative adverse outcomes, and further improvement in the long-term prognosis of heart recipients necessitates the development of strategies for risk stratification, prevention and prompt treatment of pathologic conditions in the long-term period.

The primary adverse factors affecting the long-term prognosis, aside from the irreversible risk of rejection, are cardiac graft cardiopathy and extracardiac complications brought on by immunosuppressive therapy side effects, as well as those linked to compromised cardiac reflexes, heart autonomic denervation, and chronic subclinical activation of the inflammatory system, which impairs vascular endothelium function [3].

According to our hypothesis, the indicators characterizing the elasticity of the arterial wall of large arteries can be used as noninvasive predictors of adverse outcomes and markers of various complications. The simplicity, reproducibility and low cost of the study of morphological properties of large arteries and physiological assessment of blood flow parameters using ultrasound suggests a high potential for their routine use [4–7].

In a previous single-center prospective observational study, it was shown that graft rejection in heart recipients is linked to changes in the elastic properties of the common carotid artery (CCA); the CCA arterial stiffness is increased in all types of acute graft rejection, and then decreases against the therapy [8, 9]. It was also found that the evaluation of the elasticity index of the common carotid artery, another ultrasonographic metric, can be used to assess the extent to which different factors negatively impact the main arteries in recipients of solid organs [10].

The **objective** of this study was to investigate the prognostic value of the local noninvasive elasticity index of the CCA in HT recipients.

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MATERIALS AND METHODS

The results of this study are based on analysis of the data obtained during case follow-up at Shumakov National Medical Research Center of Transplantology and Artificial Organs of 101 HT recipients who underwent orthotopic heart transplantation from March 2000 to April 2015.

All patients after transplantation received combined immunosuppressive therapy including tacrolimus, mycophenolic acid and glucocorticoids, as well as necessary adjuvant therapy as indicated.

Arterial wall elasticity indices were measured during routine examination after HT surgery between February 2013 and May 2015.

The exclusion criterion was the presence of signs of cardiac graft rejection detected by endomyocardial biopsy or acute infectious diseases.

The structural and functional characteristics of the CCA wall were determined using the Vivid S70N ultrasound diagnostic system with a 9 MHz linear multifrequency sensor measuring the thickness of the intima-media complex, determining the carotid-femoral pulse wave velocity (PWV), and calculating the elasticity index, hereinafter referred to as iCOMPL (**i**ndex **COMPL**iance). The vascular wall elasticity index was calculated using the formula.

$$iCOMPL = [(D_{dia}^2 - D_{sys}^2)/D_{dia}^2]/[(P_{sys} - P_{dia})/P_{sys}],$$

where D_{sys} and D_{dia} are systole and diastole CCA diameters, respectively; P_{sys} and P_{dia} are systolic and diastolic blood pressure levels.

Event-free survival was studied based on assessment of the time to occurrence of the combined endpoint, which included patient death (from all causes), clinically significant cardiac graft dysfunction requiring repeat HT, and clinically significant cardiac graft ischemia associated with transplant coronary artery disease (TCAD) with indications for coronary angioplasty.

Statistical processing of the study results was performed using the Wizard Pro software package (Version 1.9.49, MacOS). The Shapiro–Wilk test was used to check the normality of distribution of values. Student's t test was used to assess the reliability of differences in quantitative indicators that satisfied the normal distribution assumptions; in other situations, the Mann–Whitney U test was used. Differences in qualitative characteristics were assessed by constructing conjugation tables and their subsequent analysis using the chi-squared test. The Kaplan–Meier approach was used to evaluate event-free survival, and the log-rank method was employed to compare survival curves. In all statistical analytic methods used in the study, differences were considered reliable at $p < 0.05$.

RESULTS AND DISCUSSION

The predictive value of the CCA elasticity was examined in 101 heart recipients. Most patients had end-stage chronic heart failure, which was caused by dilated cardiomyopathy in 51 patients and ischemic cardiomyopathy in 33 patients. The patients included 80 males and 21 females; recipient mean age was 47.9 ± 1.9 years. The study included individuals not younger than 15 and not older than 78 years of age who survived 30 days after surgery.

Carotid ultrasound was performed on average 469.91 ± 280.65 days after HT. The median iCOMPL of the CCA in this heart recipient sample was 0.044 mm^2/mmHg. The recipients were divided into 2 subgroups depending on the value of elasticity index values above or below the median (0.044) (Table).

Patients with high elasticity (iCOMPL >0.044 mm^2/mmHg) did not differ on average from recipients with low iCOMPL in terms of age, sex, number of patients with a previous history of CHD, duration of post-HT follow-up. No significant differences were also found in common carotid artery intima-media thickness (CCA-IMT) and PWV, while the difference in iCOMPL was statistically significant ($p < 0.001$).

The overall follow-up was 3010.8 ± 280.0 days (126 to 8652 days, 95% CI: 2730.9–3290.8 days). During

Table

Comparative characteristics of heart recipients depending on the iCOMPL of the CCA

Indicator	iCOMPL <0.044 mm^2/mmHg	iCOMPL >0.044 mm^2/mmHg	Significance of differences (p)
Total	50	51	–
Number of females	12	9	0.432
Age	46.9 ± 3.5	46.8 ± 4.3	0.953
Number of patients with a history of coronary artery disease	16	17	0.268
Time after OHT until indicators are determined	532.8 ± 246.0	484.7 ± 125.5	0.729
CCA-IMT (mm)	0.76 ± 0.06	0.78 ± 0.04	0.689
PWV (m/s)	14.7 ± 1.6	13.3 ± 1.8	0.241
COMPL (m^2/mmHg)	0.029 ± 0.002	0.082 ± 0.013	**<0.001**

Note: CAD, coronary artery disease; OHT, orthotopic heart transplantation; CCA-IMT, common carotid artery intima-media thickness; PWV, pulse wave velocity; COMPL, common carotid artery elasticity index.

the follow-up, the combined endpoint (death, heart re-transplantation, and TCAD requiring coronary angioplasty) of the cardiac graft developed in 61 patients within 2754.0 ± 346.8 days (153 to 5226 days, 95% CI: 2407.3–3100.8 days).

In the recipient subgroup with a low estimated iCOMPL, mean follow-up was 2677.0 ± 402.1 days (95% CI: 2274.9–3079.1 days), 33 adverse events developed between 153 and 4,337 days, mean time-to-event was 2475.8 ± 479.9 days, 95% CI: 1995.8–2955.7 days.

In the subgroup with high estimated iCOMPL, mean follow-up was 3338.1 ± 381.7 days (95% CI: 2956.4–3719.8 days), 28 adverse events developed between 378 and 5.226 days, mean time-to-event was 3250.1 ± 647.5 days, 95% CI: 1995.8–2955.7 days).

Kaplan–Meier survival curves in subgroups with elasticity values greater and less than the distribution median are shown in the Figure.

Comparison of event-free survival curves revealed a significantly more favorable prognosis in heart recipients with estimated iCOMPL higher than 0.044 (mm^2/mmHg) ($p = 0.03$). At the same time, the study of the relationship between adverse event-free survival and age, sex, intima-media thickness, and pulse wave velocity did not reveal any significant dependence.

The findings of this study therefore suggest that a relatively low estimated iCOMPL of the CCA is a predictor of earlier development of adverse events in heart recipients, such as patient death, clinically significant heart graft dysfunction that required repeated HT, and clinically significant heart graft ischemia linked to TCAD with indications for coronary angioplasty, in heart recipients who do not exhibit morphological and immunohistochemical signs of heart graft rejection.

Previously, we had studied the properties of the index reflecting the degree of carotid arterial wall stiffness (iRIG), which was calculated based on ultrasonographic morphometric and Doppler parameters of the common carotid artery – CCA diameters in systole and diastole, peak systolic and end-diastolic velocity and blood flow acceleration time under the influence of systolic pulse wave [9]. That index, however, took longer to calculate even though it was designed to accurately reflect the true arterial wall stiffness. The elasticity index formula used in this work requires measurement of only two parameters – CCA diameters in systole and diastole, without the need for Doppler ultrasound of intravascular blood flow velocity parameters.

In previous studies, we have demonstrated that heart graft rejection is accompanied by changes in the elastic properties of the wall of the main arteries, in particular the CCA, and we established a vascular wall stiffness index linked to the risk of graft rejection [11]. Research has shown that, with effective rejection treatment, changes in the CCA elastic properties in rejection may be functional in nature and reversible [8].

The pathogenetic relationship between iCOMPL determined in this work with long-term prognosis may be down to the fact that arterial elasticity is dependent on both the tone of smooth muscle cells and the severity of remodeling, which is in turn characterized by the quantity and quality of connective tissue fibers, calcinosis, severity of inflammation, and cellular composition of the arterial wall. The endothelium plays an important role in regulating the vascular tone. Increased circulating blood volume, pulse wave asynchrony, sympathetic stimulation, activation of inflammation and action of proatherogenic factors are accompanied by endothelial dysfunction and, consequently, decreased arterial elasti-

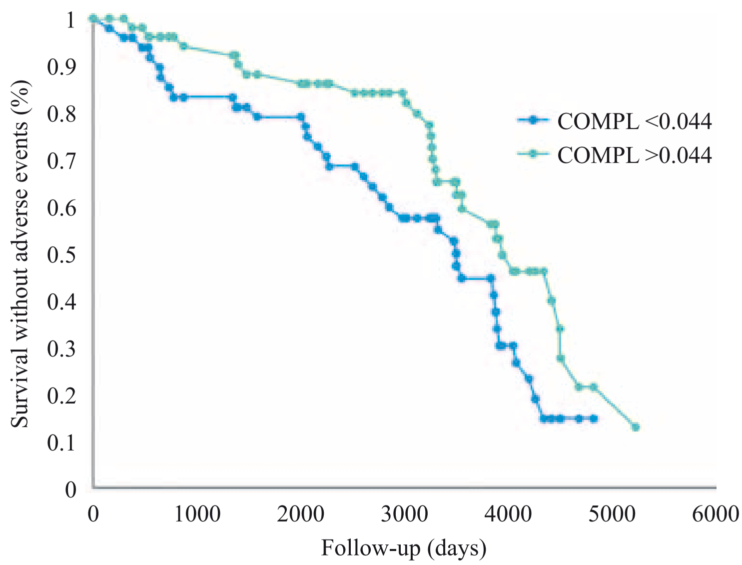

Fig. Kaplan–Meier event-free survival curves in subgroups of patients with different CCA wall elasticity (iCOMPL, vascular wall elasticity index) city. In other words, the mechanisms leading to adverse events – cardiac graft cardiopathy and its complications, TCAD development and progression, atherothrombosis, irreversible cardiac graft dysfunction requiring retransplantation, and patient death – are, to varying degrees, directly or indirectly associated with decreased elastic properties of the wall of large arteries.

CONCLUSION

The iCOMPL of the CCA, which was developed and tested during the study, is a noninvasive and easily reproducible predictor of adverse events in the long-term post-HT period, which can be used in clinical practice for the purpose of risk stratification in heart recipients.

The authors declare no conflict of interest.

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