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QT and QT-Peak Dispersion in Cardiac Allograft Vasculopathy

A. Study Purpose and Rationale

Human cardiac transplantation, pioneered in the 1960's by Christiaan Barnard and polished by Norman Shumway in the 70's and 80's, is now a indispensable tool for endstage heart failure. The International Society for Heart and Lung Transplantation's 2012 registry data again shows that we are continually improving outcomes on all major fronts (Stehlik et al., 2012). That said, the pace of improvement in long-term survival has slowed since the 80's and 90's, prompting the question, "What more can we do?"

Outside of the immediate perioperative phase, the largest risk for death for cardiac transplant recipients is infection (within the first year) or graft failure (between 1 and 3 years). After that phase, however, malignancy (potentiated by the immunosuppresive regimen) and cardiac allograft vasculopathy emerge as major sources of morbidity and mortality.

Cardiac allograft vasculopathy (CAV) is an accelerated form of coronary artery disease (CAD) that is characterized by panarterial concentric fibrous intimal hyperplasia along the length of the coronary vessels and concentric medial disease in the microvasculature(Ramzy et al., 2005). Pathogenetically distinct from native heart CAD, it is driven by a host of both immunologic and nonimmunologic factors including HLA mismatch, cellular rejection, antibody-mediated rejection, endothelial activation, donor or recipient CAD, hyperlipidemia, insulin resistance, ad infinitum.

It is shockingly prevalent: at 1, 5, and 10 years post-transplantation, its prevalence among survivors was 8, 30, and 51%, respectively. Survival varies, but in one older study of 54 patients with ≥ 40% stenosis of at least one vessel, 5 year survival was only 17% (Keogh et al., 1992)

Therapeutic options are improving, and include but are not limited to variation of immunosuppression using everolimus or sirolimus, PCI, CABG, and retransplantation as a last resort (Matos et al., 2005)

Diagnosis, however, remains problematic. Due to the surgical denervation of the donor heart, recipients are usually unable to feel ischemic pain, thus may experience repetitive silent infarcts. "Gold standard" diagnosis is performed with coronary angiography or intravascular ultrasound (IVUS) , however these are costly and invasive. In recent years, dobutamine stress echocardiography has become the de facto screening tool (Sade et al., 2008), however this too is expensive and may not be a typical component of routine surveillance.

Previous work has explored the role of QT dispersion (a proxy measure for ventricular repolarization abnormalities) in predicting coronary artery vasculopathy and found a significant association: patients found to have CAV had, on average, markedly elevated QTD's relative to their baseline, while CAV-free controls did not. (Ali, et al. 2001). However, further statistical characterizations of these distributions

was not offered in that study, thus the degree of overlap is difficult to determine. Moreover, QT peak dispersion has been found to be more reliable under certain circumstances (Masaki et al., 2006) As a more easy-to-use screening tool would offer earlier detection of CAV, I propose further investigation to explore these potentially useful metrics. I hypothesize that patients with CAV per IVUS / angiography will be significantly more likely to have an elevated QTD or QTPD.

B. Study Design and Statistical Analysis

A retrospective analysis will be performed on: All available patients ≥ 18 years of age in the Columbia transplant series who have been diagnosed with CAV by angiography or IVUS and have a baseline EKG within 2-4 weeks of their transplantation as well as a dobutamine stress echocardiogram and EKG within the 12 months preceding their diagnosis will be included. Preliminary estimates put this population at approximately 100. Post-transplant controls with no evidence of CAV will be recruited and matched for time-since-transplant.

There will be no crossover or randomization due to the nature of the study. Given prior work suggesting an average QTD increase of 42.8% in the CAV population, I used an arbitrary cutoff of 25% to define a "significant increase." As this is a screening test, a shift in the mean is less relevant than its ability to distinguish between populations. Results will be analyzed with a chi-square test for proportions. With a study population of 100 and recruiting controls at a 1:1 ratio, and assuming a 20% frequency of "significant increases" in the control population, we will be powered at 80% to detect a frequency of QTD increases of <6% or > 39% in the CAV population.

Alpha error - 0.05
Beta error - 0.2

C. Study Procedure

Two blinded reviewers will manually measure the QT, QTD, and QTPD for the subjects' baseline resting EKG and DSE resting EKG. A third reviewer will be available to arbitrate disagreement. A kappa value will be calculated to measure interobserver agreement.

Extrasystolic and postextrasystolic beats will be excluded from individual analysis. EKG's in which the T wave is not clearly definable in at least 6 of 12 leads will be excluded, as will complete bundle branch blocks.

D. Study Drugs

None

E. Medical Device

N/A

F. Study Questionnaires

None

G. Study Subjects

Inclusion / Exclusion: Per above

H. Recruitment of Subjects

No new patients will be recruited for this retrospective analysis.

I. Confidentiality of Study Data

All data will be kept confidential and de-identified

J. Potential Conflicts of Interest

No disclosures

K. Location

N/A

L. Potential Risks

N/A

M. Potential Benefit

Given the nature of this retrospection after use of the gold standard test, few potential benefits to be immediately expected, however patients may benefit from development of future screening tools.

N. Alternative Therapies

N/A

O. Compensation

N/A

P. Costs

N/A

Q. Minors

Excluded

R. Radiation

Although patients will have been exposed to radiation during their catheterization, no new risks will be posed by this review.

Sources

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