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SUDDEN DEATH AFTER PEDIATRIC HEART TRANSPLANTATION

Analysis of data from the Pediatric Heart Transplant Study Group

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Abstract

BACKGROUND

Sudden death is a well-recognized complication of heart transplantation. Little is known about the incidence and risk factors for sudden death following transplant in children. The purpose of this study was to determine the incidence of and risk factors for sudden death.

METHODS

Retrospective multi-center cohort study using the Pediatric Heart Transplant Study Group (PHTS) database, an event driven registry of children <18 years of age at listing undergoing heart transplantation between 1993 and 2007. Standard Kaplan-Meier and parametric analyses were used for survival analysis. Multivariate analysis in the hazard-function domain was used to identify risk factors for sudden death after transplant.

RESULTS

Of 2491 children who underwent heart transplantation, 604 died of which 94 (16%) were classified as sudden. Freedom from sudden death was 97% at 5 years and the hazard for sudden death remained constant over time at 0.01 deaths per year. Multivariate risk factors associated with sudden death include black race (HR 2.6; p<0.0001), UNOS Status 2 at transplant (HR 1.8; p=0.008), older age (HR 1.4 per 10 years of age; p=0.03), and an increased number of rejection episodes in the first post-transplant year (HR 1.6 per episode; p=0.03).

CONCLUSION

Sudden death accounts for one in six deaths after heart transplant in children. Older recipient age, recurrent rejection within the first year, black race, and UNOS status 2 at listing were associated with sudden death. Patients with one or more of these risk factors may benefit from primary prevention efforts.

BACKGROUND

Sudden death is a well-recognized mode of death after heart transplantation. Studies from adult heart transplant recipients report that between 9.7% and 58% of all post-transplant deaths are classified as sudden, with most reports putting the number between 15% and 40%.(1–5) Sudden death has been independently associated with cardiac allograft vasculopathy (CAV), acute cellular rejection, presence of Quilty lesion on endomyocardial biopsy (EMB), African-American ethnicity, and left ventricular dysfunction.(2, 4, 6–9) Several studies have suggested that primary prevention efforts, such as increased rejection screening and implantable cardiac defibrillator (ICD) placement, should be considered for these high-risk populations. (2, 5, 8, 10, 11)

Little is known about the incidence and risk factors for sudden death following heart transplant in children. Single institution experiences and Pediatric Heart Transplant Study (PHTS) registry data suggest that somewhere between 13% and 23% of deaths after heart transplant are sudden.(7, 12, 13) However, no focused pediatric analyses have been performed to examine the incidence of sudden death in children after transplant nor have multivariable risk factors for sudden death been delineated which could identify high-risk populations that may benefit from primary prevention efforts. The purpose of this study was to determine the incidence and risk factors for sudden death in children after heart transplant in hope of improving survival for pediatric heart transplant recipients.

METHODS

Study Population and Data Source

Children who underwent orthotopic heart transplantation in the United States between January 1, 1993 and December 31, 2007 were identified retrospectively using the PHTS Database. The PHTS Database is a prospectively maintained database of all patients <18 years of age listed for heart transplant at 31 international heart transplant centers. Demographic and clinical information are forwarded to the University of Alabama at Birmingham Medical Center Data Coordinating Center where they are reviewed and entered. Children who underwent heart re-transplantation or multi-organ transplantation were excluded from the analysis. All patients were followed from the time of heart transplant until death or the last day of observation on December 31, 2007. Institutional Review Board approval or a waiver was obtained at each site. Informed consent was obtained when required by individual Institutional Review Boards.

Study Definitions and Outcome Measures

The specific aim of the study was to identify the incidence and risk factors for sudden death among children undergoing heart transplant. All transplant centers categorized death using standard data collection forms as described on the PHTS website (http://www.uab.edu/ctsresearch/phts/). The PHTS Manual of Operations utilizes the American Heart Association sudden death definition, which is: "Death resulting from an abrupt loss of heart function (cardiac arrest). The victim may or may not have diagnosed heart disease. The time and mode of death are unexpected. It occurs within minutes after symptoms appear." The endpoint of sudden death was over-read by consensus of two authors (SC, CSA) using all available patient data provided to the registry. The primary outcome variable was time to death. Patients were censored at the time of re-transplant. All clinical and demographic variables were defined at the time of transplant unless otherwise specified. Race/ethnicity data, rejection episodes, and cause of death were analyzed as reported by the individual transplant centers. Risk factor analysis was carried out in a sub-group of patients conditional upon survival to one year allowing for the addition of number of episodes of rejection to the model. Risk factors examined included indication for heart transplantation, mechanical support status, surgical history at listing, clinical condition at listing (renal insufficiency, failure to thrive, etc.), pre-transplant hemodynamics, and donor characteristics. All risk factors that were significant in multivariable analysis are reported.

Statistical Analysis

Summary statistics are presented as median (interquartile range [IQR]) or number (percent). Patient characteristics were compared using Fisher's Exact test for categorical variables and the student t-test for continuous variables. Univariate relationships between patient characteristics and post-transplant death were evaluated using the log-rank test. Standard Kaplan-Meier and parametric analyses were used for survival analysis. Multivariate analysis in the hazard-function domain was used to identify risk factors for sudden death after transplant. Risk factors that were statistically significant at the 0.05 level were retained in the final model. Data was analyzed using statistical software SAS version 8.2 (SAS Institute Inc, Cary, NC).

RESULTS

Subjects

Between January 1993 and December 2007, a total of 2,491 children underwent heart transplantation and were entered into the PHTS database. Table 1 summarizes the characteristics of the study cohort, at the time of transplant, grouped by whether or not the patients experienced a sudden death. Overall, the median age of children who experienced sudden death was 6.1 years (IQR 12.3), 50% were female, 30% were black, 38% were transplanted as United Network for Organ Sharing (UNOS) status 2, 13% were on ventilator support, 6% were on ECMO and 5% were on VAD support at the time of transplant.

Table 1

Baseline characteristics, at the time of heart transplant, of the study cohort grouped by whether or not the patient experienced a sudden death (N=2491).

Patient Characteristic	Sudden Death (N=94)	All Others (N=2397)
Age, years (Median, IQR)	6.1, 12.3	3.2, 11.8
Weight, kg (Median, IQR)	18.3, 28.4	12.5, 30.8
Gender, Female, *n* (%)	47 (50)	1030 (43)
Race, *n* (%)		
Black	28 (30)	373 (16)
White	53 (56)	1753 (73)
Other	13 (14)	271 (11)
Diagnosis of CHD, *n* (%)	51 (54)	1253 (52)
Intravenous inotropic support, *n* (%)	43 (46)	1260 (53)
Ventilator support, *n* (%)	12 (13)	463 (19)
VAD support, *n* (%)	5 (5)	169 (7)
ECMO support, *n* (%)	6 (6)	161 (7)
UNOS Status 2, *n* (%)	36 (38)	457 (19)
Year of Listing, *n* (%)		
1993–1997	51 (54)	653 (27)
1998–2002	32 (34)	783 (33)
2003–2007	11 (12)	961 (40)

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IQR, interquartile range; CHD, congenital heart disease; VAD, ventricular assist device; ECMO, extra-corporeal membrane oxygenation; UNOS, United Network for Organ Sharing;

During the study period there were a total of 604 deaths (24%) of which 94 (16% of total deaths) were classified as sudden death. Table 2 shows the number of pediatric deaths grouped by time interval since heart transplant. During the first year post-transplant 33 of 335 deaths (10%) were categorized as sudden, between 1 and 5 years post-transplant 39 of 166 (23%) of deaths were sudden, between 6 and 10 years 19 of 85 (22%) were sudden; beyond 10 years 3 of 18 (1%) of deaths were sudden.

Table 2

Classification of death stratified by time interval post heart transplant. Percentages utilize total number of deaths within a given column as the denominator.

	Time Post-Transplant – N (%)				
	Overall (N=604)	**0–11 mo (N=335)**	**1–5 yr (N=166)**	**6–10 yr (N=85)**	**>10 yr (N=18)**
Sudden Death	94 (16)	33 (10)	39 (24)	19 (22)	3 (17)
Acute Rejection	104 (17)	47 (14)	34 (20)	20 (24)	3 (17)
Infection	89 (15)	64 (19)	18 (11)	7 (8)	0 (0)
PTLD	13 (2)	4 (1)	3 (2)	3 (4)	3 (17)
Myocardial infarction	51 (8)	5 (1)	21 (13)	20 (24)	5 (28)
Non-specific graft failure	80 (13)	70 (21)	9 (5)	1 (1)	0 (0)
Other	173 (29)	112 (34)	42 (25)	15 (17)	4 (22)

PTLD, Post transplant lymphoproliferative disorder

Freedom from sudden death

Figure 1 depicts the freedom from sudden death for children undergoing heart transplantation using the Kaplan-Meier methodology and the instantaneous mortality hazard from sudden death as a function of time since transplant. Freedom from sudden death was 98% at 1 year, 95% at 5 years and 92% at 10 years post-transplant. The hazard for mortality from sudden death remained constant over the time period post-transplant at 0.01 deaths per year.

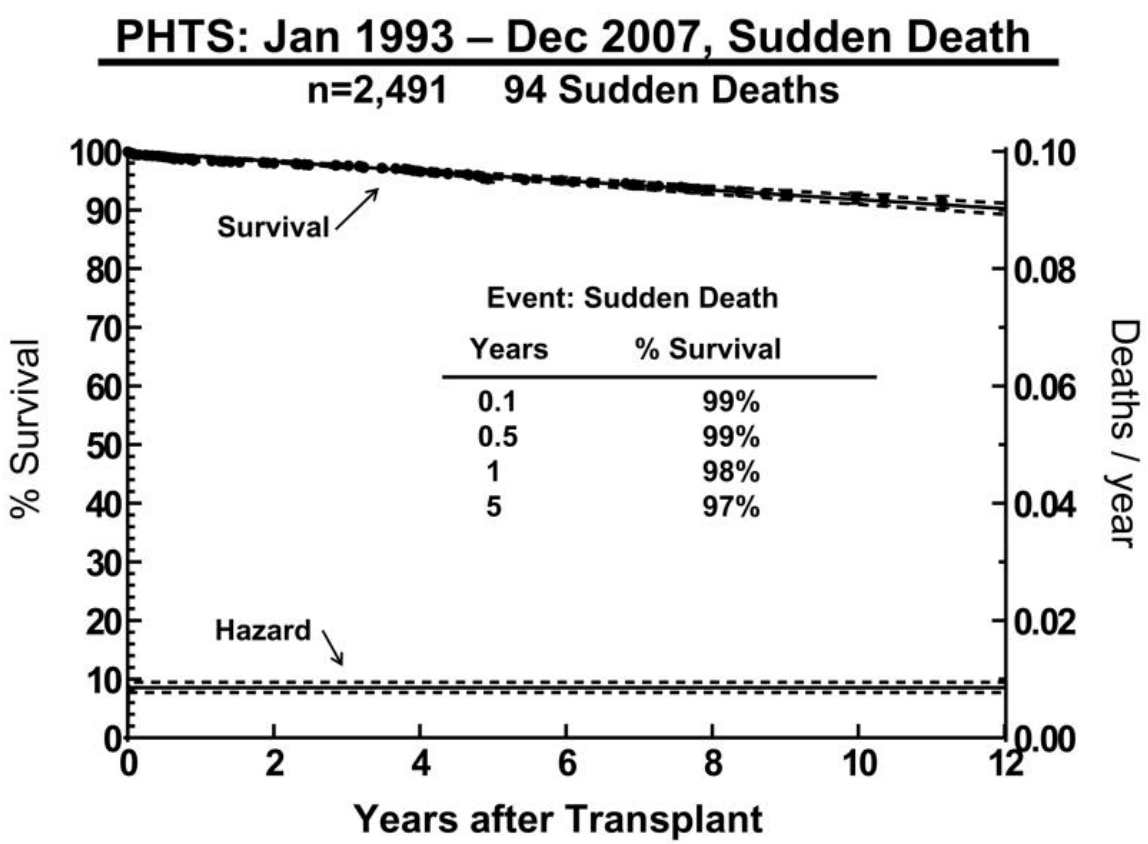

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Figure 1

Kaplan-Meier freedom from sudden death and hazard of sudden death post-transplant.

Risk factors for sudden death at the time of heart transplant

Table 3 summarizes the univariate and multivariate risk factors for sudden death after pediatric heart transplantation for the entire cohort. When compared to patients who did not experience sudden death (N=2390), the univariate predictors of sudden death included older recipient age, black race, UNOS Status 2 at transplant, shorter graft ischemic time, and older donor age. Multivariable predictors of sudden death included black race (HR 2.61; $p < 0.0001$), UNOS Status 2 at transplant (HR 1.80; $p=0.008$) and older recipient age (HR 1.39 for each additional 10 years; $p=0.03$).

Table 3

Risk factors at the time of transplant associated with subsequent sudden death (N=94 of 2491).

	Univariate Risk Factors		Multi-variate Risk Factors	
	HR	**p-value**	**HR**	**p-value**
Patient Characteristics				
Age[a]	1.51	0.0007	1.39	0.03
Gender, Female	1.49	0.06		
Black race	3.95	<0.0001	2.61	<0.0001
Ventilator support	0.08	0.36		
VAD support	1.17	0.75		
ECMO support	1.42	0.47		
UNOS Status 2	2.30	0.0006	1.80	0.008
Donor Characteristics				
Age[a]	1.31	0.02		
Female gender	1.39	0.12		
Black race	0.94	0.82		
Graft ischemic time[b]	0.85	0.03		
Year of transplant[c]	0.6	0.06		

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HR, hazard ratio; VAD, ventricular assist device; ECMO, extra-corporeal membrane oxygenation; UNOS, United Network for Organ Sharing;

[a]HR for each additional 10 years of age
[b]HR for each additional 2 hours of ischemic time
[c]HR for patients transplanted in 2005 compared to a reference group of patients transplanted in 1995

Risk factors for sudden death conditional upon survival to one year post-heart transplant

A subgroup analysis of patients who survived to one year post-heart transplant is summarized in Table 4. Older donor age, black race, UNOS Status 2 at transplant, older donor age, shorter graft ischemic time and an increased number of rejection episodes in the first year after heart transplant were significant univariate risk factors for sudden death after heart transplant. Multivariate modeling showed black race (HR 2.39; p=0.002), older recipient age (HR 2.39 for each additional 10 years; p=0.0003) and an increased number of episodes of graft rejection in the first year after transplant (HR 1.63 per additional episode; p=0.03) as the most important risk factors for sudden death.

Table 4

Risk factors associated with sudden death (N=61) after heart transplant conditional upon survival to one year (Patients without sudden death N=1805).

	Univariate Risk Factors		Multi-variate Risk Factors	
	HR	**p-value**	**HR**	**p-value**
Patient Characteristics (at time of transplant)				
Age[a]	1.94	<0.0001	2.14	0.0003
Female gender	1.20	0.48		
Black race	4.27	0.0001	2.39	0.002
Ventilator support	0.80	0.53		
VAD support	1.21	0.77		
ECMO support	2.30	0.17		
UNOS Status 2	2.56	0.002		
Donor Characteristics				
Age[a]	1.68	0.0005		
Female gender	1.13	0.65		
Black race	0.66	0.24		
Graft ischemic time[b]	0.80	0.02		
Year of transplant[c]	0.57	0.13		
Rejection episodes in the first year after heart transplant[d]	2.35	0.001	1.63	0.03

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HR, hazard ratio; VAD, ventricular assist device; ECMO, extra-corporeal membrane oxygenation; UNOS, United Network for Organ Sharing;

[a]HR for each additional 10 years of age
[b]HR for each additional 2 hours of ischemic time
[c]HR for patients transplanted in 2005 compared to a reference group of patients transplanted in 1995
[d]HR for each additional episode of rejection in the first year

Number of risk factors correlates with freedom from sudden death in pediatric heart transplant recipients

Utilizing variables that were significant in multivariate analysis, freedom from sudden death was modeled based on the number of pre-transplant risk factors (Figure 2). For patients who had all three risk factors (recipient age > 1 year, black race, and UNOS Status 2 at transplant), the freedom from sudden death was 78% at 10 years. Freedom from sudden death was also modeled using number of

episodes of rejection in the first year post-heart transplant (Figure 3). This model suggests that patients with two or more episodes of rejection in the first year are at increased risk for sudden death in the 1–5 year post-transplant period. Patients who had two episodes of rejection in the first year had the worst freedom from sudden death beyond 5 years post-transplant.

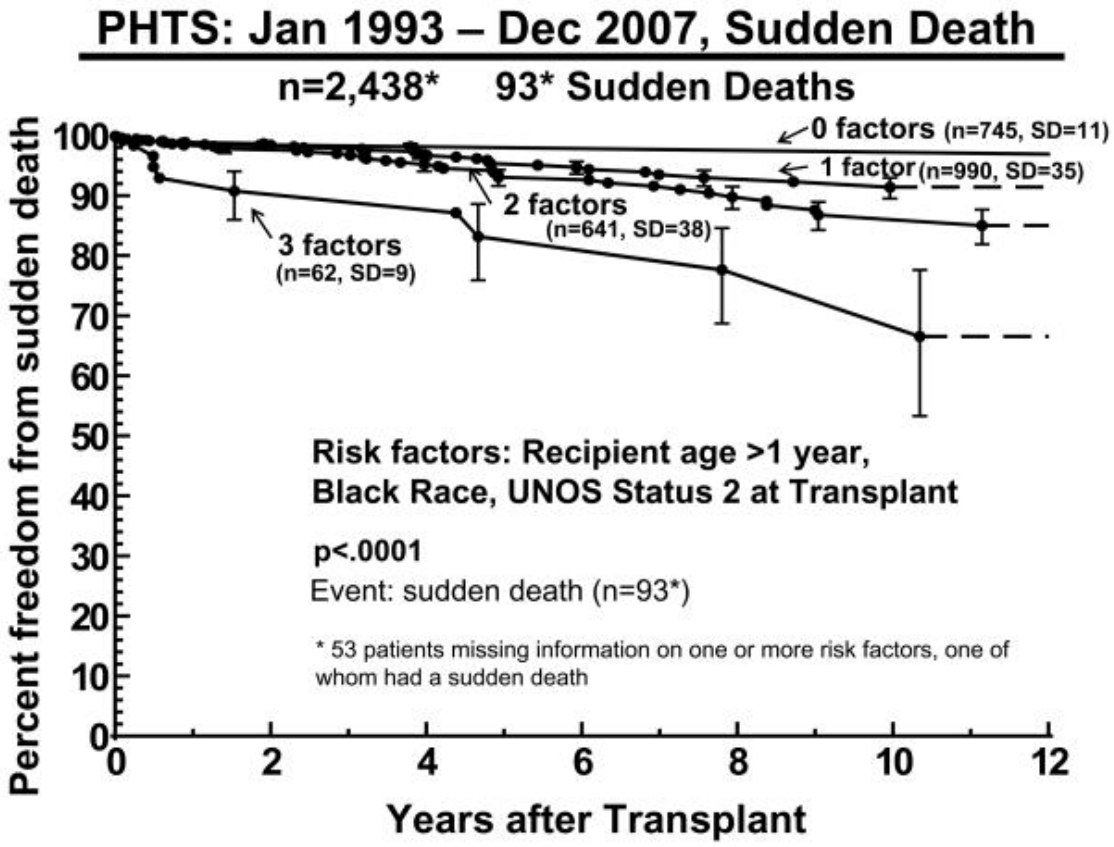

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Figure 2

Kaplan-Meier freedom from sudden death post-heart transplant stratified by number of pre-transplant patient risk factors. Risk factors used in the model were recipient age > 1 year, black race, and UNOS Status 2 at transplant.

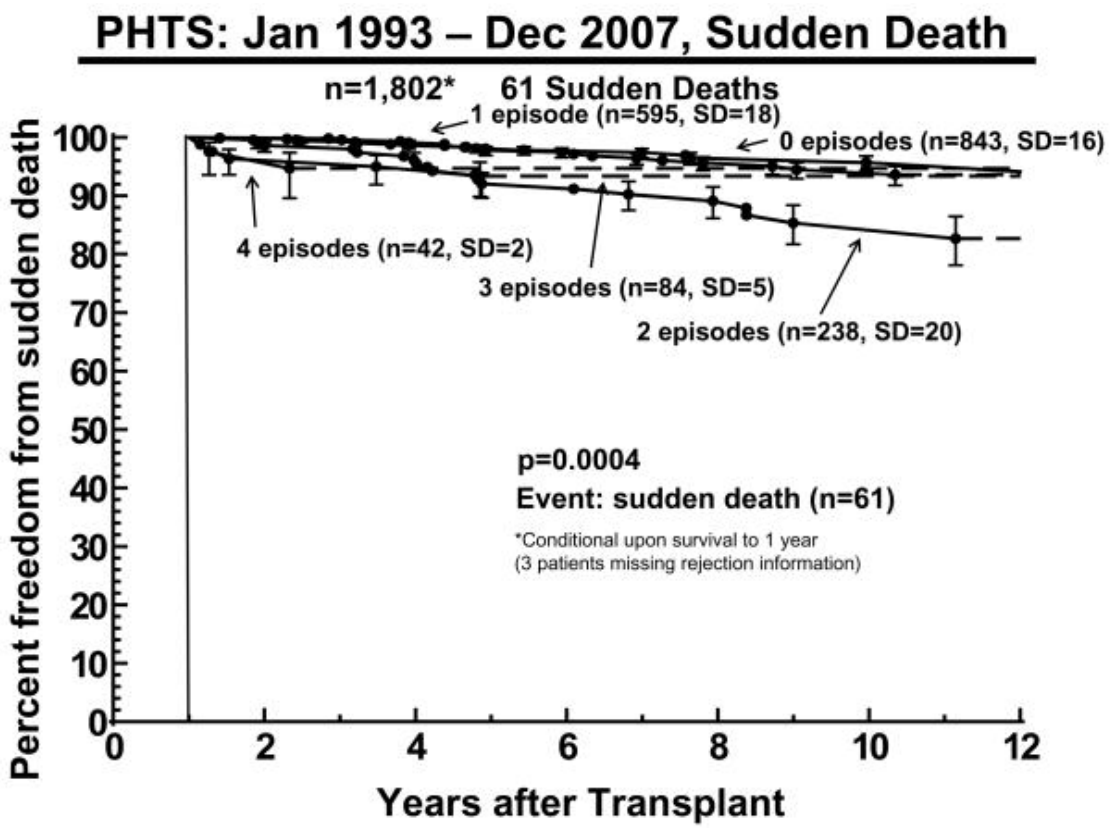

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Figure 3

Kaplan-Meier freedom from sudden death post-heart transplant stratified by number of episodes of rejection in the first year post-transplant.

DISCUSSION

Summary

In this study we found that, while the overall incidence of sudden death is low, sudden death accounts for one in six post-heart transplant deaths amongst pediatric recipients. The risk of sudden death remains constant over time at 0.01 deaths per patient year. We identified black race, UNOS Status 2 at time of transplant, older age, and an increased number of rejection episodes in the first year after heart transplant as independent risk factors for sudden death in pediatric heart transplant recipients.

The proportion of deaths classified as sudden in the present analysis is consistent with previous pediatric reports. Zuppan *et.al.* retrospectively examined the causes of death in 421 pediatric heart transplant recipients at Loma Linda University Medical Center over a 20 year period.(12) Thirty-nine of the 169 deaths (23%) were classified as sudden. Prior reports from the PHTS database estimated that 13% of deaths were sudden.(7) We systematically classified patients and found that 16% of all deaths were sudden in our cohort. The incidence of sudden death after heart transplantation in children is approximately half the incidence reported in adults. Adult heart transplant series have shown that approximately 35% of post-transplant deaths occur suddenly.(2, 3, 5) In addition, the overall incidence of sudden death at 5 years post transplant is reported to be 5% in adults.(5)

Acute cellular rejection is an established cause of sudden death in both adult and pediatric heart transplant recipients.(5, 8, 12, 14, 15) In addition, early rejection is associated with decreased graft survival and increased 5 year mortality.(16, 17) Adult series have identified acute cellular rejection in the first year as an important risk factor for sudden death in heart transplant recipients.(2, 8) Therefore, it is not surprising that a history of rejection within the first year after heart transplant is associated with an increased risk of sudden death. This may be due to a primed immune system capable of recurrent episodes of rejection or to the sequelae of early severe rejection, such as cardiac allograft vasculopathy. In fact, acute cellular rejection (56%) and cardiac allograft vasculopathy (CAV) (23%) accounted for the majority of cases of sudden death in the pediatric series from Loma Linda.(12)

We were unable to find an association between sudden death and CAV in our cohort as has been described in reports of risk factors for sudden death in adult heart transplant recipients.(2, 8, 9, 14) CAV is a well established risk factor for graft loss and death in pediatric series.(12, 18, 19) One pediatric case series found a very high incidence of sudden death or aborted sudden death in patients with CAV.(20) We believe that this lack of association may be due to a combination of low prevalence of CAV in our series and PHTS form coding requirements. The reported annual incidence of CAV in the PHTS cohort varies between 2 and 10% depending on the post-transplant year and is below 5% in the first post-transplant year.(18) By examining sudden death as a time varying hazard based on risk factors present one year after heart transplant, the incidence of CAV is too low to be assessed as a meaningful risk factor. Alternatively, we could have examined the cause of death in patients who died suddenly. However, since sudden death is listed as a cause of death on PHTS data collection forms, frequently no secondary cause of death is cited. Despite our inability to associate CAV with sudden death in the current study, we believe that CAV plays a role in the pathogenesis of sudden death after pediatric heart transplantation.

We found black race to be one of the strongest predictors of sudden death in our study. Black race has been associated with late rejection and graft failure and continues to be an important risk factor for worse outcomes after pediatric heart transplantation.(13, 21–24) Since acute cellular rejection is the underlying cause of sudden death in several series and black race has been associated with acute cellular rejection, we were not surprised that black race was associated with sudden death.(7, 12) Studies suggest that socioeconomic status plays a role in the higher incidence of rejection and graft loss in blacks; however race remains an important predictor even after controlling for this covariate.(21, 25, 26) Investigators have speculated that an increase in the number of HLA mismatches in black recipients and a predisposition to a pro-inflammatory host environment may contribute to decreased graft survival in black heart transplant recipients.(22–24, 27)

While black race and a history of early rejection appear to be risk factors for sudden death, transplantation early in life appears to be protective. This finding is expected as patients transplanted in infancy have fewer episodes of late rejection and improved late graft survival.(12, 13, 15) It is possible that tolerance of the allograft by the relatively immature immune system in younger patients leads to fewer episodes of rejection with a resultant decrease in the incidence of sudden death.(28)

We found the association of transplantation as a UNOS Status 2 with sudden death surprising, but consistent with findings from prior studies.(25) There is no clear pathophysiologic basis for why patients transplanted as a UNOS Status 2 would be at increased risk for sudden death, or when viewed in the inverse manner, why meeting pre-transplant criteria to qualify as a Status 1 would be protective from sudden death. This leads us to speculate that patients who are transplanted as a Status 2 may experience more rapid memory fatigue regarding how sick they were pre-transplant. This may adversely affect compliance with immunosuppressive medications. If such a phenomenon did occur, non-compliance could lead to acute rejection and sudden death.

Persistence of pulmonary hypertension after heart transplantation, a possible risk factor for sudden death, also deserves consideration. This variable is not collected in the PHTS database following transplant and therefore would not have been identified as a risk factor in this study design. However, we did not find an association between pre-transplant PVR and sudden death.

Role of Implantable Cardiac Defibrillators

Primary and secondary prevention efforts for sudden death in heart failure patients have traditionally focused on ventricular arrhythmia. However, the epidemiology of arrhythmia in the post-transplant population is markedly different than the heart failure population. Ventricular tachyarrhythmias can be seen in the context of acute cellular rejection, CAV, and LV dysfunction, all of which have been linked to sudden death in pediatric and adult studies.(5, 8–10, 12, 29) Vaseghi *et.al.* examined the mode and mechanisms of death in a single institution cohort of adult heart transplant patients.(5) By defining any death up to 24 hours after onset of symptoms as sudden and using all available data sources, the investigators documented the first abnormal rhythm at the time of death in 26 patients. Only 4 patients (10% of the cohort) experienced ventricular tachycardia (VT) or ventricular fibrillation (VF), rhythms which are typically responsive to electrical cardioversion. It is possible that that some patients who experienced paroxysmal VT/VF may have been missed with this study design if they did not have an ICD in place. The authors reported that patients who experienced VF were most likely to have experienced rejection or sepsis while patients with CAV and myocardial ischemia were more likely to experience pulseless electrical activity. It has been suggested that cardiac denervation in transplant patients may be partially responsible for the decreased incidence of VT/VF. (29–32)

In adult heart transplant patients, there does seem to be a role for ICDs in highly selected patient populations. Tsai *et.al.* reported that among of 36 adult heart transplant recipients with an ICD in place, 8 patients had an appropriate ICD discharge.(10) All 8 patients had received ICD implantation for CAV with > 50% obstruction of at least one large epicardial coronary artery. Because the data in support of CAV as a risk factor for sudden death in pediatric heart transplant recipients is not strong, the adult transplant experience with ICDs is not directly applicable to pediatric patients. However, in patients with advanced CAV, an increased frequency of arrhythmia screening via Holter monitoring may be warranted.

Limitations

The study has several limitations related to the study design. First, this was a retrospective analysis and is vulnerable to ascertainment bias. However, because the PHTS registry is prospectively-maintained, captures a large majority of North American transplants and is regularly audited, it is unlikely that ascertainment bias played a significant role in the findings of the study. Second, the diagnosis of sudden death was made clinically by transplanting centers using standard data collection forms and therefore could be susceptible to misclassification bias. Two potential study misclassification scenarios merit consideration; (1) an unwitnessed death at home could have been preceded by several days of a rejection prodrome for which the patient did not seek medical attention, leading clinicians to perceive the event as sudden even though it was not; (2) a sudden death event occurring in the context of myocardial infarction which may not have been coded as sudden according to the PHTS Manual of Operations which disallows reporting of sudden death if there is evidence of myocardial infarction. While the first is an example of random misclassification that biases the results toward the null, the second is an example of non-random bias that may account, in part, for why we found no association between coronary artery vasculopathy and sudden death. Nevertheless, we believe the broader findings of the present study are valid because transplanting centers were provided with a single, widely-accepted clinical definition of sudden death and consensus classification of deaths as sudden would have properly reclassified some of the deaths which were both sudden, and due to myocardial

infarction, based on the totality of the available clinical information. Lastly, because the prevalence of CAV in our population was relatively low at 1 year post-transplant, type II statistical error could contribute to a lack of association between CAV and sudden death.

Implications

The findings of this study have several important implications. First, while the overall incidence of sudden death is low (Figure 1); sudden death accounts for 16% of pediatric transplant deaths overall, a considerable fraction of the overall mortality after pediatric heart transplant. Our findings identify specific high-risk subgroups where targeted primary prevention efforts may be beneficial. Figure 2 displays freedom from sudden death stratified by the number of pre-transplant risk factors (black race, UNOS Status 2, recipient age greater than 1 year). The risk of sudden death is approximately 15% at 5 years in patients who carry all three pre-transplant risk factors. In addition, patients can be stratified post-transplant based on the number of episodes of early rejection (Figure 3). This reinforces the concept that patients who experience early rejection are at higher risk for sudden death. In patients who have several risk factors, strategies aimed at reducing the risk of graft rejection, such as increased frequency of rejection screening, increased intensity of immunosuppression, more frequent follow up visits, patient and family education to minimize non-adherence, and intensive patient and family education about the early signs of rejection, are likely to be of benefit.

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Footnotes

Disclosures: The authors have no disclosures or conflicts of interest.

Disclosure statement

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