COLOR DOPPLER IN THE STUDY OF THE BREAST: HOW DO WE PERFORM IT?

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Doppler color en el estudio de la mama: ¿Cómo lo hacemos nosotros?

Abstract: The contribution of color Doppler sonography in the study of breast cancer remains a topic of discussion. However, in the daily clinical practice it has become an indispensable tool, and an integral part of the breast ultrasound (US). The aim of this paper is to demonstrate its utility based on the available evidence as well as on our experience. We describe the technical considerations necessary to conduct a good study, the Doppler signs of benignity/malignancy in focal lesions of the breast, and the benefits of its routine use in day-to-day practice. In our experience, it is an useful tool for this purpose. Nevertheless, its diagnostic impact as described in the literature is variable. To evaluate its real usefulness, prospective studies along with standardization of the evaluation techniques would be required.

Keywords: Angiogenesis, Breast Neoplasms, Doppler sonography, Breast Ultrasound, Vascularity.

Resumen: La contribución del Doppler color en el estudio de la mama sigue siendo un tema en discusión. No obstante, en la práctica clínica diaria se ha convertido en un instrumento indispensable, formando parte integral del Ultrasonido (US) mamario. El objetivo de este artículo es demostrar su utilidad según la evidencia disponible y a través de nuestra experiencia. Se describen las consideraciones técnicas indispensables para realizar un buen estudio, los signos Doppler de benignidad/malignidad en lesiones focales de la mama y las ventajas de su uso rutinario en la práctica diaria. En nuestra experiencia es una herramienta útil para este propósito; sin embargo, su impacto diagnóstico descrito en la literatura es variable. Para evaluar su real utilidad, se requiere de la realización de estudios prospectivos y de la estandarización de la técnica.

Palabras clave: Angiogénesis, Neoplasia mamaria, Ecografía Doppler, Ultrasonido mamario, Vascularidad.

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Introduction

The role of color Doppler sonography in breast disease remains a controversial issue(1-3). No solid evidence is available due to lack of large-scale population studies; therefore, there are no prospective randomized controlled studies available. Results—largely obtained from small series—are heterogeneous, being conclusions not always reliable. Due to absence of clearly defined standards, evaluation of breast lesion vascularity is currently optional in BI-RADS US lexicon(4-7).

Even so, with technological advances in the transducer industry and because of the experience gained in breast ultrasound (US), Doppler technique currently enjoys an ever-increasing utilization. The purpose of this paper is to analyze the
use of color Doppler ultrasound in breast pathology in the light of available evidence, and to describe, according to our experience, how it can improve the performance of B-mode US in the routine examination of the breast.

Technical considerations
High-frequency transducers (ideally 12-18 MHz) capable of evaluating signal in vessels less than 0.1 mm in diameter with low-velocity flow are needed. Different Doppler modalities for evaluating breast lesions such as power Doppler, spectral Doppler, color Doppler with or without contrast medium injection are used.

Color Doppler US is an easy-to-use tool, available in most ultrasonic imaging devices today. It provides information about the presence of vascularization in tissues; it allows to depict the flow direction, and to distinguish a vein from an artery, according to the spectral type of curve observed.

In order to demonstrate very slow flows, it is necessary to apply minimal pressure on the breast, thus avoiding compression of the blood vessels. Additionally, it is necessary to adjust some parameters to obtain an optimal staining of blood vessels [PRF between 700-1,000 Hz, wall filter as low as possible (50 to 100Hz max.), appropriate algorithm to remove motion artifacts, maximum gain (85-90%), medium persistence, box without angulation].

Power Doppler US is an optimal technique for detecting slow flow in small vessels since it is Doppler angle independent, thus being highly advantageous in breast lesion evaluation. It is estimated to yield 2 to 5 times higher sensitivity than color Doppler, although this assertion has not been confirmed in our practice. Its disadvantages are: increased number of artifacts and lack of information about the speed and direction of blood flow, thus hindering proper differentiation between arteries and veins.

Spectral Doppler measurement of blood flow could theoretically help in characterizing breast masses; it has shown a high velocity and pulsatility with a systolic peak higher in malignant masses than in benign lesions. However, outcomes depend on other factors (e.g., histology of the lesion) and these measurements are difficult to reproduce since they are operator- and equipment-dependent, exhibiting a wide inter-observer variability.

As a line of research, we attempt to demonstrate breast mass microcirculation by adding a contrast medium injection to increase color Doppler US sensitivity. However, even after injection of microbubbles overlap between hypervascular benign lesions and malignant hypovascular masses persists, which explains its limited use.

Due to their simplicity, color Doppler and power Doppler sonography have continued to gain popularity in daily practice.

Capability of color Doppler US in differentiating benign nodules from malignant lesions
While benign breast lesions exhibit mature native blood vessels of harmonious architecture, malignant tumours secrete angiogenic factors that stimulate the growth of abnormal blood vessels. Neoangiogenesis is thought to be caused by the protein angiogenin that generates a local vascular network highly dense in capillaries, and arteriovenous loops and shunts. The new vessels are tortuous, of irregular calibre and thin walls, with no smooth muscle.

Dynamic breast MRI seeks to demonstrate tumor neovascularization with injection of gadolinium, since these abnormal vessels are early impregnated with the contrast. In color Doppler US it is not possible to identify the capillaries, while afferent and intra-tumoral vessels of greater size can be clearly visualized. Therefore, it can be assumed that an increased vascularization on color Doppler sonography increases the likelihood of masses malignancy. However, hypervascularity in a breast lesion by itself may not be an adequate predictor of malignancy, since there is much overlap between the irrigation of benign and malignant lesions.

When considering only the masses “vascularized or not vascularized nature” of the mass as a criterion of malignancy, results show low sensitivity, specificity, and predictive values. Therefore, it is evident that increased vascularity on color Doppler sonography can not be considered as the sole factor to establish the diagnosis of malignancy and that the contribution of this technique should be viewed as an additional element, complementary to bidimensional ultrasound for analyzing afferent vessels and internal vascularization of breast masses.

In several studies, semiological criteria have been established to distinguish benign from malignant lesions, according to location and morphology of the detected vessels.

Doppler signs of benignity
Benign nodules, classified as BI-RADS category 3, exhibit well defined sonographic signs on B-mode ultrasound: oval lesions, with well circumscribed contours, oriented parallel to the skin or with up to 2-3 soft lobulations. Hyperechogenicity is another element suggestive of benignity. Additionally, in this type of breast lesions the following Doppler signs indicate benignity:

• Capsular blood vessels of straight or curved path, with regular caliber and harmonious distribution (Figure 1). They are a common
finding in benign lesions such as fibroadenomas\textsuperscript{(18)}.

• The finding of “parallel artery and vein” (Figure 2) is another sign of benignity, according to our experience. An artery accompanied by its vein at the peripheral or central area of the mass denotes a normal anatomical condition. These native vessels are different from the tortuous, disorganized and non-hierarchical neo-vessels resulting from tumoral angiogenesis. In our series, even in review, 98.5% of nodules exhibiting this finding were benign (140/142). Usually seen in fibroadenomas, it can also be found in other benign lesions such as papillomas, lactating adenoma, intramammary lymph nodes, etc.

• The avascular nature of a lesion with benign morphologic appearance\textsuperscript{(18)}, BI-RADS US category 3, without color signal, often corresponds to a cyst with thick content or to a fibroadenoma, without neoangiogenic capacity (Figure 3a). According to our experience, in most cases this sign means benignity. On the other hand, we may note that with current technology for treating masses of suspicious or doubtful morphology (BI-RADS category 4b, 4c and 5) we are not always able to visualize intra-lesional vessels; we only perceive afferent tortuous neo-vessels, indicative of malignancy (Figure 3b). In this context, the apparent “avascularity” should not be interpreted as a sign of benignity.

As for the number of afferent blood vessels, benign lesions tend to have one peripheral vascular pole\textsuperscript{(18)}.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure1}
\caption{Capsular vessels with regular caliber, curved/straight path and harmonious distribution is a common finding in benign lesions such as fibroadenomas.}
\end{figure}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure2}
\caption{Sign of “parallel artery and vein”: an artery accompanied by its vein at the peripheral or central area of a mass denotes a normal anatomical condition (a). It is an infrequent finding (12\% in our core biopsies), but of high predictive value for benignity; it is seen in fibroadenomas, papillomas, intramammary lymph nodes, lactating adenomas, among others (b).}
\end{figure}
Doppler signs of malignancy

Breast masses classified as indeterminate or suspicious on B-mode images (BI-RADS 4 and 5) have irregular shape and contours, with spicules or are microlobulated, are higher than wide, often contain microcalcifications and may create posterior acoustic shadowing or echogenic halo by desmoplastic reaction\(^{(24)}\). In such lesions, the following additional features suggest malignancy on color Doppler images:

- Presence of central vessels in absence of capsular vessels\(^{(25)}\) (Figure 4a). When a large percentage of the lesion is covered with colored pixels (Figure 4b), it is usually indicative of a malignant or papillomatous mass.
- The feeding or intra-nodular tortuous arteries, of chaotic distribution and variable caliber due to irregular branching, correspond to the typical neo-vessels resulting from tumoral angiogenesis\(^{(25)}\) (Figure 5).
- Afferent vessels entering the mass perpendicularly, without passing through capsular vessels represent a finding highly suggestive of malignancy\(^{(2,18,25)}\) (Figure 6).
- The large number of afferent vascular pedicles, along with the high intra-nodular vascular density, correlate with tumor aggressiveness and metastatic risk according to several authors\(^{(21)}\) (Figure 7 and 3b). Santamaria\(^{(26)}\) found a linear relationship between tumor size, number of afferent vessels, and axillary metastases. According to the theory proposed by Byers et al.\(^{(27)}\), one of the factors involved in neoplastic dissemination is the movement of tumor cells or emboli from the tumor into the lymphatic
Figure 5. The intralesional tortuous neovessels, of chaotic distribution and variable caliber due to irregular branching, strongly increase the BI-RADS US score of a breast mass.

Figure 6. Penetrating afferent vessels entering the node directly, without passing through capsular vessels represent a finding highly suggestive of malignancy.

Figure 7. The large number of afferent vascular pedicles, appears to correlate with tumor aggressiveness and metastatic risk.

vessels or veins that have a laminar flow. This theory suggests that the more abundant the tumor vascularization, the greater the shear forces induced on tumor cells by laminar flow, thus favouring detachment of tumoral cells.

Using these suspicion criteria, color Doppler imaging yields a variable sensitivity for cancer detection, estimated at 68-99% and a specificity of 43-97%, PPV of 58 to 88%, and NPV of 80 to 100% according to different studies. This major inconsistency among different studies may be explained by differences in the techniques used (color Doppler, color Power angiography or contrast injection).

While registration of pulsed Doppler parameters generally offers no specific elements to discriminate benign from malignant lesions, according to Del Cura et al., nodal malignancy is highly probable when diastole disappears or when it is inverted.

Benefits of routine use of color Doppler sonography

Color Doppler sonography has become an indispensable tool and is currently an integral part of US breast imaging techniques.

Provided that adequate imaging technology has been applied, the above mentioned Doppler findings allow a better characterization of breast masses BI-RADS 3 and 4, whose percentage of risk of cancer is highly variable (less than 2% and 3 to 94%, respectively). Although there is no solid evidence but the opinion of some experts in this imaging technique, color Doppler sonography allows a better selection
of lesions requiring histological study in day-to-day work. If we accept the hypothesis that the presence of “benign” Doppler signs reinforce the benign appearance of masses, it is possible to “reduce” the BI-RADS score of a likely benign/indeterminate lesion on B-mode images and thus to recommend its monitoring by using imaging techniques (e.g., in masses BI-RADS 3 and 4 A) (Figure 8a).

On the contrary, the typical “malignant” US color Doppler sign increases the level of suspicion of lesions previously classified as probably benign/indeterminate, supporting the need for histological verification\(^{(2,6)}\) (Figure 8b).

Therefore, if we were capable of more accurate discrimination between likely benign or indeterminate nodules, we could reduce unnecessary biopsies. In the classic study by Stavros\(^{(29)}\), the rate of biopsies with benign versus non-benign results (= malignant and high-risk lesions) is 5 to 1. In the study by Buchberger et al.\(^{(30)}\), this ratio is even higher, 6.3 to 1. In our current practice (364 core biopsies in 2010) this ratio is 1.7 to 1, a result thought to be largely due to the routine use of color Doppler sonography.

In addition to characterization of breast masses, color Doppler examination helps in different situations, such as:

- To distinguish a fat lobule from a solid breast mass (Figure 9a); while the first exhibits avascular architecture, it is possible to demonstrate vessels in the real mass (if they are detectable by color Doppler analysis).
- To recognize an intramammary lymph node (Figure 9b), based on its hilar vascularization.
- To suspect metastatic adenopathies, due to development of capsular vessels, which is an almost pathognomonic sign for metastatic tumor involvement (Figure 9c).
- To discriminate between a vascularized tumor and a cyst with thick content (Figure 9d), based on its avascular nature.
- To identify intracystic tumors and intraductal papilomas (Figure 10), on the basis of tumor vasculature. These are highly irrigated lesions, where differentiation between benign and malignant variants is not possible by ultrasonography. Exceptionally, older lesions may appear poorly or not vascularized, due to infarctions\(^{(2,7)}\).
- Milk of calcium calcifications, located in microcysts or ducts can be identified as such on color Doppler sequences by viewing the twinkling artifact (Figure 11).
- The periductal or pericystic acute inflammatory process is demonstrated by the hypervascularity in these structures. The great parietal and perilesional hyperemia is also typical of breast abscesses and overinfected retroareolar cysts (Figure 12).
- Lesion evaluation with color Doppler studies before performing biopsies under US guidance is highly helpful. If numerous blood vessels or large arteries are present, it is advisable to use vasoconstrictors (e.g., epinephrine) together with local anesthesia so as to decrease the chance of bleeding.

Figure 8. The identification of an indeterminate mass with benign Doppler sign (a), such as avascularity, allows us to recommend ultrasound follow-up rather than biopsy. A Doppler suspicious sign (e.g., numerous intra-nodal vessels without capsular vessels) in a mass characterized as indeterminate in gray-scale sonography (b) increases suspicion and therefore it is recommended to indicate biopsy.
**Figure 9.** Some applications of color Doppler sonography: To distinguish a fat lobule from a solid breast mass (a): while the first generally exhibits avascular architecture, it is possible to demonstrate vessels in the real mass. To recognize an intramammary lymph node (b), based on its hilar vascularization. Metastatic adenopathies are entirely hypoechoic and develop capsular vessels (c), almost pathognomonic sign for metastatic tumor involvement. To discriminate between a cyst with thick content (d) and a vascularized tumor, due to the avascular nature of the cystic.

**Figure 10.** Color Doppler ultrasonography is helpful in identifying intracystic tumors and intraductal papillomas, because of tumor vascularization (a, b, c). Even in small tumors, the vascular stem can be visualized with color Doppler imaging (b). A papilloma appearing poorly vascularized (c) or avascular, is an unusual finding; this is due to infarction of older breast lesions.
Recommendations

The American College of Radiology, in its first publication on the BI-RADS US\(^4\) included evaluation of the vascularity of breast lesions and their vicinity, without establishing the mandatory use of color Doppler US.

Its routine use was recommended in our last National Consensus Resolution (2009), thus supporting the generalized opinion that color Doppler sonography is a tool deemed to be an integral part of the breast US to optimize the study of breast lesions.

Conclusions

Using an appropriate equipment, color Doppler sonography allows a better characterization of breast masses, thus reducing the number of unnecessary biopsies.

Its diagnostic impact varies among the available studies, thus posing a need for standardized evaluation techniques and parameters to be considered. Studies providing further evidence about its actual contribution are still scarce; meanwhile, its use is recommended.
References


