A preliminary study of quantitative analysis of tissue perfusion using contrast-enhanced ultrasound in the evaluation of the severity of acute pancreatitis

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Abstract

Background

Acute pancreatitis (AP) is a lethal disease with high mortality. Early diagnosis and evaluation of the severity of pancreatitis is crucial for the prevention a treatment of AP. The clinical value of contrast-enhanced ultrasound (CEUS) in evaluating the severity of acute pancreatitis by quantitative analysis of the tissue perfusion and the areas of pancreatic parenchymal necrosis is little known.

Methods

60 acute pancreatitis patients (AP group) and 30 volunteer (control group) were selected, the AP group was further divided into subgroup, the mild acute pancreatitis (MAP) group and the severe acute pancreatitis (SAP) group. All received CEUS examination, the differences of the parameters of time-intensity curve (TIC) between group AP and Control were analyzed. The receiver operating characteristics (ROC) curve of CEUS in diagnosing AP and SAP were drew, then calculated the best cut-off point of CEUS for the diagnosis of AP.

Results

Compared to group Control, there was a marked increase in AT and TTP, while a dramatic decrease in PI and AUC in group AP (all $P < 0.05$), no significant difference of WT and S was observed. After analysis of PI and AUC of those two subgroup AP patients, it was much higher in MAP group than SAP group, in contrast, the TTP decreased markedly(all $P < 0.05$), no significant difference of AT,WT and S was found. Next, we found that the sensitivity, specificity and diagnostic coincidence rate were 96.7%, 73.3% and 85.0% respectively, when the $AUC \leq 727.2\text{dBs}$ was used as the standard for the diagnosis of AP; and the sensitivity, specificity and diagnostic coincidence rate were 93.3%, 73.3%, and 83.3%, respectively when $PI \leq 11.41\text{ dB}$ was used as the standard for the diagnosis of SAP. Finally, we found that there was no significant difference in the detection of pancreatic parenchymal necrosis between CEUS and contrast-enhanced computed tomography (CECT).

Conclusions

CEUS could provide an objective and powerful basis for the early diagnosis of SAP, and also detect necrotic areas of pancreatic parenchyma early, quickly and accurately, which provide an available tool for clinic to early detection and assessment of the severity of acute pancreatitis.

Background

Acute pancreatitis (AP) is a disease with potentially lethal out-come^[1]. AP can be divided into mild acute pancreatitis (MAP) and severe acute pancreatitis (SAP), which is an inflammatory disorder of the pancreas that has been clinically defined as a common form of acute abdominal pain^[2-4]. MAP has a good prognosis and few complications with low mortality. However, SAP accompanied by serious complications is reported to have a high mortality rate^[5, 6]. Although SAP accounts for only 15–25% of AP cases, its mortality rate may be as high as 15-48.4%^[7]. Early diagnosis and evaluation of the severity of pancreatitis is crucial in AP management. As a continuous injury mechanism, pancreatic microcirculation disorder runs through the whole process of pancreatitis development and is an important factor in the transformation of hemorrhage and necrosis. Therefore, early detection of pancreatic microcirculation changes is the key to evaluate the severity of pancreatitis^[8, 9].

Contrast enhanced ultrasound (CEUS) is a new technique which can display imperceptible blood-vessel and tissue perfusion of microcirculation, and can also provide information on the vascularization of the pancreatic parenchyma and can differentiate between areas of inflammation and areas of necrosis^[10].

CEUS takes advantage of its special features: the high contrast and spatial resolution, the use of a blood-pool microbubble contrast agent and the real-time, dynamic evaluation of tissue enhancement, filtering the background tissue signals^[11]. The introduction of CEUS has led to major improvements in the diagnostic capabilities of ultrasound (US)^[12]. CEUS is less expensive compared to computed tomography(CT) and magnetic resonance imaging(MRI) and is able to significantly improve the accuracy of US, allowing better characterization and staging of pancreatic pathologies^[13].

CEUS may improve the detection and delimitation of the necrotic areas, which appear completely a vascular^[14]. Unfortunately, in the literature there are no studies comparing CEUS with CT in the quantitative evaluation and follow-up of AP. At this moment, CT remains more effective than CEUS, in particular in grading the stage of the disease.

The prospective study included 60 patients with pancreatitis, all of whom were performed CEUS examination and applies the time-intensity curve (TIC) quantitative analysis. The purpose is to explore the perfusion characteristics of pancreatic tissue by CEUS, evaluating the clinical value of CEUS in AP diagnosis, which achieves early identification of SAP, evaluating its severity and providing reliable imaging basis for clinical treatment and efficacy evaluation.

Methods

A randomized controlled trial was conducted to compare the CEUS parameters of AP, thus determining the best cut-off point between AP and SAP, and evaluating the diagnostic value of CEUS.

Patient data

This study was a prospective study. It was conducted in accordance with the Declaration of Helsinki, and with approval from the Ethics Committee of Tianjin Nankai Hospital (Tianjin, China). Written informed consent was obtained from all participants. In total, 60 inpatients given a clinical diagnosis of AP (30 patients with MAP and 30 patients with SAP) at Tianjin Nankai Hospital from May 2014 to September 2016 were selected for this study. All patients were taken the examination by CEUS.

Inclusion criteria

The inclusion criteria for cases of AP were mainly based on the Chinese guidelines for diagnosis and treatment of AP [15].

MAP group: acute persistent abdominal pain (a few had no abdominal pain), serum amylase activity increased (few without increase), no local complications (pancreatic necrosis, pseudocyst, pancreatic abscess). No organ failure; Ranson score < 3; APACHE II score < 8; Balthazar CT grading below grade II; Chinese CT classification is A, B, C.

SAP group: acute persistent abdominal pain (a few had no abdominal pain), serum amylase activity increased ≥ 3 times the upper limit of normal value, and patients with one of the following: local complications (pancreatic necrosis, pseudocyst, pancreatic abscess); Organ failure; Ranson score ≥ 3 ; APACHE II score ≥ 8 ; Balthazar CT grade II or above; Chinese CT classification was D and E.

Exclusion criteria

After laboratory examination and imaging examination, patients were clinically diagnosed with chronic pancreatitis, or patients with acute onset of chronic pancreatitis and pancreatic cancer.

CEUS examination

The PHILIPS iU22 (Philips Medical Systems, Bothell, WA, USA) ultrasonographic system with a corresponding C5-1-MHz transducer was used. The ultrasonographic system was quipped with harmonic contrast pulse sequencing technology. The contrast agent used was SonoVue (Bracco SpA, Milan, Italy), which is a suspension of stabilized sulfur hexafluoride microbubbles.

The CEUS program was at a low mechanical index (MI), MI was set at 0.05. A 1.2–1.5 ml volume of contrast agent suspension (SonoVue) was administered as a bolus injection through the median cubital vein, followed by flushing with 5 ml saline solution. After an 8–15 sec delay, the pancreatic parenchyma began to undergo enhancement. The real-time contrast-enhanced image obtained after contrast agent injection was recorded on a hard disk, and the injection times were calculated simultaneously [16]. The CEUS image data were analyzed with QLAB 10 advanced ultrasound quantification software, and the TIC was obtained.

The TIC parameters include: 1. Arise time (AT): time to begin enhancement. 2. Time to peak (TTP): the time to reach the peak. 3. Wash-time (WT): the total withdrawal of the contrast agent from the pancreatic parenchyma. 4. Peak intensity (PI): the perfusion volume at the peak time. 5. The slope of the ascending

branch of the curve (sharpness, S): it is related to the rapid degree of tissue perfusion and clearance. 6. Area under the curve (AUC): it is proportional to the average blood flow in the area of interest.

Statistical analysis

SPSS 22.0 and Graph Pad Prism8 software were used for statistical analysis of the data. Measurement data conforming to normal distribution were expressed as mean $\pm$ standard deviation ($M \pm SD$), and measurement data not conforming to normal distribution were expressed as median (M). Two independent samples t-test and paired t-test were used as statistical methods. For all analyses, values of $P < 0.05$ were considered statistically significant. Drawing the receiver operating characteristics (ROC) curves for statistically significant parameters; The best cut-off point of AP and SAP was found according to the highest critical point of the Youden index, and the sensitivity, specificity and coincidence rate were calculated [17].

Results

General characteristics

30 patients in the AP group including 43 males and 17 females, aged 24–71 years old, with an average age of (49.5 ± 11.7) years old. 30 patients in the control group, including 17 males and 13 females, aged from 32 to 77 years old, with an average age of (52.5 ± 10) years old. Among the 60 AP patients, 22 (36.7%) had biliary pancreatitis, 17 (28.3%) had alcoholic pancreatitis, 5 (8.3%) had binge-eating pancreatitis, 15 (25%) had hyperlipidemia pancreatitis, and 1 (1.7%) had unknown cause. Among the 30 cases of MAP, only 1 case developed secondary pulmonary infection, while 2 cases developed SAP secondary heart failure, 4 cases developed acute respiratory distress syndrome (ARDS), 3 cases developed pulmonary infection, 3 cases developed shock and 5 cases developed renal insufficiency (Table 1).

Table 1
Comparison of clinical outcomes (complications) between MAP and SAP(n/%)

Group	Pulmonary infection	Heart failure	ARDS	Shock	Renal insufficiency
MAP(<i>n</i> = 30)	1(3.3)	0(0)	0(0)	0(0)	0(0)
SAP(<i>n</i> = 30)	3(10)	2(6.7)	4(13.3)	3(10)	5(16.7)

Quantification of pancreatic perfusion in AP patients by time-intensity curves

After analyzing the TIC parameters, it indicated that AT and TTP in AP group were much higher than those in control group (9.64 ± 1.50 vs 8.57 ± 0.96 s, 16.21 ± 3.47 vs 12.92 ± 3.51 s, all $P < 0.05$), in contrast, the value of PI and AUC in AP group decreased significantly compared to those in control group (10.90 ± 2.82 vs 16.19 ± 3.85 dB, 560.73 ± 190.97 vs 867.39 ± 243.53 dBs, (all $P < 0.05$), which make it available to

identify the AP patients, there was no significant difference of WT and S between the AP group and control group (Table 2, Fig. 1, Fig. 3).

Table 2
Comparison of TIC parameters between AP group and control group (M $\pm$ SD)

Parameters	AP (<i>n</i> = 60)	Control(<i>n</i> = 30)	<i>t</i>	<i>P</i>
AT(s)	9.94 $\pm$ 1.87	8.57 $\pm$ 0.96	3.761	< 0.001
TTP(s)	16.21 $\pm$ 3.47	12.92 $\pm$ 3.51	4.221	< 0.001
WT(s)	46.16 $\pm$ 6.34	49.27 $\pm$ 7.38	-1.92	0.064
PI(dB)	10.90 $\pm$ 2.82	16.19 $\pm$ 3.85	-7.406	< 0.001
S	1.57 $\pm$ 0.78	1.44 $\pm$ 0.71	0.640	0.528
AUC(dBs)	560.73 $\pm$ 190.97	867.39 $\pm$ 243.53	-6.538	< 0.001

Quantification of pancreatic perfusion in the subgroup of AP patients by time-intensity curves

Next, to determine whether the CEUS could grade the stage of the AP patients, we evaluate the value of TIC between the AP patients, who were divided into the MAP and SAP based on the clinical guideline. We found that TTP increased dramatically in SAP patients (17.52 $\pm$ 2.52 *vs* 14.90 $\pm$ 3.82 s, *P* < 0.05), both PI and AUC in SAP group decreased significantly (9.40 $\pm$ 2.54 *vs* 12.40 $\pm$ 2.26 dB, and 453.81 $\pm$ 141.54 *vs* 667.64 $\pm$ 174.69 dBs, respectively, all *P* < 0.05). No significant difference of AT, WT and S was found between the SAP group and MAP group (Table 3, Fig. 2, Fig. 4).

Table 3
Comparison of TIC parameters between SAP group and MAP group (M $\pm$ SD)

Parameters	MAP (<i>n</i> = 30)	SAP(<i>n</i> = 30)	<i>t</i>	<i>P</i>
AT(s)	9.64 $\pm$ 1.50	10.24 $\pm$ 2.18	-1.245	0.218
TTP(s)	14.90 $\pm$ 3.82	17.52 $\pm$ 2.52	-3.128	0.003
WT(s)	47.22 $\pm$ 5.37	48.36 $\pm$ 6.39	-1.82	0.163
PI(dB)	12.40 $\pm$ 2.26	9.40 $\pm$ 2.54	4.831	< 0.001
S	1.61 $\pm$ 0.68	1.55 $\pm$ 0.78	-1.126	0.637
AUC(dBs)	667.64 $\pm$ 174.69	453.81 $\pm$ 141.54	5.209	< 0.001

The diagnostic value of quantitative parameters of CEUS TIC in AP and SAP

After calculating the area under the ROC curve of the all TIC parameters, we found that AUC was the most powerful parameter for the diagnosis of AP, the area under the ROC curve was 0.87(95%CI: 0.802–0.943). The best cut-off point was 727.2 dBs according to the Youden index. When choosing $AUC \leq 727.2$ dBs as the standard for the diagnosis of AP, the sensitivity, specificity and diagnostic coincidence rate were 96.7%, 73.3% and 85.0%, respectively(Table 4, Fig. 3).

Table 4
Diagnostic value of different parameters for AP (%)

Parameters	Sensitivity	95%CI	Specificity	95%CI	Coincidence rate	Youden index
$AT \geq 9.28$ s	65.0	52.4–75.8	80.0	62.7–90.5	72.5	0.450
$TP \geq 14.61$ s	71.7	59.2–81.5	83.3	66.4–92.7	78.9	0.550
$PI \leq 15.34$ dB	83.3	72.0–90.7	80.0	62.7–90.5	81.7	0.633
$AUC \leq 727.2$ dBs	96.7	88.6–99.4	73.3	55.6–85.8	85.0	0.700

Next, we found that PI was the most powerful parameter to grade the stage of the AP patients by CEUS, the area under the ROC curve was 0.85(95%CI: 0.754–0.952). The best cut-off point was 11.41 dB according to the Youden index. When selecting $PI \leq 11.41$ dB as the standard for differentiating SAP from MAP, the sensitivity, specificity and diagnostic coincidence rate were 93.3%, 73.3%, and 83.3%, respectively(Table 5, Fig. 4).

Table 5
Diagnostic value of different parameters for SAP (%)

Parameters	Sensitivity	95%CI	Specificity	95%CI	Coincidence rate	Youden index
$TP \geq 14.58$ s	100	88.7–100	56.7	39.2–72.6	78.3	0.567
$PI \leq 11.41$ dB	93.3	78.7–98.8	73.3	55.6–85.8	83.3	0.667
$AUC \leq 481.1$ dBs	70.0	52.1–83.3	86.7	70.3–94.7	78.4	0.567

Comparison of the detection rate of peripancreatic local complications between CEUS and CECT

It is well known that CECT is the imaging modality of choice for diagnosis, staging, and detection of complications of acute pancreatitis, particularly the identification and quantification of peripancreatic necrosis. In this section, we compared the detection rate of peripancreatic local complications between

CEUS and CECT. And it showed that of 30 SAP patients, 30 cases of pancreatic necrosis, 3 cases of pseudocyst and 7 cases of peripancreatic abscess were diagnosed by CECT, all of which were also diagnosed by CEUS, and the diagnostic coincidence rate was 100%, indicating CEUS could be considered as an alternative tools for the detection of initiation and extension of the peripancreatic necrosis. (Table 6)

Table 6
Comparison of the detection rate of peripancreatic local complications
between CEUS and CECT (n = 30)

Peripancreatic complications	CECT	CEUS	Coincidence rate(%)
pancreatic necrosis	30	30	100
pancreatic pseudocyst	3	3	100
peripancreatic abscess	7	7	100

Discussion

For the method to evaluate the severity of acute pancreatitis in the past there are also many, commonly used have Ranson, Glasgow, APACHE II etc., but there are some difficulties in the actual clinical applications^[18].CECT examination has good specificity and sensitivity for the evaluation of acute pancreatitis, but there are some problems such as timing and cost. Therefore, it is still necessary to find a convenient, non-invasive, sensitive and specific early evaluation method^[19].With the development of ultrasonography and the constant update of ultrasound examination equipment, the rate of diagnosis and diagnosis of acute pancreatitis by US has reached a high level, and it is harmless, economical, convenient and easy to be accepted by patients, so it has become a routine auxiliary diagnosis and dynamic monitoring method for acute pancreatitis^[20, 21].

CEUS provides a dynamic view of the “vascular pattern” through the exclusively intravascular flow of the microbubbles, assessing the aspect of increased echogenicity through nonlinear signals from the microbubbles^[22]. The contrast agent is removed from the body by breathing through the lungs, so it can be used in patients with SAP associated renal failure. Unlike the contrast agent used in ultrasonography, the contrast agent used in CT and MRI has a short intravascular retention time, being rapidly cleared from the circulation and reaching the extracellular space, and then excreted by the kidneys^[23].

Vitali F et al. considered that the performance of CEUS in diagnosing SAP to be very good compared to CT (89% specificity, 95% sensitivity)^[24]. Our study compared the detection rate of the areas of pancreatic necrosis in SAP through CECT (gold standard diagnostic) and CEUS, and there was no statistically significant difference in diagnose accordance rate.

Analyzing the current data from literature regarding the use of CEUS in acute pancreatitis, most of them are qualitative. Till now, there are few published studies on the quantitative analysis of pancreatic tissue

perfusion and determination of diagnostic thresholds for AP and SAP [25, 26].

TIC analysis of grey scale signal changes after contrast agent injection is one of the current methods for quantitative ultrasonic study of blood perfusion [27]. Among the quantitative parameters, PI has a good correlation with tissue perfusion amount, which refers to the most significant enhancement intensity of contrast agent on the local section, reflecting the maximum dose of contrast agent reaching this section per unit time. AUC is related to the distribution volume, blood flow velocity and perfusion time of the contrast agent. When the dose and instrument conditions are controlled at a constant rate, the AUC is affected by the flow rate and distribution volume, and is linearly related to the blood flow of the substance. In other words, AUC reflects the change of blood flow volume in the blood vessel, which is one of the most valuable parameters in TIC. The PPT is the time from the beginning of the contrast agent entering the tissue to the maximum strength of the enhancement. The change of the upward slope of the curve can reflect the perfusion rate of the contrast agent entering the tissue [28].

The results of TIC analysis in our study showed that TIC in control group was characterized by a sharp arc curve with a steep ascending branch. After reaching the peak, the descending branch decreased gently compared with the ascending branch. In the AP group, TIC presented a relatively flat arc curve, with the ascending branch slowly rising and the descending branch even more slowly extending. Compared with control group, the AT, TTP and WT in AP group were higher than that in control group. The PI and AUC of the contrast agent in AP group were smaller than those in control group, because the small blood vessels and microcirculation were damaged, the blood flow was slow, the perfusion volume was reduced, and the blood flow volume in the blood vessels was reduced. And by analyzing the TIC parameters, we can draw ROC curves for statistically significant parameters. Then we can determine the best cut-off point of AP and SAP.

A limitation of this study is the relatively small number of patients and the diversity in the ultrasonographically assessed structural changes. Our study provides a more objective, rapid, and accurate diagnostic method for the diagnosis of AP and SAP. Together with other clinical and biochemical information, these ultrasonographic parameters and their statistical analysis can assist in early clinical evaluation of the severity of AP.

Conclusions

An important advantage of CEUS is the possible real-time assessment of the vascular pattern with higher temporal resolution than other imaging techniques. Besides, “SonoVue” administration can be repeated due to a better patient tolerance and a reduced incidence of adverse reactions.

Our study attests the usefulness of CEUS in detecting the area of necrosis in AP, with similar results to those of CECT. We determined the best cut-off point of AP and SAP. Thus, our study provides a more objective, rapid, and accurate diagnostic method for the diagnosis of AP and SAP, which can assist in

early clinical evaluation of the severity of acute pancreatitis. And CEUS is a useful tool in the emergency diagnosis and monitoring of severe acute pancreatitis.

Declarations

Availability of data and materials

The dataset analyzed during the current study is available from the corresponding author on a reasonable request.

Ethics approval and consent to participate

This study was carried out under the approval of the Ethics Committee of Tianjin Nankai Hospital. Informed consent was obtained from all patients prior to participation in the study.

Consent for publication

Not applicable.

Competing interests

All authors declare that they have no competing interests.

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Authors' contributions

Liang Li wrote the first draft and revision of the manuscript. Xin Xu contributed in writing CT image description part. Guangxia Wang contributed in revision of the manuscript and discussion of results. Yunfeng Cui contributed in study design, discussion of results, and approval of the final version. All authors read and approved the final manuscript.

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Figures

Figure 1

Ultrasound image of acute pancreatitis. A. CEUS and US image of AP B. TIC of AP and normal pancreas

Figure 2

Ultrasound image of severe acute pancreatitis. A. CEUS and US image of SAP. B. TIC of MAP and SAP

Figure 3

ROC curve comparison of different parameters. A. AT comparison between AP group and control group. B. TTP comparison between AP group and control group. C. PI comparison between AP group and control group. D. AUC comparison between AP group and control group

Figure 4

ROC curve comparison of different parameters. A. TTP comparison between SAP group and MAP group. B. PI comparison between SAP group and MAP group. C. AUC comparison between SAP group and MAP group