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Evaluation of the intratumoral vasculature of hepatocellular carcinoma by power Doppler sonography: advantages and disadvantages versus conventional color Doppler sonography

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Abstract
Background: To determine whether a difference exists in the relative ability of power Doppler sonography and conventional color Doppler sonography to detect the intratumoral vasculature of hepatocellular carcinoma based on lesion size and location.
Methods: Sixty patients with 88 hepatocellular carcinoma lesions that showed tumor staining on angiography and were enhanced on dynamic computed tomography were evaluated. Power Doppler sonography and color Doppler sonography were used to detect the intratumoral vasculature, and their sensitivity to blood flow was evaluated.
Results: Power Doppler sonography showed a superior detection rate for lesions smaller than 2 cm and located 4–8 cm from the abdominal surface in the right hepatic lobe as compared with color Doppler sonography ($p < 0.01$). Neither power Doppler sonography nor color Doppler sonography depicted the intratumoral vasculature of lesions located more than 8 cm from the abdominal surface ($n = 14$). Both color Doppler imagings exhibited a low detection rate for lesions in the left hepatic lobe ($n = 31$, $p < 0.01$).
Conclusions: Power Doppler sonography should be applied in the evaluation of small or intermediate depth lesions because it is more sensitive to these lesions than color Doppler sonography, but it is not useful for left lobe and deep lesions.

Key words: Color Doppler sonography—Comparative study—Hepatocellular carcinoma—Liver, neoplasm—Power Doppler sonography.

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Doppler sonography is very useful for evaluating blood flow without exposing patients to radiation and without the requirement for contrast material. Color Doppler sonography has been used to differentiate hepatocellular carcinoma from other kinds of hepatic nodules [1, 2, 3, 4, 5, 6, 7], to evaluate the response of nonsurgically treated hepatocellular carcinoma [8, 9], and to guide percutaneous ethanol injection for large hepatocellular carcinoma [10]. Tanaka et al. differentiated hepatocellular carcinoma from other kinds of hepatic nodules based on the finding of a basket-pattern vascular network on color Doppler sonography that is characteristic of hepatocellular carcinoma [1]. Tanaka et al. demonstrated intratumoral vasculature on color Doppler sonography in residual hepatocellular carcinoma lesions after transcatheter arterial chemoembolization [8]. Lencioni et al. confirmed residual intratumoral vasculature on color Doppler sonography as evidence of incomplete percutaneous ethanol injection therapy for hepatocellular carcinoma [9]. But color Doppler sonography has some limitations because of its relatively low sensitivity to blood flow [1, 3, 8, 9, 11], and color Doppler sonography cannot depict the intratumoral vasculature of left lobe and deep hepatocellular carcinoma lesions.

Power Doppler sonography was developed to overcome the limitations of conventional color Doppler sonography, with preliminary studies suggesting that power Doppler sonography is superior to conventional color Doppler sonography in evaluating the intratumoral vascularity of liver tumors [12, 13, 14]. Theoretically, power Doppler sonography is also affected by ultrasonic attenuation and tissue motion [15, 16]. We investigated these obstacles to identify to which kind of hepatocellular carcinoma lesions power Doppler sonography should be applied as an alternative to conventional color Doppler sonography.

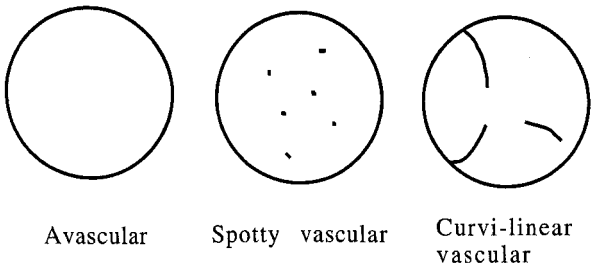


Fig. 1. Types of vascular pattern with power Doppler sonography.

Materials and methods

The following hepatocellular carcinoma lesions were selected for this study: (a) lesions that were depicted on gray-scale ultrasonography and were examined with color Doppler sonography and power Doppler sonography before undergoing angiographies and biopsies, and (b) lesions that showed tumor staining on angiography and on dynamic computed tomography at the arterial phase.

Subjects

Between December 1995 and July 1997, the intratumoral vasculature of 88 angiographically hypervascular hepatocellular carcinoma lesions in 60 patients was evaluated using color Doppler sonography and power Doppler sonography. The subject population comprised 45 men and 15 women, aged 50–84 years (mean = 68.97 years). Fifty-three patients had HCVAb, three patients had HBsAg, and four patients were uninfected by hepatitis viruses. Histologic diagnoses of hepatocellular carcinoma were obtained for eight lesions by following ultrasonogram-guided percutaneous biopsies. The remaining 80 lesions were diagnosed clinically by examining the history of viral hepatitis and by interpreting characteristic angiographic and dynamic computed tomographic findings. The experimental protocol was designed and performed according to the principles of the Helsinki Declaration. The subjects gave their full informed consent.

Doppler procedure

Color Doppler sonography and power Doppler sonography studies were performed by using color Doppler ultrasound equipment (LOGIQ700 GE Medical Systems, Milwaukee, WI, USA) with electrical probes at Doppler frequencies of 2.5, 4.0, and 5.0 MHz. Hepatocellular carcinoma lesions 4 cm or smaller from the abdominal surface were examined with a Doppler frequency of 5.0 or 4.0 MHz. Lesions larger than 4 cm from the abdominal surface were studied with a Doppler frequency of 4.0 or 2.5 MHz. Color gain was adjusted to the highest value at which the color image was not affected by artifacts, and the color-coded area was restricted as much as possible to maximize the color sensitivity and frame rate for both color Doppler imagings. The pulse repetition frequency and bandpass filter were selected to optimize the detection of weak signals as follows. The former ranged from 4 to 10 KHz, and the latter ranged from 16 to 63 Hz for color Doppler sonography. For power Doppler sonography, the ranges were 4–7 KHz and 80–140 Hz, respectively. All intratumoral color signals were analyzed by Doppler spectral analyses. The sample volume for spectral analysis varied from 2 to 4 mm. The pulse repetition frequency was adjusted to obtain the frequency shift of blood flow. Doppler examination was performed by one of the two authors (K.K. or N.H.). Color and power Doppler ultrasonography and spectral examinations were recorded on a Magneto Optical disc present within the system. The recorded images recalled on the system imaging monitor were judged by three radiologists (K.K., N.H., Y.F.) who determined by consensus whether the lesions had intratumoral vasculatures. Hepatocellular carcinoma lesions were judged to have intratumoral vasculatures if it showed color signals that were confirmed to be pulsatile waveform by Doppler spectral analysis. Intratumoral vasculature on power Doppler sonography was classified into three types: avascular, spotty vascular, and curvilinear vascular (Fig. 1). Avascular lesions had no intratumoral vasculature on power Doppler sonography (Fig. 1). Both spotty and curvilinear vascular lesions had an intratumoral vasculature. Spotty vascular lesions had a dotted color signal, whereas curvilinear vascular lesions had a straight or curved color signal (Fig. 1). Examiners and judges of Doppler examination were not aware of the results of any dynamic computed tomographic (CT) and angiographic studies.

Table 1. Detection rate of intratumoral vasculature by location of lesions

	Right lobe (n = 57)	Left lobe (n = 31)
Power	41 (71.9%)	13 (41.9%)
Color	31 (54.4%)	9 (29.0%)

Numbers indicate vascular lesions, including those with spotty and curvilinear vascular patterns

Dynamic CT and angiography procedures

Using a power injector (Auto enhance, Nemotokyorindo, Kyoto, Japan), 2 mL/kg of iopamidol 300 (Iopamiron Nihon Schering, Japan) was infused at a rate of 3 mL/s through a 20-gauge venous access catheter placed into an antecubital vein. Helical scanning of the entire liver was begun at either 30 (arterial phase) or 120 (equilibrium phase) s after the start of the infusion. All scans were obtained with a helical CT scanner (ProSeed GE Medical Systems, Milwaukee, WI, USA) with 10-mm beam collimation and 10-mm/s table speed.

Digital subtraction angiography was performed with a DFP-60A unit (Toshiba, Tokyo, Japan) with use of 5-F catheters. At first, 20–30 mL of iopamidol 300 (Iopamiron Nihon Schering) was injected at 4–5 mL/s at the level of the right, left, or proper hepatic arteries. Catheterizations and injections were repeated so that the whole liver parenchyma could be imaged, if accessory or replaced hepatic arteries were found. Tumor staining on CT and angiography was judged by consensus by two radiologists (M.F., D.Y.) who were not aware of the results of the Doppler examination.

Evaluation of factors affecting color Doppler imaging

We evaluated factors affecting the ability to detect intratumoral vascularity such as location of lesions in the liver, greatest tumor diameter, and depth of lesions. Location refers to which hepatic lobe the lesions occupied. Greatest diameter was measured on a gray-scale ultrasonogram. Depth refers to the distance between the abdominal surface and the center of the lesion. A minimum depth was chosen for this study by multidirectional scanning.

There were 57 lesions (64.8%) in the right hepatic lobe and 31 lesions (35.2%) in the left hepatic lobe. The 88 hepatocellular carcinoma lesions were 0.8–5 cm in diameter (mean = 2.01 cm). Specifically, 57 lesions (64.8%) were $\leq$2 cm, and 31 lesions (35.2%) were $>$2 cm. Thirty lesions (34.1%) were superficially located (i.e., the depth of lesion was $\leq$4 cm), 44 lesions (50%) were intermediately located (i.e., the depth of lesions was $>$4 cm and $<$8 cm), and 14 lesions (15.9%) were deeply located (i.e., the depth of lesions was $>$8 cm).

Statistical comparison was performed with the chi-square test, Fisher's exact probability method, and the McNemar test, with $p < 0.05$ indicating a statistically significant difference.

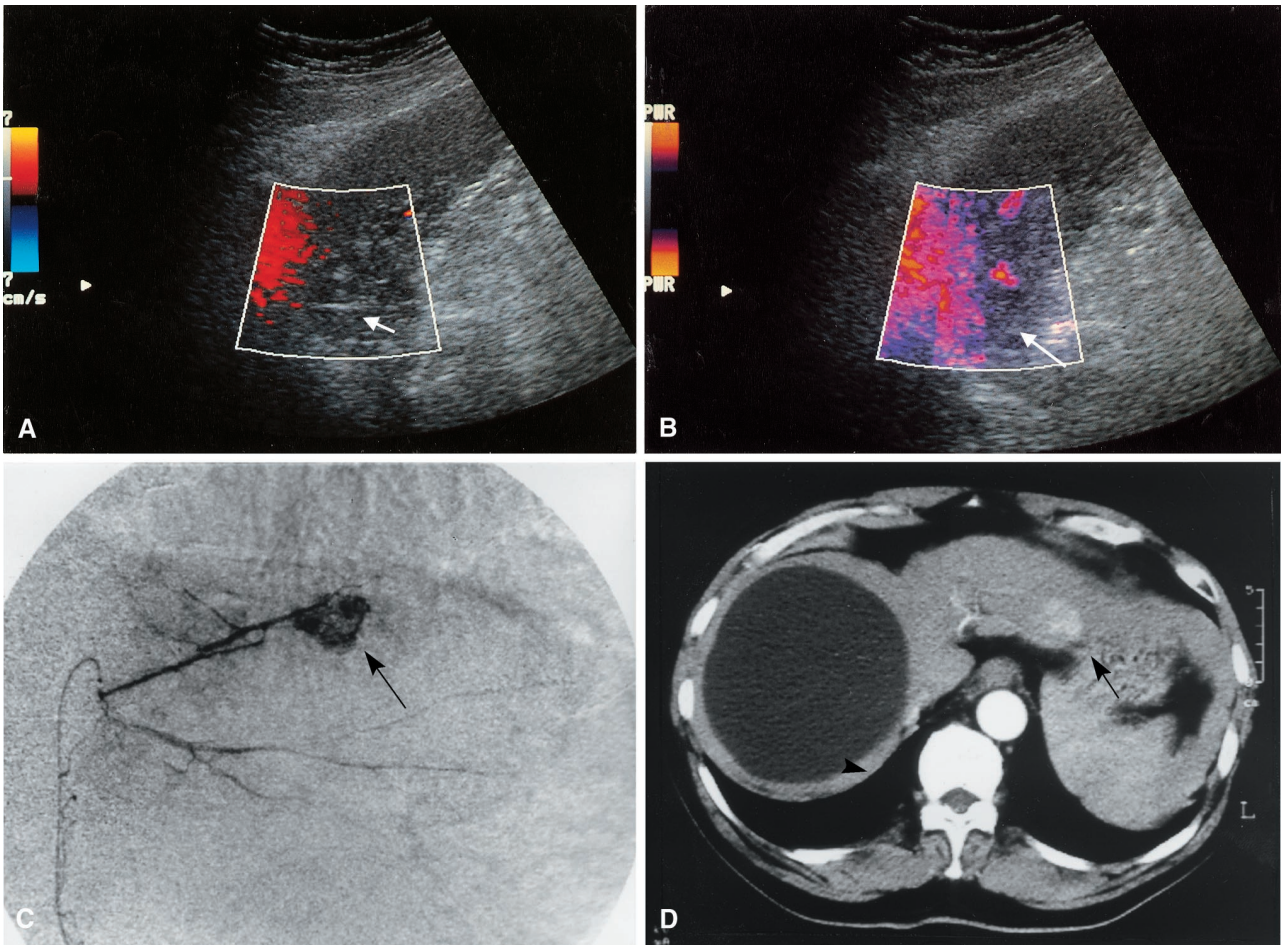


Fig. 2. Hepatocellular carcinoma in the left hepatic lobe, 1.8 cm at its greatest diameter and 9 cm deep. (**A**) Color Doppler sonography and power Doppler sonography (**B**) show longitudinal images of the left hepatic lobe. A flash artifact buries a lesion (*arrow*). **C** Digital subtraction angiogram shows tumor staining (*arrow*). **D** Dynamic computed tomography shows nodular enhancement (*arrow*) in the arterial phase. A huge liver cyst is depicted in the right hepatic lobe (*arrowhead*).

Table 2. Detection rate of intratumoral vasculature by the greatest diameter for each hepatic lobe

	≤2 cm	>2 cm
Right lobe		
n	34	23
Power	22 (64.7%)	19 (82.6%)
Color	13 (38.2%)	18 (78.3%)
Left lobe		
n	23	8
Power	7 (30.4%)	6 (75.0%)
Color	5 (21.7%)	4 (50.0%)

Numbers indicate lesions in which vascularity was detected, including those with spotty and curvilinear vascular patterns

Results

Location of lesions

Detection rates of intratumoral vasculature according to lesion location is presented in Table 1. The detection rates in the right hepatic lobe were clearly higher than those in the left hepatic lobe on both color Doppler imaging methods ($p < 0.01$ for power Doppler sonography, $p = 0.023$ for color Doppler sonography, chi-square test). In the left hepatic lobe, motion caused by the heart beat disturbed the effective use of both color Doppler imaging methods (Fig. 2). Power Doppler sonography was significantly superior to color Doppler sonography in the right hepatic lobe ($p < 0.01$, McNemar test) but not in the left hepatic lobe ($p > 0.1$, McNemar test).

Greatest diameter

Detection rates of intratumoral vasculature according to the greatest diameter are presented in Table 2. Power Doppler sonography exhibited a superior detection rate for small lesions compared with color Doppler sonography ($p < 0.01$, McNemar test), but there was no statistical superiority between color Doppler sonography and

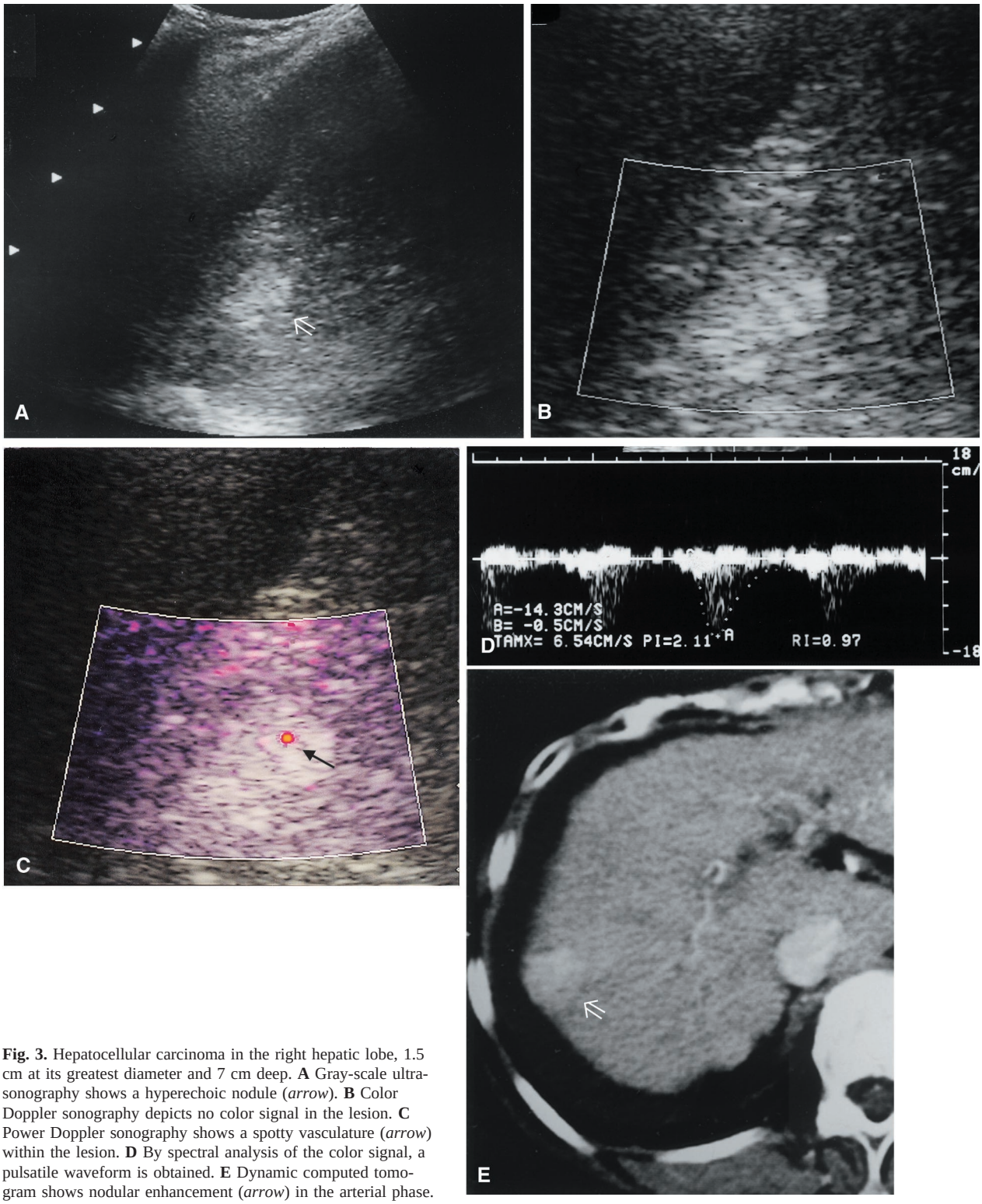


Fig. 3. Hepatocellular carcinoma in the right hepatic lobe, 1.5 cm at its greatest diameter and 7 cm deep. **A** Gray-scale ultrasonography shows a hyperechoic nodule (*arrow*). **B** Color Doppler sonography depicts no color signal in the lesion. **C** Power Doppler sonography shows a spotty vasculature (*arrow*) within the lesion. **D** By spectral analysis of the color signal, a pulsatile waveform is obtained. **E** Dynamic computed tomogram shows nodular enhancement (*arrow*) in the arterial phase.

power Doppler sonography for large lesions in the right hepatic lobe ($p > 0.1$, McNemar test). The greatest diameter statistically affected the capability of color Doppler sonography ($p < 0.01$, chi-square test) but did not affect that of power Doppler sonography in the right hepatic lobe ($p > 0.1$, chi-square test; Fig. 3).

Table 3. Detection rate of intratumoral vasculature analyzed by the depth for each hepatic lobe

	Superficial	Intermediate	Deep
Right lobe			
n	16	29	12
Power	16 (100%)	25 (86.2%)	0 (0.0%)
Color	16 (100%)	15 (51.7%)	0 (0.0%)
Left lobe			
n	14	15	2
Power	10 (71.4%)	3 (20.0%)	0 (0.0%)
Color	9 (64.3%)	0 (0.0%)	0 (0.0%)

Numbers indicate lesions in which vascularity was detected, including those with spotty and curvilinear vascular patterns

There was no statistical difference between power Doppler sonography and color Doppler sonography in evaluating lesions with regard to size in the left hepatic lobe ($p > 0.1$, McNemar test).

Depth

The detection rates of intratumoral vasculature according to depth are presented in Table 3. Power Doppler sonography was superior to color Doppler sonography in the evaluation of intermediate lesions ($p < 0.01$, McNemar test; Fig. 3), but there were no statistical differences between color Doppler sonography and power Doppler sonography for either superficial or deep lesions in the right hepatic lobe. Both color Doppler imagings depicted the intratumoral vasculature of all superficial lesions but none of the deep lesions in the right hepatic lobe (Fig. 4).

There was no statistical difference between power Doppler sonography and color Doppler sonography in the left lobe regarding the depth of lesions ($p > 0.1$, McNemar test).

Gradient in the signal on power Doppler sonography by size and depth

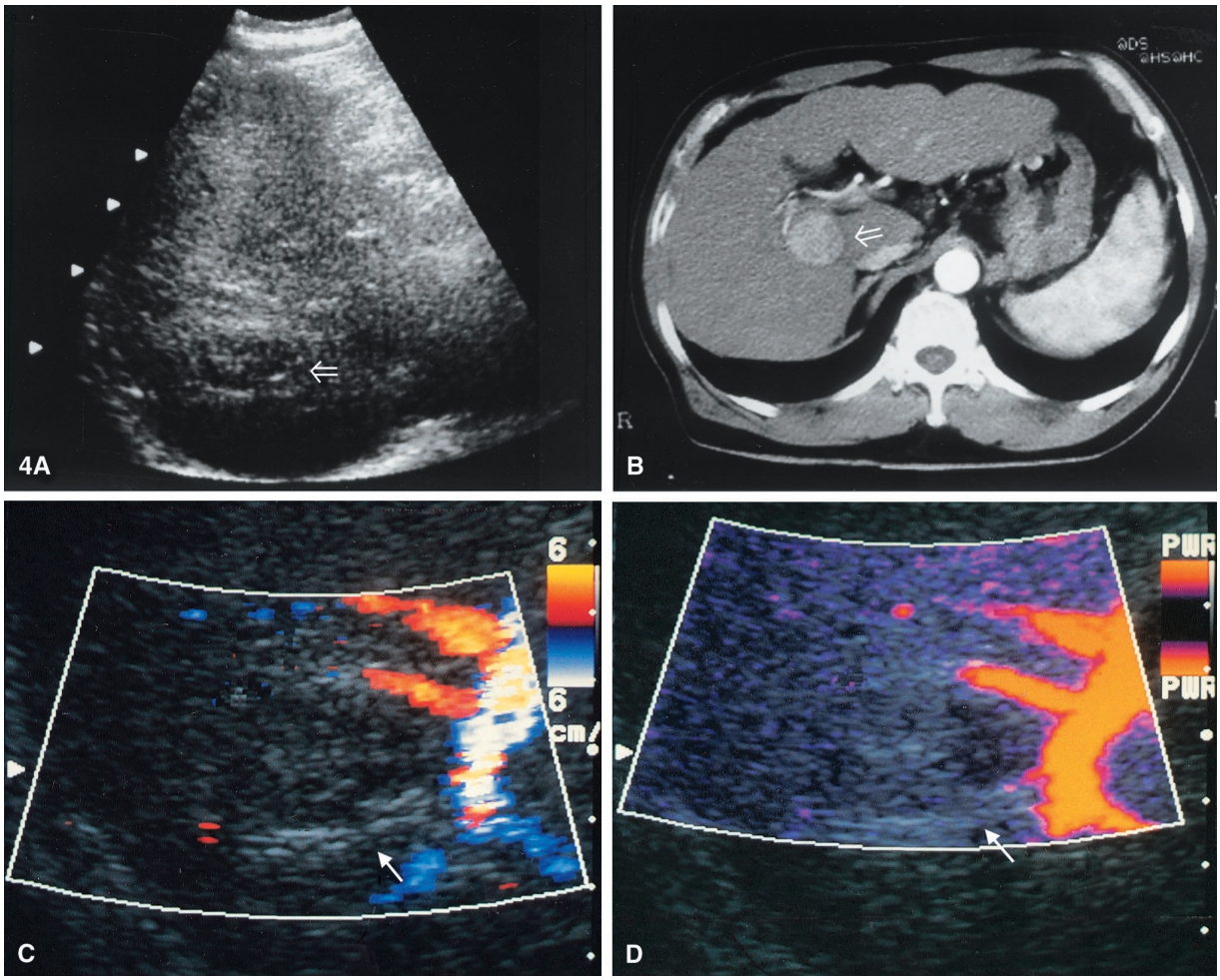
The vascular pattern of power Doppler sonography findings according to greatest diameter and depth is shown in Figure 5 and in Table 4.

In the right hepatic lobe, superficial lesions tended to be curvilinear vascular, and none of the deep lesions had intratumoral vasculature regardless of their greatest diameter. Twenty-five of 29 intermediate lesions had an intratumoral vasculature, whereas small lesions of intermediate depth tended to be spotty vascular in the right hepatic lobe ($p < 0.01$, Fisher's exact probability method was used and the numbers of avascular and spotty vascular were summed for the analysis; Fig. 3). In the left hepatic lobe, superficial lesions also tended to show an avascular pattern.

Discussion

Although color Doppler sonography noninvasively depicts the intratumoral vasculature of hepatic nodules, it has some limitations including noise, which can overwhelm the flow signal, angle dependence, and aliasing [15]. Power Doppler sonography was developed to overcome the limitations of conventional color Doppler sonography. Conventional color Doppler sonography is based on mean Doppler frequency shift, whereas power Doppler sonography displays the integrated power of the Doppler signal in color flow mapping [15, 16]. Power Doppler sonography is relatively angle independent, does not alias, and has an extended dynamic range that increases the sensitivity in comparison with conventional color Doppler sonography [15, 16]. In fact, preliminary studies have indicated that power Doppler sonography is more sensitive to the vasculature of hepatocellular carcinomas [12, 13], normal kidneys [15], and normal testes [17] than conventional color Doppler sonography. Theoretically, however, power Doppler sonography also has some limitations in that the flow detection for power Doppler sonography depends on the target's depth and flash artifacts [15, 16]. Deep lesions should also be negative on vascular on power Doppler sonography because ultrasonic attenuation reduces its sensitivity. In addition, tissue motion causes flash artifacts that overwhelm true signals. Because of its high sensitivity to motion, power Doppler sonography has been presumed to be more susceptible to flash artifacts than conventional color Doppler sonography [15, 16]. Power Doppler sonography showed poor sensitivity for deep lesions and lesions in the left hepatic lobe in this study, and this result was consistent with the theory [15, 16]. In addition, small lesions of intermediate depth tended to have a lower grade vascular pattern in this study. The amount of color signal on power Doppler sonography decreased gradually before it vanished.

Unfortunately, hepatocellular carcinomas generally originate in cirrhotic liver, which strongly attenuates ultrasound [18, 19]. For this reason, ultrasonic attenuation should markedly decrease the depiction rate of the intratumoral vasculature of deeply located hepatocellular carcinomas. A contrast agent for color Doppler sonography has been developed that can be delivered by intravenous injection because of its capability to pass through the transpulmonary capillaries [20]. This contrast agent contributes to the depiction of intratumoral vasculature by color Doppler sonography in deeply located hepatocellular carcinoma [21]. Use of a contrast agent may aid power Doppler sonography like conventional color Doppler sonography, but the contrast agent works effectively only for a few minutes after injection [21, 22], which is insufficient to observe patients with multiple nodules. Advances to overcome the limitations of power Doppler sonography and contrast agents are expected.



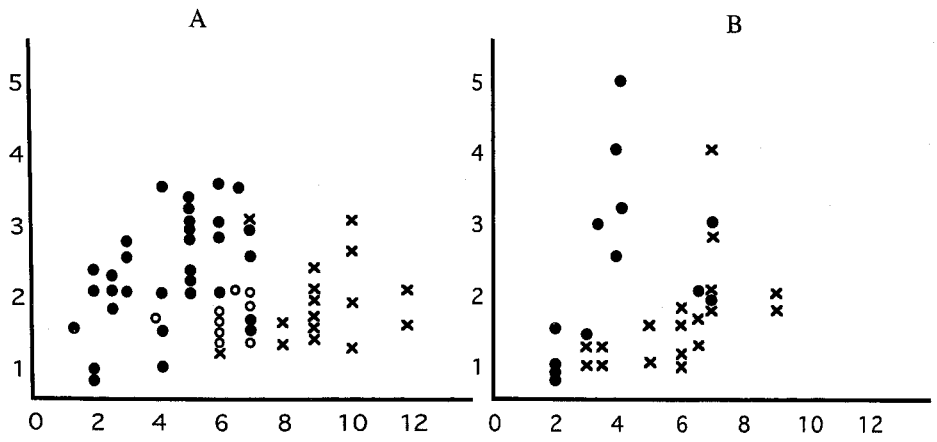


Fig. 4. Hepatocellular carcinoma in the right hepatic lobe, 2.5 cm at its greatest diameter and 10 cm deep. **A** Gray-scale ultrasonography shows a hypoechoic nodule (*arrow*). **B** Dynamic computed tomography shows nodular enhancement (*arrow*) in the arterial phase. Color Doppler sonography (**C**) and power Doppler sonography (**D**) show no color signal within the lesion (*arrow*).

Fig. 5. Gradient in the signal on power Doppler sonography by greatest diameter depth for each hepatic lobe. **A** Right hepatic lobe. **B** Left hepatic lobe. Axial bar indicates depth (cm), and the vertical bar indicates greatest diameter (cm). * avascular; *open circle* spotty vascular; *solid circle* curvilinear vascular.

Power Doppler sonography was more sensitive to small or intermediate-depth lesions than conventional color Doppler sonography in this study. Power Doppler sonography may differentiate hepatic nodules and evaluate the response of nonsurgically treated hepatocellular carcinomas more effectively if applied to small or intermediate-depth lesions, but it is not useful for deep or left lobe lesions because of attenuation and flash artifact.

Conventional color Doppler sonography was relatively insensitive to blood flow, although it was sensitive to large and superficial lesions, similar to power Doppler sonography. Conventional color Doppler sonography

Table 4. Gradient in the signal on power Doppler sonography by greatest diameter and depth for each hepatic lobe

		Superficial	Intermediate	Deep
Right lobe				
n		16	29	12
≤2 cm	Avas	0	3	9
	Spot	1	8	0
	CL	9	4	0
>2 cm	Avas	0	1	3
	Spot	0	0	0
	CL	6	13	0
Left lobe				
n		14	15	2
≤2 cm	Avas	4	10	2
	Spot	0	0	0
	CL	5	2	0
>2 cm	Avas	0	2	0
	Spot	0	0	0
	CL	5	1	0

Numbers indicate each vascular pattern lesion. Avas, avascular; spot, spotty vascular; CL, Curvilinear vascular

may also be a useful noninvasive vascular detection tool because it can depict flow direction, which power Doppler sonography cannot. For instance, conventional color Doppler sonography can easily depict a characteristic centrifugal spoke-wheel vascular pattern in focal nodular hyperplasia [23, 24], but power Doppler sonography cannot.

In summary, power Doppler sonography can evaluate small or intermediate-depth hepatocellular carcinomas more effectively than conventional color Doppler sonography, but it is less satisfactory for left lobe or deep lesions because of limitations caused by attenuation and flash artifact.

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