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Original Article

Effects of isometric contraction of the quadriceps on the hardness and blood flow in the infrapatellar fat pad

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Abstract. [Purpose] This study aimed to clarify the influence of the isometric contraction of the quadriceps (ICQ) with low intensity on the circulation in the infrapatellar fat pad (IFP). [Participants and Methods] The participants were 7 males and 5 females, with an average age of 21.5 ± 1.4 years. IFP hardness was measured using shear wave ultrasound elastography and Biodex. Tissue oxygenation was measured via near-infrared spectroscopy using oxygenated hemoglobin (O2Hb), deoxygenated hemoglobin (HHb), and total hemoglobin (cHb) as indices. The mean values were calculated for three periods: 1 min of rest immediately before the exercise task (before ICQ), the lower limit of the 10 sets during the exercise task (during ICQ), and 3–4 min after the exercise task (after ICQ). IFP hardness was compared between resting conditions and ICQ, and tissue oxygenation was compared before, during, and after ICQ. [Results] ICQ significantly increased IFP hardness. Tissue hemoglobin, O2Hb, and cHb decreased significantly during ICQ and increased after ICQ compared to that before ICQ. HHb decreased during ICQ and recovered significantly after ICQ. [Conclusion] In healthy participants, low-intensity ICQ increases the hardness and oxygenation of the IFP. This study may partly explain the unknown pain relief mechanism of exercise therapy.
Key words: Infrapatellar fat pad, Isometric contraction of the quadriceps, Oxygenation

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INTRODUCTION

Pain in knee osteoarthritis (KOA) is an important factor leading to reduced activities of daily living and a poor quality of life[1)]. The cause of pain is thought to be inflammation of the synovium and other parts of the knee[2)]. However, a study has recently suggested that fibrosis of the infrapatellar fat pad (IFP) can also induce pain[3)]. The IFP is a flexible structure with a rich vasculature as it receives its blood supply from the arterial vascular network, and is innervated by several nerve endings[4)]. It also plays a role in buffering mechanical stress as it fills the gaps in the knee[5)]. Fibrosis of the IFP prevents the buffering of the mechanical stresses encountered during knee motion. Furthermore, impingement of the fibrotic IFP during knee motion can induce knee pain[4, 6)]. Therefore, prevention of IFP fibrosis is important to reduce knee pain during motion in patients with KOA.

Fibrosis commonly occurs in renal failure and pulmonary fibrosis[7, 8)]. Recently, hypoxia due to vascular remodeling, abnormal blood flow, and imbalance between oxygen demand and supply have been shown to cause fibrosis[7, 9)]. This is because persistent hypoxia in cells increases the expression of vascular endothelial growth factor and connective tissue growth factor under the influence of the hypoxia-inducible factor present in the nucleus, leading to increased neovascularization and

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fibrosis[10]. KOA also causes abnormal increases in neovascularization in the IFP, synovium, and capsule[11], and hypoxia in the synovium and articular cartilage has been reported[12, 13]. Studies have discussed the relationship between KOA, hypoxia, and circulatory disturbance[11, 12]. Thus, it is likely that abnormal blood flow and hypoxia occur in KOA, even before the occurrence of pathological IFP fibrosis. Moreover, improvement in hypoxia may prevent fibrosis; however, there are no studies on hypoxia improvement in the IFP via therapeutic exercises.

As a general therapeutic exercise for KOA, quadriceps strengthening exercises are recommended by the Osteoarthritis Research Society International guidelines[14]. The effects of strengthening exercises on KOA include pain relief, joint stabilization by increasing muscle strength[15], and suppression of inflammation by increasing anti-inflammatory cytokines in the joint[16].

We focused on isometric contraction of the quadriceps (ICQ) muscle in the knee extension position, which is a frequently performed exercise for patients with KOA. Previous studies have reported that ICQ during straight leg raise exercises may have a pain-relieving effect even at a low load of 25% or less of the maximum intensity[15, 17]. However, the mechanism of this effect remains unclear. The effects of ICQ at maximum intensity have been reported to increase intra-articular pressure[18], which in turn decreases synovial blood flow[19]. We focused on the pain-relieving effect of low-intensity ICQ and hypothesized that even low-intensity ICQ increases IFP hardness due to increased intra-articular pressure and that the change in IFP hardness affects blood flow. The purpose of this study was to investigate the change in hardness and blood flow in the IFP by low-intensity ICQ.

PARTICIPANTS AND METHODS

Twelve healthy young adults participated in this study (seven males and five females) with an average age of 21.5 ± 1.4 years, average height of 165.0 ± 8.3 cm, and average weight of 62.0 ± 14.5 kg. The inclusion criteria were as follows: (i) no pain in the dominant knee; (ii) no history of orthopedic or neurological disease; and (iii) no current use of dietary supplements or medications.

This study was approved by the ethics committee of our institution (approval number: 2019-47). The purpose of this study was explained in writing to all participants, and their written informed consent was obtained before the study was conducted.

Biodex System3 (Biodex Medical Systems, Shirley, NY, USA) was used to measure the maximum isometric muscle strength of the quadriceps muscle at 10° of knee flexion, with the trunk and thigh fixed on the measurement side. A dynamometer was fixed on the distal lower leg, and the maximum isometric muscle strength was measured at 10° of knee flexion. The 10% intensity of the maximum knee extension was calculated, and the participants performed the 10% ICQ task with visual feedback.

IFP hardness with and without 10% ICQ were measured using the 10-MHz linear probe of the Aplio300 ultrasound machine (Canon Medical Systems, Tokyo, Japan). IFP hardness was defined as the elastic modulus calculated using shear wave elastography (SWE).

The measurement position of the IFP was two transverse fingers outside distance from the midpoint of the line connecting the lower border of the patella and the tibial tubercle, and the probe was applied to the patellar tendon in the longitudinal direction.

The region of interest for SWE was randomly set at three points within the IFP, the values of which were averaged (Fig. 1). The average shear elastic modulus from three regions of interest at random was calculated and compared with and without 10% ICQ.

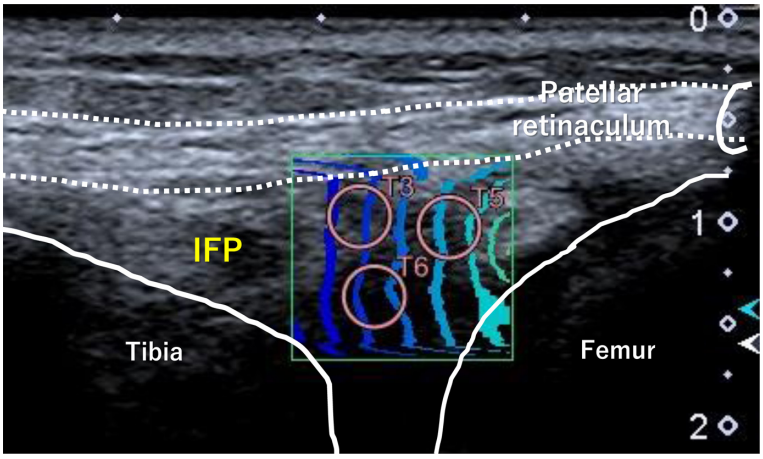

Fig. 1. Method of measuring IFP hardness via SWE.
IFP: infrapatellar fat pad; SWE: shear wave elastography.

Tissue oxygen was measured using near-infrared spectroscopy (NIRS) (NIRO200, Hamamatsu Photonics, Hamamatsu, Japan). A laser diode with three wavelengths (775, 810, and 850 nm) was used as the light source, and a photodiode was used as the light receiver. The sampling interval was set to every 2.0 s.

The maximum depth of the NIRS measurement was 50% of the distance between the transmitter and receiver of the probe[20]. In this study, the distance between the transmitter and receiver was set to 3.0 cm, and the probe was applied across the center of the patellar tendon after confirmation of the IFP by ultrasonography, considering that the estimated depth was 1.5 cm.

NIRS uses the modified Beer–Lambert method, which follows the principle of absorbance change at each wavelength to automatically calculate oxygenated hemoglobin (O2Hb); deoxygenated hemoglobin (HHb); and the sum of the two, total hemoglobin (cHb). A decrease in O2Hb indicates ischemia, an increase in O2Hb indicates hyperemia, and an increase in HHb above O2Hb indicates congestion. The probe was covered with a light-shielding sheet, an accessory of this measurement system, to prevent noise due to external light, and fixed to the skin at the patellar tendon.

O2Hb, HHb, and cHb data before, during, and after ICQ were recorded. Before ICQ was defined as the mean resting value at 1 min before ICQ, during ICQ was defined as the mean minimum value of 10 times the ICQ, and after ICQ was defined as the mean resting value 3–4 min after ICQ (Fig. 2).

Hardness measurements were performed on 10 participants; two measurements were taken for the same participant on the same day with an interval of at least 2 h, and the intra-examiner reliability was determined by the intraclass correlation coefficient (ICC)(1,1).

For blood flow measurement, two measurements at intervals of at least 3 h were taken for nine participants, and the intra-inspector reliability was determined by ICC(1,2). The ICCs for hardness and blood flow were based on the criteria of Landis et al., with 0.41–0.60 being "moderate", 0.61–0.80 being "substantial", and ≥0.81 being "almost perfect"[21]. To further clarify the measurement and chance errors in the measurements, the standard error of the mean (SEM) and the confidence interval of the minimal detectable change (MDC_{95}) were calculated.

All statistical analyses were performed a priori using the Shapiro–Wilk test. Since the values of hardness change showed a normal distribution, a paired t-test was performed. As each hemoglobin index did not show a normal distribution, the Friedman test was performed in three phases (before, during, and after ICQ), and the Wilcoxon test with Holm's correction was performed as a post hoc test. Statistical analysis was performed using the free software R.2.8.1, and the significance level was set at $p<0.05$.

RESULTS

ICC, SEM, and MDC_{95} for hardness and blood flow measurements are shown in Tables 1 and 2, respectively. The reproducibility of the hardness measurement was "almost perfect", and the reproducibility of the blood flow measurement was "substantial" for the after ICQ O2Hb and HHb and "almost perfect" for others.

The results of hardness change and circulation of IFP during ICQ were shown in Table 3. The IFP hardness increased significantly from Rest to ICQ. The tissue hemoglobin decreased significantly from before to after ICQ for O2Hb, HHb and cHb, but increased significantly from before to after ICQ for O2Hb and cHb. HHb did not differ significantly from before to after ICQ.

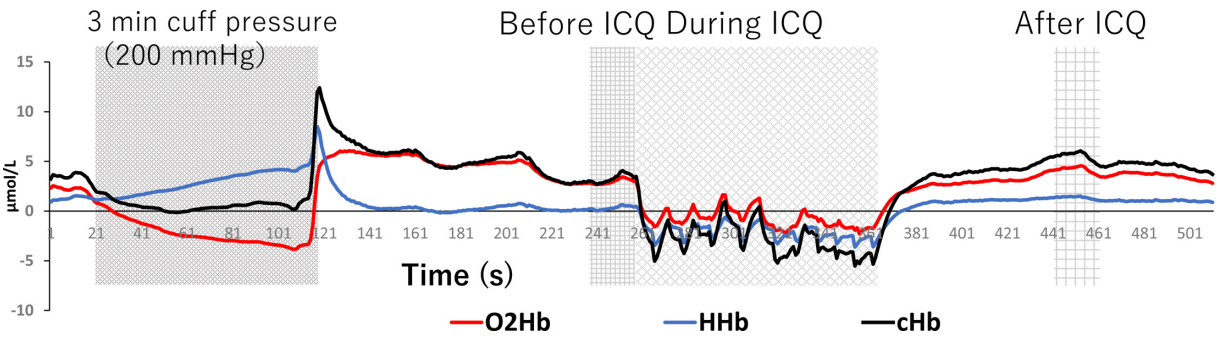

Fig. 2. Protocol for measuring blood flow in the IFP.
To standardize the resting hemoglobin levels, all participants underwent a 3-min arterial blood flow interruption immediately before the start of the experiment. Blood flow deprivation was performed by applying a pressure of 200 mmHg within 30 s using a pressure band attached to the thigh of the right leg. After 3 min of blood flow interruption, the patient rested for approximately 7 min until the O2Hb waveform became constant. This was followed by a 10-s ICQ (10% intensity of the maximal isometric contraction) and a 3-s rest, for a total of 10 sets. After the exercise task, the participants were asked to rest again for 5 min, and changes over time were observed. IFP: infrapatellar fat pad; ICQ: isometric contraction of the quadriceps; O2Hb: oxygenated hemoglobin; HHb: deoxygenated hemoglobin; cHb: total hemoglobin.

Table 1. Reproducibility of IFP hardness measurement

Rest				ICQ			
ICC	95% CI	SEM	MDC_{95}	ICC	95% CI	SEM	MDC_{95}
0.84	0.51–0.96	0.90	2.51	0.98	0.94–0.99	4.21	11.68

IFP: infrapatellar fat pad; ICQ: isometric contraction of the quadriceps muscle; ICC: intraclass correlation coefficient; CI: Confidence interval; SEM: standard error of the mean; MDC_{95}: minimal detectable change.

Table 2. Reproducibility of blood flow measurement in IFP

		ICC (1,2)	95% CI	SEM	MDC_{95}
Before ICQ	O2Hb	0.94	0.61–0.97	1.10	3.04
	HHb	0.91	0.46–0.96	0.63	1.74
	cHb	0.96	0.73–0.98	1.21	3.35
During ICQ	O2Hb	0.91	0.67–0.98	1.25	3.47
	HHb	0.89	0.38–0.95	0.58	1.62
	cHb	0.95	0.68–0.98	1.65	4.57
After ICQ	O2Hb	0.80	0.10–0.91	0.59	1.62
	HHb	0.77	0.03–0.90	0.27	0.74
	cHb	0.81	0.13–0.92	0.66	1.84

IFP: infrapatellar fat pad; ICQ: isometric contraction of the quadriceps muscle; ICC: intraclass correlation coefficient; CI: Confidence interval; SEM: standard error of the mean; MDC_{95}: minimal detectable change; O2Hb: oxygenated hemoglobin; HHb: deoxygenated hemoglobin; cHb: total hemoglobin.

Table 3. Change in IFP hardness and each hemoglobin index in each period

	Before ICQ	During ICQ	After ICQ		p value
IFP hardness (kPa)	7.0 ± 2.2	62.0 ± 30.1	-		p<0.01
O2Hb (mol/dl)	0.60 (−0.50, 1.63)	−3.30 (−4.99, −0.31)	2.71 (0.91, 5.13)	Before>During, During<After, Before<After	p<0.01
HHb (mol/dl)	1.41 (−0.08, 2.67)	−0.33 (−1.69, 0.63)	1.97 (0.33, 4.80)	Before>During, During<After	p<0.01
cHb (mol/dl)	2.01 (0.59, 3.42)	−2.60 (−7.06, −0.41)	4.30 (2.56, 7.80)	Before>During, During<After, Before<After	p<0.01

The results of the Friedman test showed significant differences between each level of hemoglobin index (p<0.01), with F values of O2Hb=32.70, HHb=12.90, and cHb=36.4. The results of the multiple comparison test showed that O2Hb decreased significantly from before ICQ to during ICQ (p<0.01) and increased significantly from before ICQ to after ICQ. HHb also decreased significantly from before ICQ to during ICQ (p<0.01), but there was no significant difference from before ICQ to after ICQ. cHb showed the same results as the O2Hb. IFP hardness is shown as mean and standard deviation, and hemoglobin is shown as median and interquartile range. ICQ: isometric contraction of the quadriceps muscle; O2Hb: oxygenated hemoglobin; HHb: deoxygenated hemoglobin; cHb: total hemoglobin.

DISCUSSION

Our study results showed an increase in IFP hardness with ICQ. Moreover, the IFP became ischemic during ICQ, but then exhibited oxygenation by a hyperemic response.

To the best of our knowledge, this is the first study to examine the effect of ICQ, an exercise therapy for KOA, on the oxygen dynamics of the IFP. In muscle tissue, blood flow disturbance and muscle fatigue are related[22], and muscle blood flow reduction and hypoxia are involved during isometric contraction, which affects muscle fatigue[23]. Furthermore, with regard to therapeutic exercises, there are reports of quadriceps muscle strengthening exercises under restricted blood flow for KOA, which improved muscle strength despite not increasing the muscle cross-sectional area[24], and muscle strengthening exercises at 30% of maximum intensity have been effective in improving muscle strength and pain[25]. Alterations in the blood flow during therapeutic exercises have been shown to improve pain and muscle strength. Recently, it has been found that excessive neovascular proliferation[11] and fibrosis[3], which are thought to be progressive due to circulatory disturbances,

are factors contributing to pain in patients with KOA. However, no previous studies have examined the blood flow in the connective tissue near the knee. Thus, the oxygenation of the IFP by low-load ICQ in this method is a new finding.

The IFP is an adipose tissue surrounded by the femur, tibia, patella, and patellar ligament. Therefore, it can be considered that compressive stress is applied to the IFP due to external factors. Kinematically, when the knee is extended more than the 20° flexion position, the femur moves forward and the tibia is externally rotated, thus strengthening the joint's conformity[26]. Additionally, the IFP moves from the posterior direction to the anterior direction in the knee extension position compared to the flexion position[27]. Therefore, when ICQ is applied in the knee extension position, the patella is pulled proximally, and the patellar ligament and patellar support are tensed, which is thought to act as a compressive force on the IFP anteriorly. This led us to believe that ICQ increased IFP hardness.

It was found that 10% ICQ increased IFP hardness. We hypothesized that the increase in IFP hardness with ICQ would compress the blood vessels in the same region and that repetitive ICQ would increase the blood flow after ICQ. Previous studies have reported that skeletal muscle stretching results in a transient ischemic state followed by a hyperemic response[28] and that blocking blood flow with an ejection zone and then releasing it results in increased arterial blood flow and a hyperemic response during reperfusion[29]. These reports differ in terms of the site and method of the ischemic state compared to the present study. However, these and our study are similar in that the blood vessels in the tissue were temporarily ischemic. In the present study, the IFP became ischemic during ICQ as its hardness increased and showed a hyperemic response after ICQ, suggesting that ICQ promoted blood circulation and oxygenation of the IFP.

Since it is not necessary to use high-intensity contractions to fluctuate IFP hardness and blood flow, ICQ may be an effective exercise therapy to prevent IFP fibrosis from a period of high pain, such as in elderly patients or after total knee arthroplasty. Further, IFP oxygenation achieved by low-load ICQ may explain part of the unknown pain relief mechanism of exercise therapy for KOA.

First, this study involved young and healthy participants. Therefore, it is not clear whether the same changes in blood flow will occur when the IFP is fibrotic and stiff, as in patients with KOA. Second, the NIRS measurement in this experiment required the participants to adhere to the exercise task and rest for approximately 20 min in the same position. Since we were able to only confirm changes over time with reproducibility in this study of up to 1 min after 3 min of the recovery period after the exercise task, it was difficult to confirm changes beyond that time. Third, although the hyperemic response after the exercise task revealed in this study may have been affected by the change in IFP hardness, we were unable to assess the effect of the autonomic nervous system before and after the exercise.

In young healthy adults, ICQ, a common exercise therapy for KOA, increased IFP hardness even at loads as low as 10% of the maximal contraction strength. In addition, after ischemia during the exercise task, oxygenation by hyperemic response was achieved after the end of the exercise task rather than before it. In the future, it is necessary to verify whether the same effect can be achieved in patients with actual KOA using ICQ via this procedure.

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Conflict of interest

The authors have no conflicts of interest to declare, pertaining to this study.

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