

# In Patients With Acute Myocardial Infarction, the Impact of Hyperglycemia as a Risk Factor for Mortality Is Not Homogeneous Across Age-Groups

JOSÉ CARLOS NICOLAU, MD, PHD<sup>1</sup>  
 CARLOS VICENTE SERRANO JR., MD, PHD<sup>1</sup>  
 ROBERTO ROCHA GIRALDEZ, MD<sup>1</sup>  
 LUCIANO MOREIRA BARACIOLI, MD<sup>1</sup>  
 HUMBERTO GRANER MOREIRA, MD<sup>1</sup>  
 FELIPE LIMA, MD<sup>1</sup>

MARCELO FRANKEN, MD<sup>1</sup>  
 ROBERTO KALIL, MD, PHD<sup>1</sup>  
 JOSÉ ANTONIO FRANCHINI RAMIRES, MD,  
 PHD<sup>1</sup>  
 ROBERT P. GIUGLIANO, MD, SM<sup>2</sup>

**OBJECTIVE**—To assess the impact of hyperglycemia in different age-groups of patients with acute myocardial infarction (AMI).

**RESEARCH DESIGN AND METHODS**—A total of 2,027 patients with AMI were categorized into one of five age-groups: <50 years ( $n = 301$ ),  $\geq 50$  and <60 ( $n = 477$ ),  $\geq 60$  and <70 ( $n = 545$ ),  $\geq 70$  and <80 ( $n = 495$ ), and  $\geq 80$  years ( $n = 209$ ). Hyperglycemia was defined as initial glucose  $\geq 115$  mg/dL.

**RESULTS**—The adjusted odds ratios for hyperglycemia predicting hospital mortality in groups 1–5 were, respectively, 7.57 ( $P = 0.004$ ), 3.21 ( $P = 0.046$ ), 3.50 ( $P = 0.003$ ), 3.20 ( $P < 0.001$ ), and 2.16 ( $P = 0.021$ ). The adjusted  $P$  values for correlation between glucose level (as a continuous variable) and mortality were 0.007, <0.001, 0.043, <0.001, and 0.064. The areas under the ROC curves (AUCs) were 0.785, 0.709, 0.657, 0.648, and 0.613. The AUC in group 1 was significantly higher than those in groups 3–5.

**CONCLUSIONS**—The impact of hyperglycemia as a risk factor for hospital mortality in AMI is more pronounced in younger patients.

*Diabetes Care* 35:150–152, 2012

Elevated glucose level (GL) is an independent risk factor for mortality in patients with acute myocardial infarction (AMI) (1–3), in part related to its adverse effects on microcirculation and left ventricular remodeling (4). Particularly in older people, hyperglycemia is a common complication that increases the risk of death (5). However, less is known about the impact of hyperglycemia in younger patients with AMI. Furthermore, the comparison of the impact of GL in different age-groups, particularly in very elderly adults (>80 years) versus younger adults (<50 years), has not been well studied and is the primary focus of this study.

## RESEARCH DESIGN AND METHODS

Retrospective analysis of 2,027 patients (median age 64 years, 71.8% men) with AMI, hospitalized in a single tertiary center, and included prospectively in a dedicated databank.

### Age-groups

Patients were divided into five age-groups: <50 years (group 1,  $n = 301$ ),  $\geq 50$  and <60 years (group 2,  $n = 477$ ),  $\geq 60$  and <70 years (group 3,  $n = 545$ ),  $\geq 70$  and <80 years (group 4,  $n = 495$ ), and  $\geq 80$  years (group 5,  $n = 209$ ). Hyperglycemia was defined as first glucose measurement  $\geq 115$  mg/dL ( $n = 1,025$ ). The time

between symptoms beginning and the glucose measurement was obtained in 1,752 patients; the median time for the population was 29 h and similar across the groups ( $P$  value = 0.642). The primary clinical outcome was in-hospital mortality.

### Statistical analyses

Categorical variables are described as numbers and percentages and continuous variables as median (25th, 75th percentiles) or mean  $\pm$  SD.

For the correlation between hyperglycemia and hospital mortality, the  $\chi^2$  test was used, with the Mann-Whitney  $U$  test used for the correlation between GL (as continuous variable) and mortality. The mean GL among the groups was compared with ANOVA. Stepwise logistic regression method was applied for the comparison between hyperglycemia as a categorical variable or GL (continuous variable) with mortality (dependent variable). Two different models were developed. The first model included age, hyperglycemia (or GL), sex, ST-elevation AMI, and a history of angina, dyslipidemia, relatives with coronary artery disease, smoking, hypertension, heart failure, diabetes, stroke, coronary artery bypass surgery, percutaneous coronary intervention (PCI), and myocardial infarction. The second model included the previous variables plus primary PCI, nonprimary PCI, coronary artery bypass surgery, and fibrinolytic use during the in-hospital phase. Because there was no significant correlation between LDL or HDL and mortality, and the  $P$  interactions for these variables and hyperglycemia or GL regarding mortality were nonsignificant, neither LDL nor HDL was included in the models.

To analyze the accuracy of GLs in predicting in-hospital deaths, receiver operating characteristic (ROC) curves were constructed for each group and compared with the DeLong method.  $P$  values <0.05 were considered significant; MedCalc version 11.4.4 statistical software (MedCalc Software, Mariakerke,

From the <sup>1</sup>Heart Institute (InCor), University of São Paulo Medical School, São Paulo, Brazil; and the <sup>2</sup>Thrombolysis in Myocardial Infarction (TIMI) Study Group, Brigham and Women's Hospital, Boston, Massachusetts.

Corresponding author: José Carlos Nicolau, corjnicolau@incor.usp.br.

Received 27 June 2011 and accepted 23 September 2011.

DOI: 10.2337/dc11-1170

© 2012 by the American Diabetes Association. Readers may use this article as long as the work is properly cited, the use is educational and not for profit, and the work is not altered. See <http://creativecommons.org/licenses/by-nc-nd/3.0/> for details.

Belgium) was used for the ROC curve comparisons, and SPSS 16.0 (SPSS Inc., Chicago, IL) was used for the other analyses.

**RESULTS**—The mean GLs (in mg/dL) for groups 1–5 were, respectively,  $125.8 \pm 62.7$ ,  $139.5 \pm 69.4$ ,  $143.9 \pm 69.6$ ,  $143.7 \pm 69.8$ , and  $136.7 \pm 72.1$ . In comparison with group 1, the *P* values for groups 2–5 were, respectively, 0.052, 0.002, 0.003, and 0.398.

GLs were significantly higher among patients who died in hospital compared with survivors in all age-groups. Moreover, the mean difference in GL between deceased and survivors was larger in the youngest population when compared with the eldest population ( $65.6 \pm 16.2$  vs.  $22.9 \pm 11.1$  mg/dL, *P* < 0.001). The adjusted *t* ratios (*P* values) for groups 1–5 in the first model (only baseline variables) were, respectively, 2.96 (*P* = 0.003), 4.47 (*P* < 0.001), 2.04 (*P* = 0.042), 3.48 (*P* < 0.001), and 1.85 (*P* = 0.064); for the second model (baseline variables + in-hospital interventions), the respective figures were 2.71 (*P* = 0.007), 4.47 (*P* = 0.007), 2.04 (*P* = 0.042), 3.48 (*P* < 0.001), and 1.85 (*P* = 0.064).

By univariate analyses, the odds ratios (*P* values) for in-hospital mortality in patients with hyperglycemia were the following for groups 1–5: 7.22 (*P* = 0.001), 3.17 (*P* = 0.038), 3.15 (*P* = 0.003), 3.31 (*P* < 0.001), and 2.07 (*P* = 0.021), respectively. In the first adjusted model (baseline variables), the respective group figures were 6.93 (*P* = 0.004), 3.21 (*P* = 0.046), 3.42 (*P* = 0.004), 3.20 (*P* < 0.001), and 2.25 (*P* = 0.013). In the second adjusted model (baseline + in-hospital variables), the figures were 7.57 (*P* = 0.004), 3.21 (*P* = 0.046), 3.50 (*P* = 0.003), 3.20 (*P* < 0.001), and 2.16 (*P* = 0.021), respectively.

The results of the area under the ROC curves (AUCs) are depicted in Table 1,

with best results obtained for the youngest population (AUC = 0.785) and the lowest AUC in the eldest population (AUC = 0.613).

**DISCUSSION**—The main finding of our study is the observation that hyperglycemia in patients with AMI is a better predictor for mortality in younger patients than in the elderly population. The increased mortality related to hyperglycemia in AMI patients has been linked to different pathophysiologic mechanisms (6–8), such as increased oxidative stress, inflammation, and activation of stress-responsive kinases. Moreover, hyperglycemia is strongly correlated with impaired coronary flow before reperfusion and has been associated with enhanced thrombin formation, platelet activation, and fibrin clot resistance to lysis. In addition, hyperglycemia has been linked to increased sensitivity to ischemia-reperfusion injury (9,10). Since the individual response to these processes (among others) varies with age, this could explain, at least in part, our results.

Another explanation for our findings (not exclusive of the previous) relates to the importance of age itself as a risk factor for mortality. Since advanced age is a strong independent risk factor for mortality in patients with AMI, hyperglycemia may have a relatively greater importance in younger populations and a weaker impact in the elderly population.

#### Clinical implications

There have been conflicting results regarding the clinical benefit of intensive glucose control in AMI patients (11–13). Several possible explanations for the lack of consistent benefit with intensive glucose management have been proposed, but the leading hypothesis is that it leads to a higher incidence of hypoglycemia,

which is quite deleterious in AMI patients (14). Our results add another nuance to this debate: intensive glucose control may have different effects depending on the age of the patient.

**CONCLUSIONS**—The value of hyperglycemia as a risk factor for in-hospital mortality in patients with AMI is not homogeneous, with a greater relative impact on mortality in the younger population. This finding may have clinical implications regarding the therapeutic approach to hyperglycemia in patients with AMI (15).

**Acknowledgments**—No potential conflicts of interest relevant to this article were reported.

J.C.N. contributed to every aspect of the manuscript and is responsible for the contents of the article. C.V.S., R.R.G., L.M.B., H.G.M., F.L., M.F., R.K., and J.A.F.R. contributed to discussion and critical revision of the manuscript for important intellectual content. R.P.G. contributed to every aspect of the manuscript.

The authors are indebted to Ms. Deborah Gurski (Thrombolysis in Myocardial Infarction [TIMI] Study Group, Brigham and Women's Hospital) for her assistance during the preparation of the manuscript.

#### References

- Falciglia M, Freyberg RW, Almenoff PL, D'Alessio DA, Render ML. Hyperglycemia-related mortality in critically ill patients varies with admission diagnosis. *Crit Care Med* 2009;37:3001–3009
- Capes SE, Hunt D, Malmberg K, Gerstein HC. Stress hyperglycaemia and increased risk of death after myocardial infarction in patients with and without diabetes: a systematic overview. *Lancet* 2000;355:773–778
- Goyal A, Mahaffey KW, Garg J, et al. Prognostic significance of the change in glucose level in the first 24 h after acute myocardial infarction: results from the CARDINAL study. *Eur Heart J* 2006;27:1289–1297
- Nicolau JC, Maia LN, Vítola J, et al. ST-segment resolution and late (6-month) left ventricular remodeling after acute myocardial infarction. *Am J Cardiol* 2003;91:451–453
- Kosiborod M, Rathore SS, Inzucchi SE, et al. Admission glucose and mortality in elderly patients hospitalized with acute myocardial infarction: implications for patients with and without recognized diabetes. *Circulation* 2005;111:3078–3086
- Deedwania P, Kosiborod M, Barrett E, et al.; American Heart Association Diabetes Committee of the Council on Nutrition, Physical Activity, and Metabolism. Hyperglycemia and acute coronary syndrome: a scientific

**Table 1—ROC curves according to analyzed age-groups**

Age-group (years)	AUC	95% CI	<i>P</i> value
Global	0.655	0.617–0.693	<0.001
<50*	0.785	0.697–0.873	<0.001
≥50 and <60	0.709	0.551–0.867	0.004
≥60 and <70	0.657	0.576–0.738	0.002
≥70 and <80	0.648	0.585–0.710	<0.001
≥80	0.613	0.525–0.701	0.012

The AUC revealed a close relationship between age and predictive value of GLs for in-hospital mortality. The AUC for the global population was 0.655, and once again the best result was obtained for the youngest population (AUC = 0.785); in a descending way among the groups, the least predictive result was obtained for the oldest population. \**P* = 0.035 vs. aged 60–69; *P* = 0.013 vs. aged 70–79; *P* = 0.007 vs. aged >80; other comparisons statistically nonsignificant.

- statement from the American Heart Association Diabetes Committee of the Council on Nutrition, Physical Activity, and Metabolism. *Circulation* 2008;117:1610–1619
7. Ray KK, Cannon CP, Morrow DA, et al. Synergistic relationship between hyperglycaemia and inflammation with respect to clinical outcomes in non-ST-elevation acute coronary syndromes: analyses from OPUS-TIMI 16 and TACTICS-TIMI 18. *Eur Heart J* 2007;28:806–813
  8. Pesaro AE, Nicolau JC, Serrano CV Jr, et al. Influence of leukocytes and glycemia on the prognosis of patients with acute myocardial infarction. *Arq Bras Cardiol* 2009;92:84–93
  9. Timmer JR, Ottervanger JP, de Boer MJ, et al.; Zwolle Myocardial Infarction Study Group. Hyperglycemia is an important predictor of impaired coronary flow before reperfusion therapy in ST-segment elevation myocardial infarction. *J Am Coll Cardiol* 2005;45:999–1002
  10. Undas A, Wiek I, Stępien E, Zmudka K, Tracz W. Hyperglycemia is associated with enhanced thrombin formation, platelet activation, and fibrin clot resistance to lysis in patients with acute coronary syndrome. *Diabetes Care* 2008;31:1590–1595
  11. Malmberg K. Prospective randomised study of intensive insulin treatment on long term survival after acute myocardial infarction in patients with diabetes mellitus. DIGAMI (Diabetes Mellitus, Insulin Glucose Infusion in Acute Myocardial Infarction) Study Group. *BMJ* 1997;314:1512–1515
  12. Malmberg K, Rydén L, Wedel H, et al.; DIGAMI 2 Investigators. Intense metabolic control by means of insulin in patients with diabetes mellitus and acute myocardial infarction (DIGAMI 2): effects on mortality and morbidity. *Eur Heart J* 2005;26:650–661
  13. Marfella R, Di Filippo C, Portoghese M, et al. Tight glycaemic control reduces heart inflammation and remodeling during acute myocardial infarction in hyperglycemic patients. *J Am Coll Cardiol* 2009;53:1425–1436
  14. Svensson AM, McGuire DK, Abrahamsson P, Dellborg M. Association between hyper- and hypoglycaemia and 2 year all-cause mortality risk in diabetic patients with acute coronary events. *Eur Heart J* 2005;26:1255–1261
  15. Qaseem A, Humphrey LL, Chou R, Snow V, Shekelle P; Clinical Guidelines Committee of the American College of Physicians. Use of intensive insulin therapy for the management of glycemic control in hospitalized patients: a clinical practice guideline from the American College of Physicians. *Ann Intern Med* 2011;154:260–267