Preconditioning Reduces QTc Value in Patients with First Non-ST-Segment Elevation Myocardial Infarction (NSTEMI)

Christodoulos E. Papadopoulos, M.D., Haralampos I. Karvounis, M.D.,
Georgios E. Parharidis, M.D., and Georgios E. Louridas, M.D.

From the First Department of Cardiology, AHEPA University Hospital, Aristotle University of Thessaloniki, Greece

Background: Preinfarction angina (PA) consists a strong clinical correlate to ischemic preconditioning (PC) and seems to occur in a bimodal time course. The aim of the study is to evaluate the impact of both forms of PC on QTc value representing myocardial electric stability, in patients with a first NSTEMI.

Methods: Forty-eight patients, with first NSTEMI and poor or no collateral development were enrolled in the study. QTc at admission and discharge were recorded. All patients had comparable admission QTc values and were divided into three groups according to the absence or presence and exact timing of preinfarction angina. The first group consisted of 20 patients who did not report PA (PA–, representing no PC effect); the second group of 12 patients with reported PA within 12 hours prior to admission (12h PA+, representing the classic form of PC); and the third group of 16 patients reporting PA within 12 to 48 hours prior to admission (48-hour PA+, representing the delayed form of PC). The primary outcome was determined as the effect of PA on QTc value at discharge.

Results: Discharge QTc values were significantly reduced in both (PA+) groups compared to (PA–) group (412 ± 50 vs. 455 ± 53 ms, $p = 0.015$ and 417 ± 29 vs. 455 ± 53 ms, $P = 0.033$, respectively). Both groups of (PA+) patients compared to (PA–) patients suffered no arrhythmic events during their hospitalization (0/12 vs. 6/20, $P = 0.04$ and 0/16 vs. 6/20, $P = 0.02$).

Conclusions: Both forms of preconditioning, similarly and significantly reduce QTc value at discharge in patients experiencing a first NSTEMI, suggesting possible protection from future arrhythmic events.

A.N.E. 2003;8(4):275–283

preinfarction angina; preconditioning; QTc; cardioprotection

QTc and QT dispersion have been broadly evaluated as prognostic factors for sudden death and future arrhythmic events in patients with coronary heart disease and especially those experiencing acute myocardial infarction.^{1,2} Although there is much debate upon the significance, reliability and further clinical implication of these indices,³ results of a large number of prospective trials were controversial upon their predictive value on major arrhythmic events and practical value on survival assessment.^{4,5,6}

Ischemic preconditioning, first described by Murry et al., confers to myocardial cell resistance to ischemic injury that follows brief episodes of myocardial ischemia.⁷ There are a number of conditions in the clinical setting correlating to exper-

imental ischemic preconditioning such as preinfarction angina, percutaneous transluminal coronary angioplasty (PTCA), coronary by pass grafting (CABG), and warm up angina.⁸ Prospective as well as retrospective studies have demonstrated, that preinfarction angina in the setting of acute transmural myocardial infarction, may reduce enzymatic infarct size,^{9–16} preserve left ventricular function,^{14,15} and improve short and long term prognosis.^{10,12,14,15} Limited reports have documented infarct size limitation in the setting of NSTEMI.¹⁷ All these studies postulated ischemic preconditioning as the major explanation of preinfarction angina protective mechanism, but most of them did not look upon collateral development, which may be the main reason for the afforded protection.

The preconditioning phenomenon is encountered in two forms: the classic one lasting for two to 3 hours and a delayed form of protection appearing at 24 hours and lasting for about 48 hours, called the second window of protection.^{8,18}

The aim of our study is to evaluate and compare the effect of both forms of clinical preconditioning on QTc value in NSTEMI patients, assessing a possible antiarrhythmic myocardial protection effect.

METHODS

Study Patients

We studied 66 consecutive patients with first NSTEMI who were admitted to our Coronary Care Unit. Forty-eight patients, who fulfilled the following predetermined criteria, comprised the study population.

Inclusion criteria were: (1) typical angina-like chest pain at admission, lasting more than thirty minutes and not exceeding six hours (in order to record true peak levels of myocardial necrosis markers), (2) ST segment depression ≥ 0.1 mV or the appearance of new negative T waves ≥ 0.1 mV, in at least two contiguous leads on the surface ECG and raised biochemical markers of total serum CPK and CPK-MB values (CPK > 195 IU/L, CPK-MB > 16 IU/L), (3) absence of any Q waves and/or no development of new Q waves in any ECG lead, and (4) collateral circulation graded 0 to 1 according to Rentrop classification¹⁹ on coronary angiography, which was performed during the patient stay in the Unit.

The exclusion criteria were: (1) advanced age (above 75 years), (2) any known history of coronary heart disease, (3) any known history of terminal illness, malignancy or systemic disease, (4) any known history of previous congestive heart failure (CHF), (5) diabetic patients being on glibenclamide treatment, (6) collateral circulation graded more than 1 according to the Rentrop classification and (7) all patients with possible left ventricular hypertrophy, pericarditis, myocarditis, early repolarization, electrolyte disturbances and patients being treated with digitalis, conditions which may mask ECG changes resulting from infarction development.

Design and Procedures

The primary outcome of the study was the effect of both forms of preconditioning by means

of "early" and "late" preinfarction angina on QTc value of NSTEMI patients at discharge.

In order to test our hypothesis first we had to document the "true" existence of ischemic preconditioning in our study population, by looking upon the effect of preinfarction angina on enzymatic infarct size by assessing CKMB release.

All patients enrolled in the study were admitted to the Coronary Care Unit of our hospital. Detailed history taking and complete physical examination was undertaken by an attending Cardiologist who was blinded to the study protocol. Killip class was assessed.

Special interest was drawn to the detection of angina attacks, which took place within the last 48 hours (detecting the classic preconditioning phenomenon presence and the possible second window of protection). Such attacks were determined as typical chest pain episodes at rest or stress lasting less than 20 minutes and having the same character such as the final admission episode.

Patients were divided into three groups according to the absence or presence of preinfarction angina. Patients not reporting preinfarction angina were determined as the group with no preconditioning effect. Patients who reported angina within 12 hours prior to admission ("late" angina) were evaluated for the classic preconditioning protection while those who reported angina in between 12 and 48 hours ("early" angina) were determined as the group protected by the delayed form of preconditioning (second window).

Age, gender, coronary risk factors as well as any current drug treatment were recorded. Elderly as well as diabetic patients being on glibenclamide treatment were excluded from the study, due to the possible inhibition of the preconditioning phenomenon.^{20,21,22} In patients describing prodromal angina, the number of angina attacks, their mean duration, their exact time of occurrence, from the time of admission and the mean time of the last ischemic episode to presentation were recorded.

A standard 12-lead electrocardiogram (ECG) was performed in every patient, which was interpreted by two separate readers for detection of the specific ECG inclusion criteria. The number of leads showing ST segment or T wave changes and the possible infarct location were recorded. ECGs were obtained every morning till discharge.

Two independent readers blinded to the clinical data calculated manually QTc value, using Bazett's formula, using a simultaneous 12-lead recording at

a paper speed of 25mm/sec, at admission and discharge. The point of T wave offset was defined by the return of the T wave to the baseline. If a U wave was present, the T wave offset was defined as the nadir between the T and U waves. The QTc interval was defined as the average of the QTc intervals of three consecutive beats in each of the ECG leads.²³

We performed a series of statistical analyses in regards to the outcome, comparing patients with both forms of preconditioning versus patients without preconditioning.

In order to assess the impact of ischemia on QTc, we divided our patient population into two groups according to the magnitude of ischemia. We arbitrarily set two different criteria for ischemia severity: First, the type of ischemia appearance on the ECG (either ST depression as major ischemia or negative T waves as minor) and second the number of ECG leads in which ischemia was evident. We calculated the average number of abnormal ECG leads of our population and set two groups: One with more abnormal leads than the average number and the other with less abnormal leads, representing major and minor ischemia respectively. We then performed another series of statistical analyses in regards to QTc value on admission and discharge, comparing preconditioned versus non-preconditioned patients with major or minor "admission" ischemia, in order to elucidate the impact of ischemia on QTc shortening or lengthening.

We have finally processed ECG data and calculated QTc values at the time of ECG resolution, indicating ischemia resolution. This point of time was determined as the time that ECG first reached its final configuration. We performed a series of statistical analyses with regard to QTc value comparing once more, preconditioned versus no preconditioned patients with major and minor ischemia.

Blood samples for measuring creatine kinase MB fraction (CPK-MB) plasma levels, were taken on admission, then every 8 hours for the first day and subsequently every morning till discharge. Infarct size reduction reflecting the protection afforded by preinfarction angina was evaluated by comparing mean peak CPK MB values of all groups.

During their hospitalization all patients underwent coronary angiography after informed consent, in order to assess the severity of coronary heart disease and estimate collateral development. Angiographies were performed on days 2 and 3, in order to assess collateral development consisting a major inclusion criterion of the study. Two experienced interventional cardiologists, blinded to the clinical data, interpreted cine films. Significant angiographic coronary artery stenosis was defined as an area of narrowing >50%. The number of the diseased vessels, the proximity of the culprit lesion according to the existing ACC/AHA guidelines for coronary angiography²⁴ and approximate ejection fraction were estimated. Finally, collateral circulation was assessed using the Rentrop classification.

All patients were treated with the standard medical therapy for unstable angina. PTCA and CABG were performed in accordance with the existing ACC/AHA guidelines.^{25,26} During hospitalization, any of the following events were recorded: (1) episodes of recurrent ischemia, defined as typical chest pain episodes, followed by ECG changes being responsive to nitrates, (2) development of congestive heart failure (CHF), defined as pulmonary edema with typical audible rales > 1/3 of lung fields followed by a diagnostic chest X-ray pattern, (3) reinfarction, defined as new onset chest pain, followed by new ECG changes and/or a new elevation of serum markers of myocardial necrosis, (4) any arrhythmic event, defined as any atrial tachyarrhythmia, ventricular fibrillation or tachycardia or any kind of atrioventricular block, which was thought not to be drug related, (5) frequency of PTCA and CABG, and finally 6) death.

The study complied with the Declaration of Helsinki and was approved by the Institutional Committee on human research of our hospital.

Statistical Analysis

The baseline characteristics in the comparison groups were compared by *t*-test and chi-square test where appropriate. Univariate analysis of the comparison groups in relation to the outcome was performed by *t*-test. Statistical significance was defined as a P value < 0.05 and all data are reported as mean value $\pm$ SD.

All data analyses were performed by StataCorp. 1999. *Stata Statistical Software*: Release 6.0. College Station, TX: Stata Corporation.

RESULTS

Eighteen patients out of 66 were excluded from the study population: Eight had angiographically proven collateral circulation greater than 1, three were older than 75 years, two had a history of myocardial infarction, two had a history of pulmonary

edema, two were diabetics on glibenclamide, and one had end stage renal failure.

Forty-eight patients entered the study protocol and were divided into three groups according to the methods of the study: the first group (PA–) consisted of 20 patients with no recorded symptoms before experiencing the major ischemic episode which led them to the Emergency Department; second (PA + 12) and third groups (PA + 48) consisted of 12 and 16 patients respectively, who reported new onset prodromal angina ("late" or "early") representing patients with possible protection by the classic and delayed form of preconditioning.

The mean time to presentation was 3 ± 1.6 and 2.9 ± 1.8 hours for the (PA+) groups and 3 ± 1.2 hours for the (PA–) group respectively; the mean duration of angina attacks was 14 ± 5.8 minutes. In the (PA + 12) group 6 patients reported one to four preinfarction angina episodes while the rest above 5. In the (PA + 48) group preinfarction angina severity was comparable: nine patients with 1 to 4 and 7 with above 5.

All three groups did not differ significantly in terms of baseline characteristics, as shown in Table 1. No significant differences in the interpretation of admission ECGs were recorded and infarct location did not differ significantly between the three groups. There were not statistically significant differences concerning estimated ejection fraction, Killip class, the proximity of the culprit lesion, and the overall severity of coronary heart disease, evaluated by the number of the diseased vessels. All patients had collateral circulation graded 0–1 according to the Rentrop classification.

Table 2 shows drug treatment before admission and therapy received after diagnosis of NSTEMI. There were non statistically significant differences between the two groups.

Preconditioning effect on infarct size: Infarct size limitation in the (PA+) groups was confirmed by assessing mean peak CPK MB release and by comparing the analogous CPK MB release in the (PA–) patients. Both forms of preconditioning similarly

Table 1. Demographics

	(PA + 12) Group (N = 12)	(PA + 48) Group (N = 16)	(PA–) Group (N = 20)	P value
Age (years)	58 ± 12	62 ± 13	60 ± 8	NS
Male (%)	9 (75)	11 (68)	17 (85)	NS
Current smoking (%)	9 (75)	11 (68)	16 (80)	NS
Hyperlipemia (%)	9 (75)	14 (87)	18 (90)	NS
Diabetes mellitus (%)	2 (16)	4 (25)	4 (20)	NS
Hypertension (%)	7 (58)	14 (87)	15 (75)	NS
Family history (%)	5 (42)	7 (44)	8 (40)	NS
Admission ECG data				NS
ST depression (%)	7 (58)	11 (68)	12 (60)	NS
Negative T waves (%)	5 (42)	5 (32)	8 (40)	NS
Anterior location (%)	9 (75)	11 (68)	13 (65)	NS
Inferior location (%)	1 (8)	1 (6)	3 (15)	NS
Lateral location (%)	2 (16)	4 (25)	4 (20)	NS
Coronary angiography data (%)				NS
One-vessel disease	7 (58)	10 (62)	15 (75)	NS
Two-vessel disease	5 (42)	4 (25)	3 (15)	NS
Three-vessel disease	0 (0)	2 (12)	2 (10)	NS
Left main artery disease	0 (0)	0 (0)	1 (5)	NS
Collateral grade 0 (%)	9 (75)	12 (75)	16 (80)	NS
Collateral grade 1 (%)	3 (25)	4 (25)	4 (20)	NS
Ejection Fraction (%)	58 ± 11	55 ± 7	54 ± 8	NS
Killip class I (%)	11 (92)	14 (87)	16 (80)	NS
Killip class II (%)	1 (8)	2 (12)	4 (20)	NS

Plus-minus values are mean $\pm$ SD. (PA + 12), patients with classic PC effect; (PA + 48), patients with delayed PC effect; (PA–), patients with no PC effect.

Table 2. Drug Treatment before Admission and During Hospitalization

Medications (patients %)	(PA + 12) Group (N = 12)	(PA + 48) Group (N = 16)	(PA-) Group (N = 20)	P	(PA + 12) Group (N = 12)	(PA + 48) Group (N = 16)	(PA-) Group (N = 20)	P
Aspirin	2 (16)	3 (18)	3 (15)	NS	12 (100)	14 (87)	20 (100)	NS
Beta blockers	2 (16)	5 (31)	6 (30)	NS	11 (91)	14 (87)	18 (90)	NS
ACE inhibitors ^a	3 (25)	5 (31)	7 (35)	NS	6 (50)	7 (43)	10 (50)	NS
Ca ⁺⁺ blockers	2 (16)	3 (18)	4 (20)	NS	2 (16)	3 (18)	4 (20)	NS
Nitrates	0 (0)	0 (0)	0 (0)	NS	12 (100)	16 (100)	20 (100)	NS
Statins	3 (25)	2 (12)	5 (25)	NS	10 (83)	10 (62)	18 (90)	NS
Diuretics	0 (0)	2 (12)	1 (5)	NS	0 (0)	2 (12)	4 (20)	NS
Antidiabetics ^b	2 (16)	4 (25)	3 (15)	NS	2 (16)	4 (25)	3 (15)	NS
Insulin	0 (0)	0 (0)	1 (5)	NS	0 (0)	0 (0)	1 (5)	NS
AT1 inhibitors ^c	0 (0)	0 (0)	0 (0)	NS	1 (8)	3 (18)	3 (15)	NS
LMWH ^d	0 (0)	0 (0)	0 (0)	NS	10 (83)	15 (93)	19 (95)	NS
Clopidogrel	0 (0)	0 (0)	0 (0)	NS	4 (33)	3 (21)	4 (20)	NS
Amiodarone	0 (0)	0 (0)	0 (0)	NS	1 (8)	2 (12)	3 (15)	NS
IIb IIIa inhibitors	0 (0)	0 (0)	0 (0)	NS	2 (16)	3 (18)	5 (25)	NS

^aAngiotensin converting enzyme inhibitors. ^bExcept glibenclamide. ^cAngiotensin receptors AT1 inhibitors. ^dLow Molecular Weight Heparine. (PA + 12), patients with classic PC effect; (PA + 48), patients with delayed PC effect; (PA-), patients with no PC effect.

and significantly reduced CPK MB release documenting equal and significant myocardial protection. Figure 1 represents our results.

Preconditioning effect on discharge QTc value: Although admission QTc values in all three groups were comparable, a significant reduction of discharge QTc values was documented in both preconditioned groups. Table 3 reviews all the relevant data.

Figure 1. Both forms preconditioning (PC) effect on infarct size assessed by CPK MB release. CPK MB represents creatine phosphokinase MB fraction; (PA + 12), patients with classic PC effect; (PA + 48), patients with delayed PC effect; (PA-), patients with no PC effect; CPK MB (PA + 12) = 34 ± 9 IU/L; CPK MB (PA + 48) = 48 ± 28 IU/L; CPK MB (PA-) = 116 ± 81 IU/L.

Impact of preconditioning and severity of ischemia on QTc value: In our study population the average number of ECG leads showing abnormal ischemic deflections on admission, was 4 ± 1.2. We compared QTc values on admission and discharge of preconditioned versus no preconditioned patients facing major or minor ischemia using two different criteria: first by the main admission ECG pattern (ST depression as major, negative T wave as minor) and secondly by the number of abnormal admission ECG leads (>4 as major, <4 as minor) (Table 4).

Same series of statistical analyses at the time of ECG resolution (mean time 2 ± 1.1 days) revealed no significant differences in QTc values between all studied subgroups (Table 5).

Preconditioning effect on in-hospital events: Both forms of preconditioning reduced significantly arrhythmic events; additionally the delayed form reduced the incidence of recurrent angina. There was no evident effect on the incidence of death, congestive heart failure, reinfarction and frequency of PTCA or CABG (Table 6).

It is clear that during hospitalization there is a significant lower incidence of arrhythmic events in both groups of preconditioned patients, no matter the severity of the ischemic stimuli (a finding that is consistent with the analogous QTc shortening at discharge) and we conclude that there might be a correlation between arrhythmogenicity and absence of preinfarction angina.

Table 3. Both forms Preconditioning Effect on Discharge QTc value

	PA– N = 20	PA + 12 N = 12	P	PA– N = 20	PA + 48 N = 16	P
QTc admission (ms)	417 ± 59	432 ± 19	NS	417 ± 59	440 ± 38	NS
QTc discharge (ms)	455 ± 53	412 ± 50	0.015	455 ± 53	417 ± 29	0.033

(PA + 12), patients with classic PC effect; (PA + 48), patients with delayed PC effect; (PA–), patients with no PC effect.

DISCUSSION

QTc and QT dispersion is thought that may serve as a measure of variability in ventricular recovery time and may be a means of identifying patients at risk of arrhythmias and sudden death after acute myocardial infarction.^{1–3} Preinfarction angina being a clinical analogue of ischemic preconditioning shares a well documented protective effect in the setting of acute transmural myocardial infarction by reducing infarct size, preserving left ventricular function and improving short and long term prognosis.^{9–16} Preconditioning seems to occur in a bimodal time course in the experimental setting.²⁷ The early form of protection wanes rapidly and is succeeded by a delayed phase of cardioprotection lasting for up to three days.^{8,18} Evidence for delayed preconditioning in human heart in vivo is sparse and limited.²⁸

The present prospective study demonstrates that both forms of preconditioning in the clinical setting exert some electrophysiologic effect in NSTEMI patients by reducing equally discharge QTc value and in-hospital arrhythmic events, implicating another possible cardioprotective effect of this phenomenon and documenting a similar efficacy of the

classic versus the delayed form of preconditioning protection.

The beneficial effect of preinfarction angina may be explained by several mechanisms including mainly preconditioning and collateral development.

Ischemic preconditioning, first described by Murry et al.,⁷ confers to myocardial cell resistance to ischemic injury that follows brief episodes of myocardial ischemia. In the clinical setting, pain is thought to be mediated, at least in part, by adenosine which is a well-established mediator of preconditioning, acting on special A1 receptors and stimulating afferent sensory pathways.²⁹ Thus it is possible that adenosine released during episodes of angina could trigger preconditioning cascade.

All patients enrolled in our study were angiographically proven to have poor or no collaterals (0–1 grade, according to the Rentrop classification). Subendocardial viability in contrast with the rest of myocardial wall is far less dependent to collateral circulation and in the case of severe ischemia, cell death occurs first in the subendocardial zone,⁷ according to a wavefront of cell death which moves subsequently from this zone toward the

Table 4. Preconditioning Effect on QTc, According to the severity of “Primary” Ischemia, on Admission and Discharge

Deflection Type Criteria	QTc (PA–) (ms)	QTc (PA+) (ms)	P	Lead Number Criteria	QTc (PA–) (ms)	QTc (PA+) (ms)	P
Major ischemia on admission	406 ± 65	428 ± 35	NS	Major ischemia on admission	420 ± 60	431 ± 20	NS
Minor ischemia on admission	440 ± 39	445 ± 25	NS	Minor ischemia on admission	442 ± 40	444 ± 36	NS
Major ischemia at discharge	464 ± 57	424 ± 45	0.048	Major ischemia at discharge	473 ± 60	420 ± 48	0.02
Minor ischemia at discharge	433 ± 37	405 ± 28	0.07	Minor ischemia at discharge	437 ± 40	409 ± 19	0.04

(PA–): patients with no PC effect, (PA+): patients with both forms of PC effect.

Table 5. Preconditioning Effect on QTc Value According to the Severity of "Primary" Ischemia after ECG-Ischemia Resolution

Deflection Type Criteria	QTc (PA-) (ms)	QTc (PA+) (ms)	P	Lead Number Criteria	QTc (PA-) (ms)	QTc (PA+) (ms)	P
Major ischemia on admission	440 ± 32	428 ± 36	NS	Major ischemia on admission	441 ± 41	423 ± 51	NS
Minor ischemia on admission	431 ± 41	418 ± 23	NS	Minor ischemia on admission	439 ± 28	421 ± 40	NS

(PA-): patients with no PC effect, (PA+): patients with both forms of PC effect.

subepicardial region.³⁰ In addition patients that are more prone to collateralization, such as those with previous history of coronary heart disease, left ventricular hypertrophy and conditions promoting chronic hypoxia (COPD) were excluded from the study population. For the aforementioned reasons it is unlikely that collateral development may explain the beneficial effects of preinfarction angina in our study design.

In our study, assessing myocardial infarct size by CPK MB release evidenced preconditioning presence. We found that preconditioned patients compared to patients with no prodromal angina had significant smaller values of CPK MB, thus smaller infarcts. Additionally, the efficacy of both forms on myocardial salvage was comparable giving evidence for the existence of a delayed phase of cardioprotection in humans. Our observation of infarct size reduction, assessed by myocardial serum markers measurement, is consistent with several prospective and retrospective studies in the literature focusing on the preinfarction angina effect on myocardial infarction.^{9-17,28} Additionally we observed that both forms of preconditioning exerted similar beneficial effects on the occurrence of arrhythmic events during hospitalization and documented a significant reduction of recurrent angina

and a trend for less congestive heart failure appearance in patients protected by the delayed form of preconditioning.

Heart-corrected QT interval represents an ECG index which is easily available, inexpensive, easy to perform, and is thought to have some prognostic power as a risk marker for future arrhythmic events in coronary heart disease patients. QT interval has been proposed as a marker of heterogeneous repolarization and electrical instability increasing the propensity for ventricular fibrillation². Large-scale trials though reported controversial results concerning the prognostic power of this index.⁴⁻⁶

Our study showed that both forms of preconditioning similarly and significantly reduce discharge QTc value of NSTEMI patients, giving evidence of a new cardioprotective mechanism of this phenomenon in the clinical setting of myocardial infarction. Our results also indicated that this effect was independent of the severity of the ischemic stimuli. Interestingly, we found no correlation of the preconditioning phenomenon with the QTc value on admission and at electrocardiographic ischemia resolution, no matter what the magnitude of ischemia. Finally, our observation of significant reduction of in-hospital arrhythmic events in both

Table 6. In-hospital Outcome of Preconditioned versus no Preconditioned Patients

In-hospital Events	PA- N = 20	PA + 12 N = 12	P	PA- N = 20	PA + 48 N = 16	P
Recurrent angina	12/20	4/12	NS	12/20	4/16	0.04
Arrhythmic events	6/20	0/12	0.04	6/20	0/16	0.02
Pulmonary edema	4/20	0/12	NS	4/20	0/16	0.06
Reinfarction	2/20	0/12	NS	2/20	0/16	NS
Death	1/20	0/12	NS	1/20	0/16	NS
PTCA	2/20	2/12	NS	2/20	4/16	NS
CABG	2/20	0/12	NS	2/20	0/16	NS

(PA + 12), patients with classic PC effect; (PA + 48), patients with delayed PC effect; (PA-), patients with no PC effect.

groups of preconditioned patients, led us to the conclusion that there might be a correlation between arrhythmogenicity and QTc lengthening.

There are some reports in the literature implicating the protective electrophysiologic effects of ischemic preconditioning on human myocardium during the ischemia-reperfusion injury model, reflected by QTc and QT dispersion shortening. Okishige et al. concluded that the gradual decrease in QT dispersion provoked by coronary artery occlusion and reperfusion during coronary angioplasty may be associated with electrophysiologic effects of preconditioning.³¹ Additionally, other investigators showed analogous results using the same preconditioning model^{32,33} which seemed to increase ischemic myocardium electrical stability. A recent study documented preinfarction angina protection against out-of-hospital ventricular fibrillation in patients with acute occlusion of the left coronary artery implicating preconditioning as the major antiarrhythmic protective mechanism.³⁴

Botsford et al. suggested that ischemic preconditioning might exert its antiarrhythmic effect through reduction of the substrate for reentrant arrhythmias during ischemia (dispersion of repolarization) via effects on endocardial monophasic action potentials.³⁵ Other mechanisms, which may contribute to the electrophysiologic effects of preconditioning include intracellular potassium loss through potassium channel opening, inhibition of intracellular acidosis and anaerobic glycolysis and decrease of intracellular calcium ion accumulation during severe ischemia.^{34,36}

Study Limitations

The number of the patients enrolled in the present study is relatively small compared with other similar studies. Anyway we think that the strict inclusion and exclusion criteria we have used and the general design of the study offer a good level of reliability. Additionally there is the possibility for information bias concerning the presence or absence of preinfarction angina as well as preinfarction angina characteristics (timing, duration). However, it is very unlikely that under- or over-reporting of preinfarction angina has influenced our results having in mind that QTc evaluation was blinded to all clinical data. Finally, to determine more efficiently the specific effects of preinfarction angina on major in- and out-of-hospital events, a larger prospective study is needed.

Detection of silent ischemia, which may influence our results, was not feasible, because none of the patients could have been fitted with ambulatory ECG monitoring before admission. Anyhow, patients in whom silent ischemia may occur more frequently such as elderly and diabetics, were excluded from the study population or consisted of a small minority.

Another limitation of the study is QTc assessment reliability. Additionally many studies have shown high inter- and intraobserver variability of manually measured QT dispersion³ and it is still debatable if QT dispersion represents a better repolarization ventricular status index than QTc.^{3,23}

CONCLUSIONS

Early and late preinfarction angina representing the classic and delayed form of ischemic preconditioning may exert equal electrophysiologic protective effects on human myocardium, as demonstrated by the significant attenuation of discharge QTc value in NSTEMI patients and the significant reduction of arrhythmias during their hospitalization.

REFERENCES

1. Zabel M, Klingenhoben T, Franz MR, et al. Assessment of QT dispersion for prediction of mortality or arrhythmic events after myocardial infarction: Results of a prospective, long term follow up study. *Circulation* 1998;97(25): 2543–2550.
2. Davey P. QT interval and mortality from coronary artery disease. *Prog Cardiovasc Dis* 2000;42(5):359–384.
3. Malik M, Batchvarov V. Measurement, interpretation and clinical potential of QTc dispersion. *J Am Coll Cardiol* 2000;36:1749–1766.
4. Okin PM, Devereux RB, Howard BV, et al. Assessment of QT interval and QT dispersion for prediction of all-cause and cardiovascular mortality in American Indians. The Strong Heart Study. *Circulation* 2000;101:61–66.
5. Macfarlane PW, on behalf of the WOSCOPS. QT dispersion-lack of discriminating power. (Abstract). *Circulation* 1998;98 (Suppl):I-81.
6. Brooksby P, Robinson PJ, Segal R, et al., on behalf of the ELITE study group. Effects of losartan and captopril on QT dispersion in elderly patients with heart failure. *Lancet* 1999;354:395–396.
7. Murry CE, Jennings RB, Reimer K. Preconditioning with ischemia: a delay of lethal cell injury in ischemic myocardium. *Circulation* 1986;74:1124–1136.
8. Kloner RA, Jennings RB. Consequences of brief ischemia: Stunning, preconditioning and their clinical implications (Part 2). *Circulation* 2001;104:3158–3167.
9. Ottani F, Galvani M, Ferrini D, et al. Prodromal angina limits infarct size. A role for ischemic preconditioning. *Circulation* 1995;91:291–297.
10. Kloner RA, Shook T, Pryzklenk K, et al., for the TIMI 4 investigators. Previous angina alters in-hospital outcome in

- TIMI 4. A clinical correlate to preconditioning? *Circulation* 1995;91:37-47.
11. Nakagawa Y, Ito H, Kitakaze M. Effect of angina pectoris on myocardial protection in patients with reperfused anterior wall myocardial infarction: Retrospective clinical evidence of preconditioning. *J Am Coll Cardiol* 1995;25:1076-1083.
 12. Kloner RA, Shook T, Antman E, et al., and the TIMI-9B Investigators. Prospective temporal analysis of the onset of preinfarction angina versus outcome. An ancillary study in TIMI-9B. *Circulation* 1998;99:1042-1045.
 13. Iwasaka T, Nakamura S, Karakawa M, et al., Cardioprotective effect of unstable angina to acute anterior myocardial infarction. *Chest* 1994;105:57-61.
 14. Anzai T, Yoshikawa T, Asakura Y. Effect on short-term prognosis and left ventricular function of angina pectoris prior to first Q-wave anterior wall acute myocardial infarction. *Am J Cardiol* 1994;74:755-759.
 15. Anzai T, Yoshikawa T, Asakura Y, et al. Preinfarction angina as a major predictor of left ventricular function and long-term prognosis after a first Q wave myocardial infarction. *J Am Coll Cardiol* 1995;26:319-327.
 16. Andreotti F, Pasceri V, Hackett DR, et al. Preinfarction angina as a predictor of more rapid coronary thrombolysis in patients with acute myocardial infarction. *N Engl J Med* 1996;334:7-12.
 17. Papadopoulos CE, Karvounis H, Kiotsekoglou A, et al. Effect of preinfarction angina on clinical and laboratory variables after first non-Q wave myocardial infarction. Possible evidence for preconditioning. (Abstract). *Eur Heart J* 2001;22(Suppl): 687.
 18. Baxter GF, Ferdinandy P. Delayed preconditioning of myocardium: Current perspectives. *Basic Res Cardiol* 2001;96:329-344.
 19. Rentrop KP, Cohen M, Blanke H, Phillips R. Changes in collateral channel filling immediately after controlled coronary artery occlusion by an angioplasty balloon in human subjects. *J Am Coll Cardiol* 1985;5:587-592.
 20. Abete P, Ferrara N, Cacciato F, et al. Angina-induced protection against myocardial infarction in adult and elderly patients: A loss of preconditioning mechanism in the aging heart? *J Am Coll Cardiol* 1997;30:947-954.
 21. Ishihara M, Sato H, Tateishi H, et al. Beneficial effect of prodromal angina is lost in elderly patients with acute myocardial infarction. *Am Heart J* 2000;139:881-888.
 22. Tomai F, Crea F, Gaspardone A, et al. Ischemic preconditioning during coronary angioplasty is prevented by glibenclamide, a selective ATP-sensitive K⁺ channel blocker. *Circulation* 1994;90:700-705.
 23. Statters DJ, Malik M, Ward DE, et al. QT dispersion: Problems of methodology and clinical significance. *J Cardiovasc Electrophysiol* 1994;5:672-685.
 24. Scanlon P, Faxon D, et al. ACC/AHA Guidelines for coronary angiography. *J Am Coll Cardiol* 1999;33(6):1756-1824.
 25. Hirshfeld WJ, Ellis GS, Faxon PD, et al. Recommendations for the assessment and maintenance of proficiency in coronary interventional procedures. *J Am Coll Cardiol* 1998;31(3): 722-743.
 26. Eagle AK, Guyton AR, Davidoff R, et al. ACC/AHA guidelines for coronary artery by pass graft surgery. *J Am Coll Cardiol* 1999;34(4):1262-1347.
 27. Arstall MA, Zhao YZ, Hornberger L, et al. Human ventricular myocytes in vitro exhibit both early and delayed preconditioning responses to simulated ischemia. *J Mol Cell Cardiol* 1998;30:1019-1025.
 28. Noda T, Minatoguchi S, Fujii K, et al. Evidence for the delayed effect in human ischemic preconditioning. Prospective multicenter study for preconditioning in acute myocardial infarction. *J Am Coll Cardiol* 1999;34(7):1966-1974.
 29. Gaspardone A, Crea F, Tomai F, et al. Muscular and cardiac adenosine induced pain is mediated by A1 receptors. *J Am Coll Cardiol* 1995;25:251-257.
 30. Reimer KA, Jennings RB. The "Wavefront Phenomenon" of myocardial ischemic cell death. II. Transmural progression of necrosis within the framework of ischemic bed size (myocardium at risk) and collateral flow. *Lab Invest* 1979;40:633-644.
 31. Okishige K, Yamashita K, Yoshinaga H, et al. Electrophysiologic effects of ischemic preconditioning on QTc dispersion during coronary angioplasty. *J Am Coll Cardiol* 1996;28(1): 70-73.
 32. Tomoda H, Aoki N. Prolongation of QT interval as a predictor of no-reflow induced by rotational atherectomy. *Angiology* 2002;53(4):435-441.
 33. Yunus A, Gillis AM, Traboulsi M, et al. Effect of coronary angioplasty on precordial QT dispersion. *Am J Cardiol* 1997;79(10):1339-1342.
 34. Gheeraert P, Henriques J, De Buyzere M, et al. Preinfarction angina protects against out-of-hospital ventricular fibrillation in patients with acute occlusion of the left coronary artery. *J Am Coll Cardiol* 2001;38(13):1369-1374.
 35. Botsford MW, Lukas A. Ischemic preconditioning and arrhythmogenesis in the rabbit heart: Effects on epicardium versus endocardium. *J Mol Cell Cardiol* 1998;30(12):1723-1733.
 36. Asimakakis GK, McBride KI, Medellin G, et al. Ischemic preconditioning attenuates acidosis and postischemic dysfunction in isolated rat heart. *Am J Physiol* 1992;263:H887-894.