Macros and microcirculation patterns of intrahepatic blood flow changes in patients with hereditary hemorrhagic telangiectasia

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AIM
To evaluate vascular dynamic processes in the liver of hereditary hemorrhagic telangiectasia (HHT) patients by ultrasound (US) considering quantitative analytic methods.

METHODS
The imaging features on US and contrast-enhanced ultrasound (CEUS) in 18 patients diagnosed with HHT were retrospectively analyzed. Regarding CEUS, realtime contrast harmonic imaging and sulfur hexafluoride-filled microbubbles were used.

RESULTS
HVaMs were identified in all 18 patients. By US, the two major Caselitz criteria could be detected in 55.6% patients. "Color spots" were detected in 72.2% of the cases. Respecting sonographic grading criteria
Hereditary hemorrhagic telangiectasia (HHT) is a systemic autosomal dominantly inherited affection concerning the vasculature. It is assumed a rare disorder (1/5000 to 1/10000 births) with no differentiation between race, age or sex.[1,2] HHT is definitive when more than two of the following Curaçao criteria are present: (1) “Hereditary”, meaning at least one-first degree relative with HHT; (2) “Hemorrhagic”, meaning unprompted recurrent nose bleeds; (3) “Telangiectasia”, meaning several telangiectases at typic sites: lips, oral cavity, fingers, nose; and (4) Visceral involvement, such as gastrointestinal telangiectasia, pulmonary arteriovenous malformations (VaMs), hepatic VaMs, cerebral VaMs and spinal VaMs.[3]

Hepatic VaMs (HVaMs) can be detected in circa 78% of HHT patients, but merely 8% are symptomatic.[4,5] Shunts are especially arteriovenous, merely few cases of arteriportal and portovenous shunts have been reported.[6,7] The clinical appearance comprises high-output heart failure, portal hypertension and biliary disorder.[8] Diagnosis of HVaMs is usually made in the first line by vascular ultrasound (vUS) including color coded Doppler sonography (CCDS) and Power Doppler (PD) but also by magnetic resonance imaging tomography (MRI) or by computerized tomography (CT).

The advent of contrast-enhanced ultrasound (CEUS) has greatly ameliorated the aptitude to illustrate macro- and microcirculation in focal hepatic lesions[9–15], yet, so far only one case report delineated the use of CEUS in HHT associated HVaMs.[16] To better understand US characteristics of HHT hepatic involvement we analyzed for the first time HVaMs in a group of patients (n = 18) using CEUS and supplemented qualitative data with quantitative perfusion time intensity curve (TIC) analysis.

INTRODUCTION

Hereditary hemorrhagic telangiectasia (HHT) is a systemic autosomal dominantly inherited affection concerning the vasculature. It is assumed a rare disorder (1/5000 to 1/10000 births) with no differentiation between race, age or sex.[1,2] HHT is definitive when more than two of the following Curaçao criteria are present: (1) “Hereditary”, meaning at least one-first degree relative with HHT; (2) “Hemorrhagic”, meaning unprompted recurrent nose bleeds; (3) “Telangiectasia”, meaning several telangiectases at typic sites: lips, oral cavity, fingers, nose; and (4) Visceral involvement, such as gastrointestinal telangiectasia, pulmonary arteriovenous malformations (VaMs), hepatic VaMs, cerebral VaMs and spinal VaMs.[3]

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Core tip: For the first time we analyzed contrast-enhanced ultrasound (CEUS) examination of a group of 18 hereditary hemorrhagic telangiectasia (HHT) patients regrading macro- and microcirculation. This new information could be used to sub-classify a high risk group of asymptomatic patients with therapeutic indication. With regard to the advent of new therapeutic agents, CEUS analysis can complete the required accurate cost-effective screening methods in HHT patients.

MATERIALS AND METHODS

Patients
B-mode US, vUS with CCDS/PD as well as CEUS imaging data of 18 patients were retrospectively analyzed. Diagnostic was made considering the Curaçao criteria. The database was searched for all patients in the years 2015/2016 who got vUS or CEUS examinations after being diagnosed with HHT in the Ear–Nose–Throat (ENT) department of the University Hospital of Regensburg (UKR).

This study was approved by the ethical committee of the UKR and the demand for informed consent was waived, each patient accepting injection of contrast agent for CEUS investigation.

Imaging examinations
All US investigations were accomplished with a high-end US scanner (LOGIQ E9, GE Healthcare, Milwaukee, United States). The frequency of the convex transducers ranged from 1.0 to 5.0 MHz, all being conceptualized for abdominal use. Contrast specific imaging in terms of amplitude modulation (AM) or pulse inversion harmonic imaging was installed in the US system. A sulfur hexafluoride-filled microbubble contrast agent (SonoVue, Bracco, Milan, Italy) was applied in this work. A volume of 1.0 to 2.4 mL of this agent was injected intravenously in a bolus manner via antecubital vein, followed by administration of 10 mL of 0.9% NaCl.

All US investigations were executed by one radiologist who had more than five years of experience in CEUS and conducted more than 3000 US/year over more than 15 years. Uniform imaging settings were applied and all the US methods were implemented conformable to standard protocol. An entirely exploration of the liver was achieved by vUS before...
CEUS for each patient. For CEUS a sweep technology was used for detection of contrast enhancement in the center and the peripheral parenchymal structures. The mechanical index (MI) was reduced less than 0.16, which allows effective tissue annulment to constitute nearly pure microbubble pics and prevent their destruction. Usually, the focus was placed under the target lesion. Then CEUS operating mode and a stopwatch were started coincidentally when contrast agent was applied. The CEUS clips until 120 s after the administration were recorded steadily, neither in any alteration in the machine settings nor motion of the transducer. After 120 s the transducer was moved to scan the whole liver. Baseline US images and CEUS cine clips were saved digitally on the hard disks of the US systems and transferred to an archiving system for analysis.

Image analysis
All US images and clips were interpreted retrospectively by two independent scientists who have not participated in the investigation and were uninformed about relevant clinical, laboratorial, histopathological data and the findings of other imaging procedures. Variant views on the enhancement configuration and extent were solved by agreement. The findings were analyzed in respect of suggested sonographic criteria. In 2003 Caselitz et al. proposed major (dilated common hepatic artery > 7 m; intrahepatic arterial hypervascularisation) and minor criteria (systolic Vmax of the proper hepatic artery > 110 cm/s; RI of the proper hepatic artery < 0.60; Vmax of the portal vein > 25 cm/s; tortuous course of the extrahepatic hepatic artery) to establish the diagnosis of HVaMs in patients with HHT. Positivity of two major criteria or one major criterion and at least two minor criteria were required. In 2008 Buonamico emphasized the importance of “color spots” (spotty like images in the peripheral region of the liver)\textsuperscript{[18]}. Independently, Buscarini described in 2011 four sonographic grades considering dilatation of the common hepatic artery, shunt images, sonographic evidence of heart failure or portal hypertension, systolic Vmax of the hepatic artery and RI (EASL guidelines 2015)\textsuperscript{[19,20]}

The CEUS phase was categorized into arterial (8-30 s from contrast agent application), portal (31-120 s) and late (121-360 s)\textsuperscript{[10,11,13]}. The intraductal enhancement intensity was compared to the neighboring liver parenchyma and was divided into hyper-, iso-, hypo- and non-enhancement in compliance to the lately published guideline\textsuperscript{[9]}. The enhancement configurations were subdivided into homogeneous and heterogeneous.

In order to perform TIC analysis eight regions of interest (ROIs) with a diameter of 5 mm were placed in the perfused hepatic artery, portal vein, shunt region and hepatic parenchyma, two ROIs per region. The investigation of the grayscale value represents the perfusion curves in dB. For quantitative investigation, the area under the curve (AUC) and time to peak (TTP) was considered. After calculation of the mean value regarding the two ROIs/region, the percentage in relation to AUC of the hepatic artery (100%), respectively to TTP of the portal vein (100%) was evaluated.

Statistical analysis
The statistical analysis was carried out using Prism 6 software (Graphpad, La Jolla, CA, United States). The continuous data were expressed as mean ± SE of the mean. The comparison between quantitative data was assessed using one way ANOVA. \(P\) values less than 0.05 were regarded statistically significant.

RESULTS

Basic characteristics
The patients were two men and sixteen women, with a mean age of 59.4 ± 12.1 years (range, 21-83 years) at the time of HVaM diagnosis. HVaMs could be identified in all 18 patients. Coexisting disorders like for example aneurysm of the mesenteric vein (\(n = 1\)), ectatic V. cava (\(n = 1\)), ectatic Aorta abdominalis (\(n = 1\)), thrombosis of V. porta with cavernous transformation (\(n = 1\)), focal nodular hyperplasia (\(n = 1\)), hepatic cysts (\(n = 4\)), biloma (\(n = 1\); Figure 1), cholecystolithiasis (\(n = 3\)), sludge in the gall bladder (\(n = 1\)), ascites (\(n = 1\)), splenomegaly (\(n = 1\)), hepatomegaly (\(n = 1\)), steatosis hepatis (\(n = 4\)), high-flow angiomas (\(n = 2\); Figure 2) were present in certain patients. There was no evidence for malignant lesions in the patients. The shunts were situated in the central area (hilum) of the liver (\(n = 13\)), the left lobe of the liver (\(n = 6\)) and segment 8 of the liver (\(n = 10\)), respectively (Table 1).

Findings on B-mode, CCDS and PD
In our 18 patients, the mean value of the diameter of the common hepatic artery was 11.5 ± 2.7 mm. Intrahepatic arterial hypervascularization was identified in 61.1%. Systolic Vmax of the proper hepatic artery was on average 111.0 ± 38.6 cm/s and diastolic Vmax 47.6 ± 15.4 cm/s. RI averaged 0.58 ± 0.04 and Vmax of the portal vein 28.9 ± 6.5 cm/s. In 83.3% of HHT patients, tortuous course of the extrahepatic artery could be demonstrated. “Color spots” were detected in 72.2% of the cases and portal hypertension in 27.8%. HVaMs were particularly arteriovenous and arterioportal (61.1%) while 38.9% were singularly arteriovenous and 16.7% showed even all three HVaMs (arteriovenous, arterioportal and portovenous). Left accessory artery was found only in 3 patients (16.7%). Hepatic veins appeared dilated in 72.2% of cases, while mean diameter of the portal vein was 11.9 ± 2.3 mm.

Taken together, positivity of two major Caselitz criteria could be described in 55.6% patients while
Microcirculation patterns on CEUS - TIC analysis

Quantitative perfusion analysis within hepatic artery, portal vein, shunt region and hepatic parenchyma (two ROIs per region) was performed. In order to better compare the AUC and TTP values we investigated the percentage in relation to AUC of the hepatic artery (100%), respectively to TTP of the portal vein (100%). Obvious significant differences ($P < 0.0001$) in AUC values was found between the four areas, to the effect that highest values were determined in hepatic artery (100%), next in the shunt region (83.9% ± 13.2%), subsequent in the portal vein (54.2% ± 12.6%) and the lowest values were identified in the liver parenchyma (35.2% ± 13.8%).

Concerning TTP (Figures 4 and 6), the fastest maximal enhancement could be detected in the hepatic artery (69.8% ± 33.2%), following the shunt region (87.6% ± 29.3%), the hepatic parenchyma (102.5% ± 22.7%) and finally the portal vein (100%) ($P < 0.02$).

62.5% of the cases with only one positive major criterion had at least 2 positive minor criteria. Buscarini grading criteria were as follows: grade 1 (22.2%), grade 2 (16.7%), grade 3 (44.4%), grade 4 (16.7%) (Tables 2 and 3, Figures 3-5).

Macrocirculation patterns on CEUS

All the 18 patients showed quick and early hyperenhancement during the arterial phase (Figure 1). During the portal and late phases isoenhancement was detected in 16 cases, hyperenhancement in 2 cases. The hepatic cysts showed no enhancement during all the phases. There was no evidence for any “wash out” phenomenon, and thus no hint for a malignant lesion. The areas of hepatic sclerotization showed late enhancement of the portal vein. In two patients several hepatic lesions with quick hyperenhancement and lacking “wash out” phenomenon could be demonstrated, consistent with high-flow angiomas (Figure 4).

Figure 1  HVaM in a 46-year-old woman. B-mode and dynamic images detected in the arterial phase of contrast-enhanced ultrasound (CEUS) (A-D) compared to contrast enhanced magnetic resonance imaging tomography (MRI) (E) and computerized tomography (CT) (F) images. Intrahepatic arterial hypervascularization with tortuous hepatic artery in segment IV, VI, VII and VIII of the liver. Enhanced mean diameter of the hepatic artery (14.4 mm) intra- and extrahepatic. Intrahepatic non/ hypoechoic (B-mode), hypodense (CT) and hypointense (MR; T1-phase) lesion without enhancement (CEUS) in segment V, VI of the liver corresponding most likely to biliary.
Figure 2  High-flow angiomas in a 21-year-old woman. B-mode and contrast-enhanced ultrasound (CEUS) images. Intrahepatic hypoechoic and isoechoic lesions in segment IV, V and VIII of the liver detected by B-mode ultrasound (A and B), showing in CEUS early hyperenhancement during arterial phase without “wash out” phenomenon in portal and late phases (C).

Table 1  Basic characteristics of 18 patients with hereditary hemorrhagic telangiectasia

| Case No. | Gender (M/F) | Age (yr) | HVaMs (yes/no) | Coexisting lesions | Malignant lesions (yes/no) | Location HVaMs |
|----------|--------------|----------|----------------|-------------------|---------------------------|----------------|
| 1        | F            | 83       | Yes            | -                 | No                        | Diffuse        |
| 2        | F            | 60       | Yes            | -                 | No                        | left hepatic lobe; segment 8 |
| 3        | F            | 75       | Yes            | Aneurysm of the mesenteric vein | No                        | Hilaum         |
| 4        | F            | 50       | Yes            | -                 | No                        | Hilaum         |
| 5        | F            | 36       | Yes            | FNH; cholecystolithiasis | No                        | Hilaum         |
| 6        | F            | 75       | Yes            | Sludge in the gall bladder; Ectatic V. cava; ascites | No                        | Hilaum         |
| 7        | F            | 58       | Yes            | Cholecystolithiasis | No                        | Hilaum         |
| 8        | F            | 65       | Yes            | -                 | No                        | Hilaum         |
| 9        | F            | 66       | Yes            | Splenomegaly      | No                        | left hepatic lobe; segment 8 |
| 10       | F            | 52       | Yes            | Steatosis hepatitis | No                        | Segment 8      |
| 11       | F            | 76       | Yes            | Cholecystolithiasis; Hepatic cysts | No                        | Hilaum         |
| 12       | F            | 49       | Yes            | Steatosis hepatitis | No                        | Hilaum; segment 8 |
| 13       | F            | 55       | Yes            | Steatosis hepatitis; Hepatic cysts | No                        | Segment 8      |
| 14       | M            | 72       | Yes            | -                 | No                        | Hilaum         |
| 15       | F            | 21       | Yes            | High-flow angiomas | No                        | Hilaum         |
| 16       | M            | 69       | Yes            | High-flow angiomas | No                        | Segment 8      |
| 17       | F            | 62       | Yes            | Ectatic Aorta abd.; hepatic cysts; Hepatomegaly; Steatosis hepatitis | No                        | Hilaum; segment 8 |
| 18       | F            | 46       | Yes            | Thrombosis of V. porta (cavernous transformation); hepatic cysts; bilioma | No                        | Left hepatic lobe; segment 8 |
Table 2  Findings on B-Mode, color coded Doppler sonography and Power Doppler

| Case No. | Shunt type (a-v/A-p/V-p) | Portal hypertension (yes/no) | Tortuosity extrahepatic A. Hepatica (yes/no) | Vmax portal vein (cm/s) | RI hepatic artery | Vmax hepatic artery (cm/s) | Intrahepatic arterial hyper-vascularization (yes/no) | Diameter common hepatic artery (mm) |
|----------|-------------------------|-----------------------------|---------------------------------------------|------------------------|------------------|------------------------|---------------------------------|---------------------------------|
| 1        | a-v + a-p               | No                          | No                                         | 45.0                   | 0.66             | 105.5                  | Yes                             | 7.4                             |
| 2        | a-v + a-p + V-p         | Yes                         | Yes                                        | 32.3                   | 0.60             | 111.7                  | Yes                             | 19.5                            |
| 3        | a-v + a-p               | No                          | Yes                                        | 20.0                   | 0.56             | 148.1                  | No                              | 15.5                            |
| 4        | a-v                    | No                          | Yes                                        | 20.0                   | 0.55             | 96.0                   | Yes                             | 9.5                             |
| 5        | a-v                    | No                          | No                                         | 44.0                   | 0.59             | 81.0                   | No                              | 9.7                             |
| 6        | a-v + a-p               | No                          | Yes                                        | 36.0                   | 0.56             | 145.5                  | Yes                             | 13.8                            |
| 7        | a-v + a-p               | No                          | Yes                                        | 40.0                   | 0.52             | 60.2                   | Yes                             | 14.2                            |
| 8        | a-v + a-p + V-p         | Yes                         | Yes                                        | 18.0                   | 0.51             | 109.2                  | Yes                             | 13.7                            |
| 9        | a-v                    | No                          | Yes                                        | 22.8                   | 0.55             | 86.7                   | Yes                             | 13.2                            |
| 10       | a-v                    | No                          | Yes                                        | 27.0                   | 0.62             | 92.5                   | No                              | 13.3                            |
| 11       | a-v                    | No                          | Yes                                        | 20.0                   | 0.56             | 87.9                   | No                              | 8.7                             |
| 12       | a-v                    | No                          | Yes                                        | 26.6                   | 0.64             | 245.7                  | Yes                             | 8.2                             |
| 13       | a-v + a-p               | No                          | Yes                                        | 26.9                   | 0.62             | 218.3                  | Yes                             | 9.9                             |
| 14       | a-v                    | No                          | Yes                                        | 25.4                   | 0.65             | 40.5                   | No                              | 7.8                             |
| 15       | a-v                    | No                          | Yes                                        | 27.6                   | 0.64             | 46.0                   | No                              | 12.2                            |
| 16       | a-v                    | No                          | No                                         | 25.2                   | 0.60             | 86.7                   | No                              | 10.0                            |
| 17       | a-v + a-p               | Yes                         | Yes                                        | 30.0                   | 0.50             | 123.8                  | Yes                             | 7.8                             |
| 18       | a-v + a-p               | Yes                         | Yes                                        | 29.6                   | 0.35             | 112.1                  | Yes                             | 12.0                            |

RI: Resistive index; Vmax: Peak flow velocity.

Table 3  Considered sonographic criteria in 18 patients with hereditary hemorrhagic telangiectasia

| Case No. | Buscaliti criteria (2003) | Buonamico grading (2008) | “Color spots” Buonamico (2008) (Yes/No) |
|----------|---------------------------|--------------------------|-----------------------------------------|
| 1        | 2 Major + 2 Minor         | 3                        | Yes                                     |
| 2        | 2 Major + 3 Minor         | 4                        | Yes                                     |
| 3        | 1 Major + 2 Minor         | 1                        | Yes                                     |
| 4        | 2 Major + 2 Minor         | 3                        | Yes                                     |
| 5        | 1 Major + 2 Minor         | 1                        | No                                      |
| 6        | 2 Major + 3 Minor         | 4                        | Yes                                     |
| 7        | 2 Major + 3 Minor         | 3                        | Yes                                     |
| 8        | 2 Major + 2 Minor         | 4                        | Yes                                     |
| 9        | 2 Major + 1 Minor         | 3                        | Yes                                     |
| 10       | 1 Major + 2 Minor         | 2                        | No                                      |
| 11       | 1 Major + 1 Minor         | 2                        | Yes                                     |
| 12       | 2 Major + 3 Minor         | 2                        | Yes                                     |
| 13       | 1 Major + 3 Minor         | 3                        | Yes                                     |
| 14       | 1 Major + 1 Minor         | 1                        | No                                      |
| 15       | 1 Major + 2 Minor         | 1                        | No                                      |
| 16       | 1 Major + 0 Minor         | 3                        | No                                      |
| 17       | 2 Major + 4 Minor         | 3                        | Yes                                     |
| 18       | 2 Major + 4 Minor         | 3                        | Yes                                     |

DISCUSSION

HHT is a rare autosomal dominantly inherited affection characterized by systemic vascular dilatation resulting in arteriovenous fusion in the form of telangiectases or larger vascular malformations, implicating the risk of bleeding events[21].

HVaMs can be demonstrated in most HHT patients, but merely few cases (8%) are symptomatic[4,22]. In symptomatic patients, diagnosis of HVaMs is usually made by vUS including CCDS and PD but also by MRI and CT. Due to currently efforts to identify certain risk factors for progression to the symptomatic stage and thus to sub-classify a high risk group of asymptomatic patients on the one side and the experienced benefits of angiogenesis inhibitors like bevacizumab for treatment of HVaMs on the other side, cost-effective screening of HHT patients for hepatic involvement become more and more attractive[23].

Until now, only one case report by Neye et al.[16] handled with CEUS in HHT patients. However, in this paper only microcirculation patterns were considered and described very rudimentary, without making reference to TIC analysis or reference imaging methods.

In our work we analyzed for the first time HVaMs in a group of patients ($n=18$) applying CEUS and

Reference imaging characteristics

Besides vUS/CEUS examination, in six of eighteen patients contrast enhanced MRI of the liver; in four cases contrast enhanced CT of the abdomen and in two patients angiography of the liver vessels was performed. In all cases, vUS/CEUS covered every detailed finding on abovementioned sophisticated imaging modalities, from precise localization of HHT lesions to accurately morphology characteristics of hepatic vessels right up to information about homogeneity of the liver parenchyma (Figure 1). Actually, vUS/CEUS investigations proved much more exact referring to these features, and especially in diagnosis of challenging lesions suitable for HHT, like high-flow angiomas (Figure 2).

In the two patients in which angiography of the liver vessels was performed, transarterial embolization of HVaMs was carried out repeatedly (3-4x) with successful results, monitored by CEUS three months after each investigation.

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Figure 3  Arteriovenous hepatic malformation (shunt) in a 49-year-old woman. Color coded Doppler sonography and Power Doppler images. A: Intrahepatic arterial hypervascularization with tortuous hepatic artery and aliasing in segment IV (central) and VIII of the liver as well as obvious presence of left accessory artery. Enhanced mean diameter of the hepatic artery (8.2 mm) intra- and extrahepatic and increased peak systolic velocity (245.7 cm/s) and end-diastolic velocity (85.9 cm/s); B: Image of the portal vein of the same patient, showing increased peak flow velocity (27.9 cm/s) but without elevation of the mean diameter and without signs of portal hypertension. Caselitz-Kriteria: 2 Major + 3 Minor; Buscarini grade 2; no color spots in peripheral regions.

Figure 4  Arteriovenous hepatic malformation (shunt) in a 36-year-old woman. Contrast-enhanced ultrasound image and time intensity curve (TIC) analysis. A: Intrahepatic tortuous hepatic artery in segment IV (central) and VIII of the liver being evident by early hyperenhancement during the arterial phase after injection of 2.0 mL contrast agent. Enhanced mean diameter of the extrahepatic hepatic artery (9.7 mm) without dilation intrahepatic (4.2 mm) and of the portal vein (7.5 mm); B: For TIC analysis eight regions of interest (ROIs) with a diameter of 5 mm were placed in the perfused hepatic artery (yellow, turquoise), portal vein (red, green), shunt region (orange, purple) and hepatic parenchyma (white, blue), two ROIs per region. TIC analysis showed significant lowest time to peak (TTP) and highest area under the curve (AUC) in the hepatic artery and highest TTP and lowest AUC in the portal vein and hepatic parenchyma. Appropriate to the idea that the shunt region represents mixed arteriovenous perfusion, TTP and AUC values were between those of hepatic artery and portal vein. (Caselitz-Kriteria: 1 Major + 2 Minor; Buscarini grade 1; no color spots in peripheral regions).

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adding quantitative perfusion analysis. HVaMs could be identified in all patients (100%), thus in higher percentage than in literature (78%)\(^4\) and considerably higher compared to studies dealing with only baseline US (53%)\(^{24}\). Coexisting disorders were rare, hepatic cysts and steatosis hepatis being the most frequent ones \((n = 4)\). Two patients (12.5%) presented high-flow angiomas, similar to the percentage described by other authors (12%)\(^{17}\). Focal nodular hyperplasia, described as a lesion with an enhanced prevalence in patients with HHT (2.9%) compared to general population (0.3%)\(^{24}\) could be detected only in one case in our examination setting, however with the meaning of higher percentage (6.25%). There was no evidence for malignant lesions. The shunts were situated particularly in the central area (hilum), segment 8 and the left lobe of the liver. Until now, no data regarding this aspect could be found in the literature.

Using B-Mode, CCDS and PD criteria for hepatic involvement of HHT were figured out. All patients showed dilated hepatic artery with mean diameter of 11.5 mm. In only 55.6% of our patients the two major Caselitz criteria were positive, while 16.7% of the cases did not reach diagnostic criteria for HVaMs. Buonamico reported higher sensitivity for “color spots” compared to Caselitz criteria, but 27.8% of our patients showed no spots at all. Respecting sonographic grading criteria by Buscarini E. grade 3 could be demonstrated most frequent (about 40%).

Contrary to former assumption that only few cases present arterioporal HVaMs, we find arterioporal HVaMs in more than the half of the patients (61.1%), however always in combination with arteriovenous
malformations. In 16.7% even portovenous malformations were associated as third component.

HVaMs could be demonstrated by CEUS in all patients. On CEUS macrocirculation analysis, all 18 patients showed quick and early hyperenhancement during the arterial phase and 16 isoenhancement during the portal and late phases. This finding corresponds to our microcirculation TIC analysis, showing significant lowest TTP and highest AUC in the hepatic artery and highest TTP and lowest AUC in the hepatic parenchyma and the portal vein. Appropriate to the idea that the shunt region represents mixed arterial-venous perfusion, TTP and AUC values were between those of hepatic artery and portal vein.

In all cases in which MRI, CT or angiography was performed, vUS/CEUS covered not only all subtle patterns described on mentioned methods but also proved much more accurate referring to quantitative perfusion analysis and in diagnosis of challenging lesions like high-flow angiomas or focal nodular hyperplasia. A similar benefit for vUS/CEUS investigations compared to MRI and CT was shown by our group regarding prediction of malignancy of hepatic tumors.²⁵₁

**Limitations of the study**

HVaM changes of the liver concern only a small group of patients in the daily clinical practice. For US examinations high resolution technique is necessary, for CEUS special techniques with perfusion imaging of TIC analysis which are not available in all US systems. Histological proven references were not available because of the risk of bleeding.

The knowledge about US characteristics of HVaMs increased in the last years, especially by using color coded Doppler sonography (CCDS) and Power Doppler (PD) but there are still no data about quantitative proliferation patterns. For the first time we analyzed CEUS findings of a group of 18 HHT patients regrading macro- and microcirculation. These data demonstrate significant differences in time to peak (TTP) and AUC values in the four selected regions: hepatic artery, shunt region, portal vein and hepatic parenchyma.

**Applications**

These new facts could be used to sub-classify a high risk group of asymptomatic patients with therapeutic indication. Besides, based on new emerging therapeutic agents like angiogenesis inhibitor bevacizumab, treatment of HVaMs and their complications will become more attractive in future. US/CEUS analysis can therefore fill the gap of required accurate cost-effective screening methods in HHT patients with hepatic involvement.

**Terminology**

CEUS: A sonographic procedure used to image blood perfusion in organs after intravenous injection of a microbubble contrast agent. TIC analysis: a tool which allows quantitative analysing of the CEUS perfusion images by placing regions of interest in the perfused regions of interest.

**Peer-review**

For the first time we analyzed CEUS findings of a group of 18 HHT patients regarding macro- and microcirculation. Our data demonstrate significant differences in TTP and AUC values in the four selected regions: hepatic artery, shunt region, portal vein and hepatic parenchyma.

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