Description of Longitudinal Measurement of Donor Fraction of Cell-Free DNA Following Rejection Treatment and Correlation to Clinical Outcomes

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Abstract

Purpose: Donor Fraction (DF) of cell-free DNA in transplant recipients has been correlated with rejection and allograft injury. Treatment of rejection results in a decrease in DF levels. Little is known about the clinical significance of rebound of, or increase in, DF following initial decrease associated with rejection treatment.

Methods: A cohort of 88 heart transplant recipients were prospectively followed. DF was quantified using a targeted assay, myTAlheart test (TAI Diagnostics, Milwaukee Wisconsin). 7 subjects were treated for rejection and had longitudinal samples available for analysis with serial DF levels before and treatment. Clinical end points were death, need for mechanical circulatory support (MCS), and recurrent or progressive rejection.

Results: Two patients did not demonstrate rebound in DF following treatment and did not experience near-term adverse events. Mean pre-treatment DF was 2.67% and post-treatment was 0.15%. Of the five patients who demonstrated rebound in DF, two required MCS within 19 days following DF rebound and subsequently died. One patient with DF rebound developed progression of previously present cardiac allograft vasculopathy (CAV) within 42 days following rebound. The two remaining subjects who demonstrated DF rebound did not experience clinical adverse events.

Conclusion: We found that initial treatment of rejection lowers DF in general. Rebound of DF following treatment of rejection appears to be correlated with near-term adverse clinical events. Larger studies are needed to define the precise prognostic significance of this observed treatment effect.
Early Changes in Donor Fraction Cell-free DNA in Newly Transplanted Pediatric Heart Transplant Patients

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Abstract
Purpose: Heart transplantation is an accepted therapy for children with end-stage heart disease with average survival of 15-20 years. The highest risk for graft loss remains in the first 60 days post transplantation despite several advances in the care of these patients. Measurement of percent donor fraction (DF) cell-free DNA (cfDNA) allows for extremely sensitive monitoring of graft injury and may be useful early after heart transplant to detect patients at risk for graft failure or death.

Methods: This single center study reviewed early post-transplant DF cfDNA levels in children who received heart transplantation. The outcome measure was 60 day survival. Data reviewed included demographics of donor and recipient, key operative characteristics including ischemic time and bypass time were reviewed, and recipient and graft outcomes were analyzed. Declination curves were created for each patient based on these DF cfDNA data using an estimation modeling approach.

Results: 17 patients had at least one DF cfDNA level drawn in the peri-operative period. In general, each day was associated with a significant decrease in DF (p<0.001), with a leveling off by day 8. This included 10 patients with samples on post-transplant day 0, 4 and 8 which made up the study cohort. Median (IQR) % DF cfDNA levels were 3.2% (1.81 - 5.80), 0.38% (0.22 -1.00), and 0.22% (0.38 - 0.48) at day 0, 4, and 8 respectively. 7 patients had a decline in their DF cfDNA from day 4 to day 8 whereas 3 had an increase from day 4 to day 8. All three patients with an increase in % DF cfDNA from day 4 to day 8 died within 60 days of transplant and none of the 7 with a decline over this time period died in this period. Cause of death in those three patients included complications of hyper-acute rejection, primary graft dysfunction, and infection. One patient had an increase from day 0 to day 4 which clinically corresponded to a short ischemic time (115 minutes) and an episode of acute hypotension on post-transplant day #3. This patient had a decline in DF cfDNA by day 8 and a negative biopsy on day 9.

Conclusion: DF cfDNA is associated to peri-transplant graft survival and serial monitoring in the perioperative period may be helpful in early monitoring of graft function. DF cfDNA appears to significantly decline by 8 days post-transplant.
Endomyocardial Biopsy - A Source of Heartache
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Abstract
Purpose: Donor fraction cell free DNA (DF cfDNA) was investigated as a marker for cardiac injury in cardiac transplant recipients. We hypothesized that injury from routine biopsy (bx) would produce a detectable rise in circulating DF cfDNA.

Methods: Paired blood samples from 21 asymptomatic pts were drawn pre and post surveillance bx. Percent DF cfDNA was determined using the myTAI-HEART™ test (a proprietary quantitative genotyping assay from TAI Diagnostics, Wauwatosa, WI). Excluding pts with known graft vasculopathy, cancer, mechanical circulatory support, or any cellular rejection with grade >1, 17 sample pairs were available. Biopitome size and number of bx samples taken were recorded and analyzed.

Results: DF ranged from 0.02% pre-bx through 11.1% post-bx with a median of 0.43%. Paired samples are shown in Figure 1. The DF consistently increased post-bx, with a median increase of 8.2x (range 1.5x - 213x). Pt ages ranged from 4 to 32 years (med 12). Pt weights ranged from 17 to 90 kg (med 49). Both age and weight are independently associated with DF change (p<0.01). Pts <17 of age had an average DF increase of 24x versus pts >23 with an average DF increase of 2.7x. Age and weight are correlated, thus similar effects are seen by weight at time of draw. DF change did not correlate with biopitome size (p=0.4). The time between bx and the second blood draw ranged from 1 to 36 minutes and did not appear to be correlated to DF increase. Samples drawn soon after bx had more dramatic DF increases than more delayed samples consistent with the short half life of cfDNA; the five fastest (mean 2 minutes) had an average DF increase of 19.8x, versus the five latest (mean 7.6 minutes) saw just 4.1x. Initial DF is indicative of organ health before bx. A patient with elevated DF (>0.9%) pre-biopsy saw less DF increase post-bx (p<0.01).

Conclusion: Standard endomyocardial bx induces a significant and measurable injury to the transplanted heart, influenced strongly by patient body size and pre-bx level of DF cfDNA. This serves as evidence of the tremendous sensitivity of DF cfDNA as a marker of cardiac injury.

![Box Plot](http://files.abstractsonline.com/CTRL/05/4/19f/995/109/478/3af/c3c/e81/917/3ad/56/g4388_1.GIF)