Prolonged donor ischemic time does not adversely affect long-term survival in adult patients undergoing cardiac transplantation

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Objective: With liberalization of donor eligibility criteria, organs are being harvested from remote locations, increasing donor ischemic times. Although several studies have evaluated the effects of prolonged donor ischemic times on short-term survival and graft function, few have addressed concerns regarding long-term survival.

Methods: Over the last 11 years, 819 consecutive adults underwent cardiac transplantation at Columbia Presbyterian Medical Center. Recipients were separated into the following 4 groups based on donor ischemic time: <150 minutes, 150 to 200 minutes, 200 to 250 minutes, and >250 minutes. Statistical analysis included Kaplan-Meier survival and Cox proportional hazard models to identify predictors of long-term survival.

Results: Donor ischemic time was 120.1 ± 21.1 minutes for group 1 (n = 321), 174.1 ± 14.7 minutes for group 2 (n = 264), 221.7 ± 14.6 minutes for group 3 (n = 154), and 295.5 ± 37.1 minutes for group 4 (n = 80) ($P < .001$). There were no significant differences in recipient age, donor age, etiology of heart failure, United Network for Organ Sharing status, or history of previous cardiac surgery among the groups (P = NS). Prolonged donor ischemic time did not adversely affect long-term survival, with actuarial survival at 1, 5, and 10 years of 86.9%, 75.2%, and 56.4% for group 1; 86.2%, 76.9%, and 50.9% for group 2; 86.4%, 71.0%, and 43.7% for group 3; and 86.7%, 70.1%, and 50.9% for group 4 ($P = .867$). There was no significant difference in freedom from transplant coronary artery disease among the 4 groups ($P = .474$).

Conclusions: Prolonged donor ischemic time is not a risk factor for decreased long-term survival. Procurement of hearts with prolonged donor ischemic time is justified in the setting of an increasing recipient pool with a fixed donor population.

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At New York Presbyterian Hospital–Columbia Medical Center, orthotopic cardiac transplantation has a 1-, 5-, and 10-year survival of 84%, 72%, and 53%, respectively, which is comparable to data reported by other high-volume transplant centers.[1-3] To accommodate increasing demand in the setting of a declining donor population, many transplant programs have liberalized donor eligibility criteria.[4-7] This has translated into harvesting older hearts, from more unstable donors, in more remote locations, with the latter resulting in an increase in donor ischemic time (DIT).[8]

Although several studies have evaluated the effects of prolonged DIT on short-term survival and graft function, few have addressed concerns regarding long-term survival with a substantial number of patients and adequate follow-up time.[9,10] This issue has therefore remained a concern shared by many transplant centers and has been the subject of considerable debate. Additionally, there has been some experimental data implicating prolonged DIT in the development of transplant coronary artery disease (TCAD) by inducing endothelial activation.[11,12] However, to the best of our knowledge, there have not been any clinical studies that have evaluated this issue in a large group of patients with long-term follow-up.

To help clarify the effects of DIT on long-term survival and development of TCAD, we retrospectively analyzed our transplant experience over the last decade. This study constitutes a large single-center transplant experience, with long-term follow-up, evaluating the effect of prolonged DIT on long-term survival and development of TCAD.

Patients and Methods

From January 1992 through January 2003, 937 patients underwent cardiac transplantation at New York Presbyterian Hospital–Columbia Medical Center. Pediatric recipients (<18 years at the time of transplantation, n = 118) were excluded. The remaining 819 adult recipients were separated into the following 4 groups based on length of DIT: group 1, <150 minutes (39.2%, n = 321); group 2, 150 to 199 minutes (32.2%, n = 264); group 3, 200 to 249 minutes (18.8%, n = 154); and group 4, >250 minutes (9.8%, n = 80). Group 4 contained 17 patients (2.1%) with DIT > 300 minutes and 6 patients (0.7%) with DIT > 360 minutes. All 819 recipients were included in the analysis, even patients who died in the early postoperative period. DIT was defined as the interval from application of donor aortic crossclamp to release of the recipient crossclamp.

Detection of Transplant Coronary Artery Disease

All patients underwent annual coronary angiography to evaluate for transplant coronary artery disease. The diagnosis was based on the following: (1) discrete lesions resulting in ≥50% obstruction of the proximal or midportion of major graft vessels, or (2) diffuse, concentric narrowing of whole vessels, including their branches. Reports of "luminal irregularities" were considered positive for TCAD, while reports of "mild tapering of coronary artery" were considered negative studies. If a patient had TCAD, the frequency of angiography was increased to biannually. Patients were not given routine vasodilators before coronary injections. All angiograms were reviewed by a cardiologist and compared with the previous year's films to detect the presence of luminal irregularities, discrete stenoses, loss of third-order branches, or pruning of vessels.

Donor Acceptance Criteria

Donor and recipients were matched for ABO blood type compatibility and size (generally within 20% of body weight). Prospective human leukocyte antigen (HLA) matching was not used with the exception of recipients with high levels of panel reactive anti-HLA antibodies (>20%) who underwent a prospective cross-match. Male donors less than 40 years of age and female donors less than 45 years of age met criteria as suitable donors provided there was no evidence of preexisting heart disease or impaired myocardial dysfunction by echocardiography. Older individuals also met criteria as suitable donors provided that coronary atherosclerotic lesions could be excluded, ideally by cardiac catheterization. Individuals with serologies positive for HIV, hepatitis B (hepatitis B sAg), hepatitis C, or nonprimary brain cancer were excluded from being donors.

Graft Procurement

Donor hearts were harvested from heart-beating, brain-dead individuals. Graft procurement and preservation were performed using cold University of Wisconsin solution (Viaspan; DuPont Pharmaceuticals, Wilmington, Del) and topical hypothermia. Prior to 1996, orthotopic cardiac transplantation was performed using the biatrial technique described by Lower and Shumway.[13,14] Since 1996, almost all transplants were performed using the bicaval anastomosis technique.[15,16]

Immunosuppressive Regimen

Until January 1996, all patients received cyclosporine, steroids, and azathioprine. Dosing of cyclosporine consisted of a preoperative oral dose of 3 to 6 mg/kg, followed by an intravenous dose of 1 to 2 mg/kg every 24 hours until oral intake was tolerated. Daily oral doses of 3 to 6 mg/kg were adjusted to maintain a serum level of 300 to 350 mg/mL. After 6 to 12 months, cyclosporine doses were reduced to maintain a serum level between 100 and 150 ng/mL. Azathioprine was also administered preoperatively as an oral dose of 4 mg/kg, followed by daily doses of 2 mg/kg, with adjustments in dosing made based on the patients' white blood cell count, platelet count, and hepatic function.

Since 1996, mycophenolate mofetil, starting at a dose of 1000 mg twice daily, replaced azathioprine as part of cyclosporine-based therapy. Intravenous methylprednisolone (500 mg) was administered during the operation and postoperatively with 125 mg every 8 hours for 3 doses. Prednisone was then instituted at a daily dose of 1 mg/kg and gradually tapered over 4 months to 0.1 mg/kg/d. Intravenous murine monoclonal antibody OKT3 (5 mg/d) took the place of cyclosporine for the first 4 days after transplantation for patients with severe renal dysfunction. Beginning in 1998, induction therapy using dacluzimab was added to our immunosuppression regimen in certain patients.

TABLE 1. Clinical characteristics of patients

	Group 1	Group 2	Group 3	Group 4	*P*
Recipient data					
Patient distribution	321 (39.2%)	264 (32.2%)	154 (18.8%)	80 (9.8%)	.031
Age (y)	51.9 ± 11.6*	52.1 ± 12.2	52.7 ± 11.6	49.5 ± 14.2	.453†
Range of ages (y)	18.8-67.1	18.3-70.3	19.1-70.4	20.7-66.2	.451
Gender					
Male	241 (75.0%)	203 (76.9%)	121 (78.6%)	59 (73.8%)	.833
Female	80 (25.0%)	61 (23.1%)	33 (21.4%)	21 (26.3%)	
Race					
Caucasian	246 (76.6%)	214 (81.1%)	119 (77.3%)	54 (67.5%)	.238
African American	42 (13.1%)	28 (10.6%)	23 (14.9%)	7 (8.8%)	.635
Other	33 (10.3%)	22 (8.3%)	12 (7.8%)	19 (23.8%)	.061
P value	.249†	.618	.037	.371	
Etiology of ESHD					
CAD	191 (59.5%)	148 (56.1%)	85 (55.2%)	46 (57.5%)	.534
ICM	106 (33.0%)	99 (37.5%)	60 (39.0%)	28 (35.0%)	.612
Other	24 (7.5%)	17 (6.4%)	9 (5.8%)	6 (7.5%)	.720
UNOS status					
1	262 (81.6%)	214 (81.1%)	128 (83.1%)	63 (78.8%)	.957
2	59 (18.4%)	50 (18.9%)	26 (16.9%)	17 (21.3%)	.976
Donor data					
Age (years)	32.5 ± 12.8*	32.1 ± 12.3	32.4 ± 13.4	30.2 ± 14.1	.701
Age range (years)	10.2-63.3	10.1-59.5	7.5-62.7	4.2-63.3	
DIT (minutes)	120.1 ± 21.1*	174.1 ± 14.7	221.7 ± 14.6	295.5 ± 37.1	<.001
DIT range (minutes)	42.1-149.9	150.0-199.9	200.0-249.9	250.0-396.2	.451

ESHD, End-stage heart disease; *CAD,* coronary artery disease; *ICM,* idiopathic cardiomyopathy; *UNOS,* United Network for Organ Sharing; *DIT,* donor ischemic time.
*Mean ± standard deviation.
†Variables were compared using ANOVA testing.

Exclusion Criteria

Exclusion criteria for cardiac transplantation were factors that adversely impact long-term survival (eg, cancer), increase perioperative morbidity and mortality (eg, pulmonary hypertension, recent pulmonary embolus, active infection), or affect a patient's ability to care for him- or herself (eg, untreated major psychiatric illness, recent substance abuse). Pretransplant pulmonary hypertension, defined as greater than 6 Woods units, was also considered to be a relative contraindication to transplantation. Many of these comorbidities, however, are being reevaluated, given our favorable experience in transplanting patients once perceived to be high risk (eg, diabetics).

Statistical Analysis

Data were represented as frequency distributions and percentages. Values of continuous variables were expressed as a mean ± standard deviation (SD). Continuous variables were compared using paired *t* tests, whereas categorical variables were compared by means of chi-squared tests. For all analyses, a *P* value of $<.05$ was considered statistically significant. Kaplan-Meier analysis was used to calculate survival along with a log-rank *P* value when comparing groups. Actuarial survival at 1, 3, 5, and 10 years posttransplant was calculated by constructing life tables. Significant predictors of survival were identified using multivariate Cox proportional hazard models. To further examine the relationship between prolonged DIT, advanced donor age, and survival, donor age was stratified into 3 ranges: <35, 35 to 49, and >50 years. Survival for each donor age group was then plotted within DIT groups 1 to 4. All data were analyzed utilizing SPSS 11.5 (SPSS Inc, Chicago, Ill).

Results

Distribution of Prolonged DIT throughout the 11-Year Study Period

Overall mean DIT throughout the 11-year period was 173.8 ± 58.7 (42.4-396.2). The distribution of patients with prolonged DIT was fairly equal during the course of the study period. The number of patients with associated prolonged DIT was 11 (13.8%) in 1992, 4 (5.0%) in 1993, 9 (11.3%) in 1994, 4 (5.0%) in 1995, 10 (12.5%) in 1996, 9 (11.3%) in 1997, 13 (12.6%) in 1998, 6 (7.5%) in 1999, 8 (10.0%) in 2000, 3 (3.8%) in 2001, and 3 (5.4%) in 2002.

Demographics

Recipient characteristics. Table 1 outlines baseline clinical demographics of patients in each of the 4 DIT groups. There was no significant difference in recipient age, gender, race, or etiology of heart failure among patients in the 4 DIT groups (P = NS). Mean pulmonary artery pressures were also similar among the groups (29.2 ± 11.8 mm Hg for

TABLE 2. Previous cardiac surgeries for each cohort

	Group 1	Group 2	Group 3	Group 4	*P*
Previous cardiac surgery	149 (46.4%)	139 (52.7%)	79 (51.3%)	41 (51.3%)	.671
CABG	44 (13.7%)	42 (15.9%)	29 (18.8%)	20 (25.0%)	
LVAD	73 (22.7%)	58 (22.0%)	32 (20.8%)	9 (11.3%)	
OHT	18 (5.6%)	12 (4.5%)	7 (4.5%)	1 (1.3%)	
MVR	3 (0.9%)	3 (1.1%)	0	3 (3.8%)	
AVR	2 (0.6%)	1 (0.4%)	1 (0.6%)	0	

CABG, Coronary artery bypass grafting; *LVAD,* left ventricular assist device; *OHT,* orthotopic heart transplant; *MVR,* mitral valve replacement; *AVR,* aortic valve replacement.

group 1, 27.7 ± 10.9 mm Hg for group 2, 30.3 ± 12.1 mm Hg for group 3, and 32.0 ± 13.1 mm Hg for group 4; P = .153).

United Network for Organ Sharing (UNOS) status distribution was similar for all 4 groups, with UNOS status 1 and 2 recipients distributed as 81.6% and 18.4% in DIT group 1, 81.1% and 18.9% in DIT group 2, 83.1% and 16.9% in DIT group 3, and 78.8% and 21.3% in DIT group 4 (P = NS).

There was no significant difference among the 4 DIT groups in the percentage of patients who underwent previous cardiac surgery. One hundred forty-nine (46.4%) patients in group 1, 139 (52.7%) patients in group 2, 79 (51.3%) patients in group 3, and 41 (51.3%) patients in group 4 underwent previous cardiac surgery before transplantation. The most common types of surgeries are listed in Table 2.

Donor characteristics. There was no statistically significant difference in donor age among the groups (P = NS; Table 1). DIT was similar when comparing male recipient and female recipients (174.5 ± 58.5 versus 171.5 ± 59.3 minutes, respectively; P = .596) and recipient races (172.9 ± 56.8 for Caucasian, 173.0 ± 60.7 for African American, and 181.5 ± 69.5 for other; P = .214).

Survival

Overall survival of the entire cohort is depicted in Figure 1. Actuarial survival at 1, 5, and 10 years was 86.5%, 73.4%, and 50.3%, respectively, with median survival of 10.2 years. There was no significant difference in overall survival when comparing the 4 DIT groups (P = .867; Figure 2). Actuarial survival at 1, 5, and 10 years was 86.9%, 75.2%, and 56.4% for group 1; 86.2%, 76.9%, and 50.9% for group 2; 86.4%, 71.0%, and 43.7% for group 3; and 86.7%, 70.1%, and 50.9% for group 4, respectively (Table 3). When group 4 was compared with groups 1 to 3, there was no difference in survival (P = .196). Actuarial survival at 1, 5, and 10 years posttransplant for the subgroup of patients within group 4 with DIT > 300 minutes was 82.2%, 71.7%, and 46.9%, respectively. There was no statistically significant difference in survival when this subgroup of patients was compared with the remainder of patients in DIT group 4 (P = .514) or with patients in DIT groups 1 to 3 (P = .442).

Relationship Between Donor Age, DIT, and Survival

Four hundred fifty-eight (55.9%) patients received heart from donors <35 years of age, 272 (33.2%) from donors 35 to 49 years, and 89 (10.9%) from donors >50 years. The distribution of hearts from donors of advanced age (>50 years) among the 4 DIT group was not significantly different and encompassed 11.5% (n = 37) of patients in group 1, 10.2% (n = 27) of group 2, 10.4% (n = 16) of group 3, and 11.3% (n = 9) of group 4 (P = .182). When separating recipients in each on the 4 DIT groups based on 3 donor age ranges (<35, 35 to 49, and >50 years), advanced donor age adversely impacted survival in DIT groups 1 and 3 (P = .024 and P = .038, respectively), but not groups 2 and 4 (P = .315 and P = .692, respectively; Figures 3, 4).

Predictors of Survival

Univariate analysis. By univariate analysis, recipient gender, race, and donor age were statistically significant risk factors adversely affecting long-term survival (Table 4). DIT was not an independent predictor of decreased survival (P = .353).

Mutivariate analysis. Using Cox proportional hazard models, only recipient female gender was found to be a statistically significant predictor adversely affecting long-term survival (OR 1.281, 95% CI 0.856-1.694, P = .001, SE 0.158; Table 5).

Primary Graft Failure

There was no significant difference in the incidence of primary graft failure (PGF) among the 4 groups (P = NS). PGF occurred in 2 (0.6%) patients in DIT group 1, 7 (2.7%) patients in group 2, 6 (3.9%) patients in group 3, and 2 (2.5%) patients in group 4 (P = .114).

Relationship between Prolonged DIT and Development of Transplant Coronary Artery Disease

There was no statistically significant difference in freedom from TCAD when comparing the 4 DIT groups, although

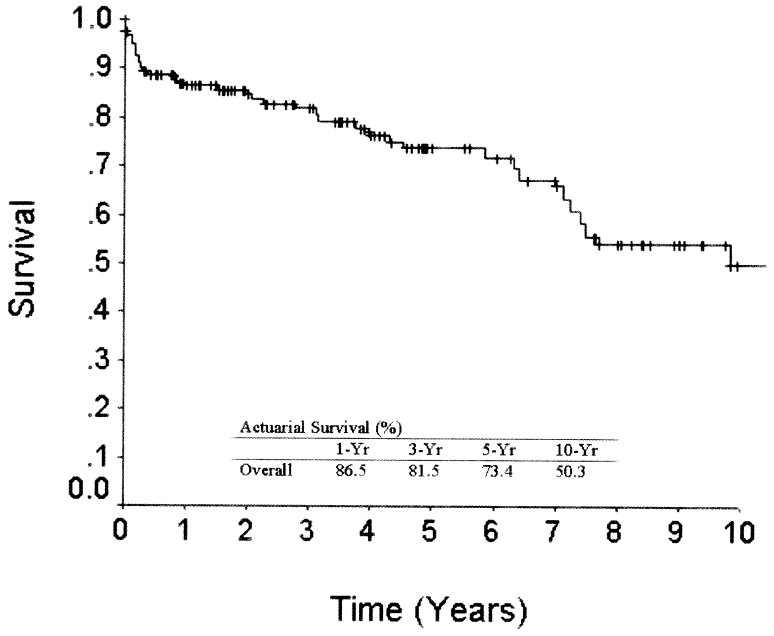

Figure 1. Overall posttransplant survival for all adult patients from January 1992 through January 2003. Median survival was 10.2 years.

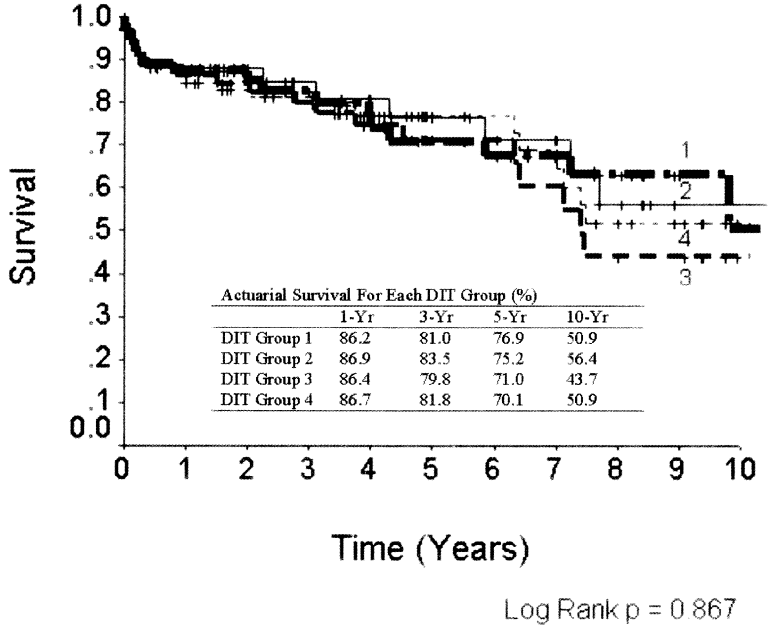

Figure 2. Survival for each DIT group. There was no significant difference in overall survival when comparing the 4 DIT groups. Median survival was 12.4 years for group 1, 10.2 years for group 2, 8.8 years for group 3, and 11.4 years for group 4.

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the incidence of TCAD was highest for patients in group 4 ($P = .474$; Figure 5). Freedom from TCAD at 1, 5, and 10 years was 98.0%, 68.9%, and 38.9% for group 1; 98.1%, 60.1%, and 38.5% for group 2; 95.7%, 70.5%, and 42.1% for group 3; and 98.8%, 57.7%, and 28.9% for group 4. When group 4 was compared with groups 1 to 3 as a composite, the difference in freedom from TCAD was still not statistically significant ($P = .202$), although median

time for development of TCAD was 5.3 years for group 4, as compared with 8.3 years for groups 1 to 3 (Figure 6).

Impact of Donor Heart Left Ventricular Hypertrophy on Survival

Data regarding donor left heart ventricular hypertrophy (LVH) were available to us beginning only in 1996. There were a total of 17 patients since 1996 who received hearts noted to have LVH on echocardiography. There was no statistically significant difference in graft function or survival when comparing these 17 patients with LVH to other patients without LVH since 1996. These 17 patients included 9 (6.9%) from DIT group 1, 3 (2.8%) from group 2, 4 (5.2%) from group 3, and 1 (1.6%) from group 4.

Discussion

Due to the overwhelming demand for organs, the definition of the "ideal donor organ" is in constant flux. In an attempt to expand the donor pool and accommodate patients awaiting transplantation, it has become commonplace to accept organs from distant locations, resulting in prolongation of DIT.

Some series have demonstrated prolonged DIT to be associated with significantly reduced postoperative left ventricular ejection fraction (LVEF), right ventricular function, and increased requirement for inotropes within the first 48 hours postoperatively.[5,8] This may be secondary to a more elaborate cytokine response or ischemia-reperfusion injury.[5] Prolonged DIT has also been associated with a trend toward increased intensive care unit and hospital stay.[5,8] However, many transplant centers believe that although prolonged DIT may have negative consequences in the immediate postoperative period, it may not adversely affect long-term survival.

The data on the impact of prolonged DIT on short- and mid-term survival are conflicting. Several studies have not found prolonged DIT to be an independent predictor of adverse outcome.[4,8,15-17] Del Rizzo and colleagues,[4] reporting on 372 patients, found that prolonged DIT (defined as ≥240 minutes) did not adversely affect posttransplant 1-year survival. Additionally, Plugfelder and associates,[17] in a series of 167 heart recipients, found no difference in 90-day graft loss or 3-month survival for recipients with prolonged DIT (≥300 minutes). When Plugfelder and colleagues[18] updated their experience on 219 patients, they again found that prolonged DIT (≥3 hours) did not adversely impact 1-year survival. Another comparative study by Mullen and coworkers[19] demonstrated no significant difference in 30-day or 90-day survival when comparing 261 recipients with DIT above and below 4 hours. However, 30- and 90-day mortality was 13% and 16%, respectively, for recipients with DIT $>$ 4 hours compared with 7% and 10%, respectively, for patients with DIT $<$ 4 hours (P = .014 and 0.027, respectively). Finally, Korner and colleagues[20] showed no difference in survival based on prolonged DIT (up to 330 minutes) at a mean follow-up time of 22 months, although data was only available for 100/834 (12.0%) patients.

TABLE 3. Actuarial survival for each DIT group

	1 year (%)	3 years (%)	5 years (%)	10 years (%)	Median (%)
DIT Group 1	86.2	81.0	76.9	50.9	12.4
DIT Group 2	86.9	83.5	75.2	56.4	10.2
DIT Group 3	86.4	79.8	71.0	43.7	8.8
DIT Group 4	86.7	81.8	70.1	50.9	11.4

Two multi-institutional studies, however, reported by the Cardiac Transplant Research Database Group, concluded that prolonged DIT was an independent risk factor for early mortality after transplantation.[21-23] These studies had a mean follow-up of 13.9 and 8.1 months, respectively.

Although there have been several studies analyzing the effect of prolonged DIT on short- and mid-term survival, there are only a few single-institutional studies that have studied the effect of prolonged DIT on long-term survival with a substantial number of patients.[4,18,24-26] Furthermore, a detailed examination of the literature reveals that there have not been any studies with a substantial number of patients that have evaluated the effects of prolonged DIT of up to 5 hours on survival. The largest single-center series to evaluate the effect of prolonged DIT on survival studied a total of 373 patients and only evaluated prolonged DIT up to 4 hours.[4] This study did not analyze whether or not DIT $>$ 5 hours adversely affected survival.

While multicenter registries have the advantage of being able to pool data on large numbers of patients and enhance statistical power, they are limited by interinstitutional variability and accurate risk stratification.[27,28] Furthermore, registries are generally composed of data from many low-volume transplant centers and relatively few high-volume centers.[29] Conclusions are made from extrapolation of data from many centers, where there may be significant differences in management strategies and ranges of experiences.[24] It is possible, therefore, that favorable results of a single large-institution experience may be masked by results from smaller centers with higher mortality rates.[24]

In our report of more than 800 patients over 11 years, we demonstrated that prolonged DIT did not significantly affect long-term survival. Prolonged DIT was evaluated for up to 5 hours in a cohort of 17 patients, a subgroup of patients in DIT group 4. We demonstrated that DIT can be safely extended to 5 hours without adversely affecting survival, a finding that to the best of our knowledge has not yet been published in the literature in a substantial number of patients.

Our investigation of the relationship between prolonged DIT and TCAD did not corroborate experimental data,

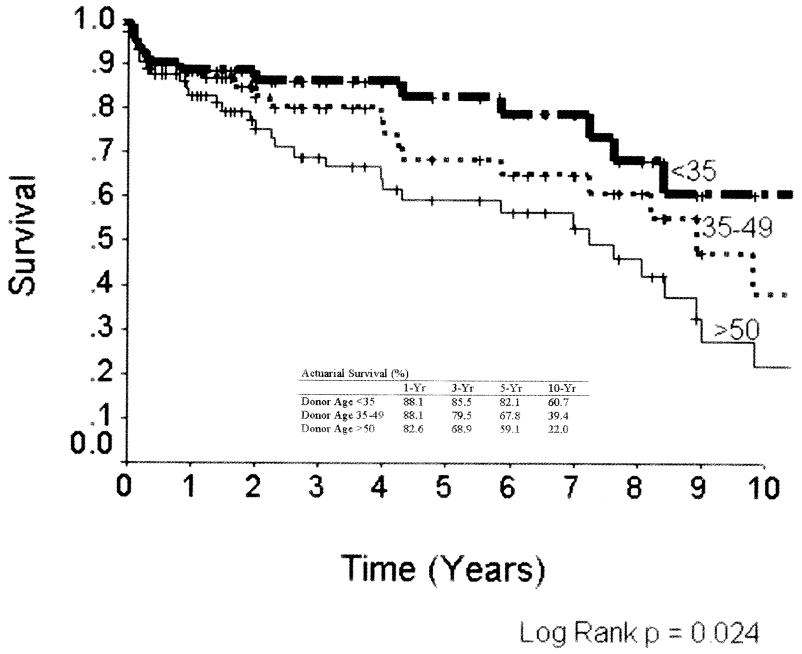

Figure 3. Effect of donor age on survival within DIT group 1. Advanced donor age adversely affected survival within DIT group 1, with median survival for patients with donor age < 35, 35 to 49, and >50 years of 11.4, 8.8, and 7.5 years, respectively.

which suggests that prolonged DIT may be implicated in the development of TCAD.[11,12,30] It should be noted, however, that there was a greater incidence of TCAD in patients with prolonged DIT (although not statistically significant).

There is some evidence that prolonged DIT, in combination with donor heart LVH, can be a risk factor for reduced graft function and survival.[31] Because data regarding donor LVH was available to us beginning only in 1996, our evaluation of this issue was limited. Although we demonstrated that there was no statistically significant difference in graft function or survival when comparing the 17 patients with LVH to other patients without LVH since 1996, we could not effectively evaluate the combined effects of donor heart LVH and prolonged DIT since there was only 1 patient who met these criteria.

Limitations of this study include those related to a retrospectively performed analysis. Identification of demographic variables, DIT, and risk factors for mortality were obtained by chart review, which has inherent limitations, such as access and accuracy of the data. Additionally, as a retrospective observational study, it is subject to selection bias and incomplete data collection. Although comparative data of the clinical characteristics indicate that DIT groups 1 to 4 were similar for several donor and recipient characteristics, as outlined in Tables 1 and 2 (recipient age, gender, race, etiology of heart failure, UNOS status, donor age, and previous cardiac surgical history), it is likely that there were additional factors that were not apparent but that may have had an important effect on the results. Additionally, interpretation of the results regarding the effects of advanced donor age on survival and the relationship between advanced donor age and prolonged DIT is limited because of the relatively small sample size of hearts from donors > 50 years. Although we demonstrated that advanced donor age adversely impacted survival only in DIT groups 1 and 3, not groups 2 and 4, it is possible that if a larger cohort of recipients who received hearts from donors > 50 years were studied by conducting a multi-institutional analysis, a different result may have been obtained. Finally, interpretation of the data regarding the relationship between prolonged DIT and development of TCAD may also be limited for the similar reason. Given the relatively small number of patients in group 4, it is possible that if a multi-institutional evaluation of development of TCAD in patients with prolonged DIT was conducted, increasing the number of patients with prolonged DIT, a statistically significant association might have been observed.

In conclusion, in our experience with 819 adult recipients over 11 years, prolonged DIT did not significantly affect long-term survival. Patients with DIT > 5 hours demonstrated similar short- and long-term survival as patients with DIT of shorter durations. Additionally, prolonged DIT was not a significant risk factor for the development of TCAD. These data have emphasized to our team that DIT can safely be extended beyond 5 hours and have made us more secure with our efforts to expand the donor pool by harvesting

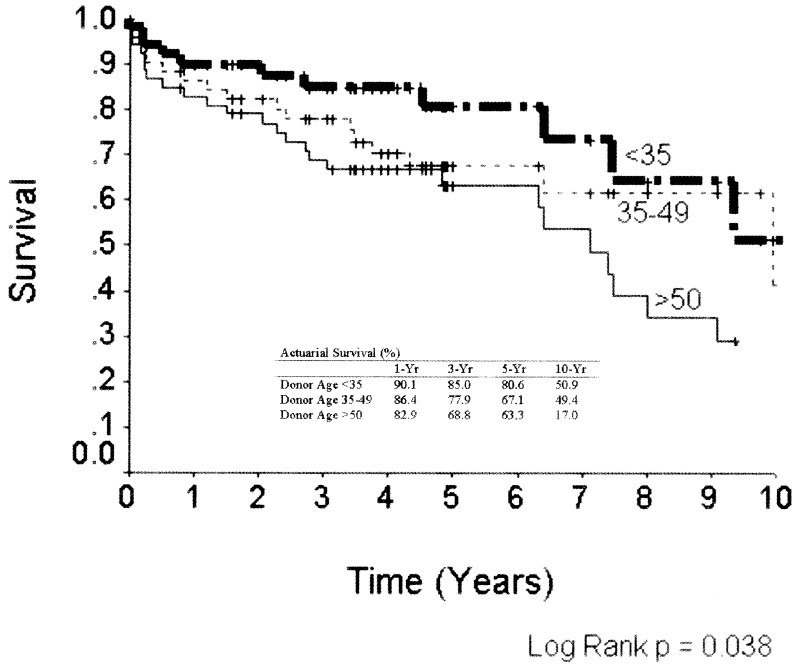

Figure 4. Effect of donor age on survival within DIT group 3. Advanced donor age adversely affected survival within DIT group 3, with median survival for patients with donor age < 35, 35 to 49, and >59 years of 10.4, 10.1, and 7.2 years, respectively.

TABLE 4. Univariate analysis of factors affecting survival

Variable	*P**
Recipient age	.946
Recipient gender	.012†
Recipient race	
Caucasian	.054
African American	.043†
Other	.686
CMV	.805
MFM	.466
LVAD	.778
DM	.309
Donor age	.034†
DIT	.353
DIT Group 1	.659
DIT Group 2	.847
DIT Group 3	.431
DIT Group 4	.434

CMV, Cytomegalovirus; *MFM,* male-female mismatch; *LVAD,* left ventricular assist device; *DM,* diabetes mellitus; *DIT,* donor ischemic time.
**P* value from Cox Regression univariate analysis.
†$P < .005$.

TABLE 5. Factors affecting survival by Cox proportional hazard models

Variable	OR	95% CI	*P*	SE
Recipient gender	1.281	0.856-1.694	.001	0.158

OR, Odds ratio; *CI,* confidence interval; *SE,* standard error.

hearts from distant locations with associated prolonged DIT.

We could not perform a statistical analysis on our relatively limited experience with DIT > 6 hours given the limitations of small sample sizes and statistical power. However, it may be time to expand the criteria for DIT to include hearts with DIT > 6 hours and evaluate the effect of DIT > 6 hours on survival, possibly by pooling data from a multicenter study. This would better define the limit to the duration that we can safely extend DIT without adversely affecting outcome.

We believe that suitability of donor hearts from distant locations should be evaluated on a case-by-case basis. Variables such as donor stability, inotropic use, and left ventricular function should be considered in the decision of whether to accept or reject a donor heart. Associated prolonged DIT should not, in and of itself, be an excluding factor given the similar long-term survival when comparing groups with different DIT. Moreover, hearts with associated prolonged DIT should not be exclusively reserved for sicker, unstable patients, as some have suggested.[21-23] In our series, there was not a tendency to implant hearts with

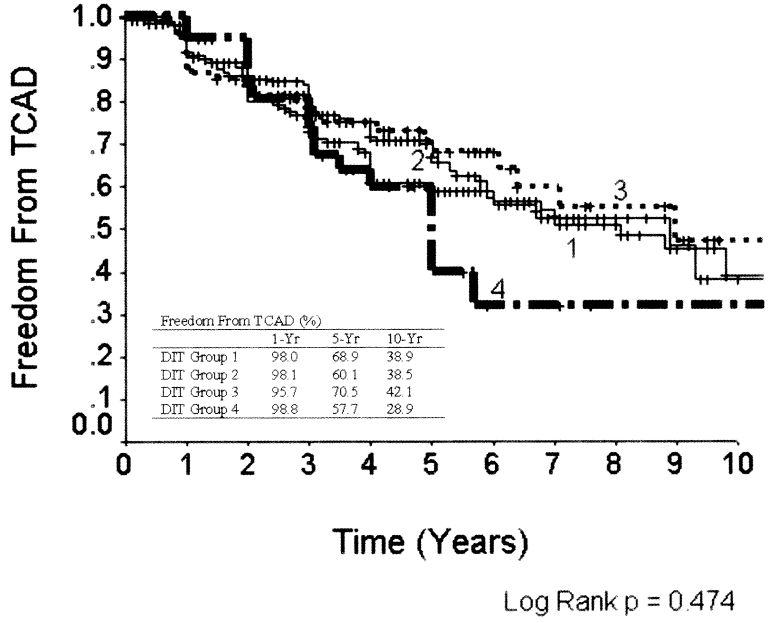

Figure 5. Effect of prolonged DIT on development of TCAD.

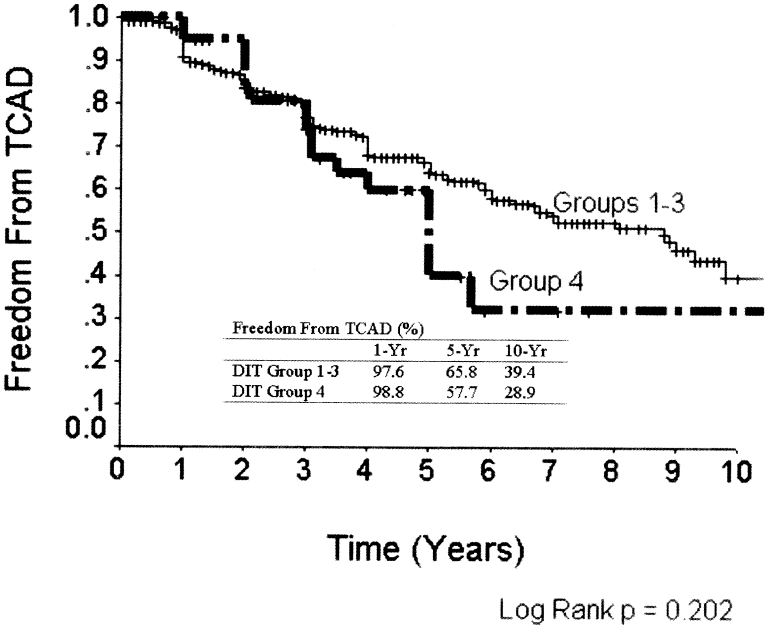

Figure 6. Effect of prolonged DIT on development of TCAD.

prolonged DIT into sicker recipients, as confirmed by the similar distribution of UNOS status across DIT groups. This may have been a contributing factor to the similarity in outcome. We believe that in view of the current donor shortage, attempts to increase the donor pool by evaluating donor hearts associated with prolonged ischemic times is warranted.

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