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Permalink

<https://escholarship.org/uc/item/43q3k3kh>

Journal

American journal of critical care : an official publication, American Association of Critical-Care Nurses, 27(2)

ISSN

1062-3264

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Publication Date

2018-03-01

DOI

10.4037/ajcc2018862

Peer reviewed

ELECTROCARDIOGRAPHIC CORRELATES OF ACUTE ALLOGRAFT REJECTION AMONG HEART TRANSPLANT RECIPIENTS

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Background Acute allograft rejection appears to be associated with increases in QT/QTc intervals.

Objectives To determine the relationship between acute allograft rejection and electrocardiogram changes in patients undergoing an orthotopic heart transplant.

Methods The study population comprised 220 adult patients undergoing heart transplant and enrolled in the NEW HEART study. Electrocardiograms obtained within 72 hours of endomyocardial biopsy were analyzed; electrocardiograms obtained fewer than 10 days after transplant surgery were excluded. Repeated-measures analysis was performed with statistical models including effects for rejection severity (mild and moderate/severe) and time trends independent of rejection status.

Results The 151 male and 69 female transplant recipients (mean age [SD], 54 [13] years) had 969 biopsy/electrocardiogram pairs: 677 with no rejection, 280 with mild rejection, and 12 with moderate/severe rejection. Moderate to severe organ rejection was associated with significant increases in QRS duration ($P < .001$), QT ($P = .009$), QTc ($P = .003$), and PR interval ($P = .03$), as well as increased odds of right bundle block branch ($P = .002$) and fascicular block ($P = .009$) occurring.

Conclusions Moderate to severe acute allograft rejection was associated with electrocardiographic changes after transplant surgery. Studies are needed to assess the value of computerized electrocardiogram measurement algorithms for detecting acute allograft rejection. (*American Journal of Critical Care*. 2018;27:145-150)

Evidence-Based Review on pp 151-152

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doi:<https://doi.org/10.4037/ajcc2018862>

The primary aim was to see if an increase in QT or QTc interval within the first 6 months after heart transplant could be used as a biomarker for acute allograft rejection.

Endomyocardial biopsy is the gold standard for diagnosis of acute allograft rejection, a major cause of early death after heart transplant in adults.¹ Typically, patients undergo frequent biopsies during the first year after transplant, to detect the early stages of rejection and administer immunosuppressant therapy. However, endomyocardial biopsy is an invasive procedure that entails risk²; thus, researchers are looking for a simple, noninvasive biomarker to identify early stages of acute rejection, with the goal of reducing the number of invasive biopsy procedures.

Researchers have demonstrated that donor hearts with a prolonged QTc interval of more than 500 milliseconds noted on their electrocardiogram were associated with acute allograft rejection in the recipient.³ In fact, a prolonged QT or QTc interval in the donor heart may be an underlying factor contributing to the development of allograft rejection.³

Study evidence suggests that acute allograft rejection causes delays in ventricular repolarization and thereby increases the duration of the cellular action potential, resulting in a longer QT interval on the electrocardiogram.^{4,5} To our knowledge, no prospective study has investigated whether such increases in the QT interval could provide early detection of acute allograft rejection.

The aim of this study was to investigate the potential benefit of electrocardiographic monitoring to predict acute allograft rejection.

Methods

The Novel Evaluation With Home Electrocardiogram and Remote Transmission (NEW HEART) study

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(National Institute of Nursing Research project no. NR012003) of electrocardiographic monitoring was conducted at 3 large heart transplant centers in the United States between 2011 and 2015: Columbia University Medical Center, New York, New York; and University of California, Los Angeles, and Cedars-Sinai, both in Los Angeles, California.⁶ This study was done in accordance with the appropriate institutional review body and carried out following the ethical standards set forth in the Helsinki Declaration of 1975.

The aims of this prospective, double-blind study were to determine whether an increase in QT or QTc within the first 6 months after heart transplant could be used as a biomarker for acute allograft rejection, and to explore additional electrocardiographic measurements that might be predictors of acute allograft rejection. Inclusion criteria required the patients be at least 18 years old, undergoing and having undergone their first heart transplant surgery, not enrolled in other research studies that conflicted with the study design, and clinically stable at time of enrollment (ie, having an ejection fraction $\geq 45\%$ and no clinical symptoms of allograft impairment).

Participants were recruited either while in the hospital for transplant surgery or during their first clinic visit after transplant surgery. After informed consent was obtained, demographic and clinical data were collected by self-report and by medical record review. Collected demographic data included age, sex, race, and ethnicity. Clinical data collected included a history of hypertension, diabetes, dyslipidemia, cause of heart failure, and the presence of a ventricular assist device or implantable cardioverter defibrillator inserted before transplant.

At the time of each endomyocardial biopsy, data from the medical record were abstracted to collect endomyocardial biopsy results. In addition, other clinical data pertinent to myocardial performance with acute rejection (ie, systolic blood pressure and level of B-type natriuretic peptide) also were collected. At all 3 participating centers, biopsies were typically performed weekly during the first 3 months of the study. Subsequently, biopsies were performed

approximately every other week for the next 3 months, and then every month or 2 for the following 6 months. Generally, 3 to 6 biopsy specimens of the right ventricular endocardium were taken to minimize false-negative tests. At each site, endomyocardial biopsy specimens were graded by clinical pathologists experienced with the heart-transplant population. The pathologists used the International Society of Heart and Lung Transplantation standards for acute rejection.⁷ The standard for mild rejection was interstitial and/or perivascular infiltrate with no more than a single focus of myocyte damage. The standard for moderate rejection was 2 or more foci of infiltrate and accompanying myocyte damage. Criteria for severe rejection included biopsy specimens with diffuse infiltrate and multifocal myocyte damage with or without edema, hemorrhage, or vasculitis.

Analyses of ECG measurements were sent to a core laboratory at the University of California, San Francisco. Trained experts performed the ECG measurements. Measurements of QT interval were obtained from 12-lead electrocardiograms recorded during routine clinical follow-up. The QT interval measurement was made from the onset of the QRS waveform to the end of the T wave. The end of the T wave was defined as the intersection of a tangent to the steepest slope of the last limb of the T wave with the baseline (Figure 1).

For calculation of QTc, the Bazett formula was used to correct for heart rate.⁸ Additional electrocardiographic measurements included RR interval, P wave and QRS duration, and PR interval, as well as assessments of cardiac rhythm, right bundle branch block (RBBB), left anterior and left posterior fascicular block, atrial enlargement, T-wave inversion, and nonspecific ST-T wave changes.

Data were analyzed by using SAS, version 9.4 (SAS Institute). Continuous variables are reported as means and standard deviations; categorical variables are reported as frequencies and percentages. Endomyocardial biopsy results were paired with electrocardiograms obtained within 72 hours of biopsy. Electrocardiograms obtained fewer than 10 days after transplant surgery were excluded to minimize immediate postoperative effects related to surgery. Repeated-measures analysis was done by using PROC MIXED for continuous dependent variables and PROC GLIMMIX for categorical dependent variables.^{9,10} Statistical models included indicator variables for rejection severity (mild and moderate to severe) and a variable for time trends independent of rejection status. A *P* value less than .05 was considered statistically significant for all analyses.

Figure 1 A tangent is drawn to the steepest slope of the last limb of the T wave; the end of the T wave is the intersection of this tangent with the baseline.

Table 1
Demographic and clinical characteristics

Variable	Proportion (%) of patients (N = 220)
Male sex	151/220 (69)
Diabetes	82/220 (37)
Hypertension	127/219 (58)
Dyslipidemia	117/220 (53)
History of smoking	102/212 (48)
Ischemic cardiomyopathy	60/218 (28)
Implantable cardioverter defibrillator	104/220 (47)
Ventricular assist device	86/220 (39)

Results

A total of 220 participants had at least 1 electrocardiogram/biopsy pair and were included in the current study (Columbia University Medical Center, n = 129; University of California, Los Angeles, n = 52; Cedars-Sinai, n = 39). The mean age of the participants was 54 (SD, 13) years; males composed 69% of the study population (Table 1). Ethnic and racial composition of the cohort was 46% non-Hispanic whites, 24% non-Hispanic blacks, 20% Hispanics, 9% Asians, and 1% other ethnicity or race. Cardiovascular risk factors were common within the cohort. Hypertension was most prevalent (58%), followed by dyslipidemia (53%), a history of smoking (48%), and diabetes (37%). Before receiving their transplant, 39% of patients had a ventricular assist device implanted and 47% had an implantable cardioverter defibrillator (Table 1). During the study period, 9 deaths occurred (4.1%). Two of the deaths were related to graft rejection.

Moderate to severe rejection was significantly associated with an increase in QTc interval.

Figure 2 Numbers of biopsy/electrocardiogram pairs.

Table 2
Unadjusted values of electrocardiographic variables^a

Variable	Rejection		
	None	Mild	Moderate or severe
RR interval, ms	644 (89)	649 (94)	609 (70)
QRS duration, ms	90 (18)	90 (18)	108 (19)
QT interval, ms	362 (34)	366 (36)	374 (48)
QTc, ms	451 (29)	453 (37)	479 (56)
PR interval, ms	147 (21)	148 (21)	154 (23)
	None	Mild	Moderate or severe
Right bundle branch block	41	50	75
Fascicular block	13	12	25
Atrial enlargement	43	36	50
T-wave inversion	32	33	50
Nonspecific ST-T changes	47	49	42

^a Values in top section are means and standard deviations, and values in bottom section are percentages of all 969 electrocardiograms by rejection status among the 220 study participants.

Among study participants, 94 patients had no episodes of rejection, 123 patients had mild episodes of rejection, and 12 patients had moderate to severe episodes of rejection; 9 patients had both mild and moderate to severe episodes of rejection. A total of 969 biopsy/electrocardiogram pairs were available: 677 with no rejection (69.9% of pairs), 280 with mild rejection (28.9%), and 12 with moderate to severe rejection (1.2%). The mean number of biopsies per patient was 4.4 (range, 1-11; Figure 2).

Table 2 lists the mean and standard deviation for measurements of QRS duration, and QT, QTc,

and PR intervals for electrocardiograms from patients classified as having no rejection, mild rejection, and moderate to severe rejection. Similarly, Table 2 lists the prevalence of RBBB, left anterior and posterior fascicular block, atrial enlargement, T-wave inversion, and nonspecific ST-T wave changes among electrocardiograms from patients with no rejection, mild rejection, and moderate to severe rejection.

Table 3 lists the results of the repeated-measures analyses for the relationship of rejection status to the specific electrocardiographic variables of interest. Moderate to severe rejection was associated with significant increases in QRS duration and prolongation of QT, QTc, and PR intervals. Mild rejection was associated with prolonged QRS and QT intervals only. Among categorical variables, RBBB and left anterior and left posterior fascicular block were associated with higher odds ratios for moderate to severe rejection, but not for mild rejection. In addition, time trends independent of rejection status were found for QRS duration (mean [SD], 0.6 [0.1] ms/mo; $P < .001$), QTc (0.8 [0.3] ms/mo; $P = .02$), and PR interval (0.5 [0.2] ms/mo; $P = .004$).

Discussion

The NEW HEART study sought to determine the potential benefit of electrocardiographic monitoring for predicting acute allograft rejection in patients undergoing orthotopic heart transplant. The results of the study demonstrate that moderate to severe acute allograft rejection is associated with electrocardiographic changes in QRS duration, and QT, QTc, and PR intervals, as well as an increased prevalence of RBBB and left anterior and posterior fascicular block.

QT and QTc have been considered promising predictors of acute rejection and mortality after heart transplant.^{4,5} In our study, moderate to severe rejection was significantly associated with an increase in QTc interval ($P = .003$). We did not have enough deaths to analyze mortality. However, in a recent study, Chang et al¹¹ found that prolonged QTc was associated with sudden cardiac death in patients who had undergone heart transplant. In their study, electrocardiogram characteristics, including JTc interval prolongation and increased heart rate, were independent predictors of posttransplant sudden cardiac death.¹¹

RBBB is a frequently reported abnormality after orthotopic heart transplant, with reported incidence from 14% to 69%.¹²⁻¹⁴ In our study, 52% of patients had RBBB. However, the clinical significance is controversial. In most studies, researchers found no association between RBBB and adverse outcomes.¹²⁻¹⁵ To our knowledge, a relationship between RBBB and rejection has been reported in only 3 studies,^{13,16,17}

Table 3
Effect of rejection status on electrocardiographic variables

Variable	Mild rejection	P value vs no rejection	Moderate or severe rejection	P value vs no rejection
	Increase from no rejection, mean (SE)		Increase from no rejection, mean (SE)	
RR interval, ms	6.2 (4.5)	.17	9.4 (17.6)	.59
QRS duration, ms	1.2 (0.6)	.049	12.6 (2.3)	<.001
QT interval, ms	3.8 (1.9)	.04	19.0 (7.3)	.009
QTc, ms	2.2 (2.0)	.27	22.8 (7.6)	.003
PR interval, ms	1.5 (1.0)	.14	8.6 (4.0)	.03
	Mild rejection	P value vs no rejection	Moderate or severe rejection	P value vs no rejection
	Odds ratio (95% CI) ^a		Odds ratio (95% CI) ^a	
Right bundle branch block	1.19 (0.98-1.43)	.07	3.82 (1.67-8.71)	.002
Fascicular block	1.24 (0.92-1.67)	.17	3.35 (1.35-8.35)	.009
Atrial enlargement	0.82 (0.64-1.09)	.17	1.27 (0.42-3.83)	.68
T-wave inversion	0.98 (0.73-1.31)	.88	1.75 (0.56-5.40)	.33
Nonspecific ST-T changes	1.16 (0.87-1.54)	.32	1.19 (0.37- 3.82)	.77

^a No rejection is reference.

but differences in definitions and relatively small sample sizes warrant caution in generalizing the results. Ferretto et al¹³ found an association between development of RBBB and early acute graft rejection; they converted the 1990 International Society of Heart and Lung Transplantation grading into points and defined rejection as a score of at least 2 points (grade 1B). The new International Society of Heart and Lung Transplantation grading of 2R for moderate rejection, as used in our study, is comparable to a grade of 3A in the old system, which limits comparisons with the study by Ferretto et al. We had 280 episodes of mild rejection, which trended toward significance in an association with RBBB ($P = .07$). Because mild rejection is not usually treated, our study findings support those of others who found that RBBB is very common and generally not associated with adverse prognosis.

To use electrocardiogram changes to predict rejection in a clinical setting, it would be necessary to have a baseline electrocardiogram without evidence of rejection that could be used for comparison of subsequent electrocardiographic changes. In our study, only 5 of the 12 episodes of moderate to severe rejection were preceded by an electrocardiogram obtained when patients were not experiencing allograft rejection. Moreover, 14% of the episodes of moderate to severe rejection occurred during the first 10 days after surgery and were not included in the analysis because electrocardiographic changes could be confounded significantly by the effects of

surgery and electrolyte imbalances that occur during the acute phase.

The low incidence of episodes of moderate to severe allograft rejection by external electrocardiographic monitoring, used to predict acute allograft rejection in the clinical setting, may be enhanced in the future by internal electrocardiographic and computerized approaches. Most rejection episodes (>95%) in our study were mild; focusing on developing personalized computerized algorithms that detect episodes of mild rejection would be useful to administer antirejection medications in a timely fashion, which could limit the extent of myocardial damage.

Evidence supporting novel, internal implantable and computerized approaches to electrocardiographic monitoring continues to be reported.¹⁸

Limitations

Although these results are encouraging, several issues limit the conclusions that can be drawn from our study about the utility of electrocardiographic measurements for identification of early allograft rejection in the context of heart transplant. First,

Episodes of rejection: 94 patients had none, 123 patients had mild ones, and 12 patients had moderate to severe ones; 9 patients had both mild and moderate to severe episodes of rejection.

only 12 episodes of moderate to severe rejection were detected; the low number precludes the ability to make meaningful estimates of sensitivity for predicting acute allograft rejection. Although we had power to demonstrate significant associations of single electrocardiographic variables with moderate to severe allograft rejection, similar multivariable analyses were not practicable. Thus, it was not possible to determine whether using a combination of electrocardiographic measurements rather than a single measurement could have enhanced the ability to predict acute allograft rejection. This remains an area of future investigation.

Conclusions

Moderate to severe acute allograft rejection after heart transplant surgery is associated with electrocardiographic changes, including increases in QRS duration and QT, QTc, and PR intervals. The odds ratio for moderate to severe rejection is also elevated for RBBB and left anterior and posterior fascicular block. Thus, it may be possible to predict allograft rejection by using computerized measurement algorithms to characterize the electrocardiograms of patients undergoing orthotopic heart transplant in the future. Additional prospective studies are needed to examine the application of computerized electrocardiographic algorithms in the posttransplant setting and the correlation with acute rejection and electrocardiographic changes over time.

ACKNOWLEDGMENTS

We thank Kate Warren and Teresa Riga for their contributions in reviewing and editing this manuscript.

FINANCIAL DISCLOSURES

This study was supported by National Institute of Nursing Research project no. NR012003.

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