Published in final edited form as:

Magn Reson Imaging. 2018 September ; 51: 113–119. doi:10.1016/j.mri.2018.04.019.

Pancreatic Stiffness Response to an Oral Glucose Load in Obese Adults Measured by Magnetic Resonance Elastography

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Abstract

Background: To test the feasibility of magnetic resonance elastography (MRE) for assessing changes in pancreatic stiffness of obese adults administered an oral glucose load.

Methods: MRE scans were performed on 21 asymptomatic obese volunteers (BMI = 27 kg/m²) before and after receiving a 75-g oral glucose load, and repeated in 7 days without a glucose load. Shear waves at 40 and 60 Hz were introduced into the upper abdomen by a pneumatic drum driver (diameter of 12 cm). Two radiologists subjectively graded the overall quality of the wave images of the pancreas using a scale from 1 to 4, in which suboptimal image quality was considered to be scores of 1 and 2.

Results: Good inter-observer agreement was found for image quality at both frequencies ($\kappa = 0.805$ for 40 Hz and 0.762 for 60 Hz). The median overall image quality score was significantly higher in 40 Hz than that of 60 Hz (4 versus 2). At 40 Hz, pancreatic stiffness in response to oral glucose had a decrease of 6.7% (pre vs post: 1.17 ± 0.13 kPa vs 1.08 ± 0.12 kPa; $P < 0.001$), whereas the change in stiffness was not significant at 60 Hz (pre vs post: 2.01 ± 0.21 kPa vs 2.02 ± 0.24 kPa; $P = 0.695$). Excellent intersession agreement was found for MRE acquisitions at 40 Hz with an overall intraclass correlation coefficient = 0.947 (95% confidence interval: 0.913–0.967).

Conclusion: MRE at 40 Hz provides good-quality wave images and high sensitivity to changes in the mechanical properties of pancreatic tissue in obese volunteers after an oral glucose load.

Keywords

magnetic resonance elastography; pancreas; glucose; obese

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Conflict of Interest:

The authors declare that they have no conflict of interest.

1. Introduction

Pancreas disorders such as pancreatitis and pancreatic cancer is one of the most frequent gastrointestinal causes for hospitalization worldwide [1]. Accurate discrimination of chronic pancreatitis, premalignant lesions, and pancreatic cancers with overlapping radiological and clinical features is highly challenging in the clinical setting [2–5]. Moreover, highly specific and sensitive imaging and/or laboratory markers that can complement the current imaging modalities are not available for the early detection of pancreatic diseases [4, 6–8].

Magnetic resonance elastography (MRE) as an emerging imaging method can measure the mechanical properties of biological tissues by imaging and processing the propagating shear waves [9, 10]. Many pathological processes, such as inflammation, fibrosis, tumor, and congestion have been shown to cause marked changes in the MRE-assessed liver stiffness, which is manifested by the changed wavelengths of the propagating shear wave traveling through diseased tissues [11, 12]. MRE studies in pancreas have also demonstrated the promise in differentiating normal pancreas from diseased ones [13, 14]. In pancreatic MRE, previous feasibility and reproducibility studies were performed at vibration frequencies of 40 and 60 Hz using a spin-echo echo-planar-imaging (SE-EPI) sequence [14–16]. However, further evaluation of the wave quality at different vibrational frequencies among individuals with different Body Mass Index (BMI) has not been investigated. The wave penetration in individuals with high BMIs tend to be inhibited by the large volumes of tissue between the MRE driver and the deep-seated pancreas [15]. Given overweight/obesity is an established risk factor for both pancreatitis and pancreatic cancer, optimizing the driver set-up for the effective wave penetration in large BMI subjects is needed [17].

In pancreas, the blood perfusion, especially to the islets, is normally coupled with insulin released in response to changes in the concentrations of blood glucose [18]. The blood glucose level increases markedly and peaks 30–40 min after the administration of a 75-g oral glucose load (OGL) [19]. Given by the fact that increased blood perfusion could affect the mechanical properties of various organs [16], we hypothesized that with the optimized driver set-up, pancreatic MRE would be feasible and sensitive for detecting changes in the pancreatic stiffness of obese volunteers in response to an OGL. To the best of our knowledge, MRE has not yet been used to investigate the effects of an OGL on the pancreas. Hence, in this study, we first evaluated the performance of different drivers for obese volunteers. Then, we used the optimized driver set-up to characterize the changes of pancreatic stiffness in response to an OGL.

2. Materials and Methods

2.1 Study participants

This prospective study was compliant with the Health Insurance Portability and Accountability Act and approved by the Institutional Review Board of our local hospital. Written informed consent was obtained from all participants, who were recruited from the community and hospital visitors and staff between March 2017 and October 2017. Participants aged 18 y with a BMI 27 kg/m² were initially enrolled. Exclusion criteria included the following: (1) history of pancreatitis or pancreatic mass; (2) pregnancy; (3)

Type 1 diabetes or evidence of glucose intolerance on a standard 75-g oral glucose tolerance test (OGTT); (4) alcohol or tobacco abuse (for excluding patients with chronic asymptomatic pancreatitis); (5) abnormal serum amylase and lipase levels; (6) abnormal pancreatic magnetic resonance imaging (MRI) findings as determined by a senior radiologist with 20 years of experience in abdominal imaging; and (7) methodological failure of MRE scan, including poor breath holding and intolerance to the driver stimulus. Finally, the study included a total of 21 obese adult volunteers (mean age: 39.7 ± 10.6 years; BMI: 30.0 ± 2.0 kg/m²; 12 male/ 9 female).

This study had 2 stages. The first stage compared the performance of 6 different drivers on 5 volunteers at both 40Hz and 60Hz, respectively. The second stage used the optimal driver evaluated in the first stage to perform MRE scans on all study participants before and after an OGL at both 40 Hz and 60 Hz.

2.2 First stage

Five of the 21 volunteers were recruited to participate. Five round pneumatic drum drivers with the diameters of 19 cm (D19), 12 cm (D12), 9 cm (D9), 7.5 cm (D7.5), and 4 cm (D4) [20] and one rectangular soft driver (19 cm×14 cm) [15] were separately placed in the middle of the upper abdomen and tightly secured with an elastic band that was wrapped around the participant (Figure 1). The D12, D9, D7.5, and D4 drivers were composed of acrylic plastic, and the drum head consisted of 0.02-cm thick polycarbonate plastic, similar to the cardiac driver reported by Kolipaka [20]. The soft driver is a pillow-like, passive driver and consists of a soft, inelastic fabric cover over a porous, springy mesh, previously used in renal and pancreatic studies [15, 21]. These 5 drivers were developed in house by the Mayo Clinic (Rochester, MN, USA) and were given to our institution, along with a service agreement. The largest D19 driver is a commercial product of MR Touch (Resoundant, Rochester, MN, USA). Briefly, the results showed that D19 and D12 produced the best wave images (details in the Results). D12 produced slightly better wave images than D19 and was used for all study participants in the second stage of the study.

2.3 Second stage

Twenty-one participants underwent 3 MRE scanning sessions (session 1: before an OGL, session 2: after an OGL, and session 3: repetition of session 1 in seven days). Each MRE session consisted of 2 MRE scans at 40- and 60 Hz. Each participant was asked to fast overnight for at least 6 hours before undergoing MRE. After the first MRE session, the participant ingested 300 mL of a solution containing 75-g of glucose over a 1-min period, and the time right after drinking was set as time zero. Thirty-five minutes later, the participant underwent the second MRE session. Between session 1 and 2, the participant was removed from the MRE table and allowed to rest. Seven days later, each participant underwent the third MRE session, which was equivalent to the first session (no ingestion of glucose solution), to test the reproducibility of MRE acquisition. The same operator performed all the exams.

2.4 MRE pulse sequence

All MR examinations were performed on a 3.0 Tesla (T) MRI scanner (Signa EXCITE HD MRI System; GE Healthcare) using an 8-channel phased-array surface coil. The three-dimensional wave field was acquired by a two-dimensional, single-shot, SE-EPI sequence with flow-compensated motion-encoding gradients. Thirty-two consecutive slices were acquired within 5 breath holds (4 of 22 sec and 1 of 11 sec) at 40 Hz and 3 breath holds (3 of 21 sec) at 60 Hz. The other imaging parameters for MRE were as follows: repetition time = 1375 for 40 Hz and 1334 for 60 Hz; the 40-Hz and 60-Hz echo times for any particular patient were the same, and ranged from about 37.7–40.5 ms, depending on the patient weight; field of view = 36–44 cm; matrix size = 96×96 ; slice thickness = 3.5 mm; phase offsets = 3.

2.5 MRE data processing and imaging Analysis

The post-processing software was integrated with the MRE pulse sequence. Within 2 minutes after MRE scanning, the wave images were processed automatically to generate tissue stiffness maps (elastograms), which quantitatively depict mechanical properties. The elastogram was created with a direct inversion (DI) algorithm as previous described [15, 22].

The acquired motion data in MRE include the 3 components (X, Y, and Z) of the vector displacement field throughout the pancreas. This motion included information about the shear and longitudinal wave propagation in the tissue. The shear wave information was isolated and the longitudinal wave information was suppressed by calculating the vector curl of the measured displacement data for each MRE time point. The Fourier transform was then applied through the time domain to isolate the curl wave information that occurred at the vibration frequency (called the “first harmonic” in MRE) and to suppress information and artifacts that were in the images at other temporal frequencies. Since the curl (or curl-filtered) wave data are used to calculate the stiffness information in the tissue, the quality of the wave information was assessed in the curl-filtered wave data.

The image quality of the wave images was then subjectively rated based on a 4-point scale. Scores 1 to 4 were defined as failure, poor, fair to good and excellent, respectively (Figure 2, Table 1). Suboptimal image quality was considered to be scores of 1 and 2. The ratings for image quality and measurements of pancreatic stiffness were assessed separately for each pancreatic subregion (head, body, and tail). Regions of interest (ROIs) were drawn within the largest dimension of each subregion, based on the magnitude of MRE images, with 1 ROI per subregion. Each ROI encompassed as much of the involved pancreatic parenchyma as possible, while avoiding the pancreatic border, large vessels, and the surrounding tissues. The ROIs were then transferred automatically to the wave images for image quality assessment and to the elastograms for stiffness measurements (kPa).

Two radiologists (primary radiologist Y.S. and secondary radiologist Y.L., with 5 and 3 years, respectively, of experience with MRE interpretation) each independently performed the pancreatic stiffness measurements and image quality assessments. They were blinded to each other's results. After the inter-observer agreements were examined, the final image

quality rating for each participant was determined by consensus; and the final stiffness estimation was derived from the mean of the 2 measurements obtained by each observer.

2.6 Statistical analysis

The pancreatic stiffness measurements and image quality ratings for each participant were organized according to the assessed subregions (pancreatic head, body, and tail), sessions (first, second and third), frequencies (40 and 60 Hz) and observers (primary and secondary). The image quality scores were expressed as interquartile range (IQR; 25th quartile- 75th quartile). The pancreatic stiffness values of each subregion were expressed as means $\pm$ standard deviation. Cohen's kappa value was calculated to assess the interobserver variability for scoring image quality. The intraclass correlation coefficient (ICC) was calculated to assess interobserver agreement and intersession agreement for stiffness measurements. The image quality scores and pancreatic stiffness values before and after an OGL and for the 2 vibration frequencies were compared by the paired Wilcoxon signed-rank test. Statistical analysis was performed using GraphPad Prism V.6.02 (GraphPad Software Inc, San Diego, CA, USA) and SPSS Version 22.0J (SPSS Inc, Chicago, IL, USA). *P* values < 0.05 were considered statistically significant.

3. Results

3.1 First Stage

With 15 subregions in 5 participants in stage 1, the image quality produced by the D4 and D7.5 drum drivers at 40 Hz showed diagnostic-quality wave images (scores ≥ 3) in 0 out of 15 and 4 out of 15 subregions, respectively. Both D9 and soft driver produced score ≥ 3 in 9 subregions. D12 and D19 produced scores ≥ 3 in all participants and all subregions, with score = 4 in 13 and 12 subregions, respectively. As shown in Figure 3, the waves generated by the small drivers (D4 and D7.5) were superficial and less parallel. D9 produced waves of adequate wave amplitude at the pancreatic body, but waves of low amplitude at other subregions. The largest driver (D19) appeared to produce waves that had the deepest penetrations and more parallel; the organs within the abdominal cavity (liver, spleen and kidneys) were all clearly illuminated. When compared with liver and spleen, the pancreas was slightly less illuminated. The second largest driver (D12) produced more parallel and deeper waves than D9, D7.5, D4 and the soft driver. These waves also showed slightly higher amplitudes of the pancreas than D19, and lower wave amplitudes of the liver, spleen, and kidneys than D19. D12 was subsequently used for the second stage of our pancreatic study.

At 60 Hz, all drivers produced waves with lower amplitude when compared with 40 Hz. D4 and D7.5 drum drivers produced scores ≥ 3 in 0 and 1 subregion, respectively. D9 produced score ≥ 3 in 3 subregions. Soft driver produced score ≥ 3 in 2 subregions. Both D12 and D19 produced scores ≥ 3 in 7 subregions.

3.2 Second stage: assessments of image quality

The overall score for image quality (median score: 4, IQR: 4–4) at 40 Hz was significantly higher than the score at 60 Hz (median score, 2; IQR: 1–3, *P*<0.001) (Figure 4). Both

frequencies showed strong interobserver agreement for image quality ($\kappa=0.805$ for 40 Hz and 0.762 for 60 Hz). Of the 63 total subregions in 21 volunteers, the 40 Hz images before and after an OGL were of diagnostic quality (scores 3–4) in 93.6% (59 of 63) and 90.4% (57 of 63), respectively. Specifically, the 10 failed subregions (total of 126 measurements) at 40 Hz (4 before and 6 after an OGL) included 3 of the pancreatic head and 7 of the tail. MRE at 60 Hz frequency produced diagnostic-quality images before and after an OGL of 42.9% (27 of 63) and 41.3% (26 of 63), respectively, which were significantly lower values than those produced by 40 Hz (both $P<0.001$).

3.3 Second stage: pancreatic stiffness measurements

The plots of the mean pancreatic stiffness values of the subregions are shown in Figure 5 and listed in Table 2. The pancreatic stiffness values at 60 Hz both before and after an OGL (pre/post: 2.01 ± 0.21 kPa/ 2.02 ± 0.24 kPa) were significantly higher than the values obtained at 40 Hz (pre/post: 1.17 ± 0.13 kPa/ 1.08 ± 0.12 kPa), both $P<0.001$. After an OGL, the overall pancreatic stiffness at 40 Hz MRE decreased (-6.7% , $P<0.001$), whereas the difference in stiffness before and after an OGL at 60 Hz was not significant ($P=0.695$). The pancreatic stiffness of each subregion after an OGL at 40 Hz was significantly lower than before an OGL ($P=0.003$ for head, $P<0.001$ for body and $P=0.002$ for tail). The stiffness changes at 60 Hz for the pancreatic head and tail were not significant ($P=0.698$ and $P=0.759$, respectively), but the changes in the body were significant, with a higher mean value after an OGL ($P=0.037$), as shown in Figure 6.

Excellent intersession (first vs third session) MRE agreement was found for acquisitions at 40 Hz, with an ICC = 0.947 (95% confidence interval (CI): 0.913–0.967, $P<0.001$), while the ICC equal to 0.704 (95% CI: 0.547–0.812, $P<0.001$) at 60Hz. The ICC for intersession (first vs second session) MRE agreement was 0.624 (95% CI: -0.082 –0.878, $P<0.001$) at 40 Hz and 0.667 (95% CI: 0.223–0.860, $P=0.004$) at 60Hz. The ICC for intersession (second vs third session) MRE agreement was 0.688 (95% CI: 0.266–0.869, $P=0.002$) at 40 Hz and 0.591 (95% CI: 0.056–0.827, $P=0.009$) at 60Hz.

4. Discussion

We have presented a multislice SE-EPI MRE protocol for the assessment of pancreatic stiffness in obese volunteers and used the protocol to examine changes in pancreatic stiffness before and after glucose intake. According to the 4-point scale wave classification developed in this study, and we found that the large drum drivers (D19 and D12) produced diagnostically useful wave images of the pancreas at 40 Hz. D12 at 40 Hz produced good-quality images for >90% of subregions, whereas it produced good-quality images for less than 50% of subregions at 60Hz. Moreover, MRE at 40 Hz could detect the small changes in stiffness induced by OGL; whereas the 60 Hz MRE produced inconsistent results due to highly dampened wave penetration. This suggests that MRE at 60 Hz may not be able to accurately characterize the pancreas stiffness in obese populations.

Currently, there is no standard to quantitatively or qualitatively assess the MRE wave data. In this study, we developed a 4-point scale classification to visually evaluate the quality of wave propagation, illumination of the pancreas on the images of the waves, and wave

magnitudes. Although visual evaluation of wave quality is a subjective process, the interobserver agreement in our study was very good. The visual evaluation of wave data has also been described by several studies that used SE-EPI MRE [9, 14, 15]. To the best of our knowledge, our study was the first to describe a 4-point scale for the semi-quantification of image quality derived from the wave data. Our scoring system should facilitate validation of wave data and direct comparisons among different driving systems.

As shown in previous studies [14, 15], the 40 Hz driving frequency has always produced better quality of wave data than the 60 Hz. Our study also found that the image failure rate at 60 Hz was over 50%, in which the 60 Hz waves cannot propagate throughout the entire deep-seated pancreas. The small drum drivers (D4 and D7.5) appeared to deliver waves superficially, showing narrow penetration and less parallel waves, with illumination only immediately under the skin or confined to the pancreatic body. The largest driver (D19) propagates waves along the bony skeleton, so that the organs near the bones such as liver, spleen, and kidneys were all well illuminated. The second largest driver (D12) appeared to produce good, balanced results showing direct propagation of waves at depth and indirect propagation via boney tissue for widely disseminated waves. However, 40 Hz produced 10 failed measurements out of the 126 measurements of subregions, involving MRE of the head and tail. This failure might due to the shorter distance to passive driver for the waves propagated to the pancreatic body as opposed to the distances the waves travel to the pancreatic head and tail.

Dittmann et al [16] addressed the hypothesis that water intake might increase vascular flow and organ perfusion, which would lead to stiffness changes in the organs of the upper abdomen. We changed the external load of water to a glucose load, which would target the pancreas. We proposed this modification for 2 reasons. First, pancreatic islets are highly vascularized. The perfusion of pancreatic islets exceeds that of the exocrine parenchyma by 5- to 10-fold [18]. The major factor affecting pancreatic blood flow with regard to the islets is the blood glucose level [23]. The MRE scan during the second session was performed 35 min after glucose ingestion, based on data from OGTTs, which should lead to a maximum increase in pancreatic blood perfusion [19]. Second, the pancreas can be deformed by a full stomach [15]. One liter of water will compress and distort the shape of a normal pancreas. Consistent with Dittmann's results, we also found that at 40 Hz, the pancreatic stiffness decreased. Previous studies have shown that the state of perfusion affects the stiffness of organs. Increased blood perfusion leads to increased stiffness of organs such as the kidney [24] and liver [25, 26], but might lead to decreased stiffness of organs such as the pancreas and spleen [16]. MRE produces the combination of a static component that reflects the stiffness of the parenchyma and a dynamic additive component, which represents the hydrostatic effect of perfusion pressure [24, 27]. Our result is consistent with Dittmann's study that the pancreas might have high tissue compliance, which produces a higher fluid to solid ratio, instead of increased inner stress. The high tissue compliance thus results in reduced shear stiffness. Therefore, MRE should be performed according to standardized protocols; otherwise the uptake of water or glucose by a tissue could produce confounding effects with regard to the diagnostic accuracy of MRE.

Our study has several limitations: 1) the study enrolled a small number of volunteer participants; 2) only two frequencies at 40 and 60Hz were investigated. A wider range of other frequencies should be evaluated in the future to identify the optimal frequency for pancreatic MRE; 3) the driver performance was only evaluated on 5 volunteers. Although our study found that both D12 and D19 produced diagnostic-quality images, further studies comparing these drivers on clinical cases are needed; 4) the assessment of image quality remained subjective and semiquantitative, and further development of a more objective method to guarantee the wave quality for SE-EPI MRE is urgently needed; and 5) obesity poses challenges for MRE, and further studies should evaluate additional factors that could affect MRE measurements, such as height, waist circumference and amount of subcutaneous fat, etc.

5. Conclusion,

we demonstrated that SE-EPI MRE of the pancreas can provide promising and stable stiffness measurements throughout the pancreas. Large pneumatic drum drivers (D12 and D19) are favorable for producing highly reproducible pancreatic SE-EPI MRE measurements from obese volunteers. Compared with the 60 Hz data, wave at 40 Hz produced better-quality wave images and was more sensitive to changes in the mechanical properties of the pancreas in response to glucose uptake.

Acknowledgments:

We thank Richard L Ehman, Jun Chen and Kevin J Glaser from the Mayo Clinic for providing the MRE system and the tailored pancreatic MRE drivers.

Founding:

This work was supported by National Natural Science Foundation of China [grant numbers: 81771802, 81771893, 81401376 and 81471718]; Outstanding Youth Foundation of China Medical University [grant numbers: YQ20160005]; National Institutes of Health [grant numbers: EB001981]; National Key R&D Program of China [grant numbers: 2016YFC0106804] and Support program for innovative talents of in universities of Liaoning Province [grant numbers: LR2016020].

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Figure 1:

Representative images of different drivers for magnetic resonance elastography of the pancreas. From left to right: soft rectangular driver, pneumatic driver with the diameter of 19 cm (a commercial product of GE MR-Touch system), and Pneumatic drivers with the diameter of 12 cm, 9 cm, 7.5 cm, and 4 cm, as well as MRE setup with the passive driver positioning.

Figure 2:

The image quality of wave images was rated based on a 4-point scale. Scores 1 to 4 were defined as failure, poor, fair to good and excellent, respectively. Suboptimal image quality was considered to be scores of 1 and 2.

Figure 3:

Representative images of magnitudes, elastograms, and wave images of the x, y, and z components of the vector displacement field generated by magnetic resonance elastography driven by pneumatic drum drivers with diameters of 19 cm, 12 cm, 9 cm, 7.5 cm, and 4 cm as well as a soft driver. The wave data produced by D19 and D12 showed adequate wave amplitude of the three components of the vector displacement field. D9 and the soft driver produced lower wave amplitude than D12 and D19. D7.5 showed some wave propagation but with low wave amplitude, and D4 produced very minimally observable waves.

Figure 4:

Four-point scale of image quality analysis of wave images produced by magnetic resonance elastography. The overall image quality of 63 subregions (head/body/tail in 21 volunteers) was rated based on a 4-point scale, as shown by the shaded bars. Scores of 1 to 4 were defined as failure, poor, fair to good and excellent, respectively, at 40 Hz and 60 Hz frequencies before and after an oral glucose load (OGL). The median overall image quality scores before and after an OGL were 4 and 2 for 40 and 60 Hz, respectively. The number of failed subregions (scores of 1 or 2) before and after an OGL was 4 and 6, respectively for 40 Hz, and 27 and 26, respectively, for 60 Hz.

Figure 5:
Effects of glucose loading on pancreatic stiffness in different pancreatic subregions at frequencies of 40 and 60 Hz. * $P<0.05$, ** $P<0.01$.

Figure 6:

Images of magnetic resonance elastography at 40- and 60 Hz frequencies. Magnitude images (first column), elastograms (second column), and wave images of the 3 components of the vector displacement field (third, fourth, and fifth columns) at 40 Hz and 60 Hz in an obese volunteer with a body mass index = 28.7 kg/m^2 before (first and third rows) and after oral glucose loading (second and last rows). The pancreas is outlined in all images. The wave images show good image quality at 40 Hz with image quality scores of 4 for 40 Hz before and after glucose, and suboptimal wave image quality at 60 Hz, with scores of 2 before glucose and 1 after glucose.

Table 1:

Description of The 4-Point Scale Used to Assess Wave Image Quality

Score	Description	
4	Excellent	Wave penetration with high wave amplitude and the waves primarily propagating along the length of the pancreas
3	Fair to good	Wave penetration with average-to-high wave amplitude and the waves mostly propagating along the length of the pancreas, but with some regions showing wave interference due to waves propagating in other directions
2	Poor	Wave penetration with low wave amplitude and wave interference in most of those regions
1	Failure	No waves observable in the pancreas

Table 2:

Magnetic Resonance Elastography Measurement of Shear Stiffness (kPa) in the Main Pancreatic Subregions (Mean±Standard Deviation) of Obese Volunteers

Frequency	Subregions	Before glucose	After glucose	<i>P</i> value*
40 Hz	Head	1.12±0.13	1.04±0.12	0.003
	Body	1.19±0.12	1.09±0.11	<0.001
	Tail	1.19±0.12	1.12±0.13	0.002
	Total	1.17±0.13	1.08±0.12	<0.001
60 Hz	Head	1.97±0.13	1.91±0.23	0.698
	Body	2.07±0.24	2.18±0.23	0.037
	Tail	1.98±0.22	1.96±0.17	0.759
	Total	2.01±0.21	2.02±0.24	0.695

* The *P* values were calculated by the paired Wilcoxon signed-rank test for each dataset before and after glucose loading.