Effects of GIK (glucose-insulin-potassium) on stress-induced myocardial ischaemia

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Abstract

Despite the evidence in experimental animal models that insulin - or GIK (glucose-insulin-potassium) - improves left ventricular function and perfusion during both acute and chronic ischaemia, clinical studies have generated conflicting results. We tested the hypothesis that pretreatment with GIK attenuates the vascular and functional effects of stress-induced myocardial ischaemia in man. Twenty-two patients with evidence of inducible myocardial ischaemia were enrolled; 11 patients with normal ventricular function underwent two dipyridamole echocardiography tests and 11 with regional contractility defects from previous myocardial infarction were submitted to two ECG exercise tests combined with ^{201}Tl myocardial perfusion scintigraphy; the tests were preceded by 60 minutes of either normal saline or an isoglycaemic GIK infusion. On stress echo, a 30% reduction in the severity of ischaemia was observed. On ECG ergometry, GIK infusion slightly increased the time to ischaemia (+0.6 min, $p=0.07$); however, the higher workload (+8%, $p=0.07$) was achieved at a similar rate-pressure plateau. On scintigraphy, an increase in ischaemic segments (+48%, $p<0.001$) was imaged mainly at the expense of viable (but non-ischaemic) and non-viable segments, which were reduced by 60%. GIK affected stress-induced left ventricular underperfusion only marginally (GIK: 39.7 ± 2.5 vs saline: 35.4 ± 2.2 units, $p<0.05$), but significantly improved its acute reversibility (-42 ± 4 vs $-25\pm4\%$, $p<0.001$).

We conclude that GIK pretreatment attenuates the effect of ischaemia on myocardial contractility, slightly improves exercise tolerance and causes a more rapid and diffuse recovery of post ischaemic reperfusion.

Keywords: insulin, myocardial ischaemia, GIK

Abbreviations

GIK: Glucose-insulin-potassium solution

Echo/NoPMI: Echo-dipyridamole stress test in patients without a previous myocardial infarction

MS/PMI: Myocardial scintigraphy in patients with previous myocardial infarction

Introduction

Insulin's direct and indirect effects on myocardial metabolism [1], vascular reactivity [2], microcirculation [3] and cell membrane potential [4; 5] are all potentially beneficial for the heart when a mismatch between blood flow and energy demand occurs. Both in isolated heart and in experimental animals - especially in the model of low-flow ischaemia [6], where residual tissue washout prevents intracellular lactate and proton accumulation -, there is evidence that insulin attenuates the mechanical consequences of ischaemia [7] and accelerates function recovery during reperfusion [6]. In addition to the lower oxygen cost of ATP (-13%) due to the shift from lipid to carbohydrate oxidation, insulin enhances anaerobic glycolysis, thereby providing the energy to fuel membrane ion exchange and to prevent intracellular Ca^{++} overload during hypoxia [8]. By directly stimulating the ATPase-dependent sodium-potassium pump [9], insulin could further stabilise myocardial membrane potential and attenuate the impaired repolarisation induced by ischaemia. In addition, insulin has been shown to favour endothelium-dependent vasodilatation of resistance arteries and the microcirculation by enhancing nitric oxide (NO) bioavailability and hyperpolarisation [2], to amplify β -adrenergic vasodilatation and to counteract α -adrenergic vasoconstriction [10]. Collectively, these actions, if extended to the coronary vasculature, would be beneficial in the setting of acute ischaemia. Despite this physiological rationale, a favourable effect of insulin in acute coronary syndromes has not emerged as clinically significant. In fact, the CREATE-ECLA study failed to show any acute positive effect of glucose-insulin-potassium infusions (GIK) in a large cohort of patients admitted for acute myocardial infarction [11]; likewise, the DIGAMI 2 study in patients with type 2 diabetes could not demonstrate a beneficial effect of insulin infusion on cardiovascular outcomes beyond plasma glucose control [12]. Possible explanations for these partially unexpected results are that insulin was always administered after the occurrence of the acute event and that the model of myocardial infarction is not the most likely to show a protective effect of insulin-induced myocardial metabolic conditioning. As elegantly demonstrated by studies in experimental animals [13], the optimal condition to show benefit from for metabolic support is when GIK precedes the event. In this regard, it is interesting that in the CREATE-ECLA study the only patients to benefit from GIK (*i.e.*, an odds ratio of 0.75 for 30-day mortality) were those undergoing primary

percutaneous angioplasty (PTCA), which was in every case performed after the start of GIK infusion (due to the small size of this subgroup, the effect did not reach full statistical significance) [11]. A recent study has also observed a smaller (-44%) troponine rise after elective PTCA if this was preceded by GIK [14]. Presumably, insulin pre-treatment protects against reperfusion damage and transient ischaemia because these are models of ischemia in which residual tissue washout is present and the changes in cell metabolism induced by insulin are more likely to be protective.

Despite the abundant experimental evidence and the long time since the seminal clinical observation of Sodi-Pallares *et al.* [15], only two studies [16; 17] have directly addressed the question, whether GIK modifies the threshold and/or the clinical severity of stress-induced ischaemia in humans; their results were not conclusive possibly because the techniques employed (ECG) did not allow the evaluation of the effect of GIK on stress-induced changes in regional myocardial perfusion and contractility.

More consistent, if preliminary, is the evidence on the effect of GIK in the model of chronic ischaemia (viability). Here, insulin infusion has been demonstrated to improve the contractility of the hypokinetic regions to a similar extent as low-dose dobutamine infusion [18; 19]. Whether this effect is entirely metabolic or also involves blood flow redistribution is unclear.

In the present study, we tested whether in patients with ischaemia on effort GIK pre-treatment alters the ischaemic threshold, the extension and/or the severity of stress-induced myocardial dysfunction in the normal myocardium and/or of the exercise-induced myocardial perfusion defects in the damaged myocardium.

Methods

Patients We recruited a total of 22 patients of either gender with a positive or suggestive exercise test (ST-segment depression ≥ 1.5 mm or ≥ 1.0 mm with symptoms of angina) (**Table 1**). Eleven patients without previous myocardial infarction underwent echo-dipyridamole testing for ischaemia (*Echo/NoPMI study*). The other 11 patients with previous myocardial infarction (>3 months) underwent exercise myocardial perfusion scintigraphy for the detection of ischaemia and viability (*MS/PMI study*). Exclusion criteria were: previous diagnosis of diabetes mellitus or a

HbA_{1c} value above the upper limit of normal (6.3%); chronic hepatic or kidney failure; hyper- or hypokalaemia; ongoing treatment with digitalis. ACE inhibitors or angiotensin receptor blockers (all the patients with previous myocardial infarction and 6 patients with myocardial ischaemia), aspirin and statins (all patients) were maintained; calcium antagonists and β -blockers were suspended on the day of the tests or 24 hours before at the discretion of the cardiologist (adopting an equal strategy on both study occasions); nitrates were withdrawn on the day of testing. After the study, all patients underwent coronary angiography. Two additional patients in whom angiography did not confirm the presence of haemodynamically significant stenoses consistent with the scintigraphic data were excluded from the study. The study was approved by the Institutional Ethics Committee and all patients signed an informed consent before participating.

Study design Each patient received two stress tests within 8-14 days. All tests were preceded by 60 min of either normal saline or GIK infusion: the latter consisted of 500 ml of a 10% glucose solution containing 10 UI of human rapid-acting insulin and 10 mEq of potassium. The infusion rate was initially set at 3 ml kg⁻¹ hour⁻¹; if plasma glucose rose >20% above baseline additional insulin was added to the infusate (in three subjects in *Echo/NoPMI*) to increase its concentration ~1.5 fold.

Dipyridamole echocardiography test Patients were invited not to eat after the dinner of the day prior to the study and reached the echo lab between 8 and 10 am the next morning. Two indwelling catheters were placed into the right arm, one for insulin and glucose (or saline) infusion in an antecubital vein and another in a hand vein for blood sampling. Another catheter was placed in the left arm for dipyridamole (Persantin, Boehringer-Ingelheim) and atropine (Atropine, Farmigee, Italia) administration. After a 15-min rest, the saline/GIK infusion was started; 2 hours later the sonographer initiated the basal acquisition, which was followed by drug infusions according to a standard format (dipyridamole 0.56 mg/kg in 4 min, followed by no infusion for 4 min after which further 0.28 mg/kg were given in 2 min followed by 2 min of no infusion; then, at min 12 and 13 atropine (0.5 mg) was infused in 30 s). Long- and short-axis images acquired through a 3.5 MHz probe (Acuson Sequoia C256 Ultrasound Instrument, Siemens, Mountain view, CA) were continuously recorded on an optic disk. The test was interrupted when a clear change in segmental left-ventricular function occurred; aminophylline (80-240 mg i.v.) and/or atenolol (5 mg i.v.) were immediately administered to restore normal wall kinetics. Segmental left-ventricular kinetics were quantitated using a score from 1 to 5

(1=normal, 2=hypokinetic, 3=akinetetic, 4=dyskinetic, 5=aneurismatic) for each of the 16 standardised left-ventricular wall segments; a global wall motion score (LV-WMS) was then calculated as the mean of these 16 values. We also calculated an index of ischaemia severity (Ischaemic Index) by summing all the changes in the wall motion score of each segment and normalising this value by the pharmacological stress expressed as the time elapsed between the start of drug administration and the end of the test (aminophylline/atenolol administration).

Myocardial perfusion scintigraphy test Bicycle ergometry started with an initial load of 25 watt followed by increments of 25 watt every 3 min. Six-lead continuous ECG was recorded throughout the test. A standard dose (3 mCi) of ^{201}Tl was injected at the onset of ischaemic ECG signs and/or at the onset of chest pain; the patient then exercised for further 30-60 s and images were acquired, according to current guidelines [20], through a SPECT apparatus in three consecutive occasions: a) immediately after interrupting the test (STRESS), b) after 3-4 hours (REST), c) and 20-30 min after a second dose (3 mCi) of Tl^{201} was injected (REINJ). Left-ventricle walls were subdivided into 20 segments and a score from 0 to 4 (0 corresponding to a normal tracer uptake and 4 to no tracer uptake) was assigned to each segment; the score was estimated by a nuclear medicine specialist (G.M.) who was blind to the presence or absence of GIK infusion. Segments with a post-stress score ≥ 2 were considered abnormal. A perfusion defect score was calculated as the sum of all the segment scores both in each patient (individual score) and in the whole group (global score). The changes between STRESS, REST and REINJ were used to quantitatively estimate the reversibility of the defects. To avoid volume overload, the GIK infusion rate was set at 40 ml/h after the first SPECT acquisition (STRESS), returned to 3 ml·kg⁻¹·hour⁻¹ one hour before the second acquisition (REST) and not changed until the end of the test.

Assays Plasma samples were collected before the GIK/saline infusion and immediately before the first two scintigraphic acquisitions (STRESS and REST) and before and at the end of the DET. Plasma glucose concentrations were monitored throughout the tests, while potassium concentrations were measured (Beckman Analyser 2) at the end of the test; plasma insulin concentration was measured within 3 months on stored (-20 C°) plasma aliquots (INSKIT, Lincos USA).

Statistical analysis Differences between two tests were evaluated with the use of the χ^2 or the Wilcoxon Signed Rank test, as appropriate.

Results

Both stress tests, echo-dipyridamole and exercise scintigraphy, were well tolerated; neither local nor systemic undesirable effects were observed during the GIK infusion. As shown in **Table 2**, during GIK plasma insulin rose to high physiological levels; in 3 *Echo/NoPMI* patients additional insulin was required to clamp plasma glucose levels. Plasma glucose and potassium levels were not different throughout tests, with the only exception of the STRESS phase in the *MS/PMI* group, during which plasma glucose tended to be higher during GIK than saline ($p<0.05$).

Echo/NoPMI - Blood pressure and heart rate during STRESS were similar in GIK and saline (**Table 3**). The test was positive for ischaemia in all saline studies and became negative in 3 GIK studies; the threshold, expressed as time since the beginning of the pharmacologic stress, rose in 7 patients, remained stable in 3 patients and worsened in one patient, giving an average increase of 22% ($p=0.06$). The frequency of ST depression and typical pain were similar in the two tests (**Table 3**). Despite the slightly higher pharmacologic load, both the severity (as indexed by the variation in wall motion score - Δ WMS) and the extension of ischaemia (as estimated by the number of left ventricular segments showing a worsening of the kinetics) tended to be attenuated by GIK, resulting in a 30-35% lower ($p<0.04$) left ventricular dysfunction as measured by the LV-WMS or the Ischemic Index (**Table 3** and **Fig. 1**).

MS/PMI - During maximal exercise (**Table 4**), blood pressure and heart rate were similar with GIK and saline; however, the same maximal rate-pressure product was achieved at a slightly higher workload (+8%, $p=0.07$) during GIK. No test became negative during GIK.

As shown in **Fig. 2**, GIK markedly changed the distribution of the tracer uptake defects detected by the myocardial perfusion scintigraphy ($p<0.001$). The increase in ischaemic segments occurred mainly at the expense of viable and/or non-viable segments. All ($n=3$) patients without viable myocardium became positive for viability in at least 2 left ventricular segments. Most (95%) of the myocardial segments that the saline test read as ischaemic were also detected as

ischaemic by the GIK test ($p=ns$, **Fig. 2**). The between-test agreement was good for normal segments (84%) but poor for both viable (29%) and non-viable (32%) segments ($p<0.001$).

We used the Global Perfusion Defect score to estimate the overall effect of GIK (on both extension and severity) independently of the segment localisation, also including minor changes in perfusion (a change in score of 1 unit). Between STRESS and REST the perfusion defect score decreased – *i.e.*, myocardial tracer uptake increased - by 24% during saline infusion and by 41% during GIK infusion ($p<0.001$), corresponding to a 70% increment in the acutely reversible defects (that is, overall ischaemia) (**Fig. 3**). Following reinjection, the tracer uptake further improved by 13% and 11% with saline and GIK respectively ($p=ns$), indicating a quantitatively similar estimate of overall viability.

The severity of ischaemia was further assessed by considering the 76 ischaemic segments on which there was agreement between the two tests. During GIK the segmental perfusion defect score at STRESS was 1 unit higher than with saline in 22 segments (from 2 to 3 in 10 and from 3 to 4 in 11) and 1 unit lower in 4 segments (from 3 to 2 in 2 and from 4 to 3 in 2 segments), yielding an 8% greater global score (239 vs 222 units, $p=ns$). In contrast, the number of segments showing a 2-unit improvement at REST was greater (38 vs 10), while the number of 1-unit gradients was lower (38 vs 65) for GIK and saline, respectively ($p<0.001$).

No regional heterogeneity was observed in the effect of GIK, all the 7 main regions of the left ventricle (anterior, antero-septal, inferior, infero-septal, lateral, infero-lateral and apical) showing a similar spatial distribution of the perfusion changes.

Discussion

GIK improved the ischaemic threshold and exercise tolerance only marginally but significantly reduced (by ~30%) the stress-induced left ventricular contractile dysfunction and accelerated the acute perfusion recovery in ischaemic regions.

During GIK, the maximal workload and maximal pharmacologic burden tolerated were 8% and 22% higher, respectively, than with saline. This result should be interpreted cautiously not only because of borderline statistical significance but also because the differences were small and the ECG signs of ischaemia were observed at similar double-product rates. The effect on exercise tolerance could be due to improved systemic haemodynamics (secondary to peripheral

vasodilatation, as seen in patients with chronic heart failure [21]) and/or to a slower rise in heart rate; this, in turn, could be the consequence of an improved skeletal muscle efficiency (*i.e.*, ATP production per unit of oxygen consumption). Thadani *et al* [17] also reported some increase in the time to angina despite the heterogeneity of the individual responses, whereas Bogaty *et al* [22] found no difference; in the latter study, however, plasma glucose was not controlled and rose from 5.7 to 9.4 mM before the exercise. Our patients also showed variability, with a change in exercise duration that was positive in 6 patients, nil in 4 and negative in 1. In any event, this modest improvement is unlikely to be of clinical relevance.

The data of the *Echo/NoPMI* study also suggest that GIK only marginally affects the ischemic threshold although it attenuates the mechanical consequences of ischemia. A 13% increase in the ischaemic threshold would be the expected if the only underlying mechanism was the improved metabolic efficiency (*i.e.*, ATP/oxygen); and such a difference, however, might have been missed given the limited sample size and the study design. In their elegant study, Bogaty *et al* [22] induced marked metabolic changes in circulating substrates, but saw no effects on the ischaemic threshold. In contrast, in perfused isolated hearts [23], complete substitution of glucose for free fatty acids (FFA) as a fuel causes a 30% improvement of cardiac efficiency, suggesting that more extreme metabolic manipulations may be more effective, possibly through additional mechanisms (*e.g.*, inhibition of futile cycles); however, the clinical relevance of these manipulations remains questionable. The large inter individual variability of the response to GIK (Figure 1), which was unexplained by the available clinical variables, however, suggest that the effect of GIK pre treatment on ischemia might be more relevant in some specific patients.

With regard to perfusion, the scintigraphic data showed that, for a similar myocardial stress (double product), extension and severity of perfusion defects were if any accentuated during GIK. However, the comparison with the control situation (saline) shows that most (76 out of 80) of the ischaemic segments (including only ischaemic and ischaemic-and-viable) on the saline test were confirmed ischaemic during GIK; the majority of the "new", *i.e.*, GIK-induced ischaemic segments (30 out of 42) were either non-viable (n=15) or viable but not ischaemic (n=15) segments on saline. Thus, the worsening of ischaemia by GIK was mostly apparent because the infusion "upgraded" chronically underperfused segments while causing a true perfusion deterioration (mostly of 1 unit) in only 12 out of 91 normally perfused segments. This interpretation is supported by the perfusion defect score. As recapitulated in Fig. 3, under stress

conditions GIK increased the perfusion defect score by 14% relative to saline, but the drop in score from stress to resting conditions was almost double with GIK. This was true regardless of whether the score was individual or global, absolute or relative, and also applied to the subset of myocardial segments that were ischaemic on both tests. That the overall ischaemic burden was not significantly increased by GIK is also confirmed by the clinical indices: mean ST-T segment depression averaged 1.5 mm during saline and 1.3 mm during GIK and angina was present in 5 patients during saline and in 3 during GIK. Provided that the two stresses induce ischaemia through different mechanisms, our data suggest that the effect of GIK on stress ischaemia is mostly metabolic. Although unlikely, we cannot exclude that GIK exerts different vascular and metabolic effect on the working myocardium depending on whether a portion of it has been damaged by a previous infarction.

The *MS/PMI* study indicates that post-stress tissue perfusion (*i.e.*, reperfusion) is improved by GIK; with regard to the mechanism(s) and consequences of this improvement we can only speculate. In the Hamster cheek pouch model, insulin has been shown to improve post-ischaemic tissue microcirculation through arteriolar vasodilatation and reduction in platelet adhesion [3]. Whether this phenomenon impacts on post-ischaemic recovery of myocardial function remains to be tested by techniques that measure absolute tissue perfusion and contractility simultaneously (*e.g.*, contrast echocardiography, magnetic resonance imaging). With regard to this, it is interesting to note that pretreatment with GIK has been shown to reduce the troponine-I rise produced by the coronary angioplasty procedure [14]. Another possible explanation, suggested by some studies [24], is that insulin might simply enhance myocardial avidity for thallium (which is handled like potassium). We think that this is unlikely for the following reasons: a) *in vivo* potassium and thallium are handled with different kinetics by the human myocardium [25], b) post-injection (stress and reinjection) thallium uptake has been shown not to be affected by insulin and to be dependent only on blood flow [26], c) delayed post-stress imaging depends on thallium redistribution (*i.e.*, loss of normal tissue and enrichment in ischaemic tissue); during this phase, GIK enhances tissue thallium wash-out from both ischaemic and normal regions [27], thereby exerting, if any, a negative effect on the sensitivity of the test to detect ischaemia [28].

The conclusion, that GIK favours postischaemic reperfusion, is strengthened by the data on myocardial viability. The global perfusion defect score on reinjection during saline (243 units) was similar to the score measured under resting conditions with GIK (258 units) (Fig. 2). On

tracer reinjection, GIK decreased the score further (to 212 units), *i.e.*, it increased myocardial perfusion. In fact, non-viable segments decreased from 31 to 13 ($p < 0.05$), being "upgraded" either to ischaemic ($n=15$) or viable ($n=5$) (Fig. 2). That GIK can recruit non-viable tissue to viability has been confirmed in a recent study comparing a modified GIK scintigraphy (co-infusion of thallium and GIK) with the gold standard technique, namely, ^{18}F -deoxyglucose uptake [29]. Again the mechanism appears to be related to myocardial energy metabolism, rather than tracer handling, since in patients with previous myocardial infarction GIK was able to improve the contractility of the myocardial segments with stable kinetic defects to an extent similar to low-dose dobutamine infusion [30].

It is important to note that our GIK protocol was essentially euglycaemic and hyperinsulinaemia was within the physiological postprandial range. In previous studies, different GIK mixtures gave rise to variable rates of both hypoglycaemia and hyperglycaemia. In the CREATE-ECLA trial [11], for example, the group randomised to GIK had significantly higher plasma glucose levels and more hypoglycaemia during the 24 hours of infusion as compared to the usual care group. Both hypoglycaemia – through sympathetic activation [31] – and hyperglycaemia – through oxidative stress [30] – can offset any beneficial effects of insulin.

In conclusion, pretreatment with GIK slightly enhances the myocardial ischaemic threshold, reduces the severity of the stress-induced contractile dysfunction and improves post-ischaemic reperfusion (reflow); in addition, it also enhances tissue viability identification.

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Legend to the figures

Figure 1 - Dypiridamole echocardiography test: individual, and mean, ischemic index value (see methods) in the Saline and GIK tests.

Figure 2 - Myocardial segment status distribution as defined by the results of myocardial stress scintigraphy in the Saline and GIK test. The arrows, whose thickness is proportional to the number of segments, illustrate the fluxes of the segments that changed status.

Figure 3 - Distribution of the perfusion defect scores (histogram and left Y axis) in all the left ventricle myocardial segments of the 11 patients and Global perfusion defect score values (dotted line and right Y axis) during the three SPECT acquisitions Stress, Rest and ReInjection.

Table 1 – Demographic and clinical parameters

		<i>Echo/NoPMI</i>	<i>MS/PMI</i>
Gender (m/f)		8/3	10/1
Age (years)		67 ± 3	64 ± 2
Hypertension (y/n)		6/5	4/10
Exercise ECG positive/suggestive		8/3	9/2
Effort angina (y/n)		10/1	5/6
Previous MI	Anterior	-	6
	Infero-lateral	-	4
	Inferior	-	2
	Apical	-	2
Angiography	One vessel	1	5
	Two vessels	4	2
	Tree vessels	6	4
Ejection Fraction (%)		59 ± 4	43 ± 2

Table 2 - Plasma concentrations of glucose, insulin and potassium

		<i>Echo/NoPMI</i>		<i>MS/PMI</i>	
		Saline	GIK	Saline	GIK
Glucose (mmol/l)	<i>Baseline</i>	6.0 ± 0.5	6.1 ± 0.6	5.4 ± 0.2	5.9 ± 0.3
	<i>Stress</i>	6.3 ± 0.3	6.8 ± 0.8	6.3 ± 0.3	7.7 ± 0.1*
	<i>Rest</i>	5.9 ± 0.2	6.1 ± 0.5	5.6 ± 0.2	5.7 ± 0.4
Insulin (pmol/l)	<i>Baseline</i>	98 ± 16	105 ± 28	78 ± 6	72 ± 6
	<i>Stress</i>	108 ± 22	1,130 ± 282*	48 ± 6	754 ± 54*
	<i>Rest</i>	98 ± 17	1,060 ± 275*	48 ± 6	652 ± 60*
Potassium (mEq/l)	<i>Baseline</i>	3.9 ± 0.3	3.8 ± 0.2	3.9 ± 0.3	4.1 ± 0.2
	<i>Stress</i>	3.8 ± 0.3	3.6 ± 0.4	3.9 ± 0.3	4.0 ± 0.2
	<i>Rest</i>	3.9 ± 0.3	3.7 ± 0.4	4.0 ± 0.3	4.1 ± 0.4

* p<0.05 vs *Baseline* by Wilcoxon Signed Rank test

Table 3 - Echocardiographic parameters during echo dipyridamole stress test.

	Saline	GIK	<i>Statistics^o</i>
SBP_{stress} (mmHg)	155 ± 6	147 ± 6	<i>ns</i>
DBP_{stress} (mmHg)	90 ± 2	89 ± 2	<i>ns</i>
HR_{stress} (bpm)	104 ± 5	103 ± 6	<i>ns</i>
Time (min)	9 ± 1	11 ± 1	<i>0.06</i>
ST depression (yes)	9	7	<i>ns</i>
Pain (yes)	9	8	<i>ns</i>
Ischemic segments δWMS	1.55 ± 0.14	1.05 ± 0.24	<i>0.06</i>
Ischemic segments (n)	2.9 ± 0.3	2.1 ± 0.5	<i>0.10</i>
LV-WMS_{stress}	1.31 ± 0.04	1.22 ± 0.06	<i>0.04</i>

SBP: systolic blood pressure; DBP: diastolic blood pressure; HR: Heart rate; δ WMS: wall motion score change; LV-WMS stress: left ventricular mean wall motion score in stress condition

^o Wilcoxon Signed Rank Test

Table 4 - Ergometry

		Saline	GIK	<i>p</i>
Heart rate (b/min)	<i>Bas</i>	68 ± 4	68 ± 3	<i>ns</i>
	<i>Max</i>	125 ± 5	125 ± 5	<i>ns</i>
SBP (mmHg)	<i>Bas</i>	139 ± 4	140 ± 5	<i>ns</i>
	<i>Max</i>	179 ± 5	180 ± 6	<i>ns</i>
DBP (mmHg)	<i>Bas</i>	84 ± 2	82 ± 2	<i>ns</i>
	<i>Max</i>	90 ± 2	88 ± 2	<i>ns</i>
RP (b/min*mmHg)	<i>Bas</i>	9,580 ± 641	9,468 ± 456	<i>ns</i>
	<i>Max</i>	22,250 ± 1,055	22,539 ± 1,194	<i>ns</i>
Time (min)	<i>Max</i>	9.4 ± 0.1	9.9 ± 0.3	<i>0.07</i>
Work (watt)	<i>Max</i>	525 ± 83	568 ± 79	<i>0.07</i>

SBP: systolic blood pressure; DBP: diastolic blood pressure; RP: rate pressure product;

Figure 1

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