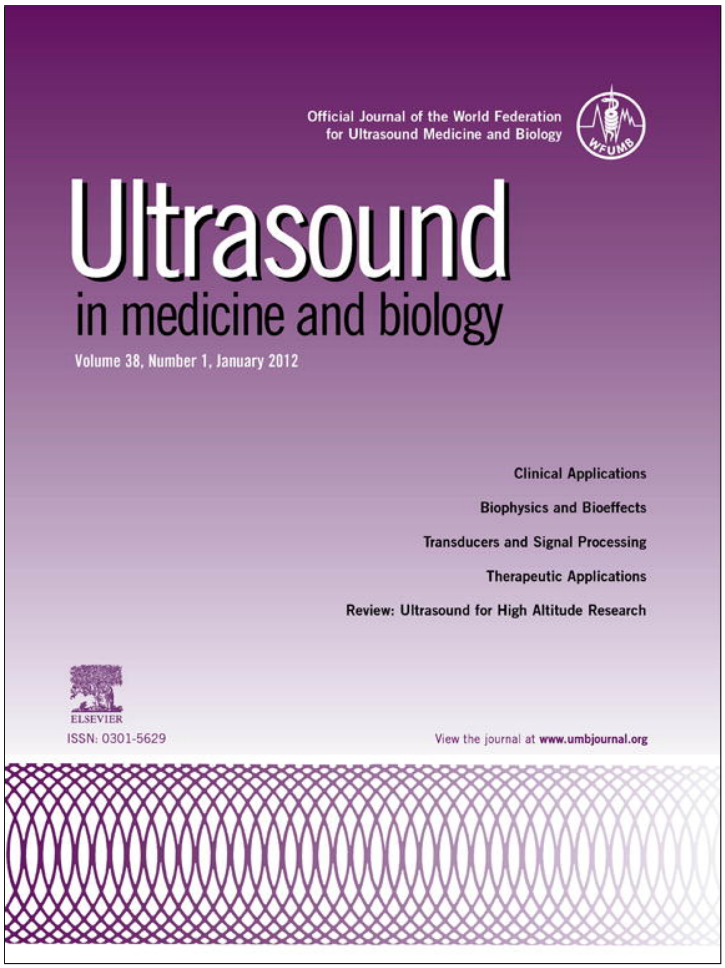

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● *Original Contribution*

SPLENIC DOPPLER IMPEDANCE INDICES ESTIMATE SPLENIC CONGESTION IN PATIENTS WITH RIGHT-SIDED OR CONGESTIVE HEART FAILURE

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Abstract—Splenic Doppler impedance indices are measurements of splenic congestion in chronic liver disease. It is not known whether they can also assess splenic congestion in patients affected by right-sided or congestive heart failure. We analyzed splanchnic hemodynamics with Doppler ultrasound and systemic hemodynamics with right-sided heart catheterization in patients with heart failure. Splenic pulsatility index (PI) was higher in patients with heart failure (48 patients) compared with healthy subjects (39 patients) (1.19 ± 0.41 *vs.* 0.73 ± 0.11, $p < 0.0001$) and was related to hepatic vein diameter ($p = 0.02$). Splenic PI was not related to systemic arterial pressure, cardiac output, systemic vascular resistance or splenic arterial resistance, whereas it was related to right atrial mean pressure ($p = 0.0003$) and to right ventricle end-diastolic pressure ($p = 0.011$) (34 patients). In conclusion, splenic PI is a measurement of splenic congestion caused by an increase in venous outflow resistance. It can estimate splenic congestion in patients with right-sided or congestive heart failure. (E-mail: massimo.bolognesi@unipd.it) © **2012 World Federation for Ultrasound in Medicine & Biology.**

Key Words: **Doppler ultrasound, Splenic pulsatility index, Spleen, Heart failure, Congestion of the spleen.**

INTRODUCTION

The measurement of Doppler impedance indices (DIIs) is a simple, noninvasive method to evaluate alterations in arterial hemodynamics. These indices are calculated as resistance index (RI = [peak systolic velocity – end-diastolic velocity]/peak systolic velocity) and pulsatility index (PI = [maximum velocity – minimum velocity]/mean velocity) (Taylor et al. 1985). DIIs are used to evaluate the hemodynamic effect of arterial stenosis and also for estimating arterial resistance of the organ downstream of the sampled vessel (Scoutt et al. 1990). These indices are essentially considered measurements of arterial resistance, but their significance varies according to the investigated organ. Splenic DIIs are increased in patients with cirrhosis and portal hypertension (Bolognesi et al. 1996), because these indices probably do not only reflect the resistance in the arterial and capillary bed of the spleen, but more likely the sum of downstream resistance, including the splenic arterial and capillary bed as well as splenic and portal venous and hepatic vascular resistance (Taourel et al. 1998). Therefore, splenic DIIs are influenced by venous congestion of the organ. We previously demonstrated that splenic PI is related to portal pressure and portal vascular resistance (Bolognesi et al. 1996, 2001), and, considering the high R^2 of the correlation ($R^2 = 0.76$), it could be a surrogate measurement of portal resistance and splenic congestion. Studies carried out by other authors confirmed this hypothesis (Piscaglia et al. 2002; Liu et al. 2006, 2007; Grgurevic et al. 2011). However, to date splenic DIIs have been analyzed almost exclusively within the context of chronic liver diseases, *e.g.*, cirrhosis with portal hypertension, hepatic fibrosis in chronic viral hepatitis, relapse of viral hepatitis after liver transplantation, acute rejection after liver transplantation and surgical liver resection in cirrhosis (Bolognesi et al. 1998; Sugimoto et al. 2002; Liu et al. 2006, 2007; Bolognesi et al. 2008; Grgurevic et al. 2011). There is no study assessing whether splenic DIIs can be used to estimate splenic congestion in other clinical conditions. Hence, it is not known whether an increase in these indices can be considered a feature of splenic congestion irrespective of its cause. Splenic congestion assessment

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may help the clinician to estimate splanchnic congestion and better understand abdominal complaints such as abdominal pain and digestive disorders.

The aim of this study was to analyze the mechanisms that determine splenic DIIs and to assess splenic DIIs in the course of heart failure, a nonhepatic disease causing splanchnic and splenic congestion.

PATIENTS AND METHODS

Design of the study

We included patients aged 18 years or older who were referred to the Department of Clinical and Experimental Medicine, University of Padua. Three study protocols were performed: (a) The analysis of the behavior of splenic DIIs in patients with heart failure, (b) the analysis of the relationships between splenic DIIs and systemic hemodynamics in patients with heart failure and (c) the analysis of the relationship between splenic DIIs and splenic arterial resistance.

In protocol (a) patients with heart failure and control subjects were included; portal vein diameter, portal blood velocity (PBV), portal blood flow volume (PBF), splenic PI, spleen size and diameter of the hepatic vein (HV) were measured.

In protocol (b) patients with heart failure (a subset of those included in protocol (a)), who underwent right-sided heart catheterization, were included; these patients underwent cardiac catheterization during complete evaluation for cardiac transplantation; in these patients, mean systemic arterial pressure (MAP), cardiac output, systemic vascular resistance, right atrial mean pressure, right ventricular end-diastolic pressure and pulmonary capillary wedge pressure were measured.

In protocol (c) patients without heart failure and normal subjects were included. In these patients, MAP, splenic blood flow, splenic vascular resistance (SplVR) and splenic PI were measured.

The enrolled patients with heart failure were those whose disease was potentially a cause of congestion/stagnation in splanchnic veins. Therefore, patients with heart failure were included if they had a syndrome of fluid retention with symptoms or signs of systemic venous congestion (Jessup et al. 2009), such as neck vein distention and systemic vein distention, ankle edema and congestive hepatomegaly. Both patients with right-sided heart failure and patients with congestive heart failure were included. All patients underwent echocardiography, chest radiograph and upper abdomen ultrasonography. N-terminal pro-B–type natriuretic peptide (NT-proBNP) was increased in all patients (Jessup et al. 2009). The *a priori* criteria for exclusion from the study were: the presence of liver carcinoma or intestinal malignancies, because the changes induced by these diseases to splanchnic resistance are not foreseeable; and atrial fibrillation, because no reliable measurement of DIIs is possible in this condition. Exclusion criteria were also: poor visualization of the upper abdomen by the Doppler method, portal vein or splenic vein thrombosis or stenosis. Indeed, vascular alterations, such as portal or arterial thrombosis or stenosis *per se* are known to modify splanchnic Doppler measurements (Dodd et al. 1994; Kok et al. 1998). The study was conducted in accordance with the guidelines of the Declaration of Helsinki of 1975. Informed consent to participate in the study was received from each person. The experimental protocol was approved by our institutional review board. In the included patients, the following measurements were obtained with ultrasound (US) technique: Diameter of portal vein and of HV, PBV and PBF; splenic PI; and spleen size. Cardiac output, systemic vascular resistance, right atrial mean pressure, right ventricular end-diastolic pressure and pulmonary capillary wedge pressure were measured invasively with right cardiac catheterization.

To examine the relationship between splenic DIIs and splenic arterial resistance, patients with chronic hepatitis, fatty liver, liver transplantation, hematologic malignancies (hematological proliferative disorders) and healthy control subjects were enrolled. The group of patients with fatty liver was selected as follows: in patients with increased echogenicity of the liver parenchyma (indicative of the presence of steatosis), anamnestic data were gathered to highlight the potential chronic alcohol use/misuse; having excluded alcohol-related etiology, patients were classified as having nonalcoholic fatty liver disease and allowed into the study. In each of these patients, splenic PI, spleen size and SplVR, according to the method specified below, were measured. Patients whose portal pressure or central venous pressure were expected to be increased, such as patients with liver cirrhosis or heart failure, were not included in the latter analysis, because an increase in splenic vein pressure cannot be neglected in the calculation of splenic arterial resistance (see the formula below).

Methods of measurements

Duplex Doppler US measurements. All subjects were examined in the morning after an overnight fast. Splanchnic hemodynamic measurements were performed with echo-color Doppler. A HDI 5000 (ATL, Seattle, WA, USA) with color Doppler sonography and a broadband curved array transducer (C5-2 40R) was used. Measurements were performed in suspended normal respiration. PBV was evaluated as the time-averaged maximum velocity multiplied by the coefficient 0.57, assuming the portal velocity profile to be parabolic (Moriyasu et al. 1986; Bolognesi et al. 1996). PBF was calculated

by multiplying PBV by the cross-sectional area of the portal vein, assuming a circular shape of the portal vein section and therefore calculated from its anteroposterior diameter (Sacerdoti et al. 1995; Bolognesi et al. 1996). The arterial DIIs of the spleen were measured as PI (Taylor et al. 1985; Bolognesi et al. 1996). We chose to use PI instead of RI because PI, taking into account the mean velocity in its calculation, is probably more sensitive to changes in velocity profile and it better reflects resistance in the distal capillary bed (Singal et al. 2010). Splenic PI values were measured near the hilum of the spleen, in one of the main branches of the splenic artery, 1–2 cm within the parenchyma of the organ, as previously reported (Bolognesi et al. 1996; Sacerdoti et al. 1997). Spleen size was estimated by the bipolar diameter because it has been shown that this measurement well reflects the volume of the organ (Rosenberg et al. 1991). HV diameter was measured in the middle hepatic vein, between 1 and 2 cm from the inferior vena cava. All examinations were performed by equally skilled operators. To decrease interobserver variability in the Doppler US results, all three US operators participated in a cooperative training program according to Sabbà et al. (1995) and Sacerdoti et al. (1997) before the beginning of the study.

Right-sided heart catheterization measurements. The procedure was undertaken in the cardiac catheterization laboratory, within one week from US evaluation. A Swan-Ganz catheter was introduced via the femoral vein under fluoroscopic guidance for hemodynamic measurements. The following hemodynamic variables were measured: right atrial mean pressure, right ventricular end-diastolic pressure and pulmonary capillary wedge pressure. Cardiac output was measured using the thermodilution technique via the Swan-Ganz catheter. Systemic vascular resistance was measured as (eqn (1)):

$$\text{Systemic Vascular Resistance}\left(\text{dyne s cm}^{-5}\right) = \{(\text{MAP [mm Hg]} - \text{Central Venous Pressure [mm Hg]}) / (\text{Cardiac Output [L/min]})\} \times 80$$

where central venous pressure was estimated by right atrial mean pressure and MAP was calculated as (eqn (2)):

$$\text{MAP} = \text{diastolic blood pressure} + 1/3(\text{systolic} - \text{diastolic arterial pressure})$$

Splenic arterial resistance measurement. Total splenic resistance can be calculated by dividing MAP by splenic blood flow. In the patients and healthy subjects included in this group, portal pressure was probably normal, and therefore we considered it acceptable to neglect it in the calculation. The measurement of splenic arterial blood flow is theoretically possible with echo-Doppler, by measuring the flow in the trunk of the splenic artery. Unfortunately, this measurement is not feasible because of methodological and anatomical problems. The methodological problems arise because Doppler measurement requires the presence of a straight tract of the vessel where the angle of incidence between the US beam and the direction of flow can be calculated, but the course of the splenic artery has no clear straight tract. Moreover, calculation of flow needs the measurement of the average velocity of the flow and of the cross-sectional area of the vessel, which are both difficult to measure in the splenic artery, because of the pulsatility of arterial flow and the variations of the cross-sectional area of the vessel with the arterial pulse. There is also the problem, because of the presence of branches of the splenic artery (*i.e.*, pancreatic branches, posterior gastric, short gastric, left gastro-epiploic arteries), that may originate downstream of the only tract of the splenic artery that might be sampled (immediately after its origin from the trifurcation of the celiac axis). To overcome these methodological problems, the flow of the splenic vein (in the left part of the retropancreatic tract), instead of the flow of the splenic artery, may be measured. The flow of the splenic vein is laminar and therefore can be measured more accurately. The flow of the splenic vein should, at least in theory, be comparable to that of the artery. However, measurement of splenic venous flow tends to overestimate the actual flow of the spleen, because the splenic vein drains blood not only from the spleen, but also partially by the stomach, pancreas and great omentum. Despite these problems, we decided to calculate SplVR by using splenic vein blood flow as an estimate of splenic blood flow.

In summary, SplVR were calculated as (eqn (3)):

$$\text{SplVR}\left(\text{dyne s cm}^{-5}\right) = (\text{MAP [mm Hg]} / \text{splenic blood flow [L/min]}) \times 80$$

Splenic blood flow was approximated by measuring flow in the splenic vein. The splenic vein was visualized in the retropancreatic tract, placing the probe transversely in the epigastric region. The pulsed Doppler sample volume was placed within the lumen, in the left tract of

the retropancreatic arc, so that the incident beam had an angle of $<60°$ (Barbara et al. 1990). The sample volume occupied about half of the lumen. The measurement was performed in suspended respiration. The average velocity of flow in the splenic vein was measured as the maximum average profile multiplied by 0.57, assuming that the flow in the splenic vein is laminar and therefore that the profile of the velocity in the vessel is parabolic (Moriyasu et al. 1986). We did not measure average velocity by spectral Doppler analysis, because in our experience, the variability of the measurement of average blood velocity by spectral Doppler analysis is significantly higher than the measurement of the maximum average profile multiplied by 0.57 (unpublished data). Splenic blood flow was calculated by multiplying the splenic blood velocity by the cross-sectional area of the splenic vein, which is considered circular and therefore calculated from its antero-posterior diameter measured at the Doppler sampling.

Statistical analysis

Results are reported as mean ± standard deviation. When data from two groups of patients were compared, Student's *t*-test for unpaired samples was used. Correlations were investigated by the least-squares method. The null hypothesis was rejected if $p < 0.05$ values were obtained.

RESULTS

Evaluation of splenic PI in heart failure

Forty-eight patients with right-sided or congestive heart failure and 39 healthy subjects were included. The clinical characteristics of patients and healthy subjects are shown in Table 1. In comparison with healthy subjects, patients with heart failure had lower PBV ($p = 0.018$) and PBF ($p = 0.002$), higher splenic PI values ($p < 0.0001$), HV diameter ($p = 0.004$) and spleen size ($p = 0.011$) (Table 2) (Fig. 1). In patients with heart failure, splenic PI was inversely correlated to PBF ($R = -0.32$, $p = 0.032$), whereas it did not correlate with portal vein diameter, PBV or spleen size. Splenic PI was also related to the diameter of HV ($R = 0.35$, $p = 0.020$). By analyzing the patients after they have been divided into two groups depending on HV diameter, *i.e.*, those with normal diameter (<10 mm) and those with increased diameter (≥ 10 mm), splenic PI was higher (1.39 ± 0.38 *vs.* 1.05 ± 0.35, $p = 0.005$), portal vein diameter was higher (10.3 ± 1.7 *vs.* 9.1 ± 1.5 mm, $p = 0.024$) and PBV was lower (13.5 ± 3.4 *vs.* 17.0 ± 5.1 cm/s, $p = 0.017$) in patients with an increased HV diameter when compared with patients with normal HV diameter.

Table 2. Echo-Doppler measurements in control subjects and in patients with heart failure

	Patients with heart failure	Normal subjects	Comparison between the two groups
Portal vein diameter (mm)	9.6 ± 1.7	10.5 ± 1.7	$p = 0.027$
PBV (cm/s)	15.3 ± 4.8	17.7 ± 4.1	$p = 0.018$
PBF (mL/min)	663 ± 237	862 ± 318	$p = 0.002$
Splenic PI	1.19 ± 0.41	0.73 ± 0.11	$p < 0.0001$
Spleen size (cm)	11.0 ± 2.1	10.0 ± 1.3	$p = 0.011$
HV diameter (mm)	9.5 ± 2.3	7.3 ± 1.3	$p = 0.004$

Relationships between splenic PI and systemic hemodynamics in heart failure

Of the 48 patients with heart failure included in the previous analysis, 34 underwent right-sided heart catheterization (male/female: 25/9; age 56 ± 12 y). In these patients, right atrial mean pressure was 9.2 ± 5.6 mm Hg, right ventricular end-diastolic pressure was 11.8 ± 5.8 mm Hg, pulmonary capillary wedge pressure was 20.1 ± 9.4 mm Hg, cardiac output was 4.2 ± 1.1 L/min, MAP was 80 ± 12 mm Hg and systemic vascular resistance was 1429 ± 396 dyne s cm^{-5}. In these patients, splenic PI was significantly correlated to the right atrial mean pressure ($R = 0.59$, $p = 0.0003$) and to the right ventricular end-diastolic pressure ($R = 0.46$, $p = 0.011$). By contrast, splenic PI was not correlated to pulmonary capillary wedge pressure, MAP, cardiac output or systemic vascular resistance.

Relationship between splenic pulsatility index and arterial resistance of the spleen

To examine the relationship between splenic PI and SplVR, 13 patients and 14 control subjects were included. The clinical characteristics of patients and control subjects included in this part of the study are detailed in

Table 1. Clinical characteristics of the patients and control subjects included in the study

	Patients with heart failure	Normal subjects	Patients included to study SplVR
Number of patients	48	39	27
Male/Female	30/18	20/19	19/8
Age (y) (mean ± SD)	62 ± 16	52 ± 12	53 ± 12
Disease (normal subjects/heart failure/NAFLD/hematologic conditions/chronic hepatitis/liver transplant)	0/48/0/0/0/0	39/0/0/0/0/0	14/0/4/2/5/2

NAFLD = nonalcoholic fatty liver disease.

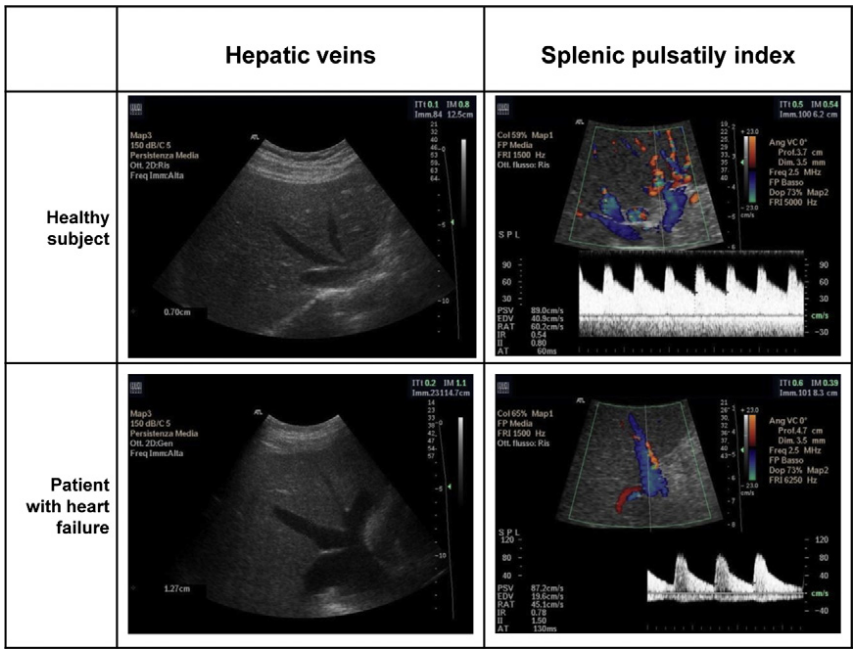

Fig. 1. Examples of splenic pulsatility index (PI) in a healthy subject and in a patient with heart failure.

Table 1. SplVR was similar in patients and in control subjects (35,644 ± 26,440 *vs.* 40,039 ± 15,896 dyne s cm^{-5}, p = NS). Splenic PI was not related to arterial resistance of the spleen (R = 0.25, p = NS).

DISCUSSION

In patients with liver cirrhosis, DIIs are indices of the degree of splenic congestion. This is evidenced by the correlation between splenic impedance indices and portal resistance on the one hand (Bolognesi et al. 1996, 2001) and portal pressure on the other (Bolognesi et al. 2001; Sugimoto et al. 2002; Vizzutti et al. 2007). The usefulness of the evaluation of splenic resistance indices in the evaluation of portal hypertension was confirmed by Piscaglia et al. (2002). These authors showed that splenic RI, which is increased in patients with liver cirrhosis, is within normal limits in patients with arterial hypertension (who we presume to have increased arterial resistance) and in hematological conditions (characterized by splenomegaly and high splenic blood flow, but normal portal resistance). These authors concluded that the assessment of splenic RI is able to distinguish the splenomegaly associated with portal hypertension from that related to other diseases with good accuracy (Piscaglia et al. 2002). However, it is not known whether splenic DIIs may be used as indices of congestion of the portal system in other clinical conditions apart from cirrhosis with portal hypertension.

We found the splenic PI values to be increased in patients with heart failure in whom splanchnic and splenic congestion are present. Splenic PI was higher in those patients with heart failure who had increased HV diameter. Considering that the increase in HV diameter is a feature of increased pressure in the inferior vena cava, responsible for liver stasis (Catalano et al. 1998), the hypothesis that splenic DIIs represent an index of splanchnic and splenic congestion even in the absence of liver cirrhosis is confirmed. In patients with right-sided or congestive heart failure, there is an increase in central venous pressure, resulting in liver and splanchnic stasis and congestion, and, in turn, in an increase in splenic PI. In these patients, splenic PI was not affected by the size of the spleen but it was inversely correlated to PBF, which was decreased in patients with right-sided heart failure compared with normal values, as opposed to what happens in cirrhosis.

Analyzing the relationships between splenic PI and systemic hemodynamics in patients with right-sided or congestive heart failure, we found that splenic PI was not related to pulmonary capillary wedge pressure, MAP, cardiac output or systemic vascular resistance, whereas it *was* related to the right atrial mean pressure (central venous pressure; index of preload) and to the right ventricular end-diastolic pressure. These results confirmed our hypothesis that splenic PI is an index of splenic congestion in heart failure and that it is independent from systemic arterial hemodynamics.

To study in depth the determinants of splenic PI, the relationship with splenic arterial resistance was also analyzed. In two previous studies, we demonstrated the relations between splenic PI values and portal venous

resistance (Bolognesi et al. 1996) and portal pressure (Bolognesi et al. 2001). On the other hand, the role of splenic arterial resistance in determining splenic PI values has not been defined. Notwithstanding the methodological limitations of the measurement of splenic arterial resistance by echo-Doppler, as specified in the Patients and Methods section, this study showed that splenic PI values do not correlate with SplVR. The significance of splenic PI as an index of splenic congestion is thus further confirmed and strengthened.

The finding that in the spleen a Doppler arterial index is mainly influenced by venous instead of by arterial hemodynamics can probably be explained by the fact that the spleen is a parenchymal organ with low arterial resistance, characterized by an arterial flow with high diastolic blood velocity. This feature, along with the particular anatomy of the spleen, probably makes the arterial DIIs sensitive to splenic venous outflow resistance even in noncirrhotic patients, such as in patients with heart failure. This measurement may also be useful to estimate splanchnic congestion, which can cause abdominal pain and digestive disorders which are often reported by patients with congestive heart failure. Further, it may be an additional feature useful for guiding diuretic therapy in these patients. Although this single study is not sufficient to propose an extensive use of splenic PI in routine diagnostics of patients with heart failure, we believe the results suggest that this index has the potential to be used as a simple index of splenic congestion in this patient population.

In conclusion, splenic PI is an index of splenic congestion caused by an increase in venous outflow resistance and it is not influenced by splenic arterial resistance. Splenic PI can be used to estimate splenic congestion in conditions such as right-sided and congestive heart failure.

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