

QT Dispersion Is Not associated with Sudden Cardiac Death or Mortality in Heart Transplant Recipients

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ABSTRACT

Background: Sudden cardiac death (SCD) has been shown to be a significant cause of death after heart transplantation. QT dispersion (QTd) is associated with SCD in several high-risk populations. We hypothesized that QTd would predict mortality and SCD in heart transplantation patients.

Methods: We examined the clinical charts and most recent electrocardiograms (ECGs) for patients who received heart transplants at Stanford University Medical Center during the period 1981-1995. QTd was measured with all 12 leads and the precordial leads. Analysis was performed by a single reader blinded to patient outcomes.

Results: A total of 346 patients who had undergone transplantation had available ECGs and known outcomes; 155 of these patients died, and 42 of these deaths were attributed to SCD. The 12-lead mean QTd was not significantly different between outcome groups: patients who survived had a 12-lead mean QTd of 58 ± 29 milliseconds and those who died had a 12-lead mean QTd of 61 ± 32 milliseconds ($P = .57$). Patients who died from SCD had a 12-lead mean QTd of 57 ± 31 milliseconds ($P = .40$), and those who died of other causes had a 12-lead mean QTd of 59 ± 34 milliseconds ($P = .36$ vs those who died of SCD). Similarly, the precordial-lead mean QTd did not differ significantly between the different outcome groups.

Conclusions: We found no correlation between QTd and SCD or mortality in heart transplant recipients. Until additional studies prove a positive association, QTd should not be used as a prognostic marker in these patients.

INTRODUCTION

Sudden cardiac death (SCD) is a well-recognized cause of death in cardiac transplant recipients [Patel 1996] and accounts for up to one-half of all cardiac-related deaths in this patient population. In a previous study, we did not

observe significant associations between electrocardiographic (ECG) predictors involving the QRS complex (including right bundle-branch block, left bundle-branch block, or QRS duration) and sudden death or overall mortality in heart transplant recipients [Marcus 2006].

The measurement of QT dispersion (QTd) is a potentially powerful noninvasive tool for predicting malignant ventricular arrhythmias and SCD. Although QTd was once thought to specifically reflect disparate refractoriness or inhomogeneity of myocardial repolarization [Statters 1994], more recent evidence suggests that QTd may be an indirect measure of general repolarization abnormalities [Malik 2000]. Regardless of the underlying mechanism, increased QTd has been associated with greater propensity to ventricular arrhythmias in patients with hypertrophic cardiomyopathy [Statters 1994], tetralogy of Fallot [Surawicz 1996], and congestive heart failure [Galinier 1998, Dublin 1999]. In addition, increased QTd has been shown to predict SCD in patients with hypertrophic cardiomyopathy or congestive heart failure and in athletes [Surawicz 1996].

Cardiac allograft vasculopathy is known to be associated with SCD [Patel 1996], and a recent study showed that development of cardiac allograft vasculopathy is associated with an increase in QTd [Ali 2001]. We hypothesized that QTd would predict SCD in heart transplant recipients. To test this hypothesis we analyzed all available ECGs of patients who had undergone orthotopic heart transplantation at Stanford University Medical Center during the period 1981-1995.

MATERIALS AND METHODS

A total of 643 heart transplantations were performed at Stanford between 1981 and 1995. A systematic review of clinical charts was performed to determine outcomes. All outcome data were obtained prior to January 1999.

SCD was defined as in-hospital death within 1 hour of abrupt onset of acute symptoms attributable to a cardiac cause, or unexpected outpatient death for which a noncardiac cause could not be identified.

ECGs were collected from the patients' clinical charts, and the most recent ECG available was used for analysis. All ECGs were obtained at a paper speed of 25 mm/second with standard 12 leads and standard amplitudes. The QT interval

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was measured manually by a single observer blinded to patient outcomes. The QT interval was measured from the onset of the QRS complex to the end of the T wave, defined as the return of the T-P baseline. If the T wave was interrupted by a U wave before return to baseline, the end of the T wave was defined as the intersection of the tangent to the repolarization slope with the isoelectric line. QTd was defined as the difference in milliseconds between the longest and shortest QT intervals in a given set of leads. QTd was considered valid if ≥ 4 leads were readable. QTds of both the entire 12 leads and the precordial leads alone were measured.

Statistical Analysis

Results are expressed as mean \pm SD. Data were analyzed using JMP software (SAS Institute, Cary, NC, USA) and Stata version 8.2 software (College Station, TX, USA). Continuous variables between outcome groups were compared using *t*-tests. Pearson product-moment coefficients were used to evaluate correlations. Multiple regression analysis was performed to control for available potential confounding variables. Differences were considered statistically significant for *P*-values (2-sided) $\leq .05$.

RESULTS

A total of 346 patients who had undergone heart transplantation had available ECGs and known outcomes. The mean age at the time of heart transplantation was 50 ± 14 years. Of the 346 patients, 155 died, and 42 of these deaths were attributable to SCD. The ECGs were performed a mean 5.5 ± 3.7 years after transplantation and 300 ± 443 days before death. Outcome data were obtained at mean follow-up time of 9.6 ± 3.5 years after transplantation.

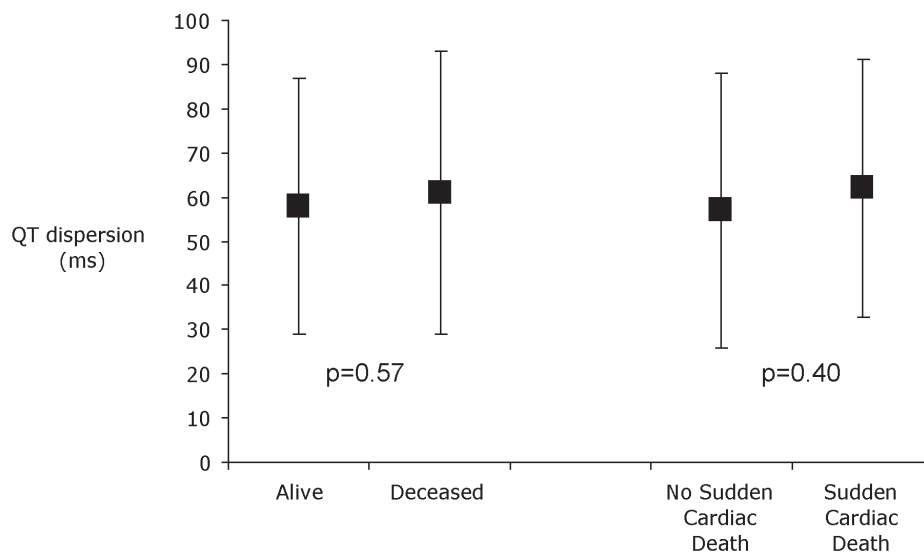
12-Lead Mean Corrected QT Intervals

12-Lead mean corrected QT (QTc) intervals did not correlate with patient age ($r = 0.038$), but the mean QTc intervals did significantly correlate with time since transplantation ($r = 0.15$, $P = .0054$). None of the mean QTc intervals were significantly different between the different outcome groups. The mean QTc interval of those who remained alive was 429 ± 29 milliseconds, and the mean QTc for those who died was 424 ± 68 milliseconds ($P = .27$). The mean QTc of those who died of SCD was 429 ± 36 milliseconds ($P = .95$ compared to the QTc of those without SCD), and the mean QTc interval of those who died of other causes was 423 ± 48 milliseconds ($P = .53$ vs those who died of SCD).

12-Lead Mean QTd

A total of 318 12-lead ECGs had ≥ 4 leads readable for the evaluation of QTd (ECGs for 184 surviving patients, 134 deceased patients, and 37 deceased patients who suffered SCD). The 12-lead QTd did not correlate with age ($r = -0.0215$, $P = .69$) or time since transplantation ($r = -0.042$, $P = .44$). None of the 12-lead mean QTd values were significantly different between the different outcome groups (Figure). The mean QTd of surviving patients vs deceased patients were 58 ± 29 and 61 ± 32 milliseconds, respectively ($P = .57$). The mean QTd of those who suffered SCD was 57 ± 31 milliseconds ($P = .40$ vs patients without SCD), and those who died of other causes had a mean QTd of 59 ± 34 milliseconds ($P = .36$ vs those who died of SCD).

Multilinear regression analysis controlling for age and time since transplantation (time from transplantation to the date of the ECG) did not significantly influence these results.



Mean 12-lead QT dispersion (QTd) for alive and deceased patients and for patients with and without sudden cardiac death (SCD). Y error bars denote SDs.

Precordial-Lead Mean QTd

A total of 304 ECGs had ≥ 4 precordial leads readable for interpretation of QTd. Of the patients included in this group, 181 remained alive at the follow-up date, 123 had died, and 35 suffered SCD. The mean QTd of the precordial leads was not significantly different between these groups. The mean QTd of the precordial leads of those who remained alive was 41 ± 24 milliseconds, and the mean precordial lead QTd of those who died was 44 ± 26 milliseconds ($P = .29$). For those who died of SCD, the mean precordial lead QTd was 40 ± 20 milliseconds ($P = .28$ compared to those without SCD). The mean precordial lead QTd of patients who died from causes other than SCD was 46 ± 28 ($P = .24$ compared to those who suffered SCD).

DISCUSSION

This study is the first to evaluate a possible correlation between QTd and clinical outcomes in heart transplantation patients. As demonstrated in our cohort and in patients previously described by Patel et al [1996], SCD is a frequent cause of cardiac death in heart transplantation patients. A simple marker that could reliably predict SCD would be invaluable. Because measurement of the difference between the shortest and longest QT intervals on a standard ECG is a simple and easily performed procedure, QTd has appropriately been described as “low-tech, low-cost” [Somberg 2002]. Unfortunately, we were unable to demonstrate a correlation between QTd and SCD or overall mortality in heart transplant recipients. There are several potential explanations for our findings.

One explanation for the lack of correlation of QTd with SCD and mortality in our study is that the transplanted heart is a unique substrate that itself might affect the utility of QTd. Although reinnervation of the transplanted hearts is known to occur to some extent [Hunt 2001], the relative lack of innervation of these hearts may affect autonomic tone such that QTd becomes less reliable. In addition, the mechanism of SCD in heart transplantation patients has not been elucidated. Neither our definition of SCD nor that reported by other investigators [Patel 1996] required documentation of a cardiac arrhythmia. Although the sudden, unexpected nature of death in these patients is certainly consistent with ventricular tachyarrhythmia, sudden deaths attributable to other causes (eg, bradyarrhythmias or events related to allograft rejection) have not been excluded. As a presumed marker of heterogeneity of ventricular repolarization, QTd is specifically a marker for ventricular tachyarrhythmias; therefore, QTd may be irrelevant to the mechanism of SCD in heart transplantation patients.

Our negative findings may also be related to, or even support, the theory that QTd is a poor marker for arrhythmia or SCD. Several reviews have questioned the clinical utility of QTd [Surawicz 1996; Statters 1994], and others have questioned whether QTd in fact does represent dispersion of ventricular repolarization [Malik 2000; Lee 2001]. Publication bias is a possible explanation for the many positive studies on QTd that have been previously reported. In one of the largest studies on the subject to date, Brendorp et al [2001] recently

showed that QTd had no prognostic value in patients with congestive heart failure and reduced left-ventricular systolic function. Clearly, this issue remains controversial: Somberg and Molnar [2002] recently provided a review in defense of the reliability of QTd as a true marker of increased heterogeneity of repolarization, citing practical problems with measurements and reproducibility as explanations for the negative findings.

Our study methods may also explain the negative findings. Our study was designed to maximize sensitivity, consistency, and applicability. Neither consensus nor evidence exist to support a particular number of readable leads required to deem QTd valid. Many studies do not mention the number of readable leads required in their methods, and others consider QTd valid only if ≥ 9 leads are readable [Brendorp 2001]. To allow for inclusion of a high number of total ECGs (in the hope of finding a positive correlation), we included ECGs with ≥ 4 readable leads. To further increase sensitivity, we analyzed both the full 12 leads and the precordial leads alone (which some authors purport to have independent value [Malik 2000; Statters 1994]), but our results failed to show a significant difference in either analysis. To maintain consistency, we used a single reader to manually measure QT intervals. Internal consistency was demonstrated by the different absolute values between the mean 12-lead QTd (range 58-65 milliseconds) and mean precordial-lead QTd (range 40-46 milliseconds) analyses showing no significant differences between the outcome groups within each analysis. An important limitation of our study, however, was that reproducibility (either intrarater or interrater variability of the QT measurements) was not tested.

Although the size of our study was comparable to many other studies of QTd, our sample size may have been insufficient to detect a meaningful difference. No absolute QTd result is known, by itself, to be pathologic. From the 12-lead mean QTd measurements, our study had an 80% power to detect a statistically significant difference of 14 milliseconds ($P < .05$) between surviving patients and SCD patients. The fact that many positive studies investigating QTd demonstrated differences greater than 14 milliseconds indicates that our sample size was sufficient [Malik 2000]. Interestingly, all of the QTd values from our patients fell into the same range as that reported in 8455 healthy subjects of various ages [Malik 2000].

With the hypothesis that QTd would provide an easy, readily available, and inexpensive marker of SCD in heart transplantation patients, we designed our study to be immediately applicable. Therefore, we used only standard 12-lead ECGs, we did not correct the QTd for the heart rate, and we did not use an automated system to measure the QTd. Some investigators have recommended the use of 24-hour recordings of QTd and automated QTd measurement [Somberg 2002], but neither has proven to offer greater validity, and both take away from the attractive convenience of an individual physician determining QTd from the standard 12-lead ECG. Although some investigators have recommended correcting the QTd for heart rate, results of a recent study suggest that this procedure is not necessary [Vassilikos 2001].

The retrospective nature of our study is certainly a limitation. We used the most recent ECG available for each patient, which in deceased patients was the ECG closest in time to the patient's death. The timing from transplantation was not uniform. If the risk of arrhythmia does manifest via QTd on an ECG, the optimal timing for obtaining this measurement is not known. Ideally, a prospective study would account for confounding differences in timing by performance of serial ECGs, allowing for comparison of ECGs obtained at similar times after transplantation and before death.

A final potential limitation of our study is the depth of statistical analysis and lack of inclusion of possible confounding conditions. We were unable to obtain detailed historical data related to transplant rejection, vasculopathy, diabetes, hypertension, and beta-blocker use on a sufficient number of patients to provide meaningful analyses. Given our negative findings from the primary analysis, however, we did not feel that subgroup analyses would be crucial to this already specialized group of patients. Our findings did not change after analyses that controlled for age and time since transplantation. One area of future research might expand on the work of Ali et al [2001] by focusing specifically on clinical outcomes and QTd in heart transplantation patients with vasculopathy.

CONCLUSIONS

We found no correlation between QTd and SCD or mortality in heart transplantation patients. Until additional studies conclusively demonstrate a positive association, QTd should not be used as a prognostic marker in these patients.

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