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1 **Examination of Pelvic Floor Muscle Elasticity in Patients with Interstitial**
2 **Cystitis/Bladder Pain Syndrome Using Real-time Tissue Elastography**

3

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33 Yui Abe-Takahashi: Data collection, management, data analysis, manuscript

34 writing/editing

35 Takeya Kitta: Protocol/project development, manuscript writing/editing

36 Mifuka Ouchi: Data collection, manuscript writing/editing

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- 40 Nobuo Shinohara: Protocol/project development, manuscript writing/editing

41

42 **Abbreviations**

- 43 ANOVA, analysis of variance
- 44 BMI, body mass index
- 45 IC/BPS, interstitial cystitis/bladder pain syndrome
- 46 ICPI, Interstitial Cystitis Problem Index
- 47 MPQ, McGill Pain Questionnaire
- 48 SF-36, MOS 36-Item Short-Form Health Survey
- 49 ICSI, O’Leary-Sant Interstitial Cystitis Symptom Index
- 50 PFM, pelvic floor muscle
- 51 RTE, real-time tissue elastography
- 52 SR, strain ratio
- 53 SWE, shear wave elastography
- 54 SUS, striated urethral sphincter

55 VAS, Visual Analogue Scale

56 2D, 2-dimensional

57

58

59 **Abstract**

60 **Introduction and hypothesis**

61 The aim was to compare pelvic floor muscle (PFM) elasticity between interstitial
62 cystitis/bladder pain syndrome (IC/BPS) patients and healthy women using real-time
63 tissue elastography.

64 **Methods**

65 The subjects were 17 IC/BPS female patients (IC/BPS group; age 34-84 years), 10
66 healthy middle-aged women (Middle-aged group; 50-80), and 17 healthy young adult
67 women (Young group; 23-37). The target sites of elastography were the striated
68 urethral sphincter (SUS) and adipose tissue as the reference site; muscle elasticity was
69 calculated as the strain ratio (SR) of the SUS to the reference site. Evaluations were
70 performed at rest and during PFM contraction. The IC/BPS group completed lower
71 urinary tract symptom and pain questionnaires. SUS SR was compared among the
72 three groups. SUS SR at rest and during PFM contraction was compared among the
73 three groups with the *t*-test and the Wilcoxon test. Associations between questionnaire
74 results and SUS SR were evaluated by correlation analysis.

75 **Results**

76 There was no significant difference in age between the IC/BPS and Middle-aged

77 groups, but the Young group was significantly younger than the other groups ($p < 0.001$).
78 SUS SR at rest was significantly higher in the IC/BPS group than in the Middle-aged
79 ($p = 0.014$) and Young groups ($p = 0.002$). Furthermore, in the IC/BPS group, there was
80 no significant difference in SUS SR between at rest and during PFM contraction. SUS
81 SR was not significantly correlated with questionnaire results for lower urinary tract
82 symptoms.

83 **Conclusion**

84 SUS SR at rest was significantly higher in the IC/BPS group than in the Young and
85 Middle-aged groups.

86

87 **Key words**

88 Elasticity, Strain ratio Interstitial Cystitis/Bladder Pain Syndrome, Pelvic floor muscles,
89 Real-time tissue elastography

90

91 **Brief summary**

92 Pelvic floor muscle strain ratio was significantly higher in the interstitial
93 cystitis/bladder pain syndrome group than in the young and middle-aged groups

94 **Introduction**

95 Interstitial cystitis/bladder pain syndrome (IC/BPS) is a collective term for a chronic
96 debilitating condition characterized by chronic urologic pelvic pain, bladder pain,
97 frequency, and urgency associated with lower urinary tract symptoms [1]. A previous
98 study reported that the best estimate of the prevalence of clinically confirmed probable
99 IC/BPS in women was 300 cases per 100,000 [2]. Furthermore, the incidence of
100 IC/BPS has been shown to be higher in women, with a male to female ratio of 1:5.8 [3].
101 However, the etiology of IC/BPS is not fully understood, so no treatment has yet been
102 established [4].

103 In IC/BPS patients, transvaginal palpation reveals increased pelvic floor muscle
104 (PFM) tone [5,6]. Pain arising from PFMs with myofascial trigger points is believed to
105 result from an excessive release of acetylcholine from neuromuscular junctions after
106 chronic muscle hyper contraction. Pelvic floor hypertonicity, characterized by an
107 increase in the tonic activity of a pelvic floor muscle, is present in up to 85% of
108 patients with IC/BPS [7]. According to a previous report, 78% of IC/BPS patients have
109 pain in the PFMs [8], and it has been reported that manual stretching of the PFMs, such
110 as the pubococcygeus muscle, significantly improved the pain and symptoms [5]. The
111 American Urological Association guidelines report that stretching of the PFMs with

112 manual physical therapy techniques for IC/BPS patients is evidence strength grade A
113 [1]. Therefore, PFM elasticity may affect lower urinary tract symptoms and pain.

114 Recently, ultrasound elastography has received much attention as a novel imaging
115 technique that is non-invasive and easily accessible. In the field of oncology, this
116 technique has been reported to be useful for the diagnosis of cancer [9]. Ultrasound
117 elastography can be used to quantify tissue elasticity, and there are two types of
118 ultrasound elastography: real-time tissue elastography (RTE) and shear wave
119 elastography (SWE). RTE is the most widely used technique to evaluate tissue
120 elasticity. In RTE, the sonographer manually compresses the ultrasound transducer
121 against the patient's body surface. Tissue deformation, represented by strain, is
122 measured in a 2-dimensional (2D) region under the transducer (typically the full field
123 of view) and is displayed as an elastogram. Given the same amount of applied stress,
124 softer tissue in the elastogram has more deformation and therefore experiences greater
125 strain than stiffer tissue [10]. SWE is an ultrasound elastography technique that uses
126 shear waves to measure tissue stiffness quantitatively. Shear waves are tracked by
127 pulse-echo ultrasound and can be used to quantitatively calculate the tissue modulus
128 (i.e., stiffness); as the stiffness of underlying tissue increases, shear-wave speed
129 increases [11].

130 In recent years, there have been reports on the quantification of muscle elasticity by
131 SWE using the target PFM as a striated urethral sphincter (SUS) [12]. SUS provides a
132 capacity is considered a major contributor to urinary incontinence [13]. Aljuraifani et
133 al. [12] showed the relationship between muscle activity and SUS stiffness obtained by
134 needle electromyography of the levator ani muscle in healthy women has been shown.
135 The results show that SWE could remove barriers to widespread functional assessment
136 of SUS caused by the need to use invasive recording methods.

137 Quantitative assessment of PFM elasticity in IC/BPS patients has not yet been
138 reported. We hypothesized that PFM stiffness would be higher in IC/BPS patients than
139 in healthy adult women, and furthermore, that it would be significantly correlated with
140 pain and lower urinary tract symptoms. Therefore, the primary objective of this study
141 was to compare PFM elasticity between IC/BPS patients and healthy women using
142 RTE, which is widely used in clinical practice. The second objective was to investigate
143 the relationship between PFM elasticity and lower urinary tract symptoms.

144

145 **Materials and methods**

146 **Subjects**

147 This was a prospective, observational study. A convenience sample of 17 IC/BPS

148 female patients (IC/BPS group), 10 healthy middle-aged women (Middle-aged group),
149 and 17 healthy young adult women (Young group) was recruited for this study. This
150 study was conducted at the Department of Urology in our University. Seventeen
151 IC/BPS patients diagnosed with IC/BPS who visited the urologist from October 2018
152 to July 2019 were included, and 27 healthy middle-aged and young adult women
153 volunteered. The inclusion criterion for the IC/BPS group was a diagnosis of IC/BPS
154 in accordance with European and East Asian clinical guidelines on IC/BPS [14]. The
155 differential diagnosis of IC/BPS is made by cystoscopy to determine the presence of
156 Hunner lesions (reddish mucosal lesions accompanied by abnormal radial capillary
157 structures) and glomerulations (mucosal bleeding after bladder distension). All IC/BPS
158 patients underwent cystoscopic hydraulic dilatation under anesthesia. IC/BPS was
159 categorized into two subtypes based on these cystoscopic findings: IC/BPS with and
160 without Hunner lesions. Participants were excluded if they had stress urinary
161 incontinence or pelvic organ prolapse. Given this was a proof of concept study with no
162 a priori data available for sample size estimation, the sample size was based on a
163 sample of convenience. This was a prospective, observational study. The present study
164 was approved by the Scientific Ethics Committee of Hokkaido University (#018-0404),
165 and all patients provided their informed consent.

166

167 **Procedure**

168 The target PFM was the SUS in accordance with previous studies [12]. Clinically, it is
169 important to objective and quantitatively assess pelvic floor dysfunction in IC/BPS to
170 better understand the etiology of pelvic floor hypertonicity and ensure complete
171 symptom resolution. Activation of SUS has been reported in conjunction with levator
172 ani muscle during voluntary pelvic floor contractions [15]. Although ultrasound
173 imaging enables assessment of levator ani muscle function via movement of ano-rectal
174 junction and bladder neck, it cannot assess levator ani muscle of elastography. New
175 methods are required. Therefore, in this study, the target PFM was the SUS. The
176 elasticity of the SUS was quantified using a real-time ultrasound imaging device with
177 RTE functionality (ARIETTA 70, HITACHI, Aloka, Japan). Measurements were
178 performed with the patients in the supine position with an empty bladder in all cases. A
179 linear probe (frequency range: 3-7 MHz) was placed on the perineum in the
180 mid-sagittal plane such that the urethra and pubic symphysis were in view (Fig. 1, 2a).

181 First, the SUS was located by transperineal ultrasound. Transperineal elastography
182 was carried out immediately after the conventional gray-scale ultrasound image was
183 acquired. Therefore, gray-scale ultrasound and elastography images were shown

184 simultaneously. Images were obtained by applying repetitive light pressure on the skin
185 of the perineum, two or three times per second, with the probe, positioned
186 perpendicular to the skin when applying pressure. The examiner manually and
187 rhythmically pressed the transducer to the muscle while monitoring the strain graph of
188 the pressing force shown on the ultrasonic apparatus to ensure consistency (Fig. 3).
189 During the measurement, the amplitude of the up-and-down movement of the probe
190 was set to about 1-2 mm, and the speed of the probe movement was set to 1-2 times
191 per second. In this study, the ultrasound manipulation of all subjects was performed by
192 a single examiner. Measurements were taken in two conditions: at rest and during PFM
193 contraction. They were measured three times each.

194 The tissue elasticity information was displayed in color, with blue indicating hard
195 tissue, green indicating medium tissue stiffness, and red indicating soft tissue.

196 Elastic parameters used strain ratio (SR) values. Based on the principle that less
197 elastic tissue deforms more than more elastic tissue, a higher strain ratio indicates less
198 elasticity [16]. Muscle elasticity was calculated using the SR, and the region of interest
199 (ROI) was set with the SUS as the target site (A) and adipose tissue as the reference
200 site (B), and the value (B/A) was calculated by dividing the reference site by the target
201 site. The anatomical location of the SUS has been confirmed to be in the area

202 surrounding the anterior aspect of the urethra from the bladder neck [17]. The location
203 of the reference site was set in the adipose tissue, referring to previous reports [18] on
204 the anatomy of the female pelvic floor. Referring to previous studies [12], ROI A was
205 set 10 mm anterior to the urethra and 15 mm above the pubic bone (1.5 mm × 1.0 mm),
206 and ROI B was set 5-10 mm below ROI A (Fig. 2b).

207 The following questionnaires for lower urinary tract symptoms and pain were
208 selected: O’Leary-Sant Interstitial Cystitis Symptom Index (ICSI) and Interstitial
209 Cystitis Problem Index (ICPI), McGill Pain Questionnaire (MPQ), the Visual Analogue
210 Scale (VAS), and the MOS 36-Item Short-Form Health Survey (SF-36). These
211 questionnaires were completed only by the IC/BPS group. The ICSI and ICPI has been
212 proposed as a treatment outcome measure in IC/BPS. In this study, these
213 questionnaires were not administered to the Middle-aged and Young groups because
214 they were healthy, and no patients had lower urinary tract symptoms or pain. Data on
215 age, body mass index (BMI), and duration of illness for the IC/BPS group were
216 collected from hospital medical records.

217

218 **Statistical analysis**

219 Comparisons among the three groups in age, BMI, and SUS SR (at rest and during

220 PFM contraction) were analyzed using the Kruskal-Wallis test, one-way analysis of
221 variance (ANOVA), and multiple comparative studies. A nonparametric test and the
222 Mann-Whitney U test were performed by applying the appropriate significance level
223 ($0.05/3 = 0.016$), which was adjusted by post hoc Bonferroni testing. Within-group
224 comparisons of SUS SR (at rest and during PFM contraction) for the IC/BPS group,
225 Middle-aged group, and Young group were performed using the *t*-test and the
226 Wilcoxon test. Correlations between SUS SR (at rest and during PFM contraction) and
227 each of the questionnaires' (ICSI, ICPI, MPQ, VAS, and SF-36) results were examined
228 using Pearson's product-moment correlation coefficient or Spearman's rank correlation
229 coefficient. Statistical analyses were performed using the free statistical analysis
230 software R, version 2.8.1, with the level of significance set at 5%.

231

232 **Results**

233 **Sample characteristics**

234 The characteristics of three groups are presented in Table 1. A total of 44 participants
235 volunteered for this study, with median (range) ages of 74 years (34 to 84 years) for the
236 IC/BPS group, 63 years (50 to 80 years) for the Middle-aged group, and 26 years (23
237 to 37 years) for the Young group. The results of the Kruskal-Wallis test of age showed

238 a significant difference among the three groups ($p < 0.05$). Further analysis via post hoc
239 multiple comparisons showed no significant difference in age between the IC/BPS
240 group and the Middle-aged group. The young group was significantly younger than the
241 IC/BPS group ($p < 0.001$) and the Middle-aged group ($p < 0.001$). The one-way
242 ANOVA results for BMI showed a significant difference among the three age groups (p
243 < 0.05). However, further analysis by post hoc multiple comparisons showed no
244 significant differences among the groups ($p > 0.05$).

245

246 **Comparison of SUS SR among the groups**

247 The results of the Kruskal-Wallis test of SUS SR at rest showed a significant difference
248 among the three groups ($p < 0.05$). SUS SR at rest was significantly higher in the
249 IC/BPS group than in the Middle-aged group ($p = 0.014$) and the Young group ($p =$
250 0.002). There was no significant difference between the Middle-aged and Young
251 groups ($p = 0.036$). SUS SR during PFM contraction was not significantly different
252 among the three groups ($p > 0.05$) (Fig. 4).

253

254 **Comparison of SUS SR within a group**

255 In the IC/BPS group, there was no significant difference in SUS SR between at rest

256 and during PFM contraction ($p = 0.120$). In the Middle-aged group, SUS SR was
257 significantly higher during PFM contraction than at rest ($p=0.018$). In the Young group,
258 SUS SR was significantly higher during PFM contraction than at rest ($p=0.003$) (Fig.
259 4).

260

261 **Correlation between SUS SR and each lower urinary tract symptom**
262 **questionnaire in the IC/BPS group**

263 SUS SR (at rest and during PFM contraction) was not significantly correlated with any
264 of the ICSI, ICPI, MPQ, VAS, and SF-36 questionnaire results (Table 2).

265

266 **Discussion**

267 The primary objective of this study was to compare PFM elasticity between IC/BPS
268 patients and healthy women using the RTE. In this study, the IC/BPS group showed
269 significantly higher SUS SR at rest than the Young and Middle-aged groups. In
270 addition, there was no significant association between SUS SR and lower urinary tract
271 symptoms and pain in the IC/BPS group. To the best of our knowledge, this is the first
272 study investigating SUS elasticity measured using RTE in IC/BPS patients. The female
273 SUS provides an important contribution to urinary continence by compression of the

274 mid-urethra [18]. However, most methods to assess the function or dysfunction of the
275 SUS are highly invasive [e.g. needle electromyography (EMG) [19], intra-urethral
276 surface EMG [20], urethral pressure [21]]. Aljuraifani et al [12] reported that SWE has
277 the potential to be a non-invasive, real-time method for assessing SUS functionality.
278 The present results may provide a non-invasive, real-time method using RTE to
279 evaluate SUS function of the idiopathic patient.

280 In the present study, SUS SR at rest was significantly higher in the IC/BPS group
281 than in the Young and Middle-aged groups. It has been reported that the muscle
282 stiffness of the lumbar multifidus muscle at rest is significantly higher in low back pain
283 sufferers than in asymptomatic individuals [22]. This follows the common clinical
284 notion of “hypertonicity”. A previous study reported that MRI showed that IC/BPS
285 patients have pelvic floor hypertonicity, which may contribute to or amplify pelvic
286 pain [23]. In general, tissue damage causes skeletal muscles to become hypertonic by
287 exciting alpha motor neurons and stimulating muscle contraction when pain occurs
288 [24]. Based on the above, we speculated that PFM tone and SUS SR were increased in
289 IC/BPS patients due to bladder pain and the pain of organs in the pelvis. Furthermore,
290 SUS SR at rest was not significantly different between the Middle-aged and Young
291 groups in the present study. Previous studies have reported that the stiffness of limb

292 skeletal muscles is affected by aging. In the lower extremity muscle groups of the
293 quadriceps and hamstrings, aging is related to the decrease in muscle stiffness [25].
294 However, in the biceps of the upper extremity, muscle stiffness has been reported to
295 increase with age, and furthermore, muscle stiffness has been shown to decrease more
296 in women than in men [26]. The effects of aging on muscle elasticity are controversial,
297 depending on location and muscle type. In the present study, there was no relationship
298 between the SUS SR and aging. There is no previous report on the relationship
299 between SUS and age in the present study. We believe that this result requires further
300 study.

301 Comparison of SUS SR within the groups showed that the Middle-aged and Young
302 groups had significantly higher SR during PFM contraction than at rest, but no
303 significant difference was observed in the IC/BPS group. In a report examining SUS
304 stiffness using SWE in healthy adult females, it was found that SUS stiffness was
305 significantly increased with PFM contraction [12]. In the present study using RTE,
306 SUS SR was also found to increase in healthy adult women with PFM contraction. A
307 previous study showed concomitant pelvic floor muscle dysfunction in over 90% of
308 IC/BPS subjects [7]. Furthermore, it has been reported that in women with PFM
309 dysfunction, correct contraction is difficult in about 24% of cases [27]. This study

310 confirmed the movement of the PFM during PFM contraction on B-mode images
311 during SUS elasticity measurement. Therefore, correct contraction of the PFM was
312 thought to have been performed. The fact that there was no significant difference in
313 SUS SR between resting and PFM contraction in the IC/BPS group suggests that the
314 PFM tone at rest was higher in IC/ BPS patients, regardless of whether they had pain
315 or not.

316 The second objective was to investigate the relationship between PFM elasticity and
317 lower urinary tract symptoms and pain. SUS SR at rest and during PFM contraction
318 was not significantly correlated with any of the ICSI, ICPI, MPQ, VAS, and SF-36
319 questionnaire results. We had expected that SUS SR would be significantly correlated
320 with pain and interstitial cystitis symptoms. However, the present results differed from
321 our hypothesis. There was no correlation with the pain and lower urinary tract
322 symptoms questionnaires in the IC/BPS group with and without Hunner lesions.
323 Previous reports examining the relationship between other skeletal muscle stiffness and
324 pain symptoms reported that those with pain in the shoulder and lumbar area and those
325 without symptoms had higher muscle stiffness than those without pain, but there was
326 no correlation with pain [22, 28]. The reason for this is that the perception of pain is a
327 highly subjective experience and can be affected by differences in individual

328 susceptibility, as well as personality. The mechanisms of pain development are clearly
329 multi-faceted, and despite the numerous studies in healthy subjects and in pathological
330 conditions, the precise underlying neural processes are still uncertain [29].

331 The results of this study suggest the following clinical applications: it may be
332 possible to evaluate the stretching effect on SUS elasticity before and after treatment.

333 There was a limitation in this study. The linear probe used in this study can only
334 observe a depth of 4.0 cm from the body surface. Therefore, it may be difficult to
335 measure SUS elasticity in the case of obese people. The RTE used in this study also
336 detects and displays the relative stiffness of the tissue. On the other hand, SWE is a
337 technology to quantify the elasticity of the tissue as an absolute value. The relationship
338 between RTE and SWE needs to be examined.

339

340 **Conclusion**

341 The present study showed that SUS SR at rest was significantly higher in IC/BPS
342 patients than in healthy young adult and middle-aged women. The results of this study
343 suggest that it may be possible to evaluate the stretching effect on SUS elasticity
344 before and after treatment.

345

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438

439 **Figure Legends**

440 **Figure 1**

441 A linear probe placement on the perineum.

442

443 **Figure 2**

444 Method for analysis of real-time tissue elastography images. a: B mode image, b:

445 Elastography image. Images are shown at rest. The region of interest (ROI) is set with

446 the SUS as the target site (A) and adipose tissue as the reference site (B); ROI A is set

447 10 mm anterior to the urethra and 15 mm above the pubic bone (1.5 mm x 1.0 mm), and

448 ROI B is set 5 to 10 mm below ROI A.

449

450 **Figure 3**

451 The strain graph shows the average strain in the tissue as a function of pressure.

452

453 **Figure 4**

454 The comparison of striated urethral sphincter (SUS) strain ratio (SR) at rest and during

455 pelvic floor muscle (PFM) contraction is shown. White represents the Interstitial

456 cystitis/bladder pain syndrome (IC/BPS) group, gray represents the Middle-aged group,

457 and shaded lines represent the Young group. Comparisons among the three groups in
458 SUS SR were analyzed using the Kruskal-Wallis test, one-way analysis of variance, and
459 multiple comparative studies. A nonparametric test and the Mann-Whitney U test were
460 performed by applying the significance level adjusted by post hoc Bonferroni testing (*
461 $p < 0.016$). SUS SR at rest is significantly higher in the IC/BPS group than in the
462 Middle-aged group and the Young group. In the Middle-aged group, SUS SR during
463 PFM contraction is significantly higher than at rest. In the Young group, SUS SR during
464 PFM contraction is significantly higher than at rest.

465

466

467

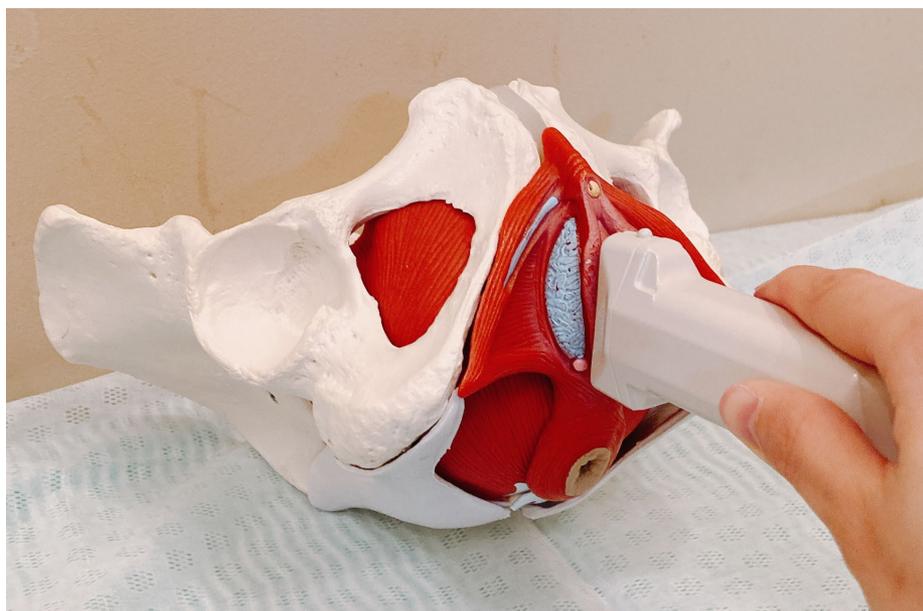


Figure 1

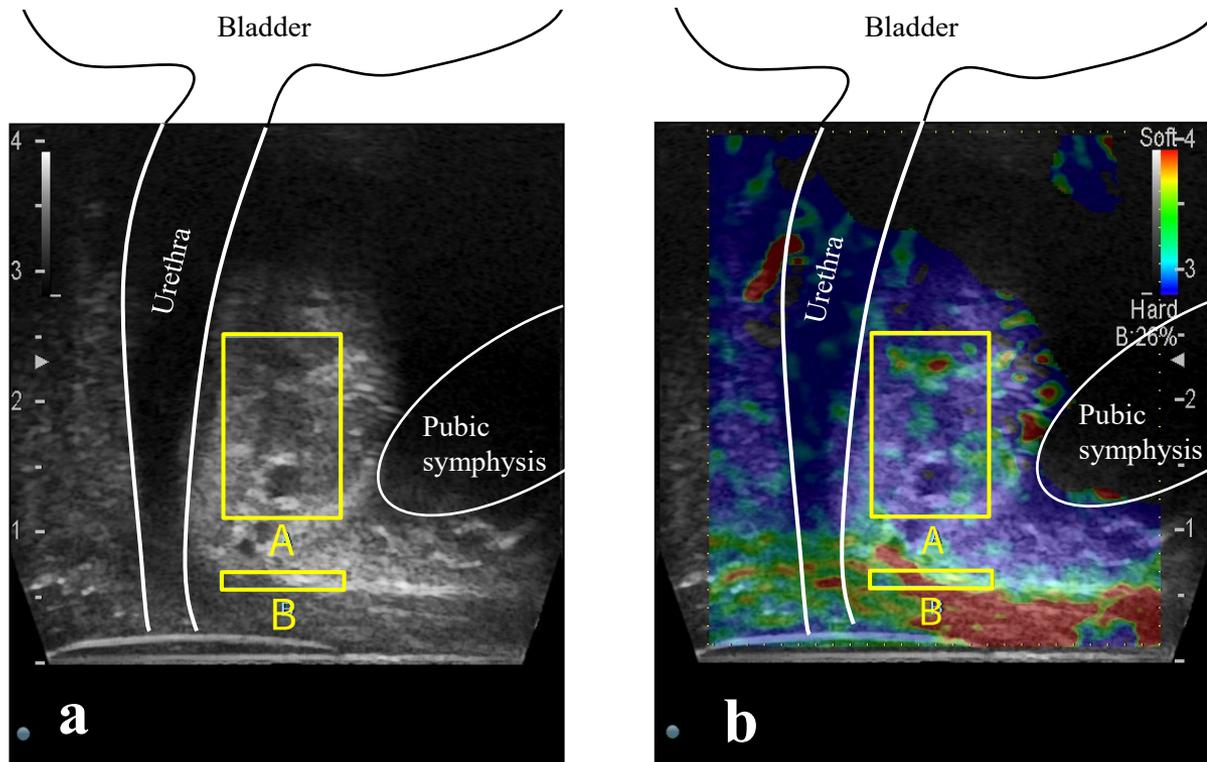


Figure 2

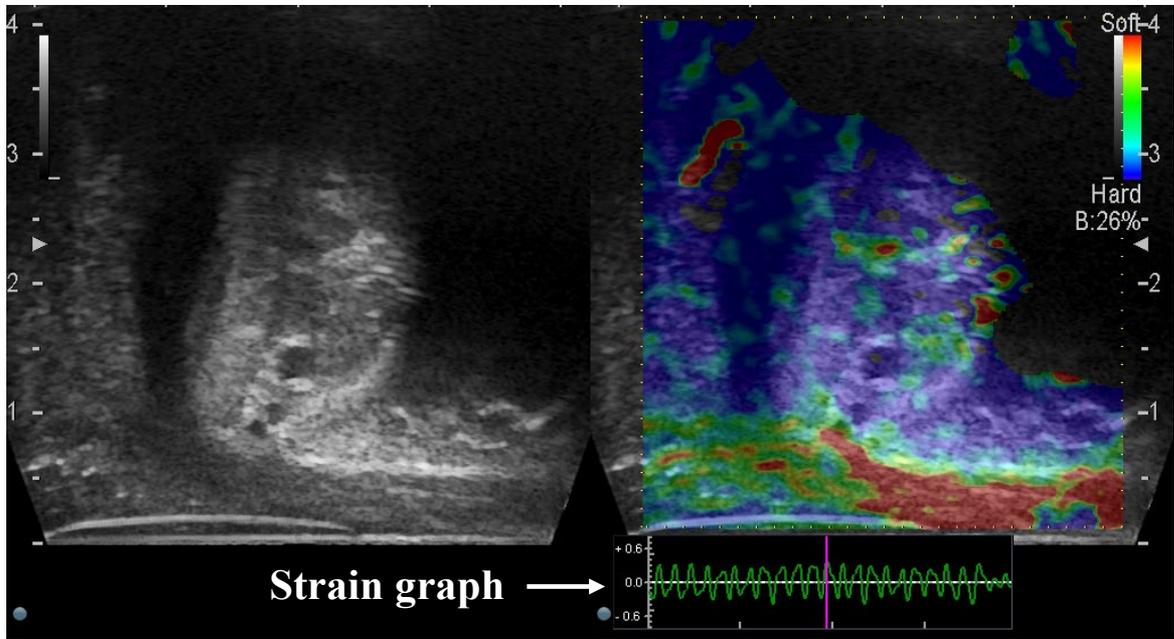


Figure 3

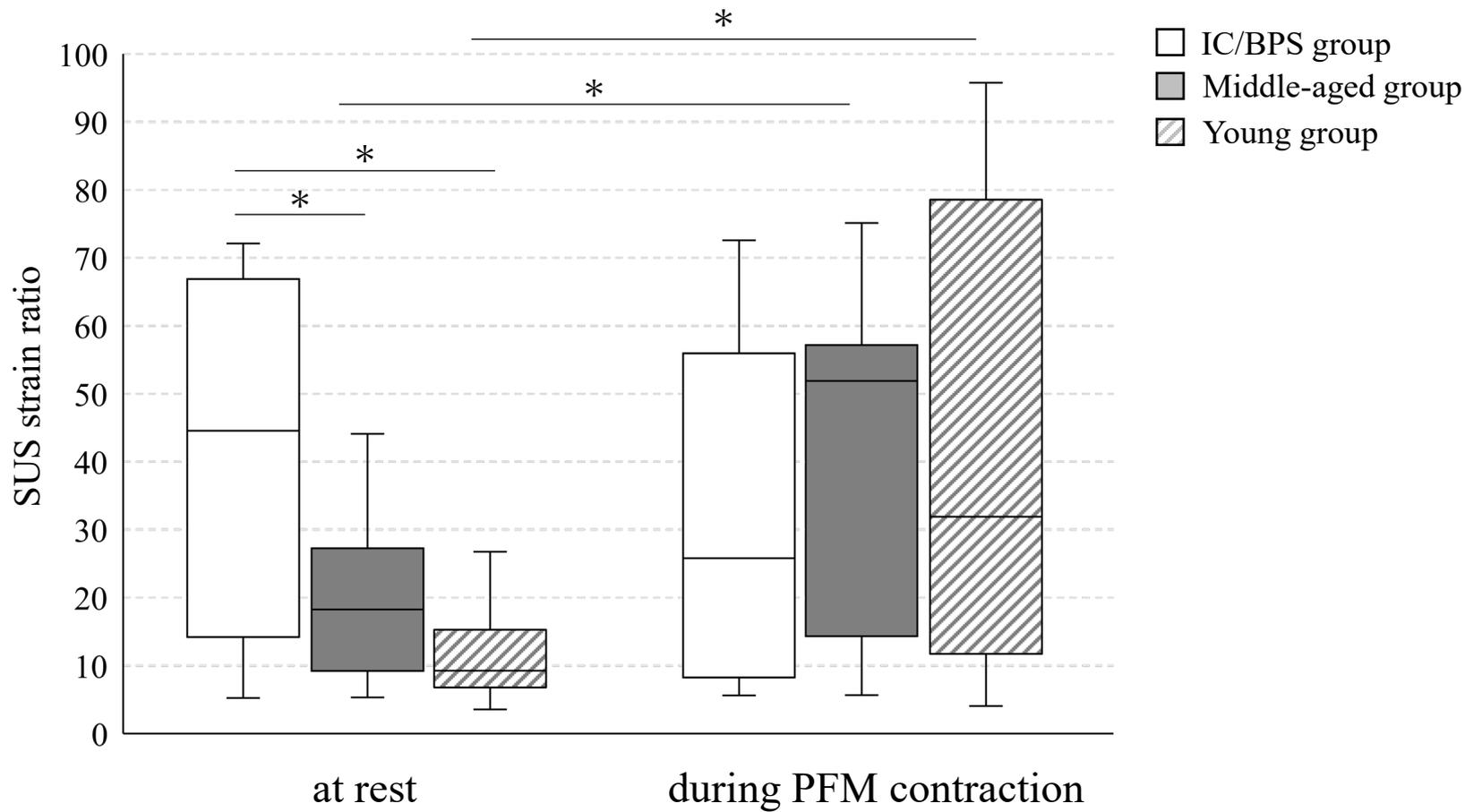


Figure 4

1 **Table 1.** Characteristics of the participants prior to the start of data collection

Characteristic	IC/BPS group (n = 17)	Middle-aged group (n = 10)	Young group (n = 17)	P value	Post hoc ^a
Age (y)	74 (34-84)	63 (50-80)	26 (23-37)	< 0.001	a, b > c
BMI (kg/m ²)	21.4 (17.6-28.3)	21.7 (20.0-26.4)	19.6 (17.5-23.4)	p = 0.04	> 0.05
Duration of illness (days)	1378 (77-5259)	—	—	—	—

2 Data are shown as medians (range).

3 BMI: body mass index, IC/BPS group: Interstitial cystitis/bladder pain syndrome female patients, Middle-aged group: healthy middle-
4 aged women, Young group: healthy young adult women.

5 ^aResults of the post hoc Mann-Whitney test with a significance level of $0.05/3 = 0.016$, which was adjusted by post hoc Bonferroni
6 testing.

Table 2. Correlation between SUS SR and each lower urinary tract symptom questionnaire in the IC/BPS group

	SUS SR (at rest)		SUS SR (during PFM contraction)	
	<i>r</i> or ρ	p value	<i>r</i> or ρ	p value
Interstitial cystitis symptom score	0.16	0.53	0.33	0.18
Interstitial cystitis problem score	0.29	0.24	0.33	0.18
Sensory	0.27	0.28	0.35	0.16
Affective	-0.09	0.71	-0.19	0.45
MPQ Evaluative	0.12	0.63	0.11	0.65
Mixed	-0.03	0.88	0.14	0.58
Total	0.12	0.62	0.24	0.34
Visual Analog Scale	0.18	0.47	0.31	0.21
Physical functioning	-0.31	0.22	-0.41	0.09
Role physical	-0.18	0.48	-0.14	0.57
Bodily pain	-0.25	0.31	-0.10	0.67
General health	-0.21	0.41	-0.37	0.14
SF-36 Vitality	-0.25	0.33	-0.33	0.18
Social functioning	0.07	0.77	0.04	0.86
Role emotional	-0.14	0.57	-0.08	0.74
Mental health	-0.36	0.14	-0.48	0.05

SUS: striated urethral sphincter, SR: strain ratio, IC/BPS: interstitial cystitis/bladder pain syndrome, PFM: pelvic floor muscle.

SF-36: MOS Short-Form 36-Item Health Survey, MPQ: McGill Pain Questionnaire.

Pearson's product moment correlation coefficient or Spearman's rank correlation coefficient