Effects of Glucose-Insulin-Potassium Infusion on QT Dispersion in Patients with Acute Myocardial Infarction

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Background: Increased QT dispersion during acute myocardial infarction (AMI) has been associated with the occurrence of ventricular arrhythmias. Also, serum potassium levels have been shown to be relevant to the arrhythmic risk in this group of patients. The aim of the present study was to assess changes in QT dispersion during infusion of glucose-insulin-potassium (GIK) during AMI.

Methods: Patients from the Pol-GIK study were analyzed retrospectively. The patients were selected from the placebo (1000 mL of 0.89% NaCl) and the GIK (1000 mL of 10% dextrose, 20–32 units of insulin, 80 mEq K⁺) groups (18 and 24 patients, respectively). QT interval duration and dispersion (the difference between the longest and shortest QT intervals) were measured at baseline, 18–24 hours into placebo/GIK infusion and 24 hours after the end of infusion.

Results: In the placebo group, plasma potassium levels changed from 4.1 ± 0.5 mmol/L at baseline to 4.6 ± 0.8 mmol/L during infusion ($P < 0.05$) and 4.6 ± 0.4 mmol/L after infusion, whereas in the GIK group the respective values were 4.0 ± 0.4 , 4.6 ± 0.3 ($P < 0.0001$), and 4.5 ± 0.5 mmol/L. QT interval duration was stable throughout the study and there was no difference between the groups. The two groups did not differ in respect to QT dispersion at any time point, the respective values were 79 ± 28 , 65 ± 25 , and 77 ± 27 ms in the placebo group, and 61 ± 35 , 60 ± 26 , and 76 ± 43 ms in the GIK group. The incidence of arrhythmias was also similar in both groups.

Conclusions: GIK, at the dose used, is unlikely to affect heterogeneity of ventricular repolarization during AMI.

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Electrocardiographic QT dispersion has been used for several years as a noninvasive clinical index of heterogeneity of ventricular repolarization. With regard to patients with acute myocardial infarction (AMI), an early increase in QT dispersion during infarction has been observed, followed by a gradual decrease over several days after an acute event.^{1–3} In some, although not all studies increased QT dispersion during myocardial infarction has been associated with the occurrence of ventricular arrhythmias.^{3,4}

Some clinical studies have shown that serum potassium levels are relevant to the risk of complex

ventricular arrhythmias in patients with myocardial infarction.^{5,6} Furthermore, experimental data suggest that changes in ion concentrations may modulate electrical heterogeneity in either non-ischemic or ischemic conditions.⁷ Interestingly, there is evidence from clinical studies that administration of potassium can decrease QT interval duration and QT dispersion in patients with heart failure or in healthy subjects treated with quinidine,⁸ as well as in patients with the chromosome 7-linked long QT syndrome.⁹ In addition, in patients with renal failure, hemodialysis has been shown to affect the magnitude of QT dispersion as

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a result of changes in plasma electrolyte concentrations.¹⁰ However, to our knowledge, the effects of potassium supplementation on QT dispersion in patients with AMI have not yet been studied. This issue is particularly interesting in view of the fact that administration of glucose, insulin, and potassium (GIK) has been suggested to suppress arrhythmias during AMI.^{11,12}

Recently, a large multicenter prospective trial has been published in which GIK was administered to patients admitted with an AMI (Pol-GIK).¹³ In the present study a subpopulation of the Pol-GIK patients have been studied retrospectively with regard to changes in QT dispersion during intravenous administration of GIK.

METHODS

Study Group

The study group consisted of 42 patients with an AMI, taken from a local Pol-GIK database at the Department of Cardiology, Postgraduate Medical School, Warsaw, Poland. The patients were randomly selected from the placebo and the GIK groups (18 and 24 patients, respectively). The clinical characteristics of the study groups are shown in Table 1.

Electrocardiographic Measurements

QT interval duration and corrected QT interval duration (according to Bazett's formula) were measured from 12-lead ECG recordings at a tape speed of 50 mm/s. The measurements were performed manually after twofold magnification with a magnifying glass. The QT interval was measured from the beginning of the QRS complex to the return of the T wave to the isoelectric line. In the presence of the U wave, the end of the T wave was defined as the lowest point between the T and the U wave. QT interval dispersion was defined as the difference between the longest and the shortest QT interval. It was measured from 6 precordial leads (V₁-V₆) or from all 12 leads (I-V₆).

Study Protocol

Eligible patients with an AMI (a chest pain lasting > 30 minutes and typical ischemic ECG changes within 24 hours of onset) were randomized to the GIK (1000 mL of 10% dextrose, 20-32 units of insulin, 80 mEq K⁺) or the placebo (1000

Table 1. Baseline Clinical Characteristics of the Study Groups

	Placebo n = 18	GIK n = 24	P <
Females/males (n)	10/8	12/12	NS
Age (years)	61 ± 11	59 ± 12	NS
History of smoking (n)	10	14	NS
Coexisting diseases (n)			
hypertension	8	11	NS
heart failure	1	2	NS
previous MI	3	5	NS
hyperlipidaemia	3	4	NS
diabetes (not on insulin)	1	2	NS
Time from onset of symptoms to randomization (hours)	5.6 ± 1.9	6.0 ± 2.2	NS
Concomitant medication (n)			
aspirin	18	24	NS
thrombolytic therapy	12	15	NS
beta-blockers	13	18	NS
ACE-inhibitors	9	11	NS
digitalis	1	2	NS
diuretics	5	7	NS
antiarrhythmic agent	3	5	NS

MI = myocardial infarction; ACE = angiotensin converting enzyme.

mL of 0.89% NaCl) groups. GIK or placebo were administered as an intravenous 24-hour infusion at a rate of 42 mL/hour. QT interval duration and dispersion were calculated at baseline, 18-24 hours into placebo/GIK infusion, and 24 hours after the end of placebo/GIK infusion.

Statistical Analysis

Analysis of variance for repeated measures (followed by post-tests with Bonferroni's correction) was used for statistical comparisons of QT interval duration and dispersion at various time points during the study. An unpaired Student *t*-test was used to assess differences between the two groups. Clinical characteristics of the study groups were compared using Fisher's exact test. A P value < 0.05 was considered statistically significant. All data are expressed as mean ± SD.

RESULTS

Biochemical Parameters

There was no difference between the placebo and the GIK groups in respect to peak creatinine

kinase (905 ± 430 vs 898 ± 393 IU/L, respectively) or peak glutamic oxaloacetic transaminase (130 ± 66 vs 142 ± 73 IU/L) levels. In the placebo group, glucose levels were 124 ± 22 , 111 ± 16 , and 115 ± 22 mg% at baseline, 18–24 hours into placebo infusion and 24 hours after the end of infusion, respectively. The respective values in the GIK group were 122 ± 21 , 110 ± 22 , and 104 ± 18 mg%. In the placebo group, plasma potassium levels changed from 4.1 ± 0.5 mmol/L at baseline to 4.6 ± 0.8 mmol/L during infusion ($P < 0.05$) and 4.6 ± 0.4 mmol/L after infusion, whereas in the GIK group the respective values were 4.0 ± 0.4 , 4.6 ± 0.3 ($P < 0.0001$) and 4.5 ± 0.5 mmol/L. Finally, plasma sodium concentration was stable throughout the study, the respective values being 140 ± 3 , 142 ± 3 , and 141 ± 4 mmol/L in the placebo group and 142 ± 4 , 143 ± 3 , and 143 ± 3 in the GIK group.

Electrophysiological Effects of GIK Infusion

The results of electrophysiological measurements are shown in Tables 2 and 3. QT interval duration was stable throughout the study and there was no significant difference between the groups. Similarly, the placebo and the GIK groups did not differ in respect to QT dispersion (either corrected or not) at any time point.

Arrhythmic Events

There was no difference between the groups with regard to arrhythmic events. Nonsustained

ventricular arrhythmias and/or conduction disturbances occurred in four patients (22%) in the placebo group and in six patients (25%) in the GIK group. Resuscitated cardiac arrest due to ventricular fibrillation was reported in one patient (5%) in the placebo group and one patient (4%) in the GIK group.

DISCUSSION

Electrocardiographic QT dispersion is thought to be a noninvasive index of heterogeneity of ventricular repolarization. Indeed, there is evidence that dispersion of monophasic action potential duration and recovery time correlates with QT dispersion.^{14–17} Accordingly, the lack of any effect of GIK infusion on QT dispersion in the present study suggests that GIK infusion (i.e., potassium supplementation) does not affect heterogeneity of ventricular repolarization in patients with AMI in contrast to patients with the long-QT syndrome, heart failure, or those treated with quinidine.^{8,9} This observation is consistent with the final results of the Pol-GIK study that GIK treatment does not improve survival and clinical course in patients with AMI.¹³ This conclusion, however, requires some comment.

In the above-mentioned study in patients with heart failure,⁸ the same amount of potassium as in the present study was administered over a shorter period of time and potassium chloride was infused in 0.9% saline rather than as a GIK solution. Although the baseline and final serum potassium concentrations were similar in the two studies, it

Table 2. Values of Corrected QT Interval Duration (ms) in the Placebo and the GIK Groups at Baseline, 18–24 Hours into Placebo/GIK Infusion and 24 Hours After the End of Placebo/GIK Infusion (Recovery)

	Placebo (n = 18)			GIK (n = 24)		
	Baseline	Infusion	Recovery	Baseline	Infusion	Recovery
Lead I	433 ± 54	417 ± 43	425 ± 45	407 ± 44	409 ± 30	420 ± 41
Lead II	445 ± 37	421 ± 39	434 ± 40	420 ± 40	420 ± 35	430 ± 38
Lead III	410 ± 43	431 ± 51	432 ± 50	419 ± 40	418 ± 40	433 ± 43
Lead aVR	415 ± 29	420 ± 44	419 ± 54	404 ± 37	414 ± 32	424 ± 31
Lead aVL	411 ± 35	426 ± 57	394 ± 43	401 ± 36	422 ± 36	433 ± 39
Lead aVF	429 ± 34	410 ± 47	425 ± 38	417 ± 31	424 ± 34	431 ± 40
Lead V ₁	438 ± 60	412 ± 29	410 ± 24	408 ± 35	414 ± 42	419 ± 38
Lead V ₂	443 ± 37	437 ± 42	437 ± 45	420 ± 58	431 ± 27	438 ± 36
Lead V ₃	443 ± 48	437 ± 61	449 ± 52	426 ± 50	426 ± 28	445 ± 35
Lead V ₄	438 ± 60	435 ± 57	447 ± 53	429 ± 47	424 ± 36	462 ± 52
Lead V ₅	425 ± 46	439 ± 46	433 ± 54	431 ± 49	428 ± 28	434 ± 39
Lead V ₆	433 ± 46	440 ± 47	435 ± 51	425 ± 46	431 ± 39	439 ± 51

Table 3. Values of QT Interval Dispersion (ms) in the Placebo and the GIK Groups at Baseline, 18–24 Hours into Placebo/GIK Infusion and 24 Hours After the End of Placebo/GIK Infusion (Recovery)

	Placebo (n = 18)			GIK (n = 24)		
	Baseline	Infusion	Recovery	Baseline	Infusion	Recovery
V ₁ –V ₆	55 ± 32	55 ± 28	66 ± 35	41 ± 30	41 ± 22	67 ± 46
I–V ₆	79 ± 28	65 ± 25	77 ± 27	61 ± 35	60 ± 26	76 ± 43

Dispersion was calculated either for 6 precordial leads (V₁–V₆) or for all 12 leads (I–V₆).

cannot be excluded that the concentration of potassium infused as well as the form of potassium infusion can affect its electrophysiological effects. With regard to the latter possibility, it has been reported that insulin (contained in the GIK solution in the present study) may exert direct electrophysiological effects in its own right by affecting membrane polarization and individual ion currents.^{18–20}

In addition, some experimental results suggest that changes in potassium concentration can affect electrical dispersion in the whole heart in nonischemic conditions when potassium levels are lowered to hypokalemic values.⁷ It is likely, therefore, that restoration of normokalemic potassium levels can reverse hypokalemia-induced electrophysiological changes. This situation, however, is different from that in the present study, when GIK was infused to patients with baseline normokalemia. In addition, the experimental results suggest that it is hypomagnesemia rather than hypokalemia that affects ischemia-induced dispersion of repolarization.⁷ It may suggest that KIG should be administered together with magnesium to reduce QT dispersion produced by AMI. Indeed, it has been reported that administration of GIK with magnesium is likely to decrease morbidity²¹ and administration of magnesium alone decreases QT dispersion and the incidence of ventricular arrhythmias in patients with AMI.^{22,23}

Finally, as discussed by Apstein and Opie,²⁴ although meta-analytic studies of a number of smaller trials have suggested mortality benefit,²⁵ it is only the South American trial that has been large enough to show a mortality benefit of a GIK infusion.¹² In contrast, the Pol-GIK study has produced a negative result.¹³ The two chief differences between these two studies are the higher risk of mortality of the patients chosen for the "positive" trial and the higher dose of GIK that was used. Interestingly, the "positive" study suggests that GIK is likely to suppress arrhythmias in patients

with AMI.¹² It is possible, therefore, that in order to exert beneficial antiarrhythmic electrophysiological effects, GIK has to be administered at a high enough dose and to patients at the greatest risk of death.

CONCLUSIONS

The present study has demonstrated that GIK, at the dose used, is unlikely to affect heterogeneity of ventricular repolarization during AMI. However, the main limitation of this study is its retrospective character. To clarify this issue, it would be necessary to conduct a larger prospective study in which a higher concentration of GIK would be administered together with magnesium to patients in the acute phase of myocardial infarction.

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