

ANGIOTENSIN CONVERTING ENZYME INHIBITORS EFFECT ON QT DISPERSION IN CHRONIC MYOCARDIAL INFARCTION PATIENTS

Ioana Mozos¹, Carmen Cristescu²

REZUMAT

Scop: Aprecierea influenței inhibitorilor enzimei de conversie (IEC) asupra parametrilor variabilității activității ventriculare la pacienții cu infarct miocardic cronic. **Material și metode:** Au fost comparați parametrii variabilității activității ventriculare într-un lot de 16 pacienți cu infarct miocardic cronic (IMC) cărora li s-au administrat IEC cu valorile obținute la alți 16 pacienți care nu au beneficiat de acest tratament. **Rezultate:** S-au obținut diferențe semnificative statistic între cele două loturi de pacienți pentru dispersia QT (QTd): 94 ± 46 ms la pacienții tratați cu IEC comparativ cu 170 ± 100 ms la pacienții care nu au beneficiat de IEC, $p=0,048$, dispersia JT corectată (JTdc): 12 ± 8 ms comparativ cu 25 ± 13 ms, $p=0,013$, valorile maxime ale intervalului QT (QTcmax): 104 ± 25 ms comparativ cu 123 ± 22 ms, $p=0,017$ și valorile maxime ale intervalului JT (JTcmax): 77 ± 16 ms comparativ cu 84 ± 14 ms, $p=0,00053$. **Concluzii:** Administrarea IEC la pacienții cu IM afectează repolarizarea ventriculară, reducând riscul aritrogen. Efectul de reducere a QTd se explică prin scăderea semnificativă a QTcmax, dar nu și a QTcmin. Reducerea dispersiei repolarizării ventriculare poate fi pusă pe seama efectului protector al IEC asupra remodelării ventriculului stâng postinfarct. **Cuvinte cheie:** infarct miocardic, inhibitori ai enzimei de conversie, dispersia QT.

ABSTRACT

Aim: The aim of this study was to estimate the influence of angiotensin converting enzyme inhibitor (ACEI) therapy on the ventricular variability parameters in chronic myocardial infarction patients. **Material and methods:** The ventricular variability parameters were compared in 16 chronic myocardial infarction patients who received ACEI therapy with values obtained in other 16 patients. **Results:** Statistically significant differences were obtained for QT dispersion: 94 ± 46 ms in the patients treated with ACEI compared to 170 ± 100 ms in patients who didn't receive ACEI, $p = 0.048$, heart rate corrected JT dispersion: 12 ± 8 ms compared to 25 ± 13 ms, $p=0,013$, and the maximal values for the QT interval: 104 ± 25 ms compared to 123 ± 22 ms, $p = 0.017$ and the maximal values of the JT interval: 77 ± 16 ms compared to 84 ± 14 ms, $p = 0.00053$. **Conclusions:** ACEIs in chronic myocardial infarction patients affect ventricular repolarisation, reducing arrhythmia risk. The reduction of QTd is due to a significant decrease of QTcmax, but not of QTcmin. The decrease of ventricular repolarisation dispersion may be due to the protective effect of ACEI on postmyocardial left ventricular remodeling.

Key Words: myocardial infarction, angiotensin converting enzyme inhibitor, QT dispersion

INTRODUCTION

Angiotensin converting enzyme inhibitors (ACEI) are known to reduce postinfarction remodeling effects.¹

QT dispersion (QTd) calculation using 12 lead ECG represents a quantitative noninvasive

method to determine myocardial repolarisation inhomogeneities.²⁻⁴ QTd is considered a marker of ventricular arrhythmia risk and of sudden death.⁵ The idea to use QTd to evaluate myocardial repolarisation heterogeneity, was reactualised in 1990 by Campbell.⁶ Cardiologists considered the method because it was very simple and medical literature was invaded by articles about QTd in cardiac and extracardiac diseases.

Prolonged QTc and QTd indicate shift of sympathetico-vagal balance towards sympathetic predominance and reduced vagal modulation, increasing dispersion of ventricular repolarisation. It could be associated with autonomic modulation of the sinus node due to conditions like hypertension, myocardial infarction or congestive heart failure.⁷

¹ Department of Physiopathology, Faculty of Medicine, ² Department of Pharmacology, Faculty of Pharmacy, Victor Babes University of Medicine and Pharmacy, Timisoara

Correspondence to:
Ioana Mozos, Department of Physiopathology, 14 Spl. T. Vladimirescu, Timisoara
Email: ioana_mozos@yahoo.com

Received for publication: Mar. 22, 2005. Revised: Nov. 16, 2005.

QTd > 80 ms indicates loss of synchronisation of repolarisation favouring arrhythmogenic reentrant mechanisms.

The aim of this study was to evaluate the significance of QTd changes due to ACEI in chronic myocardial infarction patients.

MATERIAL AND METHODS

Thirty-two chronic myocardial infarction patients, ambulatory or from the ASCAR Clinic were included in the study. (Table 1) 16 of the 32 patients were given ACEI therapy: Captopril, Enalapril (enalapril maleate) or Monopril (fosinopril). 12 lead ECG was performed using a Siemens-Megacart electrocardiograph, at a paper speed of 25 mm/s. Chronic myocardial infarction was diagnosed considering the criteria of the Joint European Society of Cardiology and of the American College of Cardiology Committee for the Redefinition of Myocardial Infarction (any QR wave in leads V₁ through V₃ ≥ 30 ms, abnormal Q wave in lead I, II, aVL, aVF or V₄ through V₆ in any two contiguous leads and at least 1 mm in depth).⁸ The most important exclusion criteria were: bundle branch block, atrial flutter or fibrillation in the moment of the ECG recording and hydroelectrolytic imbalances.

Table 1. Clinical characteristics of the chronic MI patients.

Characteristics	The ACEI patient group	Patients who didn't receive ACEI
Age (years)	65±17	63±14
Women	12%	15%
Cardiovascular risk factors	Hypertension 25% Diabetes mellitus 19% Obesity 24% Smokers 60% Cardiovascular family history 27%	Hypertension 15% Diabetes mellitus 10% Obesity 11% Smokers 56% Cardiovascular family history 15%
Arrhythmias	Atrial fibrillation 12% Past atrial flutter 6% Premature ventricular contractions 6%	Sinus tachycardia 24% Premature atrial contractions 12%
Therapy	Class III antiarrhythmic drugs 31% Nitrates 96% Diuretics 95% Beta-blockers 63% Calcium-blockers 12% Perc. angioplasty 12%	Class III antiarrhythmic drugs 11% Nitrates 100% Diuretics 92% Beta-blockers 70% Calcium-blockers 24% Digitalis 8%

The ECGs were examined by two independent

observers, who weren't informed about the clinical data, and the following parameters were calculated and determined: QTd (the difference between the maximal and minimal value of the QT interval in the 12 leads), QTdc (heart rate corrected QTd), mean QT duration (QTm), JTd (the difference between maximal and minimal JT interval), JTdc (heart rate corrected JT dispersion), mean JT interval duration in the 12 leads (JTm), the maximal JT interval duration (JTc_{max}), the minimal JT interval duration (JTc_{min}), QRSdc (heart rate corrected QRS dispersion, which is the difference between QRS_{max} and QRS_{min}), the maximal values for the heart rate corrected QRS complex (QRS_{cmax}), and the minimal values of the heart rate corrected QRS complex (QRS_{cmin}).

The QT interval was measured from the beginning of the QRS complex through the end of the T wave and the JT interval from the J point through the end of the T wave. All dispersions were calculated considering at least 8 leads for each patient, eliminating the leads in which the end of the T wave could not be exactly determined, or in which there was a low amplitude or isoelectric T wave.

In each lead two QT intervals were measured and the arithmetic mean between the two was calculated. The values obtained for QTd were heart rate corrected, using the Bazett formula (QTc = QT/√RR), and QTdc resulted. QTm and JTm were calculated for each patient as the arithmetic mean of the QT and JT interval values in each lead.

RESULTS

The values obtained for the dispersion parameters are presented in Table 2.

Table 2. The values obtained for the QT, JT and QRS interval variables.

Variable	Values obtained in the ACEI group (in ms)	Values obtained in the group without ACEI (in ms)
QTd	94±46	170±100
QTdc	24±15	34±24
QTm	405±80	441±59
QTcmax	104±25	123±22
QTcmin	77±16	97±21
JTd	12±8	25±13
JTm	300±34	302±59
JTcmax	77±16	84±14
JTcmin	51±11	58±10
QRS _{cmax}	55±24	50±30
QRS _{cmin}	21±4	17±10
QRSdc	17±12	34±24

Significant differences were obtained when comparing QTcmax in the ACEI patients and the chronic myocardial infarction patients who didn't benefit of ACEI therapy ($p=0.017$). (Table 3) Significant differences were obtained for JTc_{max}, JTdc, QTdc and QTd as well.

Table 3. Differences of dispersions and intervals between the ACEI group and the chronic myocardial infarction patients who didn't receive ACEI therapy.

Compared parameters	p value	Significance
QTd	0.048	Statistic significant differences (s)
QTdc	0.045	s
QTm	0.63	Unsignificant differences (ns)
QTcmax	0.017	s
QTcmin	0.128	ns
JTcmax	0.00053	s
JTcmin	0.088	ns
JTdc	0.013	s
JTm	0.59	ns
QRSmax	0.264	ns
QRSmin	0.109	ns
QRSdc	0.663	ns

ACEI therapy leads to significant differences for echocardiographic determined ejection fraction (EF), end-systolic volume (ESV) and end-diastolic volume (EDV). (Table 4)

Table 4. The values obtained for left ventricular EF, ESV and EDV in chronic myocardial infarction patients who benefited of ACEI therapy.

Echocardiographic parameter	Values in ACEI patients	Values obtained in patients who didn't receive ACEI therapy	Values obtained for p with the t Student test
EF of the LV	56±14	48±19	0.017
EDV	52±10	91±27	0.0082
ESV	35±18	57±18	0.0084

DISCUSSIONS

The values obtained for the analysed dispersions and intervals were lower in ACEI patients, compared to those who didn't receive ACEI therapy. Several medical articles mention decrease of QTd after ACEI therapy.^{1,8,9}

Kassotis compared QTd in 105 MI patients, which had never been treated with an ACEI and 51 patients,

which were started on enalapril within 24 hours of presentation.¹ There was no significant difference in the baseline QTd, heart rate, QTc_{min}, and QTc_{max} between the two groups. On days 3-4 the QTd in the treatment group was 39.2 ± 19.4 ms, as opposed to 84.4 ± 31.2 ms in the control group. This reduction in QTd was accounted for by a significant difference in the QTcmax. The QTd shortened in both groups on days 6-7 with a QTd of 30 ± 17.5 ms in the treatment group and a QTd of 54.1 ± 26.3 ms in the control group. There was a significant difference in EF between the two groups with the ACEI treated group exhibiting a lower EF. The beneficial effects of ACEI occur early following administration of the drug. The reduction in sudden cardiac death conferred by ACEI therapy may be attributed to its effect of reducing the degree of ventricular dispersion of repolarization following a myocardial infarction.

Ranade showed that the normalized QTd after 2 months of ACE therapy decreased from 16 ± 4 to 12 ± 3 ms, a 25% reduction in dispersions. QTd also decreased from 61 ± 14 to 47 ± 12 ms and QTc dispersions decreased from 71 ± 18 to 52 ± 14 ms.⁹ After 2 months of ACE inhibitor therapy, heart rate slowed significantly and there was a negative correlation between ejection fraction and QTd. The study also found no correlation between ACE level, percent converting enzyme inhibition, and QTd. The effects of ACE therapy appear early on in terms of repolarization changes. The decrease in QTd may explain the reduced sudden death mortality in patients with heart failure who are treated with ACE inhibitor therapy.

Sredniawa described also the beneficial effect of angiotensin-converting enzyme inhibitors and beta-adrenolytic therapy on QT dispersion.¹⁰

Early treatment with captopril during acute myocardial infarction for 4 weeks can significantly reduce long-term total mortality.¹¹ The results showed a lower 4 week mortality in the captopril group. Captopril in early acute myocardial infarction is safe and beneficial. This results suggest a protective effect of early treatment with captopril on left ventricular remodeling. This study also demonstrates that mortality decreased significantly in the anterior infarct group.

The maximum effect may be seen after four years with trandolapril, and it is maintained for up to 10-12 years. The mechanism is probably prevention of remodeling and stabilizing heart disease.¹²

However, each patient benefited of other drugs besides ACEI, which is the most important limit of this study. Beta-blockers are known to decrease QTd

and QTdc, as a possible antiarrhythmic mechanism of this drugs.¹³ The percent of patients treated with beta-blockers was higher in the group who didn't receive ACEI. This is the reason why we consider that beta-blockers didn't influence significantly the results of the study.

Sotalol and amiodarone have controversial effects in coronary patients: some authors found a decrease of QTd, others consider that QTd is not modified.¹⁴⁻¹⁸ Amiodarone is also known for its repolarisation prolonging effect, blocking the potassium, sodium and calcium channels.¹ Some authors consider that QTd could be used as a method to asses the effectiveness of class III antiarrhythmic drugs.¹⁹

Digoxin therapy increases repolarisation dispersion, and this could have contributed to the increase of QTd in the group who didn't receive ACEIs. Nitrates, calcium-blockers and diuretics do not influence QTd. Hypokalemia, hypocalcemia or hypomagnezemia may increase QTd, and this is the reason why patients with hydroelectrolytic imbalances were excluded from the study.^{13,20}

QTdc is significantly higher in hypertensive patients compared to healthy controls, but the percent of patient with hypertension is higher in the ACEI group, so it could not explain the differences.²¹ The same situation is found in type 2 diabetes mellitus and obesity, which are also known to increase QTd.^{22,23}

CONCLUSIONS

ACEI therapy, administrated in myocardial infarction patients, impairs ventricular repolarisation, demonstrated by the significant lower values for QTcmax, JTcmax, JTdc, QTdc and QTd, compared to the values obtained for the same parameters in patients who didn't receive ACEI therapy, reducing arrhythmia and sudden cardiac death risk. The decrease of QTd and JTdc can be explained by the significant decrease of maximal values of those intervals. The decrease of the ventricular repolarisation dispersion is due the protective effect of ACEI therapy on postinfarction left ventricular remodeling.

REFERENCES

1. Kassotis J, Mongwa M, Reddy CV. Effects of angiotensin-converting enzyme inhibitor therapy on QT dispersion post acute myocardial infarction. *Pacing Clin Electrophysiol* 2003;26: 843-8.
2. Day CP, Mc Comb JM, Campbell RWF. QT dispersion: an indication

- of arrhythmia risk in patients with long QT intervals. *Br Heart J* 1990;63:342-4.
3. Mirvis DM. Spatial variation of QT intervals in normal persons and patients with acute myocardial infarction. *J Am Coll Cardiol* 1985;5:625-31.
4. Zabel M, Portnoy S, Franz MR. Electrocardiographic indexes of dispersion of ventricular repolarization: an isolated heart validation study. *J Am Coll Cardiol* 1995;25:746-52.
5. Bruyne MC, Hoes AW, Kors JA, et al. QTc dispersion predicts cardiac mortality in the elderly. The Rotterdam study. *Circulation* 1998;97:467-472.
6. Malik M, Batchvarov VN. Measurement, Interpretation and Clinical Potential of QT Dispersion. *J Am Coll Cardiol* 2000;36(6):1749-66.
7. F Lambardi. The QT interval and QT dispersion „the smaller, the better”. *European Heart J* 1998;19:1279-81.
8. K. Thygesen, J.S. Alpert. Myocardial infarction redefined – A consensus document of The Joint European Society of Cardiology/ American College of Cardiology Committee for the Redefinition of Myocardial Infarction. *European Heart Journal* 2000;21:1502-13.
9. Ranade V, Molnar J, Khokher T et al. Effect of angiotensin-converting enzyme therapy on QT interval dispersion. *Am J Ther* 1999;6(5):257-61.
10. Sredniawa B, Musialik-Lydka A, Pasyk S. Measurement dispersion of the QT interval and its significance in different diseases. *Pol Merkuriusz Lek* 2001;11(61):52-5.
11. Lisheng L. Long term mortality in patients with myocardial infarction impact of early treatment with captopril for 4 weeks. *Chinese Medical Journal* 2001;114(2):115-8.
12. Wayne Kaznar. Trace: Early ACE inhibitor use in MI has long-term mortality benefit. *Today in Cardiology*. 2004;6:101-3.
13. Bonnar CE, Davie AP, Caruana L, et al. QT dispersion in patients with chronic heart failure: β blockers are associated with a reduction in QT dispersion. *Heart* 1999;81:297-302.
14. Faber TS, Malik M, Zehender M. QT Dispersion im Oberflaechen-Elektrokardiogramm. Methodik und klinische Bedeutung. *Intensivmedizin und Notfallmedizin* 1998;35(7):641-6.
15. Cui G, Sen L, Sager P, et al. Effects of amiodarone, sotalol and sotalol on QT dispersion. *Am J Cardiol* 1994;74: 896-900.
16. Sicouri S, Moro S, Litovsky S, et al. Chronic amiodarone reduces transmural dispersion of repolarization in the canine heart. *J Cardiovasc Electrophysiol* 1997;8:1269-79.
17. Grimm W, Steder U, Menz V, et al. Effect of amiodarone on QT dispersion in the 12-lead standard electrocardiogram and its significance for subsequent arrhythmic events. *Clin Cardiol* 1997;20(2):107-10.
18. Merot J, Charpentier F, Poirier JM, et al. Effects of chronic treatment by amiodarone on transmural heterogeneity of canine ventricular repolarization in vivo: interactions with acute sotalol. *Cardiovasc Res* 1999;44(2):303-14.
19. Lighezan D, Lighezan R, Hilbel T, et al. Effects of D-sotalol on QT interval dispersion. *Cercetari Experimentale si Medico-Chirurgicale Nr. 4/1999: 286-289.*
20. Jain H, Avasthi R. Correlation between dispersion of repolarization (QT dispersion) and ventricular ectopic beat frequency in patients with acute myocardial infarction: a marker for risk of arrhythmogenesis. *Int J Cardiol* 2004;93:69-73.
21. Saadeh AM. Relation between age, ventricular arrhythmia, left ventricular hypertrophy and QT dispersion in patients with essential hypertension. *Acta Cardiol* 2004;59(3):249-53.
22. Veglio M, Bruno G, Borra M, et al. Prevalence of increased QT interval duration and dispersion in type 2 diabetic patients and its relationship with coronary heart disease: a population-based cohort. *J Intern Med* 2002;251(4):317-24.
23. Gupta AK, Xie B, Thakur RK, et al. Effect of weight loss on QT dispersion in obesity. *Indian Heart J* 2002;54:399-403.