White Paper

Ultrasound Micro Angiography (UMA) in the Liver

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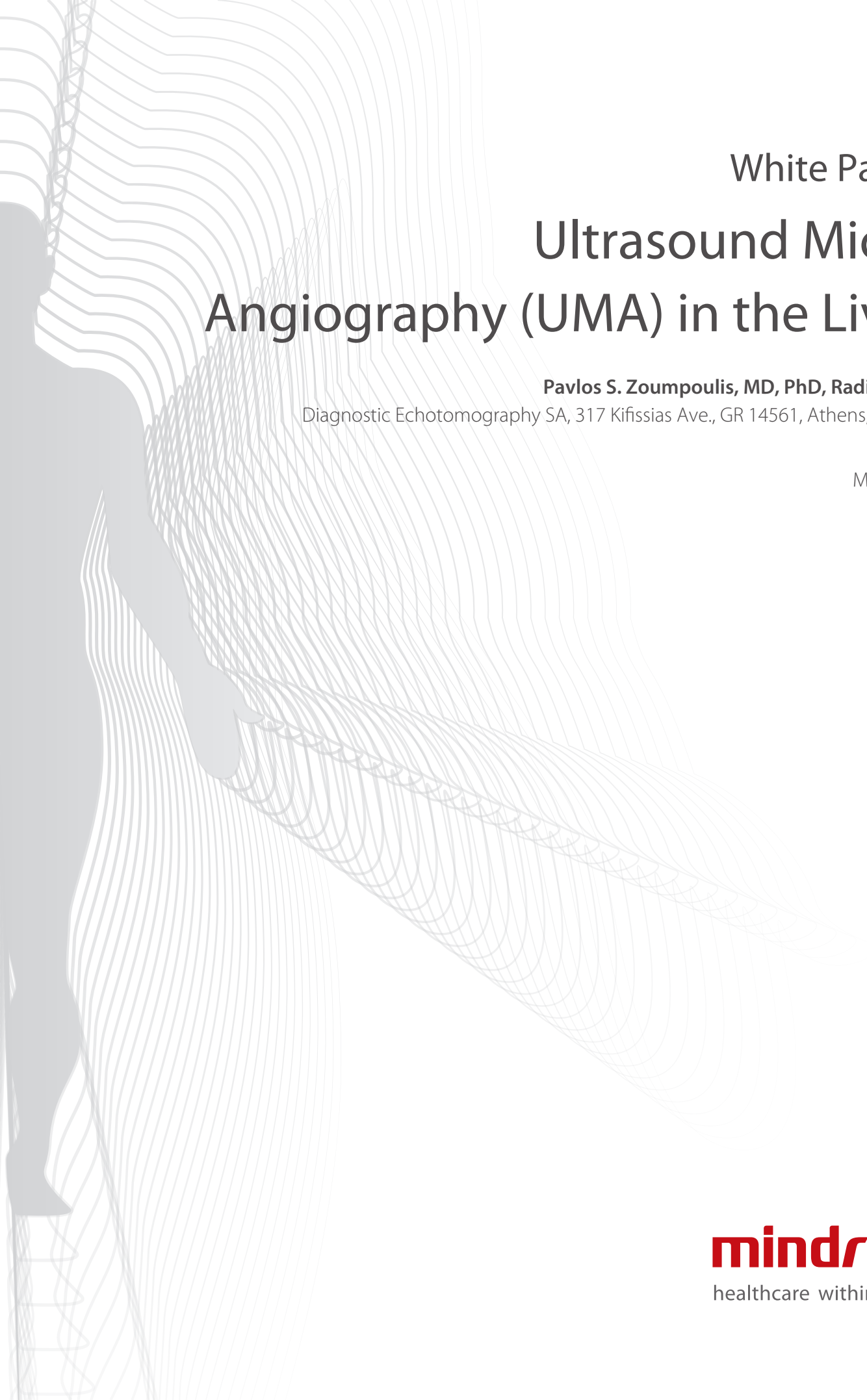

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Introduction

Aim of this White Paper is to discuss the value of the Ultrasound Micro-Angiography (UMA) feature available in Mindray Ultrasound (US) systems and provide clinicians with a guide on its use on the Liver. This document does not replace the Color Doppler Guidelines found in the literature [1] but serves as a guide for Mindray US system UMA users.

Angiography for Diagnostic Purposes

Angiography is a medical imaging technique used for blood vessel lumen visualization. It mainly involves hemodynamic information visualization, concerning arteries, veins, and heart chambers. Angiography is useful in clinical conditions related to blood flow, direction, and tissue perfusion, such as Coronal Disease, Portal Hypertension, Macula Lutea, advanced diabetes and malignant tumors.

Ultrasound Angiography

Ultrasound Angiography is a non-invasive, radiation-free examination that uses Ultrasound Doppler techniques to visualize vessel hemodynamics. Color Doppler provides information concerning blood flow direction and mean velocity. Conventional color Doppler applications may be limited from the aliasing effect, angle dependency, and reduced low flow sensitivity. Power Doppler applications provide density and red blood cells power information, mainly used for small vessel low flow visualization [2]. Spectral Doppler is a Fast Fourier Transformation application, which provides a graphical visualization of flow velocity over time. Ultrasound angiography is useful in clinical fields like Carotid Arteries, Mesenteric Vessels, Peripheral Arteries, Veins, and Tumors.

Ultrasound Micro-Angiography

Ultra-micro-angiography (UMA) is a Doppler technique aiming to improve vessel identification. It is characterized by enhanced sensitivity for low-velocity blood flow visualization. Conventional Color Doppler applications utilize focused waves and cannot typically distinguish signals from slow-moving tissue and blood flow, which reduces their performance in detecting micro-vessels. UMA technology, on the other hand, uses plane and divergent waves allowing faster sampling rate and, therefore, improved sensitivity. Moreover, a wall-filtering algorithm allows precise distinction of low-speed blood flow from low-speed tissue movement, therefore, accurately displaying micro-vessels. UMA may, hence, improve Color Doppler diagnostic performance for diseases characterized by micro-vascularization or angiogenesis (i.e., malignant neoplasms) [3].

The UMA feature includes three sub-modes, cUMA, pUMA, and sUMA. cUMA simultaneously visualizes the B-Mode and color information for low-velocity micro-vessels. pUMA displays Power Doppler information and has a directional option. sUMA provides high spatial resolution visualization of micro-vessels and allows the examiner to adjust background transparency (grades 0-4). Grade 0 only displays vasculature information, while grade 4 displays both vascular and B-Mode information with the brightest B-Mode setting. Even though the sUMA sub-mode is the most sensitive and may visualize the smallest vessels with slow velocity blood flow, it does not provide blood flow direction information like the cUMA and pUMA sub-modes. The UMA feature may be combined with the Glazing Flow feature to provide a 3D view of vessels leading to a more detailed visualization. Moreover, UMA allows vessel detectability quantification through Color Pixel Percentage (CPP).

The UMA feature provides additional hemodynamic diagnostic information for the Liver. Vascularization and neo-angiogenesis are crucial diagnostic findings that are more reliably visualized through UMA, which provides holistic imaging for both arteries and veins, leading to differential benign/malignant diagnosis.

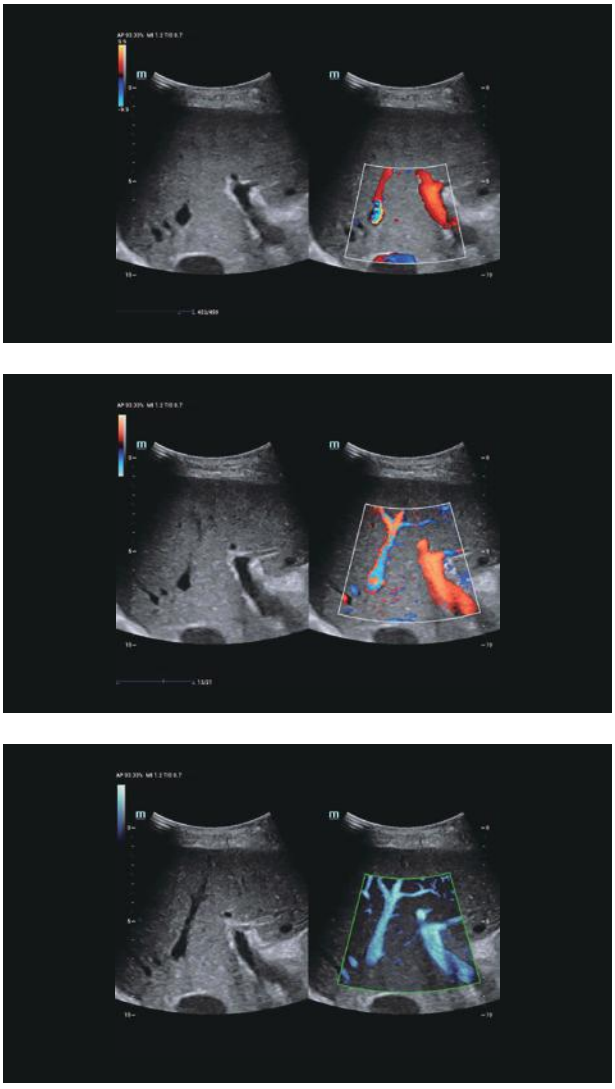


Figure1: Normal flow in the PV and the right HV using the cUMA, pUMA and sUMA sub-modes.

Liver

Ultrasound Doppler is an effective and non-invasive method for evaluating Liver vasculature, through patency and blood flow direction and velocity assessment. It is a part of every abdominal Ultrasound examination. Recognizing normal or abnormal waveforms of hepatic vessels contributes to the diagnosis of various Liver conditions that characteristically affect Liver waveform patterns [4].

The UMA feature is sensitive and precise in distinguishing low-speed blood flow from low-speed tissue movement. This strength renders UMA a useful feature for the Liver, an organ mainly vascularized by veins. Specifically, the UMA feature is valuable in Portal Hypertension cases and in focal Liver lesions differentiation.

Anatomy and Physiology relative to Liver Hemodynamics

The Liver is categorized into hepatic segments, each receiving blood from the portal triad, namely the Portal Vein (PV), Hepatic Artery (HA) and Biliary Tract [5].

The PV provides 75% of the Liver blood supply and is shaped from the junction of the superior mesenteric and splenic veins. It drains the upper and middle parts of the gastrointestinal tract, pancreas, gallbladder, and spleen [6]. In the normal Liver, the blood in the PV flows towards the hepatic parenchyma, while its velocity and the PV diameter fluctuate following the phases of the respiratory cycle.

The HVs drain blood to the Inferior Vena Cava (IVC) and are divided into three branches, the right, left, and middle HVs [7]. The typical morphology of the HVs involves the right HV and a common trunk for the middle and left HVs [8].

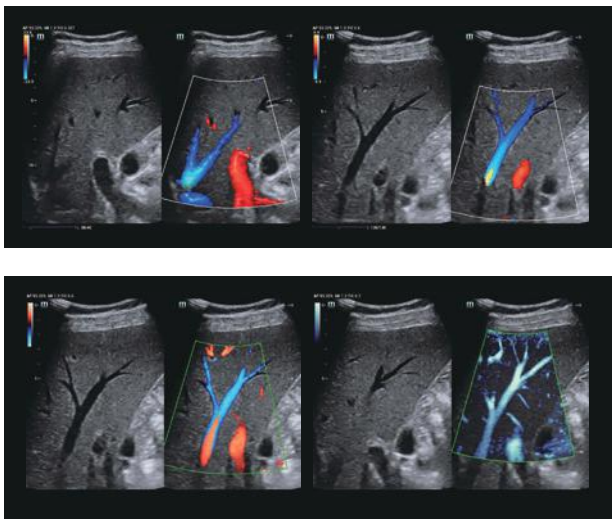


Figure 2: Normal flow in the right HV and its branches using the Glazing Flow Color Doppler and cUMA, pUMA, and sUMA sub-modes.

In Cardiac insufficiency cases, significant increase of the IVC and HVs diameters occurs. The diameters do not fluctuate and do not follow the phases of the respiratory cycle. The increased diameter is an important finding as elevated pressure in the HVs may significantly increase Liver Elastographic measurements, due to the pressure applied on the Hepatic parenchyma.

UMA has limited value in cardiac insufficiency cases because the increase in IVC and HVs diameters is so significant that can be reliably assessed through B-Mode. The examiner should consider that the IVC and HV dilatation causes an increase Liver Elastography measurements and may lead to pre-hepatic PH.

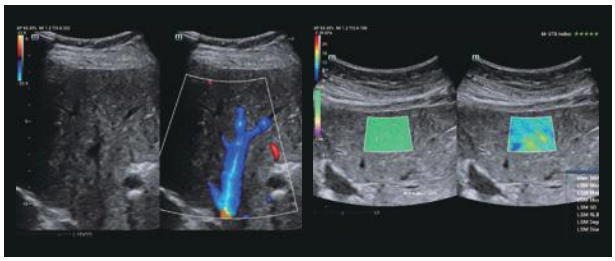


Figure 3: HV Dilatation often caused by cardiac insufficiency is an important finding because it may lead to an increase of Liver Elastography measurements.

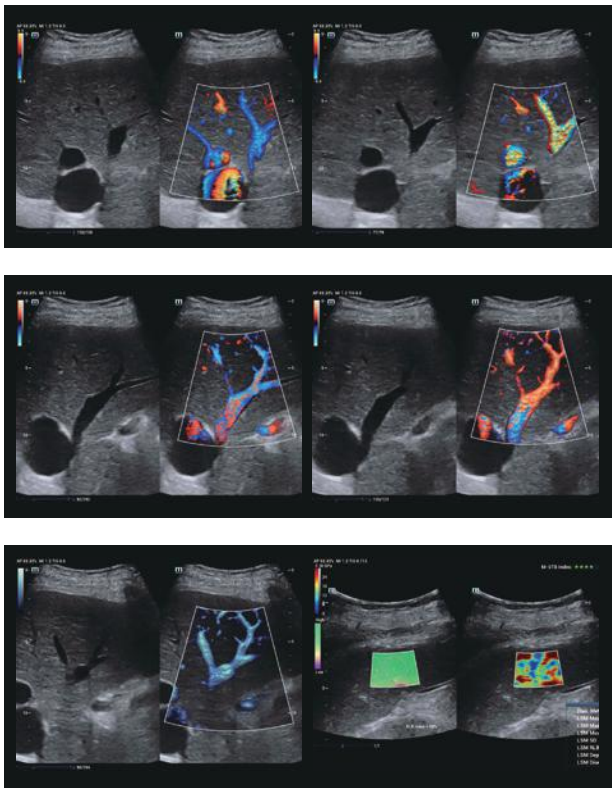


Figure 4: Case with Cardiac insufficiency and HVs dilatation. The UMA feature visualizes all the HV branches, displaying both the hepatopetal and hepatofugal flow. This change in flow results in varying pressure exercised on the Liver parenchyma and, therefore, in varying and increased Liver stiffness values.

The Hepatic Artery (HA) provides 25% of the Liver blood flow, comprising most of the oxygenated blood flowing to the Liver [9]. The IVC is formed from the juncture of the right and left common iliac veins. It drains blood from the retroperitoneal space towards the HVs [10]. In normal Livers the inferior vena cava has a diameter of approximately 1.7 – 2.1 cm, which fluctuates following the phases of the respiratory cycle [11, 12].

Hepatopetal flow is the blood flow towards the Liver parenchyma through the PV [13]. Hepatofugal flow is the blood drainage from the Liver towards the PV [13]. It occurs when the PV pressure is increased in Portal Hypertension cases [14]. In such cases, portosystemic shunts are opened, the PV is narrowed, and the HA diameter and flow are increased [15].

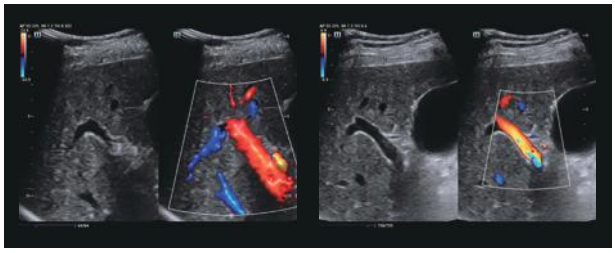
Portal Hypertension (PH)

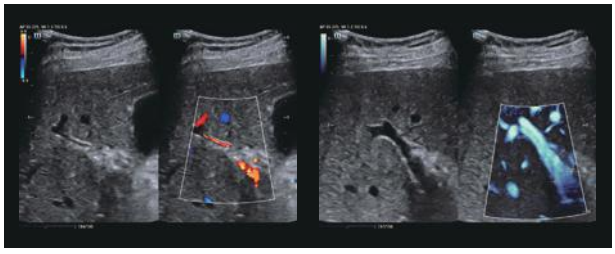
Portal Hypertension refers to an abnormal blood pressure elevation in the portal system. It is typically caused by cirrhosis and an increase in HV pressure gradient, with a greater than 5 mm Hg pressure difference between the PV and the IVC [16, 17]. PH is considered clinically significant when the PV pressure is greater than 10mm Hg [17]. The HV pressure gradient is considered the reference standard for PH diagnosis but is an invasive procedure requiring hepatic vessel catheterization [18]. Color Doppler applications are a non-invasive alternative that can reliably detect abnormalities in the Liver Hemodynamic behavior [19].

US Color Doppler for Portal Hypertension

Ultrasound Doppler applications can evaluate blood flow direction and detect collateral vessels. Relative measurements involve PV and splenic vein velocities, flow directions, as well as resistive and pulsatility indices of the arterial Hemodynamics.

In PH patients the diameter of the portal vein and its branches increase. The diameter does not fluctuate and does not follow the phases of the respiratory cycle [20].





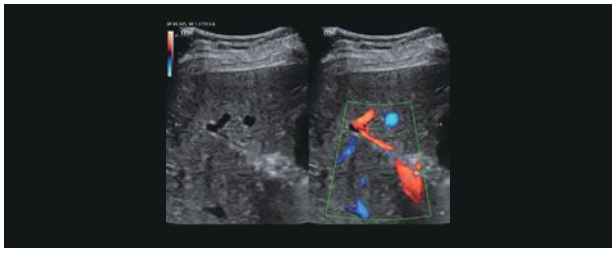
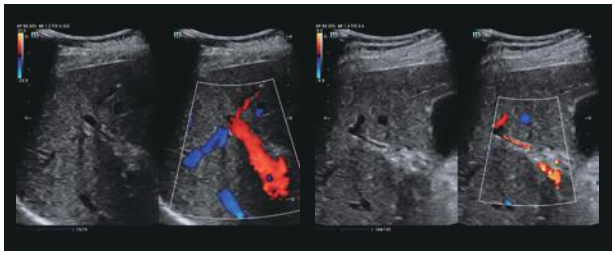


Figure 5: A dilated PV and an increased diameter HA and HA branches, visualized by the Color Doppler feature combined with Glazing Flow and the cUMA, pUMA, and sUMA sub-modes.

The Liver is vascularized mainly from the PV but also from the HA. In normal Livers, the HA diameter is approximately 1,5-2,5mm, while the arterial flow and resistive index is normal (0.50–0.70).

In Cirrhotic Livers an increase of HA diameter (3-4,5mm) is often observed. The arterial flow is usually normal, but the resistive index may be affected [21, 22]. The dilatation and the consequent important increase of the HA volume of flow occurs because the Liver' s only vascularization source is the HA as the vascularization from the PV is importantly reduced due to the effects of PH.

To reliably measure the HA diameter, the HA blood flow should be adequately visualized. The colored blood visualization of conventional Color Doppler features often expands beyond vessels' wall due to pulse movement. The UMA feature can help in visualizing the blood flow in all vessels, including small ones, avoiding motion artefacts. Specifically, the UMA feature can reliably visualize the entire HA and accurately measure its diameter.



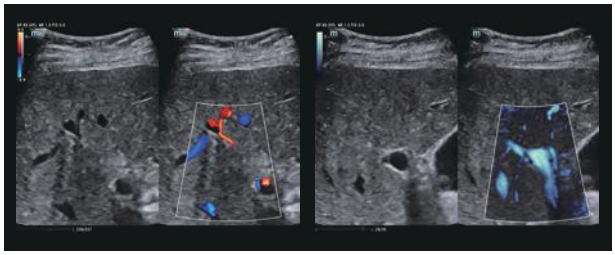


Figure 6: The HA in front of the PV and the HA bifurcation, visualized by the Color Doppler feature and the cUMA and sUMA sub-modes.

The left gastric vein (LGV) has an important role in venous drainage of the stomach. The LGV typically drains into the portal vein (PV) or splenic vein [23, 24]. LGV evaluation can be challenging due to its several anatomic variants. Specifically, LGV hemodynamic evaluation can be performed through Color Doppler. LGV, however, is challenging to detect in non-PH cases due to its small caliber. In Cirrhotic cases, on the other hand, the LGV is easier to visualize through US, while inability to visualize it is mainly associated with bowel gas artifacts and obesity. In PH cases the reversed LGV flow is a common finding, which may be identified by Color Doppler [17].

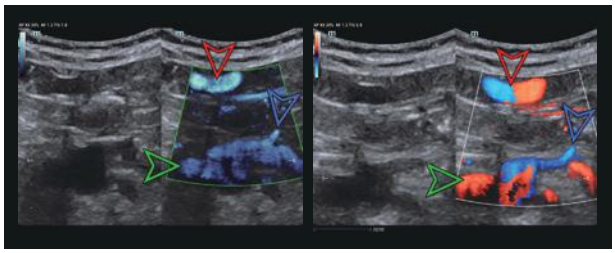


Figure 7: Reversed flow in the LGV (starting from the splenic vein), and epigastric varices visualized by the UMA pUMA, and sUMA sub-modes. Red: Epigastric variceal vein, Green: Dilated splenic vein, Blue: Left gastric vein.

In initial phase PH cases, the blood flows from the Splenic veins through the PV towards the hepatic parenchyma (hepatopetal flow). In severe PH cases the blood flow in the PV may cease completely and then hepatofugal flow and PV thrombosis may occur.

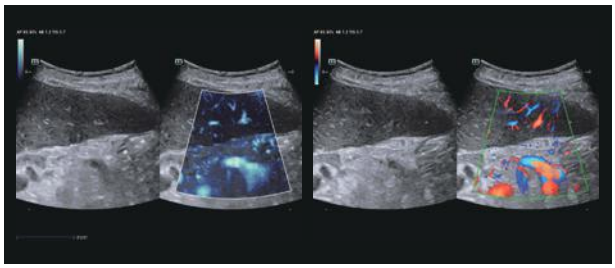
Figure 8: Reversed flow in the PV visualized by the cUMA sub-mode.

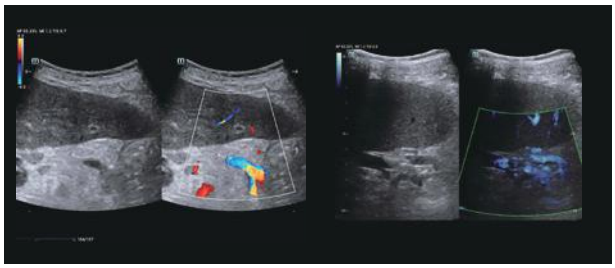
The visualization of varices of various anatomic positions (esophageal, gastric, abdominal wall, umbilical, splenogastric, splenorenal, retroperitoneal) is essential for PH staging and for applying appropriate treatment. The examiner should consider the anatomic positions of the portosystemic shunts to focus the US beam and visualize the blood flow through Color Doppler. Since B-Mode alone is not diagnostic, the presence of flow is pathognomonic for the diagnosis of varices [17, 25]. The derivations' (varices) diameter is often very small and the flow is barely visible.

UMA in Portal Hypertension

Blood flow quantification, regarding in the entire Portal Syste or in a part of it, is crucial for assessing PH severity and coordinating treatment to avoid life-threatening hemorrhages. In all these circumstances conventional Color Doppler Ultrasound applications often fails to visualize collaterals and PV thrombosis, especially in its early stages.

Detecting collaterals is an important criterion for PH staging. The UMA feature being more sensitive than the conventional Color Doppler, allows the visualization of slow flow and, therefore, of collateral vessels [3]. UMA can detect small varices with slow blood flow in all anatomic positions that varices may be developed. Specifically, UMA can detect small varices in very challenging conditions such as splenogastric and retroperitoneal varices. Combining the UMA and Glazing Flow features renders the collateral visualization very realistic since it provides the examiner with a 3D view.





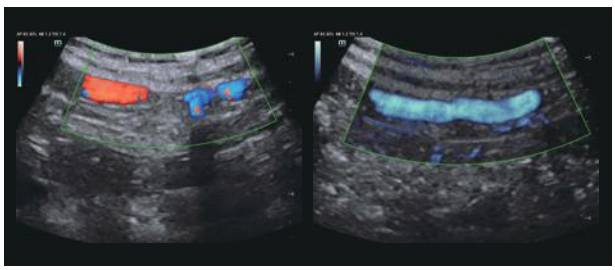


Figure 9: Varices on the inferior border of the left Liver lobe and periumbilical varices, visualized by the cUMA, pUMA, and sUMA sub-modes.

In Portal Hypertension patients the PV blood flow is often slow, which may lead to stagnation. This condition favors the formation of thrombi, aggravating the PH effects and completely blocking the PV. PV thrombosis may complicate thrombotic treatments regarding the gastric and esophageal varices. Moreover, PV thrombosis may be partial, meaning that a part of the lumen is patent and/or one of the branches preserves blood circulation. UMA' s sensitivity in detecting and visualizing slow blood flow renders the feature ideal for diagnosis of PV thrombosis. Absence of flow in a part of the PV means formation of thrombi, often on the vessel wall. Moreover, UMA is very sensitive in detecting and quantifying blood flow in the recanalized thrombosed PV. Combining the UMA and Glazing Flow features provides the examiner with a spectacular 3D visualization of recanalized thrombosed PV.

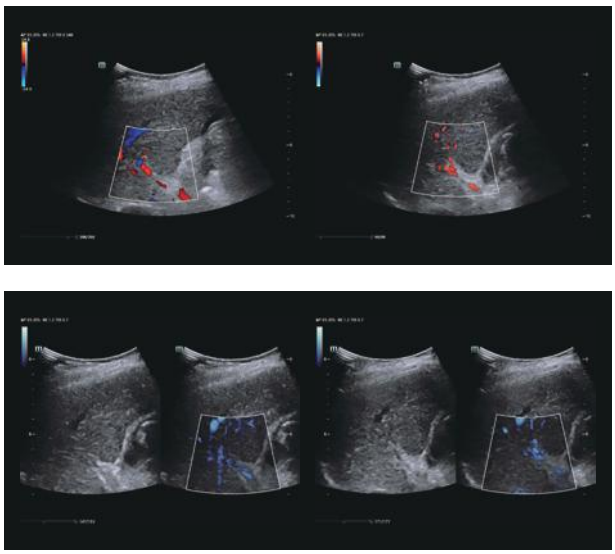


Figure 10: PV thrombosis and partial recanalization, visualized by the Color Doppler feature and the pUMA and sUMA sub-modes.

Focal Liver Lesions Hemodynamic Study:

Focal Liver lesions (FLLs) are abnormal Liver tissue areas [26]. Benign FLLs include cysts, Adenomas, Focal Nodular Hyperplasia and Hemangiomas. Malignant FLLs include Hepatocellular Carcinomas (HCC), Cholangiocarcinomas and Metastases. Benign-malignant FLL differentiation is a clinical challenge. Ultrasound plays an important role in FLL detection and differentiation either through Contrast Enhanced Ultrasound (CEUS) or through Color/Power Doppler [27-30]. Color Doppler applications produce real-time information on a lesion' s Hemodynamic behavior but are limited due to their insufficient capacity to detect slow flows [31-39]. UMA, being more sensitive in slow blood flows, can reliably visualize very small vessels, thus contributing in the FLL differential diagnosis.

Hemangiomas

Hemangiomas are the most common benign tumor of the liver, consisting of multiple vascular channels of varying size supported by fibrous interstitium [40-42].

Typical Hemangiomas are characterized by hyperechoic in B-Mode appearance and clear margins, while the hemodynamic study provides limited diagnostic information [42]. On the other hand, morphology alone is not sufficient for confirming the diagnosis of atypical Hemangiomas [42]. For example, relatively hypoechoic lesions in fatty infiltration livers are often challenging. In such challenging anatomic conditions or in obese patients, conventional Color Doppler is often not applicable, and the UMA feature may play a critical role in differential diagnosis. Specifically, Hemangiomas have no visible internal vessels since the blood is often stagnated. The feeding artery may be recognized in the periphery of the tumor only through UMA.

In Livers with Steatosis, differentiating spared hypo-echoic "lesions" from atypical hypo-echoic Hemangiomas is often challenging. UMA can play an important part in this issue by reliably visualizing small veins and arteries within such "lesions". If such vessels are visualized the examiner may assume that the "lesion" is spared liver parenchyma since Hemangiomas are not traversed by vessels.

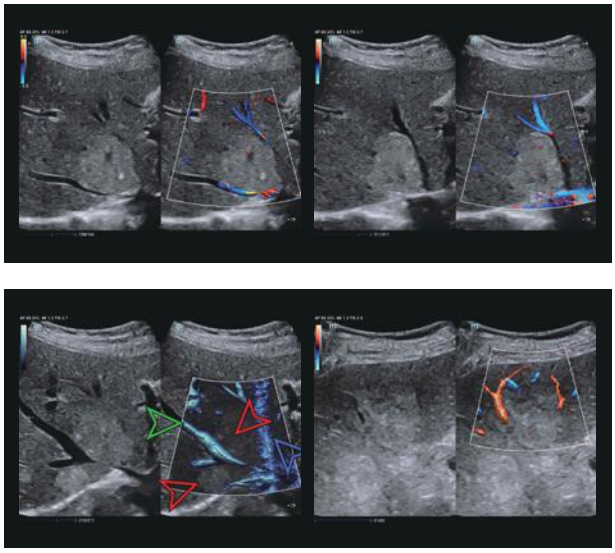


Figure 11: Patient with multiple Hemangiomas in both Liver lobes. Two of the Hemangiomas are visualized here through sUMA, pUMA and cUMA sub-modes. Normal vessels surround both lesions. The lesions neither invade the vessels nor cause thrombosis (typical for Hamangiomas), indicating a benign lesion. In lesion 2 the feeding artery is visualized through the pUMA sub-mode. Red: Hemangiomas, Green: Normal HV, Blue: Artefact.

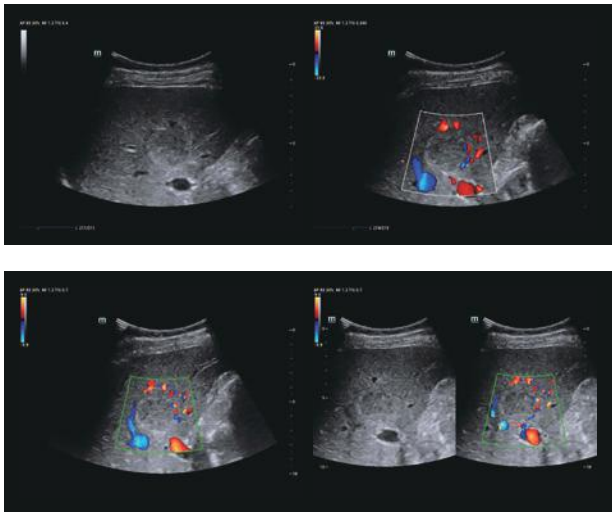
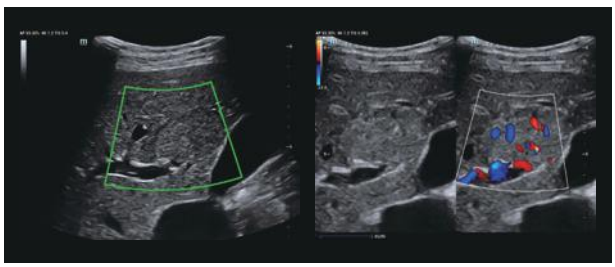


Figure 12: Atypical iso-echoic Hemangioma and its feeding artery in a fatty infiltration Liver, visualized by the Color Doppler feature and the cUMA sub-mode.

Focal Nodular Hyperplasia (FNH)

FNH is a proliferation of non-neoplastic hepatocytes that are abnormally arranged, as a hyperplastic response to an area of vascular malformation or venous thrombosis, and frequently associated with a central fibrous scar and anomalous arteries [40, 43].

FNH are hyper-vascular lesions with a very characteristic vascular pattern. They are surrounded by an arterial and venous plexus and a wheel-like vascular system converges towards the fibrotic center of the tumor. These vessels cannot easily be visualized through conventional Color Doppler because they cannot fit in a single US section. All central, periphery and spoke-wheel pattern vessels, characterizing FNH, are tortuous and often have slow blood flow. This typical pattern may be visualized in its entirety through the UMA feature, through which all arterial and venous flows are easily distinguished. Moreover, combining UMA with the Glazing Flow feature can help the examiner acquire a very realistic 3D view of converging vessels towards the center of an FNH nodule.



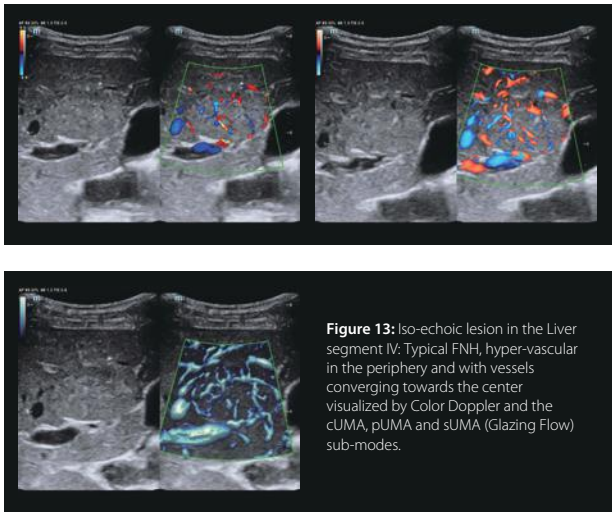


Figure 13: Iso-echoic lesion in the Liver segment IV: Typical FNH, hyper-vascular in the periphery and with vessels converging towards the center visualized by Color Doppler and the cUMA, pUMA and sUMA (Glazing Flow) sub-modes.

Hepatocellular Carcinoma (HCC)

HCC is the most common primary malignancy of the liver, most of which occur on a background of cirrhosis. HCC with expansile growth is nodular, and frequently encapsulated. HCCs with infiltrative growth show an indistinct margin. Such HCCs are often characterized by invasion and thrombosis of PV branches [40].

Every malignant tumor is characterized by the formation of neo-vessels. The vein and artery morphology typically presents stenosis, dilatations, obliterations, and arterio-venous anastomoses, forming an anarchic structure of tortuous vessels. Some of the vessels involved in such structures of hyper-vascular HCCs have slow flow and can be, therefore, reliably visualized through UMA. Moreover, UMA may reliably visualize small, thrombosed PV branches, characterizing HCC.

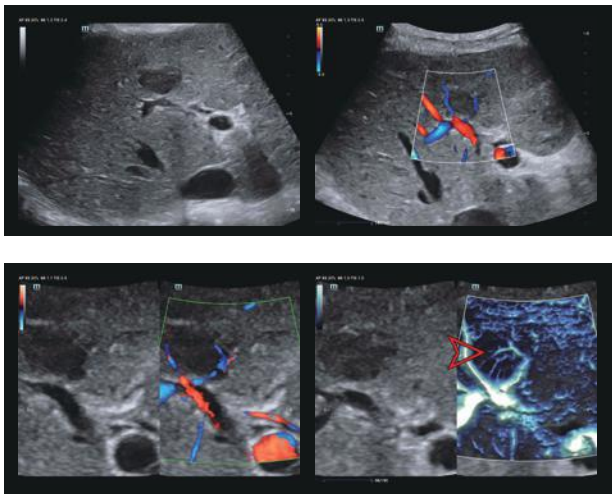


Figure 14: Hypo-echoic HCC in a Cirrhotic Liver. The lesion is hyper-vascular mainly in its periphery (basket pattern). Anarchic neo-vessels are reliably visualized by the cUMA, pUMA and sUMA (Glazing flow) sub-modes. Sometimes in order to visualize small neoplastic vessels the user should increase color gain. This could create artefacts like in the top of sUMA (Glazing flow) image. Red: Neoplastic vessels.

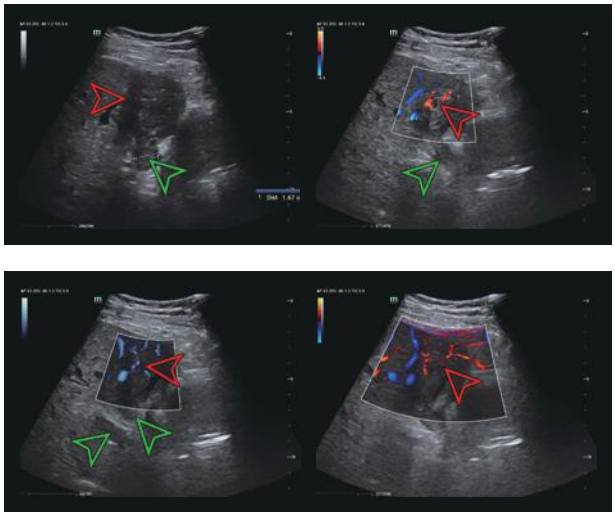


Figure 15: Typical HCC with dilated, stenotic, and obstructed neo-vessels, invading and thrombosing the PV, visualized by the cUMA and sUMA sub-modes. Red: HCC, Green: Thrombosed PV

Metastases

Metastases are also malignant tumors characterized by, mainly peripheral, neo-vessels [40]. These vessels can be more reliably and accurately be visualized through UMA than with conventional Color Doppler features.

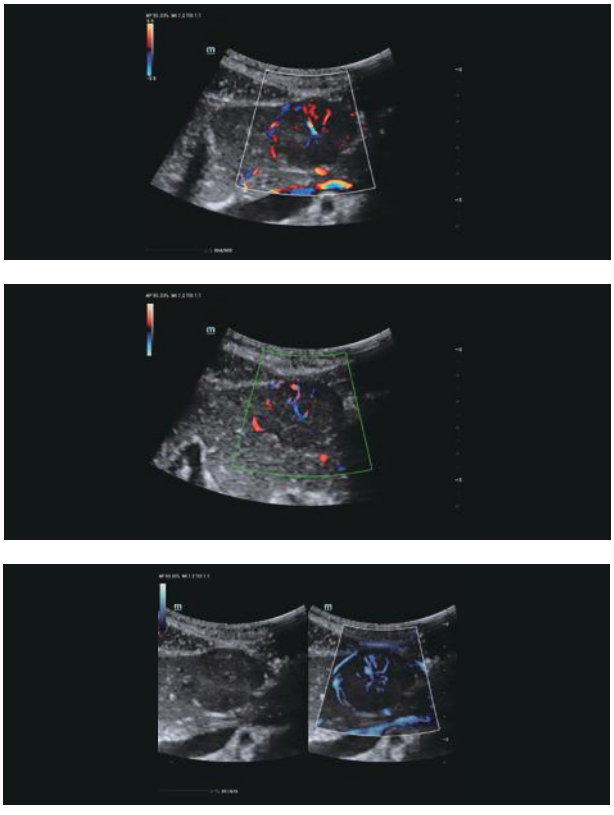


Figure 16: Hyper-vascular Liver metastasis with vessels in the hypo-echoic peripheral halo and neo-plastic tortuous vessels.

Conclusion

Concluding, UMA can contribute to detecting collaterals and small varices in Portal Hypertension cases and in challenging anatomic conditions. Furthermore, the UMA feature may have a very important contribution to the differential diagnosis of FLL, where Contrast Enhanced US (CEUS) examinations currently play a major role. Since a tumor' s vessels morphology and topography is the principal criterion for FLL differential diagnosis, the UMA feature could be very useful in the situations where CEUS is not applicable.

UMA step-by-step application

1. The probe should be as stable as possible during UMinations. he patient should be instructed to hold his/her breath.

2. Locate the target lesion through B-Mode. Zoom when necessary and enable the UMA feature using the touchscreen.

3. Adjust the UMA ROI to include the entire lesion and adjacent tissue.

4. Switch between cUMA, pUMA, and sUMA sub-modes. Use the Glazing Flow feature when appropriate.

5. Adjust frequency scale, gain, and wall filter to acquire the optimum image quality and reduce motion artefacts.

- Use as high frequency as possible without compromising US beam penetration. As frequency increases more micro-vessels may be detected.
- In the pUMA and sUMA sub-modes reduced scale leads to increased sensitivity for low velocity vessels.
- Increased wall filter frequency may reduce motion artefacts.

Interesting Liver UMA Cases

Case 1

Liver Hemangioma, 36-year-old female Patient

Clinical Information: Asymptomatic

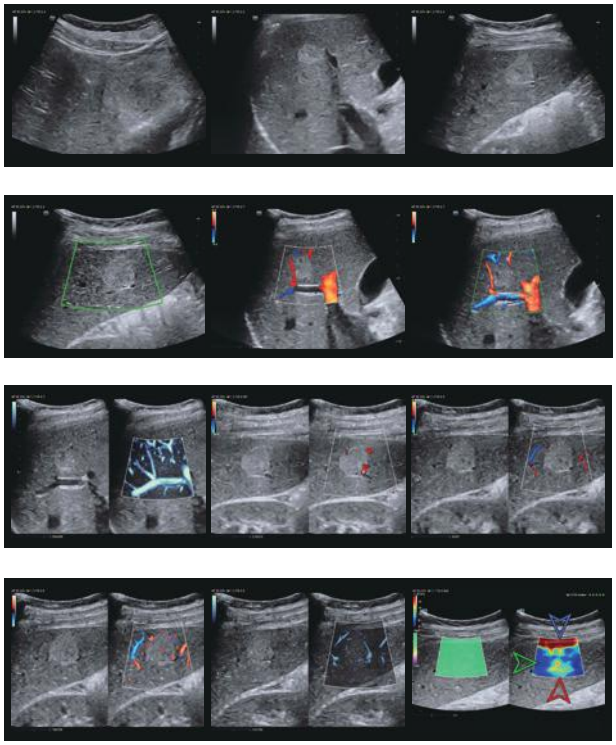
Imaging information: Previous CT with contrast examination showed hypo-dense lesions, which slowly became hyper-dense after the contrast injection

Biochemical information: normal Liver biochemical findings

Ultrasound information: many hyper-echoic lesions in both Liver lobes. The biggest lesion has a hypo-echoic part (clots)

Elastography information: the lesions are stiffer than the normal parenchyma. The particular STE image accurately delineates one of the small Hemangiomas

UMA information: normal Liver vessels surrounding the lesions. The feeding artery is visible. No vessels within the lesions



Indicators: Red: Small Hemangioma, Green: Normal Liver Parenchyma, Blue: Artefact

Case 2

Focal Nodular Hyperplasia, 35-year-old female Patient

Clinical information: Asymptomatic

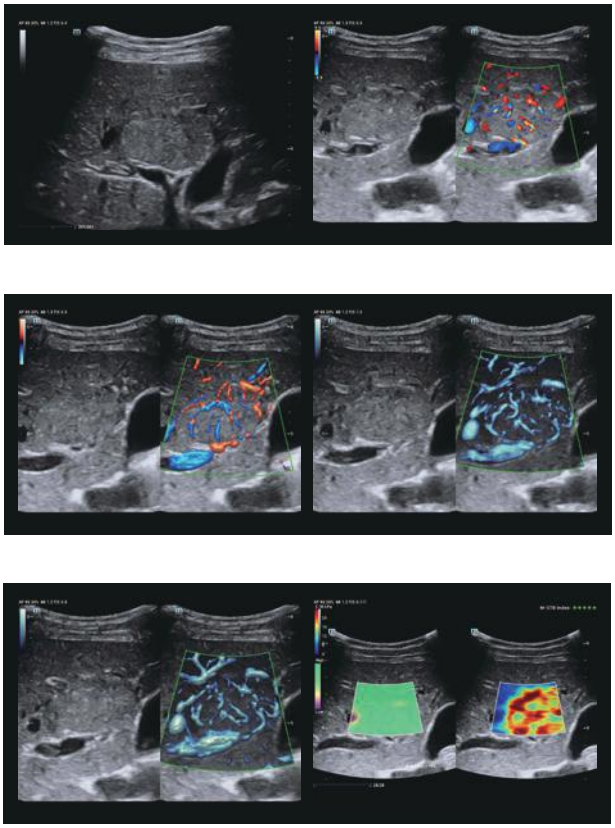
Imaging information: Previous CT examination showed a hyper-vascular tumor (adenoma or atypical hemangioma)

Biochemical information: normal Liver tests

Ultrasound information: iso- and discreetly hyper-echoic lesion pushing the branches of the PV, no invasion

Elastography information: the lesions are stiffer than the normal parenchyma

UMA information: circular peripheral vessels (arteries and veins). Some of the vessels are converging in a non-central point in the lesion, typical for FNH



Case 3

Portal Vein Thrombosis with Recanalization, 45-year-old female Patient

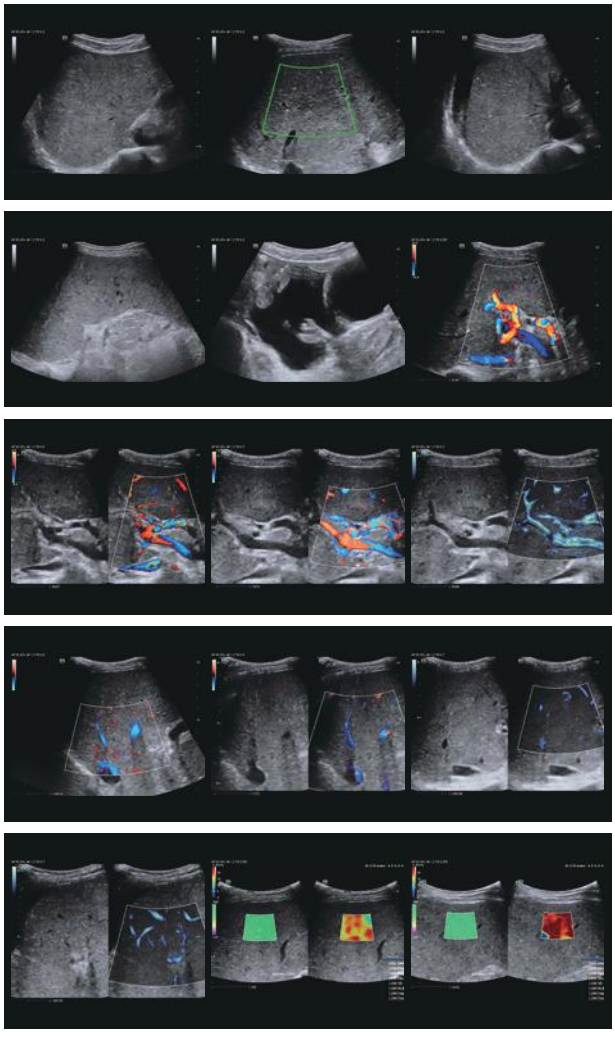
Clinical information: myelohyperplastic syndrome, Budd Chiarri syhndrome, Portal Hypertension, Ascites

Biochemical information: transaminases and bilirubin elevation

Ultrasound information: Hepatomegaly and splenomegaly, Liver heterogeneity and Caudate Lobe hypertrophy, thin Hepatic Veins, ascites

Elastography information: elevated Liver elastographic measurements (21 kPa), elevated Spleen elastographic measurements (31 kPa)

UMA information: Hepatic Veins thrombi, stenoses and dilatations, reversed Portal Vein flow, Hepatic Artery dilatation



Case 4

Chronic Hepatopathy,Budd Chiarri, Portal Vein Recanalization, 15-year-old male Patient

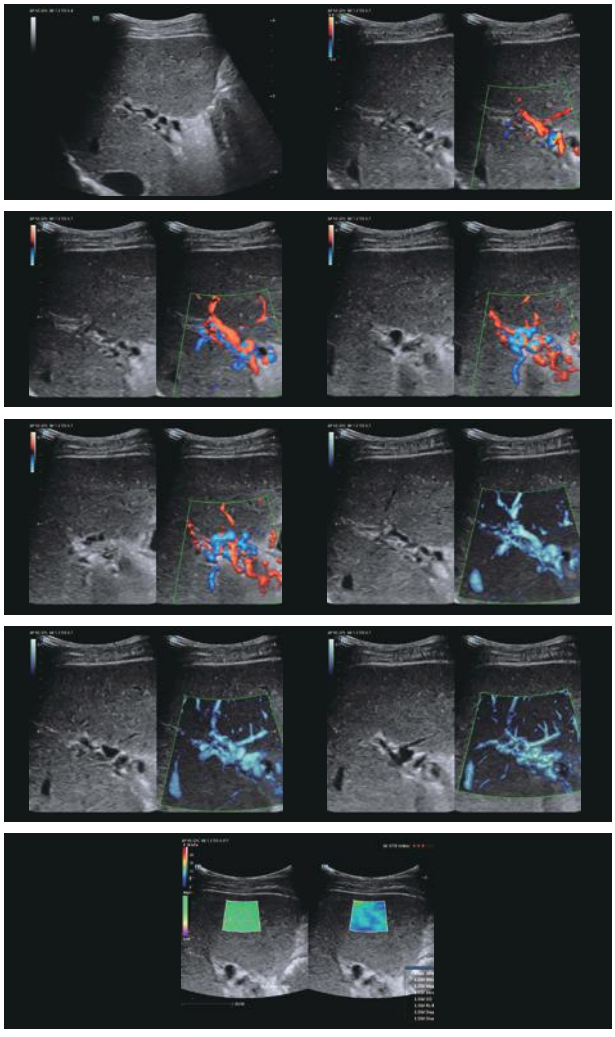
Clinical information: B thalassemia, splenectomy, PV thrombosis, Portal Hypertension with gastric varices

Imaging information: Previous CT examination showed PV thrombosis with no PH signs

Biochemical information: transaminases elevation

Ultrasound information: tortuous vessels with hepatopethal flow in the PV anatomic position. The increased Liver Elastographic measurements are due to pressure exercised on the Liver by the dilated varicose veins caused by PH

UMA information: the entire PV cavernous formation is only visible through the UMA feature, and specifically through the Glazing Flow. One branch of the cavernous formation is rectilinear and is characterized by hepatopetal flow, hemodynamically replacing the thrombosed PV, and resolving the PH issue.



Case 5

ALD, Liver Cirrhosis, Portal Hypertension, Varices,
55-year-old male Patient

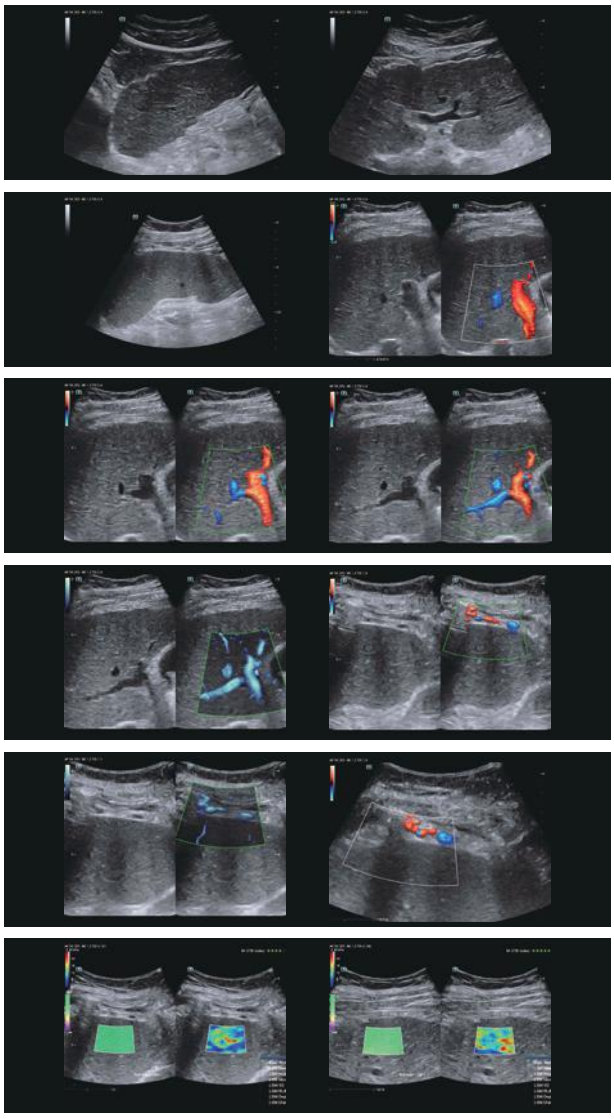
Clinical information: History of encephalopathy and ascites, Portal Hypertension with gastric varices

Imaging information: Previous endoscopy examination showed esophageal and gastric varices

Biochemical information: transaminases elevation

Ultrasound information: hepatomegaly, caudate lobe hypertrophy, Liver lobulations, splenomegaly. Elevated Liver stiffness measurements (14,74 and 15,37 kPa) typical for Cirrhosis.

UMA information: Dilatation and normal hepatopethal flow in the non-thrombosed PV. Dilated tortuous veins surrounding the Liver left lobe.



Case 6

Multi-focal Hepatocellular Carcinoma, 62-year-old male Patient HCV patient

Clinical information: no symptoms

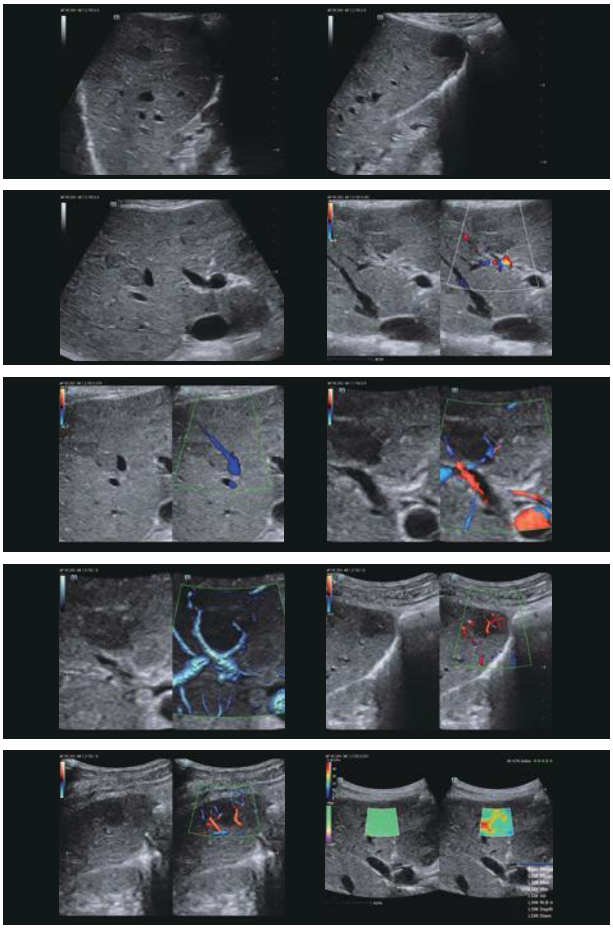
Imaging information: Previous CT examination showed hypo-dense, vascularized tumors in both Liver lobes

Biochemical information: AFP elevation

Ultrasound information: several hypo-echoic lesions mainly in the right Liver lobe. Elevated Liver stiffness measurements (31,45 kPa). Differences in stiffness between the lesions and the normal parenchyma.

Elastography information: elevated Liver elastographic measurements (31 kPa) due to Liver Cirrhosis.

UMA information: The lesions' vascularity is not reliably visualized through the conventional Color Doppler. However, the lesions appear hyper-vascular through the UMA feature and the pUMA, cUMA and sUMA sub-modes. The hyper-vascularity is very prominent in the lesion' s periphery (basket pattern). The UMA feature also visualizes stenotic and/or dilated neo-vessels within the lesions.



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