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Long-term glucose insulin potassium infusion improves systolic and diastolic function in patients with chronic ischaemic cardiomyopathy

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Summary

We assessed the effects of glucose-insulin-potassium (GIK) using echocardiography, right ventricular catheterisation and myocardial scintigraphy with 99mTc sestamibi in stable patients with ischaemic cardiac dysfunction.

Methods: Thirty male patients with stable coronary disease (SCD) and an ejection fraction (EF) <40% were studied for systolic and diastolic function. Glucose 30%, 300 insulin units and KCl 6 g/l were infused at 1 ml/kg per hour for 24 hours. Haemodynamic, echocardiographic and myocardial scintigraphy measurements were recorded at rest on completion of the GIK infusion.

Results: A significant increase in EF was observed (32.1 ± 7.8% and 43.3 ± 11.6%, p <0.01). A significant prolongation was seen in the diastolic filling periods (365 ± 52 msec and 428 ± 70 msec, p <0.05). A significant decrease in pulmonary capillary wedge pressure was measured (22.2 ± 5.3 and 17.1 ± 4.3, p <0.01) and a significant decrease in stress score (SS) was observed (13 ± 7 and 11 ± 5, p >0.05).

Conclusion: Our present work suggests that GIK infusion improves systolic and diastolic function in patients with SCD and an ejection fraction <40%. Further studies are needed to determine whether long-term GIK infusion could be useful for therapeutic strategies in patients with chronic ischaemic coronary diseases.

Key words: ischaemic cardiomyopathy; GIK infusion

Introduction

Glucose appears to be the preferred energy substrate for the myocardium during ischaemia and reperfusion. Glucose-insulin-potassium (GIK) solutions have been shown to limit ischaemic damage in experimental models and clinical studies of ischaemia [1, 2]. To the best of our knowledge, in all GIK trials to date, GIK solution was used only for a short period, and diastolic function was seldom evaluated. Glucose uptake and glycolytic ATP production are important determinants of tissue viability, especially when the heart is compromised by reduced flow [3, 4]. Beneficial effects of GIK infusion have been demonstrated in patients in the acute phase of myocardial infarction and during cardiac surgery. The aim of this study was to assess the effects of a long period of GIK infusion on systolic and diastolic left ventricular parameters measured by echocardiography, right ventricular catheterisation and myocardial scintigraphy in stable patients with ischaemic dysfunction.

Methods

Our study group consisted of 30 men aged from 42 to 75 years (mean age: 53 ± 15 years). All patients presented with severe LV dysfunction with an ejection fraction (EF) <40% and an average NYHA class of 2.1 ± 0.5. They had a history of myocardial infarction in the preceding 6 months and at least one vessel disease documented by coronary angiography. None of the patients had a left main stenosis, valvular heart disease or diabetes mellitus. All patients were in normal sinus rhythm and any cardiac medication was continued.

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After baseline recordings were obtained, GIK solution was given as glucose 30% with 300 insulin units and 6 g of potassium chloride per litre at an infusion rate of 1 ml/kg per hour for 24 hours.

Blood glucose concentrations, heart rate, systolic and diastolic blood pressure were determined every hour during the 24 hours. Two echocardiography studies were performed on each patient. Both were obtained at rest, the first before and the second on completion of the GIK infusion. Transthoracic echocardiography was performed using a Vingmed CFM 800 model USG device with a 2.5 MHz transducer. The peak velocity of early rapid filling (E wave) and the peak velocity of atrial filling (A wave) were recorded, and the E to A ratio (E/A) was calculated. End diastolic volume (EDV), end systolic volume (ESV), stroke volume (SV) and ejection fraction (EF) were calculated using end diastolic and end systolic diameters taken from the basal part of parasternal long axis sections. Isovolumetric relaxation time (IVRT), diastolic filling period (DFP) and ejection time (ET) were also calculated using a Doppler technique. Left ventricular inflow velocities were calculated by continuous wave Doppler from apical four space sections. Haemodynamic parameters, pulmonary artery pressure and pulmonary capillary wedge pressure were measured using a Swan-Ganz catheter via the subclavian vein. Myocardial scintigraphy was performed using a GE.Millenium square. Each myocardial segment was visually graded using a semi quantitative scoring system, in which 0 = normal, 1 = mildly reduced, 2 = moderately reduced, 3 = severely reduced, 4 = upset uptake. Using this scoring system a summated stress score (SS) was calculated. A stress score less than 4 was considered normal, 4 to 8 mildly abnormal, 8 to 13 moderately abnormal and more than 13 severely abnormal [5]. Tomograms were divided into 20 segments, stress score was defined as the sum of each segment score divided by the number of interpreted segments [6]. The same examiners were used before and after GIK infusion and they were blind during both assessments.

Data were expressed as mean±standard deviation (S.D.). Statistical analysis was performed by paired-t test. Statistical significance was considered acceptable for $p < 0.05$.

Results

During the GIK perfusion and follow-up period, no serious adverse symptoms were observed in echocardiography, in particular no arrhythmia or severe hypotension. No significant haemodynamic changes were observed during the GIK infusion or during the follow-up period. A significant increase in EF was observed (32.1 ± 7.8% and 43.3 ± 11.6%, p <0.01). A significant prolongation was seen in the diastolic filling periods (365 ± 52 msec and 428 ± 70 msec, p <0.05). No significant relation was found in IVRT (89.3 ± 21.6 msec and 93.6 ± 17.1 msec). Echocardiography parameters at rest before and after 24 hour of GIK-infusion are summarised in table 1. A significant decrease in pulmonary capillary wedge pressure was measured (22.2 ± 5.3 and 17.1 ± 4.3, p <0.01). Haemodynamic parameters at rest before and after 24 hour of GIK-infusion are presented in table 2, a significant decrease in stress score (SS) was observed (13 ± 7 and 11 ± 5, p >0.05) as shown in table 3. The overall characteristics and comedications of patients are summarised in table 4.

Table 1

Echocardiography parameters at rest before and after 24 hour of GIK-infusion (values are mean ± S.D.).

	At rest prior to infusion	After 24 hour of GIK infusion	P
IVRT (ms)	89.3 ± 21.6	93.6 ± 17.1	NS
DFP (ms)	365 ± 72	428 ± 70	<0.05
ET (ms)	252.8 ± 33.8	270.4 ± 25.5	NS
LVEDV	108.2 ± 20.9	106.3 ± 11.3	NS
LVESV	72 ± 16	63 ± 19	<0.05
SV	34 ± 7	45 ± 9	<0.05
EF %	32.1 ± 7.8	43.3 ± 11.6	<0.05
FS %	20 ± 2.1	27 ± 2.1	<0.05
Peak E (cm/s)	62 ± 13	67 ± 11	NS
Peak A (cm/s)	73 ± 22	69 ± 15	NS
E/A	0.78 ± 17	0.75 ± 13	NS
MDT (ms)	279 ± 42	242 ± 45	NS

Abbreviations: IVRT, isovolumetric relaxation time; DFP, diastolic filling period; ET, ejection time; LVEDV, left ventricular end-diastolic volume; LVESD, left ventricular end-systolic diameter; SV, stroke volume; SF, shortening fraction; EF, ejection fraction; A, mitral flow velocity at the time of atrial contraction; E, initial peak mitral flow velocity; E/A, ratio of peak mitral velocity to mitral flow velocity at the time of atrial contraction; MDT, mitral deceleration time; NS, non significant

Table 2

Haemodynamic parameters at rest before and after 24 hour of GIK-infusion (values are mean ± S.D.)

	at rest prior to infusion	after 24 hour of GIK infusion	P
Blood sugar (mgr/dl)	101 ± 13	107 ± 11	NS
HR (beats/min)	68 ± 9	65 ± 11	NS
SBP (mm Hg)	98 ± 12	105 ± 12	NS
DBP (mm Hg)	60 ± 9	61 ± 11	NS
PAP (mm Hg)	42 ± 13	35 ± 9	<0.05
PCWP (mm Hg)	22.2 ± 5.3	17.1 ± 4.3	<0.05

HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; PAP, Pulmonary artery pressure; PCWP, pulmonary capillary wedge pressure; NS, non significant

Table 3

Result of myocardial scintigraphy with 99mTc sestamibi at rest before and after 24 hour of GIK-infusion (values are mean ± S.D.).

	at rest prior to imfusion	after 24 hour of GIK infusion	P
Stress score	13 ± 7	10 ± 5	<0.05

Discussion

Use of GIK solutions in acute ischaemic MI has been shown to limit ischaemic damage in experimental models and in some clinical studies such as ECLA and DIGAMI [1, 2, 7, 8]. To the best of our knowledge these studies investigating the use of GIK-infusion in ischaemic cardiomyopathy were done in small groups using a short-period of GIK infusion (approximately 2–4 hours). The present study investigated the effects of a long period of GIK administration in ischaemic cardiomyopathy on myocardial viability and monitored the haemodynamic changes. It has been reported that the use of GIK in experimental studies does not result in a decrease in systemic vascular resistance [9, 10]. A recent clinical study suggested a direct stimulatory effect of insulin on endothelial production of NO without haemodynamic changes [11]. GIK therapy has been shown to have a beneficial effect on ventricular late potentials (VLPs) by improving the electrical stability of the heart. VLPs are known to correlate with an increased risk of ventricular tachycardia and sudden cardiac death in acute myocardial infarction during the early period [12].

Table 4

Overall characteristics and comedications of the patients.

	(n = 30)
Age (years)	53 ± 15
female/male	0 / 30
Average of NYHA	2.1 ± 0.5
Hypertension	8 (26%)
Hyperlipidaemia	12 (40%)
Diabetes mellitus	0
Smoker	11 (36%)
Beta-blocker	21 (70%)
Aspirin	30 (100%)
Nitroglycerine	3 (0.1%)
ACE-inhibitors	28 (93%)

LV dysfunction is generally studied using pharmacological inotropic stimulation and echocardiography or MRI [13], in spite of the fact that several studies have demonstrated the therapeutic benefit of GIK on the post-ischaemic heart. Unfortunately drug companies have shown little interest in producing a GIK-infusion. This may be due to the fact that GIK solution is cheaper and easily prepared. The use of varying doses of GIK infusion in different clinical studies may also be one of the reasons why it is not routinely industrially manufactured

To date both clinical and experimental studies using GIK solution have been performed only as short-period studies. We aimed to evaluate the effects of long-term GIK administration in ischaemic cardiomyopathic patients. Our results suggest that infusion of GIK enhances left ventricular ejection fraction whilst decreasing pulmonary capillary wedge pressure and end systolic volume indexes. These findings suggest a metabolic effect of GIK on the chronic ischaemic myocardium. Analysis of regional wall motion shows that the increase in ejection fraction is secondary to improvements in the infarcted zone [14]. These findings may lead to improved long term survival in patients with cardiomyopathy. The mechanism of action of GIK infusion may be that the solution acts as a polarising agent, promoting electrical stability and providing metabolic support [2]. It has been reported that an important meta-analysis of all GIK trials in AMI showed a reduction in mortality of 28% [15]. In our study we found that infusion of GIK reduced myocardial SS. These results suggest that the viability of the ischaemic myocardium depends on the glucose supply [1, 16,]. The improvement in contractile function also suggests that insulin can be internalised by myocardial cells and activates the SR Ca^{2+} ATPase by binding to SR membranes [17, 18]. Tune et al's experi-

mental study reported that insulin given alone improved contractile function during moderate ischaemia without increasing O_2 consumption [19].

The increased values of LVEF in our study were comparable with the results of Cottin et al. [2]. However their patient group (n = 12) was small and they did not evaluate the results using invasive parameters. We performed our study in 30 patients, and we evaluated invasive parameters such as PAP and PCWP by right heart catheterisation. We found a significant decrease in PAP and PCWP. These decreases may be due to the improvement in LV and the increased LV contractility. On the other hand, we found a significant increase in DFP in the evaluation of diastolic functions. This indicates that GIK infusion improves not only the systolic but also the diastolic function.

Pulmonary hypertension is an important problem in patients with cardiomyopathy. As GIK infusion leads to a decrease in PAP, administration of GIK in patients with cardiomyopathy may be therapeutic.

Conclusion

Our present work suggests that GIK infusion improves systolic and diastolic function in patients with SCD and ejection fraction <40%. In addition it reduces myocardial SS and PCWP. Further studies are needed to determine if long-term GIK infusion could be a useful option in the development of therapeutic strategies in patients with chronic ischaemic coronary diseases.

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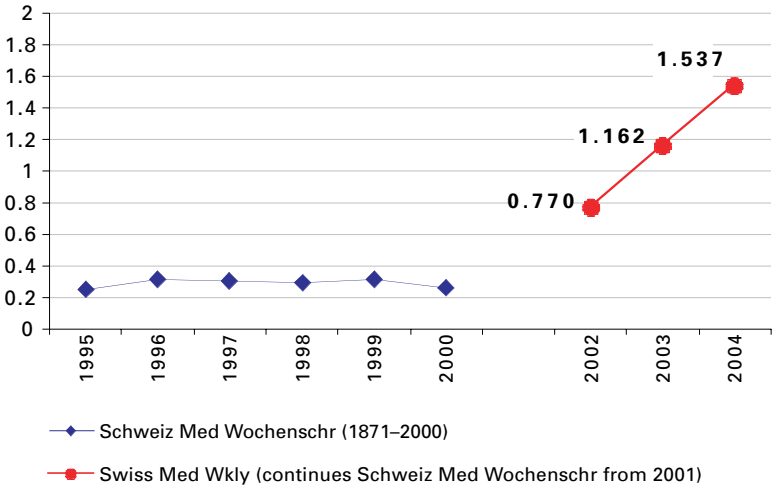

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