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Elisabetta Buscarini
Guido Manfredi
Alessandro Zambelli
Gastroenterology Department,
Center for the Diagnosis,
Therapy and Surveillance of HHT,
Maggiore Hospital,
Largo Dossena 2,
26013 Crema, Italy
E-mail address: ebuscarini@rim.it

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New signs and old applications of echo-color-Doppler should always be compared to a gold standard

To the Editor:

We thank our colleagues for the comments to our paper, which allow us to better clarify some aspects regarding the US diagnosis of liver involvement in hereditary hemorrhagic teleangiectasia (HHT) patients.

In our study, we described a new Doppler sign, called 'color-spot', particularly suitable for identifying small hepatic arterio-venous malformations (HAVMs) and verified its accuracy using multislice CT (MSCT) as gold standard [1]. Moreover, we clearly distinguished the *color-spots* found in the peripheral subcapsular region of the liver from '*hepatic hypervascularization*', a sign previously reported by Caselitz et al. [2]. Both are suggestive of small HAVMs and provide a greater diagnostic sensitivity for HAVMs in HHT when compared to previously published extrahepatic parameters.

It must be emphasized that the diagnostic sensitivity and accuracy of previous ultrasound (US) findings [2–4] cannot be defined since their results were not systematically compared to a gold standard; in fact, Doppler-negative HHT patients have never been systematically compared with other techniques. Ours is the first controlled study to assess the diagnostic accuracy of Doppler US for diagnosis of HAVMs in HHT with respect to MSCT as a reference technique. According to Buscarini et al., the use of CT as gold standard is debatable, as we employed a 4-detector CT scanner which is not the best available technology; however, these authors did not consider that our prospective study was conducted over a four-year period. Having initiated our study with a 4-detector CT scan and in order to avoid inter-equipment variability [5], we preferred to prospectively study a large patient sample maintaining the same methodology, even if meanwhile a more sophisticated 16-detector scan had become available (moreover, our HHT-experienced radiologists have not found any difficulties in identifying tiny vascular abnormalities with both CT scanner systems).

The two signs (*color-spot* described by our group and *peripheral hypervascularization* reported by Buscarini et al. [4]) are two distinct echo-color-Doppler parameters. The *color-spot* sign appears in the presence of isolated spotty-like images with a high blood-flow velocity and a resistive index (RI) less than 0.45. It corresponds to a point on a very small peripheral tortuous arterial vessel where, due to a Doppler angle close to zero, the high Doppler frequency shift overcomes the threshold of detection, thus giving rise to a visible spotty-like image (whereas the remaining tract of the vessel, characterized by an unfavourable Doppler angle, undergoes a reduction in the intensity of the ultrasound

signal, thus remaining undetected). This 'spot effect' is peculiar of very small vessels while tortuous vessels of larger size (such as 1st and 2nd degree branches of the hepatic artery, often protruding into the peripheral liver region) can be detected in their entire length with color Doppler, occasionally as a 'spider-like' sign, corresponding to the "*peripheral hypervascularization*" described by Buscarini et al. [4]. Therefore, the images of *peripheral hypervascularization* should not be considered as a superimposition of our *color-spot* images. Hence, our *color-spot* is a new Doppler sign and not, as suggested by these authors, merely a previously-reported sign with a new name. In fact, in our cohort, we can affirm that the majority of HAVM-patients (122/128, 95%) received a positive Doppler-based diagnosis by means of the new *color-spot* sign, thus reaching a prevalence similar to that detected by MSCT (84%). Given the very small size of many liver AVMs [6], we can also conclude that *color-spots* represent a sign revealing the presence of small liver AVMs even earlier than Buscarini's *peripheral hypervascularization*, since the latter sign requires the visualization of the entire vessel tract to be detected (and consequently only abnormalities involving larger vessels can be depicted).

We clearly defined the term *hypervascularization* as a "highly evident appearance of the *main* hepatic artery branches in the portal spaces; the higher flow velocities generated by the shunts determine tortuosity and enlargement of these vessels, evidenced by color-Doppler as tones varying in intensity from bright red to yellow orange" [1]. In the majority of our patients, this sign was observed in absence of any extrahepatic signs or intrahepatic B-mode-signs. Therefore, only in a few cases was it concomitant with evident hepatic artery (HA) dilatation, strongly increased HA flow velocity and other B-mode-signs included in grades 2–4 of the classification reported by Buscarini [4]. Rather, hypervascularization seems to even indicate an only moderate increase of blood flow velocity in HA branches which might be secondary to numerous subcapsular, low-RI, micro-AVMs with little haemodynamic impact, which accounts for its use as a sign suggestive of small AVMs. Therefore, it cannot always be suggestive of "obvious, prominent vascular abnormalities".

Our results clearly show that intra-hepatic signs (both *color-spots* and *hypervascularization)* have a better sensitivity and accuracy than extrahepatic ultrasonography parameters (95–82% vs 40%, and 90–81% vs 50%, respectively). Regarding this point, Buscarini et al. noted that we utilized the cut-off values reported by Caselitz et al. [2] particularly the HA diameter of >7 mm, and stated that this cut-off might be affected by a selection bias, and, consequently, determine "the risk of a low diagnostic sensitivity when applied to the screening of a general HHT population". The use of a lower cut-off is suggested, as proposed in their classification, (HA > 6 mm in grade 1 and HA diameter >5 mm–<6 mm in grade 0+) [4]. Therefore, to dispel their concerns, in the present letter we report our data on intra-hepatic signs with respect to the HA diameter, taking into account both cut-offs (Caselitz [2] and Buscarini [4], Table 1).

As shown, the use of a lower hepatic artery diameter cut-off (>6 mm, grade 1) would not determine a significant increase in HAVM-positive patients (from 46/128 to 65/128 pts), and consequently in the sensitivity of HAVM detection of our cohort (from 35% to 50% sensitivity). Utilizing an even lower cut-off (>5 mm, grade 0+) would definitely permit an increase in HAVM-positive patients (from 65/128 to 104/128 pts), and thus in the sensitivity (although to a lesser extent than the intra-hepatic parameters, 80% for HA diameter vs 95% for color-spot), but would also determine a decrease in specificity and accuracy (64% and 77% for HA diameter vs 68% and 90% for color-spot), given the evident overlapping with MSCT-negative patients (together with non-HHT subjects and non-HHT-related cirrhotic patients).

On the other hand, to avoid such a decrease in specificity, Buscarini et al. [4] included their grade 0+ among the grid of parameters also requiring the detection of another extrahepatic parameter (namely, hepatic artery resistive index (HA-RI) < 0.55). In the table, the results based on HA-RI show that a very low sensitivity value

Table 1
Color-spot, hypervascularization and hepatic artery RI (<0.55) in MSCT+/MSCT− patients according to HA diameter cut-off (mm)

Parameters	HA > 7	HA > 6/⩽7	HA > 5/⩽6	HA ⩽ 5	Total
MSCT+ patients	46	19	39	24	128
Color-spot	46	19	36	21	122
Hypervascularization	46	18	29	13	106
HA-RI < 0.55	12	2	4	4	22
MSCT− patients	1	2	6	16	25
Color-spot	0	1	3	5	9
Hypervascularization	0	1	3	2	6
HA-RI < 0.55	0	0	2	1	3

Abbreviations: MSCT = multislice computer tomography; RI = resistive index; HA = hepatic artery.

(13%) would result. Actually, the majority of cases without dilatation of HA (using both Caselitz and Buscarini's thresholds) had both *color-spot*s and *hypervascularization*, thus further supporting our statement that intra-hepatic parameters have a better sensitivity and accuracy than extrahepatic ultrasonography parameters due to their ability to permit the diagnosis of even very small AVMs in their early stage of development. Evidently the presence of more severe vascular involvement determines an angiodynamic remodelling and gross abnormalities which can be detected on B-mode ultrasonographic study (mainly enlargement of HA in the extrahepatic tract and 'double channel aspect' in the portal spaces).

In conclusion, in this first controlled, prospective study, we have demonstrated that the diagnosis of HAVMs in HHT can reliably be made by merely using intra-hepatic parameters and does not require evidence of extrahepatic abnormalities. The latter are useful to grade the haemodynamic impact of HAVMs and the possible effect on liver angioarchitecture and clinical significance. We disagree with Dr. Buscarini's final comment in which she states that "Doppler US diagnosis of liver VMs in HHT requires a combination of extrahepatic and intra-hepatic findings, which can provide a diagnostic accuracy ranging between 95% and 99% for different observers" [7] because in the absence of a standard reference technique, data on sensitivity and accuracy cannot be considered reliable.

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Carlo Sabbà
Paolo Buonamico
Gennaro Mariano Lenato
Arnaldo Scardapane
University of Bari, Dimimp, Policlinico, Piazza Giulio Cesare Bari 70124, Italy
**Tel./fax: +39 080 5478708*
E-mail address: c.sabba@dimimp.uniba.it

Francesco D'Ovidio
University of Bari, Department of Statistics, Bari, Italy

Maurizio Pompili
Catholic University of Sacred Heart, Rome, Department of Internal Medicine, Rome, Italy

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Prevalence of hepatitis C in Romania: Different from European rates?

To the Editor:

We have read with much interest the review by Esteban et al. on the changing epidemiology of hepatitis C virus (HCV) infection in Europe [1]. Hepatitis C has become a major public health problem worldwide with significant geographical and temporal heterogeneity. The burden of HCV infection in Romania is an area of great concern for at least three main reasons: (1) based on scarce and outdated information, Romania is considered the European country with the highest prevalence rate (double that of Spain or Greece, for example); (2) Romania is one of the most important sources of migrant population towards Western Europe, in particular to countries such as Spain and Italy, therefore altering the decreasing trend of HCV prevalence in these countries; (3) last but not least, there is an urgent need for a national strategy for the active detection and control of the silent epidemic of HCV-infected population in Romania. Although HCV infection is a major public health problem in Romania, its prevalence in the general population and its routes of transmission are largely unknown. Before 1989, during the communist era, data on the prevalence of viral hepatitis in Romania were scarce. The reported prevalence of HCV infection in Romania