Electrocardiographic changes during dobutamine stress testing in patients with recent myocardial infarction: relation with residual infarct artery stenosis and contractile recovery

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Objective — The identification of viable but jeopardized myocardium after acute myocardial infarction (AMI) is of great importance for selecting patients who could benefit from a revascularization procedure.

The aim of the study was to determine the accuracy of the dobutamine stress electrocardiogram (ECG) 1) for detecting significant stenosis of the infarct-related artery and 2) for predicting the occurrence of contractile recovery.

Methods and results — Ninety-four patients underwent dobutamine stress ECG and quantitative angiography within the first week after AMI. A follow-up resting echocardiogram was obtained in all patients at 1 month. Significant stenosis of the infarct-related artery was detected in 76 patients and functional recovery occurred in 56 patients. Dobutamine stress induced ST-segment elevation in 44 patients, ST-segment depression in 17 and T-wave normalization in 34. Increase in QT dispersion and dobutamine ST elevation were more sensitive than chest pain and ST-segment depression (79% and 53% vs. 24% and 17%, respectively; $p<0.05$) for detecting significant infarct-related artery stenosis. Four independent variables were selected for predicting contractile recovery: ≥20 ms increase in QT dispersion from baseline to low-dose dobutamine ($p = 0.00016$), dobutamine-induced ST-segment elevation ($p = 0.0009$), elective angioplasty of the infarct-related artery ($p = 0.001$) and T-wave normalization ($p = 0.005$).

Conclusions — The analysis of predischarge dobutamine stress ECG is useful for predicting residual stenosis of the infarct-related artery and contractile recovery in the affected area. QT dispersion changes during the test are the most accurate parameter. *(Acta Cardiol 2004; 59(1): 11-16)*

Keywords: *myocardial infarction – coronary stenosis – dobutamine – electrocardiography.*

Introduction

After acute myocardial infarction (AMI), the identification of viable myocardium at jeopardy is clinically important, because of its prognostic and therapeutic implications[1]. Stress echocardiography or scintigraphy are most frequently used as a diagnostic tool, but they are operator dependent or expensive[2,3]. In this clinical setting, the potential role of exercise or dobutamine electrocardiogram (ECG) has recently emerged[4-7]. During pharmacological stress, the ECG signal to noise ratio is significantly better than during dynamic exercise. Three stress-induced ECG changes are possibly related to myocardial viability: T-wave normalization[4], ST-segment elevation[5,6] and an increase in QT dispersion[7]. However, the link between these ECG characteristics and the occurrence of contractile recovery has not yet been fully elucidated[8,9]. Jeopardized myocardium in the affected area implies collateral-dependent viable myocardium or salvaged myocardium perfused by a coronary artery exhibiting reduced flow reserve[2]. The present study was designed to determine the accuracy of several dobutamine-induced ECG changes 1) for detecting significant stenosis of the infarct-related

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artery and 2) for predicting the occurrence of contractile recovery.

Methods

Study patients

A total of 121 consecutive patients admitted for a first AMI were prospectively recruited for the study. AMI was diagnosed by an increase in creatine kinase and creatine kinase MB myocardial enzymes to at least twice the normal values in the clinical setting of typical chest pain lasting more than 30 minutes and acute ST-segment elevation. No contraindications to graded dobutamine infusion were present: post-infarction angina, heart failure, uncontrolled systemic hypertension or ventricular arrhythmias. All patients underwent resting echocardiography, dobutamine-stress testing and coronary angiography. Twenty-seven patients were excluded because of an uninterpretable dobutamine test: the target heart rate was not reached in 17, severe arrhythmias occurred in 3 and 7 patients had a non-interpretable ECG. The final study population consisted of the 94 remaining patients (82 men and 12 women), with a mean age of 59 ± 12 years. The infarct ECG location was anterior in 35 patients, lateral in 6, and inferior in 53. The mean peak level of serum creatine kinase was 2,107 ± 976 IU/l. Fifty-nine patients (63%) were treated with thrombolytic therapy but none underwent primary angioplasty of the infarct-related vessel. The study was approved by the Research Ethics Committee of our institution; informed consent was obtained in all patients.

Stress test

Stress dobutamine-ECG was performed 4 ± 2 days after admission. Beta-adrenergic-blocking agents were withdrawn 24 hours before the test. A 12-lead ECG was continuously monitored and recorded every minute. Blood pressure was measured at each stage by an arm-cuff sphygmomanometer. Dobutamine was administered in doses of 5 and 10 μg/kg/min for 3 minutes each, followed by increments of 10 μg/kg/min every 2 minutes, up to a maximal dose of 40 μg/kg/min. Atropine (0.25 mg to a maximum of 1 mg) was added if the target heart rate (85% of maximum predicted heart rate) was not reached with dobutamine alone. End points of the test were: target heart rate, limiting chest pain and significant (≥2 mm) ST-segment depression. A follow-up resting echocardiogram was recorded 1 month later in all patients and contractile recovery was defined to be present when wall thickening increased by at least 1 score in 2 contiguous segments of the affected area.

Electrocardiographic analysis

ST-segment, T-waves and QT characteristics were analysed in the infarct-related ECG leads, as previously described[7,9]. During stress test, ST-segment elevation was defined as new or worsening ≥1 mm, 80 ms after J point, in ≥2 contiguous infarct-related leads. T-wave normalization was defined as present when inverted T-waves at rest became upright during stress in ≥2 infarct-related leads. QT interval was measured from the onset of QRS to the end of T-wave. QT dispersion was defined as the difference between the maximum and minimum QT intervals. QT dispersion was calculated at baseline, at low-dose dobutamine and at peak stress. The QT dispersion differences between low-dose dobutamine and rest and between high and low-dose dobutamine were also calculated. Since QT dispersion does not change with heart rate, heart rate-corrected QT dispersion was not calculated[10].

Coronary angiography

Quantitative coronary angiography and left ventriculography were performed in all patients within 1 week after the dobutamine test. Quantitative measurements of coronary stenoses were performed with the use of the CAAS system (Cardiovascular Angiography Analysis System, Philips Integris-Medical System, Eindhoven, The Netherlands). Mean global left ventricular ejection fraction was 47 ± 15%. End-diastolic volume and end-systolic volume were 102 ± 39 ml/m^2 and 61 ± 42 ml/m^2, respectively. Significant stenosis of the infarct-related artery (≥50%) was observed in 76 patients. Persistent occlusion of the infarct-related artery was observed in 14 patients. Mean residual stenosis of a patent infarct-related artery was 70 ± 19%. Elective angioplasty of the infarct-related artery was performed in 56 (60%) patients who had ≥60% stenosis. The results of stress testing were not used for the decision to perform the procedure. Fifteen patients had multivessel disease (double-vessel disease in 9 and triple-vessel disease in 6).

Statistical analysis

Data are expressed as mean ± SD. Student's t test was used to assess differences between mean values and categorical variables were compared with chi-square test and Fisher's exact test when appropriate. To detect independent variables associated with functional recovery, a multivariate logistic regression procedure was performed according to the unmodified forward selection stepwise analysis (STATISTICA version 5). In this case, the variable that had the most significant relation with dependent outcome was selected first for

inclusion in the model. At the second and subsequent steps, the set of variables (clinical, angiographic and ECG variables) remaining at each point was evaluated, and the most significant was included if it significantly improved the prediction of outcome. The algorithm ceases to select variables when there was no further significant improvement in the prediction. Statistical significance was defined as $p \leq 0.05$. Reproducibility of QT dispersion measurements has been published previously [7].

Results

Stress electrocardiographic characteristics

On the ECG recorded at rest, pathologic Q waves were present in 75 patients, negative T-waves in 45 and ST-segment elevation in 19. Heart rate increased from baseline to low and high-dose dobutamine (71 ± 12 vs. 93 ± 9 vs. 131 ± 11 beats/min, respectively; $p < 0.001$). Dobutamine infusion significantly increased QT dispersion from baseline to low-dose and high-dose dobutamine (69 ± 19 vs. 84 ± 16 vs. 104 ± 24 ms; $p < 0.0001$). Significant ST-segment elevation occurred during stress in 44 patients (47%): 31 patients had new ST-segment elevation and the 13 remaining patients showed increased ST-segment elevation as compared with baseline. ST-segment depression was observed in 17 patients and T-wave normalization in 34.

Prediction of significant infarct-related artery stenosis

There were no significant differences between QT dispersion on the baseline ECG in patients with or without significant stenosis of the infarct-related artery (67 ± 19 vs. 74 ± 17 ms). The increase in QT dispersion was significantly greater in patients with significant infarct artery stenosis. Both the difference in QT dispersion between high-dose dobutamine and rest (40 ± 31 vs. 14 ± 24 ms; $p = 0.002$) and the difference between high-dose and low-dose dobutamine (26 ± 28 vs. 3 ± 20 ms; $p = 0.0018$) were higher in patients with significant infarct stenosis. Table 1 shows the sensitivity, specificity, predictive value and accuracy of stress-ECG findings for the prediction of significant stenosis of the infarct-related artery. Both an increase in QT dispersion (≥30 ms from baseline to high-dose dobutamine and ≥10 ms from low-dose to high-dose dobutamine) and dobutamine ST-segment elevation were more sensitive than the occurrence of dobutamine-induced chest pain and ST-segment depression (79%, 68% and 53% vs. 24% and 17%, respectively; $p < 0.05$). Specificity and positive predictive values were not significantly different for all stress-ECG features. The increase in QT dispersion from baseline to high-dose dobutamine was greater in patients with multivessel disease than in those with single-vessel disease (69 ± 26 vs. 29 ± 28 ms; $p < 0.0001$). A ≥50 ms increase in QT dispersion from baseline to high-dose dobutamine had a sensitivity of 73%, a specificity of 75%, a positive predictive value of 35%, a negative predictive value of 94% and an accuracy of 75% for predicting the presence of multivessel disease (figure 1).

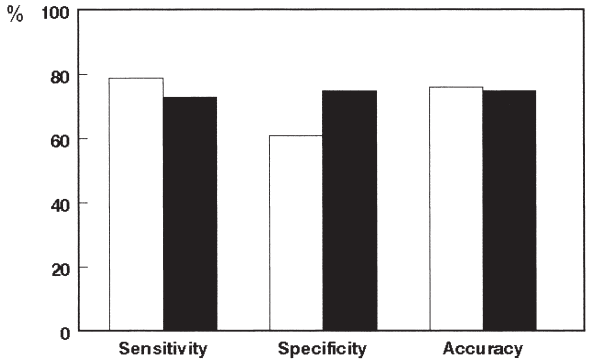

Fig. 1. – Bar graph showing sensitivity, specificity and accuracy of an increase in QT dispersion from baseline ECG to high-dose dobutamine by ≥30 ms for detecting significant infarct artery stenosis (white bar) and by ≥50 ms for multivessel decease (black bar).

Table 1. – *Value of dobutamine-induced ECG changes for predicting significant stenosis of the infarct-related artery*

(n)	Sensitivity	Specificity	PV +	PV –	Accuracy
Chest pain (22)	24 (18/76)*	78 (14/18)	82 (18/22)	19 (14/72)	34 (32/94)*
T-wave normalization (34)	36 (27/76)*	61 (11/18)	79 (27/34)	18 (11/60)	40 (38/94)*
ST-segment depression (17)	17 (13/76)*	78 (14/18)	76 (13/17)	18 (14/77)	29 (27/94)*
ST-segment elevation (44)	53 (41/76)	84 (15/18)	93 (41/44)	30 (15/30)	60 (56/94)
Diff QTd Peak – rest ≥30 ms (67)	79 (60/76)	61 (11/18)	90 (60/67)	41 (11/27)	76 (71/94)
Diff QTd Peak – low-dose ≥10 ms (56)	68 (52/76)	78 (14/18)	93 (52/56)	37 (14/38)	70 (66/94)

d = dispersion, Diff = difference, n = number of patients, PV = predictive value, * $p < 0.05$ vs. Diff QTd and ST-segment elevation.

Predictors of contractile recovery

Table 2 presents clinical, ECG and angiographic findings in patients with and without contractile recovery. Recovery of contraction was observed in 56 (60%) patients. There were no significant differences between groups in age, gender, site of infarction, proportion of Q wave infarction, the use of thrombolytic therapy and baseline wall motion score index. Peak level of creatine kinase was lower in patients who recovered (1,881 ± 886 vs. 2,441 ± 1,017 IU/l; p = 0.012). Elective coronary angioplasty was more frequently performed in patients who showed contractile recovery (41 of 56 vs. 15 of 38; p = 0.001). QT dispersion on the baseline ECG was shorter in patients with contractile recovery. QT dispersion increased by 21 ± 10 ms from baseline to low-dose dobutamine in patients with contractile recovery and only by 8 ± 19 ms in patients without recovery (p = 0.0012). An increase in QT dispersion by ≥20 ms allowed the best distinction between groups (p < 0.00001). Contractile improvement was also more frequent in patients with stress-induced T-wave normalization, and ST-segment elevation. Using multivariate analysis, 4 independent variables were selected stepwise: an increase in QT dispersion by ≥20 ms from baseline to low-dose dobutamine (χ^2 = 15.3; p = 0.00016), dobutamine-induced ST-segment elevation (χ^2 = 11.8; p = 0.0009), elective angioplasty of the infarct-related artery (χ^2 = 11.4; p = 0.001), and T-wave normalization (χ^2 = 8.4; p = 0.005). A ≥20 ms increase in QT dispersion from baseline to low-dose dobutamine had a higher sensitivity for predicting contractile recovery than dobutamine-induced ST-segment elevation or T-wave normalization (86% vs. 66% vs. 45%, respectively; p < 0.05) (figure 2). Specificity was not significantly different for dobutamine-induced ST-segment elevation, T-wave normalization and QT dispersion changes (82% vs. 76% vs. 61%; respectively). The accuracy of QT dispersion changes and of ST elevation was greater than that of T-wave normalization (76% vs. 72% vs. 57%, respectively; p < 0.05).

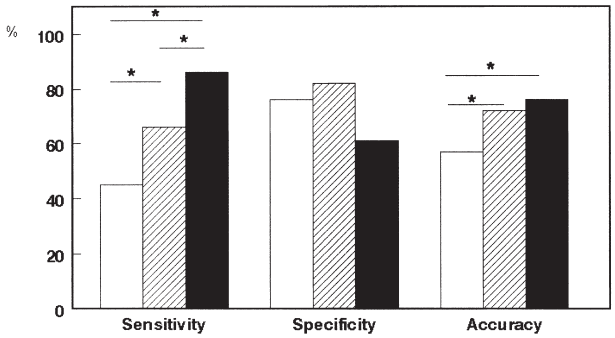

Fig. 2. – Bar graph showing sensitivity, specificity and accuracy of dobutamine-induced T-waves normalization (left bar), ST-segment elevation (middle bar) and an increase of QT dispersion from baseline ECG to low-dose dobutamine by ≥20 ms (right bar) for predicting the occurrence of functional recovery. * p < 0.05

Discussion

This study shows that after AMI, the analysis of predischarge stress ECG is useful for predicting residual stenosis of the infarct-related artery and contractile recovery in the affected area. Changes in QT dispersion during graded infusion of dobutamine were the most accurate parameter for this purpose. The clinical value of dobutamine-induced chest pain or ST-segment depression was modest. Stress-induced ST-segment

Table 2. – *Comparison between patients with and without functional recovery*

Data	Recovery (n = 56)	No recovery (n = 38)	P value
Age (years)	60 ± 12	59 ± 11	NS
Gender (% male)	47 (84)	35 (92)	NS
Anterior infarction	17 (30%)	17 (45%)	NS
Thrombolytic therapy	32 (57%)	27 (71%)	NS
Peak CK (IU/l)	1,881 ± 886	2,441 ± 1,017	0.012
Baseline score index	1.36 ± 0.21	1.40 ± 0.26	NS
Residual stenosis of the IRA (%)	75 ± 19	64 ± 18	0.012
Elective angioplasty	41 (73%)	15 (39%)	0.001
Q-waves	46 (82%)	29 (76%)	NS
Negative T-wave	32 (57%)	13 (34%)	0.03
QTd at baseline (ms)	64 ± 16	74 ± 21	0.018
Dobutamine test			
QTd at low-dose (ms)	85 ± 18	82 ± 15	NS
Diff QT d low-dose – rest (ms)	21 ± 10	8 ± 19	0.0012
Diff QTd ≥20 ms at low-dose	48 (86%)	15 (39%)	< 0.00001
T-wave normalization	25 (45%)	9 (24%)	0.038
ST-segment elevation	37 (66%)	7 (18%)	0.00001

CK = creatine kinase, d = dispersion, Diff = difference, IRA = infarct-related artery.

elevation was a sensitive marker of viable myocardium but its sensitivity to predict significant residual stenosis was moderate.

Significant stenosis of the infarct-related artery and multivessel disease

After AMI, ischaemic myocardium usually reflects the presence of significant residual stenosis of the infarct-related artery[2]. Several studies have assessed the relation between dobutamine-induced ECG changes and the presence of jeopardized myocardium in the affected area. T-wave normalization in the infarct-related leads during dobutamine infusion has been identified as an accurate marker of ischaemia in patients with non-Q wave AMI[11]. In Q wave AMI, Lombardo et al. have demonstrated that T-wave normalization was specifically associated with ischaemic myocardium when developed at high-dose dobutamine[4]. In our study, the positive predictive value of T-wave normalization for detecting significant infarct stenosis was good (79%), but its negative predictive value was very low (18%). We have recently found a good relationship between ST-segment elevation and the observation of a biphasic response during dobutamine administration[9]. In the present study, the sensitivity and the specificity of dobutamine ST-segment elevation for predicting significant infarct artery stenosis were similar to those reported by Smart et al[12]. No study has assessed the accuracy of QT dispersion changes during dobutamine stress testing for the identification of infarct artery stenosis. In patients with significant infarct artery stenosis, QT dispersion increased significantly during graded infusion of dobutamine. This increase was more sensitive and accurate than dobutamine-induced chest pain or ST-segment depression. Our results confirm and extend recent observations indicating that an increase in QT dispersion immediately after exercise was more sensitive for detecting ischaemic myocardium than ST-segment depression[13]. The increase in QT dispersion was even higher in patients with multivessel disease. These data suggest that the degree of heterogeneity of ventricular repolarization is determined by the extent of stress-induced myocardial ischaemia.

Contractile recovery

In the present era of thrombolysis, the incidence of transmural infarction and left ventricular aneurysm has largely decreased. Most patients develop an incomplete infarction, with an admixture of subendocardial necrosis and salvaged subepicardium. Several studies have recently found an association between stress-induced T-wave normalization[14], ST-segment elevation[15] or an increase in QT dispersion[7] and the presence of myocardial viability. Few studies have shown the usefulness of stress-induced ECG changes for predicting improvement of function after AMI. Recently, we[16] and others[17] have found that recovery in regional function was more frequent in patients with than in patients without dobutamine-induced ST-T segment changes. However, no investigation has assessed the accuracy of QT dispersion changes during dobutamine infusion for the prediction of contractile recovery. In our study, stepwise multivariate analysis selected an increase in QT dispersion of ≥20 ms from baseline to low-dose dobutamine as the best predictor of functional recovery. The sensitivity of dobutamine ST-segment elevation (66%) tended to be lower but was not significantly different to that observed in our previous investigation (74%)[16]. T-wave normalization was also a less sensitive marker of myocardial viability as previously demonstrated[4]. It should be emphasized that these results are not necessarily applicable to patient populations infrequently treated by revascularization after AMI. In this study, elective angioplasty of the infarct-related artery also emerged as an independent predictor of functional recovery. Indeed, persistence of a significant infarct artery stenosis may preclude functional recovery[18].

Limitations

Our observations pertain only to patients with small or moderate infarct size. Wall motion analysis was done by a semi-quantitative method rather than by quantitative techniques, but this method remains the standard. Coronary angiography was not repeated at follow-up. Thus, restenosis or reocclusion cannot be excluded: this could have resulted in lack of recovery in some patients. However, repeated catheterization is not indicated in an asymptomatic patient. It is also possible that the measurement of QT interval cannot always be assessed in every lead and the terminal portion of the T-wave may be difficult to determine. In the present study, QT intervals were assessable in ≥8 leads in all patients. The duration of the dynamic changes in QT dispersion during recovery was not examined. Correction of QT interval is plagued by controversy due to the weakness of the classical Bazett's formula[19]. Since QT dispersion does not change with heart rate, heart rate-corrected QT dispersion was not calculated.

Conclusions

In patients with uncomplicated AMI, the identification of viable but jeopardized myocardium is of great importance for selecting patients who could benefit

from a revascularization procedure. Dobutamine stress echocardiography has been widely validated in this clinical setting. However, the interpretation of the test remains difficult in some patients with low echogenicity or with subtle changes in wall thickening. Our study shows that careful ECG observation, especially dynamic changes in QT dispersion during graded infusion of dobutamine provides an accurate and cost-effective strategy for detecting the presence of significant infarct artery stenosis and for predicting functional recovery after AMI.

References

1. Carlos ME, Smart SC, Wynsen JC, Sagar KB. Dobutamine stress echocardiography for risk stratification after myocardial infarction. *Circulation* 1997; **95:** 1402-10.
2. Piérard LA, De Landsheere CM, Berthe C, Rigo P, Kulbertus H. Identification of viable myocardium by echocardiography during dobutamine infusion in patients with myocardial infarction after thrombolytic therapy: comparison with positron emission tomography. *J Am Coll Cardiol* 1990; **15:** 1021-31.
3. Marwick T, D'Hondt AM, Baudhuin T, Willemart B, Wijns W, Detry JM, Melin J. Optimal use of dobutamine stress for the detection and evaluation of coronary artery disease: combination with echocardiography or scintigraphy, or both. *J Am Coll Cardiol* 1993; **22:** 159-67.
4. Lombardo A, Loperfido F, Pennestri F. Significance of transient ST-T segment changes during dobutamine testing in Q wave myocardial infarction. *J Am Coll Cardiol* 1996; **27:** 599-605.
5. Stiles GL, Rosati RA, Wallace AG. Clinical relevance of exercise-induced ST-segment elevation. *Am J Cardiol* 1980; **46:** 931-6.
6. Yamagishi H, Akioka K, Takagi M. Exercise four hour redistribution thallium-201 single photon emission computed tomography and exercise induced ST-segment elevation in detecting the viable myocardium in patients with acute myocardial infarction. *Heart* 1999; **81:** 17-24.
7. Lancellotti P, Bilge AR, Mipinda JB, Piérard LA. Significance of dobutamine-induced changes in QT dispersion early after acute myocardial infarction. *Am J Cardiol* 2001; **88:** 939-43.
8. Bodi V, Sanchis J, Llacer A. ST-segment elevation on Q leads at rest and during exercise: relation with myocardial viability and left ventricular remodeling within the first 6 months after infarction. *Am Heart J* 1999; **137:** 1107-15.
9. Piérard LA, Lancellotti P, Kulbertus HE. ST-segment elevation during dobutamine stress testing predicts functional recovery after acute myocardial infarction. *Am Heart J* 1999; **137:** 500-11.
10. Malik M, Batchvarov VN. Measurement, interpretation, and clinical potential of QT dispersion. *J Am Coll Cardiol* 2000; **36:** 1749-66.
11. Elhendy A, Geleijnse ML, Salustri A, van Domberg RT, Cornel JH, Arnese M, Roelandt JR. T-wave normalization during dobutamine stress testing in patients with non-Q wave myocardial infarction: a marker of myocardial ischemia. *Eur Heart J* 1996; **17:** 526-31.
12. Smart SC, Knickelbine T, Stoiber TR, Carlos M, Wijnsen JC, Sagar B. Safety and accuracy of dobutamine-atropine stress echocardiography for the detection of residual stenosis of the infarct-related artery and multivessel disease during the first week after myocardial infarction. *Circulation* 1997; **95:** 1394-401.
13. Naka M, Shotani I, Koretsune Y, Imai K, Akamatsu Y, Hishida E, Kinoshita N, Katsube Y, Sato H, Hori M. Occurrence of sustained increase in QT dispersion following exercise in patients with residual myocardial ischemia after healing of anterior wall myocardial infarction. *Am J Cardiol* 1997; **80:** 1528-31.
14. Schneider CA, Helmig AK, Baer FM. Significance of exercise-induced ST-segment elevation and T-wave pseudonormalization for improvement of function in healed Q-wave myocardial infarction. *Am J Cardiol* 1998; **82:** 148-53.
15. Margonato A, Chierchia SL, Xuereb RG, Xuereb M, Fragasso G, Cappelletti A, Landoni C, Lucignani G, Fazio F. Specificity and sensitivity of exercise-induced ST-segment elevation for detection of residual viability: comparison with fluorodeoxyglucose and positron emission tomography. *J Am Coll Cardiol* 1995; **25:** 1032-8.
16. Lancellotti P, Seidel L, Hoffer E, Kulbertus HE, Piérard LA. Exercise versus dobutamine-induced ST elevation in the infarct-related electrocardiographic leads: clinical significance and correlation with functional recovery. *Am Heart J* 2001; **141:** 772-9.
17. Elhendy A, Cornel JH, Roelandt JRTC. Relation between ST-segment elevation during dobutamine stress test and myocardial viability after a recent myocardial infarction. *Heart* 1997; **77:** 115-21.
18. Barilla F, Gheorghiade M, Alam M. Low-dose dobutamine in patients with acute myocardial infarction identifies viable but not contractile myocardium and predicts the magnitude of improvement in wall motion abnormalities in response to coronary revascularization. *Am Heart J* 1991; **122:** 1522-31.
19. Malik M, Camm AJ. Mystery of QTc interval dispersion. *Am J Cardiol* 1997; **79:** 785-7.