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Unfavorable Outcome of Heart Transplantation in Recipients With Type D Personality

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Background: The role of personality in heart transplantation (HTx) remains largely unknown. We examined the distressed personality (Type D) as a predictor of outcomes in patients suffering from end-stage heart disease who underwent HTx.

Methods: Using the DS14 scale, 51 patients (75% men; 54.1 ± 9.7 years of age) were diagnosed as Type D or non-Type D in the pre-transplant period. End-points of this prospective follow-up study (mean 5.4 years) were mortality and allograft rejection (Grade $\geq 3A$ rejection, rejection-free days after HTx).

Results: At baseline, 15 patients were diagnosed as Type D and 36 as non-Type D; they did not differ in recipient or donor characteristics. At follow-up, there were 8 deaths; the mortality rate of Type D recipients was 33% vs 8% for non-Type Ds ($p = 0.036$). Two deaths were due to early post-operative complications and were excluded from further analyses. Type D recipients had a 10-fold higher mortality rate after hospital discharge (5 of 15, or 33%) as compared with non-Type D recipients (1 of 34, or 3%) ($p = 0.013$, adjusting for age and gender). Among surviving recipients, the rate of Grade $\geq 3A$ rejection for both groups was 40% vs 27%, respectively ($p = 0.45$). The first episode of rejection was diagnosed, on average, after 14 days in Type D recipients vs after 50 days in the other patients ($p = 0.032$). The risk of unfavorable outcomes (death, Grade $\geq 3A$ rejection, or number rejection-free days ≤ 14) was greater in Type D recipients (12 of 15, or 80%) than in non-Type Ds (13 of 34, or 38%), adjusting for other risk factors (odds ratio: 6.75; 95% confidence interval: 1.47 to 30.97) ($p = 0.014$).

Conclusions: Type D personality independently predicted mortality and early allograft rejection, and should be accounted for when planning interventions to achieve optimal outcomes after HTx. *J Heart Lung Transplant* 2007;26:152-8. Copyright © 2007 by the International Society for Heart and Lung Transplantation.

Heart transplantation (HTx) has become the most effective treatment for patients suffering from end-stage heart disease, with 5- to 7-year survival rates approaching 77% and 75%, respectively.^{1,2} The scarcity of donor hearts, on the one hand, and the progressive improvement in heart failure management,³ on the other, demand that transplant physicians critically evaluate heart transplant candidates. Justification for HTx im-

plies that a better prognosis and improved quality of life for a given patient are anticipated when compared with optimized medical/electrical therapy.⁴

Further improvement in survival after HTx will depend on a better understanding of risk factors and the development of intervention strategies to modulate them. A major contributor to poor outcomes is acute allograft rejection. Female-to-male mismatch, donor and recipient age, allograft ischemia time, cause of brain death, cytomegalovirus (CMV) status, HLA sensitization and HLA mismatch have all been implied as risk factors for acute rejection.⁵⁻⁸ Behavioral factors such as non-compliance with therapy and depression have also been related to acute rejections and poor prognosis post-HTx.⁹⁻¹¹ Persistent symptoms of psychologic distress are prevalent among HTx patients^{11,12} and have a negative impact on compliance.^{13,14} Little evidence has been published to date, but there is some indication that these symptoms might also predict long-term mortality after HTx.¹⁵⁻¹⁷

Importantly, recipients have shown differences with regard to whether distress decreases after HTx,¹⁸ and personality influences both post-transplant distress and

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non-compliance.^{19,20} One study also found that post-HTx mortality was increased in recipients who were characterized by chronic stress and inhibition in interpersonal situations.²¹ These characteristics closely resemble those of the distressed personality (Type D); that is, Type D denotes the joint tendency toward negative affectivity (chronic negative emotions) and social inhibition (inhibited self-expression toward others), and has been related to mortality and poor health status in cardiovascular patients.^{22–26} However, other investigators did not find an association between distress and outcomes after HTx,²⁷ and the exact role of personality in this context remains largely unknown.¹⁹

Type D patients are vulnerable to chronic forms of distress, given their high scores on both the negative affectivity and social inhibition personality traits²⁸; that is, they experience more feelings of dysphoria, anxiety and irritability, and tend to inhibit the expression of emotions/behaviors to avoid the disapproval from others (Table 1). Previous research has shown that Type D predicts adverse cardiac events and poor quality of life in patients with coronary heart disease^{22,24} and peripheral arterial disease,²⁶ and also predicts poor outcomes after coronary artery stent implantation²³ or coronary artery bypass grafting surgery.²⁵ However, the present study is the first to examine the effect of Type D personality as assessed in the pre-transplant period on

long-term clinical outcomes after HTx. Patients were followed prospectively from the time of transplantation to study Type D personality as a predictor of mortality and acute rejection.

METHODS

HTx Recipients

Subjects included 51 adult patients who underwent HTx at the University Hospital of Antwerp between February 1995 to October 2004, and who were assessed for Type D before transplantation. There were 38 (75%) male heart transplant recipients; the average age at HTx was 54.1 ± 9.7 years (range 26 to 74). In the majority of patients, ischemic cardiomyopathy was the cause of heart failure (26 of 51, or 51%); idiopathic cardiomyopathy was present in 37% of patients (19 of 51). There were no sensitized patients (panel-reactive antibodies [PRA] >10%) or patients on assist device at the time of transplantation. Five patients were transplanted urgently. The standard immunosuppressive regimen consisted of induction therapy with rabbit anti-thymocyte globulin, followed by triple therapy (calcineurin inhibitor, azathioprine or mycophenolic acid and steroids). Endomyocardial biopsies were scheduled weekly for 6 weeks, biweekly until Month 3 and monthly thereafter until 6 to 8 months. Thereafter, the procedure was conducted every 6 weeks until Year 1. Rejection therapy (methylprednisolone 1 g for 3 days or oral taper) was initiated for acute rejection of Grade 3A or higher.

Table 1. Type D Personality

	Negative Affectivity	Social Inhibition
<i>Definition</i>	Tends to experience negative emotions across time/situations.	Tends to inhibit emotions and behaviors in social interaction.
<i>Symptoms</i>	Often feels unhappy, tends to worry; easily irritated; lacks self-esteem.	Tends to be closed, reserved; tends to keep others at distance.
<i>Assessment</i>	DS14 Negative Affectivity sub-scale (7 items; score ≥ 10 as cut-off). sample items: “I am often irritated,” “I often feel unhappy,” “I often find myself worrying about something.”	DS14 Social Inhibition sub-scale (7 items; score ≥ 10 as cut-off). sample items: “I often feel inhibited in social interactions,” “I am a closed kind of person.”
<i>Type D^a personality</i>	Predicts death/myocardial infarction in patients with coronary heart disease, ²² following stent implantation, ²³ and controlling for symptoms of stress. ²⁴ Predicts poor health-related quality of life in coronary patients, ²² following coronary artery bypass grafting surgery, ²⁵ and in patients with peripheral artery disease. ²⁶	

DS14: Type D Scale, 14-items.²⁸

^aPatients are diagnosed with a Type D personality if they have a score of ≥ 10 on both the Negative Affectivity and the Social Inhibition sub-scales.

Type D Assessment

In the pre-transplant period, all patients completed the DS14 scale as a standard measure of Type D personality.²⁸ The DS14 is self-administered and takes only a few minutes to complete. The 14 items of this scale are answered on a 5-point response scale ranging from 0 (false) to 4 (true). Seven of these items refer to “Negative Affectivity,” or the tendency to experience negative emotions in general (e.g., *I am often down in the dumps* or *I often find myself worrying about something*). The remaining 7 items refer to the patient’s level of “Social Inhibition,” or the tendency to inhibit the expression of emotion/behavior in social relationships (e.g., *I am a closed kind of person* or *I often feel inhibited in social interactions*). These personality scales are reliable (Cronbach’s $\alpha = 0.88/0.86$) and stable over time. According to previously published cut-off scores, patients were diagnosed as Type D if they scored ≥ 10 on both the Negative Affectivity and Social Inhibition scales.²⁸

Outcomes Measures

The average time of follow-up was 5.4 years (SD = 2.8, range 1 to 10 years). The primary end-point in this study was death from natural causes. Early mortality post-HTx

has been related to acute rejection.^{7,8} The onset and severity of acute biopsy-proven rejection (BPR), as indicated by the time from transplantation to the development of the first rejection episode (regardless of rejection severity) and the incidence of a rejection episode rated as Grade $\geq 3A$, were secondary end-points. Finally, the composite end-point of death, the incidence of rejection Grade $\geq 3A$, or early rejection was used to examine the risk of unfavorable outcomes after HTx.

Clinical Risk Factors

Several pre-transplant recipient and donor characteristics have been associated with long-term mortality and acute rejection after HTx. These include advanced recipient and donor age, cause of brain death, allograft ischemia time, urgent transplantation, female-to-male mismatch, number of HLA mismatches, recipient CMV-seropositive status, CMV mismatch, pre-transplant diabetes mellitus and serum creatinine levels.⁴⁻⁸ Pulmonary vascular resistance (Wood units) was recorded to account for pulmonary hypertension, and body mass index as a proxy measure of cachexia. These clinical risk factors and the pre-HTx cardiac diagnosis were included as potential confounding factors in statistical analyses.

Statistical Analyses

Cross-tabulation (dichotomous variables) and the independent-sample *t*-test (continuous variables) were used to examine whether Type D and non-Type D recipients differed with regard to baseline characteristics, incidence of rejection episodes of Grade $\geq 3A$, and time from transplantation to the development of the first rejection episode. Cox regression analysis was used to examine the effect of Type D personality on post-HTx mortality. Advanced recipient age, advanced donor age and female-to-male mismatch have been identified as important risk factors in several reports,⁴⁻⁸ and do predict post-HTx mortality above and beyond depressive symptoms.¹⁶ These risk factors and Type D were entered at the same time into a logistic regression model to determine whether Type D independently predicted unfavorable outcomes.

RESULTS

Baseline Characteristics of Type D Recipients

Based on their pre-transplant personality scores, 15 patients (29%) were diagnosed as Type D and 36 (71%) as non-Type D. The indication for HTx (ischemic or idiopathic cardiomyopathy) was not related to personality. Type D and non-Type D recipients did not differ on any of the examined clinical risk factors for mortality and rejection after HTx (Table 2); that is, the diagnosis of Type D personality was not significantly associated

with recipient age, donor age, cause of donor brain death (trauma or cerebrovascular accident [CVA]), allograft ischemia time, urgent transplantation, gender and HLA mismatches, pre-transplant CMV status and CMV mismatch, diabetes mellitus, serum creatinine levels, body mass index or pulmonary hypertension.

Type D and Mortality

After 5.4 years of follow-up, there were 8 deaths from natural causes. These included 2 in-hospital deaths (primary graft failure, $n = 1$; cardiac tamponade, $n = 1$) and 6 out-of-hospital deaths after successful transplantation (cancer, $n = 3$; lung embolism, $n = 2$; disseminating aspergillosis, $n = 1$). None of the pre-transplant recipient and donor characteristics were significantly associated with post-HTx mortality (data not shown). However, Type D recipients had a 4-fold higher mortality rate (5 of 15, or 33%) compared with non-Type D recipients (3 of 36, or 8%) ($p = 0.025$).

The 2 in-hospital deaths were due to early post-operative complications that should not logically be impacted by personality, and were therefore excluded from further analyses. Of note, Type D recipients had a 10-fold higher mortality rate after hospital discharge (5 of 15, or 33%) compared with non-Type D recipients (1 of 34, or 3%) ($p = 0.008$).

Cox regression analysis indicated that Type D personality independently predicted out-of-hospital death, adjusting for recipient age at HTx and gender ($p = 0.013$).

Type D and Allograft Rejection

Among the surviving heart transplant recipients, the rate of moderate to severe acute rejection (i.e., rejection episode rated as Grade $\geq 3A$) was 40% in Type D recipients vs 27% in non-Type Ds, but this difference was not statistically significant ($p = 0.45$). However, Type D recipients were at a significantly increased risk for early rejection; that is, the first rejection episode was diagnosed, on average, at >50 days post-HTx (SD = 91) in non-Type D recipients but already after 14 days post-HTx (SD = 6) in Type D recipients ($p = 0.032$).

Type D and Unfavorable Outcomes After Successful HTx

Using death, moderate to severe rejection or early rejection as a composite end-point, 25 recipients had unfavorable outcomes (24% died, 52% had a rejection of Grade $\geq 3A$, and they averaged only 14 days from HTx to incidence of first rejection episode).

Of note, 80% of Type D recipients had unfavorable outcomes after HTx as compared with 38% of non-Type Ds ($p = 0.007$) (Figure 1). Logistic regression analysis indicated that Type D personality was an independent predictor of unfavorable outcomes (OR = 6.75), adjusting for recipient age, donor age and female-to-male mismatch (Table 3a). Adjustment for any of the

Table 2. Baseline Characteristics of Type D Patients

Baseline characteristics	Personality type		<i>p</i> -value
	Type D (<i>n</i> = 15)	Non-Type D (<i>n</i> = 36)	
<i>Cause of cardiac pathology before HTx</i>			
Ischemic cardiomyopathy	53% (8)	50% (18)	0.39
Idiopathic cardiomyopathy	27% (4)	42% (15)	
Other cardiac conditions	20% (3)	8% (3)	
<i>Risk factors for mortality/rejection</i>			
Recipient age (mean ± SD)	52.5 ± 12.0 y	54.8 ± 8.6 y	0.43
Donor age (mean ± SD)	35.1 ± 15.3 y	34.2 ± 12.0 y	0.82
Donor brain death			
CVA	27% (4)	28% (10)	0.94
Trauma	73% (11)	72% (26)	
Allograft ischemia time	161.2 ± 47.9 min	146.7 ± 40.2 min	0.28
Urgent transplantation	13% (2)	8% (3)	0.62
Recipient gender (male)	67% (10)	78% (28)	0.41
Female-to-male mismatch	20% (3)	19% (7)	0.96
HLA mismatches (<i>n</i>)			
2	8% (1)	6% (2)	0.71
3	23% (3)	14% (5)	
4	46% (6)	34% (12)	
5	15% (2)	26% (9)	
6	8% (1)	20% (7)	
Recipient CMV ⁺	53% (8)	58% (21)	0.74
CMV status mismatch	29% (4)	15% (5)	0.26
Diabetes pre-HTx	20% (3)	17% (6)	0.78
Diabetes post-HTx	40% (6)	36% (13)	0.79
Creatinine (mean ± SD)	1.31 ± 0.40 mg/dl	1.76 ± 2.99 mg/dl	0.57
Body mass index (mean ± SD)	25.3 ± 2.9	25.2 ± 3.1	0.95
Pulmonary hypertension ^a	2.10 ± 1.18	2.23 ± 1.48	0.76

Number of subjects in parentheses.

CMV, cytomegalovirus; recipient CMV⁺, recipient positive for CMV IgG.

^aPulmonary vascular resistance expressed as Wood units.

other clinical risk factors did not change this finding (Table 3b); that is, Type D personality predicted unfavorable outcomes above and beyond recipient and donor characteristics that previously have been associated with long-term mortality and acute allograft rejection after HTx.

DISCUSSION

The findings of the present study indicate that the timely identification of Type D personality might be an issue to consider when providing optimal care to HTx patients. Recipients diagnosed with a Type D personality before transplantation had a significantly increased risk of long-term mortality post-HTx. Patients with a Type D personality also had a greater propensity for acute rejection. The difference in the incidence of moderate to severe acute rejection between Type D and non-Type D recipients (40% vs 27%, respectively) was not statistically significant, but Type D recipients were at a significantly increased risk for early rejection.

Type D personality predicted unfavorable outcomes (long-term death, moderate to severe rejection or early rejection) above and beyond established risk factors in HTx.^{4–8} Many transplant centers do not routinely evaluate recipients in terms of personality; hence, the exact role of personality in HTx is largely unknown.¹⁹ Our findings suggest that researchers need to account for Type D personality when planning studies on the long-term outcomes of transplantation in their patients.

These findings, however, need to be interpreted with some caution. The number of transplantation recipients in this study was relatively small, and all of the patients were transplanted in one HTx center. The small number of subjects is a double-edged sword. Mortality was a relatively rare event in this sample and the present findings need to be confirmed in future research. However, the Type D effect was large enough to require only a small number of patients to become statistically significant, suggesting that we may be dealing with a significant risk marker.²⁹ By analogy, initial observations on Type D and

Figure 1. Unfavorable outcomes after HTx, stratified by Type D personality. Number of patients with unfavorable outcomes (bold) and total number of HTx recipients are presented on top of each bar.

mortality in a small sample of coronary patients²⁹ were confirmed shortly thereafter in a larger study of patients.³⁰ In recent years, more studies have provided corroborating evidence for the detrimental effect of Type D in coronary heart disease.²²⁻²⁴ Because statistical associations did emerge, despite the low power, additional exploration in confirmatory research on Type D and HTx is warranted. The single-center nature of the present study also calls for more prospective research in other transplantation centers to examine the reproducibility across different transplantation settings.

Type D and non-Type D recipients did not differ on any of the known risk factors for mortality and rejection after HTx, including age, allograft ischemia time, female-to-male and HLA mismatches, CMV status, renal failure, diabetes, body mass index and pulmonary hypertension. We also found that established risk factors such as advanced recipient age and donor age⁴⁻⁸ did not explain away the association between Type D and unfavorable outcomes. Several other pre-transplant factors may also be involved as determinants of outcomes after HTx,⁵ and future research needs to examine whether Type D still is an independent predictor if more of these factors are being included. Finally, the standard assessment of personality in the pre-transplant period and the prospective design are strengths of this study.

Previous research showed that Type D has an adverse effect on the prognosis and quality of life of patients with coronary heart^{22,24} and peripheral arterial²⁶ disease, including patients recovering from stenting²³ or bypass surgery.²⁵ The present findings suggest that Type D may have an adverse effect on outcomes of HTx as well. Type D personality refers to a broad and stable personality construct, and is not likely to change with the mere experience of transplantation. For example, we have shown previously that cardiac rehabilitation is an effective therapy for improving mood and health status in cardiac patients, but that these treatment-related clinical improvements do not result in changes in the Type D personality traits.²⁸ Reassessment of Type D personality in future follow-up research is indicated to test the notion that a Type D patient is not likely to convert to a non-Type D patient due to clinical improvements after successful HTx.

Although some studies have suggested an association between symptoms of psychologic distress and mortality post-HTx,¹⁵⁻¹⁷ others argued against this relation.²⁷ The present findings add to a growing body of evidence that indicates the relevance of psychologic factors in

Table 3. Unfavorable vs Favorable Outcome After Successful HTx

	Unfavorable outcome (N = 25)	Favorable outcome (N = 24)
Outcome variables		
Mortality rate (n)	24% (6)	0% (0)
Moderate to severe rejection (n)	52% (13)	0% (0)
Rejection-free days (mean ± SD)	14.1 ± 9.5	66.1 ± 102.9
Predictors of outcome		
	Odds ratio	95% CI p
(a) Multivariate analysis^a		
Recipient age	0.99	0.93–1.07 0.91
Donor age	1.04	0.98–1.09 0.20
Female-to-male mismatch	1.27	0.36–4.52 0.71
Type D personality	6.75	1.47–30.97 0.014
(b) Other recipient/donor characteristics		
Donor brain death		0.71
Allograft ischemia time		0.28
Urgent transplantation		0.08
Recipient gender (male)		0.74
HLA mismatches		0.69
Recipient CMV ⁺		0.54
CMV status mismatch		0.98
Diabetes pre-HTx		0.62
Diabetes post-HTx		0.78
Creatinine		0.32
Body mass index		0.89
Pulmonary hypertension		0.12

Number of subjects in parentheses.

^aDeath, rejection episode Grade ≥3A, or number of days from HTx to the incidence of the first rejection episode post-HTx ≤2 weeks coded as 1.

the context of HTx. Persistent symptoms of psychologic distress are prevalent among HTx patients,¹¹ and may have a negative impact on compliance with medical therapy and prognosis.^{9,10} However, data on personality traits among HTx populations are sparse,¹⁹ and the present findings confirm previous evidence suggesting that post-HTx mortality may be increased in recipients who experience chronic stress and social inhibition.²¹ Hence, our findings support the notion that psychologic factors require continuous attention in the long-term care of post-HTx patients.¹¹ Symptoms of psychologic distress are prevalent among HTx patients,^{11,12} but recipients differ greatly in the extent to which they experience distress.¹⁸ Individual difference variables such as Type D personality may help to predict the susceptibility for persistent symptoms of psychologic distress among patients who have undergone HTx.

The DS14 scale²⁸ is a valid, brief, self-report measure with little response burden that can be easily scored by health-care providers. However, it should be clear from the outset that we do *not* consider Type D to be a relative contraindication for HTx. Rather, we would argue that the present findings might have important implications for clinical research and practice aimed at further improving the outcomes of HTx. Inclusion of the DS14 as a routine measure would allow transplantation teams to target potentially vulnerable patients who may benefit from additional behavioral intervention.¹⁹ Preliminary findings have suggested that such an intervention has a beneficial effect on patients' psychologic adjustment to HTx³¹ and is useful in motivating HTx patients to engage more in health-promoting activities.¹¹

Although this was not the focus of the present study, it is important to speculate about potential pathways that may explain the link between Type D and outcomes after HTx. Optimal outcomes after HTx can only be obtained if patients adhere to a lifelong therapeutic regimen and attend regular clinical checkups.³² However, psychologic distress increases the risk of non-adherence,^{13,14} which, in turn, has been related to acute rejections and unfavorable prognosis post-HTx.^{9,10} Of note, Type D patients are especially prone to chronic psychologic distress.²⁵ This study did not include compliance data, but it is important to examine whether medication non-compliance would explain the poor prognosis of Type D patients.

Type D personality has been associated with increased circulating levels of tumor necrosis factor- α (TNF- α) and its soluble receptors 1 and 2 in patients with chronic heart failure.^{33,34} Comparable mechanisms may apply to HTx recipients; that is, associations between pro-inflammatory cytokine levels and increased risk of rejection might be related to increased psychologic distress. TNF- α is a potent pro-inflammatory cytokine that is produced in cardiac allografts, and

has been associated with the development of cardiac allograft vasculopathy,³⁵ cardiac allograft hypertrophy³⁶ and right ventricular failure³⁷ in heart transplant recipients. Evidence has also suggested that a statin-mediated decrease in TNF- α expression may have a beneficial effect on survival and rejection post-HTx.³⁸

In conclusion, our findings underscore the potential role of psychologic factors, and of Type D personality in particular, in the clinical course and aftercare of cardiac transplant recipients. The timely recognition of recipients subject to an increased risk of poor outcomes is crucial for ensuring optimal care before and after HTx. Accumulating evidence suggests that psychosocial issues also need to be assessed carefully in the pre-transplant period, including the role of personality. The present findings clearly suggest a potential role for Type D personality in this context.

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