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Reduced Incidence of Hypertension After Heterotopic Cardiac Transplantation Compared With Orthotopic Cardiac Transplantation

Evidence That Excision of the Native Heart Contributes to Post-Transplant Hypertension

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OBJECTIVES This study was designed to test the hypothesis that heterotopic heart transplant (HHT) patients have lower blood pressure than orthotopic cardiac transplant (OCT) patients because their native heart is involved in blood pressure homeostasis.

BACKGROUND Hypertension occurs more frequently after OCT than after liver or lung transplantation, suggesting that transplantation of the heart itself contributes to post-transplant hypertension.

METHODS Blood pressure and related measurements in 233 OCT and 38 HHT patients were studied retrospectively post-transplant.

RESULTS Systolic blood pressure (SBP) was persistently lower among HHT patients (means 121 vs. 137, 126 vs. 137, 125 vs. 139, and 128 vs. 143 mm Hg at month 3 and years 1, 3, and 5 respectively, $p < 0.005$). Left ventricular and aortic systolic pressures were also lower (130 vs. 143 mm Hg, $p = 0.01$ and 129 vs. 142 mm Hg, $p = 0.01$). Multivariable analysis with age, gender, body mass index, creatinine, steroids, cyclosporine, use of antihypertensive medication, donor left ventricular ejection fraction, donor weight, and type of transplant as covariables showed HHT to be independently associated with a lower SBP at each time point (beta-coefficients −16.2, −12.1, −13.3, and −14.2 mm Hg, $p < 0.01$). The adjusted hazard ratio for the development of systolic hypertension among HHT compared with OCT patients was 0.59 (95% confidence interval 0.39 to 0.91, $p = 0.017$).

CONCLUSIONS Heterotopic heart transplant patients had lower SBP than OCT patients, consistent with the hypothesis that the native heart continues to contribute to blood pressure homeostasis. (J Am Coll Cardiol 2004;44:1254–60) © 2004 by the American College of Cardiology Foundation

Hypertension develops early after cardiac transplantation and can be difficult to manage (1,2). Cyclosporine contributes to post-transplant hypertension through activation of the sympathetic nervous system (3), nephrotoxicity (4), and inhibition of endothelium-dependent vasodilation (5). However, other factors such as cardiac innervation may play a role, because the incidence of hypertension in liver (45%) and lung (66%) transplant patients receiving cyclosporine is lower than in heart transplant patients (95% at 5 years) (1,6,7).

Evidence for the role of cardiac innervation in cardiovascular homeostasis comes from human and animal studies. Autotransplantation in dogs results in increased plasma volume (8), and human heart transplant recipients have blunted responses to salt or volume loading (9). They also respond to central blood volume reduction with an attenuated increase in sympathetic activity (10).

Two types of heart transplantation are performed. The orthotopic cardiac transplant (OCT), in which the recipient's heart is removed and replaced by a denervated donor heart, is the commonest. An alternative is the heterotopic heart transplant (HHT), in which the recipient heart and its innervation remain intact and the donor heart is placed in the right hemithorax with the donor and recipient left ventricles functioning in parallel (11). Heterotopic heart transplant is often performed when the donor organ is smaller than the recipient heart or when pulmonary artery pressures are elevated (12).

We hypothesized that because HHT leaves the native heart intact, its use may be associated with less hypertension than is OCT.

METHODS

Patients. Clinical records and echocardiograms of 271 adult cardiac transplant patients transplanted at our institution between 1991 and 1999 who survived longer

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Abbreviations and Acronyms

CI = cardiac index
HHT = heterotopic heart transplant
OCT = orthotopic cardiac transplant
SBP = systolic blood pressure

than three months were examined. Of these, 233 had undergone OCT and 38 HHT. The ethics committee gave approval.

The OCT and HHT groups were well matched in terms of age, gender, size, indication for transplantation, pre-transplant blood pressure, use of angiotensin-converting enzyme inhibitors, previous history of hypertension, and pre-transplant renal function calculated according to Cockcroft and Gualt (13) (Table 1). As expected, donor weight was lower in HHT than in OCT patients (mean 36 vs. 64 kg, $p < 0.0001$). Of the 38 HHT patients, 23 underwent HHT because of donor-recipient size mismatching and 15 because of elevated systolic pulmonary artery pressures. The latter patients' pre-transplant systolic blood pressures did not differ significantly from those of patients who received HHT on the basis of size mismatch alone (109 ± 19 mm Hg vs. 107 ± 12 mm Hg).

Table 1. Pretransplant Characteristics for OCT and HHT Patients

	OCT (n = 233)	HHT (n = 38)	p Value
Men	200 (86%)	29 (76%)	0.133*
Women	33 (14%)	9 (24%)	
Mean age (yrs)	47.6 ± 10.6	48.2 ± 9.9	0.76†
Age range (yrs)	18–70	23–65	
Ethnicity			
Caucasian	208 (89%)	35 (92%)	0.61‡
Asian	16 (7%)	3 (8%)	
Other	9 (4%)	0 (0%)	
Pretransplant diagnosis			
Ischemic heart disease	123 (53%)	21 (55%)	0.52‡
Dilated cardiomyopathy	63 (27%)	12 (32%)	
Congenital heart disease	13 (6%)	0 (0%)	
Viral myocarditis	12 (5%)	3 (8%)	
Other	22 (9%)	2 (5%)	
Systolic blood pressure (mm Hg)	109 ± 17	108 ± 18	0.81†
Diastolic blood pressure (mm Hg)	70 ± 11	69 ± 11	0.45†
History of previous hypertension	24/225§ (11%)	6/37§ (16%)	0.48*
Number of patients receiving angiotensin-converting enzyme inhibitor	183/224§ (82%)	32/36§ (89%)	0.35*
Serum creatinine (μmol/l)	112 ± 27	107 ± 22	0.21†
Estimated creatinine clearance‖	78 ± 22	84 ± 27	0.15†
Body mass index (kg/m^2)	24.8 ± 4.2	25.8 ± 3.25	0.17†

Values are n (%) or mean ± SD. *Chi-square test. †Student *t* test. ‡Fisher exact test. §Number/number for which data available. ‖Estimated creatinine clearance calculated according to Cockroft and Gault (13).

HHT = heterotopic heart transplantation; OCT = orthotopic cardiac transplantation.

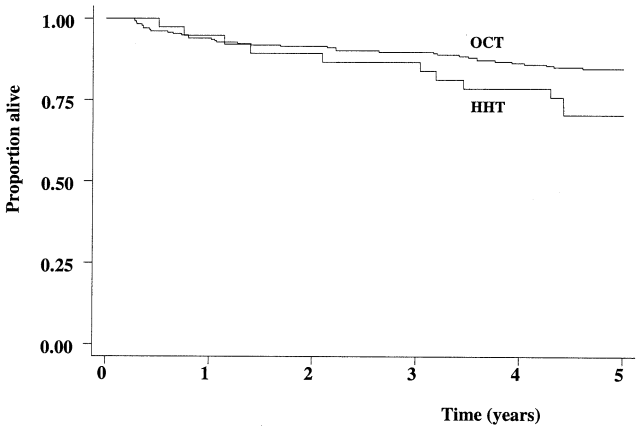

Figure 1. Survival beyond three months and up until five years in orthotopic cardiac transplantation (OCT) and heterotopic heart transplantation (HHT) patients studied; log-rank test p = 0.044.

All patients received triple-therapy immunosuppression (cyclosporine, azathioprine, and corticosteroids). Patients unable to tolerate cyclosporine, or patients with several early rejection episodes, were converted to tacrolimus. When possible, steroids were reduced and eventually withdrawn from three months after transplant. Antihypertensive agents were angiotensin-converting enzyme inhibitors, doxazosin, calcium channel blockers, diuretics and, rarely, beta-blockers. Both OCT and HHT patients were treated if their blood pressure was persistently >140/90 mm Hg (14).

Data were available for 253, 209, and 126 patients at years 1, 3, and 5 respectively, owing to death or follow-up <1, 3, or 5 years. Figure 1 shows survival beyond three months. Survival after HHT was slightly worse than after OCT, related in part to donor-recipient size mismatch (12).

Measurements. Noninvasive blood pressure was measured with an oscillometric technique using the Datascope Accutorr Plus (Montvale, New Jersey), recommended by the European Society of Hypertension (15). Readings >140 mm Hg were measured again for confirmation. Native aortic valve opening in HHT patients was

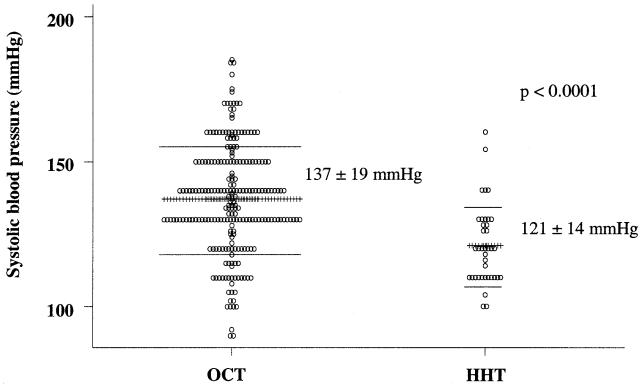

Figure 2. Systolic blood pressure in orthotopic cardiac transplantation (OCT) and heterotopic heart transplantation (HHT) patients three months post-transplantation. Figures and lines are means ± SD.

Table 2. Blood Pressure and Other Posttransplant Characteristics in OCT and HHT Patients

Variable	OCT	HHT	p Value
Systolic blood pressure (mm Hg)			
Month 3	137 ± 19 (233)	121 ± 14 (38)	<0.00001*
Year 1	137 ± 15 (217)	126 ± 15 (36)	<0.00001
Year 3	139 ± 19 (179)	125 ± 11 (30)	0.0002
Year 5	143 ± 20 (102)	128 ± 17 (24)	0.001
Diastolic blood pressure (mm Hg)			
Month 3	88 ± 13 (233)	86 ± 14 (38)	0.3*
Year 1	89 ± 11 (217)	85 ± 11 (36)	0.041
Year 3	90 ± 11 (179)	88 ± 8 (30)	0.28
Year 5	91 ± 11 (102)	88 ± 14 (24)	0.26
Antihypertensive agents per patient			
Month 3	0.89 ± 0.75 (232)	0.62 ± 0.68 (37)	0.04*
Year 1	1.1 ± 0.9 (215)	0.7 ± 0.6 (35)	0.009
Year 3	1.2 ± 1.0 (177)	1 ± 0.93 (30)	0.48
Year 5	1.2 ± 0.89 (102)	1.1 ± 0.76 (23)	0.8
Percentage on 1 or more antihypertensive agent			
Month 3	19 (43)	11 (4)	0.35†
Year 1	72 (155)	60 (21)	0.15
Year 3	72 (128)	67 (20)	0.5
Year 5	75 (77)	78 (18)	0.78
Donor heart ejection fraction (%)			
Month 3	72 ± 7 (216)	70 ± 17 (35)	0.16*
Year 1	73 ± 6 (208)	71 ± 14 (33)	0.18
Year 3	73 ± 7 (170)	72 ± 8 (27)	0.69
Year 5	73 ± 6 (96)	72 ± 8 (22)	0.66
Percentage receiving steroids			
Month 3	73 (168)	59 (22)	0.08†
Year 1	45 (97)	50 (17)	0.36
Year 3	20 (35)	17 (5)	0.7
Year 5	14 (14)	22 (5)	0.33
Percentage receiving cyclosporine			
Month 3	89 (207)	95 (36)	0.29†
Year 1	82 (177)	91 (32)	0.22
Year 3	81 (142)	80 (24)	0.9
Year 5	83 (85)	96 (22)	0.36
Daily cyclosporine dose (mg/kg)			
Month 3	4.8 ± 1.9 (172)	4.6 ± 1.6 (33)	0.59*
Year 1	3.8 ± 1.3 (171)	4.0 ± 2 (30)	0.49
Year 3	3.0 ± 0.9 (131)	3.0 ± 1 (23)	0.9
Year 5	2.8 ± 1 (78)	2.6 ± 1 (21)	0.32
12-h post dose cyclosporine level (ng/ml)			
Month 3	300 ± 120 (207)	317 ± 119 (36)	0.43*
Year 1	202 ± 79 (177)	227 ± 83 (32)	0.1
Year 3	154 ± 43 (142)	175 ± 71 (24)	0.05
Year 5	150 ± 45 (171)	163 ± 59 (27)	0.2
Percentage receiving tacrolimus			
Month 3	11 (25)	5 (2)	0.3†
Year 1	18 (39)	9 (9)	0.17
Year 3	19 (34)	13 (4)	0.9
Year 5	16 (16)	4 (1)	0.17
Rejection episodes per patient	1.53 ± 1.64 (232)	2.13 ± 2.04 (38)	0.046*
Mean number of treatments with high-dose methylprednisolone per patient	1.94 ± 1.7 (232)	2.68 ± 2.24 (38)	0.012*
Mean number of augmented immunosuppression treatments per patient	2.33 ± 2.24 (232)	3.13 ± 2.8 (38)	0.052*
Median number of augmented immunosuppression treatments per patient	2.5 (232)	2 (38)	
Serum creatinine (μmol/l)			
Month 3	143 ± 48 (230)	136 ± 35.4 (38)	0.4*
Year 1	154 ± 44 (217)	144 ± 27 (36)	0.18
Year 3	161 ± 64 (174)	152 ± 30 (30)	0.42
Year 5	158 ± 70 (98)	194 ± 185 (22)	0.13

Continued on next page

Table 2 Continued

Variable	OCT	HHT	p Value
Measured creatinine clearance adjusted for body surface area (ml/min)			
Year 1	54 ± 22 (170)	54 ± 14 (19)	0.96*
Year 3	56 ± 19 (135)	60 ± 28 (23)	0.46
Year 5	56 ± 20 (76)	53 ± 21 (20)	0.64
Body mass index (kg/m^2)			
Month 3	25.2 ± 3.9 (194)	25.6 ± 3.6 (33)	0.58*
Year 1	26.7 ± 4.4 (208)	26.9 ± 4.1 (31)	0.95
Year 3	27.6 ± 4.5 (164)	27.5 ± 4.6 (28)	0.96
Year 5	28.0 ± 4.7 (94)	28.1 ± 5.3 (21)	0.93

Values are mean ± SD (number per group) or percentages (n). *Student *t* test. †Chi-square test.
Abbreviations as in Table 1.

assessed by echocardiography. Hemodynamic data measured at cardiac catheterization were available for 46 OCT and 24 HHT cases. Acute rejection was diagnosed histologically and graded according to International Society of Heart and Lung Transplantation criteria (16). Rejection episodes were treated with augmented immunosuppression (three daily doses of 1 g methylprednisolone). Rabbit antithymocyte globulin and/or OKT3 were also used in cases of rejection associated with hemodynamic compromise.

Statistical methods. For univariate analyses, two-tailed Student *t* test was employed to test for differences between means and Pearson's chi-square or Fisher exact test (if expected frequencies were five or less) to determine differences in proportions. Paired *t* tests were employed for analysis of matched data.

Multivariable regression models were constructed with SBP as the dependent variable using a stepwise backwards method. Results were expressed as beta-coefficients and a p value of <0.05 was considered significant.

Survival analysis was performed using life tables and Kaplan-Meier methods and the log-rank test was used to determine significance. The development of hypertension (SBP ≥140 mm Hg or treatment with antihypertensive agent[s]) over time was also examined using the Kaplan-Meier technique (17); Cox method was used to generate a hazard ratio (18). Analyses were performed using STATA 7 (Stata Corp., College Station, Texas).

RESULTS

Systolic blood pressure was lower in HHT than in OCT patients at all time points (Fig. 2, Table 2). When corrected for multiple testing (Bonferroni correction), all p values remained <0.05. Other than at one year, diastolic blood pressure did not differ between the two groups. Invasively measured left ventricular and aortic systolic blood pressures were also lower in HHT patients (Table 3).

Heterotopic heart transplant patients required fewer antihypertensive agents than OCT patients, particularly at month 3 and year 1. Thus, the higher SBPs seen in OCT patients were in spite of greater use of antihypertensive agents.

Use of tacrolimus (associated with less hypertension than cyclosporin) (19) was similar between the two groups. Acute rejection and treatment with augmented immunosuppression occurred more frequently among HHT patients (mean number of rejection episodes greater than grade 1B 2.13 vs. 1.53, $p < 0.05$) (Table 2). Heterotopic heart transplant patients also received high-dose steroids more often than did OCT patients (mean number of treatments 2.68 vs. 1.94, $p = 0.012$) (Table 2).

In keeping with heterotopic grafts and their stroke volumes being smaller than orthotopic grafts, cardiac index (CI) was significantly lower among HHT compared with OCT patients (Table 3). Because a limited number of CI measurements were available (28 OCT and 12 HHT at year 1 or 3), CI was not included in the multivariable analysis. Subjects for whom CI data were available were also analyzed separately: CI and SBP were both lower among HHT patients, even when age, gender, and year after transplantation were matched between HHT and OCT subjects (mean CI 2.02 ± 0.38 l/m/m^2 vs. 2.97 ± 0.5 l/m/m^2 [paired *t* test $p = 0.006$], mean SBP 124 ± 13 mm Hg vs. 142 ± 16 mm Hg [paired *t* test $p = 0.002$]). After matching HHT and OCT patients on the basis of CI, SBP was still lower in HHT patients than in OCT patients: mean SBP 127 ± 13 mm Hg vs. 143 ± 20 mm Hg ($p = 0.02$) in 13 HHT and 13 OCT patients matched for CI (mean CI 2.22 ± 0.31 and 2.2 ± 0.32), indicating that the lower SBP seen among HHT patients was not due to lower CI. Subgroups of HHT patients were examined at year 1 and results are shown in Table 4.

Adjusted beta coefficients for the effect of HHT compared to OCT on SBP are shown in Table 5 and did not differ greatly from unadjusted values. In patients receiving cyclosporine, 12 h post-dose cyclosporine levels did not significantly affect SBP (data not shown).

The proportion of patients with systolic hypertension was always less in HHT than OCT patients (Fig. 3). The hazard ratio for the development of hypertension (adjusted for age, gender, and body mass index using the

Table 3. Left Ventricular Pressures, Aortic Pressures, and Cardiac Index Values in 24 HHT and 43 OCT Patients

	OCT	HHT (Donor Heart)	p Value
Left ventricular systolic pressure (mm Hg)	143 ± 20 (40)	130 ± 18 (24)	0.01
Left ventricular diastolic pressure (mm Hg)	12 ± 5 (41)	13 ± 6 (23)	0.4
Systolic aortic pressure (mm Hg)	142 ± 20 (43)	129 ± 17 (23)	0.01
Diastolic aortic pressure (mm Hg)	85 ± 12 (43)	88 ± 9 (23)	0.26
CO (l/min)	5.17 ± 1.2 (31)	4.1 ± 0.8 (12)	0.006
CI (l/min/m^2)	2.6 ± 0.6 (28)	2.22 ± 0.4 (12)	0.05
Years post transplant	1.13 ± 0.5	1.17 ± 0.6	0.8

Values are mean ± SD (total number for whom data available), p values refer to Student *t* test results.
CI = cardiac index; CO = cardiac output. Other abbreviations as in Table 1.

Table 4. SBP in Different Subgroups of Heterotopic Transplant Patients

	Total Number	Mean SBP (mm Hg)	p Value
Pace linked	16	124 ± 15	0.62
Not pace linked	20	127 ± 15	
Native aortic valve closed	18	125 ± 16	0.66
Native aortic valve open	12	122 ± 15	
Native left ventricular ejection fraction <20%	13	129 ± 16	0.33
Native left ventricular ejection fraction ≥20%	14	124 ± 13	

SBP values are mean ± SD and p values refer to Student *t* test results. By sensing the donor right ventricle and pacing the native right atrium after a timed delay adjusted so that recipient systole coincides with donor diastole, paced linkage causes the two hearts to contract out of phase (24).
SBP = systolic blood pressure.

Cox method) in HHT compared with OCT patients was 0.59 (95% confidence interval 0.39 to 0.91, p = 0.017).

Figure 4 shows SBP in two patients who underwent HHT followed some months later by OCT in the native heart position. The findings are discussed later.

DISCUSSION

The greater incidence of hypertension among OCT recipients may be due to the loss of cardiac inputs to blood pressure homeostasis. In keeping with this hypothesis, we found SBP to be lower in HHT patients (whose native hearts remain in situ) than in OCT patients until five years after transplant.

Possible mechanisms by which the native heart contributes to blood pressure homeostasis are through cardiopulmonary baroreceptors and the release of natriuretic peptides. Cardiopulmonary baroreceptors are located within the myocardium and provide tonic inhibition of sympathetic outflow to the heart and peripheral circulation, and lower blood pressure when filling volumes are adequate (20). When this tonic inhibitory input is disrupted, baroreflexes are impaired (10). Natriuretic peptides are released in response to myocardial stretch or when the myocardium has undergone remodeling and actions include natriuresis, diuresis, and vasodilation (21). Both atrial natriuretic peptide and brain-type natriuretic peptide concentrations are elevated after OCT (22). As HHT patients possess two hearts, they may have higher natriuretic peptide levels.

Vascular pathology could predispose to the development of post-transplant hypertension; however, when post-transplant blood pressures in patients with pre-transplant ischemic heart disease was compared with blood pressure in patients of other pre-transplant diagnoses, there was no difference (data not shown).

Arterial blood pressure in a HHT recipient could be influenced by the parallel function of the donor and native left ventricles. In practice, however, the native left ventricle of patients who have undergone HHT usually does not contribute significantly to cardiac output, and the native aortic valve often does not open at all (23). Subgroup analysis of HHT patients to determine whether aortic valve opening might have contributed to the lower SBP showed there was no difference in SBP between those whose aortic valve opened and those whose valve did not. Similarly, paced linkage (24) did not cause any difference in SBP. These observations support the view that the lower blood pressure observed in the heterotopic group was not due to HHT itself, but was related to the presence of the native heart.

Diastolic blood pressure did not differ significantly between the two groups. This could result from the physiology of HHT where asynchronous beating of donor and recipient hearts prevents blood pressure from returning to minimum after donor diastole because recipient systole has already commenced.

The heterotopic transplant patients as a whole experienced more rejection episodes requiring treatment with augmented immunosuppression than the OCT group. This may be due to the fact that more HHT patients had been weaned from maintenance steroids by three months after transplantation (41% of HHT patients vs. 27% of OCT patients) (Table 2).

Analysis of hemodynamic data for a subgroup of patients demonstrated that CI was lower in the heterotopic patients, probably owing to the smaller size of the donor heart and a greater incidence of rejection in the HHT group. However, a comparison of HHT and OCT patients matched for CI still demonstrated the difference in SBP.

In two cases, we had the opportunity to examine blood pressure after HHT and then after OCT in the same patient. As the heterotopic organ remained in situ after OCT, this resulted in two denervated hearts. Immunosuppression was with cyclosporine throughout and both patients experienced a rise in SBP after OCT (Fig. 4).

The retrospective nature of the study means that complete hemodynamic data were not available for all patients and natriuretic peptide levels were not measured. Differences in donor-recipient size mismatching between the

Table 5. Unadjusted and Backward Stepwise Multiple Regression Models

Model	Beta Coefficient (SE), p Value			
	Month 3	Year 1	Year 3	Year 5
Unadjusted				
HHT	−16 (3.2), <0.0001	−11.6 (2.7), <0.0001	−14.0 (3.7), <0.0001	−15 (4.5), 0.001
Backward stepwise				
HHT	−16.2 (2.4), <0.0001	12.1 (3.1), <0.0001	−13.3 (3.9), 0.001	−14.2 (5), 0.006
Body mass index (kg/m^2)	+0.74 (0.32), 0.02	+0.54 (0.22), 0.016	+0.64 (0.3), 0.032	
Steroids (yes or no)		+7.13 (1.9), <0.0001		
Age (yrs)		+0.18 (0.1), 0.046		+0.5 (0.2), 0.008
Male gender				+12.8 (5.2), 0.016

Variables were: type of transplant, age, gender, body mass index, steroids, serum creatinine, cyclosporine, donor left ventricular ejection fraction, donor weight, and number of antihypertensive agents Blank cells correspond to variables that were not significant at specific time points. Although systolic blood pressure was normally distributed, a number of explanatory variables were not. Results remained unchanged after repeating the analysis on data that had been appropriately transformed. To ease interpretation, results using the untransformed data are presented.

Abbreviations as in Table 1.

OCT and HHT groups mean they were not directly comparable; however, donor weight was included in the multivariable model. Although treated blood pressure was studied, the difference in SBP was consistent at all time points and the number of antihypertensive agents used was included in the multivariable model. Also, the higher SBP seen in OCT patients was despite greater treatment with antihypertensive agents.

Further studies are required to determine the exact mechanism by which the native heart acts to reduce blood pressure in the HHT group.

Conclusions. Heterotopic heart transplant patients had lower SBP, measured both invasively and noninvasively than OCT patients, managed with the same immunosuppression protocol in the same center. Multivariable analysis confirmed that HHT was independently associated with lower SBP compared to OCT. This is consistent with the hypothesis that the native heart continues to play a role in blood pressure homeostasis after HHT and that its removal in OCT contributes to the development of post transplant hypertension.

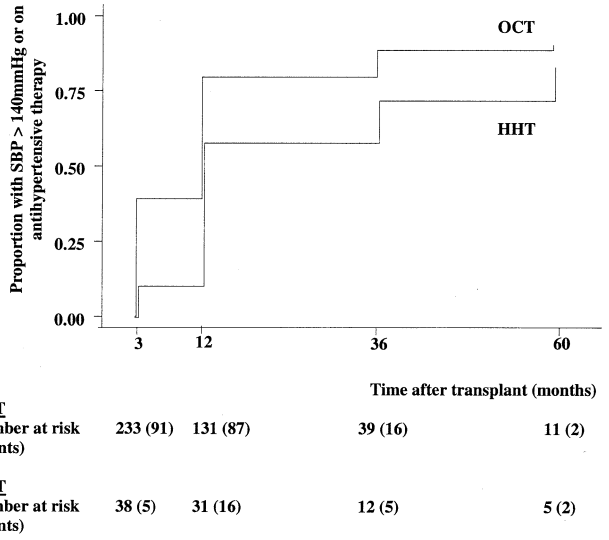

Figure 3. Proportion of orthotopic cardiac transplantation (OCT) and heterotopic heart transplantation (HHT) patients with systolic blood pressure (SBP) ≥140 mm Hg (or receiving antihypertensive treatment) over time, p = 0.001. Figures are numbers at risk (number of events).

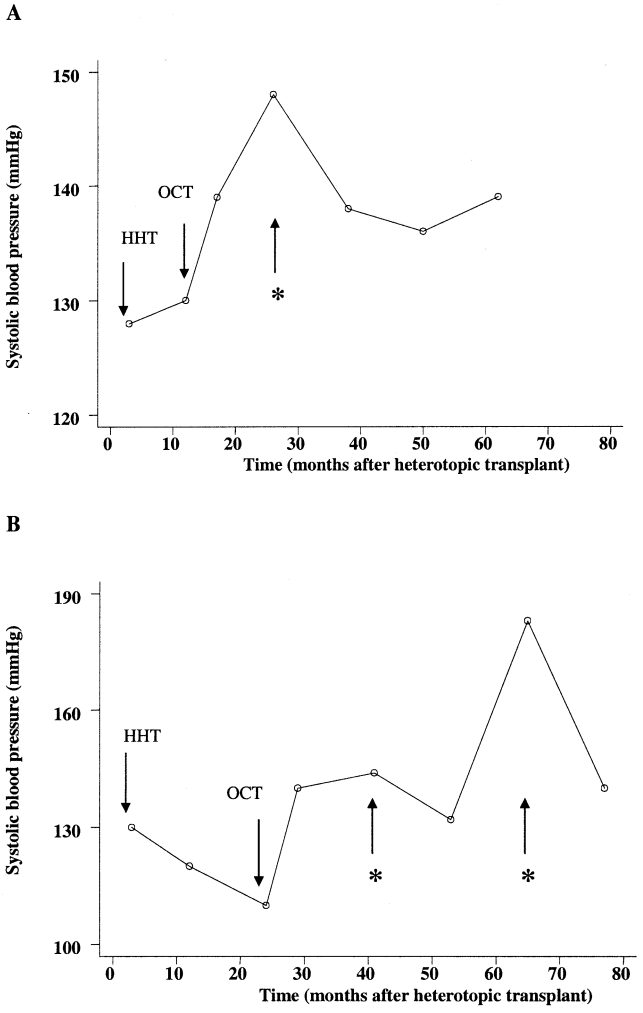

Figure 4. Systolic blood pressure in two patients who underwent heterotopic heart transplantation (HHT) followed by orthotopic cardiac transplantation (OCT). **(A)** 32-year-old man; **(B)** 45-year-old man. * Introduction of antihypertensive agents.

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