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Ultrasound-Based Noncontrast Microvascular Imaging for Evaluation of Breast Lesions: Imaging Techniques and Review of Diagnostic Criteria

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Abstract

Vascularity plays a pivotal role in the progression of breast lesions and may be associated with their aggressiveness and likelihood of being malignant. Contrast-enhanced imaging techniques are necessary to evaluate vascularity due to the limited sensitivity of conventional color Doppler techniques, in which motion artifacts are eliminated using wall filters. However, in this process, low-flow signals from small vessels also get removed unintentionally. Advancements in technology have revolutionized the way ultrasound images are generated, resulting in tremendous improvements in Doppler imaging techniques. The new, ultrasound-based noncontrast microvascular imaging techniques overcome the limitations of conventional Doppler, and are highly sensitive for detecting microvessels and low flow. The resultant high Doppler sensitivity leads to detection of vascularity in more breast lesions. It is important for radiologists to understand the imaging principles and the clinical implications of the new techniques, to optimally utilize them and aid correct diagnosis. Angio-PLUS is one such recent advancement, which uses unfocused or plane waves and three-dimensional wall filtering to analyze tissue motion in time, space, and amplitude domains that effectively distinguish between blood flow and tissue. The information is beneficial for assessing the lesion vascularity without using contrast. This article aims to explain the Doppler imaging techniques, their clinical applications, scanning methods, and review the common Doppler-based diagnostic criteria used in the evaluation of breast lesions.

Keywords

- ultrasound-based microvascular imaging
- Angio-PLUS
- breast lesions
- breast cancer
- Doppler imaging

Learning Objectives

After reading the article, the reader will have knowledge about:

1. The differences in the imaging principles of conventional Doppler versus newer ultrasound-based microvascular imaging (MVI) techniques.
2. The optimal scanning technique for performing noncontrast MVI.
3. Doppler-based diagnostic criteria for evaluating breast lesions.
4. Limitations of the MVI techniques.

Introduction

Ultrasound (US) is commonly used for breast imaging. Over the last decade, advancements in computer processing

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power, graphic boards, and parallel computing have allowed ultrafast imaging with high frame rates.[1] Advances in Doppler techniques have sparked interest in assessing lesional vascularity. The technical innovations aim to achieve faster, artifact-free scanning with preserved sensitivity to signals from small low-flow vessels while also providing higher spatial resolution for better visualization of microvessels.[2–4] US-based microvascular imaging (MVI) can be of two types based on contrast media use.[5] Noncontrast MVI techniques utilize intelligent wall filtering systems for preserving the "real" slow flow signals and selectively remove the "clutter" generated by movements and respiration-related artifacts. Several US-based noncontrast MVI techniques are evolving simultaneously, and various vendors are employing comparable methods, albeit with some variations, to attain enhanced speed and spatial resolution. Angio-PLUS (AP); SuperSonic Imagine, Aix-en-Provence, France. superb microvascular imaging(SMI)[4] Canon Medical Systems (Tokyo, Japan), MicroFlow imaging (Philips Healthcare, Eindhoven, The Netherlands), and MV Flow (Samsung Medison, Seoul, South Korea).[5] are among the noncontrast MVI techniques that are currently being utilized. A summary of the Doppler imaging principle would help us understand the limitations of previous techniques and how recent technological advancements have revolutionized imaging today.

Imaging Principle of Conventional Color Doppler

Ultrasonic Doppler signals are generated from blood flow and tissue motion (pulsation, respiratory and patient movements), which constitute the "clutter." Conventional color Doppler imaging (CDI) uses serial-focused US beams to penetrate tissue. The low flows (3–5 cm/s) approximately match tissue motion velocity[6] and the single-dimensional wall filter cannot distinguish between blood flow and motion artifacts, leading to the elimination of low-velocity flow signals.[2–4] Signal-to-noise ratio to display small vessels (<1 mm) is low,[7] and frame rates are limited to a few hundred images per second,[8] which deteriorate further as the region-of-interest (ROI) width increases.[9] Conventional Doppler has three acquisition modes[10]: CDI detects flow, mean velocity, and direction within the color box; Spectral Doppler imaging (SDI) quantifies flow velocity and power Doppler imaging (PDI), a second-generation Doppler technique that measures Doppler signal strength regardless of speed or direction of moving cells.[11] PDI is thrice as sensitive to low flow rates as CDI but is highly susceptible to tissue motion, which degrades image quality.[2] Hence, traditional Doppler US has notable limitations, necessitating a well-calibrated filtering system to distinguish blood flows from surrounding tissues.

Technical Innovations and the Principle of Microvascular Imaging

The new "MVI" techniques are third-generation Doppler techniques,[2] designed to surpass conventional filters, distinguishing tissue artifacts from low flow, and preserving flow signals.[11] AP (Plane Wave Ultra-Sensitive Imaging) technique uses unfocused or plane waves and parallel processing to achieve ultrafast imaging.[12] The initial commercial release of the first ultrafast US scanner occurred in 2009.[1] Multiple plane waves with various steering angles are sent at high frame rates (up to 20–30 kHz) to continuously interrogate each tissue pixel with a high sampling rate (5–10 times faster than color Doppler). This is done instead of reconstructing images from a single-plane wave transmission.[12] The plane-wave compounding technique achieves ultra-high image quality[1] and enables complete blood flow mapping of the field of view. It allows access to fine velocity measurements at the single-pixel level (down to 50 µm).[8] ►**Table 1** shows a comparison of Doppler techniques.

The AP system has two modes: real-time (AP-RT) and high-definition single acquisition (AP-HD). AP-RT achieves four to five times higher values than conventional CDI, but heating of the probe limits the firing rate. AP-HD increases data sampling by 10 to 15x compared to CDI by launching a clip at the time of flight and reviewing it offline. Ultrafast imaging with Doppler data enables smarter filters to distinguish between flow and tissue. Three-dimensional (3D) wall

Table 1 Comparison of Doppler techniques

Technique	Resolution	Key components	Modes	Typical parameters
Conventional imaging	Cannot detect flow signals from vessels <1 mm, and low flows of (3–5 cm/s)[7]	Serial-focused ultrasound beam Single-dimensional wall filtering	Color Doppler Spectral Doppler Power Doppler	Color velocity scale <5 cm/s Frames rates <100 frames/s Wall filter 50–100 Hz[6]
Superb microvascular imaging (SMI)	Display vessel diameters >0.1 mm	Three-dimensional (3D) wall filtering	Monochrome(mSMI), color (cSMI)	Velocity scale < 2.5 cm/s Frame rate 27–60 frames/ sec Color frequency 5 to 7 MHz Dynamic range-21 dB[6]
Angio-PLUS		Unfocussed or plane waves 3D wall filtering	AngioPLUS-RT) firing rate ~4-5x higher than color Doppler imaging (CDI) AngioPLUS-HT firing rate ~ time of flight of ultrasound, data sampling higher 10–15x higher data sampling	Color velocity scale <2 cm/s, frame rates up to 20–30 kHz Wall filter-medium Frame rate-medium Sampling rate 5–10x faster than Conventional Doppler

filtering is used to analyze tissue motion in time, space, and amplitude domains, providing effective differentiation.[1]

SMI is another MVI technique derived from power Doppler US. It maintains high frame rates (>50 frames per second) and removes clutter while using 3D filtering technology to separate low-flow signals from clutter signals.[4] SMI operates in two modes: color subtraction mode imaging (cSMI), which displays grayscale US and color-coded Doppler signals simultaneously, and monochrome subtraction mode imaging (mSMI), which enhances sensitivity by displaying only the vasculature and subtracting the background.[13] It can visualize microvessels (diameters >0.1 mm)[3,10] without contrast agents but cannot assess flow direction or velocity. Single or dual acquisition is possible.

Scanning Technique

Choose linear-array probes with broad bandwidth (2–10 MHz, 5–15 MHz, or 5–18 MHz, central frequency 10 MHz) based on the breast size and thickness. The depth is adjusted to include breast tissue and pectoralis major muscle, while excluding the pleura and lung. The field of view is chosen to cover the area of interest, with the focal zone adjusted to include the anterior to middle third of area of interest. If a lesion is found, the focal zone is placed at the center of the lesion. Incorrect placement of the focal zone can cause artifacts and blurring. Apply proper grayscale gain settings and time-gain compensation to optimize Doppler signal detection.

For color Doppler and AP mode, place the probe lightly on the skin, to prevent capillary compression. The color box should encompass the lesion and surrounding normal tissue, and the transducer should be held steady until the image stabilizes. Choose the plane with the most vessels as the representative image for assessment. Parameter settings and adjustments: Use medium wall filter at the lowest pulse repetition frequency (PRF) with no aliasing and highest color gain without noise. Dynamic range 21 dB, frame rate 27 to 60 fps, scale settings at 4 cm/sec. Malignant lesions often have twisted vessels visible at 4 cm/sec (velocity scale settings may be lowered below 4 cm/sec to detect smaller vessels). In some machines, direct scale control function is not available, and the scale can be controlled by changing the ROI width. Decreasing ROI width to a scale less than 2.5 cm/s enhances microvessel visibility.[3] However, a point to consider is that decreasing the ROI width or scale too much would lead to an increase in flash artifacts. Instruct patient to hold breath for 2 to 3 seconds to minimize motion.

Clinical Applications

Microvascular architecture varies in benign and malignant breast lesions.[14] Tumor growth depends on the blood vessel network development (neoangiogenesis).[15] High microvessel density (MVD) is linked with poor prognosis in high-grade, aggressive breast cancers.[16] Immunohistochemical (IHC) evaluation is the gold standard for assessing neoangiogenesis requiring biopsy to detect irregular and disordered vascular networks and arteriovenous shunts.[16] Doppler evaluation provides an opportunity for noninvasive assessment of vascularity.

Indications

1. While evaluating masses by US, Doppler evaluation is commonly done for vascularity assessment as an associated feature.
2. Recently, an evolving indication is to use Doppler evaluation to monitor response to neoadjuvant therapy in breast cancer.

Review of Diagnostic Criteria

One of the most commonly used criteria for assessing vascularity is the Adler's classification (AC)[17] that was developed in 1990 to classify vascularity into three levels subjectively: minimal (1–2 pixels with flow), moderate (a primary vessel and/or multiple minor vessels), and marked (4 or more vessels). However, Adler et al found poor differentiation between healthy breast tissue and cancer, indicating the need for more sensitive Doppler methods to detect small vessel flow associated with cancer. Several studies confirmed that malignant lesions exhibited increased Doppler signals due to increased vascularity,[18–20] but further Doppler feature characterization was needed to differentiate them from benign lesions.

Raza and Baum correlated vascular distribution patterns with histopathological findings and found that peripheral and central vascularity, branching vessels, and penetrating vessels (PV) were significant predictors of malignancy on CDI.[19] Lee et al found PDI to be more sensitive than CDI in detecting vascular signals,[21] but CDI continued to be preferentially used, possibly due to PDIs susceptibility to tissue motion artifacts.

Svensson et al noted that intralesional vascularity alone did not reliably predict malignancy, as both cancerous and benign (95% and 46% respectively) lesions could show vascularity due to increased Doppler sensitivity from improved US technology.[22] To improve differentiation, they developed a complex classification of vascular patterns and morphology: (1) External/peripheral only (subdivided into marginal or radial orientation), (2) internal only (marginal or radial), (3) mixed peripheral and internal (subclassified as marginal or radial), and (4) internal persistent spotty signals only. Malignant lesions had more radially aligned external vessels, with more internal connecting vessels, making breast lesions with radial rather than marginal connecting vessels suspicious.[22] Though similar to prior studies, the complexity of this classification accounted for its lower popularity compared to the simpler AC.

The 2013 breast imaging-reporting and data system ultrasound (BI-RADS US) lexicon recommended analyzing blood flow distribution as (a) absent; (b) internal vascularity (orderly or disorderly within mass or penetrating its margin); (c) vessels in the rim (marginal vessels forming part or all of a rim)[23]. Penetrating vessels are characterized as one or more blood

vessels along the edge of the mass and branching towards the center. However, the usefulness of Doppler US for distinguishing benign from malignant lesions remained unclear due to low sensitivity for detecting microvessels and low flows.

The advent of MVI techniques enabled high-resolution visualization of microvessels, renewing interest in vascularity assessment for various clinical situations. SMI and CDI were used to count the number of blood vessels in a mass[6] and determine the difference between the two results (SMI-CDI), which improved diagnostic performance for diagnosing breast cancer, but only assessed the "amount" of vascularity.[6] Yongfeng et al[24] compared SMI with PDI using semiquantitative grading, flow distribution pattern, and PV evaluation and found that cancers had central branching or diffuse distribution. SMI had higher sensitivity, specificity, and positive predictive value than PDI, and vascular pattern analysis was superior to semiquantitative grading and PV method.[24,25] SMI could demonstrate richer blood flow in malignancies by displaying peripheral and central vascularity, where CDI and PDI showed sparse punctate vessels only.[26] SMI could detect perforating vessels in avascular-CDI BI-RADS 3 or 4 masses,[27] but like CDI, it showed strong blood signals in most malignant masses and half of benign masses. Thus, semiquantitative analyses alone remained insufficient for distinguishing between benign and malignant lesions. Xiao et al[28] identified five vascular patterns: nonvascular, linear or curvilinear, tree-like, root hair-like, and crab claw-like. Malignancy was predicted by enlarged, twisted, penetrating, spiculated, or radial vessels, while peripheral annular vessels were characteristic of benign lesions. SMI had similar diagnostic performance to contrast enhanced US, but their descriptors were also complex, inhibiting widespread use.

Recent studies[29] use a three-factor system to assign "vascular imaging scores" to predict malignancy (score range: 0–13). The three factors are as follows:

(i) Vessel number scored 0 to 6.
(ii) Vessel morphology/ complexity graded as dot-like (score 1), linear (score 2), branching (score 3), or penetrating or shunting (score 4).
(iii) Distribution pattern categorized as peripheral (score 1)—all vessels at the margins or within 2 mm; central (score 2)—vessels within the lesion, or both (score 3).

PV is defined as a continuous signal extending from outside to inside lesion. Shunting vessels are capillary network connections from one or more vessels with chaotic irregularity. The SMI showed higher scores than CDI or PDI, and malignancies had higher scores than benign masses ($p < 0.001$), with a score range of 0 to 13.

The three-factor scoring system was adjusted for assessing ductal lesions[30] based on the neoangiogenesis hypothesis. The system scores vessel number (0–4), distribution (0–3), and morphology (0-3), with a maximum score of 10. Vessel number scored 1 for one to two vessels in a dilated duct, score 2 for three to four vessels, score 3 for five to seven vessels, and score 4 for more than eight vessels. Distribution is categorized as periductal (score 1), intraductal (score 2), or both (score 3). Vessel morphology (complexity) is graded as dot-like (score 1), linear-parallel to the duct without traversing its wall (score 2), and penetrating or branching traversing ductal wall (score 3). Positive malignancy criteria include more than five vessels, intraductal or intra- and periductal

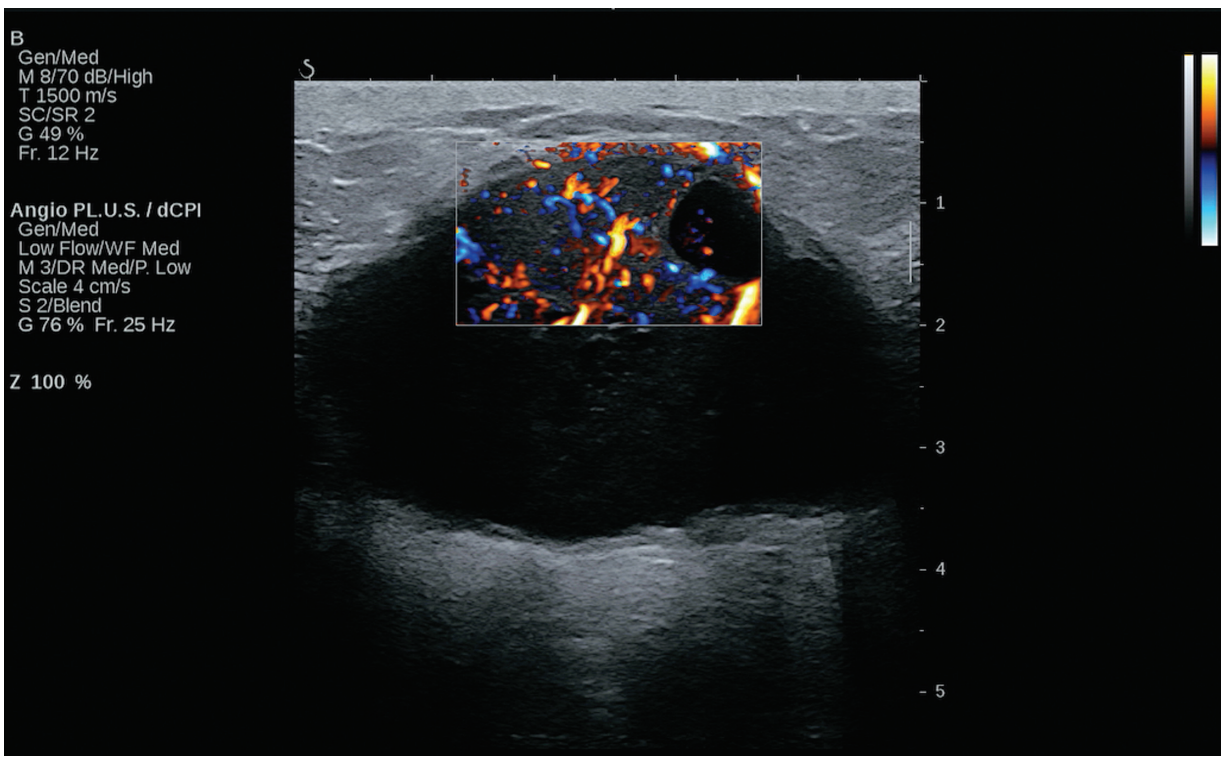

Fig. 1 Angio-PLUS image showing irregular, disordered vasculature in a malignant mass (histopathological evaluation: malignant phylloides tumor).

distribution, and penetrating or branching morphology. An optimal cutoff value for the overall vascular score suggestive of malignancy was 8. SMI was superior to CDI in evaluating BI-RADS 4 lesions, providing better vessel details and improving diagnostic efficacy.[25]

Comparative studies evaluated AP and PDI[31] using AC, distribution, and penetrating vessels, showing higher sensitivity of AP in depicting flow in benign and malignant lesions. Penetrating vessels were more frequent in malignant masses, but internal blood flow location and vessels in the rim were similar between benign and malignant lesions. On AP, high MVD lesions showed more combined distribution (60.7%) than low MVD lesions (22.2%) ($p = 0.020$), indicating its potential in predicting breast cancer prognosis. CDI features showed no significant relationship with mean vascular density on IHC.[32] ►**Figs. 1** to **6** show vascularity assessment using AP

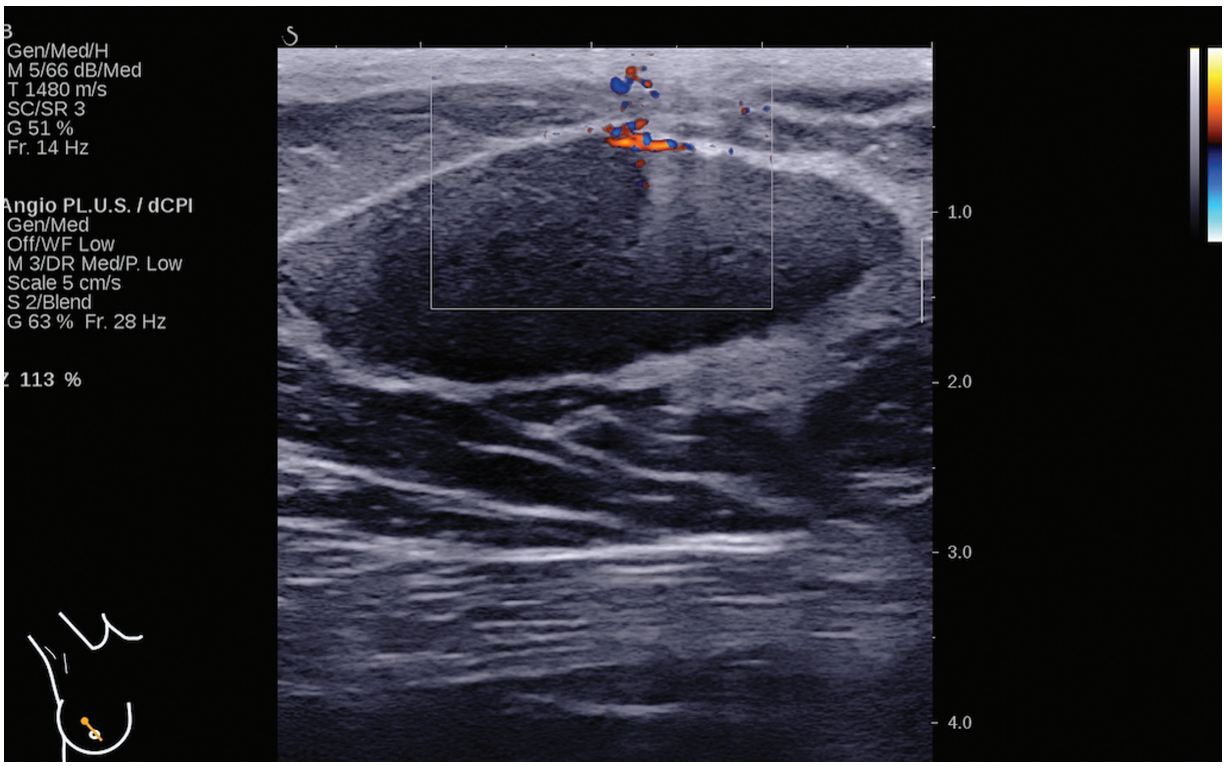

Fig. 2 Angio-PLUS image showing marginal vessels in a benign mass (histopathological evaluation: fibroadenoma).

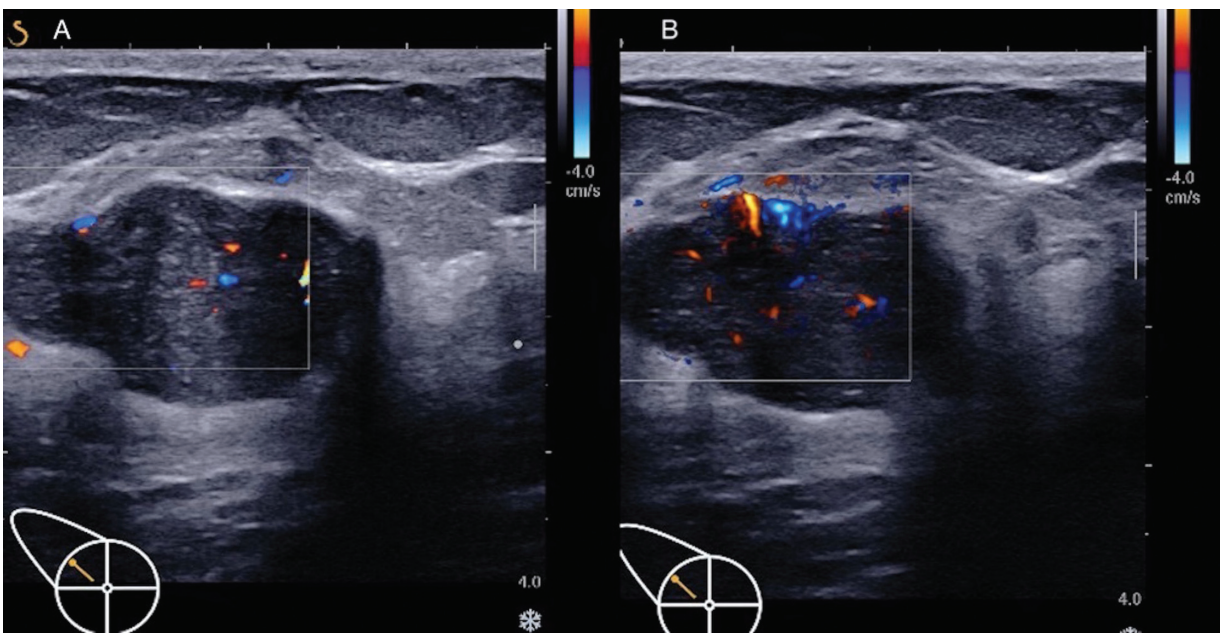

Fig. 3 Color Doppler (**A**) and Angio-PLUS (**B**) images of the same mass (histopathological evaluation: infiltrating ductal carcinoma) demonstrating richer vascularity on Angio-PLUS.

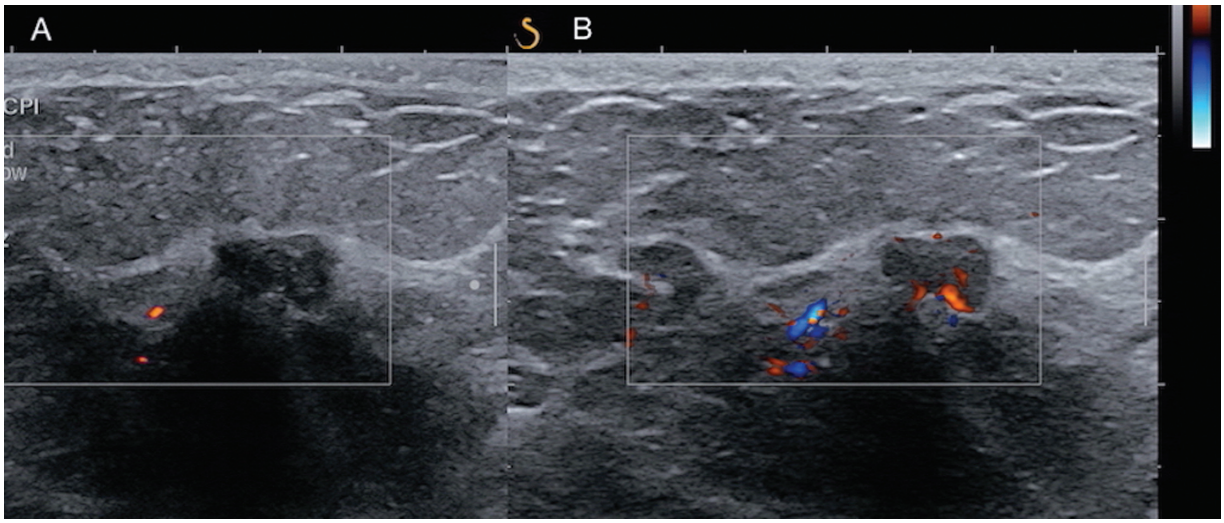

Fig. 4 Color Doppler (**A**) and a Angio-PLUS (**B**) images of a small mass (histopathological evaluation: infiltrating ductal carcinoma) demonstrating the value of Angio-PLUS in showing penetrating vessels.

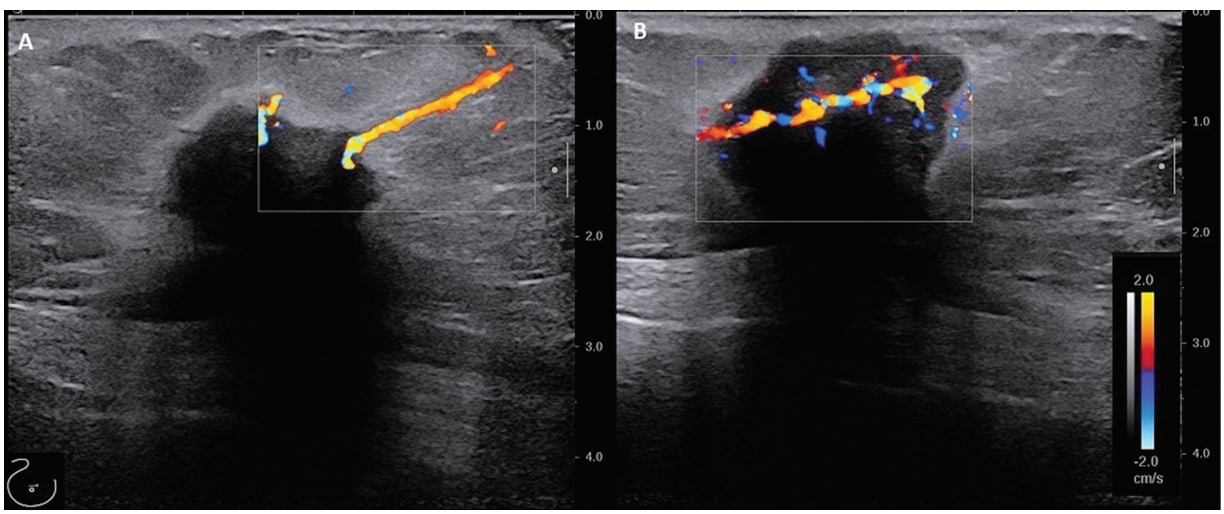

Fig. 5 Color Doppler images: (**A**) At 4 cm/sec velocity scale showing radial vessel and (**B**) at 2 cm/sec velocity scale showing twisted vessels in the same malignant mass (histopathological evaluation: infiltrating ductal carcinoma).

technique (source of images: from our study, approved by institute ethics committee).

Since operator dependency significantly limits the widely used qualitative diagnostic criteria, Park AY et al attempted additional quantitative vascularity analysis.[33] Vascular index (VI), a ratio between the pixels for the Doppler signal and those for the whole lesion, has low operator dependence. SMI-derived VI was higher in malignant masses (15.1 ± 7.3 vs. 5.9 ± 5.6) on SMI along with higher MVD ($p \leq 0.016$).[33] A recent study by Lee et al[34] reported high reproducibility of SMI-derived VI. Median VI of malignant masses was 7.6%, significantly higher than of benign masses (VI 2.6%, $p < 0.001$). The intraobserver agreement for VI was excellent regardless of the pathology, size, or depth of lesion, and interobserver agreement was excellent irrespective of the measurement interval. ►**Table 2** shows a comparison of different studies.

In summary, the four main diagnostic criteria currently used to evaluate vascularity are: AC, the presence of PV, the microvascular distribution pattern (MVDP), and the VI. The first three (qualitative) criteria are often combined to obtain an overall "vascular score." Among these four main diagnostic criteria, a recent meta-analysis[35] found that MVDP may be more effective, which may aid radiologists in choosing appropriate diagnostic criteria.

Limitations

There is heterogeneity in the literature regarding technical factors, equipment sensitivities, and the diagnostic criteria used for vascularity assessment. The widely used qualitative diagnostic criteria have the limitation of being operator dependent; quantitative methods are being explored to overcome this problem. While MVI techniques provide intricate vessel details such as numbers and complexity, they cannot give information on wash-in and wash-out kinetics, which may require contrast-enhanced studies. Additionally, it is

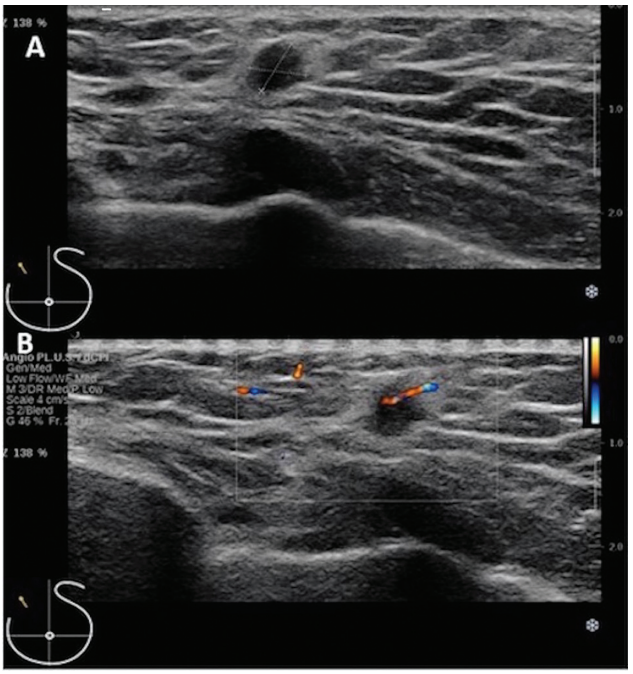

Fig. 6 Grayscale image (**A**) of a small (5.4 × 5.3 mm size mass) and Angio-PLUS image (**B**) of same mass (histopathological evaluation: infiltrating ductal carcinoma) demonstrating value of Angio-PLUS in showing intralesional vascularity.

impossible to differentiate between arteries and veins and flow direction.[36] Although AP has the potential to influence a change in the BI-RADS categorization of lesions, it is too early to say that it can reduce biopsies. The increased efficacy of SMI in extracting microvascular information may lead to an increase in false positive diagnoses.[25] Another limitation of the existing literature is that most studies had relatively large lesions, which displayed typical angiogenesis characteristics.[28] It is yet to be determined if smaller lesions with developing neoangiogenesis can be effectively depicted, and what the threshold (in terms of vessel numbers, diameters, and complexity) would be for accurately detecting newly emerging abnormal vascularity using MVI techniques. A single study noted that signals deeper than 25 to 30 mm might be challenging to detect on mSMI; however, literature is sparse regarding this limitation. Specificity could still be limited due to overlapping Doppler signs between hypervascular benign tumors (such as fibroadenomas or intraductal papillomas), hypovascular malignant tumors, (such as ductal carcinoma in situ), and small invasive carcinomas.[37]

Future Directions

Several studies indicate that adjunct vascularity assessment using MVI has the potential to aid in radiology-pathology concordance decisions, potentially leading to a reduction in unnecessary biopsies for some BI-RADS 4 A lesions.[33] Additional research is required to determine whether MVI can effectively influence a shift in BI-RADS assessment. Future studies should also investigate the potential of Doppler techniques to identify regions of elevated vascularity in nonmass lesions, such as asymmetry, architectural

Table 2 Comparison of various studies using conventional Doppler, power Doppler, superb microvascular imaging, or Angio-PLUS techniques

Authors, year	Sample size	Imaging criteria	Doppler technique	Conclusion	Limitations
Adler et al 1990[17]	55 breast masses, proven malignant	Blood flow amount(AC) Minimal, moderate, marked	CDI	Moderate to marked vascularity (82%) of cancers. CDI not sensitive to vessels < 1mm diameter. Specificity not high as >1–1.9 mm size vessels visible at tumor periphery, outside tumor, and in normal parenchyma. Poor distinction between normal breast tissue and cancer, more sensitive techniques to detect small vessel flow needed	Small sample size, only malignant masses. Flow sensitivity set at "high"—searched for high velocity flow only
Raza and Baum 1997[19]	86 solid masses (25 cancers; 38 fibroadenoma, 23 other benign)	Distribution and morphology of vessels	PDI	Distribution and morphology of blood vessels important to predict malignancy	Ultrasound was performed by 1 of 8 ultrasonographers, and interpreted by 1 of 2 radiologists. It is sometimes difficult to correctly interpret distribution and morphology of vessels on static images-presence/ absence of radiologists at the time of scan may have affected results

Table 2 (*Continued*)

Authors, year	Sample size	Imaging criteria	Doppler technique	Conclusion	Limitations
Lee et al 2002[21]	129 (54 malignant, 75 benign) but only 43 cases compared	Location (central, peripheral, both); shape (linear, irregular, branching); Penetration of doppler signals	CDI, PDI	Both peripheral and central vascularity (odds ratio, 6.0), branching vessels (odds ratio, 13.7, penetrating vessels (odds ratio, 5.4) predictors of malignancy. PDI more sensitive in detecting vascularity in 49%	Both CDI and PDI done in only 43 cases. Since CDI shows larger vessels and PDI is sensitive to smaller vessels, vascular patterns predictive of cancer differed in the 2 modalities; larger studies were needed to assess this
Svensson et al 2010[22]	117 cancers, 366 FA or FA-like benign lesions	Vascular morphology within and around lesions	CDI	Presence of mere vascularity in lesion; not good predictor of malignancy. Vascular morphology more sensitive to identify cancers. Radial vessels suspicious	Retrospective study, size of lesions not considered in analysis (sensitivity of detecting Doppler signals may be lower in smaller masses)
Ma et al 2015[6]	123 (57 Malignant, 66 benign) Mean lesion size 22.4 mm	AC- number of blood vessels in mass; SMI-CDI calculated	CDI, SMI	Malignant tumors have more vessels, SMI more sensitive than CDI in detecting flow (mean vessel number SMI 6.79 ± 3.75; CDI-3.50_1.90). AUROC for CDI = 0.73; SMI = 0.81; and SMI-CDI 0.89 (TP 51,FP 27,TN 39, FN 6)	Sample size small for quantifying optimal threshold of SMI-CDI to predict cancer. MVD by HPE not done. Comparison with the more sensitive PDI not done
Yongfeng et al 2016[24]	135	Semiquantitative grading, PV and flow distribution	SMI, PDI	Flow distribution more important than semiquantitative grading or PV for differentiating malignant lesions from benign. Sensitivity, specificity, PPV positive, and NPV value of SMI-assessed flow distribution: 85.4%, 92.6%, 83.3%. and 93.5%; compared with 70.7%, 92.6%, 80.5%, and 87.9% for PDI	Some benign lesions misdiagnosed as malignant on SMI suggesting that small size may interfere with diagnosis and it needs further studies
Xiao et al 2016[28]	132 breast masses (58 malignant, 74 benign)	5 vascular distribution patterns: Avascular, linear or curvilinear, tree-like, root hair-like pattern, crab claw-like patterns	CDI, SMI, CE-MVI	mSMI increases blood flow detection and depicts microvascular architecture. Diagnostic performance of mSMI not significantly different from CE-MVI Root hair-like and crab claw-like patterns more often seen in malignant lesions. (TP 45, FP7,TN 67, FN 13)	Single-center, study, small sample size, large tumor volumes with typical angiogenesis features. MVD by HPE not compared with SMI. Interobserver variation not assessed

(*Continued*)

Table 2 (*Continued*)

Authors, year	Sample size	Imaging criteria	Doppler technique	Conclusion	Limitations
Park et al 2018[29]	191 (99 benign, 92 malignant)	Vessel number (0-6); complexity 1-4; Distribution-peripheral 1-3; Overall score 0-13	CDI, PDI, SMI	SMI—higher vascular scores than CDI, PDI. Malignant masses have higher vascular scores than benign. ($p < 0.001$).Grayscale US+ SMI has higher diagnostic performance than Grayscale+ CDI or PDI (AUC, 0.815 versus 0.789, 0.791; $p < 0.001$	Retrospective study on patients scheduled for biopsy, causing selection bias. Single radiologist —reproducibility not known. Lesions with borderline features on HPE excluded from analysis; could have influenced diagnostic performance. MVD by HPE not done
Kim et al 2018[30]	62 ductal lesions	Number, distribution, morphology (Max. score 10). Criteria for malignancy= >5 vessels, intraductal or both intra- and periductal distribution, PV or branching vessels	CDI, PDI, SMI	Vessel number scores significantly different between SMI and CDI, but not between CDI and PDI. Optimum cutoff value of overall vascular imaging score suggestive of malignancy on ROC curve analysis was 8. (sensitivity 83.3%; specificity 87.0%, PPV 60.6%, NPV 95.6%, and AUC of 0.906)	Selection bias-ductal lesions scheduled for biopsy. Only one static image chosen for analysis, causing selection bias
Zhu et al 2019[25]	116 BI-RADS 4 lesions	Amount (AC), morphology, and distribution	CDI, SMI	SMI showed more vessel details and significantly more accurate in distinguishing malignant breast lesions (86.67%) compared with CDI (80.00%) ($P<0.001$). SMI or CDI downgraded no lesion	Single-center, limited pathological groups, interobserver difference not assessed. Selection bias as BI-RADS 3 masses not included
Jung et al 2018[31]	124 masses (44 malignant, 80 benign)	Amount (AC), distribution, and the presence of PV within mass	PDI, AP	AP more sensitive in depicting flow in both benign and malignant lesions. Internal blood flow location and vessels in the rim did not differ between benign and malignant. Penetrating vessels more frequent in malignant masses	Single institution, technical factors may vary in different equipment and institutions. Interobserver variability in interpretation possible
Kim S, Kim et al 2018[30]	55 (28 benign, 27 malignant)	vascular flow distribution and amount (AC); MVD on IHC subcategorized as high or low with reference to median	CDI, AP compared with MVD on histopathology	Flow distribution and amount different between benign and malignant. AP vascular flow distribution significantly different between lesions with low and high MVD ($p = 0.020$). Combined vascular distribution on AP correlated with high MVD(than in the low MVD lesions (17/28, 60.7 vs. 6/27, 22.2%)	Single institution, small sample size some subgroups may be poorly populated; core biopsies may not represent the entire lesion. Possible interobserver variability

Table 2 (*Continued*)

Authors, year	Sample size	Imaging criteria	Doppler technique	Conclusion	Limitations
Park et al 2019[33]	98 (57 benign, 41malignant)	Morphology distribution and PV Quantitative: Vascular index (%) (ratio between the pixels for Doppler signal and those for whole lesion, calculated by dedicated software)	CEUS, SMI compared with MVD on IHC	SMI: Malignant masses-higher VI (15.1 ± 7.3 vs. 5.9 ± 5.6), complex vessel morphology (82.9 vs. 42.1%), central vascularity (95.1 vs. 59.6%), PV (80.5 vs. 31.6%); unnecessary biopsies could be avoided in 12 category 4A masses. VI on SMI, 8.9 (80.5 sensitivity, 73.7 specificity, 0.844 AUC).US vascular parameters associated with malignancy = higher MVD ($p \leq 0.016$).*PV (TP 33, FP18, TN 39, FN 8)VI (TP 33, FP15,TN 42, FN 8)*	All lesions were BI-RADS 4 or 5. Exclusion of BIRADS 2 or 3 may cause selection bias. Generalizability not certain as study done on single US equipment by single radiologist
Lee et al 2021[34]	87masses (32 malignant, 55 benign)	VI	SMI	Median VI malignant masses (7.6) significantly higher than benign (2.6, $p < 0.001$). Interobserver agreement excellent regardless of pathology, depth, size of lesion	Small sample size, retrospective study, selection bias possible. All patients were scheduled for biopsy.VI on 2D image is not representative of total lesion vascularity. Observer bias is possible

Abbreviations: AP, AngioPLUS; AUC, area under the curve; CDI, color Doppler imaging; CEUS, contrast-enhanced ultrasound; FP,false positive; HPE, histopathological evaluation; IHC, immunohistochemistry; MVD, microvessel density; NPV, negative predictive value; PPV, positive predictive value; ROC, receiver operating characteristic; SMI, superb microvascular imaging; TN, true negative.

distortions, and microcalcifications on mammography. The higher sensitivity of MVI techniques could be valuable for assessing response to neoadjuvant therapy, especially for patients who cannot undergo MRI scans. However, limited research compares the diagnostic accuracy of SMI-derived VI with MVD obtained through histopathological evaluation.

Further studies are necessary to determine the optimal VI threshold for distinguishing between tumors. Additionally, research should explore the potential of MVI metrics in identifying associations with tumor characteristics such as size, histopathological factors, tumor grade, molecular subtypes, gene expression, and prognosis, as well as in selecting treatment options.[36] Studies comparing the diagnostic performance of AP/SMI with CEMR also warrant further investigation.

Conclusion

The literature consistently documented that malignant lesions have more vascularity than benign ones. MVI techniques have higher sensitivities, enabling microvessel display that was not possible earlier. This has paved the way for analyzing exquisite vessel details related to numbers, distribution, and complexity, which can improve the accuracy of predicting malignancy. There is some heterogeneity in the literature regarding diagnostic criteria. However, most investigations have concluded that hypervascularity, combined vascular distribution, central or penetrating vessels, complex/ branching or disordered vessel morphology are more frequent in malignant masses. Quantitative assessment by VI calculation overcomes the problem of operator dependence with dedicated software, and more research is needed to determine the optimum threshold of VI to differentiate tumors correctly.

Conflict of Interest
None declared.

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