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White paper

Microvascular Imaging Super Resolution (MVI SR) and Time of Arrival Super Resolution (TOA SR) technologies

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Introduction

Contrast-enhanced ultrasound (CEUS) leverages the nonlinear properties of ultrasound contrast agents (microspheres with a size similar to red blood cells, intravenously injected into the bloodstream) in order to detect, visualize and quantify the presence of microbubbles anywhere in the human circulation.[1] This unique ability has transformed diagnostic ultrasound into a functional imaging modality and has found numerous applications in almost every organ in the human body.[2-4]

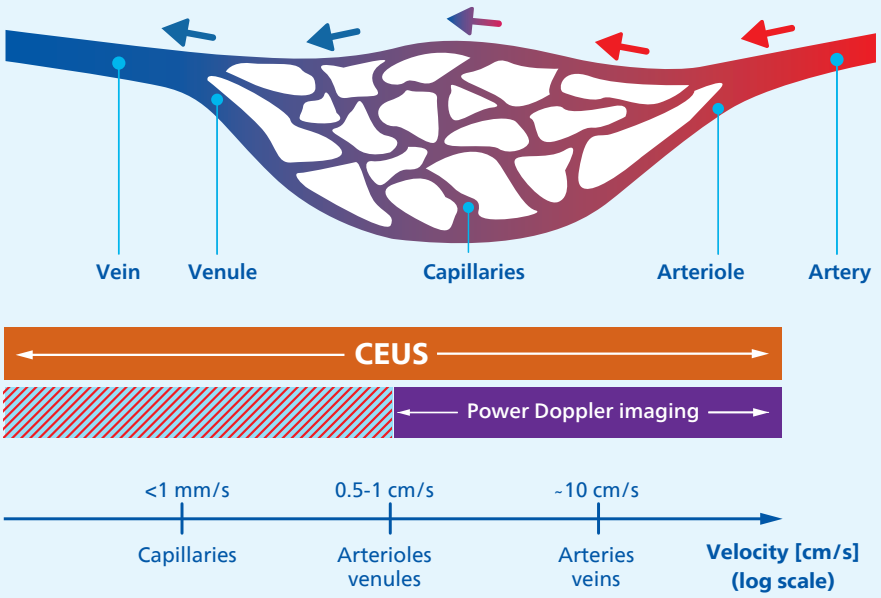

Figure 1 CEUS is able to detect blood everywhere in the circulatory system, unlike Doppler flow imaging techniques.

CEUS offers major advantages vs. Doppler techniques in detecting microbubbles in blood, irrespective of the blood flow velocity (i.e., ranging from high-velocity arterial flow to near-stationary blood flow in capillaries) as illustrated in **Figure 1**.

More specifically, Doppler blood flow imaging techniques rely on high-pass "wall" filters to separate blood flow Doppler signals from those generated by soft tissue motion and, therefore, struggle to reliably detect and visualize vessels with blood velocities comparable to tissue motion. CEUS techniques, however, rely on the nonlinear response of ultrasound contrast agents when insonified by ultrasound pulses to detect the presence of microbubbles in blood, even in extremely slow-flow conditions such as in capillaries.

As a consequence, CEUS can detect the presence of microbubbles everywhere in the circulation but cannot resolve small vessels whose dimensions are smaller than the resolution limit of the ultrasound imaging system.[5] Broadly speaking, the resolution limit of an ultrasound imaging system is directly related to its point spread function (PSF), which defines the response of the ultrasound imaging system to an ideal point source (such as a single microbubble).

The PSF is primarily determined by the frequency of the transmitted ultrasound pulses and, for typical abdominal and small part applications, it results in a spatial resolution that is 10 to 100 times lower than the resolution needed to offer clear visualization of the network of arterioles, venules and capillaries commonly referred to as the microvascular architecture.

The ability to visualize the microvascular architecture of organs and/or lesions can provide important information for the detection and diagnosis of many diseases as well as for treatment planning and monitoring in diverse clinical applications, including focal lesion characterization, renal diseases, plaque neovascularization, brain neurovascular abnormalities and skin ischemia.[5] The need for CEUS-based visualization of the microvasculature has led to the recent emergence of an entirely new and vibrant field of technical and academic research known as "super resolution CEUS," also known as "ultrasound localization microscopy."[6] The next section provides an overview of the origin, technological background and evolution of the exciting and innovative field of super resolution CEUS.

Super resolution imaging

Super resolution in fluorescence microscopy

The concept of super resolution CEUS originated in the field of fluorescence microscopy and has proven so successful that its creators won the Nobel Prize in Chemistry for it in 2014.[7,8] The super resolution advances in fluorescence microscopy were motivated by the need to achieve much higher spatial resolution than the one possible based on the imaging system's PSF.[9] The principle of "single-molecule microscopy" is illustrated in **Figure 2**, which has been adapted from Yamanaka M, et al.[10]

Principle of super resolution microscopy ("connecting the dots")

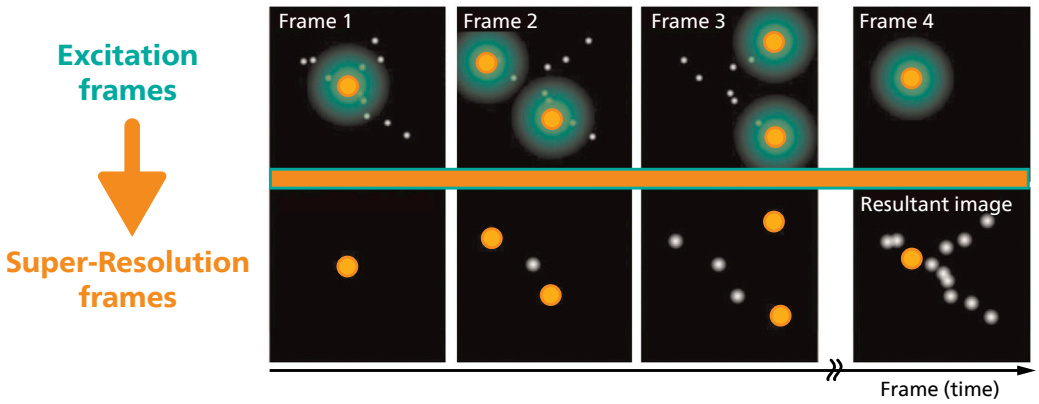

Figure 2 Super resolution microscopy uses photo switchable fluorescent probes to excite molecules in a sequential manner.

More specifically:

1. Instead of exciting all molecules at the same time, photo switchable fluorescent probes are used so that molecules are excited in a sequential manner (top row, Figure 2).
2. The responses received after each excitation (green circles in top row of Figure 2) are then "localized," i.e., are replaced by single points that correspond to the centers of their fluorescence responses (orange dots in bottom row, Figure 2).
3. Finally, the dots representing the centers of the sequentially recorded fluorescence responses are accumulated over time (left to right, bottom row, Figure 2).

The end result is an image with a spatial resolution that is an order of magnitude higher than conventional microscopy, as shown in **Figure 3** (adapted from Betzig E, et al).[9]

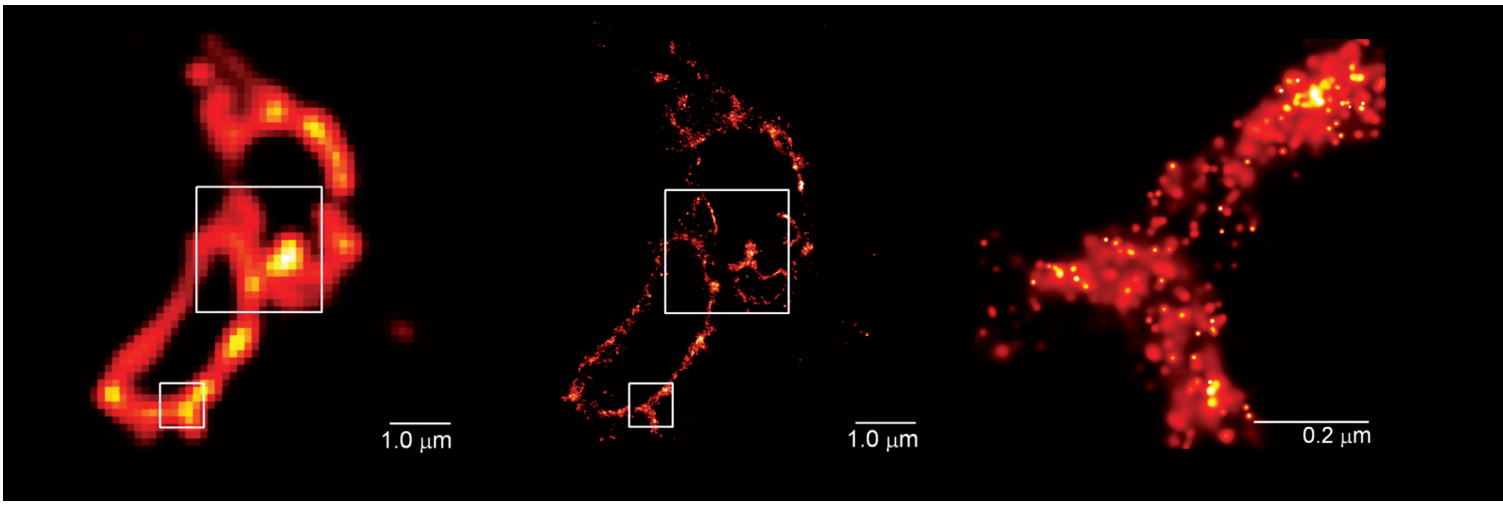

Figure 3 Super resolution microscopy results in images with much higher spatial resolution than conventional microscopy.

Super resolution in CEUS imaging (aka ultrasound localization microscopy)

Soon after super resolution fluorescence microscopy won the Nobel Prize in Chemistry, this concept was introduced for the first time in the field of CEUS imaging by two scientific papers,[11,12] which led to the emergence of a new field known as "super resolution CEUS" and/or "ultrasound localization microscopy." This field has become very popular with academic researchers and has led to a growing stream of papers published on the same topic (see Yi HM, et al[5] for a complete list of publications).

An outline of the steps involved in "super resolution CEUS" and/or "ultrasound localization microscopy" is provided below:

1. Start with a very low contrast agent dose so that CEUS images contain, as much as possible, "single" microbubbles instead of clusters of many microbubbles.
2. Replace echoes from "single" bubbles with dots corresponding to their centers, effectively resulting in an ideal PSF (i.e., a point as opposed to the blob-like PSF of CEUS imaging).
3. Accumulate all dots over time to create a map of the underlying microvasculature with a spatial resolution that is much higher (10x or more) than the resolution CEUS imaging.
4. Optionally, track the dots from one frame to the next in order to estimate the velocity and direction of the tracked microbubbles.

While the field of "super resolution CEUS" and/or "ultrasound localization microscopy" represents a groundbreaking development in CEUS, it is important to note that it does impose some strict requirements that are incompatible with the CEUS workflow adopted into clinical practice today, namely:

- Very low microbubble concentrations
- Very long acquisition times
- Very high frame rates
- Minimal motion between the transducer and the area being imaged from one frame to the next

Temporal accumulation/maximum intensity projection (MIP) CEUS imaging

One common theme of both super resolution fluorescence microscopy and super resolution CEUS imaging is the use of temporal accumulation to gradually form a complete representation of the molecular structures of interest and the microvascular architecture of a lesion or organ, respectively.

Commercially available ultrasound systems already employ temporal CEUS accumulation in the form of a maximum intensity projection (MIP) technique, which is applied to CEUS loops and displays at any given pixel and frame the maximum pixel intensity received at that pixel during all frames from the beginning of the CEUS loop to the current frame.

This MIP CEUS imaging technique, which was originally introduced by Philips Ultrasound in the early 2000s under the name microvascular imaging (MVI), is equivalent to the "long exposure" mode in photography, where the lens remains open to record the light received over a long period of time.

Two of the earliest papers to investigate the clinical applications of MIP CEUS imaging documented that this type of processing provides a better representation of the microvascular morphology of liver and breast lesions, respectively, and can help users perform more accurate and confident lesion characterization.[13,14]

MIP CEUS imaging has now become an integral part of the "toolbox" available to CEUS users, but it does have two important drawbacks that limit its clinical utility:

- Inadequate spatial resolution
- Strong motion artifacts

Microvascular Imaging Super Resolution (MVI SR)

Microvascular Imaging Super Resolution (MVI SR) is an innovative technique that bridges the gap between the CEUS MVI maximum intensity projection feature currently available in the Philips ultrasound systems and super resolution CEUS imaging (aka ultrasound localization microscopy).

MVI SR employs proprietary image processing and advanced motion compensation techniques applied to the CEUS images prior to maximum intensity projection imaging in order to address the two main limitations of MVI by offering:

- Significantly higher spatial resolution
- Substantially reduced motion artifacts

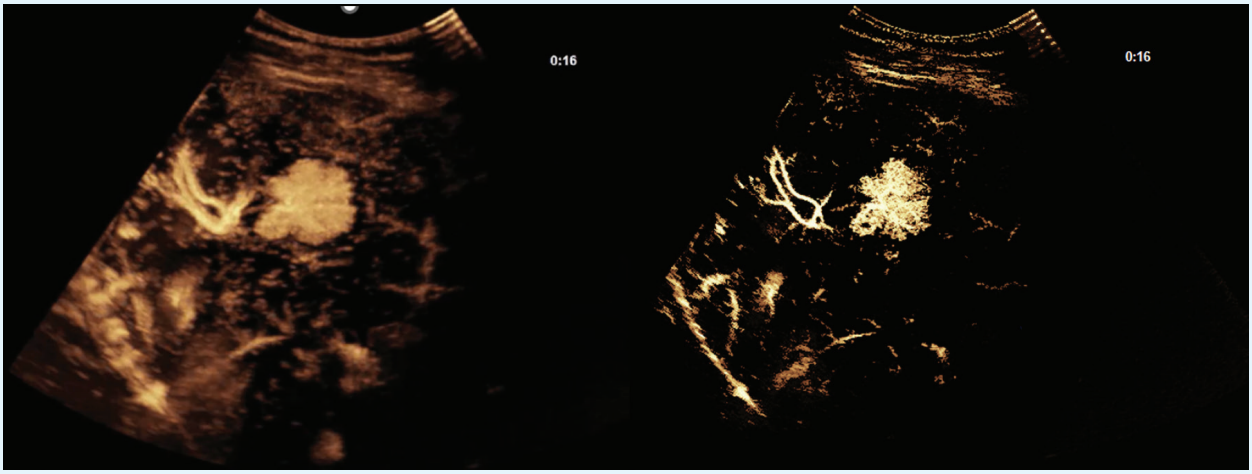

Figure 4 MVI SR demonstrates a significant increase in spatial resolution compared to MVI in this FNH benign liver lesion.

At the same time, it must be noted that this version of MVI SR currently offers spatial resolution that is not as high as ultrasound localization microscopy, but also does not suffer from its major limitations in the sense that:

- MVI SR is applied to CEUS loops acquired with standard frame rates (e.g., 15-30 Hz), whereas ultrasound localization microscopy typically needs frame rates of more than a few hundred Hz.
- MVI SR works with standard contrast agent doses, whereas ultrasound localization microscopy typically needs very low contrast agent concentrations.
- MVI SR requires short observation times of a few seconds, whereas ultrasound localization microscopy typically must operate on loops of a few minutes, when used in conjunction with very low contrast agent concentrations.

MVI SR is available on the Philips EPIQ Elite platform with the Next Gen Release software. It is implemented as part of the EPIQ MVI Q-App and can be applied to CEUS loops in post-processing (after Freeze and/or in Review).

Figure 4 illustrates the significant increase in spatial resolution offered by MVI SR (right image) relative to the legacy MVI technique (left image). Please note that the input CEUS loop used to generate both the MVI and MVI SR results was acquired by scanning a focal nodular hyperplasia (FNH) benign liver lesion.

Figure 5 provides a quantitative demonstration of the spatial resolution improvement offered by MVI SR vs. the legacy MVI results. More specifically, this figure was obtained by processing CEUS loops containing 122 vessels with both the MVI and MVI SR techniques, calculating the ratios of the mean vessel diameters measured from the MVI results over the mean vessel diameters measured from the MVI SR results and plotting the histogram of all 122 ratios. Please note that the average spatial resolution improvement of the histogram in Figure 5 was 250%.

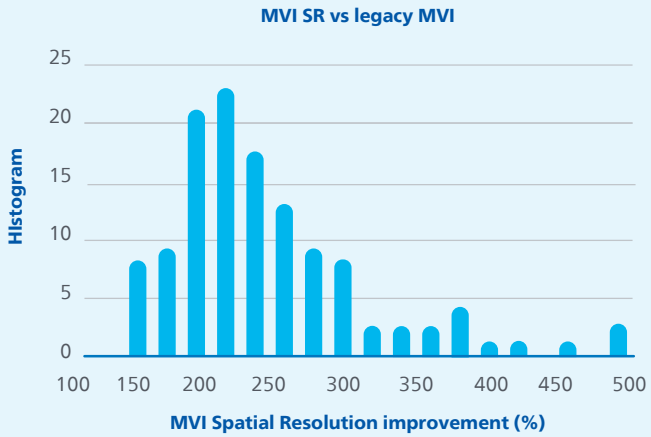

Figure 5 MVI SR demonstrates an average spatial resolution improvement of 250% compared to MVI.

Time of Arrival Super Resolution (TOA SR)

Time of Arrival (TOA), is a CEUS-based parametric mapping technique that color codes the first time each pixel receives a CEUS signal that exceeds a (typically user-selected) threshold. TOA parametric mapping was first introduced in 2007[15] and has found applications in documenting the temporal aspects of a lesion's arterial filling patterns. However, one major limitation of TOA parametric mapping is that it tends to generate images with a "patchy" appearance that cannot be easily related to the original CEUS loops from which they were derived because TOA images display only temporal estimates and do not include any amplitude-based information.

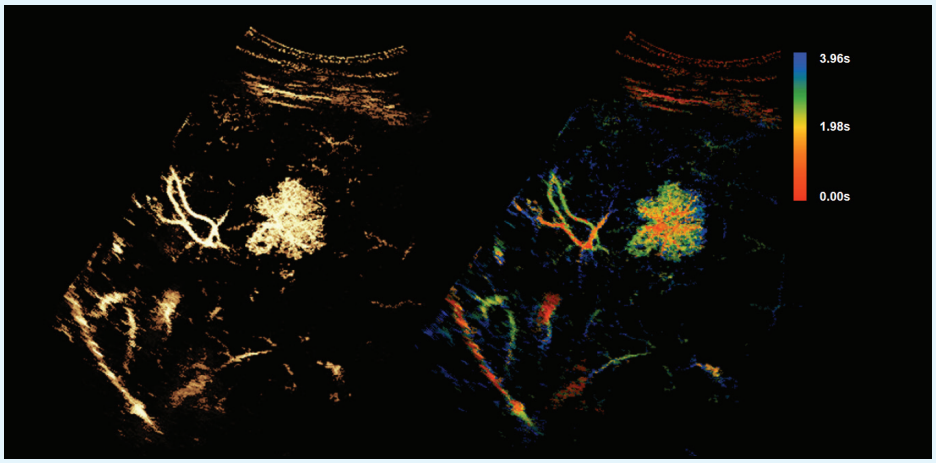

Figure 6 The TOA SR parametric mapping technique clearly documents the typical arterial filling characteristics exhibited by FNH lesions.

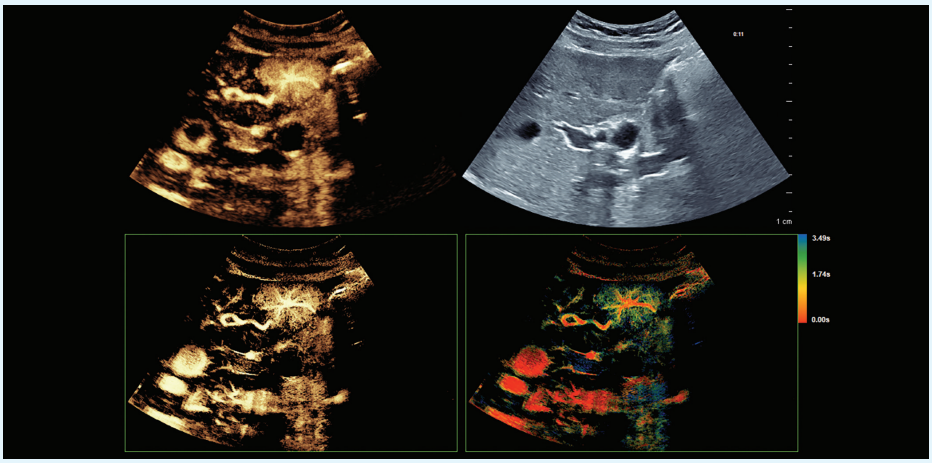

Figure 7 MVI SR provides a high-resolution representation of the FNH lesion's peak arterial enhancement pattern, while TOA SR clearly demonstrates the star-like temporal arterial filling pattern associated with FNH lesions.

Time of Arrival Super Resolution (TOA SR) addresses this limitation of TOA mapping by using a color-coding scheme in which the color hue at a given pixel is determined by the CEUS arrival time, and the color luminance is obtained from the corresponding MVI SR CEUS amplitude.

As an example, the left side of **Figure 6** shows the same MVI SR image of the FNH lesion from Figure 4, whereas the right side of Figure 6 shows the corresponding TOA SR image and illustrates the ability of the TOA SR parametric mapping technique to clearly document the typical arterial filling characteristics exhibited by FNH lesions (i.e., the star-like red pattern, indicating that contrast bubbles first arrived in the lesion's center and subsequently spread to the lesion's periphery).

MVI SR and TOA SR examples

This section provides a few more clinical examples of results provided by the MVI SR and TOA SR features.

The first example (**Figure 7**) was generated by processing the CEUS loop from another FNH lesion, after trimming the CEUS loop so that the first CEUS frame of the trimmed loop corresponds to the initial arrival of contrast inside the lesion. The top row of this figure displays one CEUS frame plus the corresponding side-by-side B-mode frame, both of which were acquired at 3.5 seconds after the beginning of the trimmed loop, whereas the bottom row displays the MVI SR and TOA SR results obtained by analyzing all the CEUS frames from the beginning of the trimmed CEUS loop to the 3.5-second mark. As can be easily appreciated from this figure, the MVI SR result provides a high-resolution representation of the FNH lesion's peak arterial enhancement pattern, while the TOA SR result clearly demonstrates the star-like temporal arterial filling pattern associated with FNH lesions. This figure also demonstrates that a single TOA SR technique can "summarize" the entire CEUS arterial phase in a single image from which it's easy to appreciate the temporal arterial filling characteristics of a given lesion, without the need to inspect all of the frames of the original CEUS loop.

The second example (**Figure 8**) follows the format of Figure 7 (top rows of each set of images: last CEUS frame and side-by-side B-mode from the trimmed loop acquired from a liver hemangioma; bottom rows: MVI SR and TOA SR results by analyzing all of the CEUS frames from the beginning of the trimmed CEUS loop to the 8-second mark) and again illustrates the ability of MVI SR to provide a high-resolution snapshot of the arterial peak enhancement pattern, plus the ability of TOA SR to "condense" the temporal arterial filling patterns of this hemangioma into a single image that is easy to interpret.

The third example (**Figure 9**) also follows the format of Figure 7 and illustrates the ability of MVI SR and TOA SR to clearly visualize the single feeding vessel of a small HCC (see white arrows in Figure 9) which cannot be seen on the original CEUS frame (top left image of Figure 9).

Finally, **Figure 10** provides an example of applying MVI SR and TOA SR to a trimmed CEUS loop of a gallbladder polyp and again illustrates the excellent single-image visualization of the peak arterial enhancement and temporal arterial filling patterns.

Image attribution

Figure 2 is adapted from Yamanaka, et al.[10]
Figure 3 is adapted from Betzig E, et al.[9]
Figures 7 and 10 are courtesy of Dr. DT Fetzer, UT Southwestern Medical Center, Dallas, Texas, USA.
Figure 8 is courtesy of Dr. Stephanie Wilson, Foothills Medical Center, Calgary, Alberta, Canada.
Figure 9 is courtesy of of Prof Dirk Andre Clevert, LMU University Hospital, Munich, Germany

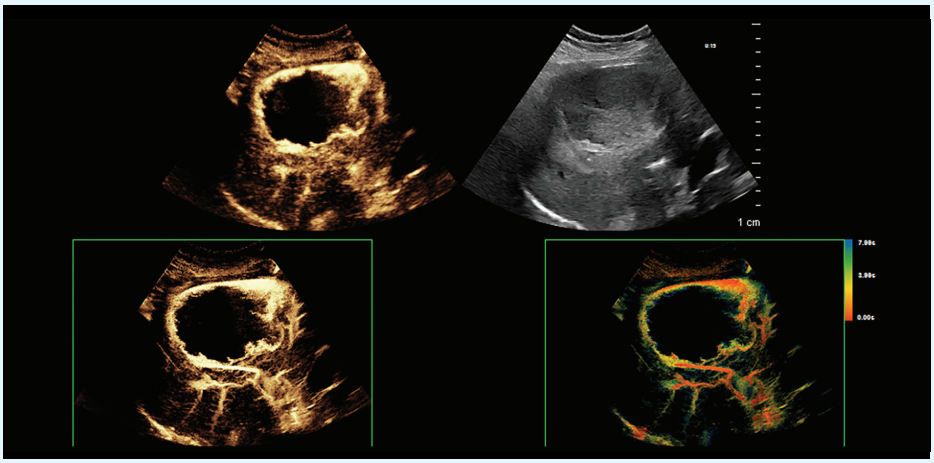

Figure 8 These examples illustrate the ability of MVI SR to provide a high-resolution snapshot of the arterial peak enhancement pattern as well as the ability of TOA SR to "condense" the temporal arterial filling patterns into a single image that is easy to interpret.

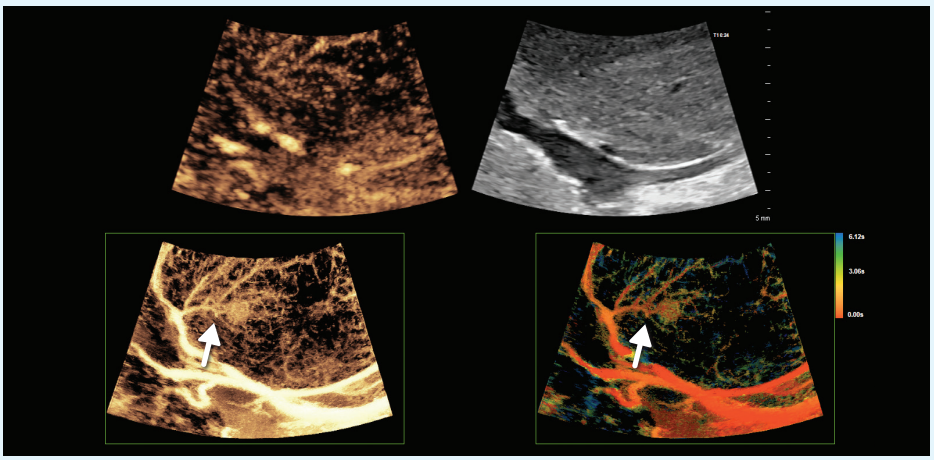

Figure 9 MVI SR and TOA SR clearly display the single feeding vessel – pointed out by white arrows - of a small HCC lesion on the right of the white arrows.

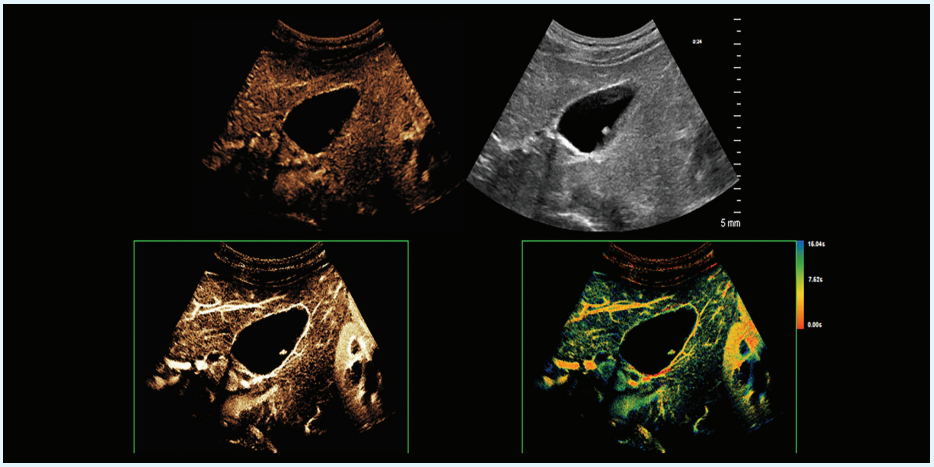

Figure 10 MVI SR and TOA SR illustrate the excellent single-image visualization of the peak arterial enhancement and temporal arterial filling patterns in this gallbladder polyp.

Summary

This white paper provided an overview of Microvascular Imaging Super Resolution (MVI SR) and Time of Arrival Super Resolution (TOA SR) breakthrough innovation features, which were introduced to the Philips EPIQ Elite platform with the Next Gen Release software and also discussed the similarities and differences of MVI SR/TOA SR vs. related existing techniques (namely, super resolution in fluorescence microscopy; super resolution in CEUS, aka ultrasound localization and maximum intensity projection CEUS imaging).

In summary, MVI SR/TOA SR is available as a post-processing Q-App tool and can be applied to any previously acquired CEUS loop.

MVI SR/TOA SR is consistent with current CEUS workflow in the sense that it performs well with current contrast agent doses, frame rates and observation times.

MVI SR/TOA SR leverages proprietary computer vision techniques and advanced motion compensation algorithms to achieve:

- Major spatial resolution improvement of more than 250% over existing maximum intensity projection CEUS imaging techniques (called microvascular imaging [MVI] on Philips ultrasound systems)*
- Significant reduction in motion artifacts compared to Philips legacy MVI (based on multiple qualitative observations), which represents a key limitation of current maximum intensity projection CEUS imaging techniques

As a result, MVI SR/TOA SR offers:

- High-definition visualization of the microvascular architecture
- Excellent visualization of the peak enhancement and, perhaps more importantly, temporal filling patterns during the arterial phase
- Clear depiction and separation of feeding vessels, which can be challenging to identify in regular CEUS and MVI loops

Initial clinical feedback regarding MVI SR/TOA SR is that its use can enhance diagnostic confidence.[16] Also, by using these features, it is straightforward to "condense" CEUS loops into single-image "summaries," which can help relatively inexperienced users to interpret CEUS exams and easily communicate the relevant findings to referring physicians.

The next step, after the introduction of the exciting MVI SR/TOA SR innovations, is to perform clinical studies in order to investigate their potential for better CEUS-based characterization of lesions and diseases as well as treatment planning and monitoring.

*Compared to previous capability.

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