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A Preliminary Investigation of Normal Pancreas and Acute Pancreatitis Elasticity Using Virtual Touch Tissue Quantification (VTQ) Imaging

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

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Background: The aim of this study was to prospectively evaluate the use of elastometry in healthy volunteers and patients with acute pancreatitis using virtual touch tissue quantification (VTQ) imaging technology performed on the pancreas.

Material/Methods: We enrolled 210 healthy volunteers and 44 acute pancreatitis patients in the study between March 2012 and June 2013. Healthy subjects were divided into 3 groups: young (18–30 years), middle-aged (30–50 years), and elderly (>50 years). VTQ was performed on the pancreatic head and body regions to obtain shear wave velocity (SWV) measurements, which were used to evaluate the elasticity values of tissues.

Results: The pancreatic head SWV value in the whole healthy group was 1.18±0.23 m/s, and that in the pancreatic body was 1.21±0.20 m/s. In patients with acute pancreatitis, the mean SWV measurements at the head were 1.18±0.20 m/s, compared to 1.25±0.19 m/s in the pancreatic body. There was no statistically significant difference between whole healthy volunteers and the acute pancreatitis group.

Conclusions: VTQ is a new method that shows promise for the quantification of pancreatic elasticity, but further studies are warranted.

MeSH Keywords: **Elasticity Imaging Techniques • Pancreas • Pancreatitis**

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Background

With increasing industrialization and improvements in living standards, the influence of lifestyle and environmental factors has recently led to a significant increase in the incidence of acute pancreatitis (AP) in China and in other countries [1,2]. It has been reported that pancreatitis can be the first symptom of pancreatic cancer and in unexplained cases of pancreatitis (roughly 10–15% of all acute pancreatitis patients), 1% of patients have from pancreatic cancer [3,4]. Delayed recognition and treatment leads to significant deleterious effects on the affected individuals and to healthcare resources generally, and investigations that aid the early discovery, diagnosis, and treatment of pancreatic diseases are therefore of particular importance.

Acoustic radiation force impulse (ARFI) imaging is an emerging and promising ultrasound-based imaging modality for the evaluation of tissue stiffness, which consists of virtual touch tissue imaging (VTI) and virtual touch tissue quantification (VTQ). When ARFI imaging is performed, the tissue in a fixed target region of interest (ROI) is mechanically excited using short-duration (less than 1 ms) acoustic pulses to generate small (1–10 μm) localized tissue displacements without the need for an external compression [5–7]. The response, monitored with ultrasound (US), is a function of Young's modulus, which provides information about tissue viscoelastic properties [5–7]. Acoustic radiation force impulse produces a vertical compression and a horizontal vibration in parenchymal tissue, which are the foundations of VTI and VTQ, respectively. By measuring the time of peak displacement at each lateral location, the shear wave velocity (SWV) within the tissue can be calculated (measured in m/s). The VTI directly presents tissue stiffness using black and white images, while the VTQ is given as an objective numerical evaluation of tissue stiffness. Increasing tissue stiffness is represented by greater SWV values as it crosses through the ROI. VTI is therefore a qualitative diagnostic tool and VTQ is quantitative to conventional US [8,9].

VTQ has turned out to be a non-invasive quantitative method that could feasibly measure tissue stiffness [10,11]. When lesions are present within the pancreas, its elasticity will change correspondingly, and therefore VTQ has potential as a diagnostic tool in pancreatic disease. This study focused on the use of VTQ technology for a range of pancreatic elasticity measurements in healthy volunteers and patients with acute pancreatitis.

Material and Methods

Volunteers

This study was performed in accordance with the ethics guidelines of the Helsinki Declaration and approved by the Ethics Committee of the Tenth People's Hospital of Tongji University. A total of 288 consecutive adult subjects were recruited at the time of their annual physical check-up or treatment in our hospital between March 2012 and June 2013. In 34 subjects the procedure failed for technical reasons because the pancreas could not be visualized or penetration of VTQ failed to reach the pancreas. According to local legislation, all subjects older than 18 years gave their verbal informed consent prior to entering the study. The committee approved the consent procedures because the noninvasive technique used in this study was incorporated in a commercially available US machine and its safety has been well documented. The consent process was documented in a separate file after the verbal informed consent was obtained. In 210 healthy volunteers (HVs), vital signs, routine blood and urine tests, blood electrolytes, electrocardiography findings, and hepatic and renal function test results were normal in all fasting subjects. Subjects were excluded from the study if they had a history of primary or secondary pancreatic disease or if there was any morphological or structural abnormality in the pancreas identified by US examination. Normal subjects were divided into 3 groups according to age: young (18–30 years; n=74), middle-aged (30–50 years; n=65), and elderly (>50 years; n=71).

Patients

Forty-four patients with acute pancreatitis were admitted to hospital within 48 h. Each patient met at least 2 of the following inclusion criteria: a) middle and upper abdominal pain that continuously radiates to the back; b) patients had amylase/lipase levels that were at least 3 times higher than the upper limit of the normal range; and c) there were morphological changes of the pancreas on imaging examinations.

Methods

We used the ACUSON S2000 US system (Siemens Medical Solutions, Mountain View, CA, USA), equipped with a curved array transducer 4C1 (a center frequency of 3.5 MHz, range: 3.0~4.5 MHz), conventional B-mode ultrasound, and ARFI elasticity imaging technology. To avoid inter-observer variability, a single sonographer with more than 5 years of experience performed the procedure. Volunteers underwent conventional US examinations in the supine position, and the pancreatic location, size, echographic appearances, shape, boundaries, and hemodynamic changes were observed. Additionally, the organ dimensions were measured in mm. As much of the pancreatic parenchyma as possible <8 cm away from the probe surface was identified as the target region of interest (box with fixed dimensions of 1×0.5 cm), and peripancreatic vessels were avoided. Subjects were asked to hold their breath, and the operator clicked "Update" after image stabilization, in accordance with the pancreas test standards of no obvious motion artifact. Brief acoustic pulses at a fixed transmission

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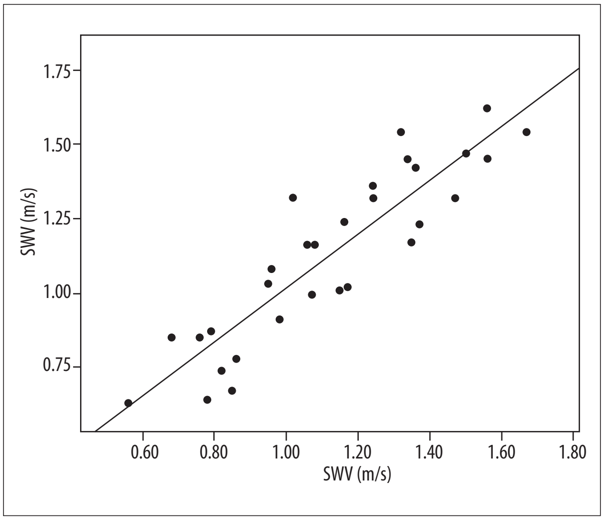

Figure 1. Correlation between the shear wave velocity (SWV) measurements acquired by the same operator for the pancreatic head in 30 healthy volunteers (r=0.900).

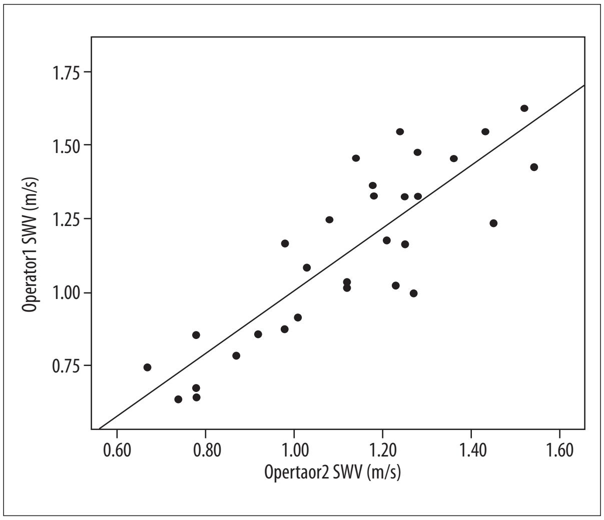

Figure 2. Correlation between the shear wave velocity (SWV) measurements acquired by the 2 independent operators for the pancreatic head in 30 healthy volunteers (r=0.854).

frequency produce a lateral SWV, which results from local tissue displacement, and this reflects transverse expansion after longitudinal compression in the region under the force. SWV values are expressed as m/s and measurement depths (cm) were recorded. In cases that were beyond the VTQ limitations of 0–9 m/s or where there was image instability, the SWV values were shown as "x.xx m/s" and remeasured. The pancreas is a retroperitoneal organ that was identified in front of the abdominal aorta, and is detected too distant from the transducer to set the ROI on the target tissue. It is a deep organ that is susceptible to being obscured by gastrointestinal tract gas. Consequently, image acquisition is not very stable. SWV values were measured 7 times in the same position, direction, and depth and with the same probe. Nevertheless, to minimize deviation, the highest and lowest values were removed and the remaining 5 measurements were averaged and used in the analysis. The "x.xx m/s" values were allocated to 0 m/s or 9 m/s, depending on the VTI image, with 0 m/s corresponding to a bright image and 9 m/s to a dark image [12].

To investigate intraobserver reproducibility, repeated SWV measurement for the pancreatic head was performed in 30 other healthy volunteers by the same operator. Interobserver reproducibility was assessed independently by 2 operators, who made SWV measurement for the pancreatic head in 30 other healthy volunteers. Both of them had similar experience in use of the technique.

Statistical analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences, version 18.0 (SPSS Inc., Chicago, IL, USA). The intra- and inter-observer reproducibility was assessed using the correlation coefficient (r) analysis. Spearman's correlation coefficient was used to demonstrate the relationships between variables. The clinical characteristics of healthy volunteers, patients with acute pancreatitis, and the SWV measurements are expressed as means ± standard deviations (SD) together with the range. Comparisons between different parts of the pancreas were made with the aid of paired t-tests, and those between different age groups were made using unpaired t-tests. A p-value<0.05 was considered statistically significant.

Results

The correlation coefficients were 0.900 for intraobserver measurement (Figure 1) and 0.854 for interobserver measurement (Figure 2) (both P<0.001).

There were 210 healthy adult volunteers (male: female, 99: 111), with a mean age of 42.02±17.37 years (range, 19–81 years) and a mean BMI of 22.09±3.03 kg/cm^2 (range, 16.4–30.4 kg/cm^2). The patients with acute pancreatitis consisted of 30 males and 14 females with a mean age of 53.76±16.78 years (range, 27–81 years) and a mean BMI of 23.98±2.71 kg/cm^2 (range, 18.8–29.1 kg/cm^2) (Table 1). The pancreatic head and body thickness were 21.20±3.59 mm (range: 11–34 mm) and 12.27±3.09 mm (range: 6–22 mm) for normal pancreas, and 24.32±2.95 mm (range: 17–29 mm) and 16.80±2.78 mm (range: 11–22 mm) for acute pancreatitis, respectively. There were 7 severe and 37 mild pancreatitis cases in the acute pancreatitis patients.

None of the normal pancreatic parenchyma mean SWV measurements were highly significantly correlated with either

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Table 1. Patient characteristics.

Groups	Age (range), year	Male/female	n
Healthy group	42.02 (9–81)	99/111	210
Acute pancreatitis group	53.76 (27–81)	30/14	44

Table 2. Correlations between head and body of normal pancreas shear wave velocities (SWVs) and sex, age, height, weight, waistline measurement, BMI, and organ dimensions.

Correlation factor	Pancreatic head SWV		Pancreatic body SWV	
	r	p	r	p
Sex	0.012	0.863	0.117	0.091
Age	–0.063	0.364	0.108	0.117
Height	0.047	0.502	–0.041	0.554
Weight	0.014	0.837	–0.013	0.854
Waist	–0.025	0.717	0.042	0.543
BMI	–0.013	0.847	–0.002	0.976
Thickness of pancreatic head	–0.032	0.646	NA	NA
Thickness of pancreatic body	NA	NA	–0.025	0.715

p<0.05 was considered statistically significant. r – correlation; NA – not applicable.

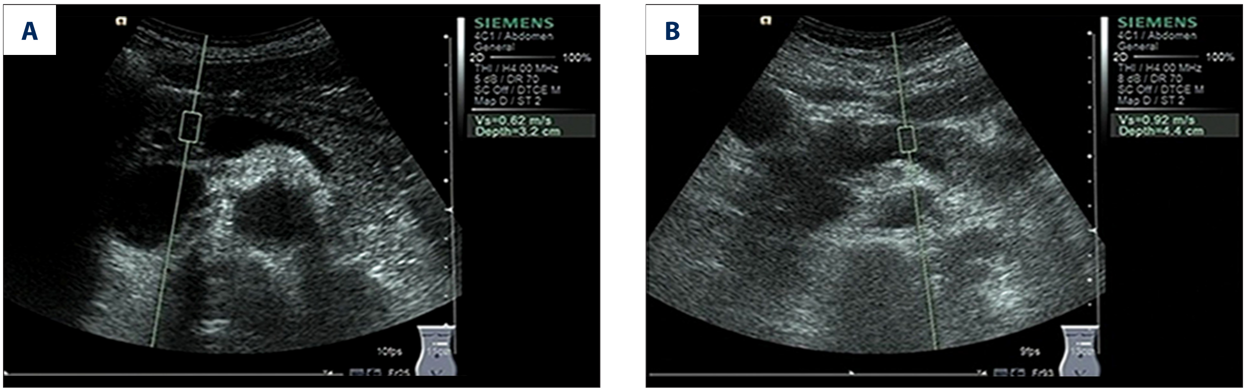

Figure 3. Measurement of the SWV of the pancreas using VTQ in healthy volunteers. The SWV at the pancreatic head (**A**) is 0.62 m/s and the SWV of the pancreatic body (**B**) is 0.92 m/s.

sex, age, height, weight, waist circumference, BMI, or organ dimensions (Table 2).

The pancreatic head SWV values in the young, middle-aged, and elderly healthy groups were 1.13±0.24 m/s, 1.15±0.23 m/s, and 1.08±0.22 m/s, respectively, whereas those in the pancreatic body were 1.17±0.19 m/s, 1.27±0.20 m/s, and 1.22±0.20 m/s, respectively. The pancreatic head SWV value in the whole healthy group was 1.18±0.23 m/s, and that in the pancreatic body was 1.21 ± 0.20 m/s (Figure 3). The SWV values did not differ between the head and body of the pancreas within or between any of the 3 age groups (Table 3) (p>0.05). In the patients with AP, the mean SWV measurements at the pancreatic head and body were 1.18±0.20 m/s and 1.25±0.19 m/s, respectively (Figure 4). These results did not differ significantly from those of the whole healthy volunteers (p > 0.05) (Table 3, Figure 5).

Discussion

Computed tomography (CT), magnetic resonance imaging (MRI), magnetic resonance cholangiopancreatography (MRCP), B-mode US, endoscopic ultrasonography (EUS), and endoscopic retrograde cholangiopancreatography (ERCP) have been widely used to investigate the pancreas and have enhanced the rate of detection of pancreatic disease. However, each method has its

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Table 3. Mean SWVs of the head and body of the pancreas in the young, middle-aged, and elderly healthy groups, and in the acute pancreatitis group ($\bar{\chi}$±s, m/s).

Groups	SWV of pancreas (m/s)	
	Pancreatic head	Pancreatic body
Healthy group	1.18±0.23	1.21±0.20
Young group	1.13±0.24	1.17±0.20
Middle-aged group	1.15±0.23	1.27±0.21
Elderly group	1.08±0.22	1.22±0.20
Acute pancreatitis group	1.18±0.20	1.25±0.19

Comparison between the head and body of pancreas, p>0.05; Comparison among any age groups, p>0.05; Comparison between healthy group and acute pancreatitis group, p>0.05.

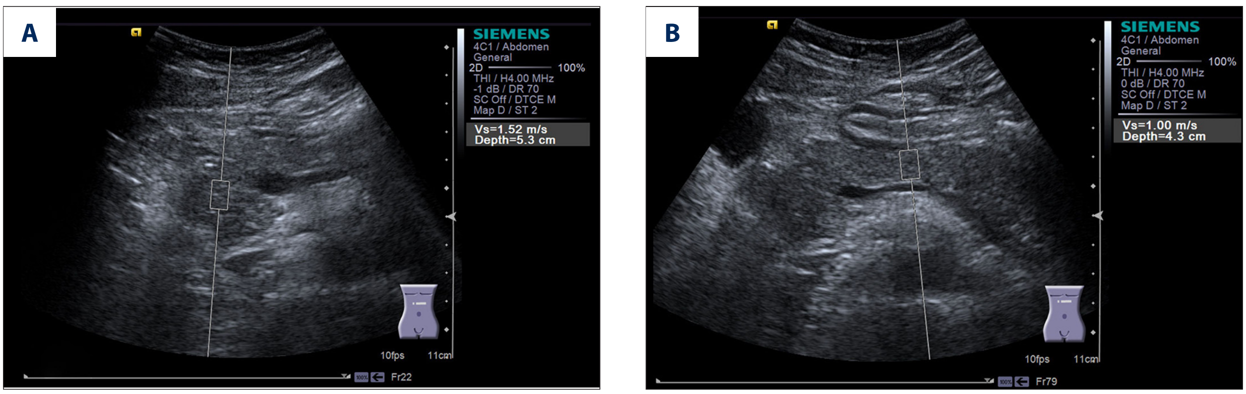

Figure 4. Measurement of the SWV of the pancreas using VTQ in patients with acute pancreatitis. The SWV at the pancreatic head (**A**) is 1.52 m/s and the SWV of the pancreatic body (**B**) is 1.00 m/s.

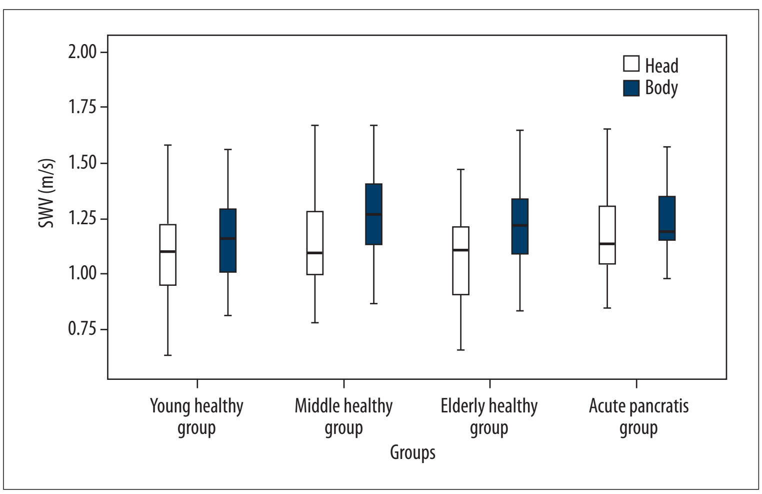

Figure 5. Box plots of the pancreatic SWVs in healthy volunteers and patients with acute pancreatitis, showing interquartile range (box), median (thick line), and range (vertical thin line) of tissue stiffness (SWV values) in head and body of pancreas in different groups.

own limitations. CT involves radiation exposure and fixed imaging, while the radiation-free MRI and MRCP can be time-consuming and expensive. It is currently difficult to justify the use of MRI for routine examinations of the pancreas. Since EUS and ERCP are invasive and generally cause considerable postoperative complications, candidates for ERCP need to be chosen carefully. Compared to these detection modalities, US imaging has distinct advantages in terms of low cost, lack of radiation, and ease of use. MRCP and B-mode US have been regarded as preferred imaging tools for screening purposes of patients with pancreatic disease, and the follow-up preferred imaging method of patients with pancreatic disease is B-mode US. Nevertheless,

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the diagnostic sensitivity of conventional ultrasound depends to some extent on the size and position of the lesion, its signal features, and the experience of the ultrasonographer. The quantitative diagnosis of pancreatic disease is relatively difficult.

Ophir et al. [13] first proposed the concept of elastography in 1991. There are 3 main types of US elasticity imaging: Real-time elastography (RTE), Transient elastography (FibroScan), and Acoustic Radiation Force Impulse (ARFI) Imaging. The real-time elastography or its combination with endoscopic ultrasound (EUS) can offer supplemental information to improve the accuracy of pancreas disease diagnosis, which presents a promising method in characterization and differentiation of the normal pancreas, as well as benign and malignant pancreatic tissues [14–18]. However, this elastography is not widely used because it is a qualitative technique based on the principle that tissue compression produces strain (displacement) within that tissue and the elastographic image acquisition is shown as strain images[19], and provide incomplete delineation of the border of lesions greater than 35 mm in diameter or of lesions too far from the transducer [20]. Transient elastography with FibroScan is one of most accurate methods and is mainly used for assessment of liver fibrosis [21]. Although the tissue stiffness measured by transient elastography is quantified and is well correlated with the fibrotic stages by biopsy specimens of the liver [22], the FibroScan method is not able to measure pancreatic stiffness because it needs at least a 6-cm depth. The ARFI technique has been recently introduced into clinical practice and can overcome the limitations of previous elastography techniques. It is operator-independent and more reproducible than conventional elastography. It can also provide estimations of local elasticity that are independent of local hardened areas of tissue. In recent decades, ARFI technology has increasingly become a focus of research. As a new examination tool, VTQ technology has the advantages of simplicity, convenience, wide availability, relatively low-cost, and it is reproducible. VTQ technology is not ready for widespread use, and its advantage will have to be confirmed by high-quality clinical studies with large sample sizes. It is currently mainly used for the investigation of various abdominal organs, breast, and thyroid [10,11,23–32]. In addition, the prostate and the uterus [33,34] have also been involved. However, the use of VTQ technology for pancreatic diseases is still in the initial stages. D'Onofrio et al. [35–37] have studied various pancreatic cystic lesions, and correctly diagnosed pancreatic cystadenoma, which mimicked a solid neoplasm at conventional imaging (US and CT), as cystic using ARFI imaging. The purpose of this study was to determine the elasticity values of the pancreas in healthy volunteers and patients with AP, which could lay the foundation for future studies of pancreatic lesions.

Elastometry in healthy adult volunteers did not highly significantly correlate with sex, age, height, weight, waist circumference, BMI, or organ dimensions. No statistically significant differences were found between the normal pancreas and AP SWVs. Mild and severe AP is characterized pathologically by edematous interstitial tissue and hemorrhage, respectively, with an inflammatory response against the former and parenchymal necrosis as a result of the latter. None of these pathological changes exert any influence on pancreas stiffness. Pancreatic fibrosis is a common feature of chronic pancreatitis (CP), in which copious fibroblast proliferation and extracellular matrix deposition can be seen histologically. Consequently, pancreatic stiffness values in CP may be higher than those in the normal pancreas, and this is in agreement with reports by Yashima et al. [38], which showed that the mean SWV values in the head, body, and tail of the pancreas were1.23±0.34 m/s, 1.30±0.34 m/s, and 1.24±0.50 m/s, respectively, in the healthy volunteers, and 1.65±0.71 m/s, 2.09±1.03 m/s, and1.68±0.84 m/s, respectively, in the CP patients. But our study finding was in contrast to the reported data of Mateen et al., which found that the mean SWV values were 1.28 m/s, 1.25 m/s, and 3.28 m/s for the normal, chronic, and acute pancreas, respectively [39]. It was further concluded that 1.63 m/s of SWV was used as a cutoff value for diagnosis of acute pancreatitis at initial hospital admission [40].

The VTQ technique is non-invasive, quantitative, and easy to perform. However, limitations are imposed by the fact that the VTQ penetration depth is restricted to 8 cm in curved array transducer, and the thick fat layer can affect the accuracy of the results when VTQ technology is applied to obese patients. In addition, the measurement is susceptible to interference from breathing. In this study, the measurement was technically not possible in 11.8% (34/288) of recruited patients for technical reasons because the pancreas could not be visualized or penetration of VTQ failed to reach the pancreas. Furthermore, the size of the sample box cannot be adjusted, which means that the sampling frame range may not be able to avoid the surrounding tissue, with consequent measurement errors. Because of medical technology advances, most cases of AP are diagnosed and treated in the early period of disease. Finally, it is difficult to correlate ARFI findings with histological findings. VTQ technology can be performed in the pancreatic head and body and was not performed on the tail in this study because imaging of the tail is also problematic with routine ultrasound.

Conclusions

In summary, VTQ is a novel elastography method, which is feasible and robust for the quantification of pancreatic elasticity. However, there was no discrimination of SWV values between in normal tissue and acute pancreatitis in this study. The possibility of VTQ having potential for differentiation in pancreatic masses as a non-invasive diagnostic tool can be assessed and verified with a large sample size in future studies.

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