

# Impact of Donor Spontaneous Intracranial Hemorrhage on Outcome after Heart Transplantation

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**Donor cause of death has been suggested to have a significant impact on cardiac transplant morbidity and mortality. Our objective was to evaluate the impact of donor spontaneous intracranial bleeding on clinical outcome after heart transplantation. A group of 160 recipients underwent cardiac transplantation from donors with spontaneous intracranial bleeding (ICB group). These were compared with 197 recipients who were transplanted from trauma donors (Trauma group). A higher 4-year mortality rate was noted in the ICB group (24% vs. 14%,  $p = 0.015$ ). ICB as a cause of donor death was an independent predictor of recipient mortality (adjusted hazard ratio 2.02, 95% CI 1.27–3.40,  $p < 0.0001$ ). Compared with the Trauma group, the ICB group had an increased incidence of post-transplant graft dysfunction during the first week of transplant (10% vs. 3%,  $p = 0.007$ ), and higher incidence of interstitial myocardial fibrosis on their endomyocardial biopsies within 4 weeks of transplant (21% vs. 9%,  $p = 0.0012$ ). There was a trend towards an increased rate of allograft vasculopathy in the ICB group (competing risks adjusted hazard ratio 1.39, 95% CI 0.90–2.13,  $p = 0.14$ ).**

**Key words:** Allograft vasculopathy, heart transplantation, intracranial bleeding

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Compared with trauma donors, donor spontaneous intracranial bleeding is associated with an increased inci-

dence of graft dysfunction and interstitial fibrosis along with poorer long-term recipient survival.

Donor cause of death has been suggested to have a significant impact on morbidity and mortality after cardiac transplantation (1). Several experimental animal models have demonstrated impairment of myocardial function and hemodynamic performance after brain death (2–4). Atraumatic intracranial bleeding, which occurs in approximately 39% of brain death donors, has been found to be a potential independent risk factor for early mortality after cardiac transplantation (5). Although the exact causes of cardiac dysfunction after brain death remain unknown, one proposed pathophysiologic mechanism is the excessive catecholamine surge that accompanies the endocrine perturbations associated with intracranial bleeding (2–4,6–8). We evaluated the impact of donor spontaneous intracranial bleeding on outcome after cardiac transplantation.

## Materials and Methods

### Patient population

Between January 1995 and December 2000, a group of 160 transplant recipients received hearts from donors with spontaneous atraumatic intracranial bleeding (ICB group). These were compared with 197 recipients who received hearts from trauma donors (Trauma group) who were involved in car accidents or sustained head trauma related to a fall or had a gun shot wound (homicide or suicide). Forty-two recipients (cause of donor death: seizure,  $n = 3$ ; asphyxiation,  $n = 3$ ; drug intoxication,  $n = 5$ ; brain infarct,  $n = 28$ ; brain tumor,  $n = 3$ ) did not meet the above criteria and were excluded from the analysis (5-year survival in this subgroup of 42 patients was 80%). Information regarding donor and recipient age, etiology of heart failure, mode of donor death, ischemia time, use of left ventricular assist device and immunosuppression was obtained from The Cleveland Clinic Foundation Cardiac Transplant Database which is approved by the Institutional Review Board of our institution.

### Endomyocardial biopsies

All patients underwent serial endomyocardial biopsies. An average of 13 biopsies was performed in each patient during the first year after transplantation as part of the routine endomyocardial biopsy surveillance protocol to monitor for acute rejection. The heart biopsy was evaluated for acute rejection, and presence of ischemic injury and interstitial fibrosis. The pathologist was blinded to the mechanism of donor brain death. No scoring or quantification of fibrosis was performed. However, this was documented on H&E stain as the presence of interstitial myocardial fibrosis excluding Quilty lesions or findings consistent with 'prior myocardial biopsy site'.

### Echocardiography

According to routine protocol, an echocardiography was done during the first week in all patients to evaluate left ventricular function.

**Coronary angiography**

Cardiac catheterization was performed at baseline (within 1 month of transplant) and annually. Coronary vasculopathy was classified as mild (coronary obstruction < 50%), moderate (coronary obstruction 50% to 70%) or severe (coronary obstruction > 70%).

**Follow-up**

The patients were followed up for a median period of 4.4 (range 0.02–7.2) years. No patients were lost to follow-up.

**Statistical analyses**

Quantitative data are presented as mean  $\pm$  SD. Categorical variables were compared using the chi-square or Fisher's exact test as appropriate. Continuous variables were compared using Wilcoxon's rank sum test.

The primary survival endpoint was all-cause death. Unadjusted differences in time to death were assessed by construction of Kaplan–Meier plots (9) and calculation of the log-rank chi-square statistic. After confirming the validity of the proportional hazards assumption by examination of weighted Schoenfeld residuals, Cox regression modeling (10) was performed to determine whether or not the cause of donor death was independently associated with recipient survival. We sought to adjust for recipient age, recipient sex, recipient race, donor age, donor sex, donor race, preoperative use of a left ventricular assist device, total ischemia time, PRA > 10 (yes or no), the type of immunosuppressive regimen, recipient diabetes, recipient hypertension, recipient hyperlipidemia and, in supplementary analyses, early recipient cytomegalovirus (CMV) disease.

As there were only 77 recipient deaths and we wished to account for 14 potential confounders, there was concern of model over-fitting (11). We therefore adopted three strategies to avoid this. First, we performed standard stepwise proportional hazards modeling using PROC PHREG but maximizing the number of allowed iterations to eight, thereby reducing the number of potential covariates to  $\leq 10$  per event. Second, we performed a propensity analysis (12,13). Here, we used nonparsimonious logistic regression (14) to model cause of donor death as a function of the 14 covariates just listed, but not as a function of recipient outcome. This enabled us to generate a propensity score for each individual patient that described the probability that the patient's donor heart came from a patient who died of an intracranial hemorrhage; this propensity score could range in value from 0 to 1. The c-statistic for the logistic model was 0.86 indicating excellent discrimination. We then divided the population into quintiles based on the propensity score and within each quintile further subdivided according to the cause of donor death. There was very good matching of baseline characteristics (as well as mean propensity score and propensity score variance) in the top four quintiles. Cox proportional hazards modeling (10) was performed among the patients in the top four quintiles of propensity score; in this analysis the only independent variables were cause of donor death and the propensity score. This approach makes it possible to effectively collapse many confounding covariates into just one, namely the propensity score, and thereby essentially eliminate concerns of model over-fitting (15).

Third, we used a bagging bootstrap approach (16). Here we used random selection and replacement to create 1000 bootstrap data sets in which each set had 80% of the number of observations as the main cohort. A Cox proportional hazards model was generated for each of these 1000 data sets using stepwise variable selection (17). Those variables that entered at least 50% of models were incorporated into a second set of 1000 bootstrap analyses to estimate hazard ratios and 95% confidence intervals.

For all three of these Cox modeling strategies we formally tested interaction terms relating cause of donor death with each of the 14 potential confounders to determine whether any effect modification was present.

A secondary endpoint was time free of angiographic evidence of graft vasculopathy. This was also analyzed by construction of Kaplan–Meier curves (9), calculation of the log-rank chi-square statistic and Cox proportional hazards modeling (10). An important problem for this endpoint was that of competing risks: a patient who died before having manifested coronary disease on an angiogram could not longer undergo a coronary angiogram that might show disease. We used formal competing risks analyses to account for this (18).

Supplementary analyses were performed to examine the association of cause of donor death with the occurrence of graft dysfunction during the first postoperative week and interstitial myocardial fibrosis during the first 4 weeks. Logistic regression modeling was used to account for potential confounders; because of the relatively small numbers of patients with these secondary endpoints and risk of model over-fitting, confounders were accounted for by adjusting solely for the propensity score for intracranial bleed as the cause of death among donors (15).

A p-value < 0.05 was considered to be significant for all analysis. Analyses were performed using the SAS 8.2 system (SAS Inc.).

**Results**

The ICB group had significantly increased donor age and more female donors compared with the Trauma group (Table 1). There were no significant differences in the immunosuppression regimens, or differences in acute cellular or acute vascular rejection.

**Survival**

During follow-up there were 77 deaths; causes of recipient death according to cause of donor death are listed in Table 2. As shown in Figure 1, survival was markedly worse among patients in the ICB group (4-year Kaplan–Meier mortality rates 24% vs. 14%, unadjusted hazard ratio 1.76, 95% CI 1.11–2.78,  $p = 0.016$ ). After adjusting for potential confounders using standard stepwise selection but maximizing the number of iterations at eight, ICB as a cause of donor death remained independently predictive of worse recipient survival (adjusted hazard ratio 2.03, 95% CI 1.24–3.32,  $p = 0.0048$ ). Similarly, in the propensity-score adjusted Cox model ICB independently predicted death (adjusted hazard ratio 1.93, 95% CI 1.02–3.64,  $p = 0.04$ ).

In the bootstrapping analysis, there were only three variables that successfully entered at least 50% of stepwise selection Cox models: recipient hypertension (91%), ICB as cause of donor death (75%) and recipient diabetes (64%). Of note, donor age only entered 14% of models while donor sex entered only 38%. Again, ICB as a cause of donor death emerged as an independent predictor of recipient death (adjusted hazard ratio 2.02, 95% CI 1.27–3.40,  $p < 0.0001$ ).

No important interactions were noted between donor cause of death and any of the considered potential confounders. In particular we found no interaction with gender mismatch. There were only 22 deaths among

**Table 1:** Baseline characteristics

Variable	Trauma (n = 197)	ICB (n = 160)	p-value
<b>Demographics and history of donor</b>			
Age, mean (SD), years	28 ± 13	44 ± 11	<0.001
Men, no. (%)	140 (71)	52 (32)	<0.001
Ischemia time (min), mean (SD)	161 ± 47	176 ± 49	0.01
<b>Demographics of recipient</b>			
Age, mean (SD), years	52 ± 14	55 ± 12	0.02
Men, no. (%)	163 (83)	132 (82)	0.95
<b>Clinical history of recipient</b>			
<b>Etiology of heart failure</b>			
Ischemic cardiomyopathy, no. (%)	110 (56)	93 (58)	0.67
Dilated cardiomyopathy, no. (%)	81 (41)	64 (40)	0.83
Other, no. (%)	6 (3)	3 (2)	0.48
Left ventricular assist device, no. (%)	65 (33)	42 (26)	0.17
Diabetes mellitus, no. (%)	41 (21)	36 (22)	0.70
Hypertension, no. (%)	98 (50)	83 (52)	0.69
Hyperlipidemia, no. (%)	101 (51)	87 (54)	0.56
<b>Immunology/rejection</b>			
CMV disease, no. (%)	14 (7)	20 (12)	0.08
Panel reactive antibodies >10%, no. (%)	30 (15)	26 (16)	0.79
Episodes of acute cellular rejection, Grade ≥ 3 A, mean (SD)	1.9 ± 2.0	1.9 ± 1.9	0.83
Incidence of acute vascular rejection (%)	16 (8)	11 (7)	0.66
<b>Medication/immunosuppressant use</b>			
Imuran/CSA/prednisone, no. (%)	49 (25)	31 (19)	0.22
MMF/CSA/prednisone, no. (%)	107 (54)	91 (57)	0.63
MMF/tacrolimus/prednisone, No. (%)	41 (21)	38 (24)	0.51

CMV: cytomegalovirus; CSA: cyclosporine; MMF: mycophenolate mofetil.

**Table 2:** Causes of death

	Trauma (n = 30)	ICB (n = 47)	p-value
Cardiac: GF/MI/SD, no. (%)	9 (30)	28 (59.6)	0.011
Malignancy, no. (%)	9 (30)	5 (10.6)	0.032
Acute rejection, no. (%)	5 (17)	5 (10.6)	NS
Infection, no. (%)	3 (10)	3 (6.4)	NS
Multiorgan failure, no. (%)	2 (6.7)	3 (6.4)	NS
Others, no. (%)	2 (6.7)	3 (6.4)	NS

GF: graft failure; MI: myocardial infarction; SD: sudden death.

male recipients who received hearts from female donors (age-adjusted hazard ratio = 0.65, 95% CI = 0.28–1.55, p = 0.34). Detailed subset analyses of patients with female/male mismatches could not be done due to the low numbers of events.

**Graft vasculopathy**

During follow-up there were 132 patients who were identified as having any angiographic evidence of graft vasculopathy. ICB as a cause of donor death was associated with a greater likelihood of vasculopathy (Figure 2). After accounting for potential confounders but before taking into account the competing risk of recipient death, ICB as a cause of donor death remained independently predictive of vasculopathy (adjusted hazard ratio 1.97, 95% CI 1.32–2.94, p = 0.0009). After taking into account the competing risk, however, ICB as a cause of donor death only tended to predict vasculopathy (competing risk adjusted hazard ratio 1.39, 95% CI 0.90–2.13, p = 0.14). The strongest independent predictor of vasculopathy in the competing risks adjusted model was donor age (p = 0.0004).

**Graft function**

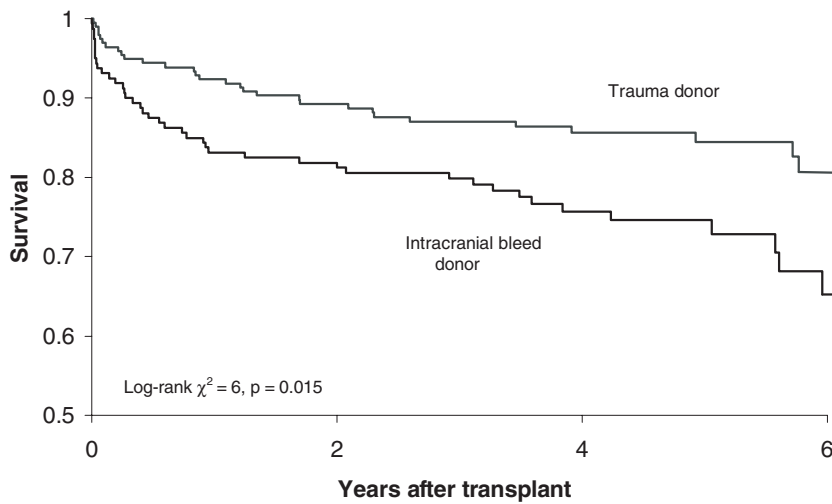
Compared with the Trauma group, the ICB group had a higher incidence of post-transplant graft dysfunction (left ventricle ejection fraction < 35%) during the first week of transplant [16/160 (10%) vs. 6/197 (3%), p = 0.007]. After adjusting for the propensity score for intracranial bleed as a cause of donor death, there remained an independent association with post-transplant graft dysfunction (adjusted odds ratio 4.22, 95% CI 1.25–14.22, p = 0.02). Hemodynamic compromise was also more common in the ICB group [12/160 (7.5%) vs. 4/197 (2%), p = 0.018].

**Myocardial fibrosis**

The ICB group showed an increased incidence of post-transplant ischemic injury complicated by the development of myocardial interstitial fibrosis on their endomyocardial biopsies during the first 4 weeks of transplant [33/160 (21%) vs. 17/197 (9%), p = 0.0012]. After adjusting for the propensity score for intracranial bleed as a cause of donor death, this association persisted (adjusted odds ratio 2.33, 95% CI 1.03–5.30, p = 0.04).

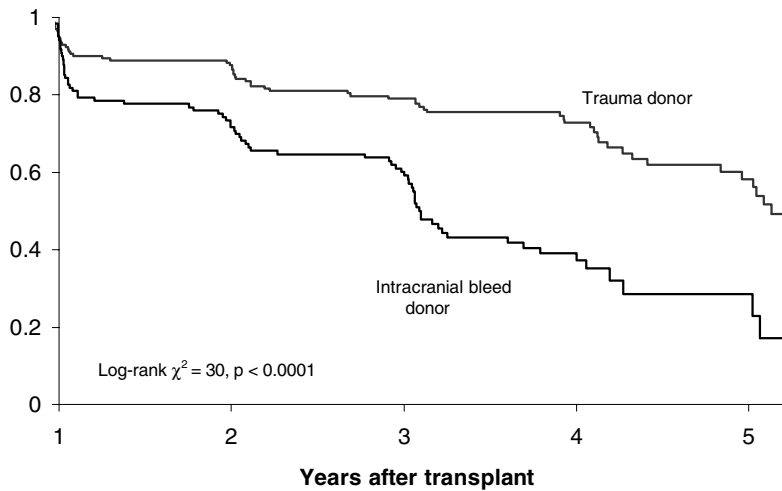
**Discussion**

Our study has several important findings. Spontaneous intracranial bleeding is associated with an increased incidence of graft dysfunction, hemodynamic compromise and myocardial fibrosis. In animal models of increased intracranial pressure, cerebral injury results in a catecholamine surge with marked perturbations of hemodynamics and histological evidence of myocardial damage (6,8). It is estimated that 10–20% of potential cardiac donors with brain injury and no previous cardiac history have evidence of severe myocardial dysfunction that exclude the heart from organ donation (19). The myocardial dysfunction accompanying brain injury has been noted to be associated with marked alterations in beta-adrenergic signal transduction as well as changes in the contractile apparatus (7). The type and extent of myocardial injuries are related to the type of brain injury. In a study of 27 patients whose hearts were systematically examined after an acute fatal episode of



Number at risk				
Trauma	197	174	118	43
ICB	160	130	82	23

Figure 1: Kaplan-Meier plot of freedom from death according to cause of donor death.



Number at risk					
Trauma (173)	166	147	123	82	33
ICB (121)	115	84	64	29	9

Figure 2: Kaplan-Meier plot of freedom from vasculopathy.

intracranial brain hemorrhage, Baroldi et al. found evidence of myocardial necrosis in up to 89% of these patients as compared with only 4% in 45 cases of fatal head trauma (4). Increased donor age is another confounding factor in the donors who die from brain injury caused by intracranial bleeding (5). This may potentially contribute to the higher incidence of post-transplant ischemic injury complicated by fibrosis. Early endomyocardial fibrosis has been described in transplant animal models and human allograft recipients and was linked to peri-transplant ischemia (20,21). Pickering et al. (21) showed that cardiac allograft fibrosis may be identified shortly after transplantation and is dependent on ischemia duration. In a recent study on serial endomyocardial biopsies in 50 cardiac transplant patients followed over 5 years, Armstrong and his colleagues (22)

showed that myocardial fibrosis develops early and remains modestly elevated 2 months after transplant, indicating that peri-transplant factors may be the cause of this fibrotic process.

Another significant finding of the study was the tendency of the ICB group to manifest an increased coronary vasculopathy progression as noted by serial coronary angiograms. Increased donor age, and the prevalence of hypertension in the ICB group have been shown to be associated with the development of severe coronary vasculopathy (23). We have previously shown that patients with peri-transplant myocardial ischemia followed by fibrosis clearly show an increased incidence of coronary vasculopathy (24). Our study also shows that patients in the ICB

group had a worse survival and die more often of cardiac-related causes with a redistribution of cause of death resulting in less malignancy as an etiological factor. It appears thus, that donor cause of death has an overall significant impact on survival.

An important limitation of our analysis is that we did not have systematic intravascular ultrasound data on all, or nearly all, of our patients (data not shown). We did find a tendency towards increased vasculopathy in the ICB group, but this was based solely on angiographic data, which has well-known inherent limitations (25). Another limitation is that we did not have data on donor hypertension, diabetes or dyslipidemias. Finally, because of small numbers, we were unable to perform detailed subset analyses on gender mismatches (26), although we did not find any important interaction between donor and/or recipient gender regarding the impact of donor ICB on recipient mortality.

**Conclusions**

We conclude that spontaneous donor intracranial bleeding is associated with left ventricular dysfunction, development of interstitial myocardial fibrosis, advanced coronary vasculopathy and poorer survival compared with trauma donors.

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