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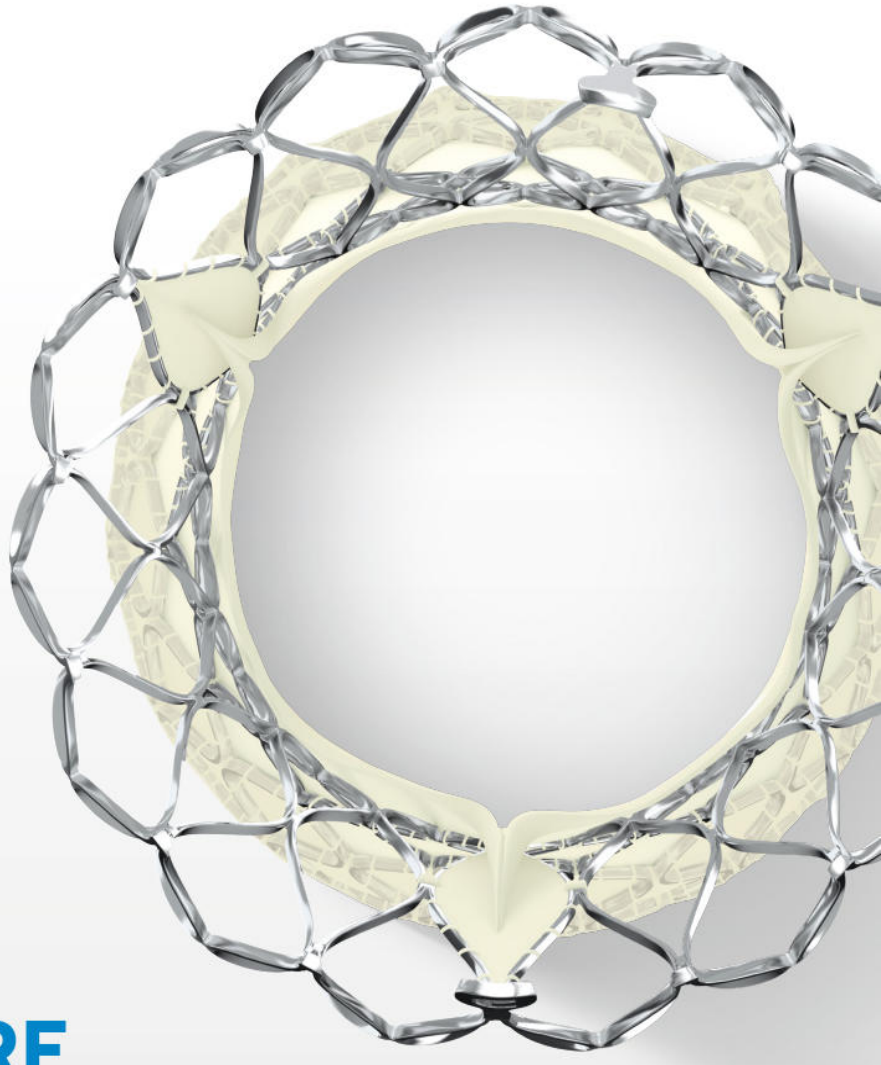

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Is Ventricular Repolarization Heterogeneity a Cause of Serious Ventricular Tachyarrhythmias in Aortic Valve Stenosis?

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Summary

Background: It is well known that there is a close relation between sudden cardiac death and serious ventricular tachyarrhythmias in patients with aortic valve stenosis (AS). QT dispersion (QTd) reflects the ventricular repolarization heterogeneity and has been proposed as an indicator for ventricular arrhythmias.

Hypothesis: This study investigated the QTd and its relevance to the clinical and echocardiographic variables.

Methods: In all, 51 patients (33 men, 18 women, mean age 56 ± 12) with isolated AS and 51 age- and gender-matched healthy controls comprised the study group. Left ventricular mass index (LVMI) was calculated by the Devereux formula, and we used continuous-wave Doppler (n = 15) and cardiac catheterization (n = 36) for the determination of the maximum aortic valve pressure gradient (PG).

Results: Corrected QTd (QTcd) (89 ± 39 vs. 49 ± 15 ms, $p < 0.001$) and LVMI (176 ± 69 g/m^2 vs. 101 ± 28 g/m^2, $p < 0.001$) in patients with AS were significantly different from those in the control group. The group of 21 patients had a significantly greater number of 24-h mean ventricular premature beats (VPB) and mean number of couplet VT episodes than did the control group ($p < 0.05$). QTcd also correlated significantly well with LVMI ($r = 0.58$, $p < 0.001$), PG ($r = 0.41$, $p = 0.003$), and number of 24-h VPB ($r = 0.56$, $p = 0.008$). With respect to symptoms (e.g., angina, syncope, and dyspnea) patients without symptoms (n = 19) displayed less QTcd (71 ± 31 vs. 100 ± 39 ms, $p = 0.007$) and less LVMI (144 ± 80 g/m^2 vs. 195 ± 57 g/m^2, $p = 0.01$) than patients with symptoms. Statistical analysis was similar for all variables with uncorrected QTd values.

Conclusion: We found that ventricular repolarization heterogeneity was greater in patients with AS than in controls. Our findings also showed that QTd in the patient group correlates well with LVMI, severity of AS, and PG. The present results suggest that serious ventricular arrhythmias in patients with AS may be due to spatial ventricular repolarization abnormality.

Key words: QT dispersion, aortic valve stenosis, arrhythmia

Introduction

It is well known that there is a close relation between sudden cardiac death and serious ventricular tachyarrhythmias in patients with aortic valve stenosis (AS).[1–4] However, although a higher prevalence of ventricular arrhythmias has been documented in patients with AS, the mechanisms underlying these arrhythmias are still not clear.

Recent studies have suggested that interlead QT variability on the surface electrocardiogram (ECG), defined as QT dispersion (QTd), may reflect regional variations in ventricular recovery of excitability. Increased dispersion of ventricular repolarization time is believed to provide a substrate that facilitates serious ventricular arrhythmias.[5–8]

Therefore, we investigated the QT dispersion—as a marker of repolarization abnormality—in patients with AS and its possible role in the development of ventricular arrhythmias in these patients. We also analyzed its relevance to the clinical and echocardiographic variables of patients with AS.

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Patients and Methods

Patients

We selected 51 patients with isolated AS (33 men and 18 women, mean age 56 ± 12 years). Exclusion criteria were other overt cardiac valve disease (except trace degree valve insufficiency and valve thickening) shown by M-mode and two-dimensional (2-D) color-Doppler echocardiography; atrial fibrillation or bundle-branch block or preexcitation; angiographically documented significant coronary artery disease (coronary angiogram obtained from 41 patients) or suspected coronary artery disease shown by thallium-201 perfusion scan, echocardiography, and ECG (10 patients); taking of oral medications which might alter QT interval; and electrolyte imbalance. A group of age-matched healthy subjects (33 men and 18 women, mean age 54 ± 13 years) with a normal physical examination, standard 12-lead ECG, and normal M-mode and 2-D color-Doppler echocardiography served as controls.

Gradient Measurements

Transvalvular aortic gradient measurements were obtained by standard left heart catheterization techniques in 36 of the 51 patients. Continuous wave Doppler technique (using the modified Bernoulli equation with Toshiba 160 SSH) was used for the other patients in whom catheterization was not performed or the catheter did not pass retrogradely.[9]

Left Ventricular Mass Index

Left ventricular end-diastolic dimensions and posterior wall and septal wall thicknesses were measured with 2-D guided M-mode echocardiography. All echocardiograms were recorded and measurements were obtained by an observer blinded to the subjects' clinical data. Left ventricular mass was calculated by the formula of Devereux *et al.*[10] and left ventricular mass index (LVMI) by dividing left ventricular mass by body surface area.

Holter and QT Analysis

Ambulatory ECG monitoring was performed in 21 of the 51 patients and in matched healthy subjects to quantify ventricular arrhythmias. QT interval and QTd measurements were calculated from a 12-lead resting ECG during sinus rhythm at a paper speed of 25 mm/s with 1 mV amplitude. The ECGs were magnified 100% with photocopy. Two blinded observer measured the QT interval from the onset of QRS to the end of the T wave, defined as a return to T-P baseline. When U waves were present, QT was measured to the nadir of the curve between the T and U waves. When the end of the T wave could not be identified, the lead was not included. A minimum of seven leads, at least three of which were precordial, was required for QTcd to be calculated. The QTc was calculated using Bazett's formula.[11] QTcd was defined as the difference between the maximal and the minimal QTc intervals occurring in any of the 12 leads.

Reproducibility

We performed a study on the variability of QT measurements. Twenty ECGs were coded and duplicated and measured blindly by two observers. We found an intraobserver variability of 1–3% and an interobserver variability of 2–4%.

Statistical Analysis

Categorical variables were compared by chi-square analysis. Continuous variables are presented as mean value ± standard deviation and compared by a two-tailed Student's *t*-test, either parametric or nonparametric as appropriate. Simple correlation analysis was used for assessment of relations between variables. A value of $p < 0.05$ was considered statistically significant. SPSS release 6.0 for MS Windows (SSPS, Inc., Cary, N.C., USA) was used for statistical analysis.

Results

There were no significant differences between the patient and control groups with regard to age and gender ($p > 0.05$). Hemodynamic, echocardiographic, ECG, and Holter data are presented and compared in Table I. Maximum QT and QTc interval, QTd and QTcd, and LVMI in patients with AS were significantly greater than those in controls. The group of 21 patients had a significantly greater mean number of 24-h ventricular premature beats and a mean number of couplet VT episodes than did the control group.

QTcd and QTd also correlated significantly well with LVMI ($r = 0.58$, $p < 0.001$; $r = 0.54$, $p < 0.001$, respectively), transvalvular aortic peak gradient ($r = 0.41$, $p = 0.003$; $r = 0.41$, $p = 0.003$, respectively), and 24-h ventricular premature beat number ($r = 0.56$, $p = 0.008$; $r = 0.53$, $p = 0.009$, respectively).

With respect to symptoms (e.g., angina, syncope, and dyspnea), patients without symptoms (n = 19) displayed less QTd

TABLE I Comparison of hemodynamic, echocardiographic, electrocardiographic, and Holter data of patients and control group

	Patient	Control	p Value
Aortic peak gradient (n = 51)	56 ± 26 (min. 31, max. 120)	—	—
Ejection fraction (n = 51)	67 ± 9	68 ± 8	NS
LVMI (n = 51)	176 ± 69	101 ± 28	< 0.001
Max QT (n = 51)	392 ± 34	365 ± 20	0.003
Max QTc (n = 51)	439 ± 33	408 ± 22	0.002
QTd (n = 51)	79 ± 36	43 ± 14	< 0.001
QTcd (n = 51)	89 ± 39	49 ± 15	< 0.001
VPB (24 h) (n = 21)	439 ± 531	97 ± 152	0.002
Couplet and VT number	6.3 ± 9.7	1.5 ± 2.6	0.031

Abbreviations: LVMI = left ventricular mass index, NS = not significant, QTd = QT dispersion, QTdc = corrected QT dispersion, VPB = ventricular premature beats, VT = ventricular tachyarrhythmia.

and QTcd (62 ± 29 vs. 90 ± 38 ms, p = 0.008; 71 ± 31 vs. 100 ± 39 ms, p = 0.007, respectively) and less LVMI (144 ± 80 g/m^2 vs. 195 ± 57 g/m^2, p = 0.01) than did patients with symptoms. However, there was no significant difference for the aortic gradient in patients with and without symptoms (51 ± 26 vs. 59 ± 25 mmHg, p > 0.05), although the symptom-positive group had a greater pressure gradient.

Discussion

Although the exact electrophysiologic mechanism of the arrhythmogenicity of AS remains unknown, a variety of hypothetical mechanisms have been put forward and, to some extent, experimentally documented:

Increased afterload imposed on the left ventricle as seen in AS causes a progressive concentric hypertrophy of the left ventricle in order to normalize systolic wall stress and preserve left ventricular function.[12] The increase in myocardial mass is produced by an increase in the size of myocytes, an increase in the number of extramyocyte cell components (connective and vascular tissue), and an increase in fibrous material and other extracellular elements, all of which can disturb intercellular flow of the electric current and can initiate reentry as a result of premature beat.[12, 13] The Framingham study showed that left ventricular hypertrophy, as demonstrated by ECG and echocardiography, is associated with an increased risk of death even in asymptomatic subjects.[14, 15] Hypertrophied myocardium can also cause the progressive prolongation of the action potential.[16] Altered cardiac repolarization and an increased dispersion of ventricular refractoriness is another electrophysiologic abnormality of the hypertrophic myocardium.[17, 18] Our findings of increased QTd values in patients with isolated AS reflect the similar results in studies comparing QTd and cardiac hypertrophy due to aortic stenosis[19] and other causes.[20] We also found a most prominent correlation between QTd and the LVMI. Consequently, myocardial hypertrophy may be the major cause of increased refractoriness of the myocardium in patients with AS.

A decrease in electric threshold has been described in isolated myocytes following mechanical stretching. Likewise, in an experimental study in which pressure load was gradually increased, the rate of ventricular ectopy increased in parallel.[21] We also found a good correlation between QTcd and maximum pressure gradient, so we can speculate that mechanical load and stretching may increase ventricular repolarization heterogeneity. Our finding of a correlation between the severity of AS, suggested by an increased aortic transvalvular gradient, and QTd may show an increased risk for serious arrhythmias in patients with severe aortic stenosis, as also suggested by other studies.[2, 19]

Ischemia and angina may occur in the absence of significant coronary artery disease, due to both increased oxygen demands by the hypertrophied left ventricle and decreased oxygen delivery from excessive compression of the smaller coronary vessels.[22] It has been shown that there is a strong relation between ischemia and QTd.[6, 8] Ischemia may be one of the causes of increased QTd and QT interval in our patients, although they had no coronary artery disease.

Angina pectoris, syncope, and heart failure are the cardinal symptoms of AS. The onset of symptoms in patients with AS is an ominous sign: survival curves show that the time of death following symptom occurrence is approximately 5 years for patients with angina, 3 years for those with syncope, and 2 years for patients with heart failure.[12] Our patients with symptoms displayed higher QTd and higher LVMI than patients without symptoms; therefore, our results may be an another explanation for why patients with symptoms have a higher risk of mortality.

We found a significantly greater mean number of 24-h ventricular premature beats and couplet VT episodes in the patient group than in the control group. These results are consistent with several investigators' observations of ventricular arrhythmias in patients with aortic valvular disease, even in the absence of coronary artery disease.[2–4] Some investigators indicated that the frequency and complexity of ventricular arrhythmias were closely related to myocardial function.[23] On the other hand, we showed that the severity of arrhythmias was more prominent in patients with AS, even though they have normal systolic left ventricular function. It has been determined that serious arrhythmias, in valvular heart disease, were most frequently noted in patients with AS who also had a higher incidence of sudden death.[24] Likewise, we found a good correlation between QTd and the number of 24-h ventricular premature beats (r = 0.53, p = 0.009).

Study Limitations

Bazett's formula for the calculation of QTc has been found to give suboptimal correction, as it includes a slight overcorrection of the QT interval for fast heart rates. However, none of the other proposed methods of rate correction for QT have been generally accepted.

Conclusion

We found that ventricular repolarization heterogeneity in patients with AS was greater than that in controls, and that patients with AS are susceptible to developing serious ventricular arrhythmias. Our findings also showed that QTd in the patient group correlates well with LVMI, severity of AS, and PG. The present results suggest that serious ventricular arrhythmias in patients with AS may be due to spatial ventricular repolarization abnormality.

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