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ORIGINAL ARTICLE

Evaluation of the definition of hyperdynamic circulation in patients with cirrhosis and ascites

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Abstract

The aim of this study was to evaluate potential criteria for defining hyperdynamic circulation in patients with cirrhosis according to the severity of ascites and its association with the activation of vasoactive systems and markers of systemic inflammation. Cross-sectional study of patients with cirrhosis and right heart catheter measurement from two different academic centers. We evaluated systemic vascular resistance (SVR)/cardiac output (CO) according to ascites severity. The first substudy evaluated the possible definition, the second validated the findings, and the third evaluated the possible mechanisms. Comparisons were performed by means of *t* test, Mann–Whitney *U* test, and analysis of variance. Finally, linear regression curves were adjusted to evaluate the relationship between CO and SVR according to the severity of ascites and compensated or decompensated stage of cirrhosis. The study included 721 patients (substudy 1, n = 437; substudy 2, n = 197; substudy 3, n = 87). Hyperdynamic circulation (HC), defined by absolute cutoffs, had no association with the presence or severity of ascites in the first two cohorts. No association was observed between HC with renin, aldosterone, or markers of bacterial translocation. Comparison of linear regression curves showed a shift of the CO–SVR relationship to the left in patients with refractory ascites ($p < 0.001$) compared to patients without ascites as well as to patients with decompensated cirrhosis ($p = 0.002$). *Conclusion*: HC according to the traditional concept of high CO and low SVR is not always present in ascites. Evaluation of the CO–SVR relationship according to the severity of ascites shows a shift to the left, suggesting that the presence of HC would be defined by this shift, independent of absolute values.

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INTRODUCTION

The development of ascites is a major hallmark in the natural history of patients with cirrhosis. Along the course of the disease, ascites is the most frequent event that marks the transition to the decompensated phase of the disease.[1] Systemic circulatory abnormalities with hyperdynamic circulation, defined by an increase in cardiac output (CO) and a decrease in systemic vascular resistance, are considered to play a central role in the development of ascites. Based on the previous vasodilation hypothesis,[2] the current systemic inflammatory hypothesis postulates that translocation of bacteria and/or bacterial products due to portal hypertension and liver failure leads to splanchnic vasodilatation, which in turn leads to activation of compensatory mechanisms, including an increase in CO and renal retention of sodium.[3] Therefore, both theories imply that hyperdynamic circulation is a condition "sine qua non" for the development of ascites.

The presence of systemic hemodynamic alterations in patients with cirrhosis has been established for over 50 years. In the milestone study from Kowalski and Abelmann,[4] an increased resting CO associated with a large stroke volume, normal blood pressure, and low peripheral vascular resistance was observed in approximately one third of patients. Since then, this constellation of hemodynamic abnormalities of cirrhosis has been named hyperdynamic circulation. Following its description, numerous studies have observed an increase in CO and/or a decrease in systemic vascular resistance (SVR) in patients with cirrhosis that are considered a hallmark of hyperdynamic circulation, and these individual alterations have been correlated with the severity of liver disease.[5–10]

Of note, a clear-cut and reproducible definition of hyperdynamic circulation has not been established, and only a few studies have evaluated its prevalence in cirrhosis.[4,10] These studies have focused on its definition based on one criterion, most commonly CO/cardiac index (CI). On the population level, numerous studies have shown that changes in individual parameters, such as CO, are associated with the severity of the disease. However, interpretation of CO in the individual patient is hindered if one does not consider loading conditions.[11] Patients with cirrhosis have typically central hypovolemia due to splanchnic vasodilation with splanchnic pooling of the blood. A more accurate evaluation would include the use of at least two parameters.[12]

Therefore, the aim of the present study was to evaluate potential criteria for defining hyperdynamic circulation in patients with cirrhosis according to the severity of ascites and to evaluate its association with the activation of vasoactive systems and markers of systemic inflammation. Finally, presence of different hemodynamic patterns according to the severity of ascites was evaluated.

MATERIALS AND METHODS

The present study was composed of three different cross-sectional substudies. All patients had evaluation of hepatic and systemic hemodynamics. The initial substudy (substudy 1, n = 437) was a secondary retrospective analysis of a prospectively collected database of patients who underwent hemodynamic measurements in Halle (Germany) between November 1995 and November 2004.[13,14] In this initial substudy, previously established known associations between classic parameters of hyperdynamic circulation and markers of severity of liver disease and survival were evaluated in order to ensure that the present study could reproduce previously attained knowledge and that the possible definition of hyperdynamic circulation was evaluated. The results obtained were then validated in a second substudy of a different population (substudy 2, n = 197), which comprised a secondary analysis of patients included in a prospectively collected database in Madrid (Spain) between May 2004 and December 2007.[15–17] Finally, a third study (substudy 3, n = 87) comprising a group of patients who underwent hemodynamic measurement in Halle (Germany) between May 2015 and April 2016 was included prospectively. In these patients, samples had been collected as part of a biodata bank aimed to evaluate the activation of vasoactive systems in patients with cirrhosis. The third substudy used these samples to validate the findings and to explore the mechanisms with a focus on markers of activation of vasoactive systems and inflammatory parameters, including the measurement of renin, aldosterone, interleukin-6 (IL-6), and C-reactive protein (CRP). There were no samples available from substudies 1 and 2.

The study centers participating in the present study routinely perform hemodynamic measurements in patients admitted with cirrhosis. The diagnosis of cirrhosis was either biopsy proven or clinically suspected and was confirmed by the presence of a hepatic venous pressure gradient (HVPG) of 6 mm Hg or greater. Indications for HVPG measurement at the Martin Luther University-Halle Wittenberg were either to establish the diagnosis of cirrhosis (by means of histology or based on the presence of portal hypertension) and/or to assess baseline portal pressure before pharmacologic therapy or before placement of a transjugular intrahepatic portal-systemic shunt (TIPS). Indications for HVPG measurement at the Gregorio Marañón Hospital included all those mentioned above but mainly in the context of evaluation for liver transplantation. In both centers, a right heart catheterization besides

hepatic vein catheterization was routinely performed in the same procedure.

Patients were considered for inclusion in the present study if they had cirrhosis and had measurements of portal and systemic hemodynamics (HVPG and right heart catheterization). Exclusion criteria included primary biliary cirrhosis (due to a possible presinusoidal component of portal hypertension), previous TIPS placement, previous liver transplantation, hepatocellular carcinoma (HCC) beyond Barcelona Clinic Liver Cancer B stage, splenic or portal vein thrombosis, and concurrent illnesses expected to decrease life expectancy to less than 1 year. Clinical characteristics and laboratory values were collected from the clinical record at the time of the hemodynamic evaluation. Ascites severity was classified as absent, diuretic responsive, and refractory according to the International Ascites Club.[18] Decompensation was defined by the presence of actual or past clinical ascites, hepatic encephalopathy, and/or variceal bleeding.[19] Waiver of informed consent was obtained for the retrospective studies. Ethic Committee approval had been obtained for the biodata bank (2012–2015). Patients included in the prospective study gave their informed consent for the biodata bank. The study followed the ethical principles of the World Medical Association's Helsinki Declaration, Seventh Revision, 2013.

Hemodynamic assessment

Right heart catheterization was conducted using a quadruple-lumen thermodilution catheter (Abbott Laboratories, Abbott Park, IL, USA) inserted into the internal jugular vein under local anesthesia, with assessment of mean arterial pressure (MAP) and heart rate using automated noninvasive monitoring (Sirecust; Siemens AG, Erlangen, Germany). Standard measurements included central venous pressure (CVP), right atrial pressure, CO, and SVR. CO was determined by thermodilution and standardized for body surface area as the CI (CI = CO/body surface area). When information on height and weight was lacking, the CI could not be calculated (subgroup 2). Measurements of CO were repeated to obtain at least three adequate curves after visual inspection. If there was a variation greater than 0.5 L/minute between the obtained values, the measurements would be repeated until a maximum of a 0.5-L/minute difference between measurements was obtained. SVR was calculated using the standard formula SVR = [(MAP – CVP)/CO] × 80. Portal pressure was determined by the HVPG as described.[20] Briefly, free and wedged hepatic venous pressures (FHVP, WHVP) were assessed following catheterization of a hepatic vein with a standard occlusion balloon catheter (Boston Scientific, Natick, MA, USA). Measurements were repeated 3 times, and the average was calculated. HVPG was substracted from the two measurements (HVPG = WHVP – FHVP).

Definition of hyperdynamic circulation

In order to account for the changes in loading conditions, a combination of both CO and SVR was used. To explore possible cutoffs of these variables to define hyperdynamic circulation in the present study, CO and SVR according to the severity of ascites to visually evaluate their association were plotted, with the assumption that the different degrees of ascites severity would tend to present a specific hemodynamic pattern (i.e., patients with refractory ascites would have a low CO and low SVR). If no cutoffs could be identified, we would define hyperdynamic circulation by an increase of CO and a decrease of SVR above and below the limits of normality, respectively (CO ≥ 8 L/minute, SVR ≤ 800 dynes [dyn]·second·cm^{-5}), which are the cutoffs provided by the manufacturers of the machines to measure CO. There are no studies in healthy humans evaluating cutoffs of CO or SVR as determined by right heart catheterization. Nevertheless, the cutoffs proposed are similar to the cutoffs for the upper limit of normal (percentile 97.5%) and lower limit of normal (percentile 2.5%) of the estimation of CO and SVR, respectively, in the general population (n = 2218) as determined by ultrasonic cardiac monitoring, a method that has been validated against pulmonary arterial thermodilution.[21] Given the fact, that SVR is a parameter that is calculated with CO and MAP measurements, the combination of other parameters that play a role in hyperdynamic circulation was evaluated using CO and MAP as well as CO and pulmonary capillary wedge pressure (PCWP) in order to test whether use of these parameters could better define the presence of hyperdynamic circulation according to the severity of ascites. In order to achieve more granularity regarding the relationship between CO and SVR, different curves were adjusted according to the severity of ascites.

Finally, cardiodynamic states were defined according to Turco et al.[10] Briefly, hypodynamic state was defined by a CI lower than 3.2 L·minute·m^{-2}, normodynamic state by a CI between (and including) 3.2 and 4.2 L·minute·m^{-2}, and hyperdynamic state by a CI greater than 4.2 L·minute·m^{-2}.

Statistical analysis

Categorical variables are described by means of percentages, and continuous variables are described by median and interquartile range (IQR). For the comparison of categorical variables, the chi-square test

was used. Whether continuous variables followed a normal distribution or not was evaluated by means of the Kolmogorov-Smirnov test. Dispersion graphs were constructed to evaluate the association between CO and SVR or MAP according to the severity of ascites. For the comparison of continuous variables, the Student *t* test and analysis of variance or Mann–Whitney *U* test and Kruskal-Wallis test, Pearson, and/or Spearman correlation according to the sample distribution were used. Missing values were not imputed. Finally, in the whole population and by means of linear regression, curves were adjusted to describe the association between SVR and CO according to the severity of ascites as well as compensated and decompensated stage of cirrhosis and compared with the extra sum-of-square F test. SPSS (version 25) and GraphPad Prism 6 were used for statistical analyses.

RESULTS

A total of 721 patients were included. Baseline characteristics of patients included in each substudy are presented in Table 1.

Substudy 1: Evaluation of the presence of hyperdynamic circulation in the German retrospective cohort

A total of 437 patients were included of which 149 (34%) had no ascites, 158 (36%) had diuretic-responsive ascites, and 130 (30%) had refractory ascites. The distribution of CO and SVR according to the severity of ascites was plotted to identify possible cutoffs of CO and SVR to define hyperdynamic circulation (Figure 1A). As expected according to the formula, an increase in CO is associated with a decrease in SVR so that a curve associating the two variables could be observed. Nevertheless, no skewness could be observed according to the severity of ascites. When CO was plotted against MAP, again, no grouping according to ascites phenotype could be observed (Figure 2A). In order to evaluate whether an inadequate cardiac performance in the context of a cirrhotic cardiomyopathy with congestion in the pulmonary circulation could explain the lack of increase in CO in patients with refractory ascites, CO and PCWP were plotted according to the severity of ascites (Figure 3A). Again, no pattern could be observed according to the severity of ascites.

Using the previously defined arbitrary cutoffs (CO ≥ 8 L/minute, SVR ≤ 800 dyn·second·cm^{-5}), only 22% of patients (n = 95) would have hyperdynamic circulation (Table S1). Indeed, there were patients with ascites and even with refractory ascites without hyperdynamic circulation (Table 2) according to this definition. Furthermore, no skewness could be observed toward a greater proportion of normal or decreased CO among the patients with refractory ascites. Both individual components as well as the presence of hyperdynamic circulation according to this definition were associated with increasing liver disease severity and portal hypertension (Table 2; Table S2), confirming published findings. Patients with increasing severity of ascites had a lower SVR (median no ascites, 992; IQR, 783–1240 dyn·second·cm^{-5}), diuretic-responsive ascites (median, 906; IQR, 731–1137 dyn·second·cm^{-5}), and diuretic-refractory ascites (median, 856; IQR, 679–1113 dyn·second·cm^{-5}; $p = 0.025$). Interestingly, no association was observed between hyperdynamic circulation according to this definition and renal function or serum sodium.

Substudy 2. Evaluation of the prevalence of hyperdynamic circulation in the Spanish cohort

The second study included 197 patients of which 75 (38%) had no ascites, 83 (42%) had diuretic-responsive ascites, and 39 (20%) had refractory ascites. Comparison of the baseline characteristics of both groups are shown in Table 1. Patients from Spain had a lower proportion of alcoholic liver disease, a higher HVPG, and lower MAP, although a lower proportion of patients had more advanced disease according to Child-Pugh stage and presence of refractory ascites. No differences were observed in the Model for End-Stage Liver Disease (MELD) score or in the individual laboratory tests of liver function.

When the CO and SVR were plotted according to the severity of ascites, patients with all degrees of ascites severity were distributed along the curve, with no particular grouping (i.e., refractory ascites and low CO) (Figure 1B). However, almost half the patients (n = 82, 42%) were on beta blockers at the time of the hemodynamic study. When the relationship between CO and SVR was plotted according to the severity of ascites in those patients without beta blockers at the time of the hemodynamic study, again no particular hemodynamic pattern could be associated with a determined clinical phenotype (Figure S1). CO was plotted against MAP. Once more, no clustering according to ascites phenotype could be observed (Figure 2B). Finally, CO was plotted according to PCWP; repeatedly, no pattern according to ascites severity could be noted (Figure 3B). In this substudy population, the prevalence of hyperdynamic circulation according to the above-mentioned definition was 22%. In contrast to the previous group, an association between the severity of ascites and

TABLE 1 Baseline characteristics of the patients in each substudy

Variable	Substudy 1 (n = 437)	Substudy 2 (n = 197)	*p* value[a]	Substudy 3 (n = 87)
Male	284 (65)	149 (76)	0.008*	56 (64)
Age, years	53 (45–62)	53 (38–59)	0.207	60 (52–67)
Alcohol related	308 (71)	102 (52)[b]	<0.001*	76 (87)
Child-Pugh class			0.013*	
A	102 (23)	35 (19)		18 (21)
B	182 (42)	107 (57)		41 (47)
C	130 (30)	47 (25)		28 (32)
Child-Pugh score	8 (7–10)	8 (7–10)		–
MELD	13 (10–17)	14 (7–18)	0.336	13 (10–17)
Decompensated	321 (73)	–	–	81 (93)
Hepatic encephalopathy			<0.001*	–
None	401 (92)	151 (80)		
Grade I–II	33 (7)	31 (16)		
Grade III–IV	3 (1)	8 (4)		
Ascites			0.031*	
None	149 (34)	75 (38)		23 (27)
Diuretic responsive	158 (36)	83 (42)		19 (22)
Refractory	130 (30)	39 (20)		44 (51)
Patients with beta blockers at the time of HD measurement	-	82 (42)	<0.001*	20 (23)
Bilirubin (mmol/L)	32 (20–70)	41 (14–79)	0.962	23 (15–44)
INR	1.3 (1.2–1.6)	1.3 (1.0–1.6)	0.052	1.3 (1.2–1.4)
Albumin (g/L)	31 (26–38)	32 (23–36)	0.896	28 (24–35)
Creatinine (mmol/L)	77 (65–96)	71 (53–88)	0.104	84 (65–129)
Serum sodium (mmol/L)	137 (133–140)	–	–	136 (133–139)
CRP (mg/L)	–	–	–	12.5 (6.5–28.6)
Renin (pg/ml)	–	–	–	554 (257–1151)
Aldosterone (pg/ml)	–	–	–	608 (458–738)
IL-6 (pg/ml)	–	–	–	19.6 (9.0–53.2)
HVPG (mm Hg)	16 (12–20)	18.5 (8.0–21)	<0.001*	20 (15–23)
FHVP (mm Hg)	12 (10–15)	8 (2.5–10.5)	<0.001*	8 (5–12)
WHVP (mm Hg)	28 (24–33)	26 (14–31)	<0.001*	28 (23–33)
HF (bpm)	78 (70–89)	70 (50–81)	<0.001*	74 (65–84)
MAP (mm Hg)	88 (78–97)	84 (68–95)	0.018*	81 (71–88)
CO (L/minute)	6.9 (5.6–8.3)	6.7 (4.3–8.2)	0.300	5.8 (4.8–7.0)
CI (L/minute/m^2)	3.8(3.1–4.6)	–	–	3.1 (2.6–3.6)
SVR (dyn·second·cm^{-5})	923 (736–1160)	938 (533–1192)	0.829	1019 (804–1272)

Note: Values shown as number (percentage) or median (interquartile range).

Abbreviations: bpm, beats per minute; CI, cardiac index; CO, cardiac output; CRP, C-reactive protein; dyn, dynes; FHVP, free hepatic venous pressure; HD, hemodynamic; HF, heart frequency; HVPG, hepatic venous pressure gradient; IL, interleukin; INR, international normalized ratio; MAP, mean arterial pressure; MELD, Model for End-Stage Liver Disease; SVR, systemic vascular resistance; WHVP, wedged hepatic venous pressure.

[a]Comparison of substudies 1 and 2.

[b]Including patients who had hepatitis C virus and alcoholic liver disease.

*Value is significant.

the presence of hyperdynamic circulation (Table S3) was observed. However, only a fraction of patients with diuretic-sensitive ascites and refractory ascites actually had hyperdynamic circulation according to this definition (n = 21/83, 25%; n = 17/39, 44%, respectively).

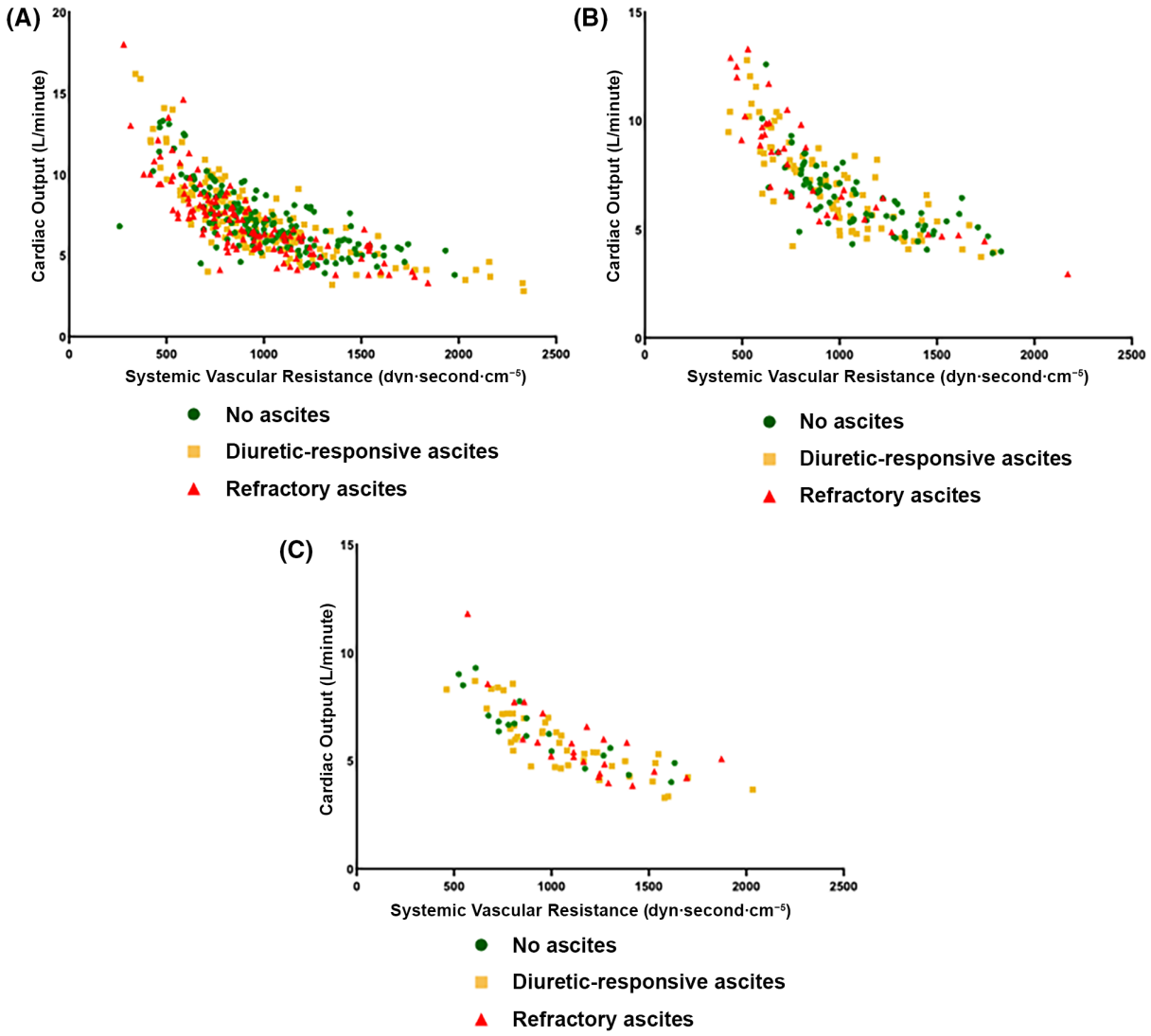

FIGURE 1 Scatterplot of the relationship of cardiac output and systemic vascular resistance according to the severity of ascites. (A) Substudy 1. (B) Substudy 2. (C) Substudy 3. dyn, dynes.

Substudy 3: Evaluation of the mechanisms in the prospective German cohort

The baseline characteristics of the patients included in this substudy are shown in Table 1. A total of 87 patients were included: 23 (27%) with no ascites, 19 (22%) with diuretic-responsive ascites, and 44 (51%) with refractory ascites. Like the two previous groups, when the CO and SVR were plotted according to the severity of ascites, no particular grouping could be observed (Figure 1C). In this last subgroup, the prevalence of hyperdynamic circulation according to the above-mentioned definition was 12%. Again, there was no association observed between the presence of hyperdynamic circulation according to this definition and the severity of ascites.

As expected, patients with increasing severity of ascites had progressively increasing serum levels of renin (p = 0.002), CRP (p = 0.02), and IL-6 (p = 0.001) (Figure S2). Significant but weak correlations confirming published results between renin, aldosterone, CRP, and CO and/or SVR were observed (Table 3). Interestingly, no association between renin and the presence of hyperdynamic circulation according to the above-mentioned definition was observed.

The patient population was classified according to the recently described "cardiodynamic states." Baseline characteristics according to this classification are shown in Table S4. No association between the presence of ascites and the cardiodynamic states was observed; no association between renin/aldosterone and the cardiodynamic states was observed. Interestingly, almost all outlying high-concentration values of renin and almost all outlying high-concentration values of aldosterone were observed in patients with hypodynamic circulation (Figure S3). When looking specifically at patients with a low cardiodynamic state (n = 44), more than half the patients had renin above the median (408 pg/

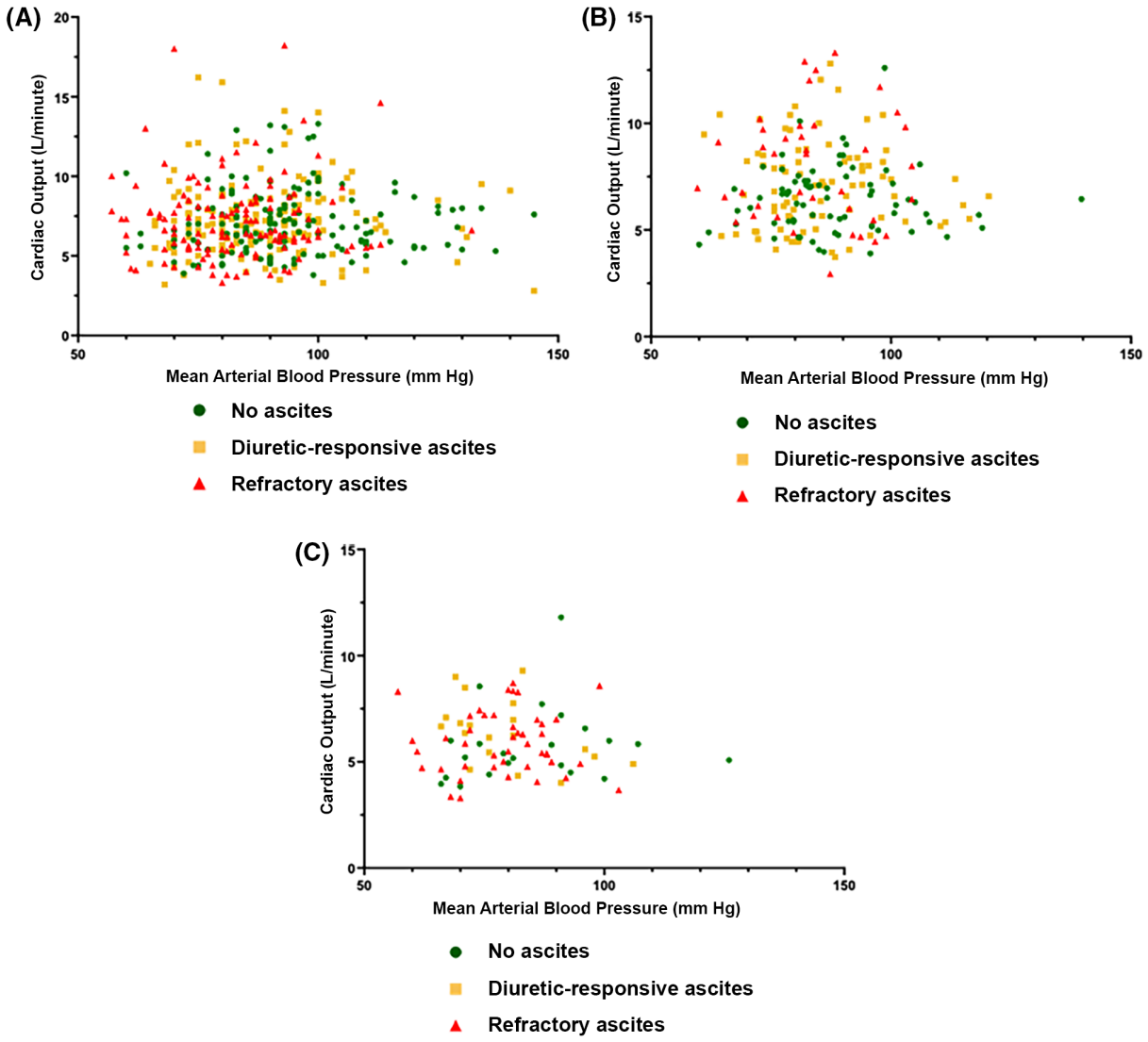

FIGURE 2 Scatterplot of the relationship of cardiac output and mean arterial pressure according to the severity of ascites. (A) Substudy 1. (B) Substudy 2. (C) Substudy 3.

ml) (n = 23) and most patients (n = 16) had refractory ascites ($p = 0.047$).

Evaluation of CO/SVR curves in the whole population

Lastly, curves describing the association between CO and SVR were fitted for each group of ascites severity, including all patients (n = 721). When these curves were compared, significant differences between patients without ascites and patients with refractory ascites ($p < 0.001$) were observed (Figure 4). Interestingly, with increasing severity of ascites, the curve shifted to the left so that with the same CO, patients with more severe ascites would have a lower SVR. No differences were observed in the slopes of the curves ($p = 0.787$). Additionally, evaluation of the relationship between CO and SVR according to the compensated and decompensated status was performed in subgroup 1. In the same line as the main findings of the study, patients with decompensated cirrhosis had a shift in the relationship to the left (Figure S4).

DISCUSSION

From a conceptual point of view, it seems clear what hyperdynamic circulation refers to; however, no clear diagnostic cutoffs have been established. This study was undertaken to evaluate how one can define hyperdynamic circulation. In order to evaluate this, we considered that patients with more severe ascites would have hyperdynamic circulation as defined by the actual hypothesis of the development of ascites.[2,3] Furthermore, given the load dependence of CO and the well-established changes in load that take place in cirrhosis,[2,3] two parameters were considered to

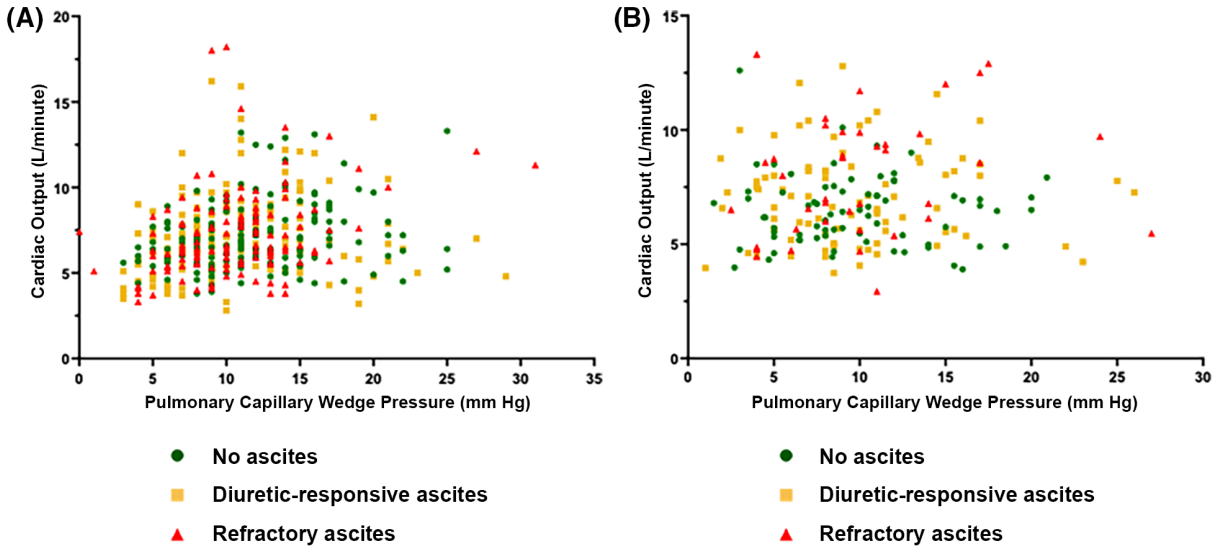

FIGURE 3 Scatterplot of the relationship of cardiac output and pulmonary capillary wedge pressure according to the severity of ascites. (A) Substudy 1. (B) Substudy 2.

TABLE 2 Comparison of patients with and without hyperdynamic circulation (CO ≥ 8 L/minute and SVR < 800 dyn·second·cm^{-5}) in the retrospective German cohort (substudy 1)

Variable	No hyperdynamic circulation	Hyperdynamic circulation	*p* value
Child-Pugh class			<0.001*
A	92 (29)	9 (10)	
B	144 (45)	38 (43)	
C	86 (27)	42 (47)	
Child-Pugh score	8 (6–10)	9 (8–11)	<0.001*
MELD	12 (9–16)	16 (13–22)	<0.001*
Decompensated	242 (71)	76 (80)	0.090
Ascites			0.414
-none	121 (36)	27 (28)	
-diuretic responsive	120 (35)	38 (40)	
-refractory	98 (29)	30 (32)	
Bilirubin (mmol/L)	29 (18–57)	49 (29–165)	<0.001*
INR	1.26 (1.12–1.45)	1.51 (1.30–1,81)	<0.001*
Albumin (g/L)	32 (27–39)	29 (25–34)	<0.001*
Creatinine (mmol/L)	77 (65–96)	74 (62–97)	0.243
Serum sodium (mmol/L)	137 (133–140)	136 (133–139)	0.364
MAP (mm Hg)	90 (80–98)	86 (75–94)	0.043*
Heart rate (bpm)	76 (68–86)	86 (75–96)	<0.001*
CO (L/minute)	6.3 (5.4 (7.2)	9.7 (8.8–11.4)	<0.001*
SVR (dyn/second.cm^{-5})	1011(866–1236)	615 (507–714)	<0.001*
HVPG (mm Hg)	16 (11–19)	18 (13–20)	0.007*

Note: Values shown as number (percentage) or median (interquartile range).

Abbreviations: bpm, beats per minute; CO, cardiac output; dyn, dynes; HVPG, hepatic venous pressure gradient; INR, international normalized ratio; MAP, mean arterial pressure; MELD, Model for End-Stage Liver Disease; SVR, systemic vascular resistance.

*Value is significant.

define hyperdynamic circulation rather than just one.[12] Interestingly, we could not identify an absolute cutoff of CO and SVR to identify patients with hyperdynamic circulation. Instead, what we observed is that there is a shift of the relationship between CO and SVR to the left in patients with refractory ascites compared to patients

without ascites, meaning that with the same CO, patients with refractory ascites would have a lower SVR. This would mean that the presence of hyperdynamic circulation would be defined by this shift rather than by absolute cutoff values. The severity of ascites was chosen to distinguish groups of patients that according to the present hypothesis should differ regarding the presence of hyperdynamic circulation. The same idea could be shown in subgroup 1 according to the presence of compensated or decompensated cirrhosis. However, the presence of hyperdynamic circulation is the consequence of the intricate balance between CO, SVR, arterial pressure, and the activation of vasoactive systems. Whether a cutoff of renin can identify those patients with hyperdynamic circulation remains unknown.

Patients with ascites have been classically divided in diuretic responsive and refractory ascites in which portal hypertension, splanchnic vasodilation, and renal sodium retention play a central role. Presence of hyperdynamic circulation is a condition sine qua non for the development of ascites according to the previous vasodilation and the actual systemic inflammatory hypothesis.[3] Indeed, the latter hypothesis states that bacterial translocation leads to splanchnic vasodilation, which in turn results in the activation of vasoactive systems, including the renin–angiotensin–aldosterone system and the sympathetic system, which leads to hyperdynamic circulation. Hyperdynamic circulation has been associated with the severity of liver disease, mainly the degree of ascites, portal hypertension as estimated by the HVPG, and hepatic insufficiency.[5–10]

However, the results of this and previous studies[10] suggest that patients with ascites can have a normal or reduced systolic function as measured by CI or CO. This phenomenon was initially attributed to an inadequate cardiac response. Theoretically, the development of cardiac function impairment takes place in patients with advanced disease in whom there is an increase in bacterial products; this impairment becomes clinically manifested under stress situations.[3,9] In the present study, this seems to apply to a subgroup of patients. Indeed, when patients were classified by their renin level, almost all patients who had the highest activation of renin also had a low or normal CI and two thirds of these had refractory ascites. However, a skewness of patients with low CO and low SVR among patients with refractory ascites, as would be expected according to this theory, could not be observed, suggesting that patients with refractory ascites are a more heterogeneous group in this regard than previously expected. Indeed, renewed attention has been given to the contribution of the lymphatic system in the development of ascites by means of fluid leakage through the capsular lymphatics (weeping liver).[22]

Although the results of this study may seem contradictory to previous data, we have confirmed all known associations of hyperdynamic circulation that had been described in the literature.[5–10] Indeed, CO, CI, and SVR were associated with the severity of liver disease, portal hypertension, and liver insufficiency. SVR was associated with the severity of ascites. Furthermore, when CO, CI, or SVR were individually analyzed, patients with greater CO or CI and/or lower SVR had higher renin, aldosterone, and CRP as would be expected. Most previous studies have evaluated the

TABLE 3 Association of CO and SVR with parameters associated with activation of vasoactive mechanisms and bacterial translocation (substudy 3)

	CO	SVR
Renin	$r = 0.184$	$r = -0.308$
	$p = 0.09$	$p = 0.004$
Aldosterone	$r = 0.214$	$r = -0.175$
	$p = 0.052$	$p = 0.114$
C-reactive protein	$r = 0.106$	$r = -0.132$
	$p = 0.331$	$p = 0.224$
Interleukin-6	$r = 0.177$	$r = -0.170$
	$p = 0.121$	$p = 0.137$

Abbreviations: CO, cardiac output; SVR, systemic vascular resistance.

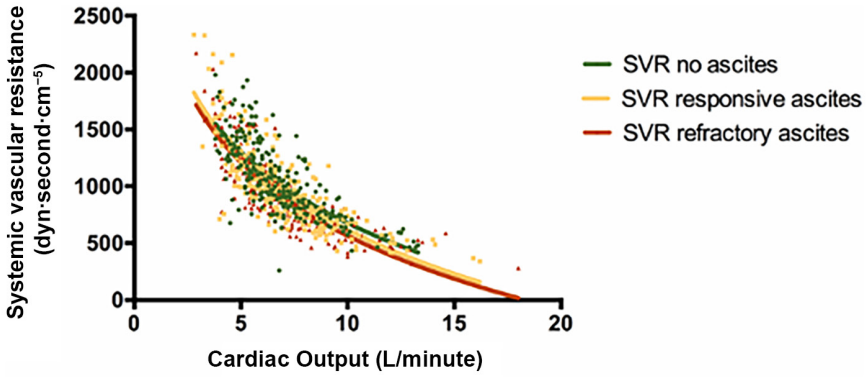

FIGURE 4 Linear regression-adjusted curves for the relationship between cardiac output and systemic vascular resistance according to the severity of ascites in the whole study population (n = 721). Analysis of variance test, 7.036; $p < 0.001$. dyn, dynes.

components of hyperdynamic circulation (that is CO, CI and SVR) individually and their association in a linear fashion in the study population. Not only did we confirm these findings, we also observed an association of the presence or absence of hyperdynamic circulation according to the arbitrary definition, taking into account both components and different parameters that reflect the severity of liver disease, such as Child-Pugh grade and MELD score. Nevertheless, no association was detected between the severity of ascites and hyperdynamic circulation according to this classical concept.

The idea that hyperdynamic circulation would be identified by a shift in the relationship between SVR and CO rather than an absolute value is mathematically sound, given the formula that associates SVR and CO, which is SVR = (MAP – CVP)/CO × 80. Because blood pressure is the third factor in the equation, these differences reflect differences in blood pressure between patients with different severity of ascites. There were no differences in the slopes of the curves, suggesting that the relationship between the three players was maintained. A similar phenomenon has been observed when classifying patients with arterial hypertension according to severity of the arterial hypertension, and this phenomenon has been proposed as an explanation for heterogeneous response to antihypertensive drugs.[23] The main implications of the study are conceptual and pathophysiological rather than directly clinical. Indeed, the presence of hyperdynamic circulation has a central role in the development of complications of cirrhosis. A better understanding of what hyperdynamic circulation is can allow us to better evaluate complications of hyperdynamic circulation, such as cirrhotic cardiomyopathy.

This study has several limitations. First, due to its cross-sectional nature, one cannot establish a temporal relationship between a clinical phenotype (i.e., refractory ascites) and a hemodynamic pattern. Additionally, we could not evaluate the hemodynamic differences between the two types of refractory ascites (diuretic resistant and diuretic intractable) or in patients with subclinical forms of ascites. Second, because the databases were not designed initially for this study, some of the information is missing. Third, all three substudies included patients who were on beta blockers. Subanalysis excluding patients on beta blockers in the prospective study showed similar results (data not shown), although due to reduced sample size, some of these differences were not significant. Furthermore, no information was available to evaluate other drugs that may impact hemodynamics, such as diuretics and albumin. The third substudy was not designed to evaluate other possible mechanisms beyond the ones included in the systemic inflammation hypothesis that could be involved in the development or worsening of ascites. Finally, although the hyperdynamic circulation shift hypothesis is mathematically sensible, the present study was not designed to further explore this finding, namely its association to activation of vasoactive systems, which would be the ultimate marker of the presence of hyperdynamic circulation. In the subgroup in which we did have a measurement of renin, an increase of renin according to ascites severity was observed, but this sample was too small to evaluate the curves.

The main strength of the study is that it includes three different, large, study populations of patients with cirrhosis from two different countries with clinical characterization and hepatic and systemic hemodynamic measurements. Despite the fact that the German and Spanish population had differences regarding etiology and some hemodynamic parameters, similar results were found. In our opinion, this strengthens our observation.

In conclusion, this study shows that, according to the present concept (high CO and low SVR), a considerable group of patients would not have hyperdynamic circulation despite the presence of ascites and even refractory ascites. Evaluation of the CO–SVR relationship according to the severity of ascites shows a progressive shift to the left, suggesting that identification of this shift would be the way to identify the presence of hyperdynamic circulation without considering absolute cutoffs.

AUTHOR CONTRIBUTIONS

Cristina Ripoll designed the study, supervised the collection of the data, did the statistical analysis, wrote the paper, and is the guarantor of the article. Luis Ibáñez-Samaniego collected the data and provided valuable intellectual input. Beatrix Neumann collected the prospective data, ran the enzyme-linked immunosorbent assays, and provided valuable intellectual input. Javier Vaquero and Robin Greinert provided valuable intellectual input. Rafael Bañares provided valuable intellectual input and critically reviewed the manuscript. Alexander Zipprich supervised the collection of data, provided valuable intellectual input, and critically reviewed the manuscript. All authors approved the final version of the manuscript.

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CONFLICT OF INTEREST

Cristina Ripoll is on the speakers' bureau of Gore and CSL Behring; she received grants from DFG. Alexander Zipprich advises and is on the speakers' bureau of CLS Behring; he is on the speakers' bureau of Gore. The other authors have nothing to report related to the topic of the study.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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