Donor Mechanism of Death and Interstitial Fibrin as Predictors of Outcome After Heart Transplantation

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Introduction

Donor innate immune responses are triggered by donor brain death. Innate immune responses activate cytokine responses including platelet activation and coagulation and may result in adverse cardiovascular outcomes (CVD). Interstitial fibrin (INTFIB) is a marker of endothelial activation and plasma leakage in both innate and alloimmune reactions. We have previously shown that INTFIB in any patient (PT) endomyocardial biopsy (EMB) is associated with a 60% increase in CVD. We hypothesized that specific donor mode of death (MOD) may be associated with various degree of immune activation and result in early INTFIB.

Methods

Donor records from Utah Affiliated Hospitals (UTAH) heart transplant program were reviewed to assess donor MOD from 1985 to 2016

Grading scale 0-3 was used to evaluate INTFIB deposition in EMB with an immunofluorescence stain and the findings were recorded in a single data base. A separate data base was maintained with information about patient demographics and survival information.

CVD was defined according to UNOS criteria as acute rejection, acute myocardial infarction, allograft vasculopathy, sudden cardiac death, heart failure, cardiogenic shock, primary allograft failure, and cardiac arrhythmia.

INTFIB and PT outcomes were analyzed using Cox proportional hazard modeling and Fishers Exact Test between various donor MOD

Results

12040 EMB from 1384 PTs had INTFIB scores
Donor MOD was available in 588 cases of local donors with ischemic times <4 hours.
There was significant association between MOD and INTFIB deposition on biopsies. Table below

Donor MOD	PT # without INTFIB	PT % without INTFIB	PT # with INTFIB	PT % with INTFIB
Drug overdose	36	34	70	66
Head gun shot wound	36	25	105	75
Intracranial hemorrhage	37	27	98	73
Motor vehicle accident	60	21	229	79*
Blunt Head Trauma	17	19	72	81*
Brain tumor surgery	0	0	14	100*

*P=00049 for those MOD versus others . Simulated p value for count data by Fishers Exact Test

INTFIB was seen mostly early after transplant with or without acute rejection. Time course for INTFIB was identical whether or not rejection was present. Figure 1 shows time course of INTFIB deposition.
INTFIB was significantly predictive of cardiovascular death by UNOS criteria. Figure 2 shows percent surviving according to fibrin and rejection status.

Figure 1

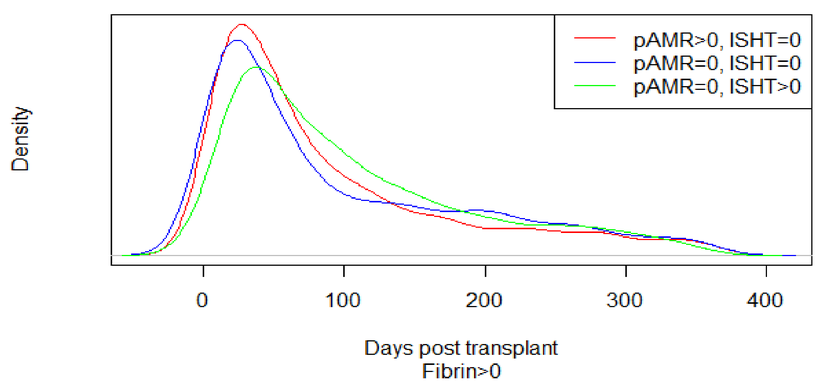
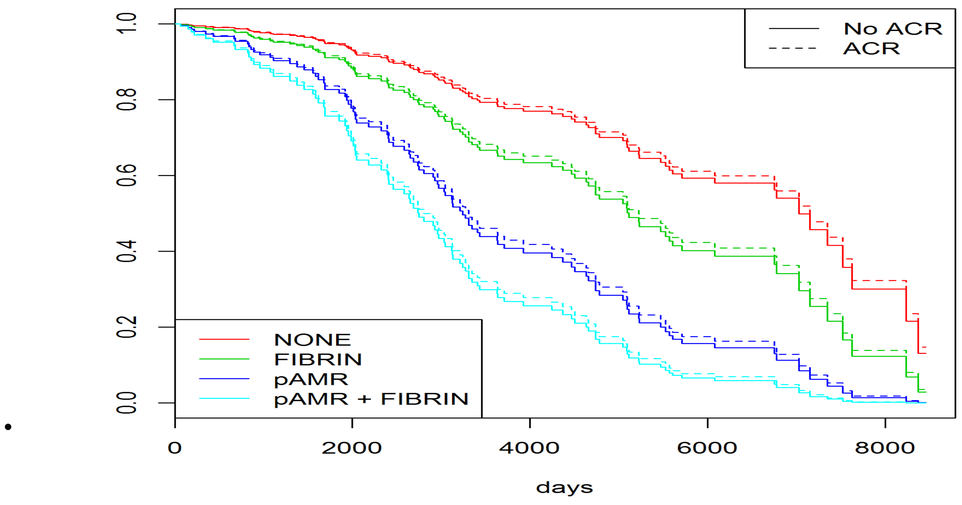


Figure 2



Conclusions

Extracellular tissue factor signaling elicits cellular activation and inflammation in a feedback loop involving coagulation and inflammation. Fibrin is an obvious hallmark of this activity. Our study confirms that INTFIB on EMB is found more commonly in hearts from donors with MODs associated with major trauma or surgery. INTFIB is most commonly seen early after transplantation, even in PTs without acute rejection. Thus, both donor and recipient factors are likely significant in determining PT inflammatory and immune responses of endothelial activation and protein leakage that are precursors to CVD.
INTFIB may be a key descriptor of this inflammatory status. Previous work has shown that INTFIB is adversely associated with PT CVD, regardless of whether rejection is present in the same biopsy.

INTFIB on PT biopsy and its relationship to donor factors should be further explored. Modification of donor management based on the inflammatory status of donors prior to transplantation may improve PT outcomes.

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The study was IRB approved at Intermountain Healthcare

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