Razavi Int J Med. 2021; 9(1): e1017 doi: 10.30483/rijm.2021.254163.1017

Published online 2021 March 30 **Original Article**

Effect of Glucose-Insulin-Potassium infusion on systolic and diastolic functions in patients with chronic ischemic cardiomyopathy

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Received 2020 December 31; **Accepted** 2021 March 07.

Abstract

Background: Ischemic cardiomyopathy is accompanied by some degrees of decreased metabolism. Therefore, the adoption of a method to facilitate cellular absorption and use of glucose may promote myocardial function and viability. Glucose-insulin-potassium (GIK) solution has been used with some successful results in acute ischemic heart disease decreasing the extent of the ischemic zone in the myocardium and promoting ventricular function.
Objectives: The current study aimed to evaluate the effect of GIK infusion on systolic and diastolic functions in patients with chronic ischemic cardiomyopathy.
Materials and Methods: The present study was carried out on a total of 25 patients with ischemic cardiomyopathy (ejection fraction<40%) with stable clinical condition referring to the Cardiac Emergency Department or Clinic of Cardiology in Ghaem hospital in Mashhad, Iran. The patients were assessed by echocardiographic indices before and after GIK administration to evaluate the effects of GIK on the systolic and diastolic functions of the heart in chronic ischemic cardiomyopathy.
Results: The male to female ratio was 4:1 in the present study. According to echocardiographic findings, left heart end-diastolic indices did not show any significant statistical changes (P>0.005); however, the diastolic function of the left ventricle significantly improved after the administration of GIK (P<0.005). Despite the fact that there was no significant change in the improvement of systolic left and right ventricular functions (P>0.005), clinical symptoms decreased due to metabolic improvements and an increase in ventricular function after GIK administration.
Conclusion: The administration of GIK solution (as an accessible and cost-effective agent) may improve ventricular diastolic function and clinical symptoms; therefore, it is suggested to use GIK as an effective therapeutic method in ischemic cardiomyopathy.

Keywords: Echocardiography; Glucose-Potassium-Insulin solution; Ischemic cardiomyopathy

Background

Left ventricular (LV) function is the main criterion determining the prognosis of ischemic heart disease (IHD) (1). Although not all the areas involved in movement impairment after an ischemic heart attack will progress to irreversible damage, LV dysfunction may progressively deteriorate with chronic IHD (2, 3). The important fact is to maintain cellular metabolism even in areas with dyskinesia (4) up to the point that they return to normal function after perfusion improvement (5). It seems that glucose is the preferred fuel for the myocardium during the ischemia and reperfusion phases. Studies reported that glucose-insulin-potassium (GIK) solution limits ischemia in experimental models and clinical investigations of patients with IHD (6, 7).

Based on available findings of GIK infusion, this infusion always has been used for a short period after acute heart ischemia focusing on the assessment of ischemic area extension and LV systolic function. Nevertheless, less attention has been paid to LV diastolic function. Glucose uptake and glycolic production of adenosine triphosphate (ATP) are important indicators of tissue survival, which are more considerable when the myocardium is in an ischemic condition (8, 9).

The benefits of GIK infusion even for the ischemic condition during heart surgery have been documented in several studies. Many patients with chronic IHD never find the opportunity for revascularization due to their underlying diseases. In these patients, medical treatment to maintain heart function is the essential part of therapy (10). In this regard, using GIK infusion in heart ischemia was beneficial, causing a reduction in the extent of infarction area and improvement of ventricular function (11, 12).

The GIK treatment reduces the effect of ischemia on myocardial contractility, slightly improves exercise tolerance, and causes a diffuse and more rapid recovery of post-ischemic reperfusion (13). In addition to GIK benefits in acute ischemia, some studies have demonstrated that GIK improves exercise tolerance and decreases ST-segment elevation during activity in patients with chronic IHD (14). The effects of cellular metabolism intervention on LV function in chronic coronary disease are not clearly perceived, although recent studies have shown evidence of improvement and common functional effects (15). In this study, we evaluated the effects of GIK infusion on diastolic and systolic heart function in patients with chronic ischemic cardiomyopathy.

Objectives

The current study aimed to evaluate the effect of GIK infusion on systolic and diastolic functions in patients

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Table 1. Frequency distribution of patients before and after glucose-insulin-potassium infusion based on left ventricular diastolic function

Left ventricular diastolic function	Before GIK infusion		After GIK infusion	
	n	%	n	%
Class I	1	4	10	40
Class II	13	52	15	60
Class III	11	44	0	0
Total	25	100	25	100

GIK: Glucose-insulin-potassium

with chronic ischemic cardiomyopathy.

Materials and Methods

In this study, it was decided to evaluate the effects of GIK infusion on the diastolic and systolic functions of the heart in patients with chronic ischemic cardiomyopathy referring to Cardiac Emergency Department and Specialty Clinic of Ghaem hospital in Mashhad, Iran, using simple sampling. The present study was carried out on a total of 25 patients (including 20 male and 5 female patients) with ischemic cardiomyopathy in stable clinical condition (NYHA class I-III) referring to Cardiac Emergency Department or Specialty Clinic of Ghaem hospital in a one-year period. The patients were admitted to the Cardiac Emergency Department for 24 h and their epidemiologic information was collected. The study subjects received their routine treatment, including diuretics, angiotensin receptor blockers, selective beta-blockers, and in some cases digoxin. The GIK solution, including 300 g glucose, 50 units insulin, and 80 mEq potassium, was administrated for the patients for 10 h with a speed of 1/5 ml/kg/h.

Serum glucose and potassium level assessment and electrocardiogram and echocardiography with Vivid 3 machine and 2-MHz probe were performed for the patients before and after GIK infusion. In echocardiography, diastolic indices before and after GIK infusion, including early and end-diastolic transmitral inflow rate (A, E), E wave deceleration, early and end-diastolic inflow of mitral annulus speed (A, E), E/A ratio, E/E ratio, slope of transmitral inflow velocity of propagation, left atrial appendage size, systolic and diastolic inflow of pulmonary veins, systolic indices (including LV end-diastolic dimension, ventricular end-systolic dimension, LV end-diastolic volume (EDV), LV end-systolic volume (ESV), LV systolic function (EF), right ventricular systolic function (including tricuspid annular plane systolic excursion (TAPSE), tricuspid annular motion speed evaluation with tissue Doppler imaging (sm), were evaluated. Then, based on diastolic findings, the patients were divided into four classes according to American College of Cardiology guidelines.

Statistical analysis

Descriptive statistics (i.e., mean, median, mode, standard deviation, and frequency distribution table) and analytical statistics (i.e., student's t-test for qualitative and quantities variables, Chi-square test, and Fisher's exact test) were used in the present study.

Results

Among 25 patients, 5 (20%) and 20 (80%) subjects were female were male, respectively. At the end of the infusion, the patients expressed improvement in clinical symptoms and shortness of breath. The serum levels of glucose and potassium did not show significant differences before and after the infusion. Left and right ventricular systolic indices demonstrated significant improvement after the infusion. Diastolic indices indicated at least one-degree improvement. The LV diameter also decreased after the infusion, which was a sign of improvement. Echocardiography indices were evaluated before and after GIK infusion. The mean values of LV EDV before and after GIK administration were 146.8±35.59 (range: 100-240 ml) and 145.1±35.0 (range: 98-238 ml) ml, respectively.

The difference between the mean values of LV EDV before and after GIK administration was not significant using paired t-test (P=0.76). The difference between the mean values of LV ESV before and after GIK infusion was not also significant using paired t-test (P=.0.66). The mean values of LV end-diastolic diameter before and after GIK administration were 66.3±6.77 (range: 51-79 ml) and 66.4±6.29 (range: 55-80 ml) ml, respectively. The means of LV end-diastolic diameter before and after GIK infusion did not indicate any significant difference using paired t-test. The mean values of LV end-systolic diameter were 53.4±6.39 (range: 64-44 ml) and 53.1±6.41 (range: 63-43 ml) ml before and after GIK infusion, respectively. The difference between the mean values of LV end-systolic diameter before and after GIK administration was not significant using paired t-test (P=0.96). The mean value of patients' ejection fraction (EF) when admitted to the hospital was reported as 34.5±5.31 with a minimum and maximum of 25% and 40%, respectively. For the evaluation of patients' LV end-diastolic function, the subjects were divided into four classes. Then, the number of patients in each class was evaluated before and after GIK administration (Table 1).

A comparison of patients' distribution based on LV diastolic function using the Fisher's exact test showed a significant difference before and after GIK administration (P<0.001). The evaluation of right ventricular systolic function indicated that the mean values of TAPSE index before and after GIK infusion were 2±0.26 (range: 1.5-2.5) and 1.9±0.26 (range: 1.2-2.4), respectively. The difference in TAPSE before and after GIK infusion was not significant using paired t-test (P=0.613). The mean values of left atrial size before and after GIK infusion were 48.7±6.19 (range: 35-60) and 42.4±5.75 (range: 35-55), respectively, with a significant difference using paired t-test was (P<0.001). The mean values of EF slope before and after GIK infusion were 29.4±4.46 (range: 21-38) and 36.4±3.62 (range: 28-42), respectively, with a significant difference using paired t-test

(P<0.001)

Discussion

The IHDs, more than any other diseases in developed countries, are responsible for mortality and disability and impose economic costs. The IHD is the most common, serious, chronic, and dangerous disease in the USA. In the USA, more than 12, 6, and 7 million individuals have IHD, angina pectoris, and one myocardium infarction, respectively. Diet high in calories and fat, smoking, and sedentary lifestyle are associated with IHD. The incidence of IHD is increasing worldwide and probably will be the most common cause of mortality around the world in the future (16).

The use of GIK infusion was based on the logic that insulin increase potassium reuptake thought sodium-potassium pomp ATPASE and increase glucose reuptake for energy production. The combination of glucose and insulin will protect the myocardium and return glycogen storage. Glucose will be consumed fast during ischemia and glycogen reduction, decrease contractility, and produce calcium (17). There are also other mechanisms suggested for myocardium protection by GIK infusion as follows:

- When blood flow reduces after ischemia, a high concentration of glucose and insulin improves ischemia and myocardium diastolic and systolic function. Furthermore, when coronary vessels dilate, the no-reflow phenomenon decreases.
- Increase in pre-glycolysis material
- Preventing non-organic phosphate and ADP increase following ischemia, ATP level, and energy release from ATP hydrolysis that even in low amounts raise free energy for cellular metabolism (18). The GIK protects the heart, has a role in the improvement of glucose uptake through GLUT1 in oxygenation by 70.5%, and decreases beta-oxidation of free fatty acids (19, 20).

Alan et al. in Turkey (2003) evaluated the effects of long-term GIK administration on the improvement of systolic and diastolic functions in patients with ischemic cardiomyopathy. The GIK effects were evaluated based on echocardiography indices, right ventricle catheterization, and myocardium scintigraphy with Technetium sestamibi in patients with a stable condition. The aforementioned study included 30 male patients with coronary diseases in a stable condition and EF of > 40%. They reported that after GIK infusion, the patients' EF significantly improved and diastolic filling time increased. Alan et al. concluded that GIK infusion is beneficial in the improvement of systolic and diastolic functions of patients with ischemic cardiomyopathy (21).

Cottin et al. also in France (2002) studied the effects of GIK on heart systolic function in patients with ischemic cardiomyopathy. The aforementioned study included 12 male patients with chronic ischemic cardiomyopathy in a stable condition and with EF of < 45%. The GIK was administrated for the subjects and hemodynamic and echocardiographic changes were evaluated. The results showed a significant decrease in wall movement index and an increase in EF. Cottin et al. concluded that GIK significantly improves heart systolic function in patients with ischemic cardiomyopathy with EF of > 45% (7).

Another study in Australia (2003) also evaluated the effects of GIK on patients with ischemic cardiomyopathy. A total of 30 patients with ventricular dysfunction caused by chronic cardiomyopathy were evaluated with dobutamine echocardiography before and after 4 h of GIK infusion. The results demonstrated improvement in wall traction index following dobutamine and GIK administration. The maximum systolic flow also showed significant improvement after GIK infusion, which was more significant than improvement after dobutamine administration. The aforementioned study reported the improvement of myocardium function in both places with normal and abnormal perfusion following GIK infusion (22).

In a study carried out by Zhu et al., the efficacy of GIK infusion in maintaining systolic and diastolic function was studied in patients with ischemia and de-perfusion syndrome in the USA in 2000. The aforementioned study was based on the rationale that GIK infusion improves heart systolic and diastolic functions in those suffering from heart dysfunction following ischemia. Zhu et al. recommended GIK infusion in patients who are at high risk for myocardial ischemia as a technique for the protection of muscles facing ischemic attacks (23).

Marano et al. also conducted a study (2000) for the evaluation of the effects of GIK infusion on myocardium function after an ischemic period. A total of 21 male patients with recent uncomplicated infarction were evaluated in rest position and 24 h after GIK infusion with myocardium scintigraphy. They showed that the patients receiving GIK infusion had significant improvement in EDV and perfusion of ischemic segments (24). Another study performed by Ramanathan et al. in Australia (2004) evaluated the efficacy of GIK infusion in LV function improvement in sheep with chronic diabetes. Heart contractility improved in 58% of those treated with GIK infusion (compared to that reported for the control group) (25).

Another study carried out by Ahmed et al. (1978) investigated the efficacy of GIK infusion in the improvement of heart function. It was demonstrated that GIK infusion in the early hours after ischemia not only improves heart function but also prevents ischemic arrhythmia (11). Harry et al. (2012) reported that GIK administration had no effect on survival; however, it will decrease in-hospital mortality and outcome rate of cardiac arrest (26). In 2007, Eiferman et al. tried to preserve heart function during ischemia with GIK infusion. They assessed myocardium function in 40 male pigs divided into two groups, with and without GIK infusion, and reported an increase in ATP consumption in cardiac cells of the group with GIK infusion (27).

Ramanathan et al. in another study (2002) assessed the effects of GIK infusion on ischemic myocardium in diabetic patients. They treated six sheep with GIK infusion after diabetes induction and observed that LV function significantly increased and improved (28). Another study (2013) reported that the intraoperative administration of GIK solution to diabetic patients with coronary artery bypass graft surgery causes more stable cardiac index, decreases the time of mechanical ventilation, and results in less atrial fibrillation onset, more stable values of potassium for normal rhythm, and less insulin to improve glycemia. All the above-mentioned items stabilize intraoperative hemodynamic and diabetic patients' recovery will be better (29).

In previous studies, the beneficial effects of GIK on myocardium function during heart open surgery have been proven. In 2017, Suhail Ahmad et al. reported that GIK infusion can significantly decrease CKMB enzyme level after surgery, duration of inotropic support, and period

of intensive care unit stay. In addition, mean ventilation time in the group receiving GIK was shorter than that reported for the non-GIK group (30, 31). Currently, with the increase in life expectancy and treatment of heart diseases, the number of patients with heart failure is increasing. The treatment of these patients has high costs. In addition to the usual treatment of heart failure (including vasodilators, diuretics, and positive inotropes), recent studies have shown the positive effects of GIK infusion on heart muscle metabolism.

Based on the above-mentioned results, low cost, simple way of GIK administration in patients with heart failure, and lack of side effects, it was decided to conduct a study with the present topic. According to numerous clinical studies, GIK infusion is capable of limiting the harmful effects of ischemia caused by acute myocardial infarction (6, 7). Two large-scale studies in this regard were conducted by ECLA and DIGAMI (32, 33). The aforementioned studies evaluated the effects of short-term GIK administration (2-4 h of infusion) on acute ischemia; nevertheless, the present study evaluated the long-term effects of GIK infusion on ischemic cardiomyopathy and assessed echocardiographic changes.

Previous studies reported that GIK does not have any effect on the reduction of systemic arterial resistance (34, 36) 31, 34; nevertheless, a recent study reported that insulin is effective in producing NO in the vessels endothelium and change hemodynamic (35). Metabolic and cellular effects have also been reported for GIK improving cellular ATP and oxygen consumption. It was also proven that GIK infusion improves ventricular delayed potentials and ventricular muscle electromechanics (36).

A total of 25 patients with EF of < 40% and proved ischemic cardiomyopathy entered the present study. The male to female ratio was 4:1, with the expected higher prevalence of IHDs in male patients similar to other studies (21, 7). Patients' echocardiographic evaluation before and after GIK infusion showed significant improvement in LV diastolic function after GIK administration. This finding is in line with the results of a study by Alan et al. in Turkey (2003) (21). A significant reduction in LV end-diastolic indices was observed in the current study consistent with the results of other studies (21, 7). These results demonstrated the metabolic effects of GIK infusion on the improvement of heart function in patients with chronic ischemic cardiomyopathy.

The analysis of GIK effects on heart tissue is indicative of its liming effects on the infarcted area (37), which increases the life span of patients with cardiomyopathy. The GIK effect mechanism could be due to its role as a polarizing material improving cellular electrical stability (38). The improvement in cardiac muscle contractility function is justified with insulin effects on Ca2 +ATP entrance into the cardiac cells. The results of the present study regarding ventricular function improvement considering the EF slope curve are in line with the findings reported by Cottin et al. (2002) (19). In the current study, it was observed that GIK improved diastolic function; however, it does not have significant effects on ventricular systolic function, which is consistent with the findings of a study by Alan et al. (2003) (18).

The GIK solution is very cheap and accessible. Most of the patients with heart failure suffered from low volume and electrolyte imbalance, as the consequences of long-term diuretic use, which can be partly compensated with the long-term administration of GIK. Different studies have shown that GIK solution can properly improve the metabolism of ischemic tissues. The results of the current study revealed that although GIK did not improve left and right ventricular systolic function, it could reduce patients' clinical symptoms with the improvement of metabolism and ventricular diastolic function. Furthermore, GIK does not increase heartbeat and contractility, thereby not increasing heart demand for oxygen. It is required to carry out larger-scale studies to establish a precise protocol for the use of GIK solution in patients with heart failure and determination of the duration and number of infusion time.

Conclusion

The GIK infusion in patients with ischemic cardiomyopathy improves heart diastolic function and clinical symptoms. The GIK infusion can be recommended as a treatment strategy for this group of patients.

Ethical considerations

Informed consent was obtained from all the patients.

Funding/Support

The present study was supported by Mashhad University of Medical Sciences, Mashhad, Iran.

Conflicts of interest

The authors declare that there is no conflict of interest.

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