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Reply:

We read with interest the letter to the editor by Huang et al., who found only a 6.3% rate of increased anti-thyroid microsomal autoantibody levels in a retrospective series of 79 patients with chronic hepatitis C. However, patients with chronic HCV infection tended to have a higher prevalence of abnormal thyroid function tests than did "healthy" controls and patients with chronic HBV infection. The prevalence of autoimmune thyroid disorders in patients with chronic hepatitis C seems to be lower in Taiwan than in France (1; Pateron et al., *J Hepatol* 1993;17:417-419). Geographical heterogeneity, genetic influence or both in autoimmune disease among different populations have been demonstrated (2) and might explain these different findings.

In a recent study (3), we found more increased anti-Gor levels in anti-HCV-positive patients with ATA than in anti-HCV-positive patients without ATA. Gor antibodies distinct from anti-HCV are supposed to have dual specificities; they target both the presumed core gene product of HCV and a host nuclear component. This cross-recognition is probably derived from homologous regions between the Gor epitope and a viral epitope on the core protein in HCV. We therefore suggest that anti-Gor is an autoantibody induced by HCV infection (4). Thus an infectious agent (e.g., HCV) could

initiate autoimmune thyroid disease by mimicking the structure of some component of thyroid tissue, by altering thyroid antigens in some way to make them more immunogenic or by activating T cells independently of antigen (5). The association between ATA and HCV seems to be not fortuitous.

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Assessment of Central Blood Volume in Cirrhosis by Radionuclide Angiography: What Does It Really Mean?

To the Editor:

The pathogenesis of fluid retention and formation of ascites in cirrhosis is still unclear, but the size of the central vascular compartment — where volume receptors and baroreceptors are located — is apparently important. We recently provided evidence that central and arterial blood volume is reduced in such patients (1, 2). Wong et al. (3), however, reported in a recent issue of *HEPATOLOGY* that the central blood volume is increased as assessed on radionuclide angiography. We have serious reservations about their conclusion. First, we are concerned about the reliability and accuracy of their radionuclide method. Second, we find their observation

incompatible with several other physiological changes observed in these patients.

Wong et al. (3) determined end-diastolic and end-systolic left ventricular volumes, stroke volume and cardiac output by means of an ECG-gated gamma-camera technique after blood pool labeling with ^{99m}Tc-pertechnetate/stannous pyrophosphate. Reference counts of venous blood were performed for calculation of the ventricular volume according to the method of Links et al. (4). This is a well-established radionuclide technique, and we do agree on the reported accuracy of the left ventricular ejection fraction and the ventricular volume (5). With this method, Wong et al. (3) found the left ventricular volume to be normal in cirrhosis, a finding we can support from the results of a study in which magnetic resonance imaging was used (Møller S, et al., Unpublished observations). We found

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stroke volumes of 88 ± 5 ml and 81 ± 8 ml in controls and cirrhotic patients, respectively, values very similar to those recorded by Wong et al.

We are seriously concerned that Wong et al. extended the standard technique for determining ventricular volume to include blood volumes of the thorax (central blood volume [i.e., blood volume in lungs, heart, and central vascular bed]). They used a single anterior large-field-of-view gamma-camera image of the thorax and calculated the ratio of the pulmonary and central vascular blood volume to the ventricular volume on the basis of specific counts in each structure. The blood volumes of the thorax were then back-calculated from the ventricular volume determined by means of the ECG-gated standard technique. In fact, this procedure requires an up to 20-fold extrapolation maneuver to get from the blood volume of the left ventricle (end-systolic volume, 63 ml; end-diastolic volume, 161 ml) to the central blood volume (3,462 ml), a procedure that is very sensitive to even minor inaccuracies and heterogeneity of attenuation. According to the authors, "The pulmonary blood volume calculation required no further attenuation correction because the cardiac ventricles and pulmonary vasculature occupy the same image plane in the thorax." This is not correct. When the same attenuation correction is used for the thorax as a whole as for the left ventricle, major errors may arise (6). In this context, it should be recalled that the distance for 50% attenuation of ^{99m}Tc -labeled photons in tissue is only about 6 cm (4). Moreover, the references Wong et al. quote for pulmonary blood estimation (6-8) specifically stress that the radionuclide technique only provides an index of the *change* in pulmonary blood volume in the single subject or animal, not an *absolute* value.

Separation of thoracic from abdominal radioactivity may also be problematic. In patients with ascites, the liver and spleen are often dislocated toward the thorax. Because the radionuclide accumulates in blood in these organs, this may easily lead to overestimation of the central blood volume as determined with that radionuclide method. Wong et al. reported an average central blood volume of 3,295 ml in their patients with ascites. Although there is general agreement that patients with ascites exhibit an expanded total blood volume (9), a central blood volume of 3.3 L is rather unlikely: Because splanchnic and other noncentral vascular areas are known to be expanded in these patients, the total blood volume would amount to extremely high and somewhat unlikely values. Unfortunately, Wong et al. did not report values for total blood volume in their patients.

Thus the radionuclide method used by Wong et al. is not suitable for measurement of the central blood volume; it is very uncertain and upwardly biased. Accordingly, Dock et al. (10) and de Freitas et al. (11) found the normal pulmonary blood volume to be 246 to 310 ml/m² in contrast to the 412 ml/m² reported by Wong et al. Reliable and accurate values of central and pulmonary blood volumes rendered by radionuclide angiography require the combination of bolus and equilibrium techniques (12, 13).

Several findings in this study (3) argue against the authors' conclusion. Their patients with ascites had decreased systemic vascular resistance and increased heart rate and cardiac output, and they showed a trend toward increased plasma norepinephrine, renin activity and aldosterone levels. These findings are typical for a hyperdynamic circulation with central underfilling, as observed in many other reports in decompensated cirrhosis (1, 9, 14, 15). Furthermore, the authors have previously reported suppression of greatly increased plasma catecholamines and augmented natriuresis after implantation of a peritoneovenous shunt in ascitic patients (16). Because this procedure leads to central volume expansion, these findings indicate that salt and water retention are at least in part due to central vascular underfilling. It seems quite difficult to reconcile these results with Wong's present finding of expanded central blood volume in cirrhosis. Moreover, the total lack of correlation between neurohumoral indicators of central blood volume and the reported values of central blood volume (3) again argues against the conclusion.

In our opinion, the report by Wong et al. (3) does not offer sufficient evidence against the contention of central vascular underfilling in decompensated cirrhosis.

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Reply:

We have read the thoughtful letter by Henriksen and colleagues and would like to offer the following clarification.

We agree with Dr. Henriksen that none of the techniques for the indirect determination of central blood volume is perfect. Each technique has its strength and weaknesses; the ultimate balance lies in the specific situation for which the method is applied. We have chosen to use the equilibrium count-based technique to calculate volume to circumvent significant noncorrectable errors of the first-pass technique (1). This is in keeping with the generally accepted principle in nuclear medicine: First-pass techniques are useful in measuring flow, and equilibrium techniques are useful in measuring volume (2).

Dr. Henriksen has employed the first-pass tracer-clearance technique by injecting radioiodinated albumin in the right atrium and collecting blood samples at 1-sec intervals in the aorta (3). The volume is calculated as $V = F \times \tau$, where V is apparent volume of distribution of tracer, F is rate of blood flow and τ is mean transit time of the tracer. This equation is based on sound theoretical physiological principles predicated on ideal circumstances that often do not exist in the real patient. The major weakness of this technique lies in the fact that for nondiffusible tracers such as albumin there is a significant nonlinearity of the equation when flow increases (2). The volume calculated by this technique represents the blood volume occupied by the tracer.

However, as flow or cardiac output increases, such as in the case in cirrhosis, there will be inadequate time for homogeneous mixing of the tracer with the total central blood volume, leading to underestimation of the true central volume. This violates one of the major assumptions that the authors themselves asserted (i.e., the requirement of complete indicator mixing [3]). One may therefore reliably predict that whenever cardiac output increases, the first-pass technique will underestimate the true volume.

Further concerns with the techniques described above include the problem of central shunts. The authors have realized this weakness and took an entire appendix to address this point. However, throughout the discussion the author assumed that a linear relationship would exist between flow, transit time and volume. This relationship again, unfortunately, does not stay linear when the flow is increased, as in the setting of central shunts. Another potential problem that was not addressed by the authors was the potential trapping or adherence of the labeled albumin to the pulmonary vascular endothelium, or extravasation of the tracer outside the intravascular space. Loss of tracer during a first-pass study will immediately lead to underestimation of the blood volume. This point was not addressed by the authors. The authors could have used labeled RBCs instead, and at the same time may have had the opportunity to try out our equilibrium technique.

To address these concerns, we have performed central blood volume calculation with the well-accepted counted-based technique. Please note that most of the recent important studies on central blood volume changes use the equilibrium blood pool method (4, 5). We

are delighted to find that Dr. Henriksen and colleagues agree with the general principles underlying this technique and with the accuracy of the left ventricular volume determinations. They were concerned that potential errors in left ventricular volume calculation might lead to huge errors in central blood volume calculation, which may be 20 times larger in quantity. However, in our laboratory and as originally described (6), the error is usually maximally in the range of 5 ml. Therefore, even if the error is maximal, we would have at most 100 ml of overestimation. This still does not explain the difference of 600 ml/m² in central blood volume between cirrhotic and normal subjects.

The authors were also concerned about attenuation differences between the central vascular structures and the heart. The authors are accurate in that the count-based equilibrium techniques must take into account the tracer attenuation factor. Tracer attenuation is proportional to the distance between the structure being imaged and the gamma camera, and the composition of the attenuating tissue—in this case, mainly the chest wall. We have taken careful attenuation correction for the left ventricle using the standard triangulation method that Dr. Henriksen has already accepted as accurate (6). We would assert that the chest wall over the heart is similar to that over the lung and great vessels; it is mostly composed of tissue containing significant amount of water. We did make an assumption that the great bulk of central blood volume in the chest is a similar distance from the camera as the heart, when the patient is in a supine position. We may argue that we may in fact underestimate the central blood volume as a result of the possibly more posterior location of the main pulmonary blood volume when the patient is supine.

The authors quoted Bell's study (7), stating that if the same attenuation was used for the lung as the heart, major errors might arise. However, Bell was studying a dog model, which has a completely different chest wall morphology, and markedly different heart and lung position from an overlying camera. Here we are studying patients. The quote that "Radionuclide technique can only provide an index in the change of pulmonary blood volume, and not absolute value" was taken out of context; the purpose of the particular study quoted was to specifically examine pulmonary blood volume ratio between the lung and heart during exercise, as an indication of exercise-induced heart failure in patients with ischemic heart disease (8).

The authors were also concerned about difficulties in separating abdominal from chest organs in the supine position in the cirrhotic patients. We use the diaphragm as the dividing line between the chest and abdomen. This is usually very distinct on the radionuclide image. Unless the authors suggest that abdominal organs can herniate through the diaphragm into the chest, contributing to extra radioactivity, this assertion is highly improbable. The authors were also concerned about the unusually high central blood volume measured. Please keep in mind, however, that this value does include all vascular structures in the chest cavity, including the

inferior vena cava above the diaphragm, all central vascular structures and all central shunts.

The authors were similarly concerned that our estimate of pulmonary blood volume of 412 ml/m² in normal subjects was too high. It is interesting that the authors have given examples in their paper of normal pulmonary blood volume as 650 ml, which for a normal person with body surface area of 1.7 m² yields a value of 382 ml/m² supporting our measurement.

Despite the emphasis that the measurement of central blood volume includes all the vascular structures in the thoracic cavity, Hendriksen et al. consider that a central blood volume of 3.3 L "is rather unlikely." It is true that we did not measure total blood volume in our patients but this has been reported in several publications. For example, Boyer et al. (9) reported blood volumes in patients with portal hypertension ranging from 78.5 to 123 ml/kg, or 5.7 to 9.6 L. Therefore a CBV of 3.3 L in such circumstances does not seem unreasonable.

We agree with the authors that, in patients with decompensated cirrhosis and ascites, the findings of hyperdynamic circulation and increased levels of sodium retaining factors speak in favor of central underfilling. However, where we disagree here is that in our view this is due to massive vasodilatation (10), leading to a greater increase in vascular capacity and an inadequate increase in intravascular blood volume, despite the intense sodium retention resulting from the vasodilatation (10). In contrast, in well-compensated cirrhotic patients, all previous publications have emphasized the tendency for an increased total blood volume in the absence of any manifestations of "underfilling" (9, 11-14). Therefore an increased central blood volume, as opposed to a decreased central blood volume as reported by the authors (3), would be in keeping with this, together with increases of plasma renin activity and serum aldosterone levels (16-18), in such patients.

Overall, we have found Dr. Henriksen's arguments interesting and thoughtful. We appreciate the opportunity to clarify these points of contention and thank them for the healthy degree of controversy and intellectual challenge.

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Complications of Transplantation for Protoporphyrin Liver Disease

To the Editor:

In a recent issue of this JOURNAL, Rank et al. (1) reported their experience with eight patients with end-stage protoporphyric liver disease in whom they found evidence of neurological dysfunction.

We would like to add the report of a 58-yr-old woman in whom liver transplantation for fulminant liver failure in erythropoietic protoporphyria was complicated by severe polyneuropathy.

In this patient, erythropoietic protoporphyria with asymptomatic liver involvement had been diagnosed 12 yr earlier. For years she had suffered from paresthesias, dysesthesias and nocturnal myoclonias of the legs. Somatosensory evoked potentials of the tibial nerve were slightly lengthened; diagnosis of a discrete polyneuropathy had been made.

In December 1992, the patient was seen with uncharacteristic abdominal pain and mild jaundice. Liver function rapidly declined, and hepatic encephalopathy (grade 3) developed. Orthotopic liver transplantation was successfully performed 5 wk after the initial presentation. The day after transplantation, respiratory insufficiency with loss of consciousness suddenly developed. The patient had to be reintubated and was artificially ventilated for 5 wk. A neurological examination immediately after reintubation revealed no abnormality. A cranial computed tomography scan did not show any pathological findings except for moderate brain atrophy.

Some days after the operation, however, the patient showed no spontaneous movement except for minimal movements of lower arms and hands. Gag and cough reflexes were absent. The electromyogram confirmed the

diagnosis of severe polyneuropathy with axonal degeneration and marked signs of muscle denervation. Six weeks after transplantation, there was still the clinical picture of an acute polyneuropathy with involvement of cranial nerves VI, VII and XII.

Considering a causal relationship between the immunosuppressant FK 506 and polyneuropathy, we changed immunosuppression to cyclosporine. Two weeks later, the patient had repeated cerebral seizures. EEG showed a diffuse cerebral functional disorder without focal changes.

With intensive physiotherapy, neurological deficits gradually improved. One year after transplantation, strength in the patient's legs is still markedly reduced. The patient is not able to walk more than 20 m, and she shows a markedly atactic gait due to polyneuropathy. Tendon reflexes of the lower limbs are still absent, and there is a considerable degree of dysesthesia and paresthesia of the legs. The patient complains of disorders of balance, orthostatic dysregulation and profuse sweating.

This case shows striking similarities to patient 4 described by Rank et al. (1) and to another case published recently by Herbert et al. (2). In all three of these patients, severe polyneuropathy with axonal degeneration and cranial nerve involvement developed immediately after liver transplantation for erythropoietic protoporphyria. Furthermore, our patient and the patient reported by Herbert et al. complained of symptoms indicating mild polyneuropathy some years before deterioration of liver function.

Considering the small number of liver transplantations for EPP reported until now, there is substantial evidence for the induction or aggravation of severe neurological dysfunction after the operation. Especially in patients with histories of mild peripheral polyneuropathy, the physician must be aware of sudden and