Is There a Role for Color Doppler Ultrasonography in Acute Cholecystitis?

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Abstract
Objective. The aim of this study was to evaluate the utility of the Pulsatility Index (PI) of the right hepatic artery, measured by color Doppler sonography, in the diagnosis of acute cholecystitis. **Methods.** Seventy-five subjects were included in this study and divided into three groups, each consisting of 25 subjects: the cholecystitis group, the asymptomatic cholelithiasis group, and normal controls. Patients with acute cholecystitis fulfilled all the diagnostic criteria as stated in the latest Tokyo Guidelines. In all patients, the right hepatic artery was detected by color Doppler ultrasound and the PI was measured. **Results**. Patients with acute cholecystitis were found to have significantly higher PI values compared to both normal controls and cholelithiasis patients. Regression analysis revealed a significant positive correlation between the PI and the cholecystitis outcome. **Conclusion.** Measurement of PI by color Doppler ultrasound represents a useful aid in the diagnostic process of acute cholecystitis. More studies are needed before this method is incorporated in the relevant guidelines.

Key Words: Cholecystitis ▪ Pulsatility Index ▪ Color Doppler Sonography ▪ Right Hepatic Artery.

Introduction

The diagnosis of acute cholecystitis relies upon a combination of clinical, laboratory and imaging findings (1). Ultrasonography (US) represents the first line imaging tool for diagnosing acute cholecystitis. Sonographic findings suggestive of acute cholecystitis are wall thickening, pericholecystic fluid and gallbladder distention. Moreover, the presence of a sonographic Murphy's sign is highly indicative of acute cholecystitis. The accuracy of US in the diagnosis of acute cholecystitis has been extensively studied; sensitivity and specificity rates of 88% and 80% have been reported, respectively (2).

Nevertheless, a subset of patients present diagnostic difficulties, rendering the diagnosis of acute cholecystitis quite challenging (3). In approximately 10% of patients US fails to provide a definite imaging diagnosis of acute cholecystitis (4). The sonographic finding of gallbladder wall thickening is common in both acute and chronic cholecystitis. In the former condition wall thickening represents an inflammatory edema of the wall on the grounds of hyperemia, while in the latter it is caused by the formation of fibrous scar tissue in the chronic setting. Furthermore, several chronic conditions, such as heart failure and cirrhosis, have been correlated with gallbladder wall thickening (5, 6). Last but not least, detection of a sonographic Murphy's sign, which is a key diagnostic finding, may be biased by analgesics administered to the patient (7).

Advances in sonographic imaging have provided the potential of overcoming these limitations of US. Color Doppler US and, more recently, power Doppler US have been used to measure several different parameters regarding blood flow in the affected area (7). The working hypothesis is that acute inflammation is accompanied by hyperemia in the affected organ. These parameters have been

evaluated in the gallbladder wall flow, hepatic artery flow, and right hepatic artery flow or, less commonly, cystic artery flow. Nevertheless, their use in the diagnosis of acute cholecystitis has not yet been widely adopted because relevant data are still scarce as well as conflicting.

The aim of this study was to evaluate the role of the right hepatic artery Pulsatility Index (PI), measured by color Doppler US, in the diagnosis of acute cholecystitis. The PI is a calculated flow parameter on ultrasound, derived from the maximum, minimum and mean Doppler frequency shifts during a defined cardiac cycle (8).

Patients and Methods

This study was performed in line with the principles of the Declaration of Helsinki of 1975 and its amendments from 1983. Permission for the study was obtained from the Institutional Ethics Committee (approval number: 75/5-6-2019, General Hospital of Amfissa). Informed consent was obtained from all individual participants included in the study. Seventy-five subjects that underwent color Doppler US of the right hepatic artery over a 1-year period were included in this study. All participants were examined after a fast of at least 6 hours. In emergency cases, where the gallbladder was found to be contracted on US examination, the patient was admitted and re-examined at least 6 hours later. Data were collected prospectively. Subjects were assigned to one of three groups, each consisting of 25 patients: (1) the control group consisting of asymptomatic volunteers with normal gallbladders; (2) the cholelithiasis group including asymptomatic patients with gallbladder cholelithiasis without any other abnormal US find-

ings; (3) the acute cholecystitis group consisting of patients with a definite diagnosis of acute calculous cholecystitis, according to the latest Tokyo Guidelines (1) (Table 1).

Patients with equivocal findings were excluded from the analysis, in an attempt to counterbalance the non-availability of pathological confirmation of acute cholecystitis. Exclusion criteria also included the following comorbidities: choledocholithiasis (due to the fact that concurrent cholangitis may affect hepatic artery velocity, thus acting as a confounding factor); pancreatitis, congestive heart failure, liver cirrhosis, renal failure, hypoalbuminemia, and hepatitis (due to the fact that these conditions are known to cause gallbladder wall thickening thus being potential confounders) (5, 6, 9); arteriosclerosis, decreased intravascular volume due to severe dehydration, and hyperdynamic circulatory state due to high fever (because PI measurement is greatly affected by the condition of the arteries, the circulating blood volume and a hyperdynamic circulation state).

All patients were examined by a single consultant radiologist using a 2.5-5.5 MHz curved array or vector transducers, and a Voluson™ S8 BT16 (GE Healthcare, Waukesha, WI) US machine. Gray-scale upper abdominal US was followed by color Doppler US of the right hepatic artery. An attempt was made to evaluate blood flow in the cystic artery, but it was only feasible in a minority of cases. The Pulsatility Index (PI) was measured in all patients. Typical PI measurements in patients with uncomplicated cholelithiasis and acute cholecystitis are shown in Figures 1 and 2 respectively. The radiologist was intentionally not informed about the laboratory results of the patients.

Table 1. TG18/TG13 Diagnostic Criteria for Acute Cholecystitis

A. Local signs of inflammation: (1) Murphy's sign, (2) RUQ mass/pain/tenderness
B. Systemic signs of inflammation: (1) fever, (2) elevated CRP, (3) elevated WBC count
C. Imaging findings: Characteristic of acute cholecystitis
Suspected diagnosis: One item in A + one item in B
Definite diagnosis: One item in A + one item in B + C

CRP=C-reactive protein; RUQ=Right upper abdominal quadrant; WBC=White blood cell count.
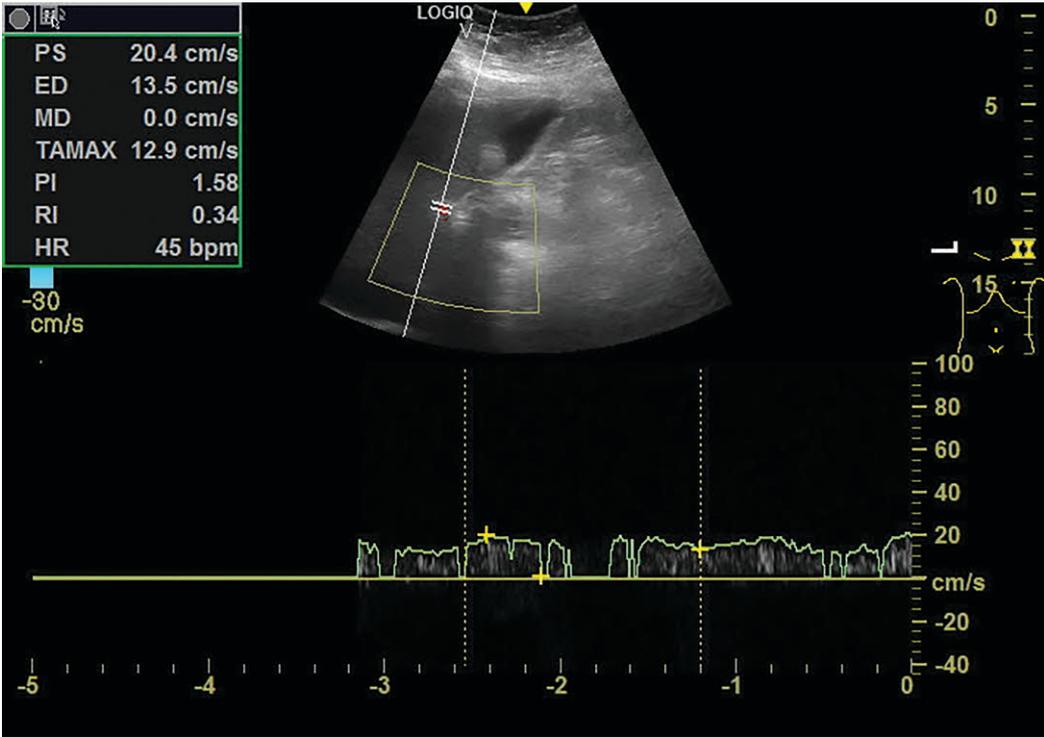
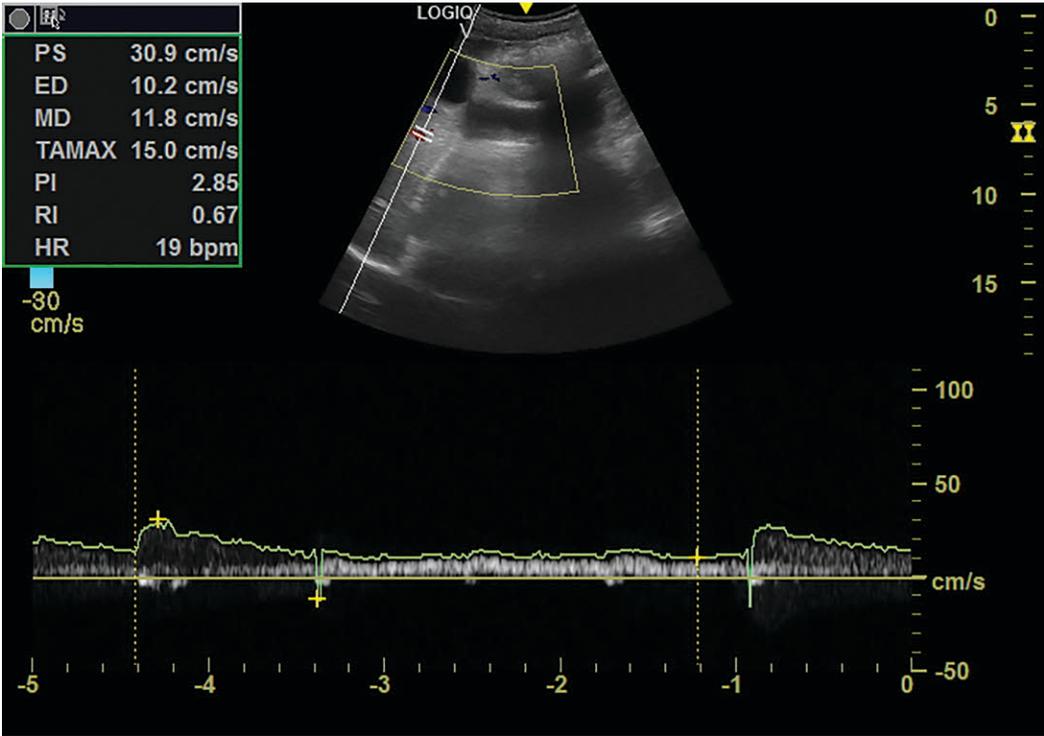Figure 1. Typical Pulsatility Index in a Patient with Uncomplicated Cholelithiasis.

Figure 2. Typical Pulsatility Index in a Patient with Acute Cholecystitis.

Statistical Analysis

Due to the lack of normality, non-parametric tests were performed. A multinomial logistic regression analysis was executed, comparing a nominal dependent variable and a continuous independent variable. All analyses were carried out using the SPSS statistical package, version 25 (Statistical Package for the Social Sciences, SPSS Inc., Chicago Ill, USA). All tests were two-sided, and statistical significance was set at P<0.05.

Results

The results of the descriptive statistics analysis are presented in Table 2.

Seventy-five subjects were enrolled in this study, with a median age of 69 years (range: 33-97 years).Twenty-five subjects were assigned to each group, as described before. All three groups were similar in terms of age and sex. Patient data are presented in Table 2. Patients in the third group fulfilled all the diagnostic criteria for acute cholecystitis. Specifically, all patients had acute right upper quadrant pain, with a positive Murphy's sign and fever (≥37.8°C); leukocyte count >10.000/μL, C-reactive protein level >0.5 mg/dl; sonographic findings suggestive of cholecystitis (cholelithiasis, thickened gallbladder wall, pericholecystic fluid and gallbladder distention). The right hepatic artery was identified in all subjects.

The median Pulsatility Index was 1.8 in both the control and the cholelithiasis group, and 2.8 in the cholecystitis group. Due to the lack of normality, the Kruskall-Wallis test revealed that the PI was statistically significant different between groups [χ^2(df2)=45.416 P<0.001]. Post-hoc analysis using the Dunn-Bonferroni test on each pair of groups showed that there was strong evidence (P<0.001, adjusted using the Bonferroni correction) of higher PI in the cholecystitis group (Mean Rank 61.68) compared to the cholelithiasis group (Mean Rank 27.46) and the control group (Mean Rank 24.86). Spearman's correlation coefficient revealed a strong correlation between PI and the group outcome (rho=0.702, P<0.001).

We performed multinomial logistic regression analysis in order to determine the correlation between the independent variable PI (which was multiplied by a factor of 10) and the dependent variable outcome (which was coded as control group=0 – reference group, cholelithiasis group=1 and cholecystitis group=2). There were no missing values and all the values were included in the analysis, including the outliers. The regression coefficients are shown in Table 3. The overall model evaluation showed an improvement over the intercept-only model (Likelihood ratio test chi-squared (df2)=79.428, P<0.001). Goodness-of-fit test yielded a chi-squared (df20)=3.847 and was insignificant (P=1.0), suggesting that the model fit the data well. According to the model, the log of the odds of a patient being diagnosed with cholecystitis was positively related to PI (P=0.006; Table 3) compared to the control group. On the other hand, there was no statistically significant correlation between PI and the outcome of cholelithiasis compared to the control group (P=0.431, Table 3). Finally, as shown in the classification table (Table 4), the model correctly predicted 92% of the cholecystitis cases and 64% of all cases.

Table 2. Patients' Demographics and Data

Characteristics	Group		
	Control (n=25)	Cholelithiasis (n=25)	Cholecystitis (n=25)
Age (years)			
Mean	57.16	61.12	79.52
Median	59.00	62.00	79.00
Range	33-87	33-87	48-97
Gender (n)			
Male	9	7	15
Female	16	18	10
Pulsatility Index			
Mean (± SD)	1.79 (±0.15)	1.82 (±0.12)	2.70 (±0.27)
Median	1.80	1.80	2.80
Range	1.50 - 2.00	1.50 - 2.00	1.80 - 3.00

Table 3. Regression Analysis Parameters Estimate with Parameter Coefficients

Group*		B	Standard error of B	Wald	Df	Sig.	Exp(B)	95% Confidence Interval for Exp(B)	
								Lower Bound	Upper Bound
Cholelithiasis	Intercept	-2.907	3.703	0.616	1	0.432	-	-	-
	PI	0.160	0.204	0.620	1	0.431	1.174	0.788	1.750
Cholecystitis	Intercept	-24.210	8.228	8.658	1	0.003	-	-	-
	PI	1.156	0.419	7.617	1	0.006	3.178	1.398	7.225

*The reference category is: control; PI=Pulsatility Index; B=Parameter B (unstandardized logisitc regression weight); Wald=test statistics χ^2; Df=Degrees of freedom; Sig=Significance;-Exp(B)=Exponentiation of B (odds ratio).

Table 4. Regression Analysis Classification Table

Observed	Predicted			
	Control (n)	Cholelithiasis (n)	Cholecystitis (n)	Percent of correct
Control	15	10	0	60.0
Cholelithiasis	15	10	0	40.0
Cholecystitis	1	1	23	92.0
Overall (%)	41.3	28.0	30.7	64.0

Discussion

Data from the present study indicate a strong correlation between right hepatic artery Color Doppler findings (PI) and acute inflammation. Significant differences in right hepatic artery PI were found between patients with acute cholecystitis and both patients with asymptomatic cholelithiasis and normal subjects. Notably, PI measurements were similar between patients with asymptomatic cholelithiasis and normal subjects. Provided that a correlation between right hepatic artery and acute cholecystitis was established by the present study, further research should aim to assess this test in diagnostically challenging cases with equivocal findings. Such difficulties usually exist in patients with a thickened gallbladder wall and comorbidities that are known to cause gallbladder wall thickening themselves, such as heart failure and cirrhosis.

PI measurement in the right hepatic artery, instead of gallbladder wall flow, is theoretically advantageous because there are cases in which severe inflammation and the resulting ischemia diminish blood flow in the gallbladder wall. In such cases color Doppler sonography may give false negative results.

The idea of correlating inflammation with hyperemia of the affected organ, detected by Doppler sonography, is not a new one (10, 11). Several reports have tried to provide a link between increased blood flow in the gallbladder and acute cholecystitis. Nevertheless, this technique has yet not gained wide acceptance, and experts are hesitant to suggest its application (12). Parameters utilized to quantify hyperemia include PI, peak velocity and resistance index. These parameters are measured either in gallbladder wall flow or in supplying arteries, namely the hepatic artery, right hepatic artery and cystic artery. The majority of studies evaluate these parameters in the gallbladder wall flow for practical purposes. Sonographic visibility of the hepatic artery was not feasible using older generation US machines. Consequently, Doppler examination of the hepatic artery for diagnosis of acute cholecystitis was first reported by Loehfelm in 2017 (7). Visualization of cystic artery flow, however, still remains rather challenging, even with modern technology. Moreover, given that PI measurement is greatly affected by the condition of the arteries, the circulating blood volume and hyperdynamic circulation state, patients with

arteriosclerosis, severe dehydration and high fever were excluded from the study.

Regarding acute cholecystitis, the discouraging preliminary results reported by McGrath et al. in 1992, showed that cystic artery flow is diminished in acute cholecystitis below the level of detection (13). Similarly, Paulson et al. suggested in 1994 that color Doppler is of little value in diagnosing acute cholecystitis (14). Jeffrey et al. focused on the length of the cystic artery visualized and its pattern of distribution, as potential diagnostic criteria for acute cholecystitis. According to these authors, despite their high specificity, these findings have quite low sensitivity, thus limiting their role in patients with cholecystitis (15). The superior flow sensitivity of Power Doppler sonography did not meet the expectation of improving diagnostic accuracy in acute cholecystitis, due to its substantial false positive rate (4).

Hayakawa et al. studied gallbladder wall blood flow in several gallbladder diseases, and concluded that maximum velocity above 30 cm/sec is indicative of cancer, but not acute cholecystitis(16). Tochio et al. found a significant correlation between a maximum flow velocity in a thickened gallbladder wall of more than 40 cm/sec, or a resistive index of less than 0.75 with acute cholecystitis in patients with cirrhosis (6). Yamashita et al. suggested that gallbladder wall flow positively correlates with the degree of inflammation in the acute setting, proposing this method for monitoring treatment success (17). Cetinkunar et al. evaluated gallbladder wall vascularity using Power Doppler, and came to the conclusion that increased vascularity correlates with the presence of adhesions, but not with operation difficulty (5). More recently Loehfelm et al. proposed that a peak systolic hepatic artery velocity of more than 100 cm/sec represents a significant aid in diagnosing acute cholecystitis (7).

A possible limitation of our study was the high percentage of subjects in whom visualization of the cystic artery was not feasible, thus excluding this data from the analysis. Establishing a diagnostic link between acute cholecystitis and cystic artery flow would have otherwise been ideal. On-going improvement in US modalities will probably render sonographic evaluation of cystic artery flow easier in the future. Another limitation of the study was the fact that US diagnosis of acute cholecystitis was not confirmed by intraoperative findings and surgical specimen histopathological examination.

Conclusion

Data from the present study indicate a strong correlation between right hepatic artery color Doppler findings and acute inflammation. Information provided by color Doppler imaging is of paramount importance in patients with a thickened gallbladder wall and comorbidities that are known to cause gallbladder wall thickening themselves. In conclusion, it is the authors' opinion that large scale studies are needed to confirm these findings and establish the role of color Doppler US in the diagnosis of acute cholecystitis in the context of ambiguous clinical scenarios. Future research should also aim to answer the question whether color Doppler findings may predict the severity of acute cholecystitis and indicate the appropriate treatment.

What Is Already Known on this Topic:
Although gray-scale US is the gold standard imaging modality for the diagnosis of acute cholecystitis, the presence of a thickened gallbladder wall due to other causes poses significant diagnostic problems. Several studies have indicated color Doppler sonography as a potential diagnostic aid in acute gallbladder inflammation, the majority of which focus on gallbladder wall blood flow.

What this Study Adds:
The results of the present study indicate a clear correlation between right hepatic artery PI elevation and acute cholecystitis. Consequently, measurement of PI by color Doppler ultrasound represents a useful aid in the diagnostic process of acute cholecystitis.

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