Glucose-Insulin-Potassium Therapy for Treatment of Acute Myocardial Infarction

To the Editor:

The meta-analysis of Fath-Ordoubadi and Beatt1 suggests a beneficial role for glucose-insulin-potassium therapy for treatment of acute myocardial infarction in nondiabetic patients, a result in accordance with the recently reported beneficial effect in diabetic patients.2

Although the exact mechanisms behind the improvement of prognosis are unclear, we would like to stress the importance of reducing free fatty acids (FAs) as a myocardial fuel by insulin administration. Normally, FA oxidation and cardiac work are closely associated. In ischemic hearts, the proportion of energy produced from FAs increases. Kudo and coworkers3 induced global ischemia of 30 minutes followed by aerobic reperfusion of 60 minutes in isolated working rat hearts. Although cardiac work after reperfusion was reduced to only 16% of aerobic values, palmitate oxidation increased to 136%. The reduced cardiac efficiency in ischemia may depend on the excessive entrance of FAs into mitochondria, leading to uncoupling of mechanical function from FA oxidation. The same phenomenon is seen with medium-chain FAs with free entrance into mitochondria.4 Normally, the access of long-chain FAs, the great majority of FAs, into mitochondria is inhibited by malonyl-CoA through carnitine palmitoyl transferase I. In the work of Kudo et al.,3 acetyl-CoA, substrate for malonyl-CoA, and malonyl-CoA levels were reduced in concert after ischemia. However, malonyl-CoA levels were much further reduced during aerobic reperfusion, although acetyl-CoA levels did not decrease further. The level of malonyl-CoA after reperfusion was only ≈1% of aerobic level. Thus, FAs probably had almost uncontrolled access into mitochondria. The activity of acetyl coenzyme-A carboxylase (ACC), the enzyme converting acetyl-CoA to malonyl-CoA, was reduced in ischemic hearts during reperfusion, explaining the lowered malonyl-CoA level after reperfusion. Cardiac dysfunction may lead to greater myocardial injury. Because glucose and insulin increase the concentration of malonyl-CoA by stimulating ACC,6 they inhibit entrance of FAs into mitochondria and consequently restrict the damage caused by the uncoupling of FA oxidation and the myocardium contraction. Thus, intensive insulin therapy both reduces FA availability by inhibiting lipolysis and prevents excessive FA entrance into mitochondria, both mechanisms that reduce FA toxicity in the ischemic heart.

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Response

We agree with Dr Ebeling and Dr Koivist and do believe that one of the main beneficial effects of GIK during ischemia, as mentioned in our article,1 is to reduce the circulating level of free fatty acids (FFAs) and inhibit their uptake and utilization by myocardial cells. The theoretical evidence for this beneficial effect is strong. However, in the clinical setting it would be very difficult to separate out the relative importance of different properties of glucose-insulin-potassium (GIK) therapy because these effects occur simultaneously and are complementary. There are several pointers indicating the importance of lowering FFAs. In our meta-analysis,1 pooled data from trials of high-dose intravenous GIK therapy, which is associated with greater reduction of circulating FFAs, showed a greater reduction in mortality after myocardial infarction than pooled results of all the trials including those using low-dose therapy. Inadequate suppression of FFAs by low-dose GIK therapy may be the reason behind the disappointing results of the recent post–myocardial infarction Polish GIK study.2 β-Blockers reduce the rate of sudden death during myocardial infarction. This action of β-blockers may be explained at least in part by their ability to reduce circulating FFAs by blunting the action of sympathetic activity during ischemia. Nicotinic acid analogues lower plasma FFAs,3 and this action is associated with reduction of extent of ST-segment depression at rest and during exercise.4 Hearts perfused with fatty acids are less able to recover after reperfusion than hearts perfused with glucose.5 The clinical implications from these points are that during ischemia, the FFA level needs to be reduced quickly and adequately. For best results, FFA levels should be reduced before reperfusion has occurred to improve the chance of myocardial recovery after reperfusion and to prevent reperfusion injury. When one uses Rackley’s high-dose intravenous regimen (infusion of 50 U of insulin and 80 mmol of potassium in 1 L of 30% glucose, administered at a rate of ≈1.5 mL·kg⁻¹·h⁻¹),6 adequate suppression of circulating FFAs can be achieved within 30 minutes. However, an initial bolus therapy followed by high-dose intravenous infusion may lead to even quicker suppression of FFAs. Finally, GIK therapy not only has a complementary role with reperfusion strategies such as thrombolysis, but its actions should also be enhanced by β-blockers. Early use of these 3 agents together may therefore have the greatest impact in reducing cardiac mortality after an acute myocardial infarction.

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Evidences are mounting to indicate that ischemic preconditioning is beneficial for the protective effects of IPC against ischemia/reperfusion injury. To the Editor:

To the Editor:

and Ischemic Preconditioning


Adenosine Pretreatment of Human Myocardium and Ischemic Preconditioning

To the Editor:

I congratulate Leeser et al1 for their innovative research. Evidences are mounting to indicate that ischemic preconditioning (IPC) can be demonstrated in human myocardium,2,3 and this has stimulated interest in its potential clinical applicability. However, their study is not the first to demonstrate that adenosine (ADO) pretreatment can protect against myocardial reperfusion injury. In 1993, ADO was infused into the right ventricle of patients undergoing CABG operations.4 It has been conclusively demonstrated for the first time that ADO pretreatment before the initiation of cardiopulmonary bypass improves postbypass cardiac function and reduces postoperative CPK release. Recently, IPC has been demonstrated to occur in organ systems other than myocardium. IPC has been demonstrated to occur in skeletal muscle of the rat and pig.5 Other organ systems such as liver,6 lung,7 brain,8 and spinal cord9 also would appear to benefit from the protective effects of IPC against ischemia/reperfusion injury.

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Dexamethasone Downregulates L-Selectin In Vitro and In Vivo

To the Editor:

We read with interest the paper by Filep et al,1 who showed that dexamethasone attenuated the downregulation of L-selectin expression induced by platelet activating factor while not affecting basal expression of L-selectin on neutrophils. They discuss that the "results appear to differ from those of Burton et al, who found that in vivo glucocorticoid treatment induced significant downregulation of both L-selectin and CD18 expression on resting bovine neutrophils. However, these effects of glucocorticoids became detectable only 8 to 16 hours and 2 to 3 days after treatment, respectively. The delayed response, combined with the fact that neutrophils reside in the peripheral blood for only a few hours, would suggest that in cows glucocorticoids affected neutrophil precursors in bone marrow rather than circulating neutrophils."

Similar to the results from previous studies in cattle1 and in rats,3 we have recently found that dexamethasone also downregulates basal L-selectin expression on neutrophils in humans, with cerebral ischemic preconditioning. Proc Natl Acad Sci U S A. 1995;92:4666–4670.


Response

The study by Lee et al1 purports to show that pretreatment with intravenous adenosine protects human myocardium during CABG. Unfortunately, there are several problems that make this conclusion untenable. First, the number of patients studied by Lee et al was small (7 control subjects and 7 adenosine-treated subjects). Second, infusion of adenosine caused significant hypotension (mean systolic arterial pressure fell by 30 mm Hg; in 2 of the 7 treated patients, systolic pressure fell below 70 mm Hg, requiring a decrease in the dose of adenosine). This hypotensive effect could have caused either global or regional (due to "coronary steal") myocardial ischemia, so that the protective effects observed after surgery could have been secondary to ischemic preconditioning rather than adenosine preconditioning. Third, since the hemodynamic parameters measured by Lee et al (cardiac index, stroke volume index, left ventricular stroke work index, etc) are highly dependent on the loading conditions, changes in these variables are difficult to interpret. Postoperative administration of vasoactive or inotropic agents could also have had a substantial impact on the results. Fourth, the decrease in the release of creatine kinase (CK) in adenosine-treated patients cannot be construed as evidence of protection against ischemia/reperfusion injury, since total CK (rather than MB-CK) was reported; the release of total CK during surgery reflects mainly the trauma to skeletal and cardiac muscle. Finally, the legend to Figure 5 in the article by Lee et al shows that CK release during the first 24 hours postoperatively was significantly greater versus prebypass in controls but not in adenosine-treated patients; the significance of this comparison is unclear. In summary, the findings of Lee et al cannot be construed as evidence that adenosine preconditioning human myocardium against ischemia.

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a lag time of 8 hours. However, this need not necessarily be due to an effect of dexamethasone on neutrophil precursors, because neutrophils recently released from the bone marrow may exhibit even higher levels of L-selectin expression. Also, the neutrophil half-life is significantly prolonged when glucocorticoids are administered, and L-selectin seems to decrease on aged neutrophils. Therefore, it is conceivable that downregulation of L-selectin expression by a direct or indirect mechanism could occur on circulating neutrophils and could also account in part for the increase in neutrophil half-life, or vice versa.

While in vitro studies can precisely define possible effector mechanisms, such as the marked inhibitory action of dexamethasone on leukotriene B<sub>4</sub> production, they often do not allow extrapolation to describe the complexity of in vivo situations. Thus, these in vitro and in vivo studies should be regarded as complementary rather than contradictory.

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Response

We thank Drs Jilma and Stohlwatz for their interest in our work. Their concern about our discussion on the possible effects of dexamethasone on neutrophil precursors is based on a misreading of our article. We did not claim that downregulation of L-selectin expression on circulating neutrophils in cattle can be exclusively attributed to an effect of dexamethasone on neutrophil precursors. Instead, we have suggested this action as a possible explanation for the apparently different results obtained in the study of Burton et al<sup>2</sup> and in our in vitro study. The statement that Dr Jilma and colleague make concerning the direct effect of glucocorticoids on neutrophils is somewhat controversial. Actually, this point is more difficult for us, since we did not have an opportunity to preview their manuscript before its publication. It is not clear how they assessed direct effects of glucocorticoids on neutrophils in humans. In particular, we wonder about a lag time of 8 hours. It is well established that glucocorticoids produce their effect on responsive cells by binding to cytoplasmic glucocorticoid receptors. The hormone-receptor complex then translocates to the nucleus and modulates transcription of specific target genes.<sup>3,4</sup> Glucocorticoid-induced de novo protein synthesis occurs within 1 to 3 hours, which would certainly not explain a lag time of 8 hours. There is also some evidence for direct effects of glucocorticoids on the function and composition of plasma membrane of target cells, but again, the maximal effects can be observed after 6 hours of incubation with glucocorticoids.<sup>5</sup> High concentrations of glucocorticoids have been implied in stabilizing cell membranes,<sup>6</sup> which can be expected to inhibit rather than facilitate L-selectin shedding.

L-selectin shedding occurs within minutes of cell activation<sup>1</sup> or treatment of leukocytes with certain nonsteroidal antiinflammatory drugs<sup>8</sup> or C-reactive protein,<sup>9</sup> which does not activate leukocytes. Inasmuch as the proteolytic enzyme (“sheddase”) appears to be a constitutively active enzyme, the formation of an appropriate three-dimensional structure of L-selectin protein near the membrane would regulate this proteolytic processing.<sup>10,11</sup> Although the enzymes and signaling mechanisms that regulate the cleavable conformation of L-selectin remain key areas of inquiry, activation of these mechanisms requires few minutes rather than several hours.

In regard to the effects of glucocorticoids on neutrophil precursors, the following should be considered. In humans, L-selectin expression increases on bone marrow granulocytes with cell maturation, and mature neutrophils recently released from the bone marrow express the highest level of L-selectin.<sup>12</sup> Burton et al<sup>2</sup> have observed “modest but significant increases in circulating immature neutrophils” in dexamethasone-treated cows. Since these immature cells express less L-selectin than mature cells, it is plausible to assume that overall decreases in neutrophil L-selectin expression (measured as mean fluorescence staining intensity) could be detected when considerable portions of mature neutrophils have been removed from the circulation and/or when the aging-related shedding of L-selectin<sup>13</sup> is augmented. While prolongation of the half-life of circulating neutrophils by glucocorticoids<sup>14</sup> is consistent with further decreases in L-selectin expression, dexamethasone-induced drop-off of neutrophils (which express unknown levels of L-selectin) from the marginating pool<sup>2</sup> would further complicate this picture. It should be noted that O’Leary et al<sup>15</sup> studied neutrophil L-selectin expression after treatment of rats with dexamethasone for 3 days (about 6× the dexamethasone-prolonged half-life of neutrophils). We have not discussed these actions in detail in our article, for we have not studied neutrophil kinetics.

Finally, while we do not agree that our report treats in vitro and in vivo studies as contradictory, we certainly agree that both in vivo and in vitro studies are necessary to investigate the mechanisms and the complexity of the actions of glucocorticoids. This was perhaps omitted from our text because it seemed obvious.

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To the Editor:

Intracoronary Doppler and Collateral Resistance

The authors' assertion is incorrect that they obtained collateral flow by measuring diastolic occlusive time velocity integral (dVi, cm). In fact they determined just an index for collateral flow that did not account for the influence of changes in general, do not respond to vasodilators may be incorrect. Intuitively, this makes sense, since coronary epicardial flow indicated by the velocity signal will finally reach the myocardial bed irrespective of the direction it has taken at the time of its detection upstream. Systolic velocity signals originating from increased epicardial backward or forward flow due to enhanced myocardial wall stress can be recognized easily by their high pitch, high peak velocity, and high acoustic intensity onset and their short duration. These signals should not be accounted for in the computation of collateral flow indices. However, all other flow velocity signals during systole should be used in the calculation of Doppler indices of collateral flow.

As a minor point, it has to be emphasized that Equation 3 in the appendix of the article is given incorrectly. It should probably read PW=−dVi+R4 (and not PW+dVi+R4).

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Response
Only a limited number of studies have been conducted on the hemodynamics of the coronary collateral circulation in humans. Consequently, the data reported in our article require confirmation by other investigators. The critical comments by Seiler are well appreciated and may stimulate further research on this topic of interest. The comments raised are addressed in numerical order.

1. The currently available technical equipment in intervention cardiology hampers the assessment of collateral vascular resistance in an angioplasty model by measurement of collateral volume flow. This requires a simultaneous assessment of both collateral blood flow velocity and the diameter of the arterial segment. It is correct that collateral flow was estimated in the study as an index using the diastolic blood flow velocity integral. The selective administration of vasodilators (adenosine or nitroglycerin) in the donor coronary artery may induce vasodilation of the recipient coronary artery. This indicates that the observed changes in collateral blood flow velocity after the administration of vasodilators in patients with spontaneously visible collateral vessels are rather an underestimated of the true alterations in volume flow and hence of the collateral vascular resistance. On the other hand, our conclusion that recruitable collateral vessels, in general, do not respond to vasodilators may be incorrect due to this phenomenon. These methodological drawbacks were addressed in the limitations section of the article.

2. The use of the diastolic blood flow velocity integral for the calculation of the collateral vascular resistance was based on the consideration that systolic blood flow velocity signals can be generated by myocardial contraction even in the absence of recruitable collateral vessels.
The interpretation of these systolic signals is rather undefined, taking into account the limited number of studies performed on this subject. The diastolic blood flow velocity integral as an index of collateral flow is arbitrary.

Table 2 of the original article depicts the alterations in the coronary blood flow velocity after the administration of vasodilators using the diastolic blood flow velocity integral as well as the total blood flow velocity integral. Bidirectional signals were added for the calculation of this total blood flow velocity integral. That table shows that the blood flow velocity alterations are not different using the diastolic or total blood flow velocity integrals.

For completeness, we have calculated the changes in collateral vascular resistance based on the total blood flow velocity integral rather than the diastolic velocity integral. Again, the following Table shows that this collateral flow index does not yield different conclusions, with the exception of the effect of nitroglycerin on the peripheral vascular resistance index of the recipient coronary artery, which shows a trend toward significance.

3. The authors apologize for the incorrect Equation 3 ($P_w = dV_i + R_4$) in the appendix that should read as: $P_w = dV_i + R_4$.

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**Effect of Adenosine and Nitroglycerin on Resistance Calculations Using Total Blood Flow Velocity Integral in Patients With Recruitable Collateral Vessels (Group 1) and Patients With Spontaneously Visible Collateral Vessels (Group 2)**

<table>
<thead>
<tr>
<th></th>
<th>Adenosine</th>
<th>Nitroglycerine</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before</td>
<td>After</td>
</tr>
<tr>
<td>$R_{coll}$, mm Hg/cm</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group 1</td>
<td>9.0±5.4</td>
<td>9.9±6.3</td>
</tr>
<tr>
<td>Group 2</td>
<td>6.1±3.6</td>
<td>5.1±3.7</td>
</tr>
<tr>
<td>$R_4$, mm Hg/cm</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group 1</td>
<td>4.5±2.2</td>
<td>4.0±1.8</td>
</tr>
<tr>
<td>Group 2</td>
<td>4.6±2.0</td>
<td>3.6±2.2</td>
</tr>
</tbody>
</table>

$R_{coll}$ indicates collateral vascular resistance index; $R_4$, peripheral vascular resistance index of the recipient coronary artery.

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