Increase in Systolic Blood Pressure during Exercise Testing after Heart Transplantation: Correlation with the Clinical Condition and Ventricular Function Assessed by Dobutamine Stress Echocardiography

Ana Fátima Salles, Cristiano Vieira Machado, Adriana Cordovil, Wagner Aparecido Leite, Valdir Ambrósio Moisés, Dirceu Rodrigues de Almeida, Antonio Carlos Camargo Carvalho, Japy Angelini Oliveira Filho

Universidade Federal de São Paulo - UNIFESP-EPM, São Paulo, SP, Brazil

Objective: Patients who underwent heart transplantation (HTX) experience a reduction in the elevation that is usual in systolic blood pressure during exercise testing. Of unknown origin, this phenomenon varies in frequency and intensity. The aim of this study was to analyze the relationship between systolic blood pressure increase (delta SBP) and clinical aspects, as well as variables measured during exercise testing (ET) and dobutamine stress echocardiography (DSE) in patients in the late post-transplantation course.

Methods: Forty-five men, mean age 49.04 ± 10.19, underwent clinical assessment, ET and DSE 40.91 ± 27.46 months after heart transplantation. Left ventricular wall motion score index and ejection fraction were assessed. Delta SBP < 35mmHg during ET was considered abnormal (SBC,1995).

Results: No significant correlation was found between delta SBP and post-transplantation time, graft ischemic time, history of rejection, diltiazem dosage, oxygen uptake, ejection fraction, and wall motion score index (WMSI). Delta SBP was normal in 17 patients (Group I) and abnormal in 28 (Group II). Patients of both groups did not differ significantly in regard to clinical features and ET and DSE results.

Conclusion: Unlike other populations, no correlation was found between delta SBP during exercise testing and clinical condition or left ventricular function in heart transplant patients. Pathophysiological factors associated with delta SBP reduction during exercise testing remain unknown.

Key words: Heart transplantation, exercise testing, echocardiogram.

Systolic blood pressure elevation (delta SBP) during exercise testing (ET) has been related to left ventricular (LV) performance[1]. In LV contractile dysfunction cases caused by ischemia or LV outflow tract obstruction, lower delta SBP values have been described[1]. In the early and late post-transplantation (HTX) course, a depressed response in SBP[2-6] and mean BP[7-9] during ET has been observed. In an analysis of consecutive ET performed after heart transplantation showed that 69% of the heart recipients showed a depressed response of SBP during exercise testing[10]; delta SBP < 35mmHg was considered abnormal (SBC,1995)[11]. The cause of SBP depressed response during ET after heart transplantation is still unclear[7]. It may be associated with graft vascular disease, one of the frequent causes of mortality among heart recipient survivors[12].

The aim of this study was to determine indicators of attenuated behavior of SBP during ET in male patients who underwent heart transplantation using clinical variables and parameters derived from ET and DSE.

Methods

Forty-five men, mean age 49.04 ± 10.19, were studied 40.91 ± 27.46 months after heart transplantation. Causes for transplantation were: idiopathic dilated cardiomyopathy (40%), chronic Chagas cardiomyopathy (33%), chronic ischemic cardiomyopathy (25%), and hypertensive cardiomyopathy (2%). Study patients were in NYHA functional class I (n = 43) and II (n = 2) and using cyclosporine A, azathioprine, prednisone, anti-hypertensive, lipid-lowering, and hypoglycemic drugs regularly. No patient showed rejection episodes exceeding grade 3A (International Society Heart Lung Transplantation) for at least two months. Mean graft ischemic time was 114.24 ± 29.73 minutes.

Symptom-limited exercise treadmill tests (TRACKMASTER TM 500-E) were conducted according to the Bruce protocol with a 13-lead ECG recording (TEB-APEX 2000). Systolic blood pressure (SBP) was measured at phase I of Korotkoff sounds and diastolic blood pressure (DBP) was measured at phase V, using a mercury sphygmomanometer. Oxygen uptake (VO_2)

Mailing Address: Ana Fátima Salles •
Rua Cantagalo, 229 - 03319-000 - São Paulo, SP, Brazil
E-mail: asalles@cardiol.br
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was estimated by regression equation[13]. Functional Aerobic Impairment (FAI) was defined by the following formula: FAI = (predicted VO_2 max – measured VO_2max) / predicted VO_2 max x 10^2. FAI values between – 27% to + 26% were considered normal[1]. Exercise test results were analyzed according to criteria established by the Brazilian Society of Cardiology[11].

During dobutamine stress echocardiography (Ultramark 9-HDI, ATL), intravenous dobutamine was infused with or without atropine[14]. Regional LV contractility was evaluated by using the 16-segment model[15], and the mean score was considered as the wall motion score index (WMSI)[15]. Left ventricular ejection fraction (EF) was determined by Simpson's method, both at rest and at peak infusion (Image Vue™ DCR™, Nova Microsonics). Resting EF values above 0.55 were regarded as normal[15]. No reference values for EF at peak dobutamine infusion are reported in the literature

All procedures (clinical evaluation, ET, and DSE) were performed by independent observers.

The correlation between delta SBP and the following variables were analyzed: post-transplantation time, graft ischemic time, diltiazem dosage, VO_2max, resting EF, peak EF, delta EF, and % delta EF. Subsequently, patients were distributed into two groups: Group I - normal delta SBP (n = 17) and Group II - abnormal delta SBP (n = 28), so that possible markers of attenuated SBP responses between clinical variables and parameters measured by ET and DSE could be studied.

Pearson's correlation coefficient and multiple linear regressions were used to evaluate the linear relationship between delta SBP and selected variables. The Student's t-test, Fisher's exact test, and Pearson's chi-square test with Yates' correction were used to compare groups I and II. The paired *t* test and McNemar's test were applied to compare resting and peak values. P values < 0.05 were considered statistically significant.

The protocol was approved by the Institutional Research Ethics Committee, and all patients signed an informed consent before entering the study.

Results

No significant linear correlation was found between delta SBP and post-transplantation time, graft ischemic time, diltiazem dosage, VO_2max, resting EF, peak EF, and EF variation in absolute and relative values (Tab. 1).

The combined analysis of 10 variables, for which multiple linear regression (resting EF, peak EF, and % EF, WMSI at rest, WMSI at peak infusion, post-transplantation time, graft ischemic time, history of rejection episodes ≥ 3 A, diltiazem dosage, VO_2max) were used, showed that no variable, at the 10% significance level, influenced delta SBP values (Tab. 2).

No significant differences were found between groups I and II regarding age, body weight, height, post-transplantation time, graft ischemic time, arterial hypertension, dyslipidemia and obesity, history of rejection ≥ 3 A, and use of prednisone, statins or diltiazem (Tab. 3).

Exercise test results are described in Table 4.Groups I and II showed similar resting heart rate (HR), resting BP, % of predicted HRmax, VO_2 max, FAI, endurance time (p = NS). Exercise testing was considered ischemic in two patients from group I and one patient from group II. SBP values at exercise peak and delta SBP were significantly lower in group II (p < 0.001).

DSE results are presented in Tables 5 and 6. Both groups underwent stress with the same dose of dobutamine and reached equivalent percentages of predicted HRmax. One patient from group I and four patients from group II required atropine co-administration.

There were no significant differences between groups with respect to: [1] WMSI and EF values at rest and at peak infusion; [2] abnormal WMSI at rest and at peak infusion; [3] presence of myocardial ischemia.

Discussion

Blood pressure is governed by a complex mechanism involving hemodynamic, neural, and hormonal factors. Its determinants are cardiac output and peripheral resistance. SBP is primarily related to factors influencing ventricular performance, namely contractility, the degree to which myocardial fibers are stretched (Frank-Starling principle), blood volume, resistance to blood ejection (afterload), and heart rate.

The SBP rises during exercise, showing a 50% increase over its baseline value at maximal exercise[16]. In this study, 62% of the patients experienced a depressed response in SBP during ET performed at late post-transplantation course. It has been suggested that abnormal delta SPB during ET is associated with reduced inotropic reserve secondary to changes in contractility caused by coronary disease, Chagas cardiomyopathy, hypertensive cardiomyopathy, dilated cardiomyopathy, and other heart diseases[1,17-19].

Our results showed no correlation between abnormal delta SBP and post-transplantation time. On average, patients had undergone heart transplantation more than three years earlier

Variable	r	P
Post-transplantation time	-0.155	0.309
Graft ischemic time	0.080	0.638
Diltiazem dosage	0.114	0.561
VO_2max	0.003	0.980
Resting EF	-0.075	0.620
Peak EF	-0.245	0.103
ΔEF	-0.160	0.293
(%) ΔEF	-0.142	0.356

r - Pearson's correlation coefficient; VO_2 - oxygen uptake; EF - ejection fraction.
ΔFE = EF at peak dobutamine – resting EF.

$$\Delta EF\ (\%) = \frac{\text{Peak EF} - \text{Resting EF}}{\text{Resting EF}} \times 100$$

Table 1 - Correlation between SBP increase during exercise test and other variables in heart transplant recipients (n = 45)

Variable	Coefficient	Standard error	p
Post-transplantation time	-0.008	0.641	0.990
Graft ischemic time	0.023	0.296	0.941
History of rejection ≥ 3 A (ISHLT)	4.349	15.037	0.779
Diltiazem dosage	0.030	0.129	0.821
VO_2 max	0.686	1.521	0.663
Resting EF	-3.671	4.100	0.394
Peak EF	1.912	3.418	0.590
ΔEF (%)	-1,365	1,886	0,488
Resting WMSI	11.557	35.385	0.751
Peak WMSI	-17.573	28.585	0.554

VO_2 – oxygen uptake; FE – ejection fraction; WMSI - wall motion score index

$$\Delta EF\ (\%) = \frac{Peak\ EF - Resting\ EF}{Resting\ EF} \times 100$$

Table 2 - Multiple linear regression results for SBP increase during exercise test in heart transplant recipients (n = 45)

and, thereby, were subject to graft vascular disease.

Graft vascular disease is the major cause of death after the first year of heart transplantation[20]. Dobutamine stress echocardiography has emerged as a promising non-invasive examination for detecting this condition[21], with sensitivity of 67% to 100%, specificity of 55% to 89.5%, negative predictive value of 90% to 100% and positive predictive value of 33% to 76%[22-25]. Graft vascular disease may cause changes in LV contractility, affecting delta SBP. The association between delta SBP and ischemia secondary to graft vascular disease is yet to be established. Myocardial ischemia incidence in groups I and II by DSE was 6% and 21%, respectively; however, no statistical significance was found between these values (p = 0.227), even though ischemia was three times higher in group II. This lack of significance may be related to the number of patients studied. Nor was significant difference found between groups I and II regarding, respectively, EF decrease at peak DSE (35.3% *vs* 17.8%) and mean EF increase during DSE (6.06 ± 16.03 *vs* 13.83 ± 17.74).

Rejection episodes are common after heart transplantation and, if repeated, may cause fibrosis and a decrease in ventricular cavity size[9]. Under dobutamine stress, Bellotti *et al*. reported normal contractility in heart transplant recipients in whom there was no rejection. In the presence of rejection, contractility was reduced[26]. Our series did not corroborate these findings, since history of rejection was similar in groups I and II (23% *vs* 18%, *p* = NS). Among the nine patients with

Variable	Group I (N = 17)	Group II (N = 28)	p
Age (years)	48.65 ± 11.58	49.29 ± 9.46	0.84
Body weight (kg)	74.71 ± 11.25	70.86 ± 9.50	0.23
Height (cm)	168.88 ± 4.47	167.29 ± 5.42	0.31
Post-transplantation time (months)	32.88 ± 15.52	45.78 ± 31.95	0.13
Graft time (min)	115.26 ± 22.90	113.55 ± 34.12	0.87
Arterial hypertension	15 (88%)	24 (86%)	> 0.99
Dyslipidemia	7 (41%)	14 (50%)	0.56
Obesity	5 (29%)	2 (7%)	0.09
History of rejection ≥ 3 A (ISHLT)	4 (23%)	5 (18%)	0.94
Use of prednisone	6 (35%)	8 (29%)	0.64
Use of statins	4 (23%)	11 (39%)	0.28
Diltiazem dosage (mg)	165 ± 58.74	160 ± 46.02	0.80

Post-transplantation time - time elapsed since transplantation; Graft time - graft ischemic time.

Table 3 - Clinical data of heart transplant recipients (n = 45)

Variable	Group I (N = 17)	Group II (N = 28)	p
VO_2max (mL/kg/min)	29.70 ± 6.20	28.94 ± 4.71	0.642
FAI (%)	18.27 ± 24.91	19.82 ± 13.24	0.787
Endurance time (min)	8.20 ± 2.46	8.21 ± 1.96	0.988
Resting HR (bpm)	101.06 ± 9.32	94.68 ± 10.97	0.052
Peak HR (bpm)	163.29 ± 21.29	154.96 ± 14.91	0.130
% HRmax.	95.29 ± 11.46	90.54 ± 7.42	0.097
Resting SBP (mmHg)	128.82 ± 17.72	134.64 ± 19.19	0.316
Peak SBP (mmHg)	176.47 ± 17.30	154.11 ± 19.72	< 0.001
ΔSBP (mmHg)	47.64 ± 8.12	19.46 ± 8.53	< 0.001
Resting SBP (mmHg)	89.71 ± 12.05	91.96 ± 9.75	0.495
Peak SBP (mmHg)	90.88 ± 13.26	85.36 ± 12.17	0.160

VO_2 – oxygen uptake; FAI - functional aerobic impairment; HR – heart rate; SBP – systolic blood pressure; DBP – diastolic blood pressure; ΔSBP = peak SBP – resting SBP.

Table 4 - Variables of exercise test in heart transplant recipients (n = 45)

history of rejection, only three showed changes in contractility, two from Group I (normal delta SBP) and one from Group II (abnormal delta SBP). No case of ventricular fibrosis or reduction in ventricular cavity was identified.

Some authors have attributed the enhanced pressure response to exercise to a late sympathetic reinnervation. Wilson et al described a trend to increased delta SBP during late follow-up of patients with evidence of marked reinnervation after heart transplantation[27].

Abnormal delta SBP values might be influenced by LV stiffness and dysfunction secondary to ventricular ischemia caused during cold preservation of the graft[28,29]. In our series, mean graft ischemic time was 114 minutes and was not correlated with abnormal delta SBP. According to Kao et al, it is unlikely that two hours of cold ischemia would cause changes in the graft capable of persisting up to 16 months post-transplantation[8].

Diltiazem hydrochloride has been frequently used for BP control after heart transplantation. In our series, 28 (62.2%) patients took diltiazem regularly at doses ranging from 60 to 240 mg/day. Drug dosage did not correlate with delta SBP during exercise testing. Both the percentage of patients on diltiazem and the dose used were similar in both groups.

No correlation was found between abnormal delta SBP and VO_2max. According to the Fick principle, VO_2 varies with HR, stroke volume, and arteriovenous oxygen difference. SBP is a function of HR, stroke volume, contractility, preload and afterload. Therefore, it would be possible to detect abnormal delta SBP in the presence of the decreased VO_2max values. Douard et al[30] found a significant correlation between SBP peak values and VO_2max. In our study, not only was this relationship not observed, but groups I and II reached equal VO_2max values. These results may have been affected by the estimated values used, calculated from formulas that were perhaps inadequate for transplant patients. Actually, the use of direct measurements of VO_2max in cardiopulmonary tests would have been more appropriate.

Overall, LV systolic performance after heart transplantation has been shown to be satisfactory at rest and during exercise. Most studies have reported normal LV values at rest and at exercise peak, during both early and late follow-up[8,9,31-37]. In our study, LV systolic function, assessed by the WMSI and EF, showed no correlation with abnormal delta SBP. WMSI and EF values were similar in patients of both groups. Our results were corroborated by other authors. Pflugfelder at al found no correlation between peak EF and peak BP during exercise in patients after thirteen months of transplantation[32].

Other clinical, ergometric, and echocardiographic measurements also failed to characterize the abnormal delta SBP group. Groups I and II shared the same clinical features, and their results were similar on ET and DSE.

Limitations - Our study has some limitations, [1] namely, the small number of patients in groups I and II; [2] and population heterogeneity regarding different etiologies.

Variable	Group I (N = 17)	Group II (N = 28)	p
Resting EF	0.65 ± 0.09	0.64 ± 0.09	0.877
Peak EF	0.68 ± 0.09	0.72 ± 0.09	0.147
ΔEF	0.03 ± 0.10	0.08 ± 0.09	0.126
ΔEF (%)	6.06 ± 16.03	13.83 ± 17.74	0.150
Resting WMSI	1.06 ± 0.24	1.13 ± 0.36	0.865
Peak WMSI	1.10 ± 0.40	1.14 ± 0.30	0.297
% HRmax.	93.53 ± 8.12	91.18 ± 7.12	0.314
Resting SBP (mmHg)	125.29 ± 16.99	135.89 ± 17.59	0.054
Peak SBP (mmHg)	132.35 ± 19.53	132.14 ± 17.50	0.970
ΔSBP (mmHg)	7.06 ± 22.85	-3.75 ± 24.37	0.147
Dobutamine (μg/kg/min)	30.00 ± 8.66	30.36 ± 8.38	0.892

FE– ejection fraction; WMSI– wall motion score index; HR– heart rate; SBP– systolic blood pressure.
ΔEF = EF at peak dobutamine – resting EF

$$\Delta FE\ (\%) = \frac{FE\ pico - FE\ repouso \times 100}{FE\ repouso}$$

ΔSBP = peak SBP – resting SBP

Table 5 - Dobutamine stress echocardiogram variables in heart transplant recipients (n = 45)

Variable	Group I (N = 17)	Group II (N = 28)	p
WMSI (resting)	1 (6.0%)	5 (17.8%)	0.385
WMSI (peak)	1 (6.0%)	7 (25.0%)	0.132
Myocardial ischemia	1 (6.0%)	6 (21.0%)	0.227
EF reduction (peak)	6 (35.3%)	5 (17.8%)	0.284

WMSI- wall motion score index; EF- ejection fraction.

Table 6 - Changes in dobutamine stress echocardiogram in heart transplant recipients (n = 45)

Conclusions

Unlike other populations, the authors found no correlation between abnormal delta SBP and clinical data plus left ventricular function in heart recipients at late post-transplantation course. A significant number of these patients progress to attenuated delta SBP during ET. The pathophysiology of this behavior remains unknown. This phenomenon is probably multifactorial in origin, reflecting a distinctive characteristic of transplanted patients.

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