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Arterial hypertension after heart transplantation

Aim	To evaluate incidence of arterial hypertension (AH) in the posttransplantation period and to identify risk factors for this complication.
Materials and methods	From January, 2010 through December, 2017, 96 heart transplantations (HT) (70 men and 26 women aged 46.5±13.9 years) were performed. During the first month following HT, 8 recipients died and were excluded from the analysis. The retrospective evaluation of results included 88 patients followed up for more than one year.
Results	For the entire post-HT period (maximum 92 months), AH was observed in 75 of 88 (85%) recipients. Post-HT AH was correlated with male gender (r=0.24; p=0.031), history of smoking before HT (r=0.45; p<0.001), history of ischemic heart disease (IHD) (r=0.28; p=0.01), older age (r=0.35; p=0.001), higher body weight index (r=0.37; p=0.0005), creatinine level (r=0.37; p=0.001), and low-density lipoprotein cholesterol level (r=0.27; p=0.04). Interrelations with other AH risk factors were not found. Most patients developed AH within the first two years after HT. During the first year, AH was diagnosed in 60% (53 of 88) of patients (relapse, 85% (n=29); newly diagnosed, 45% (n=24), p=0.0003). At two years, AH was detected in 79% (46 of 58) of patients (relapse, 53% (n=18); newly diagnosed, 53% (n=28), p=0.9). All recipients received an adequate antihypertensive therapy. 40–63% of patients required a single-drug therapy at different points of follow-up; from 29 to 45% of patients required a two-drug therapy, and 5–15% of patients required three or more drugs. During all 5 years of treatment, most patients used angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor blockers (ARBs) (70–87%) and slow calcium channel blockers (SCCB) (48–53%). The presence of AH following HT was associated with development of all cardiovascular events (CVE; r=0.31; p=0.012) whereas persistent AH, which required a combination antihypertensive treatment, was associated with a high mortality (r=0.61; p=0.015).
Conclusion	AH is a frequent complication of HT (85%), which is newly diagnosed in most patients during the first two years. AH incidence was higher for male recipients with a history of IHD, hypertension, and smoking. Approximately half of patients required only a single-drug antihypertensive therapy. After HT, the most frequently prescribed drugs included ACE inhibitors or ARBs and SCCBs (70–87% and 48–53%, respectively, depending on the time elapsed after HT). Persistent AH requiring a treatment with two or more antihypertensive drugs was associated with development of all CVEs and a higher long-term mortality.

Keywords	Heart transplantation; arterial hypertension; cardiovascular complications; essential hypertension
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The number of heart transplantation surgeries increases every year worldwide, according to the International Society of Heart and Lung Transplantation Register [1]. The inclusion criteria for heart transplant candidates have expanded recently, encompassing patients of older age and with more co-morbidities.

Hypertension is a common complication (50%–90%) after heart transplantation (HT) [2, 3]. Several factors have a potential influence on the development of hypertension after HT: chronotropic incompetence, the need for immunosuppressive therapy, endothelial dysfunction, and drug-induced nephrotoxicity. The vasoconstrictor effect of immunosuppressants (including cyclosporine and tacrolimus [2–4]) and the presence of a denervated transplanted heart provide essential inputs into the development of post-transplant hypertension [5]. The presence of hypertension is a risk factor for many complications after HT: allograft vasculopathy [6], transient ischemic attack or cerebrovascular accident [7], and mortality [1]. Therefore it is evident that the population of HT patients requires antihypertensive therapy (preferably multi-agent) [3, 5].

Our objective was to estimate the incidence of post-transplant hypertension and to determine the risk factors for this complication.

Material and methods

The study was conducted under the ethical principles of the Declaration of Helsinki. A total of 96 HTs (46.5±13.9 years old, 70 males, 26 females) were performed between January 2010 and December 2017. Eight recipients died within the first month after HT and were excluded from the analysis. The retrospective evaluation included 88 patients with a follow-up period of more than 1 year.

Patient Characteristics. The causes of chronic heart failure were coronary artery disease (CAD) (n=47, 49%), dilated cardiomyopathy (n=31, 32%), noncompaction cardiomyopathy (n=8, 8%), chronic rheumatic heart disease (n=3, 3%), arrhythmogenic right ventricular dysplasia (n=3, 3%), congenital heart disease (n=1), and cardiac sarcoidosis (n=1). Nine recipients had mechanical circulatory support implanted before HT: extracorporeal membrane oxygenation system (n=2), or biventricular circulatory support Berlin Heart EXCOR® (n=8).

Post-transplantation Care Protocol. Patients were immunosuppressed, with basiliximab 79% (n=76) or antithymocyte globulin 21% (n=20)), and received three-agent immunosuppressive therapy following HT (calcineurin inhibitors, mycophenolic acid/everolimus, glucocorticosteroids).

Patients were observed at the Almazov National Medical Research Center. Outpatient visits and/or remote consultations were carried out via telephone or the Internet at least once a month. If necessary, patients were examined and treated in the hospital. The status assessment protocol included medical history, physical examination of the patient, coronary angiography, and endomyocardial biopsy. Where necessary, additional studies were performed to exclude secondary hypertension.

Post-transplant hypertension was diagnosed at any time following HT with an increase in BP ≥130/80 mmHg, after which antihypertensive therapy was administered according to the standard treatment criteria [8, 9].

Data were processed in SPSS 21.0. All estimations of the mean were made together with the estimations of the median (Me), the lower and upper quartiles [LQ; UQ]. If the rate of a variable was less than 10, the median, minimum, and maximum values were estimated in the sample. The criterion of statistical significance of the

Table 1. Comparative characteristics of patients with post-transplant hypertension with and without hypertension

Parameters	Group of patients		p
	Patients with HT with hypertension (n=75)	Patients with HT without hypertension (n=13)	
Age, years Me [LQ; UQ]	53 [41; 57]	30 [16; 41]	0.0002
Days in waiting list, Me [LQ; UQ]	98 [31; 180]	109 [63; 267]	n/s
Male, n (%)	53 (76%)	6 (46%)	0.045
Family history of hypertension, n (%)	28 (40%)	1 (8%)	0.02
Smoking before HT, n (%)	49 (70%)	2 (15%)	0.001
Smoking after HT, n (%)	10 (14%)	1 (8%)	n/s
Obesity before HT, n (%)	9 (13%)	0	n/s
Obesity after HT, n (%)	8 (11%)	0	n/s
CAD, n (%)	38 (54%)	2 (15%)	0.01
HHD before HT, n (%)	30 (43%)	1 (8%)	0.02

HT, heart transplantation; Me, median; [LQ], lower quartile; [UQ], upper quartile; CAD, coronary artery disease; HHD, hypertensive heart disease; p, the significance of differences between groups; n/s, statistically non-significant.

Table 2. Antihypertensive therapy after heart transplantation

Treatment	Patients with hypertension			
	≤ 6 months after HT (49 of 88)	6–12 months after HT (53 of 78)	1–2 years after HT (58 of 72)	> 2 years after HT (46 of 58)
CCBs	53%	49%	48%	52%
ARBs	43%	51%	52%	54%
ACE inhibitors	27%	23%	24%	26%
Beta-blockers	12%	9%	9%	7%
Imidazoline receptor agonists	6%	7%	10%	4%
Diuretics	4%	2%	3%	4%

HT, heart transplantation; CCBs, calcium channels blockers; ARBs, angiotensin II receptor blockers; ACE, angiotensin-converting enzyme.

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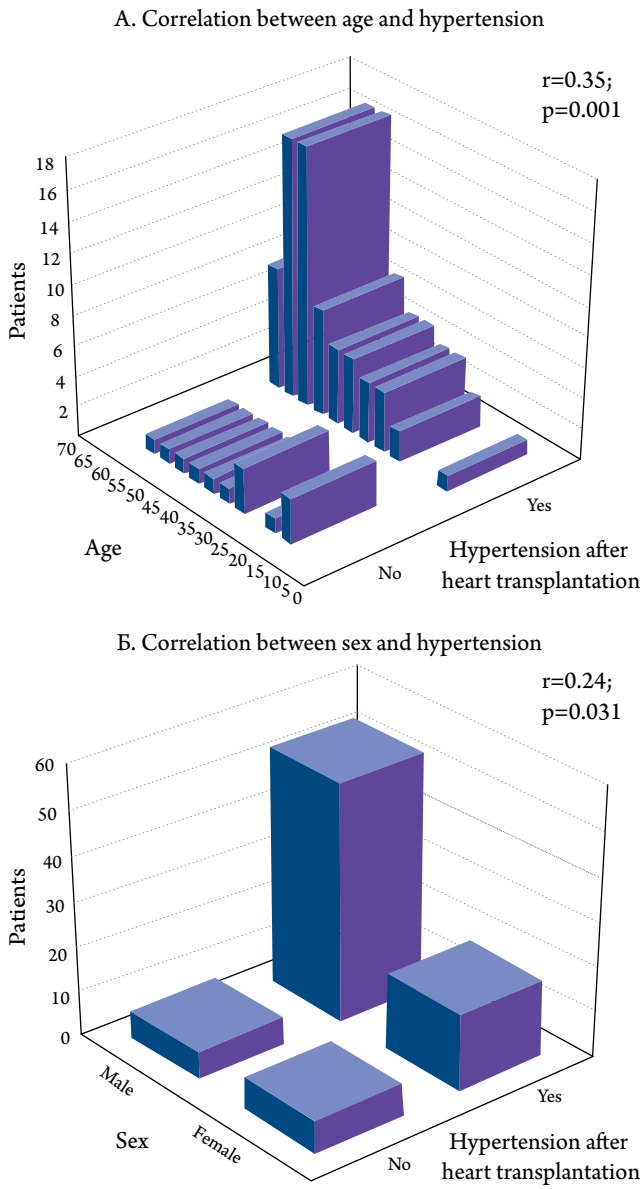
Figure 1. Factors influencing the development of hypertension after heart transplantation



findings was p <0.05, calculated using the nonparametric Mann-Whitney test for independent samples and the Wilcoxon test for dependent samples. The frequencies of binary variables were compared in unrelated groups using contingency tables and the Fisher's exact test. Correlation analysis was also performed.

Results

During the entire follow-up period after HT (maximum 92 months), hypertension was detected in 75 (85%) of 88 recipients. Their clinical characteristics are shown in Table 1. Recipients who developed hypertension were older (p=0.0002), more likely to smoke (p=0.0003), and had a higher rate of pre-HT family history of hypertension (p=0.02), hypertensive heart disease (HHD) (p=0.02), and CAD (p=0.01). This group also included more male patients (p=0.045).

The development of hypertension after HT was correlated with male sex (r=0.24; p=0.031); history of smoking before HT (r=0.45; p<0.001); history of CAD (r=0.28; p=0.01); older age (r=0.35; p=0.001); and higher body mass index (BMI) (r=0.37; p=0.0005), creatinine (r=0.37; p=0.001), and low-density lipoprotein cholesterol (LDL-C) (r=0.27; p=0.04) (Figure 1). There was no correlation with other common risk factors of hypertension.

Most patients were diagnosed with hypertension within the first 2 years following HT. During the first year, it was diagnosed in 60% (53 of 88) of patients (recurrence in 29 [33%] patients, debut in 24 [27%] patients, p=0.0003). By the second year, 79% (46 of 58) of patients had hypertension (recurrence in 18 [31%] patients, debut in 28 [48%] patients, p=0.9).

Adequate antihypertensive therapy was administered to all post-transplant patients. A total of 40%–63% of patients required single-agent therapy at different moments of follow-up, 29%–45% of patients needed two-agent therapy, and 5%–15% of patients required three or more agents. During the 5-year follow-up period, the use of angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor blockers (ARBs) was prevalent in 70%–87% of patients; calcium channel blockers (CCBs) were more commonly used in 48%–53%. Other drugs were used less frequently: beta-blockers (7%–12%), imidazoline receptor agonists (4%–10%), and diuretics (2%–4%) (Table 2).

During antihypertensive therapy for the entire follow-up period, systolic blood pressure (SBP) returned to normal in 95% of patients; diastolic blood pressure (DBP) normalized in only 60% of patients regardless of whether there was a history of hypertension (p=0.09) (Table 3). During the first 12 months, 47% of patients achieved the target levels of BP; among those in whom hypertension remained, it was due to the lack of DBP control in 84% and due to the inability to control SBP and DBP control in 16% of cases. During the first year, 76% of patients achieved BP control. Among those with uncontrolled hypertension in the first year, this was due to high levels of DBP in 75% and both SBP and DBP in 25% of patients. In 2–3 years, hypertension was controlled in 32% of patients. Increased BP is due to DBP in 74%; it is due to both DBP and SBP 26% of cases. In 4–5 years, hypertension was controlled in 31% of patients. The increase of BP was due to an isolated increase of SBP in 22% of cases, DBP in 47%, and both SBP and DBP in 31% of cases.

Following HT, the elevated levels of SBP were associated with higher levels of creatinine (r=0.28; p=0.04);

Table 3. Blood pressure levels during antihypertensive therapy depending on the history of hypertension

Parameter	Patients with hypertension after HT		p
	Positive history of hypertension before HT, m (n=45)	Negative history of hypertension before HT, m (n=30)	
SBP 6 months, mmHg, Me [LQ; UQ]	123 [111; 134]	125 [116; 134]	0.43
SBP 12 months, mmHg, Me [LQ; UQ]	119 [107; 130]	113 [105; 133]	0.80
SBP 3 years, mmHg, Me [LQ; UQ]	122 [115; 128]	122 [113; 134]	0.66
SBP 5 years, mmHg, Me [LQ; UQ]	113 [110; 116]	121 [105; 143]	0.67
DBP 6 months, mmHg, Me [LQ; UQ]	94 [86; 102]	90 [82; 96]	0.20
DBP 12 months, mmHg, Me [LQ; UQ]	88 [75; 95]	80 [76; 94]	0.78
DBP 3 years, mmHg, Me [LQ; UQ]	93 [85; 100]	90 [82; 99]	0.57
DBP 5 years, mmHg, Me [LQ; UQ]	74 [73; 79]	85 [77; 91]	0.33

HT, heart transplantation; SBP, systolic blood pressure; DBP, diastolic blood pressure;
p, significance of differences between groups; Me, median; [LQ], lower quartile; [UQ], upper quartile.

the elevated levels of DBP were associated with higher levels of creatinine (r=0.56; p=0.0006), total cholesterol (r=0.30; p=0.02), and LDL-C (r=0.54; p=0.0005).

The administration of multi-component antihypertensive therapy (two or more agents) early after HT (6–12 months) was associated with high mortality (r=0.61, p=0.015) and more frequent development of cardiac allograft vasculopathy (r=0.25; p=0.002), as opposed to patients who took only one agent to control hypertension.

In the post-transplant period, the following cardiovascular events (CVEs) were observed: cardiac allograft vasculopathy, myocardial infarction, development or progression of brachiocephalic or lower extremity atherosclerosis, cerebrovascular accident, or transient ischemic attacks. The presence of hypertension after transplantation was associated with CVEs (r=0.31; p=0.012). The analysis of relative factors found a weak correlation between the absence of DBP normalization in the period from 6 months to 3 years after HT and cerebrovascular accidents (r=0.18, p=0,04). There was no significant difference in the levels of SBP and DBP in terms of fatal outcomes (p=0.33 and 0.75, respectively). Of the predictor factors used to stratify overall cardiovascular risk, only smoking after HT was associated with high mortality (r=0.32; p=0.009), and persistent hypertension requiring multi-agent antihypertensive therapy (r=0.61; p=0.015).

Discussion

Post-transplant hypertension can develop immediately or in the long term after surgery. In our study, it occurred most commonly in the 2 years after HT. The prior international studies on hypertension following HT did not estimate the time course of the development of post-transplantation hypertension.

According to the 2017 American Heart Association Guidelines, chronic kidney disease, family history of hypertension, older age, and male sex are the risk factors for hypertension. There are also modifiable risk factors for hypertension (smoking, obesity, type 2 diabetes mellitus [DM], dyslipidemia, renal dysfunction, sedentary lifestyle) [8]. In this study, older age of recipients, male sex, smoking, and modifiable risk factors, such as higher BMI, creatinine, and LDL-C, were associated with the development of hypertension in recipients, an indication that these risk factors remain relevant following HT. We found no association of hypertension with DM and sedentary lifestyle in our population, which may be due to a small sample of patients and requires collecting more materials and performing a further investigation.

Additional risk factors contributing to the development of hypertension following HT are the age of a donor, female sex of the donor, donor's history of hypertension, elderly age of the recipient, recipient's family history of hypertension, cardiac allograft dysfunction, and chronic rejection [3, 9–11]. The donor and recipient sex mismatch, chronic transplant rejection, donor's age, and sex were not associated with hypertension in our population (p>0.05).

Antihypertensive therapy following HT is determined by the presence of a denervated transplanted heart and the need to administer multi-agent immunosuppressive therapy [10–12]. Sanchez Lazaro et al. showed the efficacy of CCBs in combination with ACE inhibitors or ARBs [10]. Shevchenko et al. observed a good tolerance of ACE inhibitors, CCBs, and diuretics administered in addition to the main drug therapy following HT [12]. In our study, ACE inhibitors/ARBs and CCBs were the most commonly used antihypertensive treatments. The prevalence of antihypertensive therapy following HT is not provided in the literature. We established that single-agent therapy was effective in about one-half of patients, every third patient needed two-agent therapy, and only

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5%–15% of patients had hypertension requiring multi-agent therapy.

According to de Souza-Neto et al., following HT patients are characterized by a more significant increase in DBP versus SBP, which can cause the deterioration of endothelial function in the post-transplant population [2]. According to our data, DBP correction in recipients is worse during antihypertensive therapy despite the normalization of SBP (Table 3). The increased DBP levels do not affect survival or the rate of long-term CVEs, which is probably due to a small sample of patients.

Persistent hypertension requiring the use of two or more antihypertensive agents may be associated with high mortality, which may be due to a combination of several predictor factors, such as higher levels of creatinine and LDL-C. However, a small amount of collected data does not allow complex analysis to be performed to identify the correlation between multiple factors affecting outcomes in these patients.

Conclusions

Hypertension is a common complication following heart transplantation (85%) and debuts within the first 2 years in most patients. Male recipients with a history of coronary artery disease, hypertension, and smoking were more likely to develop hypertension. About one-half of the patients required only single-agent antihypertensive therapy. Angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers and calcium channel blockers were the most commonly used agents following heart transplantation (70%–87% and 48%–53%, respectively, depending on the period from heart transplantation). Persistent hypertension requiring two or more antihypertensive agents was associated with all cardiovascular events and higher long-term mortality.

No conflict of interest is reported.

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