Thus, EAT seems to be associated not only with atherosclerotic burden and risk of cardiovascular disease, but also with maladaptive changes in myocardial function that increase the risk of heart failure. It is our opinion that ectopic adipose tissue, with special emphasis on EAT, greatly contribute to metabolic homeostasis and modulate activation of inflammatory cascades, therefore being a key player in cardiovascular health and disease.

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Relaxin Concentrations in Acute Heart Failure Patients

Concentración de relaxina en pacientes con insuficiencia cardiaca aguda

To the Editor,

I have read the article entitled, "Relaxin Concentrations in Acute Heart Failure Patients: Kinetics and Clinical Determinants", that appeared in *Revista Española de Cardiología.*[1] This article reports the measurement of serum relaxin in patients with acute heart failure.

I note that the authors used a commercial enzyme-linked immunoassay kit from Immundiagnostik, reporting that this is a validated assay for measuring serum relaxin. However, this assay has not been properly validated for serum relaxin, neither by the authors nor the manufacturer of the assay. No assurance has been given that serum samples dilute in parallel with authentic H2 standards. Specificity for H2 relaxin and cross-reactivity for possible interfering molecules has not been provided by the authors or the manufacturer. The sole exception is that the manufacturer reports that insulin does not interfere but no details are provided on the insulin doses tested. Although it is true that others have reported results using this assay, they also failed to report any assay validation. Because this assay relies on polyclonal antibodies, assay validation needs to be rigorous; however, it is completely absent. Thus, no valid conclusions can be drawn from the data presented in this article. The authors could have used a commercially available assay for serum relaxin that has been validated for clinical studies.[2–4]

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Relaxin Concentrations in Acute Heart Failure Patients. Response

Concentración de relaxina en pacientes con insuficiencia cardiaca aguda. Respuesta

To the Editor,

We would like to thank Dr. Stewart for his constructive contribution to the discussion of our study findings with the suggestion that failure to find a clinical determinant for of circulating relaxin concentrations in patients with acute cardiac failure could be due to the commercial assay used (Inmunodiagnostik; Bensheim, Germany).[1] Several points, however, suggest that this assay is appropriate. First, this is the most sensitive assay

on the market and the most widely used in clinical trials.[1,2] Our study had quality levels (quartile 1, 19.12; quartile 2, 108.2) within those given in the technical specifications (maximum values: quartile 1, 20.7; quartile 2, 108.5). Second, as a quality control measure, relaxin was measured in 2 women in week 12 of pregnancy, and elevated concentrations were found (351 and 402 pg/mL), that is, much higher concentrations than those found in patients with acute cardiac failure (median, 14.3 pg/mL). This is also in agreement with other studies in pregnant women (586 [295] pg/mL).[3] Finally, the assay suggested by Dr. Stewart (R&D Systems; Minneapolis, United States) has not been used in publications for measuring endogenous hormone levels; the references are pharmacodynamic studies that measure the concentration of recombinant serelaxin after intravenous infusion, reaching concentrations of the order of ng/mL, that is, higher than endogenous concentrations of the order of pg/mL. When we were designing our study, we performed tests on some samples with the proposed alternative assay, without detection of endogenous relaxin concentrations. We attributed this observation to the lower sensitivity of the alternative assay. Therefore, although we support the immunoanalysis used in our study, we cannot rule out the hypothesis put forward by Dr. Stewart that other molecules may interfere in the measurement of endogenous relaxin. These scientific letters should therefore serve to highlight the need for further studies to clarify these questions, as well as the role of endogenous relaxin in heart failure, as also indicated in our original article.

CONFLICTS OF INTEREST

D. Pascual-Figal has received speaker's fees and a research grant from Novartis, unrelated to the present study.

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Liver Imaging in Patients With Fontan Circulation

Imagen hepática de pacientes con cirugía de Fontan

To the Editor,

We read the article published by Martín-Garre[1] with interest. However, in the light of that reading, we would like to make a few comments that we believe to be important.

The Fontan procedure has been of particular benefit to infants with functional single-ventricle complexes but an inevitable consequence is systemic venous hypertension. Hepatic histology of patients with Fontan circulation usually begins with sinusoidal dilatation, parenchymal atrophy, and progressive fibrosis secondary to repetitive mechanical stretch due to persistent chronic passive venous congestion and limited cardiac output, which favors tissue hypoxia. Hepatocarcinogenesis forms part of the continuum of dedifferentiation that includes hypervascular nodules, regenerative nodules, dysplastic nodules, and hepatocellular carcinoma (HCC). Although ultrasound (US) remains inexpensive and is recommended as the first choice for the screening and surveillance of HCC by the guidelines of almost all international societies, Fontan patients have some peculiarities that must be taken into account.

First, US imaging findings in long-standing Fontan patients may be characterized by hepatomegaly, hepatic vein and suprahepatic inferior vena cava dilation, surface nodularity, increased parenchymal echogenicity, and HCC, which is usually a nodule greater than 1 cm in diameter. The classic US findings of HCC include hypoechoic nodules or mixed echogenic nodules due to tumor necrosis or fatty metamorphosis or a surrounding thin hypoechoic band indicating a capsule that is characteristic of these tumors.[2] In addition, as mentioned by Martín-Garre, the form of presentation of HCC may vary (multiplicity of nodules, small sized nodules, and "nodules within nodules").

Second, standard US can assess nodularity with variable accuracy (the sensitivity and specificity for HCC diagnosis are 60% and 93%, respectively, and are even poorer for HCC less than 1 cm). Doppler US may be used to assess portal vein flow and the presence of collateral vessels suggesting portal hypertension. In addition, color Doppler flow imaging may show hypervascularity and tumor vascular shunting. Nonetheless, both nodularity and portal flow changes are late findings and are not therefore helpful in detecting signs of early hepatic compromise,[3] which is of particular importance due to the significant impact of even mild liver disease on the outcome of cardiac surgery. Similarly, contrast-enhanced US may improve the detection of cirrhosis and may reflect the real-time dynamics of blood supply of the lesion, which is helpful in both the detection and characterization of HCCs, but again does not accurately distinguish earlier stages of fibrosis.

Third, US may be adequate for screening cirrhosis in general but is not the preferred option in Fontan patients due to the high incidence of nonmalignant vascular lesions. In fact, the presence of arterialized nodules in Fontan patients is relatively frequent and, although these nodules are benign and pathologically identifiable as focal nodular hyperplasia, they can be confused with HCC, which is increasingly reported even in the absence of frank cirrhosis.[4]

Finally, although there are no data on the precise incidence of HCC, the fact that most Fontan patients have structural hepatic