Very early administration of glucose-insulin-potassium by emergency medical service for acute coronary syndromes: Biological mechanisms for benefit in the IMMEDIATE Trial

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Aims In the IMMEDIATE Trial, intravenous glucose-insulin-potassium (GIK) was started as early as possible for patients with suspected acute coronary syndrome by ambulance paramedics in communities. In the IMMEDIATE Biological Mechanism Cohort substudy, reported here, we investigated potential modes of GIK action on specific circulating metabolic components. Specific attention was given to suppression of circulating oxygen-wasting free fatty acids (FFAs) that had been posed as part of the early GIK action related to averting cardiac arrest.

Methods We analyzed the changes in plasma levels of FFA, glucose, C-peptide, and the homeostasis model assessment (HOMA) index.

Results With GIK, there was rapid suppression of FFA levels with estimated levels for GIK and placebo groups after 2 hours of treatment of 480 and 781 μmol/L ($P < .0001$), even while patterns of FFA saturation remained unchanged. There were no significant changes in the HOMA index in the GIK or placebo groups (HOMA index: placebo 10.93, GIK 12.99; $P = .07$), suggesting that GIK infusions were not countered by insulin resistance. Also, neither placebo nor GIK altered endogenous insulin secretion as reflected by unchanging C-peptide levels.

Conclusion These mechanistic observations support the potential role of FFA suppression in very early cardioprotection by GIK. They also suggest that the IMMEDIATE Trial GIK formula is balanced with respect to its insulin and glucose composition, as it induced no endogenous insulin secretion. (Am Heart J 2016;178:168-175.)

For acute coronary syndrome (ACS) and ST-elevation myocardial infarction (STEMI), continued improvement in emergency medical service (EMS) care and in door-to-balloon times for percutaneous coronary intervention has not continued to improve in-hospital mortality.[1] An alternative avenue may be early metabolic support of ischemic myocardium. The earliest possible treatment for this in ACS and STEMI would be in the ambulance. This approach was tested in the Immediate Myocardial Metabolic Enhancement During Initial Assessment and Treatment in Emergency Care (IMMEDIATE) Trial,[2] in which glucose-insulin-potassium (GIK) infusions were given to patients with suspected ACS and STEMI. Although the primary outcome of reduced progression to MI did not meet statistical significance, prespecified secondary outcomes were improved: cardiac arrest or in-hospital mortality occurred in 4.4% of participants receiving GIK versus 8.7% receiving placebo ($P = .02$, odds ratio 0.50, 95% CI 0.28-0.90). In the biological subcohort of the trial, GIK reduced initially high levels of cardiotoxic free (nonesterified) fatty acid (FFA) levels that have been associated with cardiac arrhythmias:

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367 μmol/L (standard error [SE] = 32) with GIK versus 634 μmol/L (SE = 34) with placebo ($P < .001$).[2,3] Also in that biological cohort, the median infarct size was 2% of left ventricular mass with GIK versus 10% with placebo ($P = .01$). These findings led to the present investigation to determine the rate of decrease of FFA levels and the corresponding metabolic mechanisms of this treatment in the clinical setting.

Here we explore whether mechanisms seen in animal models might pertain to patients. The IMMEDIATE Trial found beneficial effects of out-of-hospital ambulance administration of GIK for ACS on the composite outcome of cardiac arrest or in-hospital mortality and on infarct size. Therefore, this study looked for evidence of GIK acting by metabolic mechanisms: first, by reduction of toxic circulating FFA levels[4-6] and, second, by molecular mechanisms that give GIK a unique place in cardioprotective therapy. It also considered whether these mechanisms might explain the positive outcomes in the IMMEDIATE Trial compared with the negative findings in other trials with GIK.[7]

Methods

This study was based on the Biological Mechanism Cohort of the IMMEDIATE Trial.[2] The diagram of inclusion of participants is in the primary report,[2] and details of the study design are in a methods article.[8] IMMEDIATE was a randomized, placebo-controlled, clinical effectiveness trial in 13 US EMS systems in which paramedics enrolled 871 patients age ≥ 30 with chest pain who had ≥ 75% probability of ACS by the electrocardiograph-based acute cardiac ischemia time-insensitive predictive instrument and/or STEMI detected by the thrombolytic predictive instrument. The biological mechanism subcohort (n = 143) had additional blood tests and had sestamibi scans at 30 days. Clinical end points were adjudicated independently, and primary analyses were done on an intention-to-treat basis.

Trial inclusion and exclusion criteria

Potential participants in the IMMEDIATE Trial were patients transported by EMS who were 30 years of age or older and had an out-of-hospital electrocardiogram done for signs and symptoms suggestive of ACS.[2,8]

Biological assays

Serum samples for the biological mechanism cohort were stored promptly at −20°C and held at the Clinical and Translational Research Center at Tufts Medical Center. FFA levels and fatty acid (FA) composition (ie, chain length and saturation) were measured using thin layer chromatography followed by gas chromatography with internal standards to correct for analytical losses and external standards to control for oxidative losses. Measurement of C-peptide was done with an Alpco C-peptide kit used according to manufacturer's instructions using a sandwich enzyme-linked immunosorbent assay. All analytes were measured at prespecified time points. The insulin assay was run with Siemens Coat-A-Count Insulin Radioimmunoassay (Los Angeles, CA). The assay was run according to manufacturer's instruction using an overnight incubation with 125I-labeled insulin. Radioactivity counts were measured on the Iso-Data 500 Series gamma counter.

The homeostasis model assessment (HOMA) index, an indicator of insulin resistance, was calculated as (insulin [μIU/mL] × glucose [mmol/L])/22.5.[9] Of note, in this study, HOMA was calculated with nonfasting measures.

Statistical analysis

Before analyses, distributions of continuous variables were summarized, and outliers (>5 SDs from mean) were checked for plausibility. Three values of total FFA were excluded from analyses as measurement errors. For the regression models of total FFA, 3 other values (between 1,500 and 2,000) were truncated to 1,500 to lessen the influence of these very high measures and improve model fit. Data were summarized as means and SDs, or medians and interquartile ranges, in cases of skewed distributions, or percentages and participant count in categorical variables for GIK and placebo groups separately.

To explore the relationship of changes in total FFA (and individual FA species) over time, we used a piecewise linear regression model with bends at 2 and 6 hours, including random effects for intercept terms to account for multiple measurements (up to 3) per participant done shortly after arrival at the hospital ("initial sample"), at 6 hours, and at 12 hours. The choice of the first bend was based on a review of the timing of collection of the initial sample (50% of initial samples were drawn between 1.5 and 3.4 hours of symptom onset). True times (not scheduled testing times) were used in these analyses. Because true time 0-hour pretreatment blood samples were not available, a random effect model was first run on placebo patients only, and the time 0-hour fitted value of the outcome was estimated. This constant was then subtracted from all measured values for the analysis to force a common intercept (estimated time 0-hour measure) among treatment and control subjects.

This was done to allow us to visualize and analyze the changes in FFA over time with the assumption that, because this was a randomized study, the pretreatment time 0-hour values for the GIK and placebo groups should have been equivalent. We then plotted the fitted values from this model, adding back this constant to produce plots of observed data versus the fitted values. From this model, we compared fitted values between GIK and placebo at 2 hours (median time of initial measure), 6 hours, and 12 hours. We also compared the rate of change (initial to 2 hours, 2 to 6 hours, and 6 to 12 hours) between the GIK and control groups. These

Table I. Characteristics of participants in the IMMEDIATE trial biocohort (N = 143).59.55.52

Variable	GIK (n = 68)	Placebo (n = 75)	*P* value
Age in years	64.5 ± 13.0 (68)	63.9 ± 12.8 (75)	.78
Male gender	76.5% (52/68)	69.3% (52/75)	.34
White race	97.1% (66/68)	94.7% (71/75)	.48
Body mass index	28.2 ± 5.7 (63)	29.4 ± 7.9 (70)	.33
History of MI	30.9% (21/68)	32.0% (24/75)	.89
History of CHF	5.9% (4/68)	9.3% (7/75)	.44
History of DM	17.6% (12/68)	25.3% (19/75)	.27
Distribution of DM and HbA1c levels	n = 67	n = 74	.40
a. No DM, A1c <7	79.1% (53)	68.9% (51)	
b. No DM, A1c ≥7	3.0% (2)	5.4% (4)	
c. DM, A1c <7	6.0% (4)	13.5% (10)	
d. DM, A1c ≥7	11.9% (8)	12.2% (9)	
Primary complaint chest pain	86.8% (59/68)	89.3% (67/75)	.64
Out-of-hospital systolic BP, mm Hg	141.4 ± 27.4 (68)	145.5 ± 27.5 (74)	.38
Out-of-hospital diastolic BP, mm Hg	85.4 ± 22.1 (67)	87.7 ± 22.7 (73)	.55
Out-of-hospital heart rate, beat/min	81.9 ± 23.4 (68)	79.3 ± 20.5 (74)	.48
Out-of-hospital respiratory rate, /min	18.6 ± 5.1 (65)	18.7 ± 4.5 (67)	.88
Out-of-hospital ECG ST elevation (reread by cardiologist)	67.6% (46/68)	65.3% (49/75)	.77
TIPI score	83.0 ± 15.7 (67)	83.1 ± 12.1 (73)	.99
TPI "Trigger" indicator of STEMI	30.9% (21/68)	20.0% (15/75)	.14
Elapsed times in minutes, median < q1-q3 > (n)			
Symptom to EMS arrival on scene	53 [16.5-129.5] (60)	51 [21-91] (69)	.61
Symptom onset to start of treatment	86 [51-162] (60)	81 [53-123] (69)	.61
EMS arrival on scene to hospital	31 [27-36.5] (68)	33 [27-40] (75)	.50
EMS arrival on scene to hospital (subset with symptom onset time)	30.5 [26-36.5] (60)	33 [26-38] (69)	.44
Timing of FFA samples in hours, median < q1-q3 > (n)			
Initial sample	2.4 [1.1-3.3] (65)	2.7 [.9-3.7] (67)	.10
Scheduled 6-h sample	6.1 [6.0-6.3] (62)	6.1 [6.0-6.2] (66)	.99
Scheduled 12-h sample	12.0 [12.0-12.2] (65)	12.1 [12.0-12.3] (71)	.44
Total drug infused, mL	1390 [1122-1623] (68)	1443 [1195-1667] (75)	
Duration of treatment, h	12 [11.89-12.02] (68)	12 [11.93-12.03] (75)	
Adjudicated diagnosis	n = 68	n = 75	
1. STEMI	73.5% (50)	74.7% (56)	
2. Non-STEMI infarction	11.8% (8)	16.0% (12)	
3. Angina pectoris	14.7% (10)	9.3% (7)	

Data are presented mean ± SD (sample size) with corresponding *t* test *P* value, median < 25th to 75th percentile > (sample size with corresponding nonparametric Kruskal-Wallis test *P*-value), or percentage (number) of participants with corresponding χ^2 test *P* value.
CHF, congestive heart failure; *DM*, diabetes mellitus; *HbA1c*, hemoglobin A1c; *BP*, blood pressure; *ECG*, electrocardiogram; *TIPI*, time-insensitive predictive instrument; *TPI*, thrombolytic predictive instrument.

analyses were all done using the SAS system for windows, version 12.3 (copyright 2002-2010 by SAS Institute Inc, Cary, NC; all rights reserved.

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Results

Features of the Biological Mechanism Cohort are shown in Table I, which shows comparability of the GIK and placebo groups. The effects of GIK infusion on plasma FFA concentration and the rate of change of FFA in the GIK group compared with the control group are shown in Table IIA and B for the 137 of 143 participants of the IMMEDIATE Trial Biocohort who had at least 1 valid FFA measurement. The Figure shows circulating FFA levels for those treated with GIK (blue) or with placebo (red) over time from onset of treatment (time 0). Of note, although FFA levels were significantly lower in the GIK group throughout the 12-hour infusion, the most rapid rate of change of the FFA levels was in the first 2 hours. Specifically, FFA concentrations decreased from time 0 levels to 6 hours in both groups, with a faster rate of decline in the GIK group compared with placebo ($P < .0001$) (Figure). There was no difference in the rate of decline in FFA between GIK and placebo groups over the 2-hour to 6-hour interval, or 6-hour to 12-hour interval.

The palmitic and stearic acid saturated FAs (sum of 16:0 and 18:0) as percentages of total FFA increased over time, whereas the oleic acid and linoleic acid unsaturated FAs

Table II. Overall effect of GIK infusion on FFA concentrations (μmol/L) over time

A. Comparison of fitted values at 3 key time points (n = 137 participants, 385 samples)

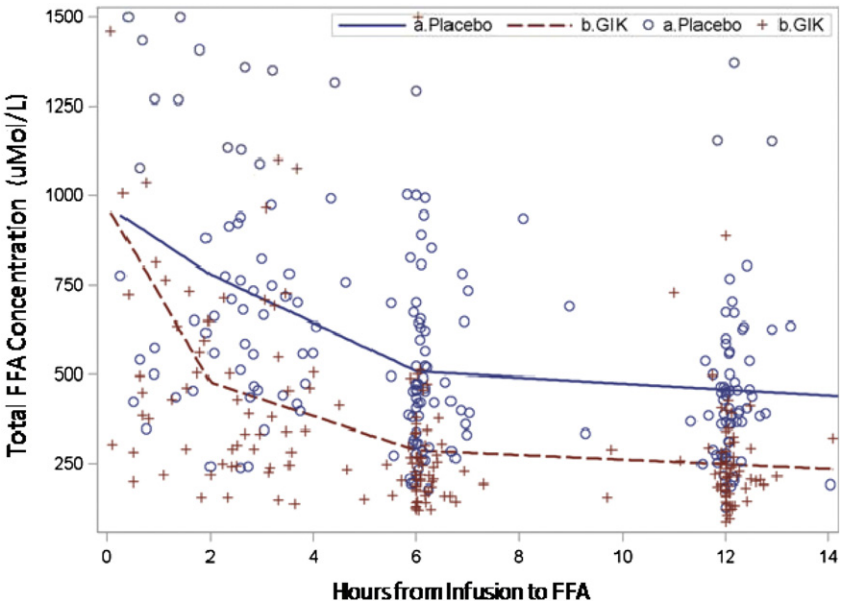
	Fitted values: mean (SE)			
Time (post start of treatment)	GIK	Placebo	Delta(G – P)	*P* value*
2 h	480.0 (47.3)	781.3 (44.3)	−301.2 (64.8)	<.0001
6 h	289.7 (29.0)	509.3 (27.3)	−219.6 (39.9)	<.0001
12 h	250.4 (24.0)	459.5 (22.5)	−209.1 (32.9)	<.0001

B. Comparison rate of change (slope) for 3 different time windows

	Estimated slopes (change in FFA per 1-h increase)			
Time (post start of treatment)	GIK	Placebo	Delta (G – P)	*P* value*
0 to 2 h	−245.7 (23.6)	−95.1 (22.1)	−150.6 (32.4)	<.0001
2 to 6 h	−47.6 (11.8)	−67.9 (11.8)	20.4 (16.1)	.21
Post 6 h	−6.6 (5.4)	−8.3 (5.1)	1.7 (7.4)	.81

GIK infusions reduced circulating FFA levels over the 12-hour infusion period (A). The rate of change was significant only in the first 2 hours of the study period (B).
*Fitted values and *P* values from a random effect mixed model (forcing common intercept to equal fitted placebo arm intercept of 971).

Figure



GIK infusions decreased mean plasma FFA concentrations from high initial levels to 6 and 12 hours in GIK (red) and placebo (blue) groups, with a faster rate of decline in the GIK group compared with placebo ($P < .0001$).

(sum of 18:1n9 and 18:2n6) decreased over time, in both GIK and placebo groups. At all time points (2, 6, and 12 hours), circulating FFAs were enriched with saturated FA and depleted of unsaturated FA in the GIK group compared with the placebo group (Tables IIIA, B and IVA, B). The largest changes in the percentage composition of both saturated and unsaturated FAs were in the 0- to 2-hour interval compared with the later intervals, with GIK having faster rates of increasing saturated FA proportions than placebo for both the 0- to 2-hour and 2- to 6-hour windows (Table IIIB). Correspondingly, the decline in the proportion of unsaturated FAs was faster with GIK compared with placebo for the 0- to 2-hour and the 2- to 6-hour periods (Table IVB).

Table III. Overall effect of GIK infusion on saturated FAs (sum of 16:0 and 18:0) (as a percentage of total FFA) over time

A. Comparison of fitted values at 3 key time points (n = 137 participants, 385 samples)

	Fitted values: mean (SE)			
Time (post start of treatment)	GIK	Placebo	Delta (G – P)	*P* value*
2 h	37.0% (1.1%)	31.6% (1.0%)	5.4% (1.5%)	.0006
6 h	43.7% (0.8%)	34.4% (0.7%)	9.3% (1.1%)	<.0001
12 h	45.6% (0.9%)	35.3% (0.8%)	10.3% (1.2%)	<.0001

B. Comparison rate of change (slope) for 3 different time windows

	Estimated slopes (change in FFA per 1-h increase)			
Time (post start of treatment)	GIK	Placebo	Delta (G – P)	*P* value*
0 to 2 h	4.3% (0.5%)	1.6% (0.5%)	2.7% (0.7%)	.0006
2 to 6 h	1.7% (0.3%)	0.7% (0.3%)	1.0% (0.4%)	.0089
Post 6 h	0.3% (0.1%)	0.2% (0.1%)	0.2% (0.2%)	.41

GIK infusions increased the percentage of saturated FA over the 12-hour infusion period (A), while increasing the rate of change over 0-6 hours of infusion (B.
*Fitted values and *P* values from a random effect mixed model intercept to equal fitted placebo arm intercept of 28.5%.

Table IV. Overall effect of GIK infusion on unsaturated FAs (sum of 18:1n9 and 18:2n6) as percentage of total FFA

A. Comparison of fitted values at 3 key time points (n = 137 participants, 385 samples).

	Fitted values: Mean (SE)			
Time (post start of treatment)	GIK	Placebo	Difference (G – P)	*P* value*
2 h	48.1% (1.3%)	54.8% (1.2%)	–6.7% (1.8%)	.0004
6 h	38.6% (0.9%)	50.6% (0.9%)	–12.0% (1.3%)	<.0001
12 h	36.8% (1.0%)	49.5% (0.9%)	–12.7% (1.4%)	<.0001

B. Comparison rate of change (slope) for 3 different time windows.

	Estimated slopes (change in FFA per 1-h increase)			
Time (post start of treatment)	GIK	Placebo	Delta (G – P)	*P* value*
0 to 2 h	–4.9% (0.6%)	–1.6% (0.6%)	–3.4% (0.9%)	.0004
2 to 6 h	–2.4% (0.3%)	–1.0% (0.3%)	–1.3% (0.4%)	.0037
Post 6 h	–0.3% (0.2%)	–0.2% (0.2%)	–0.1% (0.2%)	.61

GIK infusions decreased the percentage of unsaturated FFA over the 12-hour infusion period (A), while increasing the rate of change over 0-6 hours of infusion (B).
*Fitted values and *P* values from a random effect mixed model intercept to equal fitted placebo arm intercept of 57.9%.

A comparison of all saturated fatty acids is presented in Table V and was similar to that for saturated FA subset (sum of 16:0 and 18:0). A comparison of all mono- and polyunsaturated FAs was similar to that for the unsaturated acid subset (sum of 18:1n9 and 18:2n6) and also is presented in Table V. There was no significant difference in *trans*-fatty acids between the GIK and placebo groups at any of the 3 time points (Table V.)

The level of HbA1C, reflecting glucose intolerance and/or diabetes, was no different in GIK versus placebo infusions. The HOMA index, connoting insulin resistance, did not change over time. There were no significant differences in the HOMA index between the GIK group and placebo group (Table VI) despite the marked increase in insulin levels from the GIK infusion. Thus, the GIK infusions were not countered by insulin resistance. C-peptide levels remained unchanged over

Table V. Response to GIK infusions of other FA components as percentage of total FFA

Variable and elapsed time after start of treatment	GIK	Placebo	Difference (G – P)	*P* value*
All Saturated FA				
2 h	41.5% (1.3%)	35.1% (1.2%)	6.4% (1.7%)	.0004
6 h	50.1% (0.9%)	38.9% (0.9%)	11.2% (1.3%)	<.0001
12 h	52.4% (1.0%)	39.9% (1.0%)	12.5% (1.4%)	<.0001
Mono- and polyunsaturated fats				
2 h	55.7% (1.3%)	61.9% (1.2%)	−6.2% (1.8%)	.0008
6 h	47.0% (1.0%)	58.2% (0.9%)	−11.2% (1.3%)	<.0001
12 h	44.7% (1.1%)	57.1% (1.0%)	−12.4% (1.4%)	<.0001
trans-fatty acids				
2 h	2.8% (0.1%)	3.0% (0.1%)	−0.2% (0.2%)	.33
6 h	2.9% (0.1%)	2.9% (0.1%)	0.0% (0.2%)	.93
12 h	2.9% (0.1%)	2.9% (0.1%)	0.0% (0.1%)	.93

Data are summarized as fitted mean and SE of mean at 3 key time points for n = 137 participants (385 samples). GIK infusions increased the percentage of all saturated FAs and decreased the percentage of all unsaturated FFAs over the 12-hour infusion period. There were no significant differences in *trans*-fatty acids between the GIK and placebo groups over the infusion period.
* Fitted values and *P* values from a random effect mixed model intercept to equal fitted placebo arm intercept of 57.9%

Table VI. Response to GIK infusions of markers of insulin resistance (HOMA index, insulin levels) and C-peptide levels response (n = 143)

Variable	GIK (n = 68)	Placebo (n = 75)	*P* value
HOMA index, initial	12.99 [7.75-27.78] (39)	10.93 [7.5-16.53] (40)	.07
After 6 h of infusion	13.85 [5.46-33.33] (38)	12.74 [7.94-18.54] (44)	.74
After 12 h of infusion	12.82 [5.78-24.39] (39)	9.80 [6.13-14.29] (53)	.13
Insulin, initial levels	114.9 [66.1-160] (63)	19.1 [9.9-40. 7] (63)	<.0001
After 6 h of infusion	153.2 [71.5-265.9] (61)	22.1 [9.9-62.2] (67)	<.0001
After 12 h of infusion	122.4 [45.3-204. 6] (63)	21.4 [9.4-42.7] (69)	<.0001
C-peptide initial levels	1377 [853-2384] (43)	1193 [754-622] (41)	.15
After 6 h of infusion	1741 [696-2825] (41)	1300 [802-1875] (46)	.27
After 12 h of infusion	1351 [679-2687] (39)	1020 [712-1550] (54)	.09

Data are presented as median [25th to 75th percentile] (sample size).[28]

the infusion periods and were not different between the GIK and placebo groups (Table VI), suggesting no discernible change in endogenous insulin secretion.

Discussion

The first studies on the effects of GIK infusions in early human ACS were done by Sodi-Pallares et al[10] in 1962 and were followed by experimental exploration of the concept in animal models.[3] Infusions of GIK started soon after experimental coronary artery ligation in dogs improved early tissue metabolic and pathologic changes.[6] Subsequently, GIK was tested in a primate model of very early evolving acute myocardial infarction (AMI),[11] which showed that GIK increased the levels of myocardial high-energy phosphate compounds within 1 hour of coronary ligation.

Although there are several cardioprotective strategies for ACS,[1,3] only GIK and remote ischemic conditioning[2,12] have been tested in the ambulance. Such very early therapy should now be the therapeutic focus given the apparent lack of extensive further opportunities for benefit by additional reductions in door-to-balloon times.[1] In this study of the biological mechanisms of GIK cardioprotection, we found congruence with earlier studies in experimental models. A central hypothesis was that the high FFA levels found at the onset of symptoms of ACS[13] are substantially reduced by GIK infusion when given very early in the course of ACS in the ambulance, when the chances of saving threatened tissue and reducing cardiac arrhythmias are greatest.[2,14] Rogers et al[15] was the first to show that GIK decreases circulating FFA values in association with significant reduction in hospital mortality from AMI. Also improved by GIK was ventricular function; segmental wall motion abnormalities were reduced in association with improved myocardial glucose uptake and decreased FFA uptake.[16]

Extensive experimental and clinical results have shown the adverse effects of elevated FFA levels on the ischemic and infarcting myocardium.[6,8,11,13,17] These observations set the stage for study of the effects of GIK given within the early hours of ACS.[2] The abrupt lowering of circulating FFA values within the first 2 hours of the GIK infusion, which continued for 12 hours (Figure), was

associated with significant clinical outcome benefit, including reduction of infarct size from a median of 10% of left ventricular mass to 2% (P = .01).[2]

Mechanisms of GIK benefit

There appear to be 3 mechanisms involved in the metabolic benefit of GIK. First, excess FFA availability, and thus metabolism by the myocardium, induces oxygen wastage, as supported by experimental evidence of increased myocardial enzyme leakage in the FA-perfused rat heart.[4] Second, GIK is protective of ischemic myocardium by provision of glucose-insulin (GI) to isolated ischemic or underperfused rat heart, even in the absence of FFA.[4,18] This would suggest that stimulation of the glycolytic pathways protected the myocardium by increasing synthesis of membrane-protective glycolytic adenosine triphosphate.[19] Third, GI stimulates mitochondrial oxidative metabolism, as shown by increased levels of total high-energy phosphate compounds in the ischemic rat heart.[11] These observations suggest that elevated GI levels and depressed FFA levels work together to metabolically unload the myocardium and diminish the effect of the ischemic stress that accompanies an ACS.

FFA concentrations, insulin effects, and molecular pathways

With regard to adverse effects of high FFAs, there are several different, although overlapping, proposed mechanisms.[20] The first is the "substrate switch" hypothesis with conservation of energy.[3] GIK reduces circulating FFA levels (Figure, Table II), thereby promoting the myocardial metabolism of glucose and protective glycolysis while lessening the uptake of oxygen-wasting FFA by the heart. Second, FFA as the sole fuel for the heart can have major toxic effects on contractility and invoke serious arrhythmias.[5] Third, insulin itself can stimulate molecular paths that promote cardioprotection.[5,17] The key molecular component in GIK is insulin that acts as a mitogen to promote tolerance against ischemic cell death via the activation of innate cell-survival pathways in the heart.[21] These pathways travel via signal transducer and activator of transcription–3 and AKT,[22] crucial links in the survivor activator factor enhancement pathway that rescues from ischemic damage.[23] In addition, insulin could have activated additional protective mechanisms that are not FFA dependent such as the enzyme phosphatidylinositol kinase.[24]

Molecular subtypes of FFA

In light of arteriovenous studies on the normal human heart, the small decrease in circulating unsaturated FA levels during the GIK infusion should not be cardiotoxic even though oleic acid, C18:1 (Table IV), is the major myocardial fuel.[25] The corresponding small increase in saturated FFA (Table III) would be more than balanced by the large decrease of total FFA during the GIK infusion (Figure).

Blood C-peptide and HOMA index

C-peptide levels did not change significantly over the 12 hours of GIK infusion, suggesting that, in spite of the large glucose load in the GIK infusion, endogenous insulin secretion did not vary significantly over the 12-hour infusion. In conjunction with the relatively modest increases in glucose levels seen with GIK, this supports the suitability of the GIK recipe of Rackley[15,16] that was used in the IMMEDIATE trial. There were no significant changes in the HOMA index of insulin resistance (Table V), suggesting that the action of the infused insulin was not inhibited by the high circulating FFA levels.[9]

Contrast with the CREATE-ECLA STUDY

The large CREATE-ECLA Trial suggested that GIK infusions had no beneficial effect on patients with AMI.[7] A critical difference from the IMMEDIATE Trial was, however, that GIK was started late after the onset of symptoms of AMI (after 5 hours on average).[26] However, experimental results reviewed above suggest that the optimal timing for GIK initiation is within the first 2-3 hours, as in IMMEDIATE.[27] Furthermore, CREATE-ECLA was a non–placebo-controlled, nonblinded, open-label trial, and GIK was given after, rather than before, coronary reperfusion. Thus, we do not consider the CREATE-ECLA Trial to undermine the IMMEDIATE Trial results or this substudy; rather, it studied a different treatment approach which it suggested was not as effective as the one used in IMMEDIATE.

Future work

Although GIK infusion given in the ambulance en route to hospitals is 1 of only 2 proven interventions that appear to protect acutely ischemic myocardium, the other being remote ischemic conditioning,[12] much still remains to be clarified. Further trials of early GIK should include mechanistic studies exploring the biology underlying the cardioprotective effect of acute GIK administration in patients with ACS.

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