Validation of surrogate indexes of insulin sensitivity in acute phase of myocardial infarction based on euglycemic-hyperinsulinemic clamp

Filipe A. Moura,1 Luiz Sergio F. Carvalho,1 Riobaldo M. R. Cintra,1 Naiara V. Martins,2 Valeria N. Figueiredo,1 Jose C. Quinaglia e Silva,2,3 Osorio L. R. Almeida,2,3 Otavio R. Coelho,1 and Andrei C. Sposito1

1Cardiology Division, State University of Campinas Medical School, Campinas, Brazil; 2University of Brasilia Medical School, Brasilia, Brazil; and 3Hospital de Base do Distrito Federal, Brasilia, Brazil

Submitted 15 October 2013; accepted in final form 11 December 2013

Moura FA, Carvalho LS, Cintra RM, Martins NV, Figueiredo VN, Quinaglia e Silva JC, Almeida OL, Coelho OR, Sposito AC. Validation of surrogate indexes of insulin sensitivity in acute phase of myocardial infarction based on euglycemic-hyperinsulinemic clamp. Am J Physiol Endocrinol Metab 306: E399–E403, 2014. First published December 17, 2013; doi:10.1152/ajpendo.00566.2013.—The decrease in insulin sensitivity (IS) during myocardial infarction (MI) is recognized as a possible contributor to poor patient outcomes. Despite its potential relevance, a standardized and convenient IS assessment tool has yet to be established for said clinical scenarios. This study aimed to validate the accuracy of surrogate indexes in determining IS in acute MI patients by comparison with the gold standard reference method for measuring IS, the euglycemic-hyperinsulinemic clamp (EHC). We performed EHCs in 31 consecutive nondiabetic patients who were admitted within the first 24 h of symptoms of ST-segment elevation MI. Patients with prior diagnosis of diabetes, use of hypoglycemic agents, or a glycosylated hemoglobin (HbA1c) ≥6.5% were excluded. EHCs were performed at the second day (D2) and sixth day (D6) post-MI. Basal (12-h fasting) blood samples from D2 and D6 were used to evaluate patient blood glucose and insulin levels. We then calculated the following surrogate indexes: homeostatic model assessment of insulin sensitivity (HOMA2S), homeostatic model assessment of insulin resistance (HOMA-IR), and quantitative insulin sensitivity check index (QUICKI). The IS index measured by EHC (ISclamp) was correlated to HOMA2S, HOMA-IR, and QUICKI at D2 (r = 0.485, P = 0.009; r = −0.384, P = 0.048; r = 0.479, P = 0.01, respectively) and D6 (r = 0.621, P = 0.002; r = −0.576, P = 0.006; r = 0.626, P = 0.002, respectively). Receiver operator characteristic curves made for discrimination of ISclamp above the median in D2 and D6 depicted areas under the curve of 0.740, 0.734, and 0.760 for HOMA2S, HOMA-IR, and QUICKI, respectively. Bland–Altman plots displayed no apparent systematic error for indexes, but a propensity for proportional error, particularly with HOMA-IR. Thus, based on EHC, these simple surrogate indexes are feasible for assessing IS during MI.

ELEVATION OF PLAASMA GLUCOSE during myocardial infarction (MI) is primarily the result of increased gluconeogenesis and reduced insulin sensitivity (IS) and is strongly related to increased mortality post-MI (2). Aside from the effects of insulin on glucose and lipid metabolism, consistent data demonstrate that it has multiple direct effects on the cardiovascular system as well (4). Insulin has been shown to improve endothelial function and to have both anti-thrombogenic and anti-inflammatory effects (4, 7). Reduced IS has therefore been hypothesized to worsen outcomes of post-MI patients with hyperglycemia. To date, however, the existence of a causal link for this association remains to be proven.

The euglycemic-hyperinsulinemic clamp (EHC) has long been considered the gold standard procedure for IS assessment (5). Because of the time-consuming and labor-intensive characteristics of this technique, it is unfeasible to utilize in high-risk patients such as those during the acute phase of MI. Some simplified surrogate indexes have been validated for assessing IS in various situations of metabolic stability (1, 9, 12, 16). However, evidence is lacking as to whether these methods are adequate in measuring IS in high-stress situations such as MI. The validation for use of these surrogate indexes in said clinical scenarios will serve as the starting point in more readily and easily determining the role of IS during MI. We therefore sought to verify whether estimation of IS via surrogate indexes during MI is consistent with direct IS measurement by means of EHC.

METHODS

Patients. Consecutive ST-segment elevation MI (STEMI) nondiabetic subjects (n = 31) were enrolled in the study according to the predefined criteria of the Brasilia Heart Study (14). Inclusion criteria were as follows: 1) ≤24 h after the onset of MI symptoms, 2) ST-segment elevation of a least 1 mm (frontal plane) or 2 mm (horizontal plane) in two contiguous leads, 3) myocardial necrosis, as evidenced by an increase to at least one value above the 99th percentile above the reference limit of CK-MB (25 U/l) and troponin I (0.04 ng/ml) followed by a decline of both, and 4) absence of impediments for clinical follow-up. Patients were excluded in case of: prior diagnosis of diabetes, use of oral hypoglycemic agents, or admission glycosylated hemoglobin (HbA1c) ≥6.5%. The Regional Ethics Committee approved the study, and all patients signed an informed consent.

Biochemical analyses. Blood samples were drawn upon initiation of EHC after a 12-h overnight fast at day 2 (D2) and day 6 (D6) of STEMI. The following blood measurements were performed: glucose (Glucose GOD-PAP; Roche Diagnostics), mannheim, Germany), total cholesterol (CHOD-PAP; Roche Diagnostics), triglycerides (GPO-PAP; Roche Diagnostics), high-density lipoprotein (HDL) cholesterol (HDL cholesterol without sample pretreatment; Roche Diagnostics), insulin (Roche Diagnostics), and HbA1c (Variant II; Bio-Rad Laboratories, Hercules, CA). Low-density lipoprotein cholesterol was calculated using the Friedewald formula.

Calculations for determining surrogate indexes. The surrogate indexes chosen for this study were those that were shown to best correlate with the EHC-based IS in studies involving metabolically stable patients (1), which included homeostatic model assessment of insulin resistance (HOMA-IR), homeostatic model assessment of...
**Table 1. Clinical and treatment characteristics of study subjects**

| Subject Characteristics         | n  | Age, yr | 56 ± 8 | Male, % | 95 | Fasting glucose D2 | 95.5 (36) | Fasting glucose D6* | 84.5 (23.25) | Fasting insulin D2 | 9.1 (11.85) | Fasting insulin D6* | 8.2 (7.15) | Insulin 120 min D2 | 55.5 (39.6) | Insulin 120 min D6* | 43.7 (21.4) | Insulin 150 min D2 | 58.75 (41.53) | Insulin 150 min D6* | 45.5 (25.08) | Insulin 180 min D2 | 56 (35.95) | Insulin 180 min D6* | 46.1 (27.55) |

| RES** | GLUCOSE CLAMP VS. SURROGATE INDEXES IN MYOCARDIAL INFARCTION |

**RESULTS**

The clamp procedures did not result in any adverse effects, including episodes of hypoglycemia or hypokalemia. Ninety-

Table 2. Correlations and ROC curves between surrogate indexes and ISiClamp at D2 and D6 after myocardial infarction

<table>
<thead>
<tr>
<th>Surrogate Indexes</th>
<th>r</th>
<th>P Value</th>
<th>AUC</th>
</tr>
</thead>
<tbody>
<tr>
<td>HOMA2S D2</td>
<td>0.485</td>
<td>0.009</td>
<td>0.781</td>
</tr>
<tr>
<td>HOMA2S D6</td>
<td>0.621</td>
<td>0.002</td>
<td>0.727</td>
</tr>
<tr>
<td>HOMA2S D2 and D6</td>
<td>0.505</td>
<td>&lt;0.001</td>
<td>0.740</td>
</tr>
<tr>
<td>HOMA-IR D2</td>
<td>-0.384</td>
<td>0.048</td>
<td>0.772</td>
</tr>
<tr>
<td>HOMA-IR D6</td>
<td>-0.576</td>
<td>0.006</td>
<td>0.683</td>
</tr>
<tr>
<td>HOMA-IR D2 and D6</td>
<td>-0.456</td>
<td>0.001</td>
<td>0.734</td>
</tr>
<tr>
<td>QUICKI D2</td>
<td>0.479</td>
<td>0.01</td>
<td>0.791</td>
</tr>
<tr>
<td>QUICKI D6</td>
<td>0.626</td>
<td>0.002</td>
<td>0.712</td>
</tr>
<tr>
<td>QUICKI D2 and D6</td>
<td>0.524</td>
<td>&lt;0.001</td>
<td>0.760</td>
</tr>
</tbody>
</table>

ROC, receiver operator characteristic; AUC, area under the curve.
As shown in the Bland-Altman plots (Fig. 2), no systematic error is apparent for the comparison between EHC and surrogate indexes across a wide range of values. Linear regression analysis of the differences vs. the means of the Bland-Altman plots are also shown on Fig. 2 and are suggestive of a proportional error for all three indexes. There is a tendency for larger error in estimation of IS with the use of HOMA-IR.

DISCUSSION

This is the first study to assess both IS by EHC in patients during the acute phase of MI, and also validate the use of simplified surrogate indexes as reliable tools for measuring IS in a high-stress clinical situation like acute MI. Despite the metabolic instability of acute MI patients, we found consistent and moderate associations between ISclamp and HOMA2S, HOMA-IR, and QUICKI values. Furthermore, these values were very close to those observed in individuals at metabolically stable conditions (13).

In the very early phase of MI, IS decreases because of a rise in catecholamine, cortisol, glucagon, and cytokine levels (6). These counterregulatory hormones reach peak levels 12–18 h after MI and then decrease during the next 48 h, subsequently returning to basal (pre-MI) levels (8, 15). It was consistently observed that the association between ISclamp and the surrogate indexes was stronger at D6 than at D2. This does not, however, vary enough as to hinder the estimation of IS with the accuracy usually obtained by these methods.

Of note, we found that, in contrast to individuals in stable conditions, surrogate indexes are associated with EHC in MI patients in a nonlinear manner, i.e., a power curve pattern. This difference and the tendency for proportional error observed from Bland-Altman plots of these surrogate indexes against EHC may both be explained by the clinical scenario in which

Table 3. Agreement between ISclamp and surrogate indexes

<table>
<thead>
<tr>
<th>Measure of Insulin Sensitivity</th>
<th>Median Difference (IQR)</th>
<th>Transformation Formulas</th>
</tr>
</thead>
<tbody>
<tr>
<td>Observed</td>
<td>Predicted (HOMA2S)</td>
<td>Predicted (HOMA-IR)</td>
</tr>
<tr>
<td>HOMA2S</td>
<td>HOMA-IR</td>
<td>QUICKI</td>
</tr>
<tr>
<td>ISclamp</td>
<td>2.21 (1.64)</td>
<td>2.12 (0.94)</td>
</tr>
</tbody>
</table>

Observed and predicted values are expressed as median (interquartile range). The unit used for insulin sensitivity is \(10^{-4} \times \text{kg}^{-1} \times \text{min}^{-1}/(\mu\text{U/mL})\).
regulatory mechanisms of glucose production and uptake are overtly stimulated and potentially saturated. In addition, fasting-derived indexes primarily indicate hepatic IS, whereas EHC measurements reflect peripheral IS. Although hepatic IS is typically closely coupled with peripheral IS in humans, it is conceivable that this particular setting of acute stress may influence both in a different manner. Finally, we witnessed a very heterogeneous change in IS between D2 and D6 among patients. A step forward after this finding would be to investigate the major modulators for this discrepancy, which requires further studies with larger sample sizes.

Some limitations of our study do exist. First, because of the difficulty in performing EHCs in this clinical setting, our sample size resulted in a limited power (<20%) in assessing for the superiority of the surrogate indexes in terms of correlation to the EHC. The sample size did however yield appropriate results as to sufficiently answer the main study inquiry regarding the validity of the use of simplified surrogate indexes over the cumbersome EHC in assessing IS during acute-phase MI. In addition, we were not able to evaluate the latest version of the QUICKI index, which adjusts for fasting nonesterified fatty acid concentration because heparin administration-derived indexes primarily indicate hepatic IS, whereas EHC measurements reflect peripheral IS. Although hepatic IS is typically closely coupled with peripheral IS in humans, it is conceivable that this particular setting of acute stress may influence both in a different manner. Finally, we witnessed a very heterogeneous change in IS between D2 and D6 among patients. A step forward after this finding would be to investigate the major modulators for this discrepancy, which requires further studies with larger sample sizes.

In conclusion, compared with EHC, the surrogate indexes HOMA2S, HOMA-IR, and QUICKI are feasible in determining IS in MI patients, which was shown to be similar to that obtained in studies of patients with stable metabolic conditions. These surrogate indexes, particularly HOMA-IR, are less accurate in individuals with more pronounced reductions in IS and must therefore be interpreted with caution. This finding opens the door to considering the use of simple IS assessment tools in larger MI cohorts as to explore its relevance in the pathophysiology of MI and the potential association of decreased IS with increased patient morbidity and mortality.

DISCLOSURES
The authors declare that they have nothing to disclose.

AUTHOR CONTRIBUTIONS

REFERENCES


