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Value of QT dispersion analysis for noninvasive detection of cardiac allograft rejection

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Acute cellular rejection (AR) is a major cause of morbidity and mortality after heart transplantation (HT). It is characterized by edema, lymphocyte infiltration, and myocyte necrosis.1 Endomyocardial biopsy (EMB) is the diagnostic method of choice, as none of the noninvasive methods that have been tried have proved to be as efficient.2 However, EMB is invasive and its sensitivity is limited by its involving sampling of nonhomogenous tissue.3 and 4

The electrocardiographic QT interval indicates the total duration of ventricular activity, including depolarization and repolarization. Between-lead QT dispersion ($QT_{max} - QT_{min}$) and the analogous dispersion ($QTc_{max} - QTc_{min}$) of the "corrected" QT, $QTc = \{QT(ms)/[1000(ms^{-1}) \cdot RR(ms)]^{1/2}\}$, are measures of the spatial irregularity of myocardial electrical conduction. Both have been identified as risk markers in relation to several cardiopathies, and increased QTc dispersion has been related to increased risk of life-threatening ventricular arrhythmias and sudden death.5 and 6 For example, there is growing evidence that QT dispersion and QTc dispersion are correlated with the risk of sudden death among patients with congestive heart failure,7 left ventricle (LV) hypertrophy due to hypertrophic cardiomyopathy,8 ischemic cardiopathy,9 or mitral valve prolapse.10 QT dispersion is also increased in patients with arrhythmogenic right ventricular dysplasia.11

It has been suggested that QT dispersion may be a useful marker or predictor of cardiovascular morbidity and mortality due to complex ventricular arrhythmias in patients with rheumatoid arthritis12 or Duchenne muscular dystrophy13 or of increased risk of cardiac complications in liver transplant candidates.14 The usefulness of QT dispersion analysis in heart transplant patients is still unknown, and few studies have been done in this area. It has been suggested that cardiac allograft vasculopathy results in ventricular repolarization abnormalities that can be detected by an increase in QTc dispersion15 and that QT dispersion might serve as a noninvasive marker of resolution of allograft dysfunction.16 Here we report the results of a study of the relationship between QT dispersion and AR status as determined by EMB.

Patients and methods

Thirty consecutive patients who underwent HT between February 1995 and April 1996 and survived longer than 1 month were studied. EMB was performed every 10 days during the first and second months after HT, every 15 to 20 days during the third and fourth months, at the end of the fifth and sixth months, at various times thereafter, and whenever suspicion of AR arose. EMB specimens were graded in accordance with the International Society for Heart and Lung Transplant (ISHLT) classification.17

Each EMB was accompanied by a standard 12-lead electrocardiogram (ECG) recorded at a paper speed of 25 mm/s. A blind observer used callipers to measure QT, the interval between the onset of the QRS complex and the end of the T wave. The QT interval for each lead was calculated as the mean over three cycles, and the absolute QT dispersion (ΔQT) was calculated by subtracting the shortest of these single-lead QTs from the longest. To obtain QTc, each single-lead QT was corrected for the patient's heart rate using Bazett's formula, $QTc = \{QT(ms)/[1000(ms^{-1}) \cdot RR(ms)]^{1/2}\}$, and absolute QTc dispersion (ΔQTc) was calculated by subtracting the shortest single-lead QTc from the longest, $\Delta QTc = QTc_{max} - QTc_{min}$.

Statistical analysis

Unpaired *t* tests for comparison of means were performed to detect any connection between QT dispersion and AR, which was considered as indicated by an ISHLT EMB grade higher than 2. Analyses of variance (ANOVAs) were performed to detect any dependence of QT dispersion at first EMB on donor age group (<25 years [11 patients], 25–39 years [13 patients], ≥40 years [6 patients]) or on allograft ischemia time (50–100 minutes, 101–170 minutes, 171–240 minutes; 10 patients in each group).

Results

A total of 349 ECGs and EMBs were performed on 30 patients. Two ECG/EMB pairs were excluded from the analyses due to the EMB material being insufficient for diagnosis. We found no significant differences in QT dispersion among EMB grades (Table 1), nor between QTc dispersion and AR status: QTc dispersion was 40 ± 17 milliseconds in the AR group (n = 31) and 42 ± 23 milliseconds in the non-AR group (n = 316). QT dispersion and QTc dispersion decreased with increasing donor age group, but the between-group variation was not statistically significant ($P > 0.33$ and $P > 0.27$, respectively; see Table 2). Nor did ischemia time significantly influence QT dispersion or QTc dispersion ($P > 0.83$ in both cases; see Table 3).

Table 1. ΔQT, ΔQTc, and Their Source Parameters at Each EMB in Patient Groups Defined by ISHLT EMB Grade

ISHLT EMB	n	QT_{max} (ms)	QT_{min} (ms)	RR (ms)	ΔQT (ms)	QTc_{max} (ms)	QTc_{min} (ms)	ΔQTc (ms)
0	152	357 ± 30	321 ± 27	656 ± 79	35 ± 19	442 ± 33	398 ± 31	43 ± 24
1A	98	358 ± 26	323 ± 28	671 ± 79	35 ± 19	439 ± 32	395 ± 31	43 ± 24
1B	21	350 ± 24	322 ± 23	669 ± 64	28 ± 18	429 ± 26	395 ± 25	34 ± 22
2	45	345 ± 30	316 ± 30	656 ± 79	29 ± 16	427 ± 27	390 ± 26	36 ± 19
3A	28	345 ± 28	312 ± 25	653 ± 99	32 ± 14	429 ± 27	389 ± 30	40 ± 17
3B	3	340 ± 20	306 ± 23	643 ± 40	33 ± 11	423 ± 11	382 ± 18	41 ± 14
Total	349	354 ± 29	320 ± 27	660 ± 79	33 ± 18	437 ± 32	395 ± 30	41 ± 23

EMB, endomyocardial biopsy; ISHLT, International Society for Heart and Lung Transplant.

Table 2. QT Dispersion and QTc Dispersion at First Post-HT EMB in Three Groups of Patients Defined by Donor Age

Donor Age (years)	n	ΔQT (ms)	ΔQTc (ms)
<25	11	42 ± 31	51 ± 35
25–39	13	29 ± 21	34 ± 24
>=40	6	26 ± 20	31 ± 24
Total	30	33 ± 25	39 ± 29

EMB, endomyocardial biopsy.

Table 3. QT Dispersion and QTc Dispersion at First Post-HT EMB in Three Groups of Patients Defined by Ischemia Time

Ischemia Time (min)	n	ΔQT (ms)	ΔQTc (ms)
50–100 (T1)	10	30 ± 25	35 ± 28
101–170 (T2)	10	37 ± 33	43 ± 39
171–240 (T3)	10	34 ± 16	40 ± 19
Total	30	33 ± 25	39 ± 29

EMB, endomyocardial biopsy.

Discussion

The reproducibility of QT and QTc is controversial. Some authors have reported large variability both between successive recordings, with relative errors of 25% to 35%, and between observers (28% to 33%).18 and 19 Others have found much smaller between-observer variabilities of 5% to 7% and within-observer variabilities of 4% to 5%.20 The results seem unlikely to have been distorted by measurement variability.

The QT interval is considered to reflect cellular action potential duration. It has been suggested that myocardial necrosis and/or edema due to post-HT AR may cause ventricular repolarization inhomogeneities that would show up as abnormal QT dispersion. However, in this work, we found no correlation between QT dispersion and EMB-defined AR status. Nor were QT dispersion or QTc dispersion associated with ischemic time or donor age. These negative results suggest that the limited information afforded by QT dispersion concerning the complex electrogenesis of ventricular repolarization is insufficient for detection of such inhomogeneities as may be caused by AR at the cellular level. It should be borne in mind that there are many other factors apart from rejection that might influence ventricular repolarization in HT patients, such as left ventricular mass, systolic and diastolic blood pressures, and drug therapy.

Conclusions

The results of this study do not support proposals for the use of QTc dispersion for diagnosis of AR in HT patients.

References

1. K Sagar, A Hastillo, T Wolfgang, *et al.* Circulation, 64 (1981), p. 216.
2. M.E Billingham. J Heart Transplant, 9 (1990), p. 272.
3. R.E Nakhleh, J Jones, J.J Goswitz, *et al.* J Heart Lung Transplant, 11 (1982), p. 479.
4. J.A Vázquez de Prada. Rev Esp Cardiol, 48 (1995), p. 86.
5. P Schwartz, S Wolf. Circulation, 57 (1978), p. 1074.
6. J.T.Y Hii, D.G Wyse, A.M Gillis, *et al*. Circulation, 86 (1992), p. 1376.
7. C.S Barr, A Naas, M Freeman, *et al*. Lancet, 343 (1994), p. 327.
8. G Buja, M Miorelli, P Turrini, *et al*. Am J Cardiol, 72 (1993), p. 973.
9. P.D Higham, S.S Furniss, R.W.F Campbell. Br Heart J, 73 (1995), p. 32.
10. R.G Tieleman, H.J.G.M Crijns, A.C.P Wiesfeld, *et al.* Br Heart J, 73 (1995), p. 37.
11. M Benn, P.S Hansen, A.K Pedersen. Eur Heart J, 20 (1999), p. 764.
12. O Goldeli, E Dursun, B Komsuoglu. J Rheumatol, 25 (1998), p. 447.
13. M Yotsukura, A Yamamoto, T Kajiwara, *et al*. Am Heart J, 137 (1999), p. 672.
14. M Tallgren, K Hockerstedt, J Makinen, *et al*. Clin Transplant, 10 (1996), p. 408.
15. A Ali, M.R Mehra, F.S Malik, *et al*. J Heart Lung Transplant, 17 (1998), p. 102.
16. A Ali, M.R Mehra, F.S Malik, *et al*. J Heart Lung Transplant, 17 (1998), p. 105.
17. M.E Billingham, N.R Cary, M.E Hammond, *et al*. J Heart Transplant, 9 (1990), p. 587.
18. J Kautzner, Y Gang, A.J Camm, *et al.* Pacing Clin Electrophysiol, 17 (1994), p. 928.
19. J Kautzner, Y Gang, A.G.R Kishore, *et al*. Ann Noninv Electrocardiol, 1 (1996), p. 363.
20. J.R González-Juanatey, J.M Garcia-Acuña, A Pose, *et al*. Am J Cardiol, 81 (1998), p. 170.