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

derangements at the initiation of screening confirms that we are initiating imaging too late. Therefore, periodic imaging should be started in childhood or early adolescence.[5] The ideal screening test is gadolinium-enhanced magnetic resonance imaging (with a sensitivity and a specificity of 91% and 95%, respectively, to detect HCC)[2] at intervals of 3 to 4 years. In patients with contraindications to magnetic resonance, a computed tomography scan may be performed, although the risk of radiation exposure must be considered. Meanwhile, liver stiffness estimated by US and magnetic resonance elastography techniques may be used as a quantitative imaging biomarker for the detection, staging, characterization, and monitoring of liver fibrosis. However, the use of elastography in Fontan-associated liver disease is problematic because any altered hepatic stiffness beyond fibrosis, particularly the vascular congestion universally present in Fontan patients, may have an impact on the results.

For all these reasons, some authors recommend that patients with a Fontan procedure performed more than 10 years previously should undergo cardiac assessment, liver imaging, and even liver biopsy[4] to stay ahead of neoplastic transformation. Even after heart transplant, patients who have undergone the Fontan procedure will require vigilant screening for HCC.

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Liver Imaging in Patients With Fontan Circulation. Response

Imagen hepática de pacientes con cirugía de Fontan. Respuesta

To the Editor,

Having read with interest the letter published by Martínez-Quintana et al. concerning my publication,[1] I would like to add some comments on liver imaging findings after Fontan surgery.

First, ultrasonography is the most commonly used imaging technique for initial and follow-up liver evaluation in these children, mainly due to the lack of radiation. Hepatic parenchymal changes after the procedure, known as Fontan-associated liver disease, include liver fibrosis and cirrhosis and hepatocellular carcinoma. Although ultrasonography usually detects late changes of fibrosis and cirrhosis (such as heterogeneous parenchymal echotexture or surface nodularity), recent publications show that other findings, such as hyperechoic lesions without surface nodularity detected by high frequency transducer, may represent the early stage of fibrosis.[2] These lesions were not demonstrated by computed tomography or magnetic resonance imaging and most patients (82%) showed normal biochemical hepatic function tests, despite the presence of hepatic parenchymal changes on imaging.[2]

Second, recent studies suggest that, considering that congestion is the primary or sole trigger of liver fibrosis in these patients, ultrasound elastography may eventually become a useful noninvasive, low-cost proxy assessment of Fontan hemodynamics and a clinical means of determining which patients are at highest risk of fibrosis development.[3] Moreover, magnetic resonance elastography might prove particularly useful to evaluate progression of liver disease and have important prognostic value.[4] Furthermore, some authors conclude that magnetic resonance elastography allows earlier detection of fibrogenesis than biomarkers.[5]

Finally, with regard to contrast computed tomography and magnetic resonance imaging, heterogeneous enhancement is a common finding in cirrhotic liver. Hypervascular liver nodules are an additional important finding in patients with longstanding Fontan circulation (20%-30%), also known as focal nodular hyperplasia-like lesions.[4] The main differential diagnosis of hypervascular nodules in a cirrhotic liver should be hepatocellular carcinoma but there are few reported cases of hepatocellular carcinoma in these patients.[4] In fact, according to a recent publication, there are only 11 case reports of hepatocellular carcinoma after the Fontan procedure in PubMed.[6]

In conclusion, although ultrasonography and laboratory screening at regular intervals should be the first-line tests in the long-term evaluation of these patients, elastography and contrast studies are useful tools that should also be considered in follow-up.

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