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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. Sposito[1]

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

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Moura FA, Carvalho LS, Cintra RM, Martins NV, Figueiredo VN, Quinaglie 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 ≥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 (ISi_{clamp}) 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 ISi_{clamp} 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.

homeostatic model assessment; insulin sensitivity; euglycemic hyperinsulinemic clamp; myocardial infarction

ELEVATION OF PLASMA 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 demonstrates 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 (HbA_{1c}) ≥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 HbA_{1c} (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

All authors contributed on behalf of The Brasilia Heart Study.

Address for reprint requests and other correspondence: A. C. Sposito, Cardiology Division, Faculty of Medical Sciences, State Univ. of Campinas, 13084-971, Campinas, Sao Paulo, Brazil (e-mail: andreisposito@gmail.com).

Table 1. *Clinical and treatment characteristics of study subjects*

Subject Characteristics	
n	31
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)
ISi_{clamp} D2	2.18 (1.68)
ISi_{clamp} D6*	2.20 (1.70)
HOMA2S D2	84.30 (105.50)
HOMA2S D6*	97.25 (90.28)
HOMA-IR D2	1.86 (2.44)
HOMA-IR D6*	1.51 (2.00)
QUICKI D2	0.3462 (0.07)
QUICKI D6*	0.3543 (0.06)
BMI, kg/m^2	25.8 ± 3
Waist circumference, cm	94.4 ± 7
DM history or Hb_{A1c} >6.5%	0
Hb_{A1c}, %	5.42 ± 0.5
Hypertension history, %	48
Prior MI or stroke, %	8
CHD family histoty, %	71
Dyslipidemia, %	15
Sedentarity, %	48
Smoking habit, %	55
SBP, mmHg	145 ± 28
DBP, mmHg	91 ± 12
GFR, $ml \cdot kg^{-1} \cdot h^{-1}$	71.8 ± 12
Admission LDL-C, mg/dl	124 ± 30
Admission HDL-C, mg/dl	33.4 ± 6
Admission triglycerides, mg/dl	152 ± 85
Admission glucose, mg/dl	120 ± 18
CRP, mg/dl	
Admission	0.76 ± 0.6
5th day	6.25 ± 3.5
Delta	5.43 ± 3.8
Killip-Kimbal class I, %	100
Chemical thrombolysis, %	74
Primary PCI, %	12
β-Blocker use, %	71
Simvastatin use, %	100
Simvastatin dose, mg/day	40 ± 20

n, No. of subjects; D2, *day 2*; D6, *day 6*; ISi_{clamp}, insulin sensitivity index measured by euglycemic-hyperinsulinemic clamp; HOMA2S, homeostatic model assessment for insulin sensitivity; HOMA-IR, homeostatic model assessment for insulin resistance; QUICKI, quantitative insulin sensitivity check index; BMI, body mass index; DM, diabetes mellitus; Hb_{A1c}, glycosilated hemoglobin; MI, myocardial infarction; SBP, systolic blood pressure; DBP, diastolic blood pressure; GFR, glomerular filtration rate; LDL-C, low-density lipoprotein-cholesterol; HDL-C, high-density lipoprotein-cholesterol; CRP, C-reactive protein; CKMB, creatine kinase-MB; PCI, percutaneous coronary intervention; CHD, coronary heart disease. *Measures performed for 25 patients.

insulin sensitivity (HOMA2S), and quantitative insulin sensitivity check index (QUICKI). These indexes were calculated from a single sample of fasting levels of glucose and insulin that was collected immediately before initiation of EHC. HOMA2S was calculated with HOMA2 calculator version 2.2 (11). The other two values were calculated as follows: HOMA-IR = (I × G)/22.5, where I is fasting insulin (μU/ml) and G is fasting glucose (mg/dl); and QUICKI = 1/[log(I) + log(G)], where insulin is expressed as microunits per milliliter and glucose is expressed as millimole per liter (9, 12).

Euglycemic-hyperinsulinemic clamps. EHCs were performed at 0700 on D2 ($n = 31$) and D6 ($n = 25$) post-STEMI. Of the 31 initial patients, the second (D6) EHC was not performed in six patients (three because of MI complications and three refused to perform a second clamp). After a 12-h overnight fast, subjects were placed in a recumbent position in an adjustable bed. An intravenous cannula was inserted in an antecubital vein that was maintained by a slow saline drip, and the arm was heated to 50°C to arterialize the blood. A second cannula was inserted in an antecubital vein of the contralateral arm for infusion of insulin and glucose. After an equilibration period of 30 min, basal samples were collected for determination of plasma glucose and insulin concentrations. EHCs were then performed by infusing insulin (Novolin R; Novo-Nordisk, Bagsvaerd, Denmark) for 180 min at a rate of 7 $pmol \cdot kg^{-1} \cdot min^{-1}$. Euglycemia (~100 mg/dl) was maintained with a variable-rate infusion of 50% glucose. Blood glucose levels were measured at 10-min intervals; glucose infusion rates were adjusted as needed. The EHC-derived index of insulin sensitivity (ISi_{Clamp}) was calculated using the equation $ISi_{Clamp} = M/(G \times \Delta I)$, corrected for body weight, where M is the mean steady-state glucose infusion rate ($mg \cdot kg^{-1} \cdot min^{-1}$), G is the steady-state blood glucose concentration (mg/dl), and ΔI is the difference between basal and steady-state plasma insulin concentration (μU/ml). The ISi_{Clamp} was defined as the decrease in fractional glucose per unit increase in plasma insulin, i.e., insulin action (independent of both glucose and insulin levels) (5, 9). Upon termination of the procedure, serum potassium levels were measured as to assess for the potential need of replacement.

Statistical methods. Parametric data were expressed as means ± SE and nonparametric data as median (interquartile range). Spearman's rank correlation test was used for comparative analysis between surrogate indexes and ISi_{clamp}. Comparison of correlations was made using the method reported by Zar (17). Diagnostic performance for the panel of surrogate indexes in determining ISi_{clamp} above or below the median was assessed using the area under the curve (10) of receiver operator characteristic (ROC) curves. To be able to construct Bland-Altman plots, surrogate index results were converted to ISi_{clamp}-equivalent units of measurement. To do so, we determined the best-fit curve and applied the respective equation for the surrogate indexes as to predict ISi_{clamp}. A two-sided *P* value of 0.05 was considered statistically significant. Statistical analyses were performed using SPSS for Mac version 20.0. The authors had full access to the data, take responsibility for its integrity, and agree to the manuscript as written.

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 ISi_{clamp} at D2 and D6 after myocardial infarction*

Surrogate Indexes	*r*	*P* Value	AUC
HOMA2S D2	0.485	0.009	0.781
HOMA2S D6	0.621	0.002	0.727
HOMA2S D2 and D6	0.505	<0.001	0.740
HOMA-IR D2	−0.384	0.048	0.772
HOMA-IR D6	−0.576	0.006	0.683
HOMA-IR D2 and D6	−0.456	0.001	0.734
QUICKI D2	0.479	0.01	0.791
QUICKI D6	0.626	0.002	0.712
QUICKI D2 and D6	0.524	<0.001	0.760

ROC, receiver operator characteristic; AUC, area under the curve.

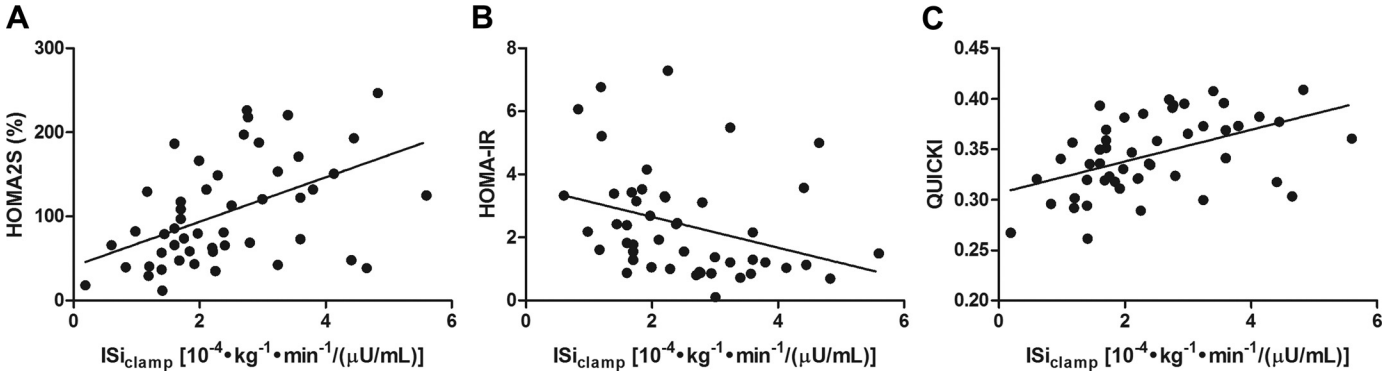

Fig. 1. Correlations between surrogate indexes and euglycemic-hyperinsulinemic clamp. Scatterplots depicting homeostatic model assessment for insulin sensitivity (HOMA2S) vs. the insulin sensitivity index measured by euglycemic-hyperinsulinemic clamp (ISi_{clamp}) (*A*), homeostatic model assessment for insulin resistance (HOMA-IR) vs. ISi_{clamp} (*B*), and quantitative insulin sensitivity check index (QUICKI) vs. ISi_{clamp} (*C*).

five percent of patients participating in the study were male, with a mean age of 56 ± 8. Clinical and metabolic characteristics of patients are summarized in Table 1. As shown in Table 2, ISi_{clamp} was correlated to HOMA2S, HOMA-IR, and QUICKI both at D2 and D6. In combining measurements obtained in D2 and D6 ($n = 56$), all indexes remained significantly correlated with ISi_{clamp}. Scatterplots of ISi_{clamp} vs. the surrogate indexes are displayed on Fig. 1. No significant differences between correlation coefficients were noted.

To test the predictive power of the surrogate indexes, ROC curves were constructed for discrimination of ISi_{clamp} above the median in both D2 and D6 combined. The areas under the ROC curve for HOMA2S, HOMA-IR, and QUICKI are shown in Table 2. Combining D2 and D6 to increase statistical power, the use of HOMA2S, HOMA-IR, and QUICKI to identify individuals with ISi_{clamp} values above the median obtained a sensitivity of 68, 67, and 65% (respectively) and a specificity of 83, 82, and 84% (respectively) at the best cut-off point of the curve. Also shown in Table 1, the median values of ISi_{clamp} and surrogate indexes suggest a tendency toward an IS increase in D6. Intraindividual change of IS from D2 to D6 was concomitant between EHC and surrogate indexes in 60, 53, and 40% for HOMA2S, HOMA-IR, and QUICKI methods, respectively.

The best-fit model for the data was a power model that predicted ISi_{clamp} from HOMA2S, HOMA-IR, and QUICKI. The conversion formulas were similar between D2 and D6 for HOMA2S ($0.299 \times HOMA2S^{0,442}$ vs. $0.241 \times HOMA2S^{0.491}$, respectively), HOMA-IR ($2.608 \times HOMA\text{-}IR^{-0,191}$ vs. $2.963 \times HOMA\text{-}IR^{-0.311}$, respectively), and QUICKI ($51.737 \times QUICKI^{2.964}$ vs. $49.877 \times QUICKI^{2.965}$, respectively). Because the D2 and D6 transformations were similar, we decided to combine them and use the resulting transformation formula (Table 3) on account that it would be based on a larger number of clamps and thus more representative.

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 ISi_{clamp} 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 ISi_{clamp} 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 ISi_{clamp} and surrogate indexes*

	Measure of Insulin Sensitivity				Median Difference (IQR)			Transformation Formulas		
	Observed	Predicted (HOMA2S)	Predicted (HOMA-IR)	Predicted (QUICKI)	HOMA2S	HOMA-IR	QUICKI	HOMA2S	HOMA-IR	QUICKI
ISi_{clamp}	2.21 (1.64)	2.12 (0.94)	2.30 (0.70)	2.11 (1.0)	0.05 (1.37)	0.01 (1.36)	0.04 (1.51)	$0.270 \times HOMA2S^{0.464}$	$2.697 \times HOMA\text{-}IR^{-0.263}$	$49.149 \times QUICKI^{2.932}$

Observed and predicted values are expressed as median (interquartile range). The unit used for insulin sensitivity is $10^{-4} \times kg^{-1} \times min^{-1}/(\mu U/ml)$.

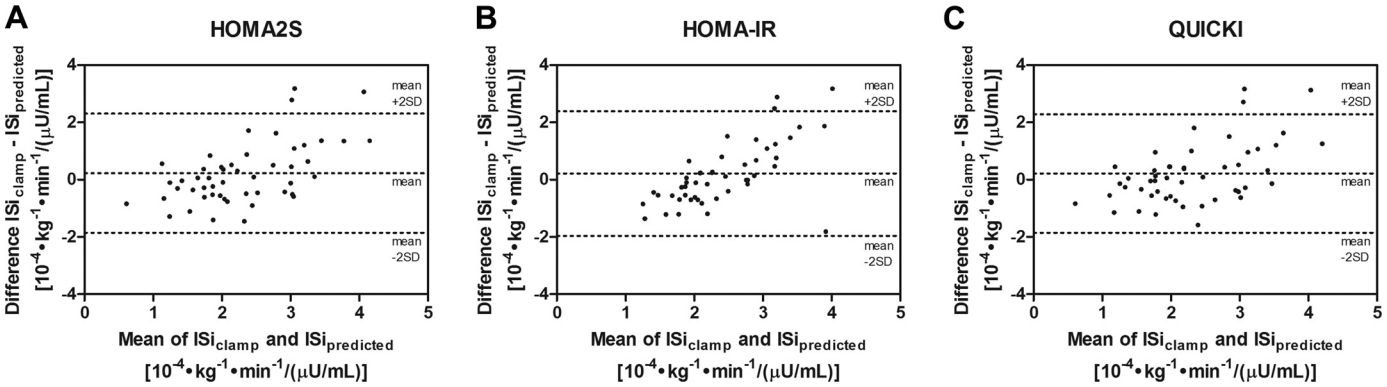

Fig. 2. Consistency between insulin sensitivity obtained by euglycemic-hyperinsulinemic clamp and surrogate indexes in acute phase of myocardial infarction. Bland-Altman plots depicting the agreement between ISi_{clamp} and the surrogate indexes HOMA2S; $\beta = 0.591$ ($P < 0.001$) (*A*), HOMA-IR, $\beta = 0.687$ ($P < 0.001$) (*B*), and QUICKI; $\beta = 0.551$ ($P < 0.001$) (*C*). ISi_{clamp} and predicted ISi_{clamp} ($ISi_{predicted}$) were measured during the euglycemic-hyperinsulinemic clamp and calculated using surrogate index values for IS by the transformation equations.

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 modified version of the QUICKI index, which adjusts for fasting nonesterified fatty acid concentration because heparin infusion, a standard procedure in MI, increases intravascular lipolysis and may misrepresent its value (3).

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.

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DISCLOSURES

The authors declare that they have nothing to disclose.

AUTHOR CONTRIBUTIONS

Author contributions: F.A.M., L.S.F.C., R.M.C., O.L.R.A., O.R.C., and A.C.S. conception and design of research; F.A.M., L.S.F.C., R.M.C., N.V.M., and J.C.Q.e.S. performed experiments; F.A.M., L.S.F.C., V.N.F., and A.C.S. analyzed data; F.A.M., R.M.C., N.V.M., V.N.F., J.C.Q.e.S., O.L.R.A., O.R.C., and A.C.S. interpreted results of experiments; F.A.M. and L.S.F.C. drafted manuscript; F.A.M., L.S.F.C., R.M.C., N.V.M., V.N.F., J.C.Q.e.S., O.L.R.A., O.R.C., and A.C.S. edited and revised manuscript; F.A.M., L.S.F.C., R.M.C., N.V.M., V.N.F., J.C.Q.e.S., O.L.R.A., O.R.C., and A.C.S. approved final version of manuscript; V.N.F. prepared figures.

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