Evaluation of New Ultrasound Techniques for Clinical Imaging in selected Liver and Vascular Applications

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THE 3 ORGINAL PAPERS ARE

1. Brandt AH, Hemmsen MC, Hansen PM, Madsen SS, Krohn PS, Lange T, Hansen KL, Jensen JA, Nielsen MB. Clinical Evaluation of Synthetic Aperture Harmonic Imaging for scanning Focal Malignant Liver Lesions. Ultrasound Med Biol 2015;41:2368-375.
2. Brandt AH, Jensen J, Hansen KL, Hansen PM, Lange T, Rix M, Jensen JA, Nielsen MB. Surveillance for Hemodialysis Access Stenosis: Usefulness of Ultrasound Vector Volume Flow. J Vasc Access 2016;17:483-88.
3. Brandt AH, Moshavegh R, Hansen KL, Bechsgaard T, Jensen JA, Lönn L, Nielsen MB. Vector Flow Imaging Compared with Pulse Wave Doppler for Estimation of Peak Velocity in the Portal Vein. Ultrasound Med Biol 2017 *Epub ahead of print*

INTRODUCTION AND BACKGROUND

Ultrasound has been a clinical imaging tool for almost 50 years. In the 1970s, the technology experienced an improvement with the introduction of real-time brightness mode (B-mode) and the superposition of Doppler data as a color overlay on the gray-scale B-mode [1]. The combination of gray-scale B-mode and color Doppler imaging permitted visualization of anatomy, while at the same time information about blood flow was given [2]. Ultrasound has, at the same time, developed from a cumbersome machine producing poor images to a portable instrument that can be moved freely around a hospital producing highly accurate anatomical images. This has required medical doctors, physicists, and engineers to work together [3] to bring ideas and development to medical ultrasound.

This thesis is part of a longstanding collaboration between medical doctors at the Department of Radiology (RAD) at Copenhagen University Hospital (Rigshospitalet), and physicists and engineers from the Center for Fast Ultrasound Imaging (CFU) at the Technical University of Denmark. CFU develop new ultrasound methods for B-mode imaging and blood flow imaging and medical doctors are validating the techniques for clinical imaging. The first study in this thesis concerns a clinical validation of the B-mode imaging technique Synthetic Aperture Sequential Beamforming combined with Tissue Harmonic Imaging (SASB-THI). SASB-THI is based on the ideas of Synthetic Aperture (SA) and Synthetic Aperture Sequential Beamforming (SASB), which were developed by CFU and validated by scanning healthy volunteers and patients with liver tumors in collaboration with RAD. Combining SASB with tissue harmonic imaging (THI) was developed by CFU as the next improvement, and its clinical validation was the natural follow-up. The second and third study addresses vector flow imaging (VFI), an angle-independent technique for blood flow imaging. VFI was developed by CFU and validated in collaboration with RAD on an experimental scanner. After this, VFI continued its expansion into a commercially available system and some early clinical studies have been performed. Continuation of the validation and deployment of VFI in everyday clinical practice is the next apparent step for the collaboration between CFU and RAD. The second study focuses on VFI's ability to gauge volume flow in arteriovenous fistulas for hemodialysis, while the third study focuses on its ability to estimate portal vein velocity.

The introduction continues with a description of the theory behind B-mode imaging followed by description of new methods for it. Later, the conventional flow technique is described vis-à-vis angle-independent blood flow imaging. The last part of the introduction addresses comparative statistics.

B-MODE

Conventional B-Mode Imaging

The conventional B-mode image comprises a number of lines. A focused pulse is emitted into the tissue; as it does, echoes are generated by reflections and scattering from the tissue elements. Once the transducer detects all echoes, an image line can be produced. Normally, information from pulses and echoes from one or several elements in the array of the transducer are used to create each image line. For creation of the full B-mode image with several image lines, the active elements are moved stepwise to the side, and a new focused pulse is emitted and echoes received until all elements have been used. None of the previous generated image lines are reused for the next full B-mode image. These conditions sets limits to the temporal resolution as the frame rate of a full B-mode image is limited by the number of image lines, the speed of sound in tissue, and scans depth. The resolution of the B-mode images turns out to be additionally limited by these restrictions, as a high number of image lines are needed for a high

resolution. To some extent, the resolution can be improved by applying multiple focused pulses; however, this reduces the frame rate [4]. Given this, the conventional B-mode technique has indisputable drawbacks.

Synthetic Aperture B-mode imaging

SA imaging is an alternative B-mode technique. SA was initially developed for radar technology [5] and suggested for use in ultrasound in 1974 [6]. SA's limitation has been its high computational requirements; however, the availability throughout the 1990s of fast computers enabled development of a fully integrated SA system [7, 8].

When using SA as a B-mode technique, one or a group of elements in the transducer emits a spherical wave. During receive mode, all elements in the transducer record echoes at the same time, as opposed to the conventional B-mode technique, where only the elements that emit are receiving. As the received echo contains information from all directions a low-resolution B-mode can be composed. From multiple low resolution images obtained from several emitted and received pulses a final high resolution image can be summed (Fig 1)[9]. Applying SA for B-mode construction can generate a higher frame rate than with conventional imaging. Furthermore, SA has proven to heighten resolution and improve penetration depth compared to a conventional B-mode technique [10].

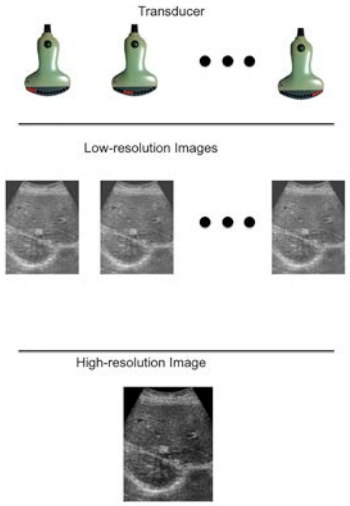

Figure 1: Illustration of Synthetic Aperture [SA]. A high-resolution image is achieved by summing low-resolution images. One or a group of elements emit a spherical wave and all elements receive the signal to acquire a low-resolution image.

Synthetic Aperture Sequential Beamforming

In 2008, Kortbek et al. purposed a solution [11] that separates the beamforming process into two stages, thereby reducing SA system computational requirements. In the first stage, beamformer scan lines are generated with a single focus point in emit and receive; in the second stage, a set of high-resolution image points combine information from multiple focused scan lines acquired in the first stage [11]. As an extra benefit of SASBs, the beamforming process reduces the data requirements to a single output signal, that is, a factor of 64 for a 64 channel system, enabling wireless RF data transfer. A wireless transducer system implemented on a commercial mobile device can be based on SASB with safe and reliable real-time data transmission [12]. SASB's ability to produce B-mode images has been validated in a blinded preclinical and clinical study, where medical doctors evaluated B-mode images of abdominal organs, and noted that SASB image quality matched conventional techniques [13, 14].

Synthetic Aperture Sequential Beamforming combined with Tissue Harmonic Imaging

Besides reducing the SA system computational load, SASB can produce sufficient acoustic energy to create harmonic components for THI. Combining SASB and THI was, thus, a logic way to go, since SASB B-mode image quality could be improved with THI (Fig 2) [15-17].

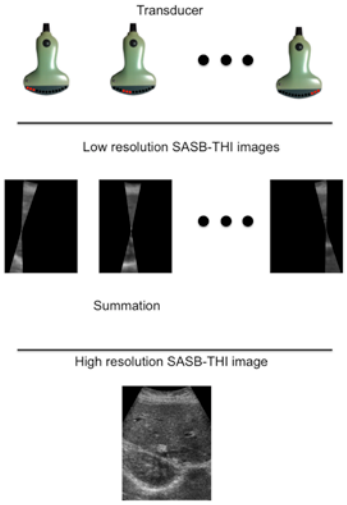

Figure: 2 Even harmonics are separated by the pulse inversion technique [15, 16], and each beam is perceived as a virtual ultrasound source emitting from the beam focal point. The received beam echoes are summed to yield the high resolution. Transmit and receive elements are identical for each emission.

THI has been used for many years in clinical imaging to improve spatial and contrast resolution, and deliver fewer artifacts. The basic theory is to image the "harmonic" signal created by the tissue. The tissue reflects the ultrasound signal with a so-called *fundamental* frequency, but also with additional frequencies termed the *harmonics* (Fig. 3). Once the fundamental and the harmonic frequencies are received, the ultrasound system can process only the latter. The harmonic frequencies build to a maximum intensity, then decay because of attenuation. The second harmonic signal is normally used for imaging [18, 19]. The combination of SASB and THI was clinically evaluated in the first study of this thesis. Patients with biopsy- or computed tomography/ magnetic resonance (CT/MR)-verified malignant focal liver lesions were scanned the day before surgery.

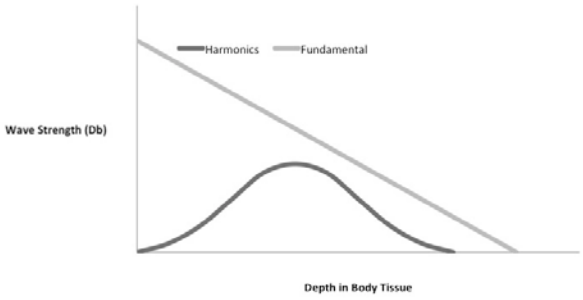

Figure 3: A schematic illustration of the strength changes of the received fundamental and harmonic waves with increasing tissue depth.

FLOW IMAGING

Conventional Flow Imaging

The standard method for evaluating flow direction is color Doppler ultrasound, while blood velocity is determined with spectral Doppler. These two techniques are widely used in flow imaging and have proven to be of great importance in evaluating, for example, hepatic vasculature [20, 21], hemodialysis vascular access [22, 23], carotid artery stenosis [24], and renal stenosis [25, 26]. A major problem with color Doppler ultrasound is that only blood flow in the direction of the emitted beam and only velocities towards or away from the transducer can be estimated, that is, in the axial direction [4]. However, frequently a vessel is located at a different beam-to-flow angle than the axial direction. The operator is obliged to adjust the transducer to an angle of less than 70 degrees to visualize flow direction. At 90 degrees no flow is seen (Fig. 4).

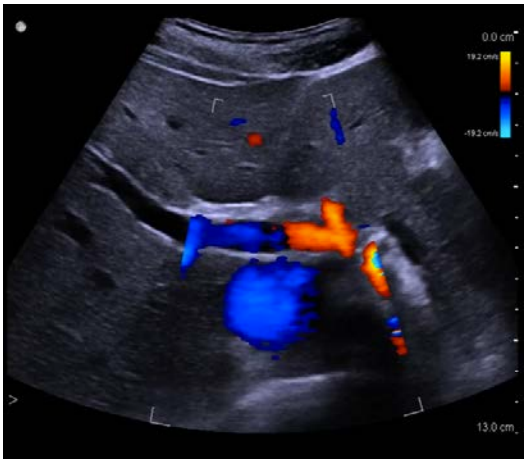

Figure 4: Color Doppler: The colors indicate the direction of the flow. Blue indicates flow going away from the transducer and red indicates flow going towards the transducer. No information about velocities is given; thus, the technique can only be used for flow direction assessment. The image shows the portal vein scanned in a subcostal position. Note that with an angle of 90 degrees no flow is seen.

In spectral Doppler, angle correction is applied when estimating velocities. Within an operator-selected range gate, angle correction is performed and a quantitative velocity value is displayed on the scanner (Fig. 5).

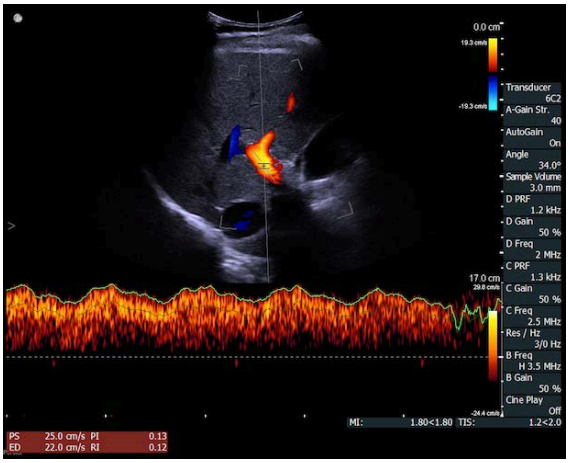

Figure 5: *Spectral Doppler* measurement of the flow in the main portal vein. The flow velocity is illustrated within a spectrogram. Angle of insonation is less than 70 degrees, indicating a reliable measurement. Flow is only measured within the range gate.

What is supposed to be the true velocity v can be determined by the equation stated below:

$$v = v_z / \cos \vartheta,$$

where v_z is the axial velocity and ϑ is the angle of insonation. The operator sets the angle, assuming that the flow is parallel to the vessel and laminar. This is certainly a simplification, since a vessel often is curved, contains branches, can be stenotic or aneurysmatic, or can contract or dilate, giving a much more disturbed flow [27-29]. The angle correction is one of the main reasons for overestimating the flow. When the angle approaches 90 degrees reliable velocity estimates cannot be achieved since *cos* (90) = 0. As with color Doppler, it is therefore necessary to achieve an angle of insonation of less than 70 degrees [30, 31]. Even though the beam-to-flow angle is less than 70 degrees, spectral Doppler overestimates the true velocity [32]. A small deviation between the beam-to-flow and the beam direction can result in a large error, when calculating the velocity v [31]. The low inter-observer variability and high inter-equipment variation is another concern with spectral Doppler [33]. Previous studies have shown poor inter-observer variability; however, a training program could improve agreement [34].

Angle-independent flow imaging

Problems with angle dependencies can be solved by vector velocity estimation, where the blood motion is found in more directions than just the axial [35]. Hence, blood flow velocities are obtained independent of beam-to-flow, which results in an improved flow understanding. Combining multiple Doppler measurements was proposed as early as 1970, and Dunmire et al., provided a full overview of the different approaches [36]. Although numerous methods combining multiple Doppler measurements have been developed and evaluated both in-vitro and in-vivo, none have become a mainstream clinical work instrument. Another approach is speckle tracking. Bohs et al. described its limitations [37], with the main one being its inability to track the axial component correctly; speckle tracking has likewise not managed to become a mainstream clinical instrument. The first technique to become a mainstream product is Transverse Oscillation (TO), which was developed by Jensen and Munk and estimates the transverse velocity and the axial velocity at the same time [38, 39]. For transmission, a conventional ultrasound pulse is emitted. The axial velocity is found similar to a conventional ultrasound technique, while the transverse velocity is found by manipulating the apodization during receive beamforming. The combination of the axial and transverse velocity can be used to calculate the vector velocity. Even though TO is now available, commercial ultrasound scanner vector techniques share the problem. None of them have had any clinical impact and both color and spectral Doppler are still the industry standard for daily clinical vascular ultrasound [40].

Vector Flow Imaging

VFI is the commercial setup for TO and provides 2-D images of the blood flow. Each pixel contains quantitative information about direction and velocity. Arrows can be superimposed in real time on the color-coded pixels for flow-profile interpretation as displayed in Figure 6. Several clinical studies from the collaboration between the RAD, and CFU have validated its use in a clinical setting. Hansen et al. found VFI obtained volume flow values in the common carotid artery comparable to magnetic resonance angiography [27, 41]. Pedersen et al. compared spectral Doppler

estimated flow angle, peak systolic velocity, end diastolic velocity, and resistive index in the common carotid artery to VFI and found significant difference in flow angle and peak systolic velocity [42]. Furthermore, Pedersen et al. found that VFI vector concentration could be used to distinguish between laminar and complex flow [43]. Hansen et al. found VFI applicable to measure volume flow in arteriovenous fistula for hemodialysis with a better reproducibility than the reference method Ultrasound Dilution Technique (UDT) [44]. For cardiac imaging, Hansen et al. showed that VFI can provide new insight into cardiac imaging regarding flow [45, 46]. Overall, VFI shows some promising results; however, final implementation in daily clinical routine has not yet been managed. This is most likely caused by the lack of TO implementation on more than a linear probe. The first implementation of TO on a commercially available convex transducer is addressed in this thesis

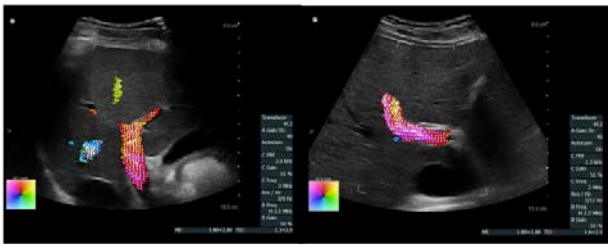

Figure 6: The figures displays the portal vein obtained with from an intercostal view [left] and subcostal view [right]. The flow looks laminar and parabolic, with shorter arrows along the vessel walls than centrally in the vessel lumen.

Vector Volume Flow

VFI can be used for volume flow calculation in arteriovenous fistula for hemodialysis; however, VFI underestimates the flow [44]. The volume flow can be found by integrating the vector-velocity profile over the cross-sectional vessel. A problem with superficial vessels such as an arteriovenous fistula is that they are easily compressed under the weight of the transducer, which will change the cross-sectional geometry. Furthermore, it is difficult for the user to place the transducer in the center intersection of the vessel and steer the ultrasound beam in the direction along one center of the epileptic geometry (Fig. 7). These errors were described by Jensen et al. and corrected for in the estimating scheme for volume flow in arteriovenous fistula in this thesis [47, 48].

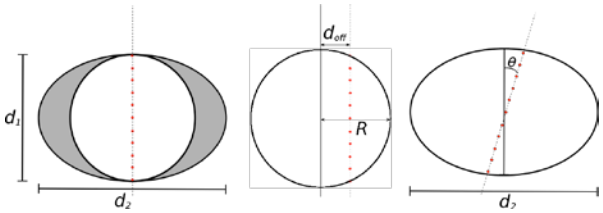

Figure 7: The figure illustrates sources of error in volume flow estimation of superficial vessels. Elliptic cross-section [left], beam-off axis [middle], and steering in an elliptic vessel [right]. The image is used by permission [47].

Vector volume is evaluated against the reference method in arteriovenous fistula volume flow determination ultrasound dilution technique (UDT) (Fig. 8) [49, 50]. UDT is an indicator dilution technique described by Krivitski and Depner [51, 52]. A known quantity of saline is added to the blood stream during a dialysis session. Changes in the resulting blood concentration as a function of time can be used to estimate volume flow. The dialysis machine is set to reverse the blood stream, recirculating some of the blood in the arteriovenous fistula [51].

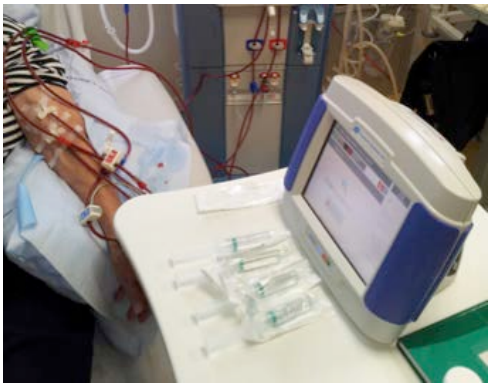

Figure 8: The figure illustrates volume flow estimation with UDT. Measurements can only be performed while the patient is in hemodialysis.

COMPARISON STATISTICS

The second and third studies compared two techniques using the generally accepted Bland-Altman analysis [53]. The limit of agreement (LOA) must be within an acceptable limit. A 30 percent error has been proposed as the acceptable LOA in a Bland-Altman analysis. However, this criterion assumes a 20 percent error on the reference method and the method being validated [54]. A precise determination of each individual method is therefore necessary before the LOA in a Bland-Altman comparison can be accepted. The comparison was based on two independent measurements with each technique. Calculation was performed as two standard deviations (STD) of the difference between two measurements of method *a* and *b* of method *x* over all included patients, divided by the mean of all measurements and multiplied by 100 to be expressed in percentage [54]. The equation for the precision calculation is given as:

$$P = \frac{2 * STD\left(x_n^a - x_n^b\right)}{\overline{x}} * 100,$$

where *n* is the number of patients, and $\overline{x}$ is the average value. After the precision of each method is determined, the excepted LOA can be calculated. The equation for the expected LOA is given as:

$$Exp\_LOA_{x,y} = \sqrt{P_x^2 + P_y^2}$$

where *P* is the precision for each method *x* and *y*. The LOA of a Bland-Altman should not be wider than expected and below 30 percent for the two methods to be interchangeable [55, 56]. For the second and third studies, analysis of interchangeability was conducted for VFI compared to the reference methods.

Aims

In study I the aim was perform a clinical comparision of a conventional imaging technique and SASB-THI using liver scans from patients with confirmed malignant focal liver cancer. The generated image sequences, SASB-THI and conventional technique videos, were evaluated by radiologists for detection of malignant focal liver lesions and to assess the image quality of SASB-THI compared with that of a conventional technique in a clinical setting.

In study II the aim was to find the agreement between volume-flow estimates by VFI and UDT, and VFI's ability to detect changes in volume flow for hemodialysis monitoring have not been stud-

ied previously. In this study, the primary aim was to analyze the agreement between UDT and VFI, and determine if VFI can detect changes in volume flow over time, compared to corresponding estimates obtained by UDT.

In study III the aim was to investigate whether the angle-independent VFI technique is an alternative to spectral Doppler for portal vein peak velocity estimation. VFI was validated in-vitro using a flowrig and in-vivo compared to spectral Doppler in two scan positions of the portal vein. Furthermore, intra- and inter-observer agreement for VFI and spectral Doppler was assessed in-vivo.

MATERIALS, METHODS, AND RESULTS STUDY I

Material and methods

Scans from 31 patients with malignant focal liver tumors were included in the evaluation. Both scans with and without visible tumors were included in the study. Diagnoses were confirmed by biopsy or computed tomography/magnetic resonance (CT/MR). The scans were performed with a conventional ultrasound scanner (UltraView 800, BK Medical, Herlev, Denmark) equipped with a research interface and an abdominal 3.5 MHz convex array transducer (Sound Technology Inc., Pennsylvania, US). The conventional technique was dynamic receive focusing combined with tissue harmonic imaging (DRF-THI). Images from the same anatomical part were recorded by SASB-THI and DRF-THI interleaved. One frame generated with SASB-THI followed one frame generated DRF-THI, giving almost simultaneously recorded images. Eight radiologists subsequently evaluated them in an image quality assessment program (IQap) that presented the images randomly side by side in real time. The imaging techniques were blinded to the evaluator. A visual analog scale (VAS) was placed at the bottom of the IQap, where the evaluator could drag a bar to the image with the preferred quality (Fig. 9). All sequences were shown twice with a different right-left position. A total of 2,032 evaluations were performed. For predicting the detection rate [sensitivity and specificity], the image sequences were shown separately where the evaluator could drag a bar to the bottom if he or she considered a tumor been present. The evaluation here was also performed in the IQap.

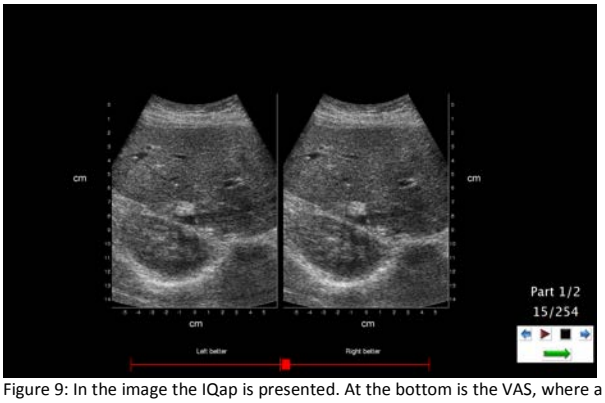

Figure 9: In the image the IQap is presented. At the bottom is the VAS, where a bar is dragged to the image the evaluator prefers. In the right corner is a control bar, where the evaluator could choose to see single image frames or a full video.

Results

The radiologist's evaluation showed no difference in preference between SASB-THI and DRF-THI in 63 percent of the evaluations. SASB-THI was favored in 16 percent of the ratings, while 21 percent favored DRF-THI. The average rating for all radiologists was -0.10 (95%CI: -0.47 to 0.26) and the statistical analysis gave a p-value of 0.63. The inter-observer variability was poor with a kappa value of 0.0045, and the intra-observer variability for each radiologist showed slight agreement with a kappa value of 0.11. Sensitivity and specificity for all rating radiologists is shown in Fig. 10. SASB-THI and DRF-THI performed similarly with regard to detection of focal malignant liver lesions (sensitivity: p=0.54, specificity: p=0.67). Inter-observer variability showed moderate agreement with a kappa value of 0.48 when rating image sequences were generated by SASB-THI, and fair agreement with a kappa value of 0.37 for images generated with DRF-THI.

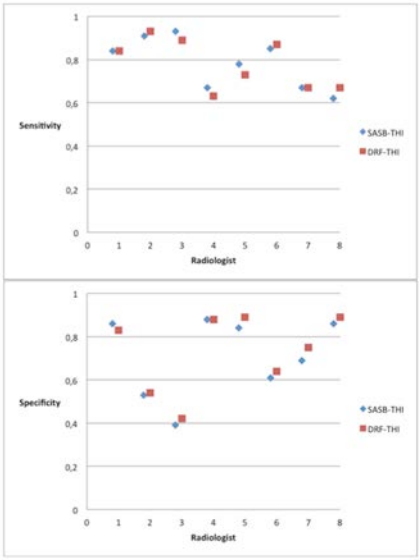

Figure 10: SASB-THI and DRF-THI sensitivity and specificity is illustrated for each radiologist.

MATERIALS, METHODS, AND RESULTS STUDY II

Material and methods

Nineteen patients with matured and functional arteriovenous fistulae were included in the study. Each patient was examined monthly over a six-month period with VFI and UDT. VFI measurements were performed on a commercial ultrasound scanner (UltraView 800, BK Medical, Herlev, Denmark) equipped with a linear transducer (8670, 9MHz, BK Medical, Herlev, Denmark). All VFI measurements were performed before the UDT measurement. Initial B-mode scans were performed for orientation. Three VFI recordings were performed with a longitudinal view at a position with laminar flow. For each recording, the color box was adjusted to cover the lumen of the arteriovenous fistula segment, and the pulse repetition frequency (PRF) was adjusted to the highest velocities without aliasing. To avoid blooming artifacts, wall filter and color gain were set to optimal filling of the vessel. Between each recording, the transducer was raised and repositioned to attain a new location. Along with the longitudinal VFI recording, an accompanying transverse B-mode recording was conducted. The transducer was not lifted between the longitudinal and transverse recording to attain the same compression. With the transverse view, two perpendicular diameters for cross-sectional area determination were measured. Diameters were measured with the built-in length gauge of the scanner, and performed from the superficial to the deep tunica intima and the corresponding mediolateral diameter. To calculate volume flow by VFI a rectangular region of at least 20 percent, the whole vessel segment was manually marked (Fig. 11). Calculation of the volume flow was based on integration of the vector-velocity

profile over the cross-sectional vessel area assuming laminar and axisymmetric flow profile. The algorithm was developed in-house [47]. UDT measurements were carried out with a Transonic HD03 Flow-QC hemodialysis monitor (Transonic Systems Inc., Ithaca, NY, US) and performed according to vendor guidelines. According to daily clinical practice, three measurements were conducted with each technique (UDT and VFI) and the average of these results was considered the volume flow of each method. The first two measurements were furthermore used for precision analysis.

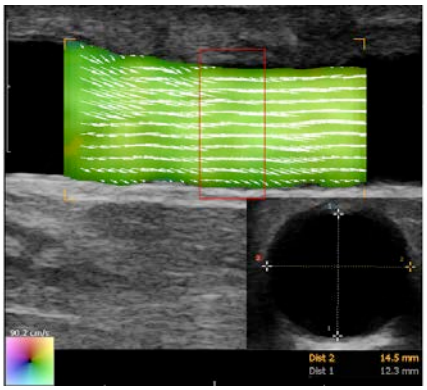

Figure 11: The longitudinal arteriovenous fistula segment measured with VFI and the 20 percent region marked for the volume flow calculation. In the right corner is an illustration of the corresponding transverse B-mode with diameter measurements.

Results

Average volume flow measured with UDT and VFI were 1,161 ml/min (±778 ml/min) and 1,213 ml/min (±980 ml/min), respectively (p = 0.3). Precision for VFI was 20 percent and the mean difference between the first and second measurement -29 ml/min (95% CI: -78 ml/min to 20 ml/min). UDT precision was 32 percent and mean difference between the first and second measurement was 28 ml/min (95% CI: -61 ml/min to 118 ml/min). There was no statistical difference between precision for VFI and UDT (p = 0.33). The differences between UDT and VFI measurements were analyzed in a Bland-Altman plot. Mean difference was -51 ml/min with LOA from -35 percent to 54 percent (mean 44.5 percent). The expected LOA calculated based on the precision for each method was 37 percent. A strong correlation was found between the UDT and VFI with an R-squared value of 0.87.
Volume flow changes were analyzed in a four-quadrant plot and with regression analysis. Inclination was 0.301 with a p-value of 0.0001. The concordance rate increased from 54 percent to 72 percent with an exclusion zone of 25 percent corresponding to the averaged precision of VFI and UDT and the threshold for referral to angiography (Fig. 12).

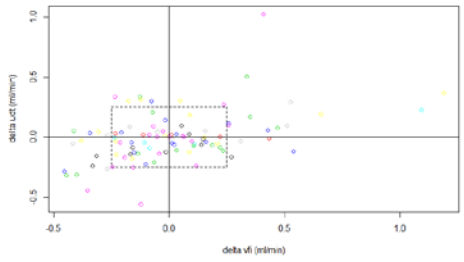

Figure 12: This illustrates the four-quadrant plot of the differences. Each color characterizes a patient and indicates the volume-flow change between sessions. Including the exclusion zone (dotted-line box) of 25 percent the concordance rose from 0.54 to 0.72.

MATERIALS, METHODS, AND RESULTS STUDY III

Material and methods

A conventional ultrasound scanner equipped with VFI (BK3000, BK ultrasound, Herlev, Denmark) and a 3 MHz convex probe (6C2, BK ultrasound, Herlev, Denmark) was used to obtain vector velocity data. For the flowrig validation, a flow system (CompuFlow 1000, Shelley Medical Imaging Technologies, Toronto, Canada) circulating a blood-mimicking fluid (BMF-US, Shelley Medical Imaging Technologies, Toronto, Canada) in a closed loop circuit was used. The pump was set to velocities from 5-49 cm/s and the convex array was fixed to a distance of 70 mm from the vessel with a diameter of 8 mm. For the in-vivo validation, 32 healthy volunteers were scanned in two positions (intercostal and subcostal). The intercostal view is preferred for velocity estimates since beam-to-flow angle of less than 70 degrees can be attained; a subcostal beam-to-flow angle of less than 70 degrees is not always possible to attain, thus giving unreliable velocity estimates with the conventional spectral Doppler. Since VFI is angle-independent, the main portal vein peak velocities should be the same regardless of scan position. For both spectral Doppler and VFI, two velocity estimates were obtained at both the intercostal and subcostal view. Between each measurement, the transducer was raised and repositioned. For the intra- and inter-observer agreement assessment, 10 of the 32 healthy volunteers were rescanned by three physicians. All scans were again performed with an intercostal and subcostal view and blinded to the peak velocity estimation displayed on the scanner. VFI peak velocity was found as the maximum velocity over at approximately 100 frames of VFI data for each measurement. Data corresponded to 5-7 heartbeats. For spectral Doppler, the peak velocity was found with the standard Doppler setup for the scanner, and maximum velocity was found over 3-5 heartbeats (Fig. 13).

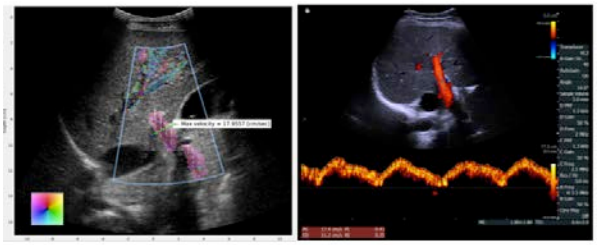

Figure 13: On the left of the image, VFI peak velocity estimation is shown for one patient, while peak velocity estimation for the same patient is shown on the right side. Notice that velocities were estimated at the same depth for both methods.

Results

In the flowrig, VFI had a precision of 3 percent with a mean bias of 0.33 cm/s. In-vivo, the precision for VFI was 18.1 percent at the intercostal view and 23.2 percent at the subcostal view, while the precision for spectral Doppler was 28.3 percent at the intercostal view and 76.8 percent at the subcostal view. Mean bias between VFI and spectral Doppler was 0.57 cm/s (p=0.38) for the intercostal view and 9.89 cm/s (p<0.001) for the subcostal view. VFI peak velocities obtained at the intercostal view were not significantly different from spectral Doppler peak velocities (p=0.38). Intercostal and subcostal VFI peak velocities were not significantly different (p=0.78), while intercostal and subcostal spectral Doppler values were significantly different (p<0.001) (Table 1).

	Mean and STD for VFI (cm/s)	*Mean and STD for spectral Doppler (cm/s)*	*P-value*
Intercostal	*20.09 / 3.19*	*20.66 / 3.77*	*0.38*
Subcostal	*19.90 / 3.87*	*29.79 / 11.45*	*<0.001*
P-value	*0.78*	*<0.001*	*-*

Table 1: Mean peak velocities and standard deviation (STD) for VFI and spectral Doppler and results from paired t-tests.

Intra- and inter-observer agreement was higher for VFI with intra-class correlation coefficients (ICC) being higher overall. ICC inter-observer values for was VFI 0.80, and for spectral Doppler 0.37, while intra-observer ICC for VFI was 0.90, and for spectral Doppler 0.86 (Table 2).

	Interobserver agreement	
	Intercostal view	Subcostal view
VFI	0.84 (95% CI: 0.53, 0.96)	0.78 (95% CI: 0.40, 0.94)
spectral Doppler	0.64 (95% CI: -0.027, 0.90)	0.27 (95% CI: -0.42, 0.73)
	Intraobserver agreement	
	Intercostal view	Subcostal view
VFI Physician 1	0.93 (95% CI: 0.71, 0.98)	0.93 (95% CI: 0.73, 0.98)
VFI Physician 2	0.77 (95% CI: 0.17, 0.94)	0.95 (95% CI: 0.81, 0.99)
VFI Physician 3	0.92 (95% CI: 0.66, 0.98)	0.88 (95% CI: 0.47, 0.97)
spectral Doppler Physician 1	0.85 (95% CI: 0.43, 0.96)	0.86 (95% CI: 0.41, 0.96)
spectral Doppler Physician 2	0.74 (95% CI: -0.51, 0.94)	0.79 (95% CI: 0.12, 0.95)
spectral Doppler Physician 3	0.60 (95% CI: -0.53, 0.90)	0.37 (95% CI: -0.57, 0.85)

Table 2: The table shows the inter- and intra-observer agreement for subcostal and intercostal view. Values are shown as interclass correlation coefficient (ICC) with 95 percent confidence interval.

DISCUSSION

The new achievements of this thesis are**:**

I. Radiologists rated the image quality and detection capability of focal liver lesions for SASB-THI to be equal to conventional imaging techniques. Consequently, it makes sense to exploit SASB's data reduction advantage to develop a wireless transducer implemented on a commercial tablet (Study I).

II. VFI has a higher precision for arteriovenous fistula volume flow determination and detects large in-between session changes similar to the reference method. VFI may therefore be regarded as an alternative method for arteriovenous fistula volume flow surveillance for hemodialysis (Study II).

III. The convex array VFI implementation for abdominal studies offers a higher precision than spectral Doppler for peak velocity estimation regardless of the portal vein insonation window. Furthermore, VFI can estimate the same peak velocity in the main portal vein with an insonation angle inapplicable for spectral Doppler. Intra- and inter-observer agreements are higher for VFI than for spectral Doppler for portal vein peak velocity estimation (Study III).

CLINICAL EVALUATION OF SASB-THI

B-mode side-by-side comparison studies

B-mode image side-by-side comparison studies are performed for new against established imaging techniques. Data is collected before the evaluation and the subsequent evaluation is often performed with a software application (e.g., IQap) created for the purpose [13]. The evaluators are instructed to assess the image quality and provide a diagnosis. For a fair comparison, the evaluators are usually blinded to technical information about the ultrasound technique that created the B-mode image [13].

For the data collection to be applicable for a side-by-side comparison, data from both techniques should be recorded as simultaneously as possible. However, for several side-by-side comparisons, data are collected with consecutive recording [57-65]. Even though the same position is held with the transducer while obtaining data, and the patient is lying still, a similar image can never be attained with consecutive data collection. Furthermore, the comparisons are often performed with still images, which does not resemble daily clinical practice as an ultrasound examination is an dynamic procedure [57-65]. Having still images reduces the clinical information and may reduce the value of the evaluation.

Our study was performed with interleaved recording of data given almost simultaneously obtained data. Moreover, during the evaluation, video sequences were shown to attain a more realistic comparison, without losing clinical information.

THI in clinical imaging

THI improves B-mode image spatial and contrast resolution, and deliver fewer artifacts [18]. For certain patient groups diagnostic information is increased, as THI displays pathology with greater clarity than a conventional B-mode image. For liver imaging, hepatic lesion visibility and characterization is improved, and a better confidence in diagnosis is provided [57, 58, 60], and focal lesions in patients with cirrhosis are detected with higher certainty [62]. The same is the case for renal imaging, as the detection rate of focal lesions, for example, renal cell carcinoma, cysts, or kidney stones, is improved due to an improved overall image quality, lesion conspicuousness, and fluid-solid differentiation [65]. In breast imaging, characterization and lesion detection is likewise improved [64], and THI is suggested for a better carotid plaque evaluation characterization [64]. Thus, THI has been shown to improve daily clinical practice and diagnostic accuracy. Therefore, combining SASB and THI was suggested to improve the former's performance [14-17].

Side-by-side comparison studies performed with SA and SASB

SA or SASB have not yet had any impact on clinical practice and diagnosis, since few studies evaluated them in side-by-side com-

parisons. Two studies by Kim et al. and Kim et al. evaluated SA as a technique for breast lesion imaging, where RF data were acquired with a conventional scanner equipped with a research package. The first study evaluated the clinical performance in a combined phantom and in-vivo study against a conventional technique. Two radiologists evaluated the B-mode images of breast tumors in 10 patients. Overall, SA was found to have an improved conspicuity, margin sharpness, contrast, and better resolution of the deeper underlying tissue. Diagnostic accuracy was similar with the two techniques [61]. The other study was a larger side-by-side comparison with 24 patients and a total of 31 breast lesions (16 malignant and 15 benign). SA was likewise found superior. Three experienced radiologists preferred SA image quality instead of the conventional technique [59].

Hemmsen et al. evaluated SASB image quality in a side-by-side comparison against a conventional technique, where the livers of healthy volunteers were scanned. The two evaluating radiologists found the joint image quality to be equal [66, 67]. In a study by Hansen et al. on SASB image quality, five radiologists evaluated 117 image sequences from patients with liver tumors. SASB was favored over the conventional technique; however, the result was not significant (p=0.18) [13].

Overall, SA and SASB B-mode imaging shows promising results, since radiologists prefer these techniques; however, the methods have not managed to improve diagnostic capabilities, even though a higher resolution and improved penetration depth are achieved [10].

The image quality of the combination between THI and SASB was pursued in study I, since both techniques' advantages could be exploited. SASB-THI was evaluated in a preliminary side-by-side comparison against a conventional technique. The liver of healthy volunteers was scanned and the combination of SASB-THI equaled the conventional technique [68]. The result was the same in our study, where liver tumors were scanned. Besides image quality evaluation, diagnostic accuracy was evaluated, with sensitivity [50-76 percent] and specificity [60-96 percent] for diagnosis of focal liver lesion with unenhanced B-mode imaging being similar to previous studies [69-71]. The results indicate that SASB-THI is capable of clinical liver scanning.

Clinical implications and future perspectives

With SA, a higher frame rate and resolution, and improved penetration, can be achieved compared to a conventional B-mode [10], while SASB allows a synthetic aperture technique to be implemented on a system with restricted capacity [72]. The combination of SASB-THI performs similarly with regard to image quality and pathology detection to a conventional technique for liver imaging; however, SASB's data reduction advantage can be used to produce a wireless transducer system with safe and reliable real-time transmission [12]. Wireless transducers improve freedom of movement and help maintain sterile conditions or simplify ultrasound-guided interventions and perioperative scanning [73]. This reduction does not lower the quality of the diagnosis, and allows the option of implementation on a hand-held tablet [12]. The combination of a wireless transducer with a relatively inexpensive commercial tablet would spread the use of ultrasound to less developed countries, as well as into emergency rooms and ambulances. Hand-held devices have moreover proven to be useful in numerous clinical conditions [74-76] and have been termed the real stethoscope [77].

A major challenge with the spread of ultrasound is the lack of user training and education. With a safe and reliable real-time transmission as demonstrated with SASB [12], an experienced user could assist a novice in acquiring and interpreting images by telesonography [78], which has already been studied in less traditional places such as patient transportation [79] and military operations [80]. The development and implementation of SASB and SASB-THI will be exciting to follow.

Limitations

Our experimental setup only allowed data collection with a navigational image from the first stage beamforming with a low frame rate and a poor image quality. The final data selection was performed after second stage beamforming in a blinded setup. Though this reduces the quality of the study, it is only minor as the selection was performed blinded. However, future data collection with SASB and SASB-THI should be performed with a real-time, second-stage beamforming. Moreover, a higher frame rate and approving algorithm [for example, speckle reduction filter] would have improved the quality. Comparison in more than one organ and with different pathologies would have further improved this study.

SURVEILLANCE OF ARTERIOVENOUS FISTULA FOR HEMODIALYSIS WITH VFI

Arteriovenous fistula surveillance

The arteriovenous fistula for hemodialysis is a surgically created connection between an artery and vein. The preferred connection is between the cephalic vein and radial artery, and it is the favorite vascular access for hemodialysis in end-stage renal disease [81, 82]. After creation, a rapid flow into the venous system gives a low-resistance circuit with highly increased blood flow, leading to vein dilation and vessel-wall thickening, which is ideal for repeated punctures and hemodialyses [81]. However, two-thirds of arteriovenous fistulae will develop varying degree of stenosis after 18 months [81, 83]. Stenosis may lead to thrombosis and access failure [81, 84]. The National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF KDOQI) has recommended monitoring patients with arteriovenous fistulae for many years [82], stating that it should be performed with regular volume flow measurements to detect stenosis. Despite this recommendation, there is an ongoing discussion on the need for regular monitoring [85-87]. Paulson et al. called the surveillance program of hemodialysis access a false paradigm based on low evidence [88], and Allon and Ribbon stated that none of the non-invasive surveillance tests available [clinical monitoring, UDT, and spectral Doppler] consistently can distinguish between vascular accesses destined to clot or remain patent [89]. However, the recommendations about regular monitoring still apply [82].

Methods for volume flow surveillance

UDT is considered the reference method for volume flow surveillance and is used commonly in comparison studies [49, 84, 90, 91]. The method is fairly simple and dialysis staff can be more easily trained [52] than with ultrasound [92]. However, UDT has variations in volume flow up to 30 percent caused by constant changes in mean arterial pressure, central venous pressure, and vascular resistance of the access circuit during each dialysis session, as well as insufficient mixing of the diluting agent (saline) in the blood [85, 90, 93].

Spectral Doppler can also be used for volume flow surveillance, but is unreliable due to operator and angle dependencies [30, 94]. Zanen et al. have reported that spectral Doppler overestimates volume flow with a bias of 1,129 ml/min between spectral Dop-

pler [average 1,958 ml/min] and UDT [average 752 ml/min] [95], while Schwarz et al. reported spectral Doppler underestimation of 30 percent compared to UDT [91]. When scanning an arteriovenous fistula, the vessel is easily compressed, creating turbulent flow, which affects the velocity estimation with spectral Doppler and may account for varying results [96].

Magnetic resonance angiography (MRA) is another method for volume flow surveillance. Bosman et al. compared UDT to MRA in hemodialysis grafts and found a good correlation (R = 0.91) [97]. However, MRA is cumbersome for the patient, time consuming, expensive, and not as available as ultrasound or UDT.

VFI for volume flow surveillance

Hansen et al. established VFI's ability to estimate volume flow in arteriovenous fistulas for hemodialysis, but found an underestimation compared to UDT of 30 percent [44]. This study found no underestimation, probably because the three sources of error described by Jensen et al. were considered in the estimation algorithm [47, 48].

The volume flow change between sessions was also considered in our study, since it often is more important than the actual estimation within a single dialysis session when identifying a stenosis. A drop of more than 25 percent may indicate stenosis and is used as advice for referral to angiography [82]. UDT may not be the best method to determine the drop in volume flow, since the measurements are performed with the dialysis needles in place. Huisman et al. reported that a different needle position could result in a between-session variation of up to 23.5 percent in radiocephalic fistulas [90]. VFI predicted large (greater than 25 percent) between-session changes in volume flow similar to UDT; furthermore, VFI precision (20 percent) was better compared to UDT (32 percent). This may indicate that VFI can estimate volume flow with more accuracy.

An emergent thrombosis evaluated with VFI was not included in our study, as angioplasty data were not considered. However, VFI was more precise, which may indicate that it can predict stenosis with more certainty. With VFI, flow characteristics can easily be determined in real time, and a part of the vessel with laminar flow can be identified. A laminar flow profile is ideal for volume flow calculation by 2D vector-flow maps of VFI [27]. Furthermore, VFI can visualize the complexity of blood flow in a manner not possible with conventional spectral Doppler and UDT [43, 98]. The flow pattern may be a new factor that should be considered when predicting imminent stenosis in arteriovenous fistulas.

Opposed to UDT, VFI adds the option of a B-mode image. A B-mode gives detailed information about the morphology of the arteriovenous fistulae and other abnormalities such as hematomas, aneurysms, and intraluminal thrombi, which should be treated and monitored to keep the hemodialysis access patent [22, 84]. Furthermore, the B-mode can be used for the construction planning of the arteriovenous fistula, for monitoring the maturation and identifying complications, which adds to the argument of educating the dialysis staff in using ultrasound [99].

Comparison analysis

UDT and VFI were compared and analyzed with Bland-Altman plots [53]; however, Crichtley et al. argued for precision should be calculated for each method before comparison [54]. By determining the precision beforehand, an excepted LOA could be calculated; the equation for precision P is given as:

$$P = \frac{2 * STD\left(x_n^a - x_n^b\right)}{\overline{x}} * 100$$

where n is the number of patients, a and b are the two measurements, and $\overline{X}$ is the average value. Given a precision of ± 20 percent for each method, the excepted LOA would be 28.3 percent using the equation for the expected LOA as follows:

$$Exp\_LOA_{x,y} = \sqrt{P_x^2 + P_y^2}$$

where P is the precision for each method x and y. Consequently, a percentage error of up to ± 30 percent of the LOA for the Bland-Altman plot should be accepted, as this is caused by the inaccuracy for each method. Expected LOA was 37 percent between UDT and VFI, and therefore higher than the suggested 30 percent. Furthermore, LOA for the Bland-Altman was higher (44.5 percent) than the excepted LOA, proving that UDT and VFI cannot be considered interchangeable. However, VFI precision [20 percent] was better compared to UDT (32 percent), indicating that the difference is caused by the inaccuracy found for UDT.

Clinical implications

A major advantage of VFI is fewer operator-dependent settings. Compared with spectral Doppler, where a beam-to-flow angle of less than 70 degrees is needed, VFI can be positioned on the arteriovenous fistula without considering the angle. This means that the operator does not have to angle the transducer, and the likelihood of compressing the arteriovenous fistula and changing the flow pattern is less. Furthermore, the operator does not have to place the range gate and to correct the angle according to flow direction. With VFI, flow is obtained over the whole vessel, and a laminar segment can easily be determined.

Limitations

One limitation was that only arteriovenous fistulas were studied. These are the preferred vascular access choice, but arteriovenous graft is the next option [82]. Approximately one-third of patients requiring a vascular access receive a graft [100]; hence, the impact of this study would be higher if grafts had been included. Furthermore, commercially available real-time volume flow estimation is still lacking; future development should focus on a user-friendly estimation scheme for use in clinical everyday life.

COMPARISON OF PORTAL VEIN VELOCITY OBTAINED BY VECTOR FLOW IMAGING AND SPECTRAL DOPPLER

Portal Vein and Spectral Doppler

Among the ultrasound parameters assessed on patients with chronic liver disease is portal vein velocity and flow direction, as portal hypertension can lead to a reduced peak velocity and in advanced stages reversed flow [101, 102]. Complications to portal hypertension [for example, ascites, esophageal and gastric varices, and splenomegaly] can be fatal [103] and spectral-Doppler-measured changes can indicate development [104, 105]. Doppler ultrasound should be repeated every time a new clinical event occurs to rule out portal vein thrombosis and hepatocellular carcinoma, which frequently exacerbate portal hypertension and clinical decompensation [106]. Portal vein flow and velocity changes are well correlated with staging of liver cirrhosis and development of portal hypertension [107]. The preferred scan position for portal vein velocity estimation with spectral Doppler

is the intercostal view, as a beam-to-flow angle of less than 70 degrees can be achieved for all patients [106]. With a subcostal view, the main portal vein can easily be visualized, but the beam-to-flow angle is often greater than 70 degrees, thus giving less precise spectral Doppler estimates (Fig. 14). Furthermore, the poor inter-oberserver agreement with spectral Doppler causes measurement errors [33, 34].

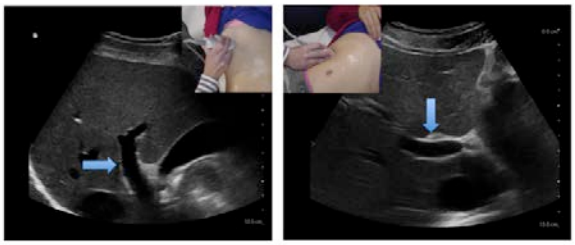

Figure 14: The intercostal view of the mean portal vein is shown on the left side, while the subcostal view is shown on the right side.

Previous comparison studies

Spectral Doppler overestimation of velocities is well known [30, 108, 109]. Tortoli et al. showed that spectral Doppler overestimates the velocities in the common carotid artery and internal carotid artery by 27 percent to 43 percent, as compared to an angle-tracking vector Doppler method and a plane wave vector Doppler method [110]. Pedersen et al. showed spectral Doppler overestimation in the common carotid artery velocity by 6.9 cm/s compared to TO [42]. The operator-dependent manual angle correction and adjustment of sample volume have a great impact on the overestimation [94]. The operator manually sets the cursor parallel to the vessel wall as it is assumed that the flow is laminar. The estimated angle is used in relation to the equation stated below to determine the velocity:

$$v = v_z / \cos \vartheta$$

where v is the true velocity, v_z is the axial velocity, and ϑ is the angle of insonation. The assumption that the flow is laminar may not be true, as well as that a single angle is involved [110]. This may be the main reason for spectral Doppler errors in velocity estimation [111, 112]. Furthermore, the error of the velocity estimation becomes bigger with increasing beam-to-flow angles mainly caused by the spectral broadening effect [108, 113].

Ekroll et al. suggested a solution to operator dependencies for spectral Doppler by combining B-mode, spectral Doppler, and vector flow using plane wave imaging and obtaining automatic vector and Doppler simultaneously [114]. This approach has potential since manual placement of the sample volume would be facilitated, thus improving the inter-observer variability. VFI has the same advantages, and inter-observer variability was improved compared to spectral Doppler in study III. The far fewer adjustments needed for VFI may be the reason for the better inter-observer agreement as compared to spectral Doppler.

A previous commercial linear array VFI implementation has shown a systematic underestimation of 10-14 percent on a flow-rig [39, 55], while the convex array VFI implementation evaluated in this study showed no underestimation compared to a flowrig. The VFI underestimation for the linear array is caused by the estimation algorithm [115], the PRF settings [116], and an inadequate temporal resolution [42]. This seems to be solved for the convex array VFI implementation as described by Jensen et al. [115].

Clinical implications

Patients suffering from chronic liver disease may benefit from the convex array VFI implementation, as correct estimates can be obtained regardless of the insonation window. Performing measurements with spectral Doppler using an intercostal view is recommended since the insonation angle is close to zero degrees [106]. Even though errors with spectral Doppler velocity estimates are well established, it is accepted as a useful method for portal peak velocity estimation and diagnosis of portal hypertension [20, 117]. With VFI, the portal blood flow examination of these patients could be more reliable, and sensitivity and specificity for portal hypertension diagnosis may even be higher. Furthermore, for the evaluation of patients with altered portal vein positions due to liver surgery or liver transplantation, the examination would be easier, as any scan position can be applied without hampering the velocity estimates.

Limitations

Some limitations with VFI must be mentioned. We found 95 mm to be the maximum scan depth. Patients are often more obese than healthy volunteers, and with a growing obesity problem in modern societies, development of VFI in terms of penetration is still needed. Nine percent of the healthy volunteers (n=3) were excluded due to this limitation, while estimates could be achieved with spectral Doppler for those patients. Thus, at the moment, VFI should be regarded as a supplement to the spectral Doppler examination. Furthermore, no real-time estimate of peak velocity is given with VFI. A commercially available, real-time, user-friendly estimation scheme is warranted. A system where the operator could indicate in which area of the vessel information of velocities should be estimated as with a spectral Doppler range gate will improve the usability.

CONCLUSION

The overall aim of this thesis was to clinically evaluate new ultrasound methods concerning B-mode and blood flow imaging. CFU has the expertise in developing ultrasound techniques, while RAD has the clinical understanding. The collaboration between CFU and RAD gives unique conditions for developing the use of ultrasound.

In the first study, we concluded that the combination of SASB and THI gives image quality and diagnostic accuracy equal to conventional imaging techniques combined with THI. The advantage of SASB data reduction can be used for development of a wireless transducer capable of working on a hand-held tablet. Furthermore, the image evaluation program must be acknowledged. The programme enables evaluation of dynamic image sequence obtained simultaneously, which is unique for the image quality program developed by CFU.

In the second study, we concluded that VFI could be used for volume flow surveillance in arteriovenous fistulas for hemodialysis. Volume flow estimates were not significantly different from values obtained with the reference method; nevertheless, while VFI was more precise, but not interchangeable with the reference method. For large volume flow changes in between hemodialysis sessions, VFI was in concordance with the reference method. A user-friendly, real-time estimation scheme for commercial use is still lacking. We advocate for the use of VFI for hemodialysis access surveillance.

In the third study, we concluded that VFI can obtain similar peak velocities as spectral Doppler in the main portal vein. Furthermore, we concluded that VFI had a better precision and could

estimate equal peak velocities with a view, which was inapplicable for spectral Doppler. Intra-and inter-observer agreement was for the first time evaluated for VFI and found better than for spectral Doppler. Results of future studies, where VFI peak velocity is estimated on patients with chronic liver disease, are definitely exciting, as VFI may heighten the diagnosis for portal hypertension as the diagnosis can be set with more certainty. The convex implementation of VFI may benefit patients and help healthcare workers in the assessment of abdominal vessel pathology.

PERSPECTIVES

Several potential clinical studies can be performed with both SASB-THI and VFI.

SASB-THI:

A study concerning SASB-THI image quality and diagnostic accuracy for more than one organ and different pathologies.

In our study, the evaluators found SASB-THI to be equally effective in liver imaging as the reference method. SASB-THI could improve diagnosis in several clinical cases as a better resolution and contrast is provided over the conventional technique. A study concerning several pathologies would therefore be beneficial.

A user experience study with a completed wireless transducer based on SASB-THI.

This study could reveal the advantages of a wireless transducer. Several clinical conductions could be facilitated.

VFI:

A large multicenter study where VFI is used for volume flow surveillance in arteriovenous fistulas by several users and dialysis centers.

VFI has the potential of replacing the reference method due to its higher precision. This study would reveal these advantages and change the way we manage patients with arteriovenous fistulas.

A comparison study, where MRA-obtained volume flow is compared to VFI estimates in arteriovenous fistulas and arteriovenous graft.

VFI has the potential to work in grafts as well. Furthermore, comparison to MRA would give a clearer indication of VFI ability to estimate volume flow in arteriovenous fistulas.

A study comparing percutaneous transluminal angioplasty data to VFI data to determine whether VFI can identify hemodynamic significant stenosis correctly.

VFI could be a more reliable method to determine stenosis due to higher precision.

A study evaluating whether vector concentration for VFI can predict arteriovenous fistula stenosis.

VFI can differentiate flow characteristics and this may be a new factor to determine upcoming stenosis.

A study validating the convex array VFI implementation on patients with varying degree of portal hypertension.

Since VFI has a higher precision than spectral Doppler for portal vein peak velocity estimation, the portal hypertension diagnosis can potentially be set with higher certainty.

A study concerning velocity estimation of other abdominal vessel were the angle independency would be an advantage (a. renalis, truncus coeliacus, a. mesenteria superior).

VFI could potentially improve diagnosis and give new insights to flow dynamics for abdominal vessel pathology.

LIST OF ABBREVATIONS

CFU: Center of Fast Ultrasound Imaging
RAD: Department of Radiology at Copenhagen University Hospital [Rigshospitalet]
B-mode: Brightness mode
TO: Transverse Oscillation
VFI: Vector Flow Imaging
SASB-THI: Synthetic Aperture Sequential Beamforming - Tissue Harmonic Imaging
SASB: Synthetic Aperture Sequential Beamforming
THI: Tissue Harmonic Imaging
SA: Synthetic Aperture
UDT: Ultrasound Dilution Technique
CT: Computed Tomography
MR: Magnetic Resonance
DRF-THI: Dynamic Receive Focusing - Tissue Harmonic Imaging
LOA: Limit of Agreement
STD: Standard deviation
IQap: Image Quality assessment program
VAS: Visual Analog Scale
LOA: Limit of Agreement
STD: Standard deviation
ICC: Intra-class Correlation Coefficients
MRA: Magnetic resonance angiography

SUMMARY

This Ph.D. project is based on a longstanding collaboration between physicists and engineers from the Center of Fast Ultrasound Imaging (CFU) at the Technical University of Denmark and medical doctors from the department of Radiology at Rigshospitalet. The intent of this cooperation is to validate new ultrasonic methods for future clinical use.

Study I compares two B-mode ultrasound methods: the new experimental technique Synthetic Aperture Sequential Beamforming combined with Tissue Harmonic Imaging (SASB-THI), and a conventional technique combined with THI. While SASB reduces the amount of data transformation, thus enabling wireless transmission, THI can improve resolution and image contrast, and creates fewer artifacts. Thirty-one patients with verified liver tumors were scanned and recordings with and without visible pathology were performed. Subsequently, eight radiologists evaluated blinded to information about the technique, which B-mode images they preferred, as well as detection of pathology. Evaluation showed that the techniques were preferred equally and tumor could be detected equally well.

Study II deals with the ability of vector flow imaging (VFI) to monitor patients with arteriovenous fistulas for hemodialysis for upcoming stenosis. VFI is an angle-independent method for determining blood flow direction and velocity. Volume can be determined by integrating the velocity profile multiplied by the cross-sectional area. Nineteen patients were monitored monthly over a period of six months, and VFI estimates were compared with the reference ultrasound dilution technique (UDT). VFI volume flow values were not significantly different from UDT and had a better precision. Concordance between VFI and UDT was high when large volume flow changes (greater than 25%) oc-

curred between dialysis sessions. However, the methods could not be regarded as interchangeable.

Study III deals with VFI's ability to determine peak velocity in the portal vein. The commonly used ultrasound method for this is spectral Doppler, which is known to overestimate peak velocity when the angle between the blood vessel and the beam is more than 70 degrees; this overestimation becomes even larger when the angle becomes larger. VFI can determine the peak velocity angle independently. Thirty-two healthy volunteers were scanned with spectral Doppler and VFI with two portal vein scan positions (intercostal and subcostal). The study showed that VFI estimates the same peak velocity as spectral Doppler. Furthermore, VFI has better precision and can estimate the same peak velocity with a scan position, where spectral Doppler cannot. Finally, inter- and intra-observer agreement is higher for VFI.

All three studies indicate that the techniques can be used in the clinic and probably will be part of everyday practice in the near future.

REFERENCES

1. Beach KW. 1975-2000: a quarter century of ultrasound technology. Ultrasound Med Biol 1992;18:377-88.
2. Tegeler CH, Kremkau FW, Hitchings LP. Color velocity imaging: introduction to a new ultrasound technology. J Neuroimaging 1991;1:85-90.
3. Newman PG, Rozycki GS. The history of ultrasound. Surgical Clinics 1998;78:179-95.
4. Jensen JA. Medical ultrasound imaging. Progress in biophysics and molecular biology 2007;93:153-65.
5. Sherwin CW, Ruina JP, Rawcliffe RD. Some early developments in synthetic aperture radar systems. Military Electronics, IRE Transactions on 1962;MIL-6:111-5.
6. Burckhardt CB, Grandchamp PA, Hoffmann H. An experimental 2 MHz synthetic aperture sonar system intended for medical use. Sonics and Ultrasonics, IEEE Transactions on. 1974;21:1-6.
7. Karaman M, Pai-Chi L, O'Donnell M. Synthetic aperture imaging for small scale systems. Ultrasonics, Ferroelectrics, and Frequency Control, IEEE Transactions on 1995;42:429-42.
8. Lockwood GR, Foster FS, editors. Design of sparse array imaging systems. Ultrasonics Symposium, 1995 Proceedings, 1995;7-10.
9. Nikolov SI, Technical University of D, Ørsted DTU. Synthetic aperture tissue and flow ultrasound imaging. Lyngby 2001, thesis.
10. Jensen JA, Nikolov SI, Gammelmark KL, Pedersen MH. Synthetic aperture ultrasound imaging. Ultrasonics 2006;44:e5-15.
11. Kortbek J, Jensen JA, Gammelmark KL, editors. Synthetic aperture sequential beamforming. Ultrasonics Symposium [IUS], 2008 IEEE International; 2-5 Nov. 2008.
12. Hemmsen MC, Kjeldsen T, Larsen L, Kjær C, Tomov BG, Mosegaard J, et al. Implementation of synthetic aperture imaging on a hand-held device. Ultrasonics Symposium [IUS], 2014 IEEE International; 3-6 Sept. 2014.
13. Hansen PM, Hemmsen M, Brandt A, Rasmussen J, Lange T, Krohn PS, et al. Clinical evaluation of synthetic aperture sequential beamforming ultrasound in patients with liver tumors. Ultrasound Med Biol 2014;40:2805-10.
14. Hemmsen MC, Hansen JM, Jensen JA, editors. Synthetic aperture sequential beamformation applied to medical imaging. Synthetic Aperture Radar, 2012 EUSAR 9th European Conference on; 23-26 April 2012.
15. Du Y, Rasmussen J, Jensen H, Jensen JA, editors. Second harmonic imaging using synthetic aperture sequential beamforming. Ultrasonics Symposium [IUS], 2011 IEEE International; 18-21 Oct. 2011.
16. Rasmussen J, Hemmsen MC, Madsen SS, Hansen PM, Nielsen MB, Jensen JA. Implementation of Tissue Harmonic Synthetic Aperture Imaging on a Commercial Ultrasound System. Ultrasonics Symposium [IUS], 2012 IEEE International; 7-10 Oct. 2012.
17. Hemmsen MC, Rasmussen J, Jensen JA. Tissue Harmonic Synthetic Aperture Ultrasound Imaging. J Acoust Soc Am 2014;136:2050-6.
18. Ward B, Baker AC, Humphrey VF. Nonlinear propagation applied to the improvement of resolution in diagnostic medical ultrasound. J Acoust Soc Am 1997;101:143-54.
19. Tranquart F, Grenier N, Eder V, Pourcelot L. Clinical use of ultrasound tissue harmonic imaging. Ultrasound Med Biol 1999;25:889-94.
20. Iwao T, Toyonaga A, Oho K, Tayama C, Masumoto H, Sakai T, et al. Value of Doppler ultrasound parameters of portal vein and hepatic artery in the diagnosis of cirrhosis and portal hypertension. The Am J Gastroenterol 1997;92:1012-7.
21. Iranpour P, Lall C, Houshyar R, Helmy M, Yang A, Choi JI, et al. Altered Doppler flow patterns in cirrhosis patients: an overview. Ultrasonography 2016;35:3-12.
22. Malik J, Kudlicka J, Novakova L, Adamec J, Malikova H, Kavan J. Surveillance of arteriovenous accesses with the use of duplex Doppler ultrasonography. J Vasc Access 2014;15:S28-32.
23. Bozoghlanian M, Lall C, Houshyar R, Helmy M, Cody ME, Bhargava P, et al. Duplex Doppler Imaging of Dialysis Fistulae and Grafts. Curr Probl Diagn Radiol 2016;45:420-8.
24. Grant EG, Benson CB, Moneta GL, Alexandrov AV, Baker JD, Bluth EI, et al. Carotid artery stenosis: gray-scale and Doppler US diagnosis--Society of Radiologists in Ultrasound Consensus Conference. Radiology 2003;229:340-6.
25. Voiculescu A, Hofer M, Hetzel GR, Malms J, Modder U, Grabensee B, et al. Noninvasive investigation for renal artery stenosis: contrast-enhanced magnetic resonance angiography and color Doppler sonography as compared to digital subtraction angiography. Clin Exp Hypertens 2001;23:521-31.
26. Rountas C, Vlychou M, Vassiou K, Liakopoulos V, Kapsalaki E, Koukoulis G, et al. Imaging modalities for renal artery stenosis in suspected renovascular hypertension: prospective intraindividual comparison of color Doppler US, CT angiography, GD-enhanced MR angiography, and digital substraction angiography. Ren Fail 2007;29:295-302.
27. Hansen KL, Udesen J, Thomsen C, Jensen JA, Nielsen MB. In vivo validation of a blood vector velocity estimator with MR angiography. IEEE Trans Ultrason Ferroelectr Freq Control 2009;56:91-100.
28. Ricci S, Diciotti S, Francalanci L, Tortoli P. Accuracy and reproducibility of a novel dual-beam vector Doppler method. Ultrasound Med Biol 2009;35:829-38.

29. Landwehr P, Schulte O, Voshage G. Ultrasound examination of carotid and vertebral arteries. Eur Rad 2001;11:1521-34.
30. Stewart SF. Effects of transducer, velocity, Doppler angle, and instrument settings on the accuracy of color Doppler ultrasound. Ultrasound Med Biol 2001;27:551-64.
31. Logason K, Barlin T, Jonsson ML, Bostrom A, Hardemark HG, Karacagil S. The importance of Doppler angle of insonation on differentiation between 50-69% and 70-99% carotid artery stenosis. Eur J Vasc Endovasc Surg 2001;21:311-3.
32. Hoskins PR. A review of the measurement of blood velocity and related quantities using Doppler ultrasound. Proc Inst Mech Eng H 1999;213:391-400.
33. Sacerdoti D, Gaiani S, Buonamico P, Merkel C, Zoli M, Bolondi L, et al. Interobserver and interequipment variability of hepatic, splenic, and renal arterial Doppler resistance indices in normal subjects and patients with cirrhosis. J Hepatol 1997;27:986-92.
34. Sabba C, Merkel C, Zoli M, Ferraioli G, Gaiani S, Sacerdoti D, et al. Interobserver and interequipment variability of echo-Doppler examination of the portal vein: effect of a cooperative training program. Hepatology 1995;21:428-33.
35. Hoskins PR. Peak velocity estimation in arterial stenosis models using colour vector Doppler. Ultrasound Med Biol 1997;23:889-97.
36. Dunmire B, Beach KW, Labs K, Plett M, Strandness DE, Jr. Cross-beam vector Doppler ultrasound for angle-independent velocity measurements. Ultrasound Med Biol 2000;26:1213-35.
37. Bohs LN, Geiman BJ, Anderson ME, Gebhart SC, Trahey GE. Speckle tracking for multi-dimensional flow estimation. Ultrasonics 2000;38:369-75.
38. Jensen JA, Munk P. A new method for estimation of velocity vectors. IEEE Trans Ultrason Ferroelectr Freq Control 1998;45:837-51.
39. Udesen J, Jensen JA. Investigation of transverse oscillation method. IEEE Trans Ultrason Ferroelectr Freq Control 2006;53:959-71.
40. Hoskins P, Kenwright D. Recent developments in vascular ultrasound technology. Ultrasound 2015;23:158-65.
41. Hansen KL, Udesen J, Oddershede N, Henze L, Thomsen C, Jensen JA, et al. In vivo comparison of three ultrasound vector velocity techniques to MR phase contrast angiography. Ultrasonics 2009;49:659-67.
42. Pedersen MM, Pihl MJ, Haugaard P, Hansen JM, Hansen KL, Nielsen MB, et al. Comparison of real-time in vivo spectral and vector velocity estimation. Ultrasound Med Biol 2012;38:145-51.
43. Pedersen MM, Pihl MJ, Haugaard P, Hansen KL, Lange T, Lonn L, et al. Novel flow quantification of the carotid bulb and the common carotid artery with vector flow ultrasound. Ultrasound Med Biol 2014;40:2700-6.
44. Hansen PM, Olesen JB, Pihl MJ, Lange T, Heerwagen S, Pedersen MM, et al. Volume flow in arteriovenous fistulas using vector velocity ultrasound. Ultrasound Med Biol 2014;40:2707-14.
45. Hansen KL, Moller-Sorensen H, Kjaergaard J, Jensen MB, Lund JT, Pedersen MM, et al. Analysis of systolic backflow and secondary helical blood flow in the ascending aorta using vector flow imaging. Ultrasound Med Biol 2016;42:899-908.
46. Hansen KL, Moller-Sorensen H, Pedersen MM, Hansen PM, Kjaergaard J, Lund JT, et al. First report on intraoperative vector flow imaging of the heart among patients with healthy and diseased aortic valves. Ultrasonics 2015;56:243-50.
47. Jensen J, Olesen JB, Hansen PM, Nielsen MB, Jensen JA, Jensen J, et al. Accuracy and sources of error for an angle independent volume flow estimator. Proceedings of IEEE International Ultrasonics Symposium: IEEE; 2014. p. 1714-7.
48. Jensen J, Olesen JB, Stuart MB, Hansen PM, Nielsen MB, Jensen JA. Vector velocity volume flow estimation: Sources of error and corrections applied for arteriovenous fistulas. Ultrasonics 2016;70:136-46.
49. Badr B, Bories P, Marais R, Frat B, Seigneuric B, Longlune N, et al. Transonic, thermodilution, or ionic dialysance to manage vascular access: which method is best? Hemodial Int 2014;18:127-35.
50. Tessitore N, Bedogna V, Gammaro L, Lipari G, Poli A, Baggio E, et al. Diagnostic accuracy of ultrasound dilution access blood flow measurement in detecting stenosis and predicting thrombosis in native forearm arteriovenous fistulae for hemodialysis. Am J Kidney Dis 2003;42:331-41.
51. Krivitski NM. Theory and validation of access flow measurement by dilution technique during hemodialysis. Kidney Int 1995;48:244-50.
52. Depner TA, Krivitski NM. Clinical measurement of blood flow in hemodialysis access fistulae and grafts by ultrasound dilution. ASAIO J1995;41:M745-9.
53. Bland JM, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. Lancet 1986;1:307-10.
54. Critchley LA, Critchley JA. A meta-analysis of studies using bias and precision statistics to compare cardiac output measurement techniques. J Clin Monit Comput 1999;15:85-91.
55. Hansen KL, Moller-Sorensen H, Kjaergaard J, Jensen MB, Lund JT, Pedersen MM, et al. Vector flow imaging compared with conventional doppler ultrasound and thermodilution for estimation of blood flow in the ascending aorta. Ultrason Imaging 2017;39:3-18.
56. Moller-Sorensen H, Hansen KL, Ostergaard M, Andersen LW, Moller K. Lack of agreement and trending ability of the endotracheal cardiac output monitor compared with thermodilution. Acta Anaesthesiol Scand 2012;56:433-40.
57. Yen CL, Jeng CM, Yang SS. The benefits of comparing conventional sonography, real-time spatial compound sonography, tissue harmonic sonography, and tissue harmonic compound sonography of hepatic lesions. Clin Imaging 2008;32:11-5.
58. Sodhi KS, Sidhu R, Gulati M, Saxena A, Suri S, Chawla Y. Role of tissue harmonic imaging in focal hepatic lesions: comparison with conventional sonography. J Gastroenterol Hepatol 2005;20:1488-93.
59. Kim WH, Chang JM, Kim C, Park J, Yoo Y, Moon WK, et al. Synthetic aperture imaging in breast ultrasound: a preliminary clinical study. Acad Radiol 2012;19:923-9.
60. Choudhry S, Gorman B, Charboneau JW, Tradup DJ, Beck RJ, Kofler JM, et al. Comparison of tissue harmonic

imaging with conventional US in abdominal disease. Radiographics 2000;20:1127-35.
61. Kim C, Yoon C, Park JH, Lee Y, Kim WH, Chang JM, et al. Evaluation of ultrasound synthetic aperture imaging using bidirectional pixel-based focusing: preliminary phantom and in vivo breast study. IEEE Trans Biomed Eng 2013;60:2716-24.
62. Tanaka S, Oshikawa O, Sasaki T, Ioka T, Tsukuma H. Evaluation of tissue harmonic imaging for the diagnosis of focal liver lesions. Ultrasound Med Biol 2000;26:183-7.
63. Yen CL, Chang HY, Huang SY, Huang YC, Jeng CM. Combination of tissue harmonic sonography, real-time spatial compound sonography and adaptive image processing technique for the detection of carotid plaques and intima-medial thickness. Eur J Radiol. 2009;71:11-6.
64. Mesurolle B, Helou T, El-Khoury M, Edwardes M, Sutton EJ, Kao E. Tissue harmonic imaging, frequency compound imaging, and conventional imaging: use and benefit in breast sonography. J Ultrasound Med 2007;26:1041-51.
65. Schmidt T, Hohl C, Haage P, Blaum M, Honnef D, Weibeta C, et al. Diagnostic accuracy of phase-inversion tissue harmonic imaging versus fundamental B-mode sonography in the evaluation of focal lesions of the kidney. AJR Am J Roentgenol2003;180:1639-47.
66. Hemmsen MC, Hansen PM, Lange T, Hansen JM, Hansen KL, Nielsen MB, et al. In vivo evaluation of synthetic aperture sequential beamforming. Ultrasound Med Biol 2012;38:708-16.
67. Hemmsen MC, Hansen PM, Lange T, Hansen JM, Nikolov SI, Nielsen MB, et al., editors. Preliminary in-vivo evaluation of synthetic aperture sequential beamformation using a multielement convex array. Ultrasonics Symposium [IUS], 2011 IEEE International; 18-21 Oct. 2011.
68. Rasmussen JH, Hemmsen MC, Madsen SS, Hansen PM, Nielsen MB, Jensen JA, editors. Preliminary study of synthetic aperture tissue harmonic imaging on in-vivo Proc. SPIE 8675, Medical Imaging 2013: Ultrasonic Imaging, Tomography, and Therapy, 867512 [March 29, 2013].
69. Beissert M, Jenett M, Keberle M. Comparison of contrast harmonic imaging in B-mode with stimulated acoustic emission, conventional B-mode US and spiral CT in the detection of focal liver lesions. Rofo 2000;172:361-6.
70. Glover C, Douse P, Kane P, Karani J, Meire H, Mohammadtaghi S, et al. Accuracy of investigations for asymptomatic colorectal liver metastases. Dis Colon Rectum 2002;45:476-84.
71. Cantisani V, Grazhdani H, Fioravanti C, Rosignuolo M, Calliada F, Messineo D, et al. Liver metastases: Contrast-enhanced ultrasound compared with computed tomography and magnetic resonance. World J Gastroenterol 2014;20:9998-10007.
72. Kortbek J, Jensen JA, Gammelmark KL. Sequential beamforming for synthetic aperture imaging. Ultrasonics 2013;53:1-16.
73. Munoz DR, Zamorano JL. Wireless echocardiography: a step towards the future. Eur Heart J 2014;35:1700.
74. Lapostolle F, Petrovic T, Lenoir G, Catineau J, Galinski M, Metzger J, et al. Usefulness of hand-held ultrasound devices in out-of-hospital diagnosis performed by emergency physicians. Am J Emerg Med2006;24:237-42.
75. Prinz C, Voigt JU. Diagnostic accuracy of a hand-held ultrasound scanner in routine patients referred for echocardiography. J Am Soc Echocardiogr 2011;24:111-6.
76. Choi BG, Mukherjee M, Dala P, Young HA, Tracy CM, Katz RJ, et al. Interpretation of remotely downloaded pocket-size cardiac ultrasound images on a web-enabled smartphone: validation against workstation evaluation. J Am Soc Echocardiogr 2011;24:1325-30.
77. Breithardt OA. Hand-held ultrasound-the real stethoscope. Eur Heart J Cardiovasc Imaging 2015;16:471-2.
78. Liteplo AS, Noble VE, Attwood B. Real-time video transmission of ultrasound images to an iPhone. Crit Ultrasound J 2010;1:105-10.
79. Garrett PD, Boyd SY, Bauch TD, Rubal BJ, Bulgrin JR, Kinkler ES, Jr. Feasibility of real-time echocardiographic evaluation during patient transport. J Am Soc Echocardiogr 2003;16:197-201.
80. Strode CA, Rubal BJ, Gerhardt RT, Bulgrin JR, Boyd SY. Wireless and satellite transmission of prehospital focused abdominal sonography for trauma. Prehosp Emerg Care 2003;7:375-9.
81. Huijbregts HJ, Bots ML, Wittens CH, Schrama YC, Moll FL, Blankestijn PJ. Hemodialysis arteriovenous fistula patency revisited: results of a prospective, multicenter initiative. Clin J Am Soc Nephrol 2008;3:714-9.
82. Clinical Practice Guidelines for Vascular Access. Am J Kidney Dis 2006;48:S176-S247.
83. Wiese P, Nonnast-Daniel B. Colour Doppler ultrasound in dialysis access. Nephrol Dial Transplant 2004;19:1956-63.
84. Whittier WL. Surveillance of hemodialysis vascular access. Semin Intervent Radiol 2009;26:130-8.
85. Paulson WD, Moist L, Lok CE. Vascular access surveillance: an ongoing controversy. Kidney Int 2012;81:132-42.
86. Casey ET, Murad MH, Rizvi AZ, Sidawy AN, McGrath MM, Elamin MB, et al. Surveillance of arteriovenous hemodialysis access: a systematic review and meta-analysis. J Vasc Surg 2008;48:48s-54s.
87. Muchayi T, Salman L, Tamariz LJ, Asif A, Rizvi A, Lenz O, et al. A meta-analysis of randomized clinical trials assessing hemodialysis access thrombosis based on access flow monitoring: where do we stand? Semin Dial 2015;28:E23-9.
88. Paulson WD, Moist L, Lok CE. Vascular access surveillance: case study of a false paradigm. Semin Dial 2013;26:281-6.
89. Allon M, Robbin ML. Hemodialysis vascular access monitoring: Current concepts. Hemodial Int 2009;13:153-62.
90. Huisman RM, van Dijk M, de Bruin C, Loonstra J, Sluiter WJ, Zeebregts CJ, et al. Within-session and between-session variability of haemodialysis shunt flow measurements. Nephrol Dial Transplant 2005;20:2842-7.
91. Schwarz C, Mitterbauer C, Boczula M, Maca T, Funovics M, Heinze G, et al. Flow monitoring: performance characteristics of ultrasound dilution versus color Doppler ultrasound compared with fistulography. Am J Kidney Dis 2003;42:539-45.
92. van Hooland S, Malik J. Hemodialysis vascular access ultrasonography: tips, tricks, pitfalls and a quiz. J Vasc Access 2010;11:255-62.

93. Heerwagen ST, Hansen MA, Schroeder TV, Ladefoged SD, Lonn L. Blood flow measurements during hemodialysis vascular access interventions--catheter-based thermodilution or Doppler ultrasound? J Vasc Access 2012;13:145-51.
94. Lui EYL, Steinman AH, Cobbold RSC, Johnston KW. Human factors as a source of error in peak Doppler velocity measurement. J Vasc Surg 2005;42:972-9.
95. Zanen AL, Toonder IM, Korten E, Wittens CH, Diderich PN. Flow measurements in dialysis shunts: lack of agreement between conventional Doppler, CVI-Q, and ultrasound dilution. Nephrol Dial Transplant 2001;16:395-9.
96. Teodorescu V, Gustavson S, Schanzer H. Duplex ultrasound evaluation of hemodialysis access: a detailed protocol. Int J Nephrol 2012;2012:508956.
97. Bosman PJ, Boereboom FT, Bakker CJ, Mali WP, Eikelboom BC, Blankestijn PJ, et al. Access flow measurements in hemodialysis patients: in vivo validation of an ultrasound dilution technique. J Am Soc Nephrol 1996;7:966-9.
98. Hansen KL, Moller-Sorensen H, Kjaergaard J, Jensen MB, Lund JT, Pedersen MM, et al. Intra-operative vector flow imaging using ultrasound of the ascending aorta among 40 patients with normal, stenotic and replaced aortic valves. Ultrasound Med Biol 2016;42:2414-22.
99. Lomonte C, Meola M, Petrucci I, Casucci F, Basile C. The key role of color doppler ultrasound in the work-up of hemodialysis vascular access. Semin Dial 2015;28:211-5.
100. Sidawy AN, Spergel LM, Besarab A, Allon M, Jennings WC, Padberg FT, Jr., et al. The Society for Vascular Surgery: clinical practice guidelines for the surgical placement and maintenance of arteriovenous hemodialysis access. J Vasc Surg 2008;48:2s-25s.
101. Davis M, Chong WK. Doppler ultrasound of the liver, portal hypertension, and transjugular intrahepatic portosystemic shunts. Ultrasound Clinics 2014;9:587-604.
102. Kok T, van der Jagt EJ, Haagsma EB, Bijleveld CM, Jansen PL, Boeve WJ. The value of Doppler ultrasound in cirrhosis and portal hypertension. Scand J Gastroenterol Suppl 1999;230:82-8.
103. Dib N, Oberti F, Cales P. Current management of the complications of portal hypertension: variceal bleeding and ascites. CMAJ 2006;174:1433-43.
104. Shastri M, Kulkarni S, Patell R, Jasdanwala S. Portal vein Doppler: a tool for non-invasive prediction of esophageal varices in cirrhosis. J Clin Diagn Res 2014;8:MC12-MC5.
105. Kayacetin E, Efe D, Dogan C. Portal and splenic hemodynamics in cirrhotic patients: relationship between esophageal variceal bleeding and the severity of hepatic failure. J gastroenterol 2004;39:661-7.
106. Berzigotti A, Piscaglia F. Ultrasound in portal hypertension--part 2--and EFSUMB recommendations for the performance and reporting of ultrasound examinations in portal hypertension. Ultraschall Med 2012;33:8-32.
107. Zekanovic D, Ljubicic N, Boban M, Nikolic M, Delic-Brkljacic D, Gacina P, et al. Doppler ultrasound of hepatic and system hemodynamics in patients with alcoholic liver cirrhosis. Dig Dis Sci 2010;55:458-66.
108. Hoskins PR. A comparison of single- and dual-beam methods for maximum velocity estimation. Ultrasound Med Biol 1999;25:583-92.
109. Park MY, Jung SE, Byun JY, Kim JH, Joo GE. Effect of beam-flow angle on velocity measurements in modern Doppler ultrasound systems. AJR Am J Roentgenol 2012;198:1139-43.
110. Tortoli P, Lenge M, Righi D, Ciuti G, Liebgott H, Ricci S. Comparison of carotid artery blood velocity measurements by vector and standard Doppler approaches. Ultrasound Med Biol 2015;41:1354-62.
111. Steinman AH, Tavakkoli J, Myers JG, Jr., Cobbold RS, Johnston KW. Sources of error in maximum velocity estimation using linear phased-array Doppler systems with steady flow. Ultrasound Med Biol 2001;27:655-64.
112. Thrush A, Evans D. Intrinsic spectral broadening: a potential cause of misdiagnosis of carotid artery disease. J Vasc Invest 1995;1:187-92.
113. Yang X, Sun C, Anderson T, Moran CM, Hadoke PW, Gray GA, et al. Assessment of spectral Doppler in preclinical ultrasound using a small-size rotating phantom. Ultrasound Med Biol 2013;39:1491-9.
114. Ekroll IK, Dahl T, Torp H, Lovstakken L. Combined vector velocity and spectral Doppler imaging for improved imaging of complex blood flow in the carotid arteries. Ultrasound Med Biol 2014;40:1629-40.
115. Jensen JA, Brandt AH, Nielsen MB. Convex array vector velocity imaging using transverse oscillation and its optimization. IEEE Trans Ultrason Ferroelectr Freq Control 2015;62:2043-53.
116. Hansen KL, Pedersen MM, Moller-Sorensen H, Kjaergaard J, Nilsson JC, Lund JT, et al. Intraoperative cardiac ultrasound examination using vector flow imaging. Ultrason Imaging 2013;35:318-32.
117. Kruskal JB, Newman PA, Sammons LG, Kane RA. Optimizing Doppler and color flow US: application to hepatic sonography. Radiographics 2004;24:657-75.