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FULL PAPER

Evaluation of gastric blood supply in diabetic patients with gastroparesis by contrast-enhanced ultrasound

¹HAO-LIN SHEN, MS, ¹SHU-PING YANG, BD, ¹KANG-JIAN WANG, BD, ¹BEI-LEI HUANG, BD, ²WEN-BAO HUANG, BD, ³JIN-ZHI WU, MS and ^{4,5}GUO-RONG LV, MS

¹Department of Ultrasound, Zhangzhou Hospital, Fujian Medical University, Zhangzhou, Fujian, China

²Department of Gastroenterology, Zhangzhou Hospital, Fujian Medical University, Zhangzhou, Fujian, China

³Department of Endocrinology, Zhangzhou Hospital, Fujian Medical University, Zhangzhou, Fujian, China

⁴Department of Ultrasound, Second Affiliated Hospital, Fujian Medical University, Quanzhou, Fujian, China

⁵Department of Clinical Medicine, Quanzhou Medical College, Quanzhou, Fujian, China

Address correspondence to: Dr Guo-rong Lv

E-mail: lgr_feus@sina.com

Objective: Improvement in regional blood flow has been shown to ameliorate diabetic gastroparesis. We compared the gastric blood supply in patients with diabetes with gastroparesis with that in healthy subjects, by using contrast-enhanced ultrasound (CEUS).

Methods: 30 healthy subjects and 40 patients with diabetic gastroparesis were enrolled. The CEUS parameters of greater curvatures of the antrum (GCOA) and lesser curvatures of the antrum (LCOA), including peak intensity (PI) and the area under the curve (AUC), were compared between the two groups.

Results: Intraclass correlation coefficient (ICC) for PI in healthy subjects measured on CEUS were 0.831–0.857 and 0.803–0.823, respectively. Intra-ICC and inter-ICC values for AUC were 0.805–0.823 and 0.813–0.815,

respectively. In both groups, no significant difference was observed in PI and AUC values of GCOA and LCOA ($p > 0.05$). The PI and AUC of GCOA and LCOA in the diabetes group were less than those in the normal group ($p < 0.05$).

Conclusion: CEUS can assess stomach wall vascularity with a high reproducibility. Microcirculation in the antrum of patients with diabetic gastroparesis is poorer than that of normal group, which is consistent with the mechanisms of diabetic neuropathy. CEUS can be used for evaluation of microvascular perfusion in patients with stomach wall disease.

Advances in knowledge: This was the first study to use CEUS for assessment of blood supply of the gastric wall and to compare microvascular perfusion between healthy individuals and patients with diabetes with gastroparesis.

INTRODUCTION

Over the past three decades, diabetes has emerged as one of the fastest-growing global epidemics.^{1,2} Patients with advanced diabetes manifest a spectrum of microvascular complications.^{3,4} These include retinopathy, nephropathy and neuropathy.^{5,6} Diabetic neuropathy has been shown to be associated with altered microvascular perfusion.^{7,8} Diabetic neuropathy may involve both the somatic and autonomic divisions of the peripheral nervous system.^{3,9} Gastric motility is closely regulated by the autonomic nervous system.^{10,11} Involvement of autonomic innervation of the gastrointestinal (GI) tract leads to gastroparesis, which can dramatically affect glycaemic control by delaying the absorption of key nutrients and impact on the efficacy of oral antidiabetic drugs.¹² Wang et al⁸ showed that measurement and improvement in regional blood flow likely contributes to the amelioration of nerve function. However, most available tests that measure gastric motility, including gastric barostat, antropyloroduodenal manometry and

scintigraphy, do not allow adequate evaluation of microvascular perfusion of the stomach wall.^{13–15}

Recently, there has been a rapid development in various ultrasound contrast agents; SonoVue (sulfur hexafluoride microbubbles) has been shown to be safe and effective and a single bolus dose of up to 4.8 ml can be administered.^{14,15} SonoVue contrast-enhanced ultrasound (CEUS) improves the ability to depict microvascular perfusion of organs and lesions and is widely used in differential diagnosis of benign and malignant focal stomach lesions.^{16–18} The use of a combination of oral and i.v. contrast agents for ultrasound imaging is referred to as double contrast-enhanced ultrasound. This approach has been used previously to assess the blood supply of gastric lesions by Shi et al.¹⁶ The contrast-enhanced time–intensity curve showed higher values of parameters such as peak intensity (PI) in malignant lesions, when compared with surrounding normal gastric tissue ($p < 0.05$); however, no difference was observed

between benign lesions and the normal gastric tissue ($p > 0.05$).¹⁶ These authors showed that CEUS can not only aid in the differential diagnosis of benign and malignant tumours by evaluation of the blood supply, but can also be used for the evaluation of microcirculation in the normal gastric wall.

CEUS has also been used to detect blood supply of the digestive tract in patients with inflammatory lesions. Use of SonoVue for imaging of inflammatory lesions of the digestive tract allows quantification of microvascular perfusion and provides a non-invasive method for characterization of inflammatory activity and for serial evaluation of treatment efficacy.^{19,20}

The feasibility of the use of CEUS to evaluate the microcirculation of the gastric wall has been well demonstrated.¹⁶ However, the use of CEUS for assessment of microvascular perfusion of the gastric wall in patients with diabetes with gastroparesis has not yet been studied. In the present study, we evaluated the utility of CEUS for assessment of blood supply to the gastric wall and to compare microvascular perfusion between healthy individuals and patients with diabetes with gastroparesis.

METHODS AND MATERIALS

This study was approved by the ethics committee (No. 20120102) at our hospital; written informed consent was obtained from all subjects.

Subjects

30 healthy volunteers (15 males, 15 females) were selected. Exclusion criteria were: GI disease, history of surgery of GI tract, hyperlipidaemia, hyperthyroidism, diabetes, valvular heart disease, hypertension, heart failure, stroke, liver or kidney dysfunction and the presence of any other significant disease. 40 patients with Type 2 diabetes (20 males, 20 females) with upper GI symptoms were recruited. All patients were diagnosed according to the 1999 World Health Organization diagnostic criteria for diabetes and were confirmed to have gastroparesis on scintigraphy.^{21,22} The main symptoms were nausea, vomiting, early satiety, postprandial bloating, anorexia and stomach pain. Mean fasting plasma glucose and haemoglobin (HbA1c) levels were $11.6 \pm 4.1 \text{ mmol l}^{-1}$ and $9.8 \pm 1.8\%$. Baseline characteristics of healthy subjects and patients with diabetes are shown in Table 1.

Methods

The ultrasound scanner iU22 (Philips Medical Systems, Bothell, WA) with C5-2 probe was used in this study. Conventional

ultrasound imaging mode was used for oral contrast imaging while contrast imaging modes (Philips pulse inversion harmonic imaging) were used for intravascular contrast imaging. The oral ultrasound contrast agent used was World instant GI ultrasound agent (Huzhou East Medical Devices, Huzhou, China); the ingredients were protein (18.6%), fat (5.5%), fibre (1.6%), water (1.5%) and carbohydrate (72.8%). The i.v. ultrasound contrast agent used was SonoVue® (Bracco SpA, Milan, Italy).

None of the subjects received any drug that affected gastric motility or smoked tobacco for at least 7 days immediately preceding the examination. The subjects were asked to fast for > 10 h prior to the examination. CEUS was performed in a random order by a physician who was blinded to the diagnosis.

Double contrast-enhanced ultrasound was performed according to the method described by Shi *et al.*¹⁶ The oral ultrasound contrast agent described earlier was suspended in boiling water to obtain a uniform paste of 400 ml. It was cooled to 37°C . Subjects ingested the agent within 3 min of preparation in an upright position. 5 min after oral contrast imaging, whole-stomach CEUS was performed with a bolus injection of 2.0 ml of SonoVue (followed by 5 ml normal saline flush) using a 20-gauge peripheral i.v. catheter under contrast imaging mode with a low mechanical index (0.09–0.21); it was captured for 180 s starting from the beginning of contrast injection. The regions of interest were selected at around the midpoints of greater curvatures of the antrum (GCOA) and lesser curvatures of the antrum (LCOA) on the short axis plane based on two-dimensional imaging (Figure 1). In order to make sure the regions of interest remained in the same point during a 3-min period, motion compensation was activated. The CEUS parameters of PI and the area under the curve (AUC) were obtained and calculated from the time–intensity curve (Figure 2). CEUS findings were analyzed using Philips QLAB software (edition 8.1.2.453561492151) by a single physician.

In order to test the interobserver and intraobserver variability, a smaller subgroup of 10 people were called back for repeat tests. The first 10 healthy subjects, who underwent CEUS in a random order by Physician A (Test 1), underwent a second ultrasound examination 2 days later by the same physician (Test 2). 2 days after the second ultrasound examination, these same 10 subjects underwent a third ultrasound examination by Physician B (Test 3).

Table 1. Baseline characteristics of healthy subjects and patients with diabetes

Groups	Age (years)	Median age (years)	Body mass index (kg m^{-2})
Healthy subjects	45.3 ± 9.5	44.5	21.3 ± 1.4
Patients with diabetes	46.6 ± 8.7	45.0	21.1 ± 1.3
<i>p</i> -value	0.552 ^a	0.468 ^b	0.666

Data are presented as mean $\pm$ standard deviation.

^aAssessed by one-way analysis of variance.

^bAssessed by Wilcoxon rank sum test.

Figure 1. (a) An image showing the regions of interest selected at the midpoint of the greater curvatures of the antrum (GCOA) and the lesser curvatures of the antrum (LCOA) on a short plane based on two-dimensional contrast imaging. (b) A schematic diagram is showing the points (*short arrow and long arrow*) chosen at the middle of GCOA and LCOA.

Statistical analysis

All data were presented as mean $\pm$ standard deviation. Between-group differences with respect to age and body mass index were assessed on one-way analysis of variance (ANOVA). Between-group differences in median age were assessed by Wilcoxon rank sum test. Intraclass correlation coefficient (ICC) was used to assess the intraobserver and interobserver variability using the following grading method: 0.21–0.4 fair; 0.41–0.6 moderate; 0.61–0.8 good; and 0.81–1.0 excellent.²³ The ICC values were calculated with 95% confidence intervals using a two-way random-effects model with single measures. The differences in PI and AUC between GCOA and LCOA were assessed by one-way ANOVA. The differences in PI and AUC between healthy subjects and patients with diabetes were assessed for statistical significance by one-way ANOVA. SPSS® v. 15.0 software (IBM Corp., New York, NY; formerly SPSS Inc., Chicago, IL) was used for data analysis; p -value < 0.05 was considered indicative of a statistically significant between-group difference.

RESULTS

Reproducibility of parameters (peak intensity and area under the curve) by contrast-enhanced ultrasound

Intra-ICC values of PI measured on CEUS were 0.831–0.857 and inter-ICC values of PI were 0.803–0.823. Intra-ICC values of AUC were 0.805–0.823 and inter-ICC values of AUC were 0.813–0.815 (Table 2).

Comparison of parameters (peak intensity and area under the curve) between patients who were normal and patients with diabetes with gastroparesis

The mean PI and AUC of GCOA in the normal group were 13.14 ± 3.27 dB and 936.38 ± 403.28 dB s, while those in the diabetic group were 10.77 ± 2.65 dB and 755.44 ± 237.45 dB s, respectively. The mean PI and AUC of LCOA in the normal group were 12.41 ± 2.70 dB and 868.40 ± 314.13 dB s, while those in LCOA in the diabetic group were 9.93 ± 2.88 dB and 672.84 ± 184.66 dB s, respectively. In both groups, PI and AUC values for GCOA showed no significant difference from those of LCOA ($p > 0.05$). PI and AUC of GCOA and LCOA in the diabetes group were less than those in the normal group ($p < 0.05$) (Table 3).

DISCUSSION

Microvascular pathological changes in diabetes lead to neuropathy, which may impact on gastric motility.¹² Ultrasound has been used to evaluate gastric dynamics by measuring the gastric volume to assess the gastric emptying time.^{24,25} However, these studies have focused only on assessment of gastric function and did not assess the microvascular system. In the present study, we describe for the first time, the use of SonoVue for studying the gastric wall microvasculature in patients with diabetes with gastroparesis.

SonoVue has a very small diameter, similar to that of red blood cells, and thus attains sufficient concentration in the microvasculature of all organs on i.v. administration. This agent is

Figure 2. Time-intensity curve for the contrast agent in the circulatory bed of the greater curvatures of the antrum (GCOA) and the lesser curvatures of the antrum (LCOA): (a) in healthy subjects, the peak intensity (PI) and area under the curve (AUC) of LCOA (*short arrow*) were 13.35 dB and 1031.60 dB s, respectively, while PI and AUC of GCOA (*long arrow*) were 10.42 dB and 914.46 dB s, respectively. (b) In patients with diabetes, PI and AUC of LCOA (*short fine arrow*) were 7.46 dB and 838.90 dB s, respectively, while PI and AUC of GCOA (*long fine arrow*) were 7.15 dB and 664.14 dB s, respectively.

Table 2. Reproducibility of parameters peak intensity (PI) and area under the curve (AUC) on contrast-enhanced ultrasound (CEUS)

Tests	PI (dB)		AUC (dB s)	
	GCOA	LCOA	GCOA	LCOA
Test 1	12.84 ± 3.20	12.03 ± 1.96	895.59 ± 352.97	778.10 ± 270.49
Test 2	12.58 ± 2.18	11.92 ± 1.56	917.02 ± 202.77	794.42 ± 175.11
Test 3	12.38 ± 2.33	12.23 ± 1.47	903.31 ± 237.66	765.42 ± 197.79
Intra-ICC	0.857	0.831	0.805	0.823
95% LOA	0.55–0.96	0.48–0.95	0.42–0.95	0.46–0.95
Inter-ICC	0.823	0.803	0.813	0.815
95% LOA	0.44–0.95	0.39–0.95	0.41–0.95	0.42–0.95

GCOA, greater curvatures of the antrum; ICC, intraclass correlation coefficient; LCOA, lesser curvatures of the antrum; 95% LOA, 95% limits of agreement.

Data are presented as mean ± standard deviation.

Between-group differences were assessed by one-way analysis of variance.

Accuracy of CEUS was assessed by ICC.

eliminated through the lungs 15 min after injection and its use is considered safe in humans.^{23,26} In addition, it does not penetrate the vessel wall or leak into the interstitial space.²⁶ Therefore, its concentration in an organ or lesion is linked to the structural and functional integrity of the microvasculature.^{23,26}

CEUS has been employed to evaluate microvascular perfusion in patients with inflammatory bowel diseases. Romanini et al¹⁹ found that quantitative parameters on CEUS provide an accurate measure of the bowel wall microvascular perfusion and could be used to predict inflammatory disease activity with a high sensitivity and specificity. Shi et al¹⁶ compared gastric lesions with the surrounding normal tissue using the contrast-enhanced time–intensity curve of microvascular perfusion. The results showed that CEUS may help differentiate benign from malignant gastric lesions.

Table 3. Comparison of parameters peak intensity (PI) and area under the curve (AUC) between healthy subjects and patients with diabetes with gastroparesis

Parameters	Healthy subjects	Patients with diabetes
GCOA		
PI (dB)	13.14 ± 3.27	10.77 ± 2.65 ^a
AUC (dB s)	936.38 ± 403.28	755.44 ± 237.45 ^a
LCOA		
PI (dB)	12.41 ± 2.70	9.93 ± 2.88 ^a
AUC (dB s)	868.40 ± 314.13	672.84 ± 184.66 ^a

GCOA, greater curvatures of the antrum; LCOA, lesser curvatures of the antrum.

Data are presented as mean ± standard deviation.

Between-group differences were assessed by one-way analysis of variance.

^a*p* < 0.05 vs GCOA.

In normal individuals, once food enters the duodenum, there is a decrease in the luminal pressure,²⁷ and the emptying of residual food from the stomach depends on the antrum–duodenal pressure difference.¹⁵ Antrum is the key gateway for gastric emptying.^{10,27} During the digestion phase, the antral position is located in the near field of ultrasound and is more stable than the gastric body in position. The GCOA and LCOA are at a certain distance from the surface and therefore may help avoid near-field artefacts. PI and AUC represent the blood volume and have been shown to provide a closer representation of blood supply.^{20,21} Thus, we chose PI and AUC of GCOA and LCOA as our indices. The intraobserver/interobserver reliability of CEUS parameters (PI and AUC) was found to be consistent in our study. In our study, no significant difference in PI and AUC was observed between GCOA and LCOA (*p* > 0.05), which reflects the fact that the density of microvasculature of LCOA is comparable with that of the GCOA.

GI motility disorders in patients with diabetes are considered to be a result of nerve damage, which is associated with systemic microvascular disease.^{3,28,29} Thus, evaluation of the degree of microvascular disease in patients with diabetes who have gastroparesis, by studying the gastric perfusion, is of much clinical relevance. In the present study, both PI and AUC of GCOA and LCOA in patients with diabetes with gastroparesis were less than those in healthy subjects (*p* < 0.05), which implies poorer gastric blood supply in patients with diabetes with gastroparesis than that in healthy individuals. This finding is consistent with the mechanisms and progression of diabetic microvascular disease. It also confirms that the abnormal gastric emptying was associated with diabetic microvascular neuropathy.

A limitation of our study was that the CEUS parameters of the entire wall of the gastric body could not be obtained. If novel methods are developed to assess these parameters, they will certainly be a value addition to the diagnostic approach and

allow a richer and more complete evaluation of gastric vasculature and function.

In conclusion, our study showed that CEUS allows for assessment of the stomach wall vascularity with a high reproducibility. The antral microcirculation in patients with diabetic gastroparesis is poorer than that in healthy subjects, which is

consistent with the mechanisms of diabetic neuropathy. CEUS can be used to evaluate microvascular perfusion in patients with stomach wall disease.

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