Variability of Gene Expression Profile Scores Does Not Predict Coronary Allograft Vasculopathy As Detected By Intravascular Ultrasound One Year Post Heart Transplant: The Mid America Experience

S. Beauchamp, K. Kennedy, H. Brandt, D. Safley, B. Austin, M. Everley, T. Khumri, S. Lawhorn, A. Magalski, B. Sperry, D. Vodnala, M. Borkon, K. Carl, G. Dryton, A. Kao

Saint Luke's Mid America Heart Institute and University of Missouri-Kansas City, Kansas City, MO, USA

INTRODUCTION

Coronary allograft vasculopathy (CAV) is a significant complication limiting long term survival post orthotopic heart transplant (OHT). The use of intravascular ultrasound (IVUS) has shown that an increase of maximal intimal thickness (MIT) of 0.5 mm or more at 1 year compared to baseline is a marker of CAV and associated with poor long term outcomes. However, IVUS is invasive and has potential complications. A noninvasive means of predicting the occurrence of CAV would be helpful.

Gene expression profiling (GEP) is a non-invasive rejection surveillance method[1] measuring the activity of a 20-gene panel (11 informative genes, 3 normalization genes, 6 control genes). The combined activity of these 11 informative genes yields a linear discriminate algorithm (LDA) score. CARGO II hypothesized that the variability in LDA score over time may indicate a more active immune system and may be associated with adverse events[2]. They evaluated a new variable: the GEP Variability Score (GVS). GVS is currently defined by calculating the standard deviation of 4 consecutive LDA scores. A high GVS (over 1.5) has been associated with a higher risk for the Invasive Monitoring Attenuation through Gene Expression (IMAGE[3]) study endpoints (death, re-transplant, and graft failure) for OHT patients within 3 years after the last GEP score[2]. In a recent study at our institution, we observed that a GVS>1.25 calculated from 3 GEP scores (directly preceding the event/most recent if no event) was associated with higher risk for IMAGE outcomes within 20 months of the most recent GEP test[4]. However, development of coronary allograft vasculopathy (CAV) risks have not been evaluated using GVS. The current study evaluated whether GVS can predict CAV as predicted by an increase of MIT on IVUS.

METHODS

PORTRAIT:

- This study is a retrospective review of 322 OHT performed at Saint Luke's Mid America Heart Institute from January 1, 2009 through December 31, 2016.
- **Hypothesis:** A GVS calculated with 3 consecutive LDA scores can predict MIT progression on IVUS on the first year study when compared to baseline.

STUDY POPULATION:

- Between 1/1/2009 and 12/31/2016, 319 patients underwent 322 OHTs at our institution.
- **Inclusions:** We included all patients who had at least 3 consecutive GEP scores beginning at month 4 and at least 2 serial IVUS exams (n=221).
- **Exclusions:** Less than 3 consecutive GEP scores after 4 months post OHT (n=26), or less than two serial IVUS exams (n=100).
- 50 out of 221 (22.6%) OHT recipients had an increase of >0.5 mm of MIT in at least 1 left anterior descending (LAD) segment at 1 year and were considered the CAV group.

DATA COLLECTION:

- LDA scores, and event data were collected on each patient.
- MIT measurements in 5 different LAD segments were collected on each patient by IVUS. Each serial exam was measured at the same 5 segments using anatomic landmarks with standardized pullback and compared to baseline.
- A patient was considered to have CAV if there was a greater than 0.5 mm increase in MIT on any serial IVUS exam when compared to 6 week baseline exam.

STATISTICAL ANALYSIS:

- GVS was calculated using the standard deviation of the 3 consecutive LDA scores at month 4, 5, and 6. Continuous variables were compared using Student's t-test.
- Categorical variables were compared using chi-square or Fisher's exact test.
- Kaplan-Meier curves were compared via log rank statistic.

RESULTS

Table 1. Baseline Demographics between CAV and No CAV Groups

Demographics	Total (n = 221)	Increase of 0.5mm in MIT from Baseline to 1 year in Any Segment		P-Value
		Yes: CAV Group (n = 50)	No: No CAV Group (n = 171)	
Age at Transplant	51.57 ± 11.76	52.92 ± 10.27	51.18 ± 12.16	0.356
Female Gender	56 (25.3%)	13 (26.0%)	43 (25.1%)	0.902
Ischemic Time (minutes)	165.99 ± 51.79	159.45 ± 51.72	167.90 ± 51.80	0.311
Pre-Transplant PVR	1.93 ± 0.78	1.85 ± 0.87	1.96 ± 0.75	0.364
Transplant Technique				0.260
Biatrial	4 (1.8%)	1 (2.0%)	3 (1.8%)	
Cabrol Modified Biatrial	115 (52.0%)	31 (62.0%)	84 (49.1%)	
Bicaval	102 (46.2%)	18 (36.0%)	84 (49.1%)	
Annuloplasty at Transplant?	211 (95.5%)	47 (94.0%)	164 (95.9%)	0.568
Female Donor to Male Recipient	51 (23.1%)	8 (16.0%)	43 (25.1%)	0.176
Donor Gender Mismatch	75 (33.9%)	16 (32.0%)	59 (34.5%)	0.742
Mean GEP Variability Score	1.20 ± 0.75	1.25 ± 0.80	1.19 ± 0.73	0.647

Figure 1. Overall Variance of GEP Variability Score

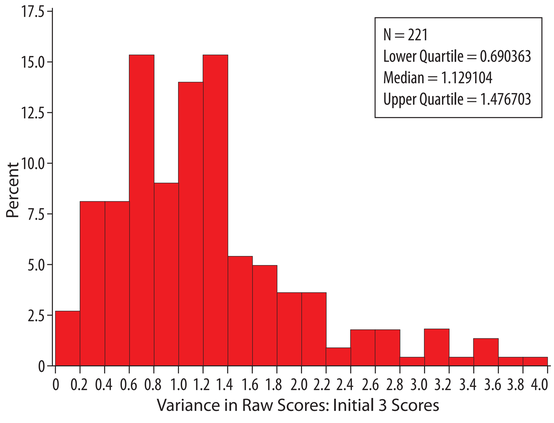
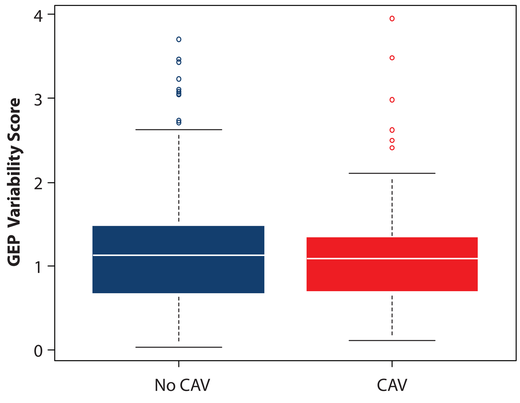


Figure 2. GEP Variability Score Comparison between No CAV and CAV Groups



REFERENCES

1. Deng MC, Eisen HJ, Mehra MR, et al. Noninvasive Discrimination of Rejection in Cardiac Allograft Recipients Using Gene Expression Profiling. American Journal of Transplantation. 2006;6:150-160.
2. Crespo-Leiro MG, Stypmann J, Schulz U, et al. Performance of Gene-Expression Profiling Test Score Variability to Predict Future Clinical Events in Heart Transplant Recipients. BMC Cardiovascular Disorders. 2015;15:120.
3. Pham MX, Teuteberg JJ, Kfoury AG, et al. Gene-Expression Profiling for Rejection Surveillance after Cardiac Transplantation. New England Journal of Medicine. 2010;362:1890-900.
4. Beauchamp SR, Carl KR, Kennedy KF, et al. High Gene Expression Profile Variability Score is Associated With Adverse Outcomes Post Heart Transplantation: The Mid-America Experience. Circulation. 2017;136:A17002.

DISCLOSURES

- **Andrew Kao:** G; C; Respicardia, CareDx, Sensible Medical, BioVentrix.

CONCLUSION

GVS did not predict CAV development on IVUS at 1 year when compared to baseline, even though this CAV marker occurred in 22.6% of patients. The variation in immune activity more than 4 months post OHT does not account for the intimal thickening observed. It may be difficult to use one immune marker of adverse outcome to predict a catheter-based marker of CAV. It is possible that these 2 parameters measure different immunologic factors.

LIMITATIONS

This study is a retrospective single-center review and thus has the inherent limitations of a non-randomized work. However, these patients were cared for using the same protocol-driven care and were not subject to any selection bias. Further mechanistic studies will be needed to further elucidate the etiology of this adverse CAV marker.