

## Homocysteine and Coronary Artery Disease

### To the Editor:

We read with great interest the article entitled «Total Concentrations of Plasma Homocysteine in Puerto Rican Patients With Ischemic Heart Disease» by Rodrigo et al.<sup>1</sup> published in the December issue of the REVISTA. Given the enormous pervasiveness of the subject, we would like to make some comments.

Firstly, in the Introduction, the authors comment that in Spain studies of ischemic heart disease have been focused more on the theory of the increase in cholesterol, and that there are no studies of homocysteine values in this population. There is a Spanish study<sup>2</sup> on this topic that reported that 26% of patients with heart disease proved to have hyperhomocysteinemia.

Secondly, the authors did not determine vitamin B<sub>6</sub>, B<sub>12</sub>, and folic acid values in cases in which deficits thereof could be a nutritional cause of hyperhomocysteinemia. It has been suggested that

approximately 60% of hyperhomocysteinemia is due to inadequate levels of 1 or more of these vitamins in the blood.<sup>3</sup> Similarly, they did not comment on the dietary habits and condition of the study population, and this is probably why there was no finding of an association between heart disease and homocysteine concentration as a side effect of long- and short-term dietary variations.<sup>4</sup> Various retrospective and prospective studies have shown the possibility that a load test would improve the ability of a fasting homocysteine measurement.<sup>5</sup> to predict the risk of heart disease.

Thirdly, the results are expressed in an unclear manner. In Table 2, the distribution of homocysteine is grouped by age, sex, smoking habits, diabetes and arterial hypertension. The authors express homocysteine concentrations for the entire population, instead of placing them in 2 categories—those with normal coronary arteries (n=10) and those that had some degree of occlusion (n=60). In Table 3, which lists the univariate and multivariate models for the different parameters that can accelerate artery occlusion, we would like to note that recent studies have concluded that using logic regression analysis in the context of small samples requires the use of exact tests (for example, the Cytel software statistical program<sup>6</sup>). The exact test, as is well known, decreases type 1 errors associated with the conflicting theories such as those described in the study. Especially when multivariate models are used in clinical studies, the precaution must be taken to maintain a balance between the number of predictors and the number of patients in the sample. In this study, there are 70 patients with a preliminary diagnosis of heart disease with only 10 in the control group (normal coronary arteries) making it impossible to use more than 1 or 2 variables at the most in prediction for or classification of the patients.

Fourthly, the sample size that the authors present is 60 patients (all with some degree of arterial occlusion) and 10 controls (normal coronary arteries). It is well known that it is complicated to determine with coronary angiography that controls are without ischemic heart disease; nevertheless, the control group might be amplified with patients who have a negative stress test. This contradicts the conclusions of the study since the impossibility of reaching conclusions is in the actual study design itself—it lacks sufficient statistical power.

Alberto Domínguez Rodríguez<sup>a</sup>,  
Pedro Abreu González<sup>b</sup>  
and Alejandro Jiménez Sosa<sup>c</sup>

<sup>a</sup>Servicio de Cardiología. Hospital Universitario de Canarias.

<sup>b</sup>Departamento de Fisiología. Universidad de La Laguna.

<sup>c</sup>Unidad de Investigación del Hospital Universitario de Canarias.

## BIBLIOGRAFÍA

1. Rodríguez JF, Escobales N, Cruz D, Banch H, Rivera C, Altieri PI. Concentraciones totales de homocisteína plasmática en pacientes puertorriqueños con cardiopatía isquémica. *Rev Esp Cardiol* 2001;54:1411-6.
2. Fernández-Miranda C, Aranda JL, Gómez González P, Díaz-Rubio P, Estenez J, Gómez de la Cámara A. La hiperhomocisteinemia es frecuente en pacientes con enfermedad coronaria. Estudio de 202 enfermos. *Med Clin (Barc)* 1999;113:407-10.
3. Selhub J, Jacques PF, Wilson PW, Rush D, Rosenberg IH. Vitamin status and intake as primary determinants of homocysteinaemia in an elderly population. *JAMA* 1993;270:2693-8.
4. Guttormsen AB, Scheede J, Fiskerstrand T, Ueland PM, Refsum HM. Plasma concentrations of homocysteine and other aminothiol compounds are related to food intake in healthy human subjects. *J Nutr* 1994;124:1934-41.
5. Bostom AG, Jacques PF, Nadeau MR, Williams RR, Ellison RC, Selhub J. Post-methionine load hyperhomocysteinemia in persons with normal fasting total plasma homocysteine: initial results from the NHLBI Family Heart Study. *Atherosclerosis* 1995;116:147-51.
6. Metha CR, Patel NR, Jajoo B. Exact logistic regression: theory, methods, and software. Cytel Software Corporation Technical Report. Massachusetts, 1993.

## Response

### To the Editor:

We appreciate the interest of our colleagues in the Canary Islands in the article presented by our group in Puerto Rico regarding the contentious subject of homocysteine plasma levels and heart disease. The study we are performing at the Puerto Rico and Caribbean Cardiovascular Center is still in process and results in the article were the preliminary analyses of the patients on whom we had complete data. At the time of writing this reply, we have accumulated data on a total of 155 patients, of which 19 are controls who have no ischemic cardiopathy. The results in these additional patients have in no way altered the values or trends discussed in our original article. We saw no correlation between homocysteine plasma values and the progressive categories and coronary angiography results. We are still recruiting patients for the study and hope to publish findings on a larger group of patients in the near future. Results for vitamin B<sub>6</sub>, B<sub>12</sub>, and folic acid levels are being obtained at this time and will also be published in the near future, as was the case in our recently published study on a colony of Rhesus monkeys (*Mucaca mulatta*).<sup>1</sup> We regret that we did not identify the homocysteine studies performed in Spain, but we limited our search to the REVISTA ESPAÑOLA DE CARDIOLOGÍA, where we could not find a single published article. We would like to comment, nevertheless, that in the study by Fernández-Miranda et al,<sup>2</sup> there was a difference in homocysteine plasma values between patients with coronary disease and the control group (11.7 μM vs 8.4 μM; *P*<.001). It should

be noted that the homocysteine plasma concentrations in the controls in the study are much lower than those reported in other studies around the world.<sup>3</sup> It is of note that in studies in which homocysteine plasma concentrations and coronary angiography have been performed in control groups, no correlation has been found between hyperhomocysteinemia and ischemic heart disease.<sup>4</sup> More notable still is that prospective studies have shown no such relationship. We understand that the problem of ischemic cardiopathy is multivariate and complex, and the relationship between factors is more important than a single isolated factor.

José F. Rodríguez<sup>a,b</sup>, Nelson Escobales<sup>b,c</sup>,  
Damaris Cruz<sup>d</sup>, Héctor Banch<sup>e,f</sup>, Cynthia  
Rivera<sup>g</sup> and Pablo I. Altieri<sup>b,c,e,g</sup>

<sup>a</sup>Departamento de Bioquímica, <sup>b</sup>Unidad de Biología Cardiovascular, <sup>c</sup>Departamento de Fisiología y <sup>d</sup>Departamento de Medicina. Escuela de Medicina. Universidad de Puerto Rico. <sup>e</sup>Departamento de Biología. Facultad de Ciencias Naturales. Universidad de Puerto Rico. <sup>f</sup>Centro Cardiovascular de Puerto Rico y el Caribe, <sup>g</sup>Departamento de Bioestadísticas, Centro de Investigaciones Clínicas-RCMI, Recinto de Ciencias Médicas. Universidad de Puerto Rico.

## BIBLIOGRAFÍA

1. Preston AM, Bercovitch FB, Jiménez BD, Rodríguez JF, Delgado-Morales W, Rodríguez CA, et al. Plasma homocysteine concentrations in a population of Rhesus Monkeys (*Macaca mulatta*): Reference ranges and accompanying plasma concentrations of folate and vitamin B<sub>12</sub>. *Contemporary Topics* 2002;41(1): 28-30.
2. Fernández-Miranda C, Aranda JL, Gómez González P, Díaz-Rubio P, Estenoz J, Gómez de la Cámara A. La hiperhomocisteinemia es frecuente en pacientes con enfermedad coronaria. Estudio de 202 enfermos. *Med Clin (Barc)* 1999;113:407-10.
3. Rodríguez JF, Escobales N, Cruz D, Banch H, Rivera C, Altieri PI. Concentraciones totales de homocisteína plasmática en pacientes puertorriqueños con cardiopatía isquémica. *Rev Esp Cardiol* 2001;54:1411-6.
4. Donner M, Klein G, Mathes P, Schwandt P, Richter W. Plasma total homocysteine levels in patients with early-onset coronary heart disease and a low cardiovascular risk profile. *Metabolism* 1998;47:273-9.