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Quantitative flow measurements for classification of ovarian tumors by transvaginal color Doppler sonography in postmenopausal patients

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ABSTRACT

Color Doppler and Duplex measurements were obtained in 83 (42 benign, 41 malignant) ovarian tumors in postmenopausal patients. An ATL UM9/HDI was used. The following flow criteria were analyzed: lowest resistance index (RI) and pulsatility index (PI), total number of arteries and number of central arteries and the maximum, mean and sum of systolic, end-diastolic and time-averaged maximum velocities of all intratumoral vessels. In 98% of malignant and in 85% of benign lesions, vessels were detected. All flow criteria showed highly significant differences between benign and malignant tumors ($p < 0.0001$). However, there was a considerable overlap between benign and malignant tumors (e.g. the median of the lowest RI was 0.62 (range 0.26–1.0) for benign and 0.40 (0.22–0.66) for malignant tumors; the median of the maximum systolic velocity was 17.5 cm/s (range 5.2–61.5 cm/s) for benign and 47.05 cm/s (14.6–105.0 cm/s) for malignant tumors).

Differentiation of malignant tumors by the lowest RI and PI, number of arteries and maximum of systolic flow velocities gave a sensitivity of 77–85%, specificity of 77–83% and accuracy of 80–84%. Differentiation was superior by calculation of the maximum end-diastolic velocities and by the summation of the systolic, end-diastolic and time-averaged maximum flow velocities: sensitivity 90–95%, specificity 83–86% and accuracy 87–91%. This study confirms that a single measurement is not sufficient for an accurate differentiation of ovarian lesions and, besides the measurement of minimum RI and PI, the measurements of flow velocities as Doppler criteria play an important role.

INTRODUCTION

The increased metabolism of neoplastic tissue requires the formation of new tumor vessels[1]. Arteries in malignancies typically lack the muscle layer and have an increased permeability. Increased vascularity and arteriovenous shunts cause decreased peripheral blood flow resistance and increased diastolic flow compared to benign lesions[2-4].

The quality of color Doppler instruments has improved dramatically over the last few years, with an increased sensitivity for detection of small amounts of blood flow. This is essential for accurate measurements of tumor vascularity and an increased number of studies have been published recently, in which color Doppler has been used for tumor differentiation[5-17]. It has even been reported that this technique might improve the diagnosis of early stage I ovarian cancers[18].

Diagnostic criteria and results of different studies show remarkable differences. Measurements of the resistance index (RI) and pulsatility index (PI) give a description of the typical flow profile. In some of the studies, this allowed an accuracy of more than 95% for the differentiation of benign and malignant tumors[11,18]. Other groups have reported that this parameter alone is not specific enough and allows only an accuracy of about 80%[5,14,19]. Differences are even more apparent when comparing the detection rate of vessels in benign ovarian tumors, in a range between 2% and 100%[4,5,7,8,10,12-17,20,21]. In order to improve the diagnostic accuracy of transvaginal color Doppler sonography, additional blood flow measurements have been performed. Some analyses have included measurements of blood flow velocity, the diastolic notch and the localization of the tumor vessels in addition to the RI and PI[21-23]. A comparison of the results is difficult because of technical differences and patient

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selection, and until now no standardized examination technique has been defined, and none of the single flow parameters is specific.

In earlier studies we made similar observations when we investigated the vascularity of breast lesions[24]. Based on our experience, we initiated a prospective study using transvaginal color Doppler sonography and Duplex measurements for the differentiation of benign and malignant ovarian tumors in postmenopausal patients. We investigated the RI, PI, the number and localization of the intratumoral arteries and measured systolic, end-diastolic and time-averaged maximum flow velocities in all of the intratumoral vessels.

METHODS

Patients

Eighty-three consecutive unselected postmenopausal patients with suspected ovarian masses were investigated preoperatively by transvaginal color Doppler sonography at the Department of Obstetrics and Gynecology of the University of Freiburg from July 1992 to July 1993. 'Consecutive unselected patients' included all postmenopausal patients undergoing an operation because of an ovarian tumor. The patients of the Department of Obstetrics and Gynecology of the University of Freiburg are highly selected and not representative of the normal population. Forty-two of the 83 tumors were benign and 41 were malignant or borderline ($n = 5$). Two of the 36 ovarian carcinomas were stage I, two stage II, 26 stage III and six stage IV. The histopathological findings and the sonographic measurements of tumor size are summarized in Table 1. Patients with benign tumors had a similar age distribution (median, 63.5; range, 50–83 years) compared to patients with malignancies (median, 64; range, 49–84 years). The clinical management was independent of the results of transvaginal color Doppler sonography.

Examination technique

Transabdominal B-mode (TAS) examination was always followed by transvaginal scanning with the patient in the supine position and with an empty bladder. For color Doppler sonography, an Ultramark 9 HDI (ATL) with a curved array vaginal probe (CIVT 5) was used, with sector angle of 150°, 4-MHz Doppler frequency and dynamic focusing between 1.2 cm and 6.9 cm. The filter was set at 50–100 Hz and, depending on the penetration depth, the pulse repetition rate was kept low. Color gain was adjusted just below the background noise level to increase as far as possible the Doppler sensitivity for low flow detection. The examination of large tumors (diameter > 10 cm) was combined with transabdominal color Doppler sonography with a curved array transducer (C3 40R; 3 MHz).

A careful survey of the vessels was made in each tumor by color Doppler. The total number of intratumoral vessels was counted and their localizations were noted at the tumor margin, in septae or centrally (i.e. at one or more centimeters) from the tumor margin in solid tumors. Additionally, detailed measurements were made on the flow velocity waveforms in all of the vessels. The angle of insonation was always adjusted to obtain the best signal, allowing for maximum flow velocity measurement. The measurements were performed more carefully than in the routine clinical procedure and great care was taken for accurate data collection, with an examination time of 30–60 min in highly vascularized tumors.

The following flow criteria were analyzed (Table 2): RI_{min}, RI_{mean}, PI_{min}, PI_{mean}, total number of intratumoral arteries and central arteries. Maximum and mean flow velocity and the sum of all flow velocities were measured and calculated in each tumor for maximum systolic (S_{max}, S_{mean}, S_{sum}), maximum end-diastolic (D_{max}, D_{mean}, D_{sum}) and time-averaged maximum velocities (M_{max}, M_{mean}, M_{sum}). The sum of all maximum systolic velocities of a tumor (S_{sum}), for example, was calculated by summation of the peak systolic velocity of each vessel in a tumor. The summation of all flow velocities in each tumor

Table 1 Histopathological diagnosis and sonographic measurement of tumor size of 83 ovarian tumors in postmenopausal patients analyzed by transvaginal color Doppler sonography

		Tumor diameter (cm)	
Histopathological diagnosis	*Number*	*Mean*	*Range*
Benign tumors ($n = 42$)			
Endometrioma	2	6.7	5.5–8
Dermoid cyst	1	5.5	
Fibroma	5	6.5	4–10
Serous cystadenoma	21	5.5	1.5–22
Mucinous cystadenoma	4	14.5	7–33
Cystadenofibroma	9	8.2	4–20
Malignant tumors ($n = 41$)			
Ovarian carcinoma	36	9.9	2–20
Borderline tumor	5	15.0	11–18

Table 2 Flow criteria investigated by transvaginal color Doppler sonography

Indices		
RI_{min}	lowest resistance index of all tumor arteries	
RI_{mean}	mean of all resistance indices of a tumor	
PI_{min}	lowest pulsatility index of all tumor arteries	
PI_{mean}	mean of all pulsatility indices of a tumor	
Vascularity detection		
Arteries	total number of tumor vessels	
Arteries-c	number of central tumor arteries	
Flow velocity analysis of tumor arteries		
S_{max}	maximum	of all maximum systolic flow velocities
S_{mean}	mean	
S_{sum}	sum	
D_{max}	maximum	of all maximum end-diastolic flow velocities
D_{mean}	mean	
D_{sum}	sum	
M_{max}	maximum	of all time-averaged maximum flow velocities
M_{mean}	mean	
M_{sum}	sum	

seemed most appropriate to express the total amount of tumor vascularity (S_{sum}, D_{sum}, M_{sum}).

The RI is defined as the difference between the maximum systolic (A) and end-diastolic (B), divided by systolic (A) flow velocity: $RI = (A - B)/A$. The PI is defined as the difference between the maximum systolic (A) and end-diastolic (B), divided by time-averaged maximum flow velocity (V_{mean}): $PI = (A - B)/V_{mean}$.

Statistical analysis

Spearman's rank correlation coefficient was calculated to analyze the relationship between age and PI_{min}, RI_{min}, S_{max}, D_{max} and S_{sum}. The distribution of the measurements in benign and malignant tumors was compared using the Mann–Whitney–Wilcoxon rank test[25]. Sensitivity, specificity and diagnostic accuracy were calculated to compare the validity of flow data for the differentiation between benign and malignant tumors. Cut-off values were derived from our data with the aim of separating the distribution of the benign and malignant tumors with the highest diagnostic accuracy, sensitivity and specificity. Therefore the given estimates of the sensitivity, specificity and diagnostic accuracy may if anything be 'too optimistic'. The statistical analysis of the number of vessels included all 83 tumors. The distribution of all the other criteria included only tumors in which at least one vessel could be detected and measured.

RESULTS

In 75 of the 83 (90%) ovarian tumors, up to 19 vessels were detected. This allowed flow measurements in 98% of the malignant and 83% of the benign tumors. No vessel could be found in one of the 41 malignancies, in one dermoid cyst and in six of 21 serous cystadenomas.

The flow data were not found to be age-dependent. The correlation coefficients between age and PI_{min}, RI_{min}, S_{max}, D_{max} and S_{sum} were between 0.18 and 0.33 in benign tumors. Correlation coefficients in malignant tumors were between 0.01 and 0.23.

The median of the flow data and the range of the distribution are provided in Table 3. All flow data show highly significant differences between benign and malignant tumors ($p < 0.0001$). However, the range of the measurements in benign and malignant tumors shows considerable overlap. This is demonstrated in the frequency distribution of RI_{min}, PI_{min}, number of arteries, S_{max}, S_{sum}, D_{max}, D_{sum} and M_{sum} (Figures 1–8). The diagnostic accuracies of all the flow criteria are different with a varying degree of overlap.

For all the flow criteria, sensitivity, specificity and diagnostic accuracy were calculated at different cut-off points to provide optimal values (e.g. 0.3, 0.35, 0.4, 0.45, 0.5 . . . for RI_{min}) (Table 4). For RI_{min}, the best cut-off point was 0.5, giving an accuracy of 81.3%. The cut-off point 0.7 for PI_{min} allowed an accuracy of 80%. The cut-off point for S_{max} was 30 cm/s, for D_{max} 10 cm/s and for M_{max} 15 cm/s, giving an accuracy of 80%, 86.7% and 82.7%, respectively.

Calculation of the average flow values in all intratumoral vessels (RI_{mean}, PI_{mean}, S_{mean}, D_{mean}, M_{mean}) was less specific compared with the selection of the vessels with the lowest RI or PI value or with the maximum systolic, end-diastolic and time-averaged flow velocity. The number of total and central tumor vessels was of equal value in differentiating between benign and malignant tumors with 82% and 84% accuracy, respectively. The summation of flow velocities in each tumor (S_{sum}, D_{sum}, M_{sum}) increased the accuracy to 90%.

Table 3 Median and range of transvaginal color Doppler measurements of 83 ovarian tumors in postmenopausal patients. For abbreviations, see Table 2

	Benign tumors (n = 42)		*Malignant tumors* (n = 41)		
Measurement	*Median*	*Range*	*Median*	*Range*	*p value**
RI_{min}	0.62	0.26–1.00	0.40	0.22–0.66	< 0.0001
RI_{mean}	0.71	0.39–1.00	0.55	0.27–0.71	< 0.0001
PI_{min}	0.98	0.31–5.84	0.53	0.25–1.22	< 0.0001
PI_{mean}	1.45	0.49–5.84	0.94	0.32–1.5	< 0.0001
Arteries	2	0–8	9	0–19	< 0.0001
Arteries-c	0	0–4	5	0–17	< 0.0001
S_{max} (cm/s)	17.5	5.2–61.5	47.05	14.6–105.0	< 0.0001
S_{mean} (cm/s)	12.9	5.2–61.5	24.3	11.3–56.6	< 0.0001
S_{sum} (cm/s)	42.0	5.0–649.0	218.5	27.0–662.0	< 0.0001
D_{max} (cm/s)	4.4	0–18.6	16.6	5.9–48.0	< 0.0001
D_{mean} (cm/s)	3.0	0–16.4	10.45	3.8–20.3	< 0.0001
D_{sum} (cm/s)	9.0	0–113.0	80.0	15.0–351.0	< 0.0001
M_{max} (cm/s)	9.3	2.0–33.4	27.85	10.1–65.5	< 0.0001
M_{mean} (cm/s)	6.4	2.0–21.7	16.5	6.8–28.9	< 0.0001
M_{sum} (cm/s)	20.0	2.0–156.0	134.5	19.0–473.0	< 0.0001

*Mann–Whitney–Wilcoxon rank test

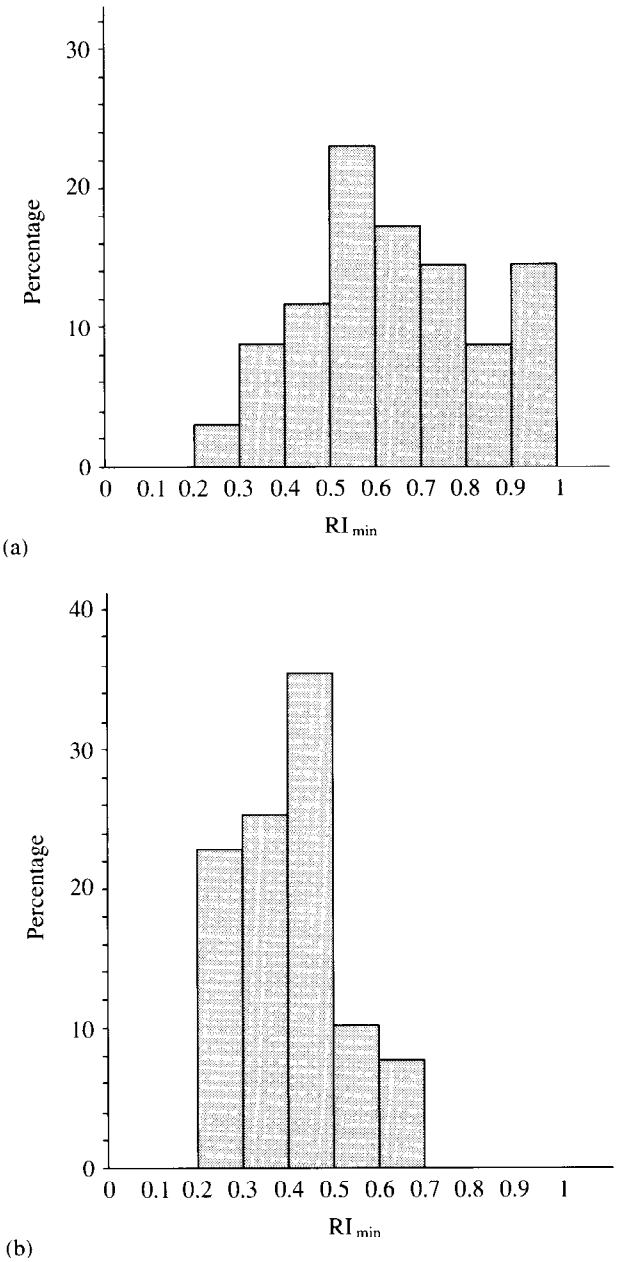

Figure 1 Distribution of the lowest resistance index (RI_{min}) in 75 benign (a) and malignant tumors (b) of postmenopausal patients

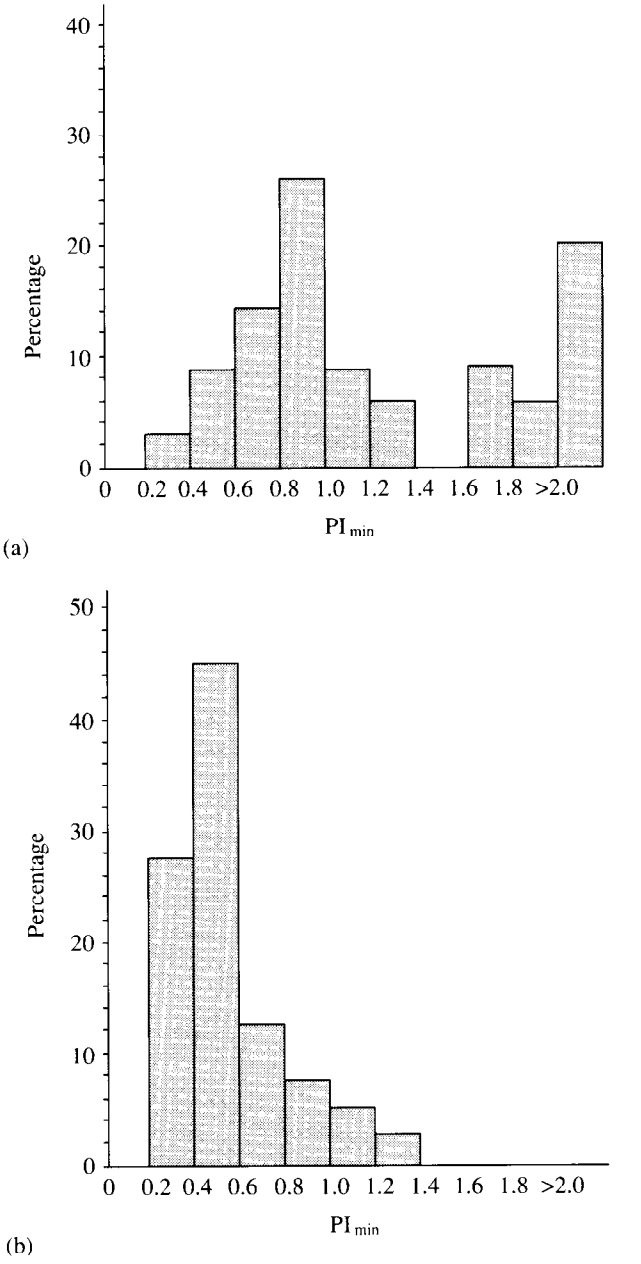

Figure 2 Distribution of the lowest pulsatility index (PI_{min}) in 75 benign (a) and malignant tumors (b) of postmenopausal patients

DISCUSSION

Most studies report abnormal tumor vessels in almost all malignant ovarian tumors[7,17,20]. In contrast, the vascularity detection described in benign tumors shows a wide discrepancy, from 2% to 100%[4,5,7,8,10,12,17,20,21]. These differences may be due to different patient selection. However, it is more likely that the discrepancies are related to different color Doppler sensitivity in the equipment. Among 83 postmenopausal patients, Kurjak and colleagues could detect vessels in 27 of 29 (93%) malignant ovarian tumors but only in 19 of 54 (35%) benign tumors[12].

Tekay and Jouppila reported that average indices, RI_{mean} and PI_{mean}, of all tumor vessels do not allow sufficient differentiation. In agreement with our results, the diagnostic accuracy was only 74–77%[14]. The accuracy of the average of the flow velocity measurements (S_{mean}, D_{mean}, M_{mean}) is lower compared to the analysis of the maximum flow velocities. Our results show that the distribution of flow data such as RI_{mean} or S_{mean} shows more overlap between benign and malignant tumors than RI_{min} or S_{max}. As a result of heterogenicity within one tumor, vessels with high flow resistance can be distinguished from typical vessels with low flow resistance. The typical flow velocities in malignancies are increased. However, in a careful examination with sensitive color Doppler equipment, one will also detect vessels with low flow velocity in malignant tumors and vessels with low resistance in benign tumors. Therefore, the differences between benign and malignant flow data are diminished if the average for all vessels is calculated.

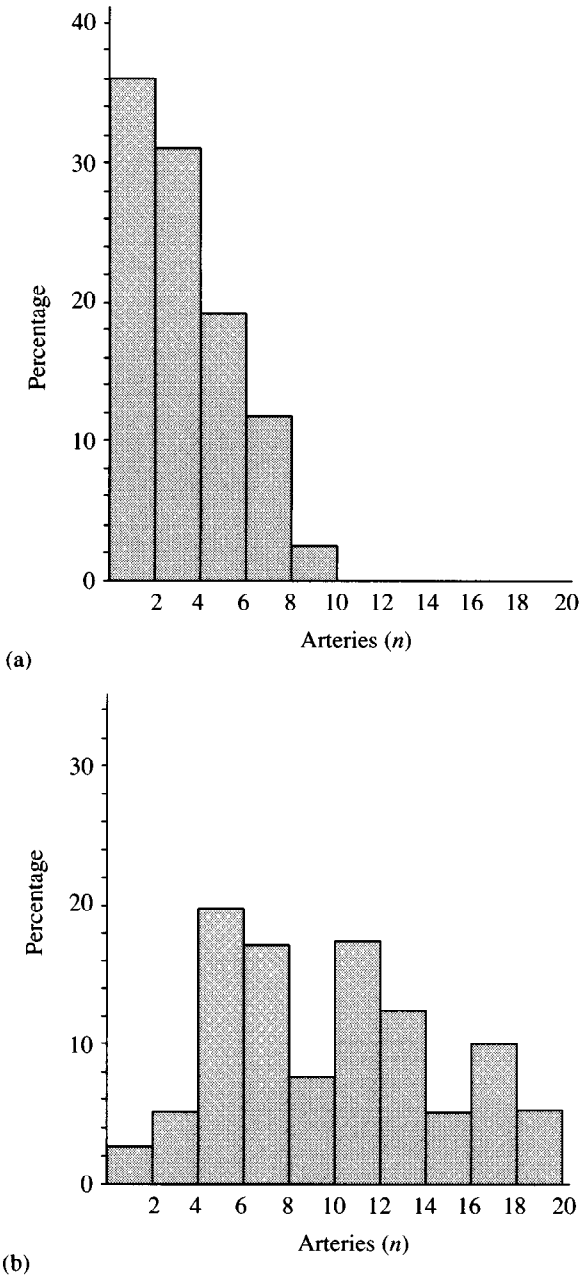

Figure 3 Distribution of number of intratumoral arteries in 83 benign (a) and malignant tumors (b) of postmenopausal patients

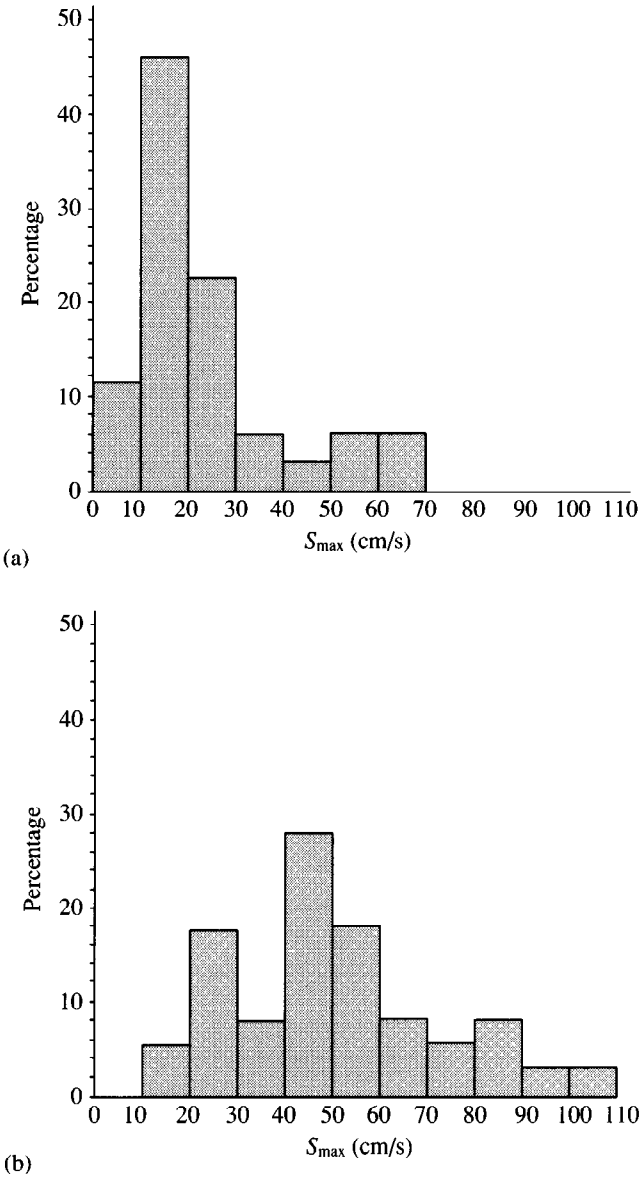

Figure 4 Distribution of maximum systolic flow velocity of all tumor arteries (S_{max}) in 75 benign (a) and malignant tumors (b) of postmenopausal patients

The correlation between RI_{min} and PI_{min} is high in benign and malignant ovarian tumors[19]. For the correlation between RI_{min} and PI_{min}, we found a coefficient of 0.99 with an accuracy of 81% for RI_{min} and 80% for PI_{min}. This allows us to use both criteria equally, which contradicts the findings reported by Kurjak and colleagues[21].

Our results are in good agreement with those of Fleischer and colleagues, who found a significant difference between PI_{min} in benign and malignant tumors, but the overlap did not allow an accurate differentiation. With the cut-off value of 1.0, the sensitivity and specificity for PI_{min} were 80% and 84%, respectively[5,6]. In contrast, Kurjak and co-workers found a very high sensitivity of 96–100%, a specificity of 97–99.8% and a diagnostic accuracy of 98–99% using 0.4 as cut-off point for the RI value[9,11]. Our optimum cut-off values are different from those used by Fleischer and colleagues[5,6] and Kurjak and colleagues[9,11]. For a cut-off value of 1.0 for PI_{min} used by Fleischer and colleagues[5,6], we reached a sensitivity of 92.5%, a specificity of 48.6% and an accuracy of 72% in this study. For a cut-off value of 0.4 for RI_{min} used by Kurjak and colleagues[9,11] we reached a sensitivity of 55%, a specificity of 88.6% and an accuracy of 72%. This demonstrates the difficulty of comparing different results and defining optimum cut-off values[26]. Flow data are operator- and equipment-dependent and need a standardized examination technique and comparable ultrasound equipment before color Doppler sonography will be established.

Often, the direction of tumor vessels cannot be determined exactly by color Doppler. Therefore, we did not perform angle corrections for Duplex measurements, in

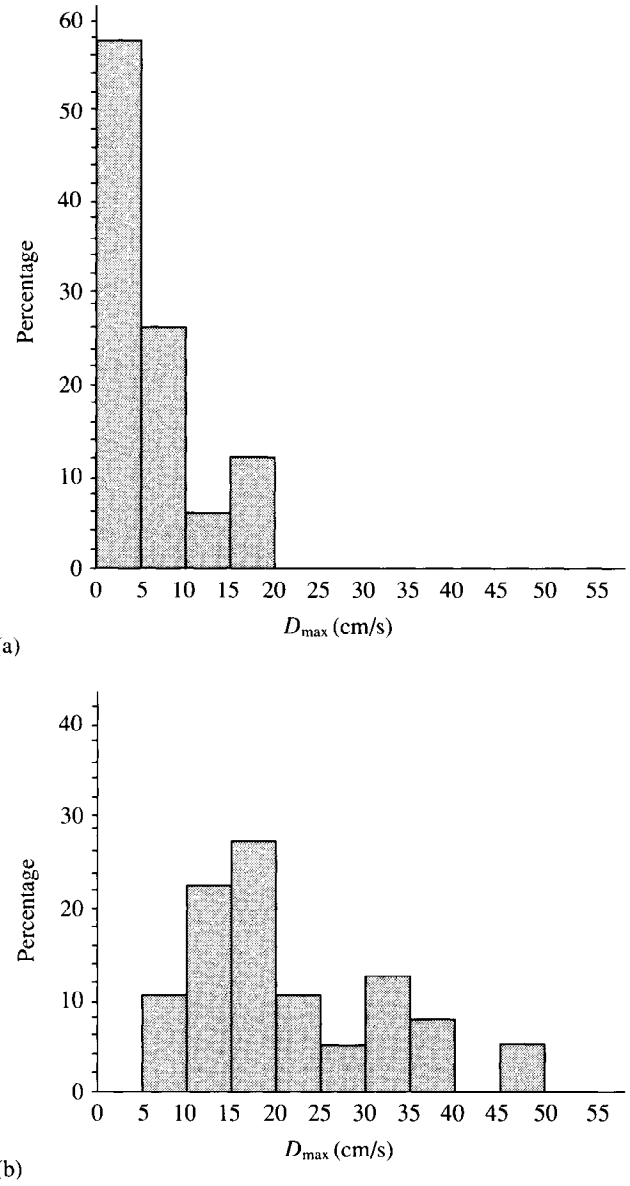

Figure 5 Distribution of maximum diastolic flow velocity of all tumor arteries (D_{max}) in 75 benign (a) and malignant tumors (b) of postmenopausal patients

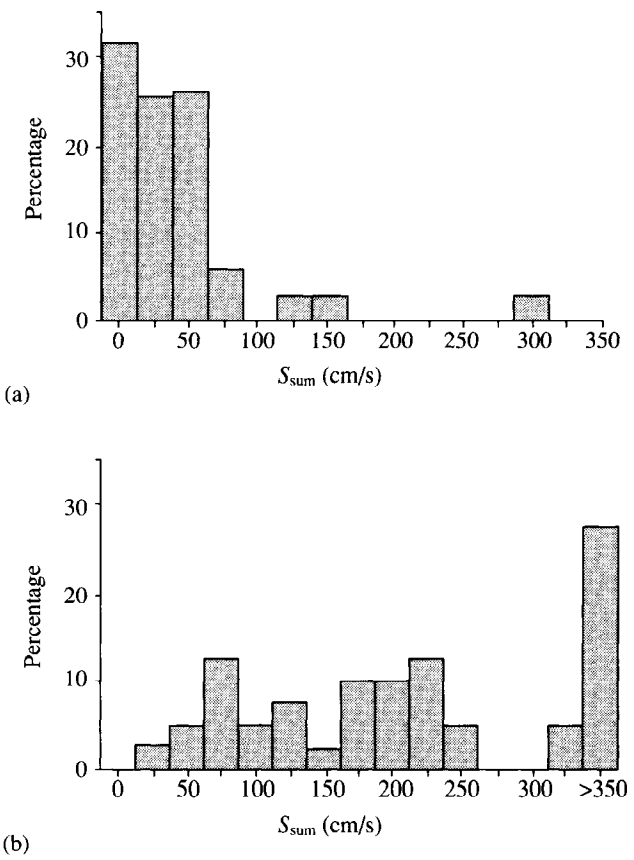

Figure 6 Distribution of the sum of systolic flow velocities of all tumor arteries (S_{sum}) in 75 benign (a) and malignant tumors (b) of postmenopausal patients

order to avoid subjective or systematic failures in the measurements. Therefore, an over-estimation of flow velocities can be excluded in our results. In accordance with our results (Table 3), Fleischer and associates[22] found, in 25 benign ovarian tumors, a mean systolic flow velocity of 17.4 cm/s (range, 3–37 cm/s) after correction for angle of insonation. Kurjak and colleagues[21] found, in 49 of 216 benign tumors, an increased average flow velocity of 20.2–27.3 cm/s, depending on the localization. Fleischer and colleagues measured an average flow velocity of 19.4 cm/s (range, 7–61 cm/s) in 25 malignant tumors[22] and Kurjak and colleagues[21] found flow velocities of 14.4–26.2 cm/s in 37 malignant tumors. Contrary to our results (Table 3), both groups did not find significant differences between flow velocities in benign and malignant tumors. Pellerito and colleagues[27] agreed with our results that malignancies tend to contain vessels with high flow velocity compared to those of benign lesions.

Although the number of intratumoral arteries and the flow velocities in these vessels are correlated (correlation coefficient between arteries and S_{max}, D_{max} and M_{max}: 0.4–0.5), the combination of both criteria should be useful for differentiation. Therefore, we summed all systolic, diastolic and mean flow velocities measured in each tumor (S_{sum}, D_{sum}, M_{sum}) and this increased the diagnostic accuracy to 90%.

Because we derived the cut-off values from our own data with the aim of separating the distribution of the benign and malignant tumors, the given estimates are probably too optimistic and have to be estimated from an independent study. Also, the cut-off values have to be tested in another study, with a larger sample size. Because transvaginal color Doppler sonography was performed by one examiner (H.J.P.), the interobserver variability also needs to be tested.

CONCLUSION

The versatile hemodynamic flow data of ovarian tumors measured in this study are able to increase our knowledge of the hemodynamic characterization and differences between benign and malignant tumors. Our results indicate that measurements of flow velocities (maximum

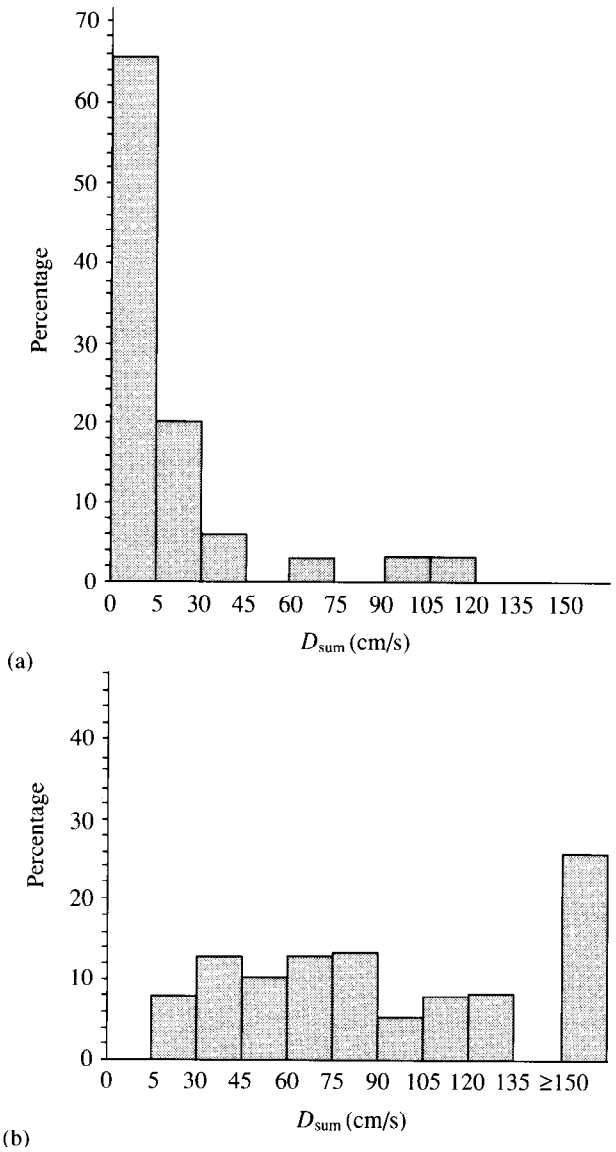

Figure 7 Distribution of the sum of diastolic flow velocities of all tumor arteries (D_{sum}) in 75 benign (a) and malignant tumors (b) of postmenopausal patients. (In (b), the last bar represents all values ≥ 150)

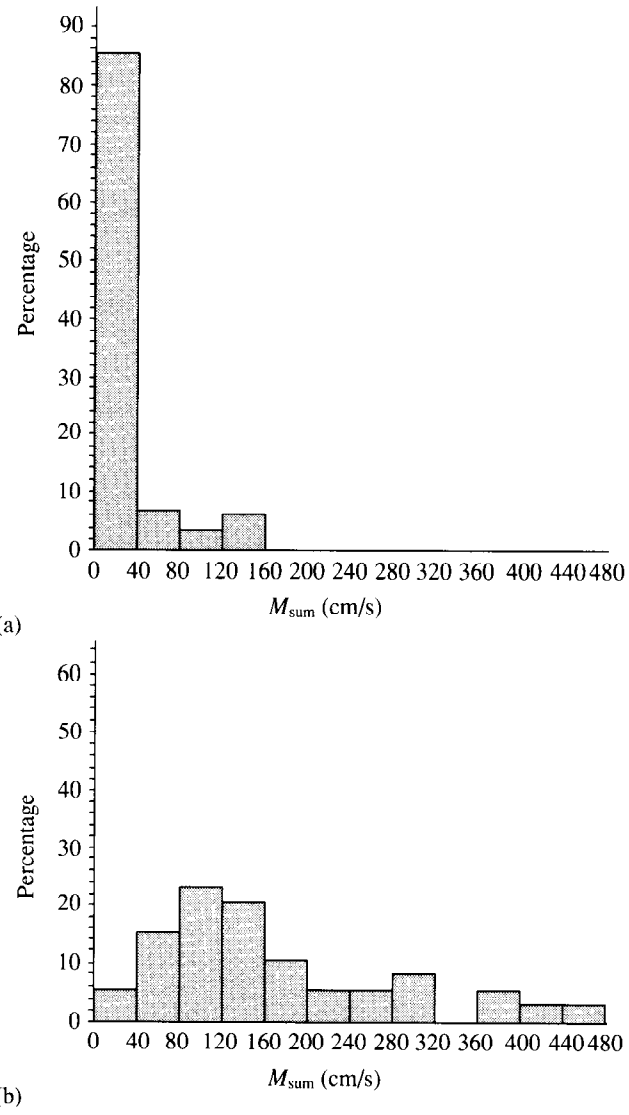

Figure 8 Distribution of the sum of time-averaged maximum flow velocities of all tumor arteries (M_{sum}) in 75 benign (a) and malignant tumors (b) of postmenopausal patients

Table 4 Validity of transvaginal color Doppler flow criteria for classification of 83 ovarian tumors in postmenopausal patients. For abbreviations, see Table 2

Measurement	*Cut-off value*	*Sensitivity* (%)	*Specificity* (%)	*Accuracy* (%)
RI_{min}	0.5	85	77.1	81.3
RI_{mean}	0.65	77.5	68.6	73.3
PI_{min}	0.7	82.5	77.2	80
PI_{mean}	1.1	77.5	77.1	77.3
Arteries	4	80.5	83.3	81.9
Arteries-c	0	85.4	83.3	84.3
S_{max}	30 cm/s	77.5	82.9	80
S_{mean}	20 cm/s	75	72.2	74.7
S_{sum}	75 cm/s	92.5	82.9	88
D_{max}	10 cm/s	90	82.9	86.7
D_{mean}	5 cm/s	92.5	75.8	82.7
D_{sum}	30 cm/s	92.5	85.7	89.3
M_{max}	15 cm/s	87.5	82.9	82.7
M_{mean}	10 cm/s	85	81.8	81.3
M_{sum}	40 cm/s	95	85.7	90.7

systolic, diastolic and time-averaged maximum velocity and summation of all flow velocities) allow a better differentiation compared to measurement of minimum resistance and pulsatility indices. Because of the overlap of different flow data, tumor differentiation with a single criterion is limited. Improved differentiation may be achieved by combining qualitative criteria such as the analysis of flow profiles[6], or by classification of vascularization types[22].

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