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QT Dispersion as a Marker of Risk in Patients Awaiting Heart Transplantation

DAVID J. PINSKY, MD, FACC, ROBERT R. SCIACCA, ENG SCD,
JONATHAN S. STEINBERG, MD, FACC*

New York, New York

Objectives. **The objectives of this study were to determine whether a signal-averaged electrocardiogram (SAECG) or measurement of interlead variability of QT intervals on an electrocardiogram (ECG) obtained at the time of wait-listing could provide prognostic value with respect to cardiac death during the waiting period.**

Background. **Because heart transplantation is a life-saving but limited resource, there remains an urgent need to identify those patients at greatest risk of dying while awaiting heart transplantation as part of the strategy to optimize the allocation of donor organs to those in greatest need. This study was undertaken to prospectively identify clinical, ECG or SAECG variables that might predict mortality during the waiting period.**

Methods. **Of 108 consecutive patients referred for heart transplant evaluation, 80 were placed on a waiting list, at which time a standard 12-lead ECG and a SAECG were recorded. In this cohort of 80 patients, QT dispersion was characterized from the 12-lead ECG as either the maximal–minimal QT interval (QTDISP) or as the coefficient of variation of all QT intervals (QTCV).**

Results. **During the 25-month follow-up period (mean time on waiting list, 201 days), the mortality rate was 27%/year, divided equally between heart failure and sudden deaths. No clinical variable identified at entry predicted mortality. QTDISP and QTCV were strong mortality predictors, with a 4.1-fold increase in mortality in patients with QTDISP >140 ms compared with those patients with QTDISP ≤140 ms (95% CI 1.1 to 14.9), whereas a QTCV ≥9% also predicted a 4.1-fold increased risk of death (95% CI 1.4 to 11.8). Although 88% of all SAECGs were abnormal, no patient with a normal SAECG died suddenly during the waiting period.**

Conclusions. **Indexes of QT dispersion provide a means of stratifying a patient's risk of dying while awaiting heart transplantation and may help to establish priority on a heart transplant waiting list.**

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Patients with end-stage heart failure can have a 40% one-year mortality rate, with an annual incidence of sudden death in outpatients exceeding 25% (1,2). Heart transplantation is often life-saving in these high risk patients, but many patients who are accepted as candidates for heart transplantation die while awaiting the transplant. Because only one in 10 patients who would benefit from transplantation actually receives a heart, owing to the shortage of donor organs, and because of the high mortality while awaiting transplantation, it would be advantageous to identify those patients at highest risk of dying during the waiting period to help establish priority on a heart transplant waiting list. In addition, each month twice as many patients are listed for transplantation as those who actually receive hearts, and waiting time for hearts has increased (3), with hearts preferentially going to deteriorating inpatient candidates (4,5). Thus, it becomes imperative not only to identify patients (especially outpatients) at high risk of dying during the waiting period, but also to identify low risk patients as part of the national strategy to optimize use of heart transplantation as a limited medical resource.

Many prognostic factors for poor outcome have been identified in patients with heart failure, including depressed left ventricular ejection fraction, low serum sodium, high levels of neurohormonal activation, advanced New York Heart Association functional class and limited exercise tolerance (6–10). More limited data have been available with respect to patients with severe heart failure who await heart transplantation. Sudden death of these patients is a vexing problem, and there exists no definitive means of predicting which patients may die suddenly, as opposed to those who succumb to progressive deterioration of ventricular function. Although a normal signal-averaged electrocardiogram (SAECG) (11–14) and the absence of inducible sustained arrhythmias by programmed electrical stimulation (15) may be associated with a

From the Department of Medicine, Columbia–Presbyterian Medical Center and *Department of Medicine, St. Luke's–Roosevelt Hospital Center, New York, New York. This work was performed during Dr. Pinsky's tenure as a Clinician-Scientist of the American Heart Association, Dallas, Texas and Dr. Steinberg's tenure as an Investigator of the American Heart Association, New York City Affiliate. Funding for these studies was derived in part from a Grant-in-Aid from the American Heart Association and the Public Health Service (HL 55397), Washington, D.C.

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Address for correspondence: Dr. David J. Pinsky, Columbia–Presbyterian Medical Center, PH 10 Stem, Room 407, 630 West 168th Street, New York, New York 10032. E-mail: djp5@columbia.edu.

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Abbreviations and Acronyms

BBB	=	bundle branch block
ECG	=	electrocardiogram, electrocardiographic
fQRS	=	filtered QRS
IVCD	=	intraventricular conduction
LAS	=	low amplitude signal at terminal portion of QRS complex
QTc	=	corrected QT interval
QTCV	=	coefficient of variation of QT intervals
QTDISP	=	QT dispersion
SAECG	=	signal-averaged electrocardiogram
V40	=	voltage of terminal 40 ms of QRS complex

low incidence of sudden death in patients with dilated cardiomyopathy, it is unclear whether these tests are useful in predicting which patients who are ill enough to require heart transplantation can survive the waiting period to receive a donor heart.

Recent studies have suggested that a standard 12-lead electrocardiogram (ECG) can provide prognostic information in some patient cohorts, especially when related to measurements of ventricular repolarization. Although QT prolongation appears to predict cardiovascular mortality in many patients (16–18), including apparently healthy individuals (19), it is not predictive in patients with left ventricular dysfunction (20). There has been a recent burgeoning interest in measuring the heterogeneity of repolarization times across the ventricular myocardium, using QT dispersion, which can be measured as the interlead variability of QT intervals on the 12-lead ECG. QT dispersion has been shown to predict sudden death in several patient cohorts, including those who are postmyocardial infarction (21) and those with ischemic cardiomyopathy (22). However, the predictive value of QT dispersion in a diverse group of patients with heart failure or those awaiting heart transplantation has not been evaluated.

Because patients accepted as candidates for heart transplantation represent a select group of patients who often do not survive the waiting period for a donor heart, there remains an urgent need to prospectively identify risk factors (at the time of heart transplant evaluation) to help assign transplant priority. This study was undertaken to determine whether clinical, ECG or SAECG variables obtained at the time of placement on the waiting list can be used to identify patients with an elevated risk of dying during the waiting period before heart transplantation. Identification of noninvasive, easily obtainable positive or negative predictors of risk could improve the strategy for allocation of the limited supply of donor organs, thereby reducing waiting lists and improving survival during the waiting period.

Methods

Patient selection. Over an 11-month period, 108 consecutive patients referred for heart transplant evaluation were asked to participate in this study, before any decision was made regarding their acceptability as a transplant candidate. Patients were enrolled after obtaining written informed consent to participate in this protocol, approved by the Institutional Review Board at Columbia–Presbyterian Medical Center. Baseline clinical variables were recorded at the time of initial evaluation, based on interviewing the patient and review of the medical records. In addition, a standard 12-lead ECG and a SAECG were obtained. Decisions regarding the patients' acceptability as heart transplant candidates (as well as decisions to remove patients from active status on the waiting list) were made independently by the heart transplant team.

12-Lead ECGs and measurement of QT dispersion. On enrollment into the protocol, standard 12-lead ECGs were obtained at a paper speed of 25 mm/s. Heart rate, QRS duration and QT intervals were measured from hard copies of the baseline ECG without knowledge of outcome data. QT intervals (23,24) were measured from the beginning of the inscription of the QRS complex until the T wave returned to the isoelectric line. If a U wave was present, the nadir of the T wave was identified as the termination of the QT interval. Rarely, notched or diphasic T waves were differentiated from T-U fusion waves. The following criteria were used (25): 1) U waves have their largest amplitude in leads V_2 and V_3; 2) U waves have $<25\%$ of the largest T wave amplitude in 98% of cases and $<50\%$ of the T wave amplitude in the same lead; 3) U wave voltage varies directly with T wave voltage; 4) U wave polarity, timing and voltage are similar when compared in contiguous leads; 5) there is typically a sudden change in slope with a notch at the T-U junction; and 6) T and U apices are separated by >0.15 s, whereas apices of diphasic T waves are <0.15 s apart. Measurements were not obtained from leads in which termination of the T wave could not be clearly identified (i.e., where isoelectric), but in all cases, a minimum of six leads were measured (ECGs were technically uninterpretable in two patients). QT dispersion was classified according to two methods (26). QT dispersion (QTDISP) was the difference between the maximal and the minimal QT intervals measured on the 12-lead ECG. The coefficient of variation of QT intervals (QTCV) was calculated according to the formula QTCV = 100 × (standard deviation of QT intervals/mean QT interval). The corrected QT interval (QTc) was determined according to Bazett's formula (27): $QTc = QT/\sqrt{RR\ interval}$. QTc dispersion was calculated in a similar fashion as QTDISP, but was corrected for the RR interval. For patients with atrial fibrillation, the QT interval was measured from the first complex of each group of three simultaneously acquired ECG leads.

Signal-averaged ECGs. The SAECGs were recorded from three orthogonal leads with a Corazonix Predictor system, using silver-silver chloride electrodes. QRS complexes were accepted after screening by a template recognition program, and acquisition continued until noise was reduced $<0.3\ \mu V$. For each SAECG obtained, three variables were analyzed after 40- to 250-Hz bandpass bidirectional filtering (28,29) to identify late potentials. These variables included 1) the filtered QRS duration (fQRS, ms), measured from the vector magnitude of the filtered leads expressed as the square root of the

sum ($X^2 + Y^2 + Z^2$); 2) the voltage of the terminal 40 ms (V40) of the fQRS complex (μV); and 3) the duration of low amplitude (<40 μV) signal (LAS) at the terminal portion of the fQRS complex (ms). Criteria for normal SAECG variables were as follows (30): 1) fQRS <110 ms; 2) V40 >20 μV; and 3) LAS <38 ms. In addition to performing outcome analyses using SAECGs from all patients awaiting heart transplantation, separate analyses were performed using those SAECGs from patients without an underlying bundle branch block (BBB) or intraventricular conduction defect (IVCD; judged to be present if the QRS complex exceeded 12 ms in duration).

Follow-up. Patients accepted as candidates for heart transplantation were followed for up to 25 months from the beginning of the study. For this cohort of patients accepted as heart transplant candidates, the primary end point was defined as cardiac death while awaiting heart transplantation. Additional end points were also identified, including the combined end point of "cardiac death or urgent transplantation" (these were patients transplanted as United Network for Organ Sharing (UNOS) status I [i.e., in the intensive care unit on inotropic support]), as well as transplantation or removal from active status on the waiting list. These end points were obtained by review of medical records, discussion with primary physicians and interviews with family members and/or friends concerning the circumstances of death. As a secondary end point, cause of death was identified as follows: Sudden death was defined as death within 1 h of the onset of new symptoms in an outpatient with previously stable symptoms (31). Congestive heart failure death was defined as progressive heart failure symptoms leading to death with or without hospitalization.

Statistics. Kaplan-Meier survival curves were computed, and univariate and multivariate analyses were performed using the log-rank test to assess the contributions of each variable evaluated with respect to outcome. All statistics were calculated based on the number of days spent on the transplant waiting list, including the time spent on the waiting list by patients who were subsequently removed from active status. Data are expressed as mean value ± SD, with $p < 0.05$ considered statistically significant. Where appropriate, odds ratios are given along with the 95% confidence interval (CI).

Results

Patients. The patient group consisted of 108 consecutive patients who were referred to the heart transplant service. Twenty-eight patients were not accepted as candidates for transplantation for the following reasons: 10 were deemed to be too well; five refused; four had concomitant diseases that precluded transplantation; five were turned down because of psychosocial reasons; one died before evaluation; and three failed to follow-up with the transplant service. The remaining 80 patients were accepted as candidates for heart transplantation and were placed on a waiting list. These 80 patients were followed up to 25 months and consisted of 63 men and 17 women (mean age 51 ± 8 years, range 25 to 67). The majority

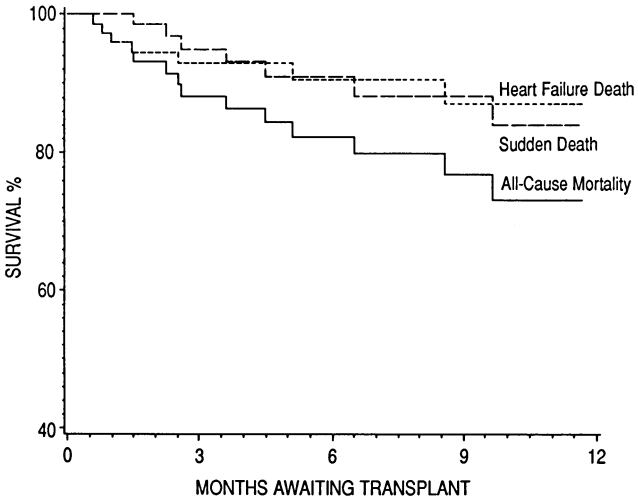

Figure 1. Survival in 80 patients awaiting heart transplantation (at time 0). All-cause mortality is shown, as well as cause-specific mortality. Congestive heart failure and sudden death were defined as described in the Methods section.

of patients (90%) were classified in functional class III heart failure by the heart transplant service. The cause of heart failure was ischemic in 44 (55%), idiopathic dilated cardiomyopathy in 33 (41%), valvular in 1 (1%) and congenital in 2 (3%). Thirteen patients were identified as having atrial fibrillation (17%). Mean left ventricular ejection fraction, determined by radionuclide or contrast ventriculography, was 19 ± 10%. Twelve patients had a history of sustained ventricular tachyarrhythmia (6 sustained ventricular tachycardia, 6 cardiac arrest), 7 had a history of syncope, and 25 were receiving antiarrhythmic therapy at the discretion of their primary physician (type IA in 11 patients, type IB in 10, combination IA/IB in 1 and type III in 3). One patient had an automatic implantable cardiovertor defibrillator, and seven were receiving beta-blockers.

Patient outcome. Of the 80 patients placed on the transplant waiting list, by the conclusion of this study at 25 months, 52 received a heart transplant (18 urgently as UNOS status I), 14 died while waiting, 13 were removed from the waiting list and 1 remained on the active waiting list. The 13 patients who were removed from active status were removed for various reasons, including improved clinical status (n = 5), patient request (n = 2), psychosocial reasons (n = 1), other illness (n = 1) and failure to follow up with the transplant clinic (n = 4). Of these patients, four were lost to follow-up, four died and five remained alive by the end of 4 years. For patients accepted as candidates for heart transplantation, the mean time on the waiting list was 201 days, and therefore the actuarial mortality rate was 27% per year during the period while awaiting heart transplantation. Mortality was high and progressive during the waiting period; by 1 month, 4% had died; by 3 months, 12% had died; by 6 months, 18% had died; and at 12 months, 27% had died (Fig. 1). Of the 14 deaths, seven were classified as sudden and seven were considered deaths due to progressive heart failure. No noncardiac deaths were identified.

Table 1. Clinical Characteristics of Patients Awaiting Heart Transplantation

	All Wait-Listed Pts (n = 80)	Survived (n = 66)	Died (n = 14)
Age (yr)	51 ± 8	50 ± 8	55 ± 5*
Men	63 (79%)	51 (77%)	12 (86%)
Etiology			
Congenital	2 (3%)	2 (3%)	0 (0%)
Valvular	1 (1%)	0 (0%)	1 (7%)
Idiopathic	33 (41%)	28 (42%)	5 (36%)
Ischemic	44 (55%)	36 (55%)	8 (57%)
NYHA functional class			
II	5%	5%	0%
III	90%	90%	100%
IV	5%	5%	0%
AF	17%	14%	3%
LVEF	19 ± 10%	20 ± 9%	19 ± 11%
Previous VTs	12 (15%)	11 (17%)	1 (7%)
Antiarrhythmic therapy	25 (31%)	20 (30%)	5 (36%)

*p = 0.05. Data presented are mean value ± SD or number (%) of patients (Pts). AF = atrial fibrillation; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; Pts = patients; VTs = ventricular tachyarrhythmias.

Risk factor analysis. *Clinical variables.* None of the clinical variables evaluated (including gender, etiology of heart failure, functional class, history of ventricular tachyarryhthmias or antiarrhythmic therapy) predicted either total (Table 1) or cause-specific mortality while on the waiting list. Of the seven patients who died suddenly, one had a history of ventricular tachyarrhythmias and two were receiving antiarrhythmic therapy. Although when evaluated as a continuous variable, age did not predict mortality risk, the mean age of those who died awaiting transplantation (55 ± 5 years) was greater than that of patients who survived the waiting period (50 ± 8 years) (p = 0.05). Left ventricular ejection fractions were uniformly low (mean 19 ± 10%) and did not predict either total or cause-specific mortality.

Standard 12-lead ECG measurements. Variables identified on the 12-lead ECG, including heart rate, QRS duration, presence of BBB, absolute value of the QT interval or the QTc, were not predictive of either total or cause-specific mortality during the waiting period (Table 2). Atrial fibrillation, which was identified in 17% of the patients awaiting heart transplantation, was not a predictor of mortality in this series (Table 3).

Table 3. Mutivariate Analysis of Clinical Variables and QT Dispersion as Predictors of Death in Patients Awaiting Heart Transplantation

	Hazards Ratio (95% CI)
Age	1.06 (0.97–1.16)
Male gender	2.04 (0.38–10.9)
Ischemic etiology	0.407 (0.11–1.56)
Previous VTs	0.429 (0.10–1.82)
Antiarrhythmic therapy	0.465 (0.06–3.81)
AF	0.503 (0.10–2.56)
QTDISP	6.77 (1.19–38.5)

CI = confidence interval; QTDISP = QT dispersion; other abbreviations as in Table 1.

Measurements of QT dispersion. In sharp contrast with standard measurements obtained from the 12-lead ECG, measurements of interlead variability of the QT interval were strong mortality predictors (Table 2). QTDISP and QTCV as continuous variables were highly predictive of mortality (p = 0.009 and p = 0.001, respectively). When patients were dichotomized into two groups—those with QTDISP ≤140 ms (short QTDISP group, n = 72) or those with QTDISP >140 ms (long QTDISP group, n = 6), the 1-year mortality differences were striking (24% vs. 56%, respectively; odds ratio 4.1, 95% CI 1.1 to 14.9) (Fig. 2A). Patients whose QTCV was >9% (long QTCV group, n = 15) had a 4.1-fold increased mortality compared with those whose QTCV was ≤9% (short QTCV group, n = 63) (95% CI 1.4 to 11.8) (Fig. 2B). (These cutpoints for long and short QTDISP and QTCV were selected by post hoc data analysis to yield predictive capability similar to that observed using continuous variables [determined by the chi-square test] after these variables were established to be mortality predictors when evaluated as continuous variables.) When the combined end point of "death or urgent transplantation" was used for analysis, QTDISP and QTCV were each significant predictors of mortality when viewed as continuous variables (p = 0.016 and p = 0.010, respectively).

When short and long QTDISP groups were compared, no significant differences were observed with respect to age,

Table 2. Electrocardiographic Characteristics of Patients Awaiting Heart Transplantation

	All Wait-Listed Pts (n = 80)	Survived (n = 66)	Died (n = 14)
HR (beats/min)	83 ± 18 (44–123)	83 ± 18 (44–123)	85 ± 17 (46–114)
QRS complex (ms)	133 ± 32 (72–200)	134 ± 32 (72–200)	126 ± 30 (92–180)
QRS complex (ms)*	102 ± 11 (72–120)	102 ± 12 (72–120)	99 ± 6 (92–108)
QT interval (ms)	416 ± 59 (308–627)	420 ± 60 (308–627)	399 ± 53 (310–489)
QTc interval (ms)	481 ± 45 (405–604)	484 ± 44 (415–604)	469 ± 51 (405–587)
QT dispersion (ms)	89 ± 39 (20–220)	85 ± 34 (20–170)	112 ± 51 (50–220)†
QTc dispersion (ms)	103 ± 42 (22–238)	98 ± 39 (22–214)	128 ± 48 (68–238)†
QT coefficient of variation (%)	7.2 ± 3.0 (1.9–16.7)	6.7 ± 2.5 (1.9–13.7)	9.3 ± 4.1 (4.5–16.7)‡

*Excluding 46 patients with bundle branch block. †p < 0.05. ‡p < 0.01. Data presented are mean value ± SD (range). HR = heart rate; QTc = corrected QT interval; Pts = patients.

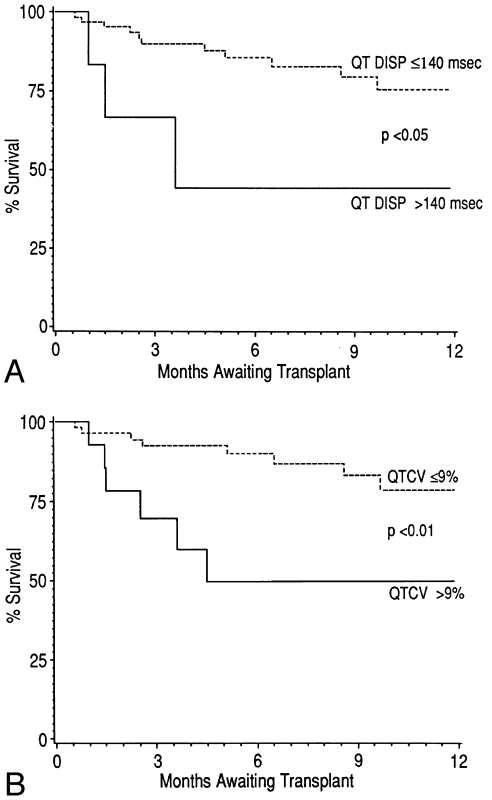

Figure 2. Effect of interlead variability of the QT interval on survival in patients awaiting heart transplantation. **A,** Effect of QTDISP (defined as the difference between the maximal and minimal QT intervals on the screening ECG) on survival in patients awaiting heart transplantation. Patients were dichotomized into two groups: six patients whose QTDISP exceeded 140 ms (at time 0) or 72 patients whose QT was ≤140 ms (at time 0). Elevated QTDISP evaluated as a continuous variable likewise predicted an increased mortality (see Results section). **B,** Effect of QTCV (calculated as 100 × [standard deviation of QT intervals]/mean QT interval) on survival in patients awaiting heart transplantation. Patients were dichotomized into two groups: 15 patients whose QTCV exceeded 9% (at time 0) or 63 patients whose QT was ≤9% (at time 0). Elevated QTCV evaluated as a continuous variable likewise predicted an increased mortality (see Results section).

gender, functional class, history of antiarrhythmic therapy, previous ventricular tachyarrhythmias or syncope or left ventricular ejection fraction. However, patients in the long QTDISP group were more likely to have an ischemic etiology of heart failure than those in the short QTDISP group ($p < 0.05$). For the short and long QTCV groups, there was no significant difference noted in any of these variables, including the etiology of heart failure. When mutivariate analysis was performed to assess the relative importance of QTDISP compared with clinical variables as predictors of mortality, only in the QTDISP group did the 95% CI not overlap unity (Table 3). Neither long QTDISP nor long QTCV predicted cause-specific mortality (Table 4). Although QTc itself was not predictive of mortality, patients who died were more likely to have an elevated QTc dispersion compared with those who survived the waiting period ($p < 0.05$) (Table 2).

Table 4. Overall and Cause-Specific Mortality as a Function of Interlead Variability of the QT Interval

	QTDISP		QTCV	
	Long (>140 ms)	Short (≤140 ms)	Long (>9%)	Short (≤9%)
No. of patients	6	72	15	63
Overall mortality	3	11	6	8
Sudden death	2	5	3	4
Heart failure death	1	6	3	4

QTCV = coefficient of variation of QT intervals; QTDISP = QT dispersion.

Because there are theoretic concerns that including patients with atrial fibrillation might result in exaggerated measurements of QT dispersion, analyses were performed in which all patients with atrial fibrillation were excluded. In these analyses excluding patients with atrial fibrillation, QTDISP and QTCV were still mortality predictors ($p = 0.025$ and $p = 0.002$, respectively). Survival analyses performed only in patients without atrial fibrillation (Fig. 3A) were similar to those performed in patients with atrial fibrillation (Fig. 1) with respect to either cause-specific or all-cause mortality. Similarly, even when patients with atrial fibrillation were excluded from analysis, patients with QTDISP >140 ms were more likely to

Figure 3. Survival in 67 patients without atrial fibrillation who were placed on a transplant waiting list (at time 0). **A,** All-cause mortality is shown, as well as cause-specific mortality. Congestive heart failure and sudden death were defined as described in the Methods section. **B,** Effect of QTDISP, according to the screening ECG, on survival in patients without atrial fibrillation. The methods are described in the legend to Figure 2.

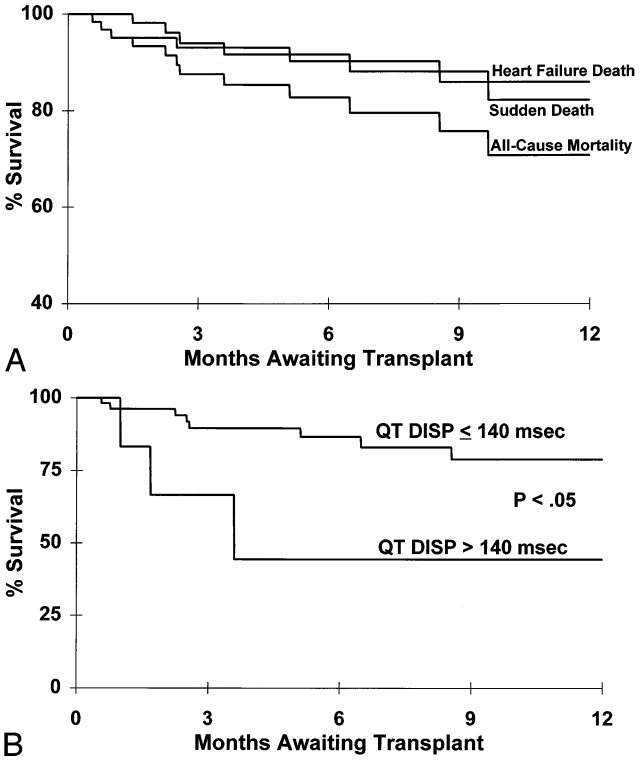

Table 5. Signal-Averaged Electrocardiographic Characteristics of Patients Awaiting Heart Transplantation

	All Wait-Listed Pts (n = 80)	Survived (n = 66)	Died (n = 14)
fQRS (ms)	147 ± 31	147 ± 31	146 ± 35
fQRS (ms)*	119 ± 17	120 ± 16	117 ± 22
V40 (μV)	27 ± 21	26 ± 19	30 ± 32
V40* (μV)	38 ± 27	36 ± 23	45 ± 42
LAS (ms)	40 ± 21	41 ± 22	37 ± 15
LAS* (ms)	34 ± 14	34 ± 15	33 ± 10

*Excluding 46 patients (Pts) with bundle branch block. Data presented are mean value ± SD. fQRS = filtered QRS duration; LAS = duration of low amplitude signal at the terminal portion of the QRS complex; V40 = voltage of the terminal 40 ms of the filtered QRS complex.

die than those with QTDISP ≤140 ms while awaiting heart transplantation (Fig. 3B). When patients with atrial fibrillation were excluded from analysis, neither clinical, ECG nor SAECG variables were predictive of either total or cause-specific mortality during the waiting period.

Signal-averaged ECG measurements. Mean SAECG data for the 80 patients on the waiting list were: 147 ± 31 ms for fQRS; 27 ± 21 μV for V40; and 40 ± 21 ms for LAS. This means that 83% of patients had an abnormal fQRS, and 53% and 46% of patients had abnormal V40 and LAS, respectively. Taken together, there was a 45% chance that all three variables were abnormal, and an 88% chance that at least one SAECG variable was abnormal. Even when 46 patients with BBB/IVCD were excluded from the analysis, there was still a 69% chance that at least one SAECG variable was abnormal (Table 5). No single SAECG variable, or combination thereof, predicted mortality, even when patients with BBB/IVCD were excluded from the analysis. However, none of the 10 patients with a completely normal SAECG died suddenly during the waiting period. There was no relation between the nature of the underlying cardiac disease and the presence of SAECG abnormalities.

Signal-averaged ECG results were not related to the QT dispersion variables. When at least one SAECG variable was abnormal compared with the criteria for a normal SAECG, QTDISP (96 ± 52 ms vs. 92 ± 67 ms) and QTCV (7.6 ± 4.4% vs. 7.8 ± 4.5%) did not differ significantly. Similar results were present in the subgroup without BBB/IVCD.

Discussion

Overview. These results demonstrate that there is a substantial mortality risk for patients awaiting heart transplantation. Nearly 20% of these patients are dead within 6 months, highlighting the need to identify risk factors at the time of placement on the waiting list. Because interlead variability of the QT interval on the ECG provides a noninvasive means for detecting spatial dispersion of repolarization (32,33), which may represent a substrate for sudden death, we evaluated the predictive value of QT dispersion for mortality during the waiting period before heart transplantation. When QT dispersion was measured from a single standard 12-lead ECG, there was a striking increased mortality risk in those patients with increased interlead variability of the QT interval measured by a variety of means. As the measurement of QT dispersion represents an easy and effective means of identifying those patients who are likely to die during the waiting period, it may serve as an important adjunct in the decision regarding priority for heart transplantation. No clinical or SAECG variable could predict either total or cause-specific mortality.

QT dispersion as a marker of risk. Of all the risk factors analyzed in this study, as well as all risk factors studied to date in a group awaiting heart transplantation, QT dispersion appears to be the one which best predicts mortality risk during the waiting period. In this study, there was a 4.1-fold increased mortality risk for those patients whose QT dispersion exceeded 140 ms, and a 4.1-fold increased mortality in those whose QTCV was ≥9%. QT dispersion may identify high risk patients with a single screening ECG, which can be performed easily, inexpensively and at sites distant from a major heart transplant center. This study adds a new dimension to previous reports indicating the usefulness of QT dispersion as a predictor of sudden death after myocardial infarction (21) in heart failure of ischemic etiology (22), as well as arrhythmia risk in the long QT syndrome (32). It is not surprising to note that values for both QTDISP (59 ± 13 ms [34], 48 ± 21 ms [35]) and QTCV (3.6% [36]) in healthy subjects (with presumably low mortality risk) reflect lower interlead variability in QT intervals than that in the patients evaluated in this study (QTDISP 89 ± 13 ms and QTCV 7.2 ± 3.0% for all patients evaluated in this study).

Prolongation of the QT interval, per se (in contrast to QT dispersion), marks cardiovascular risk in many patient cohorts, including apparently healthy subjects (19), those with alcoholic cirrhosis (16) and those with coronary artery disease (17). However, both in our series as well as in others (20,22), QT prolongation does *not* mark sudden death risk in patients with cardiac dysfunction. This is likely to reflect the fact that QT prolongation does not reflect spatial differences in myocardial repolarization times (37), which QT dispersion does (32,33).

In addition, sympathetic tone has a strong modulating role on QT dispersion. Patients with the long QT syndrome treated with beta-blockade or sympathetic denervation demonstrate a reduction in QT dispersion (35). This observation is particularly intriguing in light of the current neurohormonal hypothesis of heart failure (38), implicating activation of sympathetic tone and release of multiple neurohormones (including norepinephrine [10]) in the pathogenesis and progression of heart failure. Although further investigation is needed, it is possible that neurohormonal activation in severe heart failure may be reflected in measurements of QT dispersion, thus conceivably providing a pathophysiologic connection to overall cardiac mortality in this condition.

Although total mortality was predicted by measurements of interlead variability of QT intervals, in our group of patients with heart failure of diverse etiologies, indices of QT dispersion did not predict mechanism of death. Only in one analysis

(that of the high QTDISP group) did ischemic etiology predict a high QTDISP (>140 ms), although it did not predict mortality or mechanism of death. However, when evaluated as continuous variables, there was a trend toward the highest indices of QT dispersion in those patients who died suddenly (QTDISP 126 ± 51 ms, 99 ± 51 ms and 85 ± 34 ms; QTCV 10.0 ± 4.3%, 8.6 ± 4.0% and 6.7 ± 2.5% for patients with sudden death or heart failure or those who survived, respectively). Although our small sample size precludes a direct conclusion relating to QT dispersion as predicting mechanism of death, it is interesting to note that an even smaller study of 41 patients with only ischemic cardiomyopathy (22) showed that an increased QTDISP predicted higher sudden death risk. It is possible that sudden death is predicted by QTDISP, but in our study, the number of end points broken down by cause of death had insufficient power to detect an association. In addition, proximate mechanisms of death in heart failure are often difficult to identify, especially in outpatients. Most of our patients continued to be cared for by their primary physicians in a large geographic distribution, further hampering accurate assignment of mechanism of death. For these reasons, we chose (a priori) to use cardiac death as our primary end point. It has become increasingly common for prospective studies to use overall mortality end points, rather than cause-specific end points, to avoid bias. Although spatial differences in myocardial repolarization times (reflected by increased QTDISP) (37) may lead one to predict a higher sudden death risk due to arrhythmia, QT dispersion does not reflect arrhythmia risk as assessed by 24-h Holter recording in patients with heart failure (39).

Our technique of measuring QT intervals from hard copy ECGs is similar to that described in most studies of QT dispersion to date (26). Although in our study, no fewer than six leads were available for analysis, it must be recognized that when fewer leads are analyzed, one is more likely to obtain a spuriously low value for QT dispersion, as the true minimal or true maximal values may be missed (26). Use of QTCV, as previously described (35,36), serves as a weighted estimate of interlead variability of all measurable QT intervals. QTCV takes into account all leads evaluated as a statistical measure of dispersion, which may account for the slightly improved potency of QTCV as a mortality predictor compared with QTDISP (defined as QT_{max}–QT_{min}). The cutpoints we have used in this study to define high and low risk QTDISP and QTCV groups were established after we had determined that both measures were strongly predictive of mortality when evaluated as continuous variables. Although such a post hoc assignment of high and low risk groups does not weaken the conclusions derived from an analysis of these continuous variables, the clinical relevance of the selected cutpoints will require further study.

Clinical risk factors in the patients studied. The overall mortality we observed (27%, annualized), as well as its distribution between heart failure and sudden death, is comparable to that identified in other series of patients awaiting heart transplantation (4). More relevant to the issue of the wait for a donor heart, however, was the 12% mortality rate at 3 months and 18% at 6 months. Given the mean wait of nearly 7 months before heart transplantation in this series, similar to the 6.6-month national average in the United States (3), there is substantial attrition caused by both heart failure death and sudden death. This high mortality rate during the waiting period is particularly disturbing, given the fact that all of the patients in the current series were deemed appropriate heart transplant candidates who could have expected improved quality of life as well as an improved life expectancy (40) had they survived until the time of heart transplantation.

Evaluation of clinical variables was far less helpful in stratifying risk in the pretransplant group in our series. Although age evaluated as a continuous variable did not predict death of patients awaiting heart transplantation, compared with younger individuals, more older patients (>55 years) died during the waiting period. Advanced age is already considered an exclusion criteria for heart transplantation. Some investigators have suggested that the upper age limit be reduced below 55 years (5). Our data support the concept that older patients face a greater risk, and that this risk extends to the waiting period for heart transplantation. In this series, no other clinical markers of total or cause-specific mortality could be identified. Although we did note that QT dispersion was elevated in patients with an ischemic etiology of heart failure, etiology of heart failure did not predict mortality in our study, commensurate with the observations of others (9) that etiology does not predict mortality in patients with severe heart failure.

Signal-averaged ECG as a marker of risk. The SAECG has been proposed as a marker of risk of sudden death in a group of patients who are postmyocardial infarction (41,42), although it seems to be more useful in predicting serious arrhythmic events than death in this setting (30,41,43,44). The SAECG obtained at baseline should reflect the stable conduction characteristics of the individual patient, regardless of the degree of decompensation of heart failure (45), and so a single recording of the SAECG at entry into this study was performed. The present data show that mortality cannot be predicted by any single SAECG variable or combination thereof. This may be due in part to the high prevalence of abnormal SAECGs in this critically ill group of patients (88% in our series). A completely normal SAECG (12% of transplant candidates), however, was not associated with any instances of sudden death in the present series. This is consistent with the data of others (11–13,15,30,43), which show that in both patients with dilated cardiomyopathy or previous myocardial infarction, a normal SAECG is associated with a low risk of sudden death.

Conclusions. Patients awaiting heart transplantation have a high risk of dying during the waiting period (nearly 20% at 6 months). No clinical variable at entry (including ejection fraction) predicted mortality risk in this series. In contrast, indices of QT dispersion obtained on a single 12-lead ECG obtained at the time of placement on the waiting list provided a new means to identify patients at high risk of dying during the waiting period. Because heart transplantation candidates far

exceed available donor hearts, transplant waiting lists are growing at an alarming rate (4), and hearts are preferentially going to sicker inpatient candidates. Taken together, these data suggest that elevated QT dispersion (with its high risk of all-cause mortality) can be used to stratify patients on heart transplant waiting lists. Creation of such a risk profile would not only help to establish priority on a transplant waiting list to optimize allocation of a scarce medical resource, but also might serve to limit needless deaths of patients who die awaiting their donor heart.

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