Eur Radiol (2003) 13:68–79
DOI 10.1007/s00330-002-1413-3

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Role of power Doppler techniques and ultrasound contrast enhancement in the differential diagnosis of focal breast lesions

Received: 22 March 2001
Revised: 6 September 2001
Accepted: 28 January 2002
Published online: 7 June 2002

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Abstract The purpose of this article is to demonstrate the diagnostic impact of ultrasound in differentiating focal breast lesions with special regard on power Doppler and US contrast agents. The sonographic evaluation of breast lesions has become a standard procedure during the past 15 years. Especially the improvement of B-mode resolution and the use of high-frequency probes increased the diagnostic value of US. Assuming that the neoangiogenetic vascular architecture of solid breast lesions can be depicted reliably by color Doppler, many authors tried to differentiate between benignity and malignancy using Doppler criteria such as flow and morphologic aspects. Additionally, adjuvant techniques, such as harmonic imaging and new US contrast agents, are meant to be success-promising tools. Whereas the sensitivity and specificity of color Doppler have varied in different studies, prognostic prediction and treatment monitoring seem to be the future areas of application. To evaluate sufficiently flow signals of very small vessels with low flow velocity, the use of contrast-enhancing agents may be necessary. Nevertheless, an indispensable condition for successful Doppler-based assessment of the entity of breast lesions is the standardization of techniques, evaluation, analysis and weighting of the parameters.

Keywords Color Doppler · Power Doppler · Ultrasound contrast agent · Breast tumors

Introduction

Besides mammography, sonographic breast imaging has become a standard procedure during the past 15 years due to rapid technical evolution [1, 2, 3, 4]. Especially the improvement of B-mode resolution using high-frequency transducers up to 13 MHz, new Doppler methods, such as power Doppler and color harmonic imaging, and new US contrast agents, have taken place in routine diagnostics of the breast [3, 5, 6].

It is well documented that many different kinds of tumors are accompanied by angiogenesis. This vascularity is an important indicator as regards differential diagnosis, development, and prognosis. Several factors, such as tumor volume, doubling time, and cell cycle time, depend on the vascularity of the tumor [7]. Prior animal experimental studies proved a correlation between tumor growth and angioneogenesis in malignant [8, 9, 10], but not in the majority of the benign, tumors [11], caused by protein angiogenin which is produced by tumor cells [11]. In animal experiments, the induction of angioneogenesis is correlated to rapid tumor growth and metastasis [8, 10]. From a tumor diameter of 1 mm an intense angioneogenesis can be observed [10].

The blood vessel density of tumors can be determined by histology or immunohistochemistry. Also, it can be assessed non-invasively by color Doppler. The correlation of unenhanced sonographic blood flow measurements with histologic tumor vascularity and early metastases has been described [3, 12]. The analysis of vascularity can be used as a tool of therapy control under non-surgical treatment [13], i.e., by color Doppler [14, 15,

16, 17, 18, 19]. One of the most difficult problems of Doppler US is to evaluate sufficiently flow signals of vessels with diameters below 0.1 mm with low flow velocity, especially in organs with high-grade US absorption or in deeply located structures. Using power Doppler, only a minimal frequency shift and a minimal number of intravascular reflecting particles are necessary for sufficient measurement. But very small vessels with slow flow and few reflectors do not allow to differentiate between Doppler signals and background disturbances [20]. To avoid the assessment of artificial color pixels as intratumoral vessels, spectral Doppler curves of these color dots should be evaluated to prove arterial flow spectrum. To avoid artifacts, the gain cannot be widened too much. The visualization of tumor vascularity can be improved by US contrast agents with more exact depiction of the vascular architecture. The results of plain Doppler are not as reliable as those obtained after contrast enhancement in documenting vascularity and differential diagnosis [21, 22, 23, 24, 25].

The aim of this article is to demonstrate the diagnostic impact in differentiating focal breast lesions with special regard to power Doppler and US contrast agents.

Basic principles of tumor vascularity

During tumor growth, nutrition of tumor cells only by diffusion is possible up to diameters of 2 mm without vascular supply. From diameters of 1 mm usually an intense angioneogenesis can be observed [10]. There is a close correlation between tumor growth potential, early metastases, and angioneogenesis in malignant tumors [8, 9, 10]. The newly formed intratumoral vessels are important factors for tumor entity and prognosis. The non-physiological and rapid genesis of tumor vascularity lead to an anarchical structure compared with normal tissue; therefore, typical structural abnormalities are characteristic for rapidly growing tumors [26, 27]: irregular and variable vessel caliber, elongated and coiled vessels, reticular and anarchic vascular networks with tortuous vessel course, rings, sinusoids, arteriovenous shunts, vessel loops, disturbed dichotomous branching and decreasing of caliber, and incomplete vascular wall, especially without muscular layer. The correlation is close between vascular disorganization and grade of anaplasia of the tumor; thus, vascular structure may be a diagnostic key to evaluate the tumor entity.

Technical equipment

Usually, US examinations of breast lesions are performed with 7- to 7.5-MHz transducers. Basing on the assumption that the absence of vascularity indicates benignity and its presence malignancy, the use of a 5-MHz probe is reported to increase the sensitivity (42–62%, specificity for 5- and 7.5-MHz probes: 62%) to malignant breast tumors in both conventional color and power Doppler US [28]. In displaying vascularity in breast masses, the 5-MHz probe is reported to be superior to the 7.5-MHz probe in 24% (color mode) or 31% (power mode) [28]. Nevertheless, our experiences did not reveal a superiority of 5-MHz probes over 7.5-MHz probes in practical use, but we did not perform a controlled study concerning this subject; thus, the different Doppler quality depends possibly on the type of the transducer and of the hardware and software of the US machine. The sonographic examiner should determine the best probe for showing vascularity depending on his own US equipment. Annular arrays are the technical of choice, but new broadband linear arrays approach their quality and allow to visualize very slow flows within the breast by color Doppler [29]. Still, limitations are seen, and there is a lack of suitability of US for screening [29]. High-resolution US provides a better staging in breast features and improves the specificity of diagnosis. Staging of multifocal and multicentric carcinomas, and determination of the degree of invasion of the surrounding tissue and the ducts, can be achieved by high-resolution US. But also the visualization of benign features, such as inflammations, cysts, duct ectasia, hematomas, and mastopathy, has been improved by high-resolution US. In outcome monitoring of inflammations, B-mode and color Doppler are recommended as gold standard [29].

A problem of the color Doppler analysis of the breast tumor vascularity is an objective standardized measurement. Most authors have used subjective semi-quantitative or qualitative assessments of the vascularity; thus, comparison of the results of various prior studies is limited. Nevertheless, quantitative assessment [30] does not seem to be superior to qualitative analysis. The problem of false-positive patterns in hypervascularized benignities and the false-negative patterns in malignancies can only be solved by biopsy and not by improvement of color Doppler quantification [30]. Also, false-negative B-mode screening of the breast is not supposed to be improved by color Doppler. One of the most useful effects of contrast enhancement is to differentiate benign nodular scars from recurrent cancer during follow-up controls in postoperative scars. Also, in severe hypo- or avascular breast lesions after application of the contrast-enhancing agent, malignancy is very unlikely and follow-up control seems to be sufficient. On the other hand, patients with hypervascularized masses should undergo biopsy.

Ultrasound techniques

B-mode and spectral Doppler ultrasound

Besides mammography, B-mode US (Table 1) with transducers with a nominal frequency ranging from 7.5

Table 1 Quantitative analysis of unenhanced Doppler in breast tumors. *CD* color Doppler; *PD* power Doppler; *SD* spectral Doppler; *RI* resistive index; *PI* pulsatility index

Reference	Methods, results
[13]	Methods: CD, review article Results of quantitative analysis of Doppler US: potential help in differential diagnosis, assistance in therapy monitoring differential
[3]	Methods: 259 ductal invasive breast cancers, sonographic blood flow measurement Results of sonographic blood flow measurement: close relationship with between tumor size, lymph node, and receptor status, ploidy, and S-phase fraction
[38]	Methods: CD/SD, 116 breast lesions Results of SD: no sufficient differentiation between malignancy and benignity, color Doppler more useful
[39]	Methods: CD, 133 carcinomas, 325 benign breast lesions, 13 mastitis Results between benign vs malignant lesions: significant differences for number of tumor arteries, blood flow velocity (p<0.0001). RI: wide overlap
[40]	Methods: 106 breast lesions, duplex US Results: RI>0.7 may suggest malignancy, but wide overlap with benign lesions
[41]	Methods: 56 breast tumors, CD/SD Results of malignancies: higher RI with wider range (RI>0.6 in 81%) than benign lesions but wide overlap of range
[42]	Methods: CD/SD, 48 solid breast masses Results: peak Doppler frequency shifts in malignant higher than in benign masses (p<0.01). Spectral Doppler: possible device for differentiation of breast masses
[43]	Methods: CD/SD, 64 carcinomas, 53 fibroadenomas, 25 miscellaneous diseases Results of malignancy indicators: RI>0.80: specificity 96%, sensitivity 55%. RI difference >0.20 in vessels of one tumor: specificity 97%, sensitivity 39%
[44]	Methods: 200 healthy breasts (522 vessels), CD/SD Results of mean RI of premenopausal women: 0.64; of postmenopausal women: 0.70 (p<0.0001, but marked overlap). Variations in RI up to 0.31 in the same woman
[50]	Methods: 52 malignant, 32 benign breast lesions, CD, microvessel density (CD31 antibodies) Results of malignancy: color signals in 100% at periphery, in 27% within the tumor; benignity: color signals in 100% only at periphery; carcinomas: no significant correlation between color Doppler parameters and histologic microvessel counts (CD31)
[51]	Methods: 590 benign, 534 malignant breast lesions, CD/SD Results of carcinomas: significantly higher values of vessel number, RI, PI, peak flow velocity, but striking overlap with benign lesions
[53]	Methods: B-mode US, SD/CD, 131 solid breast masses Results of color Doppler: correct prediction in 74/63% (p<0.001); malignant lesions: greater number of vessels (p<0.001), higher maximum velocity (p<0.001). Analysis of velocity, age, size, B-mode morphology: overall sensitivity 94%, specificity 93%, positive predictive value 92%
[30]	Methods: 44 cancers, 30 benign breast lesions, CD/SD Results of all scores for cancers (except mean and peak velocity): significantly higher than for fibroadenomas (p<0.0001). Integral CD velocity was best discriminator

to 13 MHz is a widely used and well-proven imaging technique. High-frequency transducers and new techniques, such as tissue harmonic imaging, have improved the utility of B-mode US [31, 32, 33, 34, 35]. Typical B-mode signs of malignancy are irregular borders, ill-defined contours, and unchanged or decreased sound transmission [36]. Less reliable criteria are indeterminate or vertical orientation, hypoechogenicity, and complex or heterogeneous structure [36]. None of the criteria are absolutely reliable in discrimination of tumor entity. Furthermore, B-mode has been demonstrated to be able to depict intraductal spread of breast cancer [37] corresponding well to histologic findings. Whereas the diagnostic accuracy of B-mode US (85%) has been found to be superior to mammography (72%), its specificity is lower (76 vs 100%). The false-negative rates of B-mode US are reported to be 11% in unilateral and 23% in bilateral cancers [4]. The false-negative rate of mammography was lower (unilateral: 6.8%; bilateral: 16.3%). The failure rate is lower in palpable tumors, larger tumors, and with experienced sonographic examiners [4].

The analysis of spectral Doppler parameters (Table 1) contributes less to differentiation between benign and malignant lesions than color Doppler [21, 38, 39, 40, 41]. Some authors report that spectral Doppler criteria, such as the peak systolic Doppler frequency shifts which were measured to be significantly (p<0.01 to p<0.0001) higher in malignant than in benign breast masses, allow a differentiation [39, 42]. Spectral Doppler analysis leads to slightly higher specificity but lower sensitivity and accuracy using resistance and C index (RI, PI) as criteria compared with color Doppler [38]. An RI >0.7 is postu-

Table 2 Qualitative analysis of unenhanced color Doppler in breast tumors

Reference	Methods, results
[52]	Methods: 95 solid breast masses, unenhanced CD Results of peripheral curvilinear or branching signal pattern (rim sign): sensitivity 61%, specificity 70% for prediction of malignancy, negative predictive value for axillary nodal metastases: 90%
[54]	Methods: unenhanced CD, B-mode US, MRI, 99 breast cancers, 101 benign breast lesions Results of sensitivity/specificity/positive/negative predictive value: mammography 85/77/79/83%; B-mode US 95/80/81/94%; unenhanced color Doppler 82/75/72/84%; MRI 90/63/79/63%
[45]	Methods: 32 malignant, 18 benign breast tumors, unenhanced CD Results of color Doppler signals detectable in 75% of malignant and 39% of benign lesions; maximum flow velocities: malignant 67% >15 cm/s, benign 28% >15 cm/s. Positive association (p<0.05): nodal metastases and higher tumor flow velocity in T1 breast tumors
[59]	Methods: 13 benign, 11 malignant breast masses, 2D and 3D power mode, frequency shift CD scanning, videotapes Results of 3D power Doppler: stronger subjective appreciation of vascular morphology, better discrimination of malignancies than 2D images or videotapes (specificities: 85/79/71%, sensitivity: 90%)

lated to be a significant threshold (p<0.001) to indicate malignancy, but only in conjunction with gray-scale imaging [40]. Other studies have found that an RI below 0.80 is typical for benign breast lesions, a higher RI for malignancies [43]. Despite a specificity of 96%, the sensitivity is only 55% [43]. Doppler US reveals statistically significant differences (p<0.0001) between the mean RI of healthy pre-menopausal (RI=0.64) and post-menopausal women (RI=0.70) [44]. Other authors have not found any correlation between intratumoral flow velocity and lymph node metastases or clinical stage, but high flow velocity in T1 tumors is suggested to be an indicator for aggressive potential and early dissemination [45]. The results, however, have never been as reliable as those obtained by color Doppler particularly after contrast enhancement [21, 22, 23, 24]. Despite the opinion that breast malignancies have a higher RI (81% have RI>0.6) with a wider range than benign lesions [41], the wide overlap of parameters disqualifies spectral Doppler as a valuable tool in differential diagnosis [40, 41].

Another aspect of spectral Doppler may be its predictive potential [46]. The peak systolic flow velocity in spectral Doppler is postulated to be an independent prognostic factor of 5-year survival in patients with breast cancer (higher mortality in patients with higher flow velocity), whereas tumor size, tumor grade, and estrogen receptor have thwarted this goal [46]. The 5-year survival was 82.3% in patients with a tumor peak systolic flow velocity ≤0.25 m/s, but only 36.6% with values >0.25 m/s survived [46].

Color Doppler

Color Doppler (Tables 1, 2) is a widely used technique to depict the intratumoral neoangiogenesis. The proof or extent of tumor vascularity [47] are not sufficient criteria for differential diagnosis. Useful criteria are structural characteristics of tumor vessels correlating to histologic patterns. Typical color Doppler signs of malignancy are central (malignant in 86%, benign in 51% of tumors), borderline penetrating (65/34%), branching (56/22%), and disordered (42/8%) intratumoral vessels (Fig. 1) [48]. Malignant tumors are characterized by hypervascularity (92.9%), irregular and abundant vascularity (54.2%), and more than one vascular pole (Fig. 1) [49]. Benign masses show mostly only one vascular pole or avascularity (43.4%) and poor and peripheral vascularity (90%; Fig. 2) [49]. Histologic analysis revealed the correlating neovascularity penetrating the lesions from its periphery with thin-walled blood vessels and large arteriovenous shunts [45]. Nevertheless, color and power Doppler fail in differential diagnosis in numerous cases, i.e., in mucoid carcinomas, in situ carcinomas, and invasive ductal cancers with diameters <9 mm [49]. Typical benign lesions with “malignant” vascularity are hypervascularized, proliferating and juvenile fibroadenomas, and phylloid tumors [49]. A reason of failing in differential diagnosis is the missing significant correlation between the number of microvessels seen by unenhanced color Doppler and histologic microvessel density [38, 50]. Despite these pitfalls, in 92% of the malignancies, peripheral (100%) or central (27%) color signals are seen (27%) [50], but no central and only in 31% peripheral vascularity in benign tumors; however, a missing flow on unenhanced color Doppler does not exclude malignancy [41].

Additional factors, such as tumor size, influence the vascularity and weaken the prior statements [51]. A significant (p<0.0001) difference between the sizes of Doppler sonographically vascularized and non-vascularized tumors has been observed [51]. The majority of studies have shown significant differences between the presence of vascularity and the number of tumor arteries of benign and malignant lesions depicted by color Doppler (p<0.0001). A peripheral curvilinear or branching signal vascular structure pattern has been described as a predictor for malignancy (sensitivity: 61%; specific-

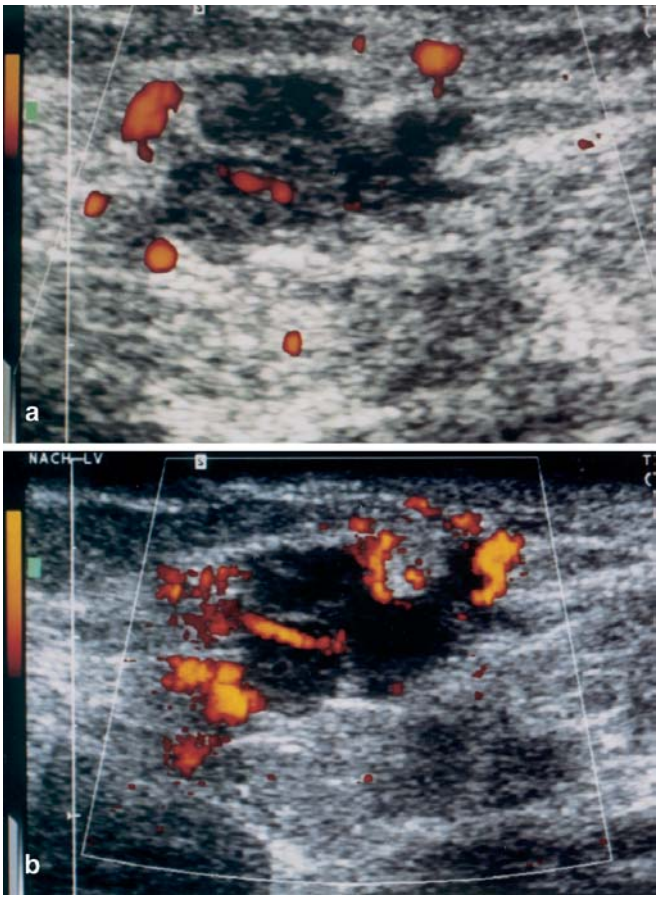

Fig. 1 **a** Plain power Doppler US shows only three paracentral intratumoral color dots representing arterial vessels. The vascular structure of this ductal invasive carcinoma cannot be analyzed sufficiently. The peritumoral vessels seem to be emphasized. **b** After application of the contrast agent, the rim-penetrating, tortuous, irregular centripetal vessels are visible as a sign of tumor neoangiogenesis. The peritumoral vascularity is lower than the intratumoral vascularity

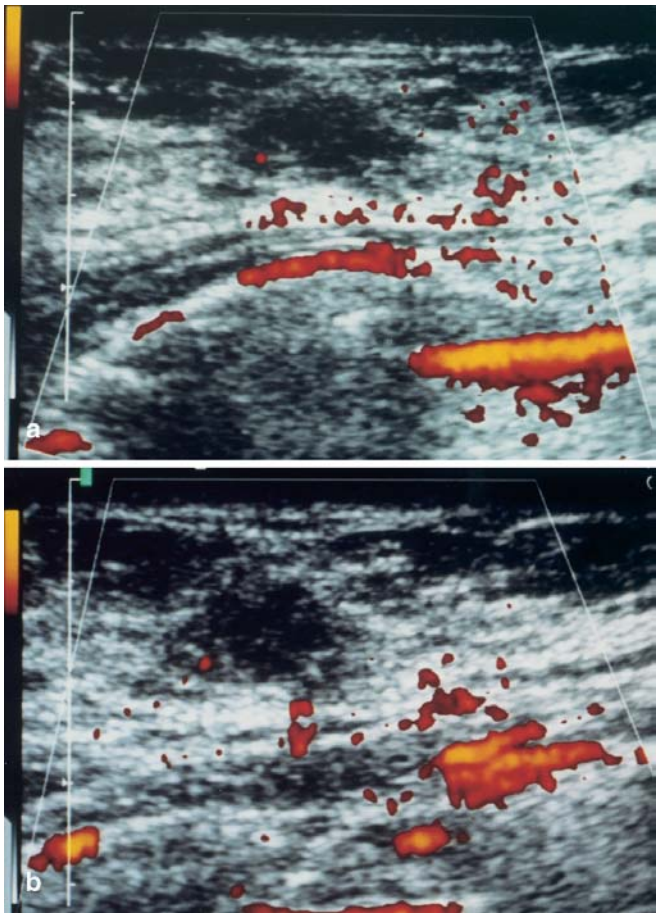

Fig. 2 **a** Before and **b** after application of the contrast agent, only one intratumoral color dot is visible. The type of vascularity with only singular or missing intratumoral vessels leads to the diagnosis "benign lesion" in this papilloma

ity: 70%) [52]. Best sonographic accuracy is obtained considering color and spectral Doppler together with mammography, tumor size, patient's age, and B-mode morphology [53].

The sensitivity of unenhanced color Doppler (82%) is believed to be inferior to mammography (85%), B-mode breast US (95%), and MRI (90%) [54]. The specificity of color Doppler (75%) was superior to MRI (63%), but inferior to mammography (77%) and B-mode US (80%) [54]. In occult breast cancer presenting with axillary metastases in 2 patients, the lesions which were not palpable and not visible on mammograms were discovered using unenhanced color Doppler [55]. Contrast-enhanced MR angiography with ultrafast gradient-echo sequences depicts the arterial and venous tumor vascularity but only of vessels with diameters >3 mm [27]. Combining all these imaging procedures, a correct classification of the tumor entity is obtained in 93.3% and may be superior to any single imaging procedure [54].

Non-invasive treatment methods, such as hormone and chemotherapy, require non-invasive, inexpensive, and simple treatment control using widely available technical tools. Various studies recommend the use of color and power Doppler to document decreasing vascularity under therapy with widened use due to development of contrast-enhancing agents [56]. Treatment is suggested to be successful in case of amount of necrosis and regression of vascularity [56].

Power Doppler

The not completely sufficient results of unenhanced color Doppler in differentiating the tumor entity, and the difficulty in depicting small intratumoral vessels, re-

Table 3 Qualitative analysis of unenhanced power Doppler in breast tumors

Unenhanced power Doppler ultrasound	
Reference	Methods, results
[28]	Methods: unenhanced CD/PD, 51 malignant, 49 benign solid breast lesions Results of CD (5- and 7.5-MHz probes): sensitivity 62/42%, specificity 62/62%; PD: sensitivity 76/51%, specificity 56/48%
[57]	Methods: unenhanced power Doppler US, 118 breast lesions Results of intratumoral flow increase compared with normal breast: highly significant (p<0.0001) for benign and malignant breast lesions; sensitivity: 74.5–78.8%, specificity: 74.6–77.8%
[58]	Methods: unenhanced color Doppler vs power Doppler imaging, review article Results of power Doppler: higher sensitivity, better vascular detailing, important in detection of flow presence and characteristics when poorly imaged with conventional color Doppler
[62]	Methods: 74 breast masses, unenhanced color/power Doppler Results: malignant masses 14–54% more vascular than benign, and five times more than surrounding tissue (benign: 2.2 times). Malignancies: strong gradient of vascularity (core >periphery >surrounding tissue), not in benign masses
[48]	Methods: 59 benign, 43 malignant solid breast lesions, unenhanced color and power Doppler US Results of power Doppler: superior to color Doppler in depiction of vascularity in 60%, equal in 40%; prediction of malignancy (color/power Doppler): sensitivity 64/77%, specificity 76/76%, accuracy 71/76%
[49]	Methods: 141 carcinomas, 112 benign solid breast masses; B-mode US, unenhanced power Doppler US Results of malignancy: hypervascularity (92.9%), irregular, and abundant (54.2%) vascularity, more than one vascular pole; benignity avascular (43.4%), poor, and peripheral vascularity (90%), mostly only one vascular pole
[47]	Methods: 33 malignant, 36 benign solid breast masses, unenhanced power Doppler US, 7- to 10-MHz transducers Results: significant overlap in vascularity of the vascular lesions in malignant and benign lesions. Power Doppler US: limited value in evaluation of solid breast masses

quires improvement in Doppler techniques. Whereas spectral and color Doppler are instruments to visualize the mean intravascular frequency shift caused by Doppler effects of flowing blood corpuscles (frequency modulated), the power Doppler mode (Table 3) depicts the intensity or energy of the Doppler signals (integrated amplitude under spectral Doppler curve) for a time period. Power Doppler reduces the temporal solution and the visualization of vessel pulsatility, and it does not show the direction or velocity of blood flow. But it depicts longer segments of smaller vessels due to holding the pixels colored for a longer time period and due to the increased signal-to-noise ratio, and it is independent of the Doppler angle. These effects of power Doppler enable the examiner to get a more complex survey of intratumoral vascular structure than by conventional color Doppler. Power Doppler depicts semiquantitatively wide lumen vessel with a higher number of scattering corpuscles more intensively than small vessels with a lower number. Despite the completely different technical bases of Doppler US and X-ray angiography, power Doppler is called "US angiography" due to its similar images as in X-ray angiography. The high sensitivity of power Doppler can de improved by use of contrast agents. Disadvantages of power Doppler are the high number of color artifacts in case of non-optimal chosen color gain, the missing possibility to differentiate reliably between arteries and veins, and the missing direct correlation between real and power Doppler sonographic vessel caliber. Power Doppler is not the most suitable method for quantitative analyses of vessel caliber (recommendation: B-mode) or quantitative flow parameters (recommendation: color or spectral Doppler).

Prior studies have demonstrated that power Doppler depicts a significant intratumoral increase in blood flow compared with the flow in normal breast parenchyma [57], particularly in carcinomas. Due to its high sensitivity, this effect is useful in small carcinomas with maximum diameters of 5 mm. The sensitivity is reported to be at least 74.5%, and the specificity 74.6% [57]. Power Doppler obtains better results than conventional Doppler in detecting vascularity of solid breast masses in 60% and similar results in 40% of the cases [48]. Some studies suggest that power Doppler is superior to conventional Doppler in diagnosing malignancy [21, 48]. The sensitivity (77%), specificity (76%), and diagnostic accuracy (76%) of power Doppler in diagnosing malignancy are found to be superior to conventional Doppler (64, 76, and 71%, respectively). Other authors have observed only a slight superiority of the power Doppler mode increasing the sensitivity from 60 to 67% and the specificity from 39 to 45% [21]. The higher flow sensitivity of power Doppler allows a more detailed depicting of vessel structure and of tissue vascularity in particular in slow and poor flow areas than color Doppler [58]. In inflamed tissue, power Doppler improves the visualization of dilated vessels. Power Doppler is able to show detailed intratumoral tortuous and irregular vessels promising an improvement of the diagnostic accuracy of color Doppler in predicting the entity of nodules. It is

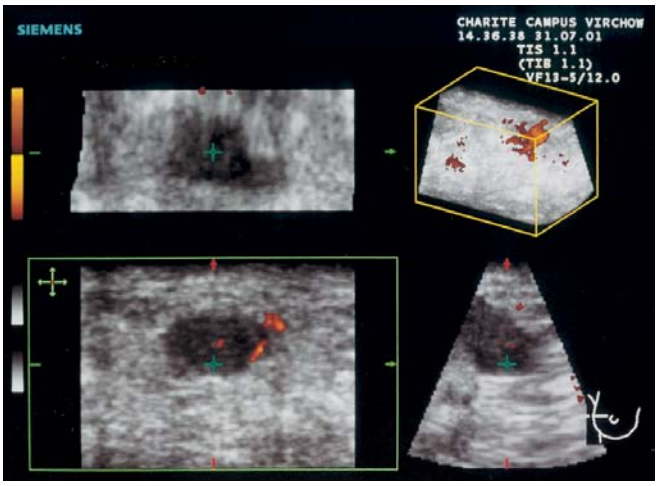

Fig. 3 A new imaging device is the 3D reconstruction of intratumoral vessels based on the primary 2D power Doppler data (Elegra, Siemens, Erlangen, Germany). The 3D imaging allows a more plastic survey about the tumor vascularity

more sensitive in showing post-therapeutic changes of intratumoral blood flow. Nevertheless, the role of power Doppler in changing therapeutic decisions has not been evaluated up to now despite its ability to improve the sensitivity in detection of blood flow compared with conventional color Doppler [58].

Besides power Doppler, other technical improvements are recommended such as low pulse repetition frequency (<1 kHz), low filters, and an amplification above the system's noise threshold to investigate low flows [49]. The sensitivity can be maximized and flash artifacts minimized by adjusting the size of the color box to be as small as possible. This is useful in differentiating breast nodules if used as an adjunct to mammography and B-mode US. Three-dimensional power Doppler displays (i.e., Fig. 3) as rotatable color volumes allow a stronger subjective appreciation of vascular morphology and a better US discrimination of malignant masses than 2D images or video mode [59]. The specificity increased from 71% (videotape) to 79% (2D) and 85% (3D) [59].

Contrast-enhanced color and power Doppler US in the differentiation of benign and malignant breast lesions

The diagnostic accuracy of color Doppler has been improved by development of power Doppler (see Table 4). Furthermore, the development of US contrast agents has opened new possibilities in depicting vessels. The usually applied contrast agent is Levovist (Schering, Berlin, Germany). Levovist is a suspension of microparticles containing 99.9% d-galactose and 0.1% palmatic acid in water. The tiny air bubbles produced by shaking the suspension have an average diameter of approximately

Table 4 Contrast-enhanced color and power Doppler studies in breast tumors

Reference	Methods, results
[7]	Methods: 47 patients, unenhanced/contrast-enhanced CD Results of criteria for malignancy with color peak density: sensitivity 55%, specificity 79%, accuracy 62%. Time to peak: sensitivity 84%, specificity 57%, accuracy 76%
[21]	Methods: 110 breast lesions, unenhanced/contrast-enhanced CD/PD Results of unenhanced color/power Doppler: specificity 39/45%, sensitivity 100/100%; enhanced: specificity 95/95%, sensitivity 100/100%; best diagnostic criterion: vascular structure
[22]	Methods: unenhanced/contrast-enhanced PD, 22 cancers/28 benign lesions (non-palpable) Results of criterion "presence of vascularity" (unenhanced/enhanced): sensitivity 36/95%, specificity 86/79%, positive/negative predictive value 67/78/63/96%
[23]	Methods: 34 patients, unenhanced/contrast-enhanced CD Results of enhanced color Doppler US: increase of diagnostic confidence, change in US diagnosis in 4 patients, increase of sensitivity/specificity to 100%
[24]	Methods: conventional/contrast-enhanced CD, 58 suspected local breast cancer recurrences Results of enhanced CD: sensitivity 94%, specificity 67%. Diagnostic accuracy: 80/90% (unenhanced/enhanced)
[60]	Methods: 10 solid breast masses, unenhanced/contrast-enhanced color flow images Results: significant correlations for enhanced US vascularity measurements and pathology (p=0.02), no correlations between unenhanced US and pathology
[63]	Methods: unenhanced/contrast-enhanced CD, 44 malignant, 24 benign breast tumors Results of best differentiation: morphological pattern, vessel course (sensitivity 95%, specificity 83%); correct distinction: postoperative scars vs recurrent tumors
[61]	Methods: 84 breast tumors, 28 post-therapeutic patients, unenhanced/contrast-enhanced CD Results of best distinction: vascular morphology and course (sensitivity 90%, specificity 81%). Clear distinction between postoperative scar and tumor recurrence
[66]	Methods: 38 suspicious scar lesion after surgery for breast cancer, contrast-enhanced Doppler Results of enhanced vs unenhanced Doppler: improved diagnostic accuracy, significant increase in visible vascularity in all recurrent tumors but in only 1 of 28 scars

2–8 μm. They are used as effective US backscatterers. The stabilizing palmatic acid inhibits destruction of the microbubbles when passing through the lung capillaries. The suspension provides a Doppler signal enhancement up to 25 dB. The concentration of the suspension is usually 300–400 mg/ml, and the volume ranges between 10.0 and 13.5 ml. The suspension has to be administered intravenously. The contrast enhancement stays for approximately 10 min. During the first minute, there may occur some so-called color blooming artifacts with overflowing vessel color. Our extensive experience has shown that the best effects are obtained during the first 5 min after application. The elimination is done the physiological way of galactose. There are no real contraindications against application.

Many studies have demonstrated the usefulness of microbubble enhancement for non-invasive evaluation of tumor neovascularity. But conventional color Doppler lacks imaging the flow in small intratumoral vessels despite using contrast agents due to the slow flow below 1 mm/s [6]. New tools, such as harmonic imaging methods and stimulated acoustic emissions detecting single scattering corpuscle signatures, open new areas in investigation of intratumoral microvessel perfusion [19, 27]. Definitive aspects for therapeutic planning are the extent of infiltration influencing directly the type and extent of surgical intervention and the prognostic prediction. Additionally, the tumor vascularity is a deciding factor for differential diagnosis and prognosis. Contrary to X-ray and MR contrast agents, the missing diffusion of US contrast agents does not allow an objective quantification of sonographically evaluated vascularity. Only semiquantitatively can the number of colored pixels or vessels in regions of interest be counted. For this purpose, power Doppler should be used. As in MRI, dynamic contrast Doppler examinations can help to differentiate the types of masses.

Several studies deal with contrast-enhanced color Doppler of focal breast lesions [21, 60, 61]. The majority of malignant tumors of the breast or other locations are hypervascularized which can be displayed by unenhanced color Doppler [38, 45, 48, 49, 50]. Nevertheless, previous studies have shown some typical pitfalls. Hypervascularized benign inflamed lesions or fibroadenomas may be mistaken for malignancies, whereas hypovascular carcinomas may be assessed falsely negative [21, 38, 49, 50]. Typical pathologic signs of malignant tumor vascularity are caliber irregularities, blood pools, arteriovenous shunts, sinusoids, and irregular courses of the intratumoral vessels [45, 48, 49]. This architecture is better visualized after application of a US contrast-enhancing agent (Figs. 1, 2, 4) [21, 22, 23, 27, 60, 61, 62, 63]. Comparing studies with unenhanced and enhanced color Doppler – despite the different methods, the use of color or power Doppler, and the various number of examined patients – the diagnostic accuracy has been improved by contrast enhancement (Figs. 1, 2, 4) [21, 22, 25, 60, 61, 62, 63]. This can be caused by better assessment of the vascular architecture of the tumors and better depiction of the hypervascularity of malignancies. Analyzing the degree of enhancement, the number of tumor vessels, the time to maximum enhancement, the morphologic pattern, and course of vessels to determine the tumor entity, the use of the contrast agent improves the differential diagnosis significantly [62]. In particular, the vascular morphology and course of vessels leads to a sensitivity of 95% and a specificity of 83% or higher [21, 62]. As in plain color Doppler, hypervascularized benign tumors are a source of false-positive patterns (Fig. 4). Using a contrast agent, power and color Doppler are equivalent (sensitivity/specificity >95%; $p<0.01$) [21].

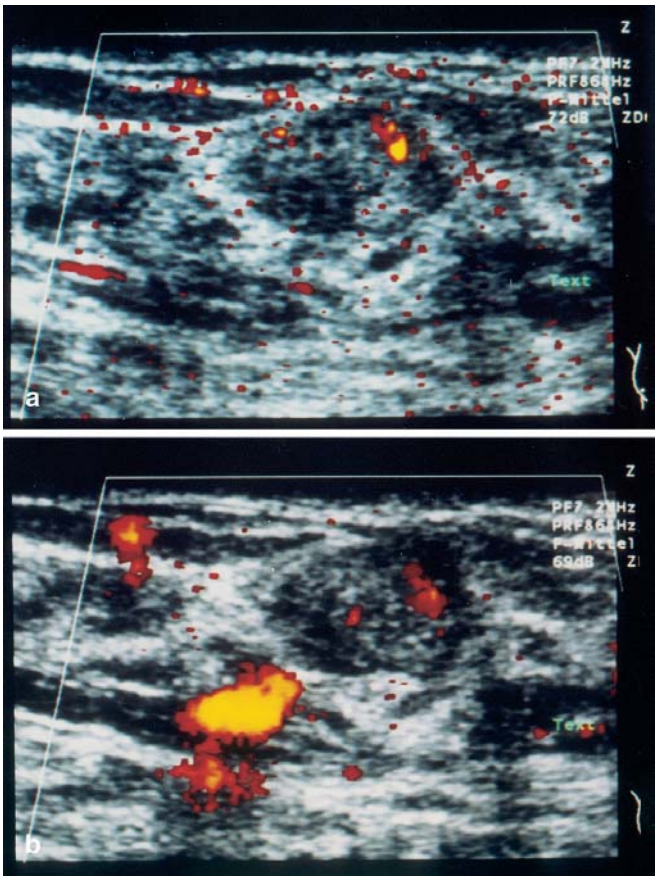

Fig. 4 **a** Using plain power Doppler, only a few intratumoral vessels are visualized without signs of malignancy and without penetrating the tumor's margin. Most of the color dots within and around the tumor are artifacts. **b** After application of the contrast agent, the number and size of intratumoral vessels does not change significantly. As a result, this fibroadenoma has to be assessed as benign considering color Doppler criteria despite its slight hypervascularity

The malignant intratumoral vascular architecture has been described as reticular or confluent dependent on the

intensity of vascularity, the use of contrast enhancement, and the Doppler settings. Some authors describe the type of vessel penetration through the tumors' margins or the peripheral (emphasized in malignancies) or central intratumoral vessel localization as criteria for distinguishing benign from malignant tumors (Fig. 1) [48, 64]. Only after application of contrast agent could a significant correlation be documented between sonographic and pathologic vascularity measurements [60]. In opposite to plain color Doppler, contrast-enhanced US flow measurements allow to determine the extent of breast tumor neovascularity well correlated with histopathologic analysis [60]. Contrast-enhanced, the rate of sonographically detectable vascularity increases in malignant lesions from 36 to 95% and in benign lesions from 14 to 21% [22]; thus, the application of contrast agent improves the visualization of the number and architecture of intratumoral vessels. This effect may lead to false-positive results in benign tumors mimicking malignant vascularity; thus, the sensitivity would be severely increased at the cost of a slightly reduced specificity. Using the presence of vascularity as criterion for malignancy, the sensitivity increases from 36 to 95% and the specificity decreases from 86 to 79% after contrast enhancement [22]. These facts may be acceptable considering the significant increase of diagnostic accuracy [21].

Considering the subjective analysis of the increase of the Doppler signal intensity, the changes in the vascular patterns, and the timing of the transit of microbubble bolus injections, the signal enhancement is greater and longer in malignant than in benign lesions [23]. Additionally to characteristic vascular morphologic features of the cancers [21], malignancies display more additional vessels visualized in relation to the lesion and a greater increase in vascular tortuosity [23]. Shunts are seen in all malignant but in no benign lesions [23]. In a prior study, the use of contrast agent changed the diagnosis in 4 of 34 patients with increasing sensitivity and specificity of US up to 100% compared with non-enhanced color Doppler [23]. The greatest increase in diagnostic accuracy by use of contrast agent seem to be obtained using vascular sonomorphologic aspects such as vessel caliber irregularities, vessel courses, and penetrating tumor feeding vessels for differential diagnosis [21, 61, 63]. In 110 breast masses an improvement of differential diagnosis was observed in 24% of the primary carcinomas, 68% of the fibroadenomas, and all local postoperative benign and malignant lesions after injection of the contrast agent compared with unenhanced color or power Doppler [21]. In another study which saw the vascular morphology and vessel course as the most reliable criterion of tumor entity, the sensitivity was 95% and the specificity 83% [61, 63]. The time to maximum enhancement and the number of tumor vessels are less reliable criteria due to pronounced overlap between benign and malignant lesions [61, 63]. A computer-assisted assessment of the color pixel density in microbubble contrast-enhanced color Doppler [7, 65] was used to measure the increase of the color Doppler signal and the transit time of the contrast agent bolus. Using a median time to peak of 50 s as criterion for malignancy, the sensitivity was 84%, the specificity 57%, and the diagnostic accuracy 76%. The criterion "color pixel density" (threshold 13%) revealed a low sensitivity (55%), specificity (79%), and diagnostic accuracy (62%). The behavior of malignant and benign lesions is significantly different with respect to degree, onset, and duration of Doppler signal enhancement, but the wide variability limits the utility of these criteria in differential diagnosis [7, 65]. Findings in malignant tumors showed a greater number of vessels and a faster and stronger enhancement after administration of the d-galactose-based contrast agent Levovist than in benign lesions with a partial overlap with results from the benign tumors [61, 63]. Although administration of the contrast agent improves evaluation of benign features on Doppler US, absolute certainty in differentiation between benign and malignant lesions cannot be achieved [61, 63].

In conclusion, the qualitative sonomorphologic aspects of vascularity are more reliable criteria of entity than quantitative spectral flow parameters and the quantification of the intratumoral vessel density. Pure quantitative parameters of tumor vascularity often lead to false-positive diagnosis, i.e., in hypervascularized benign tumors (Fig. 4). Compared with color Doppler, power Doppler is slightly superior in depicting the vascular structure. Contrast enhancement improves the accuracy, sensitivity, and specificity significantly.

Contrast-enhanced color Doppler in the differentiation of postoperative changes from recurrent tumor

The otherwise difficult distinction between postoperative scar and tumor recurrence appears to be one of the most success-promising regions of interest [61, 63, 66], in particular concerning the failure rate of mammography and B-mode US in recurrences [4]. Prior studies have shown the significant improvement of differential diagnosis by use of contrast agents in suspected postoperative recurrent carcinomas [21]. This may be an alternative method to the more expensive and less specific MRI. During the first 18 postoperative months, the nodular scars or granulomas may also be hypervascularized with decreasing tendency parallel to the increasing age of the scar [61, 63]. Criteria such as number and regularity of vessel courses before and after application of Levovist and the enhancement kinetics and intensity can be used to differentiate benign from malignant breast masses [66]. In a prior study, all scar lesions seemed to be slight or not vascularized using unenhanced color Doppler, and all but 1 of 28 after enhancement, whereas all malignant lesions showed a significant increase of visible tumor ves-

sels after contrast enhancement [66]. Other studies have confirmed that the correct distinction between postoperative scars and recurrent tumors is possible using contrast-enhanced color Doppler [61, 62, 63]. Winehouse et al. [24] concluded that contrast-enhanced color Doppler may substantially reduce biopsy rates in postoperative lesions which were suspected for local cancer recurrence (sensitivity: 94%; specificity: 67%). The contrast agent increases the accuracy from 80 to 90% ($p<0.04$) [24].

Conclusion

In a review of the literature which deals with spectral, non-enhanced, and contrast-enhanced color and power Doppler US in the differential diagnosis of solid breast lesions, over a time period of 5 years, the value of spectral Doppler decreased, whereas color- and particularly power Doppler are suggested to be of growing importance. This thesis is supported particularly by authors who used contrast agents and power Doppler imaging. The reliability of differential diagnosis, treatment monitoring, and finding recurrent tumors can be significantly improved by the use of US contrast agents. Nevertheless, an indispensable condition for successful color- or power-Doppler-based differentiation between benign and malignant breast lesions is the standardization of examination technique, and of the evaluation, analysis, and weighting of the parameters, independent of the use of US contrast agents.

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