It takes two “eyes” to see in depth

To the Editors:

We read with great interest the study published by Turco *et al.* in a recent issue of *Journal of Hepatology*, which evaluated the hemodynamic state of patients from cirrhosis. This study is particularly interesting since the whole spectrum of patients with cirrhosis was included, from patients with compensated disease to patients with refractory ascites.[1]

The actual hypothesis for the development of ascites requires the presence of hyperdynamic circulation, which is theoretically a compensatory mechanism to the splanchnic vasodilation that characterizes these patients. This was initially proposed in the 80s with the vasodilatation hypothesis[2] and further modified recently with the systemic inflammation hypothesis.[3] The former hypothesis was based on a number of studies, which showed an increase in cardiac output, a decrease in systemic vascular resistance and an increase in serum renin levels in patients with increasing disease severity. The latter hypothesis further adds to the vasodilation hypothesis in which systemic inflammation due to pathogen- and damage-associated molecular patterns play a major role in the development of splanchnic vasodilation and have additional effects on other target organs such as the brain, heart and kidney.

Nevertheless, a precise definition of hyperdynamic circulation does not exist. The study from Turco *et al.* is the first attempt to fill this gap.[1] They define cardiodynamic states based on the cardiac index (CI). According to this classification, three categories were defined: hyperdynamic with a CI above the upper limit of normality (CI >4.2 L/min/m^2), normodynamic (CI between 3.2 (general population average) and 4.2 L/min/m^2) and relative hypodynamic when the CI was below 3.2 L/min/m^2. However, from a physiological point of view, the heart is not an isolated organ which can be evaluated independently from the rest of the organism. Cardiac output (and logically CI) is a parameter which is highly dependent on the volume status of the patient.[4] Patients with a cardiac output of 8 L/min (upper limit of normal) can be completely different from a hemodynamical point of view depending on the other parameters (for example a systemic vascular resistance [SVR] of 1,500 dyn·s·cm^{-5} or an SVR of 700 dyn·s·cm^{-5}). The latter would be a truly hyperdynamic patient, while the presence of a hyperdynamic circulation could be questioned in the former case. In the present study, one can observe that on average there is a lower SVR in the groups of patients with a higher cardiac output. However, classification of patients according to two parameters such as cardiac output and blood pressure or SVR for each individual patient, would help to further tease out the subtleties in the hemodynamic changes that were observed. Similarly, the sole presence of post capillary pulmonary hypertension does not necessarily reflect the presence of left ventricular dysfunction, as it could be the consequence of an increase in preload (for example in the context of albumin infusion after large volume paracentesis).[5] Again, the evaluation of two parameters (such as post capillary pulmonary pressure and stroke work[6]) could offer a more holistic view of the situation in the individual patient. Indeed, with two “eyes” one has a greater perception of depth.

As the authors point out the presence of a lower than average CI in compensated patients is extremely interesting. This and the fact that patients with diuretic sensitive ascites have a lower than average cardiac output challenges the actual theory in which the presence of splanchnic vasodilation and hyperdynamic circulation (secondary to bacterial translocation and vascular dysfunction) are a sine qua non for the development of ascites. The authors suggest that in compensated patients, the translocation of bacterial products could be responsible for the decrease of cardiac output. Theoretically, the presence of systolic dysfunction is mainly to be seen in stress conditions and is associated with the degree of sympathetic activity and liver failure.[5] Furthermore, the typical bacterial translocation of cirrhosis occurs in decompensated disease.[7] However, it could be that other factors, namely genetic factors, favoring the translocation of pathogen-associated molecular patterns or bacteria are also present in compensated patients.[8] Unfortunately, no significant differences in C-reactive protein were observed in the different cardiodynamic states,[1] which could have supported this argument.

Despite these theoretical observations, it is clear that the classification proposed by Turco *et al.* are associated with hard clinical endpoints, which on its own justifies its use for prognostic purposes. Further studies, however, are needed to disentangle the pathophysiological implications of these findings.

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Conflict of interest

The authors declare no conflicts of interest that pertain to this work.

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Authors’ contributions

CR wrote the letter. RB and AZ provided valuable intellectual input.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhep.2018.10.028.

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Cristina Ripoll[1,*]
Rafael Bañares[2]
Alexander Zipprich[1]
[1]*First Department for Internal Medicine, Martin-Luther University Halle-Wittenberg, Halle (Saale), Germany*
[2]*Digestive Diseases and Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas Hospital General Universitario Gregorio Marañón Instituto de Investigación Sanitaria Gregorio Marañón Facultad de Medicina, Universidad Complutense, Madrid, Spain*
*Corresponding author. Address: First Department for Internal Medicine, Martin-Luther University Halle-Wittenberg, Ernst Grube Strasse 40, Halle 06120, Germany. Tel.: +49 345 557 2665, fax: +49 345 557 2253.
E-mail address: cristina.ripoll@uk-halle.de

Reply to: “It takes two “eyes” to see in depth”

To the Editor:

We appreciate Ripoll and colleagues’ comments regarding our study demonstrating that cardiac index (CI) is an independent predictor of disease outcomes in cirrhosis.[1] As stated by Dr. Ripoll and colleagues, our study is the first attempt to give a precise definition of hyperdynamic circulation by using the upper limit of normal CI (>4.2 L/min/m^2) as a cut-off. We also described a hypodynamic circulatory state (CI <3.2 L/min/m^2). Interestingly, these two states had a worse prognosis compared to patients with a normodynamic circulation (CI ≥3.2 L/min/m^2 and ≤4.2 L/min/m^2). We would like to remark that using CI (as opposed to cardiac output) or systemic vascular resistance index (SVRI, as opposed to SVR) corrects for body surface and decreases the risk of error when comparing different patients.

Ripoll *et al.* appropriately question whether adding SVRI to these cardiodynamic states could provide further granularity. We should note that, in each multivariable model assessing decompensation or survival as outcomes,[1] we introduced mean arterial pressure and this parameter was not found to be independently predictive of outcome.

Furthermore, we performed a new analysis to confirm the lack of an added predictive value of SVRI to sub-staging based on CI. To categorize patients into a “vasodilated” or “non-vasodilated” stage, we used two SVRI cut-offs: 1,700 dynes-sec/cm^{-5}/m^2 (a discriminating level often used in intensive care units) or 1,970 dynes-sec/cm^{-5}/m^2 (the lowest level of normal in adults).

Fig. 1 shows the proportion of patients in vasodilated *vs.* non-vasodilated states in the context of each of the clinical stages of cirrhosis and their circulatory subcategories. At each stage of cirrhosis, the hyperdynamic circulatory state was closely associated with a very high proportion of patients in the vasodilated state (independently of SVRI cut-off used), ranging from 90% (in compensated patients) to 100% (in decompensated patients), indicating that CI alone is sufficient to identify truly hyperdynamic patients.

Regarding the hypodynamic circulatory state, when vasodilation is determined by a SVRI cut-off of 1,700, each of the clinical stages of cirrhosis was associated with a high proportion of patients in a non-vasodilated state, ranging from 88% to 100%, indicating that in this setting CI alone is sufficient to identify a hypodynamic circulatory state. Similar results are observed when using the SVRI cut-off of 1,970, except in patients with refractory ascites, where 37% of hypodynamic patients were also vasodilated (at rest and in the supine position). This may indicate that this subgroup of patients is enriched with patients transitioning from a normo-hyperdynamic state to the hypodynamic one due to a primary deterioration of cardiac inotropic activity.[1,2]

Regarding the normodynamic circulatory state, around 25% and 60% of compensated patients with clinically significant portal hypertension (CSPH) are vasodilated, defined by SVRI <1,700 or <1,970, respectively (Fig. 1). The corresponding figures for decompensated patients were about 50% and 80%, respectively. This identifies the normodynamic group as the group where “two eyes” may provide further depth of perception.

We agree with Ripoll *et al.* that post-capillary pulmonary hypertension (pcPH) may not necessary reflect the presence of left ventricular dysfunction. Nevertheless, pcPH is a well-established definition of severe diastolic dysfunction and heart failure with preserved ejection fraction.[3–5] Although, pcPH was present in compensated patients with CSPH and in any cardiodynamic group of both the compensated and decompensated stages (see Fig. 2 in[1]), we cannot rule out that administration of an average of 46 g of albumin (after a large volume paracentesis) to patients with refractory ascites the day before the hemodynamic assessment may have increased intravascular volume above the level of maximum load tolerance of the left ventricle (and pericardium) (see Table 1 in[1]). However, data supporting this view are derived from studies where hemodynamic evaluation was performed soon after a rapid infusion of high dose of either albumin in cirrhotic patients[6] or saline in