Decreased Pulsatile Blood Flow in the Patella in Patellofemoral Pain Syndrome

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Background: Anterior knee pain without clinical and radiologic abnormalities has primarily been explained from a purely structural view. A recently proposed biologic and homeostatic explanation questions the malalignment theory. No objective measurement of the pathophysiology responsible for changes in local homeostasis has been presented.

Hypothesis: Flexing the knee joint interferes with the perfusion of the patellar bone in patellofemoral pain syndrome.

Study Design: Case control study; Level of evidence, 4.

Methods: Pulsatile blood flow in the patella was measured continuously and noninvasively using photoplethysmography. Measurements were made with the patient in a resting position with knee flexion of 20° and after passive knee flexion to 90°. In total, 22 patients with patellofemoral pain syndrome were examined bilaterally, and 33 subjects with healthy knees served as controls.

Results: The pulsatile blood flow in the patient group decreased after passive knee flexion from 20° to 90° (systematic change in position, or relative position [RP] = –0.32; 95% confidence interval for RP, –0.48 to –0.17), while the response in the control group showed no distinct pattern (RP = 0.17; 95% confidence interval for RP, –0.05 to 0.31). The difference between the groups was significant (P = .0002). The median change in patients was –26% (interquartile range, 37).

Conclusions: Pulsatile patellar blood flow in patellofemoral pain syndrome patients is markedly reduced when the knee is being flexed, which supports the previous notion of an ischemic mechanism involved in the pathogenesis of this pain syndrome.

Keywords: knee; pain; bone; ischemia; photoplethysmography

In the absence of detectable pathologic changes, anterior or retropatellar pain—which is exacerbated during sustained sitting, kneeling, ascending or descending stairs, and squatting—is defined as the patellofemoral pain syndrome (PFPS). Despite the numerous publications concerning PFPS, the basic causes and natural history of the disease are controversial. The decade-old paradigm of a purely structural and biomechanical explanation has recently been questioned, and a different etiologic theory that takes a pain mechanism into consideration has been proposed.[10] Homeostatic reactions due to ischemia are known to occur in muscle tissue,[24] and different homeostatic reactions have also been reported for tendon,[1] bone,[20] and cartilage.[31]

Several studies have investigated the links between patellofemoral dysfunction, tissue ischemia, and pain. For example, it has been shown that the intraosseous pressure in the femur and the tibia of painful knees is increased,[4] and in another study,[13] high intraosseous pressure leading to ischemia was suggested as a pain mechanism. Venous outflow, evaluated using intraosseous phlebography, is often limited in painful knees; it has been speculated that this could lead to ischemia of the knee.[3] There is also evidence of capillary ingrowth into the cartilage at the osteochondral junction in patients with chondromalacia patellae and osteoarthritis.[5] The increased vascularity (neovascularization) found in that study was concomitant with an increase in nerves containing the neurotransmitter substance-P (SP). Tissue hypoxia is a well-known trigger for the release of SP and neural growth factor (NGF), which initiate hyperinnervation. Several studies have shown that nerve fibers containing SP are present in the knee joint.[21,26,32] Selfe et al[29] summarized the growing body of evidence for the ischemic theory in patellar pain and concluded that we need to consider the influence of vascular problems. Further support for this theory is found in a recent study by Sanchis-Alfonso et al,[27] who found morphologic and ultrastructural changes associated with ischemia, including hypervascularization and increased vascular endothelial growth factor release in the lateral retinacula in painful patellofemoral malalignment.

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All perfusion in the patella is supplied via arteries descending from the popliteal artery proximal to the femoral condyles—the supreme genicular, medial superior genicular, medial inferior genicular, lateral superior genicular, lateral inferior genicular, and anterior tibial recurrent arteries (Figure 1). The intraosseous arteries are grouped into 2 main systems. The first system comprises the midpatellar vessels, which enter 10 to 12 vascular forminae located on the middle third of the anterior surface of the patella in an oblique direction. Bonutti et al[6] showed that this system provides the main supply of arterial blood to the patella. The second system arises from the polar vessels through the surface of the deep inferior patellar upward, supplying the lower third of the patella and communicating within the bone with branches of the midpatellar vessels.[11]

Photoplethysmography is a noninvasive optical technique for measuring changes in blood flow and has been used to monitor blood flow mainly in the skin[16] but also in muscle.[28,34] With a newly developed photoplethysmographic (PPG) probe, it is also possible to continuously and noninvasively study changes in pulsatile blood flow within the patella.[23]

The purpose of this study was to use this novel PPG technique to compare pulsatile blood flow in the patellae of PFPS patients with that in healthy knee controls. We hypothesized that patellar blood flow decreases with knee flexion in patients with PFPS but not in controls.

MATERIALS AND METHODS

Patients

The patients were recruited from an orthopaedic department. All participated voluntarily and gave their written informed consent. The research ethics committee approved the study. The patients were included in the study if they met the following inclusion criteria: (1) age 20 to 50 years (To avoid difficulties in differentiating between PFPS and late symptoms of apophysitis or early symptoms of osteoarthritis, patients were limited to this age range.); (2) pain duration greater than 6 months (Pain duration of more than 6 months has been proposed as a criterion in studies on PFPS to rule out short-term pain of other origin.[8]); (3) no causative explanation for the pain in clinical examination (Patellofemoral pain syndrome is clinically a diagnosis of exclusion, and the patient was excluded if the clinical examination suggested other pathologic abnormalities of the knee joint such as ligament or meniscal tears, synovial plica, tendinopathy, apophysitis, osteoarthritis, neuroma, fat pad impingement, or patellar instability.); (4) no functional (symptomatic) instability, previous injury, or surgery in the lower extremities (Instability in the lower extremity may indicate other injuries, and previous injury or surgery may cause pain similar to that of PFPS.); (5) no specific treatment for the pain during the last 12 months except for commonly used pain killers such as paracetamol or nonsteroidal anti-inflammatory drugs (NSAIDs) (Some pain treatments may affect the blood circulation. The patients were asked not to use any NSAIDs a week before the blood flow measurements.); and (6) no radiologic pathologic changes (All eligible patients were examined with plain radiographs and bone scan. Standard weight-bearing anterior and lateral views together with an axial patellar view [Merchant view] were performed. Bone scans were performed using a dose of technetium 99m given intravenously and allowed to concentrate in bone. Anterior and lateral static images of both knees using a gamma camera were obtained 3 hours after the injection. The degree of localized uptake was classified in the following groups: normal, diffusely increased, and focal. Any radiologic pathologic changes excluded the patient. However, diffusely increased uptake on bone scan was not regarded as pathologic.[22] Thirty-four percent (15 of 44) of the knees in the patient group showed diffusely increased uptake.

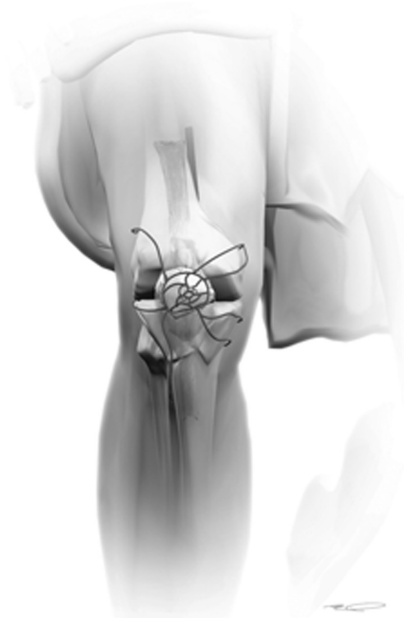

Figure 1. Extraosseous arterial supply to the patella.

Twenty-two patients with PFPS and 33 control subjects are included in the results. Bilateral pain was present in 91% (20 of 22) of the patients.

Controls

The healthy controls were selected from visitors to a health club in the same geographic area. These subjects were age- and sex-matched as closely as possible with the patient group. Potential control subjects were excluded if they had any experience of knee pain in the last 6 months or a history of previous knee trauma or surgery in the lower leg. Because of ethical reasons, no radiologic examinations were performed in the control group.

Photoplethysmography

The PPG technique requires a light source and a photodetector placed adjacent to each other. The beam of light is directed toward the section of the tissue in which blood flow is to be measured. The emitted light is reflected, absorbed, and scattered within the tissue; only a small

TABLE 1
Anthropometric Data of Subjects[a]

	Controls			Patellofemoral Pain Syndrome Subjects		
	Total	Women	Men	Total	Women	Men
Subjects (n)	33	15	18	22	13	9
Age (y)	36 (10)	33 (10)	38 (10)	33 (11)	30 (9)	37 (12)
Height (cm)	175 (11)	164 (5)	184 (6)	175 (6)	171 (4)	181 (4)
Weight (kg)	78 (16)	64 (8)	90 (12)	72 (10)	66 (7)	81 (8)
Body mass index	26 (4)	24 (4)	27 (3)	23 (3)	23 (2)	25 (4)

[a]All values shown are means, with standard deviations in parentheses.

fraction of the emitted light is received by the photodetector. The intensity of the reflected and scattered light recorded by the photodetector is assumed to be related to blood flow changes occurring underneath the probe.[17] Light penetration into the tissue increases primarily with increasing wavelength and the optical geometry of the probe, but the depth of penetration also depends on the optical qualities of the tissues of interest. A 2-channel PPG instrument (Department of Biomechanical Engineering, Linköping University, Linköping, Sweden) and a PPG probe were applied to record blood flow changes in the patellar bone continuously.[23] The patella PPG probe contains 1 near-infrared light-emitting diode (LED) at 804 nm for deep tissue monitoring of blood flow and 1 photodetector (PD). All optical components were embedded in black-colored silicon. The distance between the near-infrared LED and the PD was 25 mm. The signals were processed in an amplifier and stored on a personal computer.

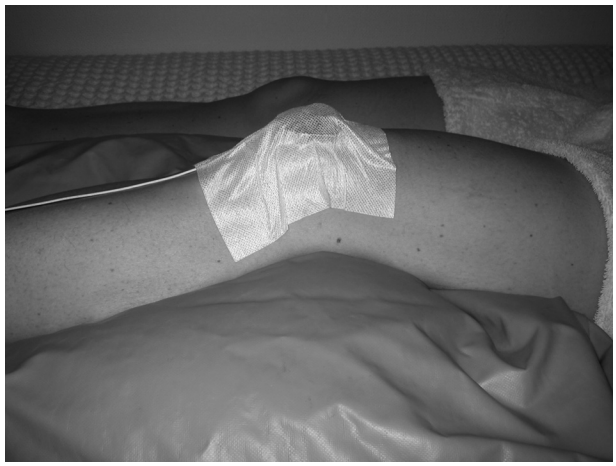

Figure 2. Photoplethysmographic probe placed on the patella with adhesive tape.

Data Collection

Basic anthropometric data were collected for all participants (Table 1). The subjects were in a supine position in a quiet room with moderate light, at a room temperature of 23°C (±1°). The PPG probe was placed over the center of the patellar bone and attached to the skin with double-adhesive tape (Figure 2).[23] After the patient had rested for 15 minutes with the knees flexed 20°, blood flow was recorded continuously from 1 minute before until 5 minutes after a passive knee flexion to 90°. Blood flow was measured with the knee fixed at both 20° and 90° of flexion using a vacuum pillow (AB Germa, Kristianstad, Sweden) (Figure 2). One measurement was made on each knee. No patient reported knee pain during the measurements. All measurements were made by one of the authors (J.N.). The mean amplitude of the pulsatile component of the PPG signals before (baseline) and after passive knee flexion was measured using an analyzing software (Daquhura 1.3, Linköpings Tekniska Högskola, Linköping, Sweden). The PPG signal was analyzed by a second author (L.-G.L.), who was blind to the origin of the recordings.

Statistical Analysis

The mean value and standard deviation were calculated for anthropometric data. For statistical analysis, the mean value of the individual bilateral measurements was used. Differences in blood flow between individual pairs of measurements—based on assessments before and after the intervention—are expressed in percentages of resting values, and the results are presented as the median and interquartile range. The Mann-Whitney *U* test was used to analyze differences in blood-flow signals between patients and controls.

The joint distribution of paired measurements of PPG recordings is illustrated in a scatter plot (Figure 3) and represents the pattern of change in values between 20° and 90° of flexion in the knee. Because a pattern of change can include both individual variations and, in case of treatment effect, a systematic component of change, we used a statistical method that could identify and separately measure the systematic component of change.[30] This pattern of change was statistically evaluated to identify possible systematic changes in PPG signal values that are in common for the group of patients. The difference between the proportions of change toward higher and lower values at flexion of 90° compared with the values at 20° defines the measure of systematic change in position (relative position [RP]). The possible values for RP range between –1 and +1. Values close to 0 represent a systematic negligible change from one session to another, a positive value for RP indicates a systematic change from a lower to a higher value, and a negative RP indicates a change from a higher to a lower value. The RP value is separately reported with corresponding 95%

confidence intervals (95% CIs) for patients and controls. The level of significance was set at $P < .05$. Statistica 7.1 (StatSoft Inc, Tulsa, Okla) was used for descriptive statistics and statistical analyses of group differences. SYSRAN 1.0 for Matlab 6 (OrdStat AB, Stockholm, Sweden) was used to calculate the values of RP and the corresponding 95% CI.

RESULTS

The distribution of paired PPG signal measurements shows that the decrease during knee flexion at 90° compared to knee flexion at 20° that was seen in most (19 of 22) PFPS patients (Figure 3B) was not observed among the control subjects (Figure 3A). Apart from the individual variation in change that is demonstrated in the figures, the statistical evaluation indicates the presence of a systematic change toward lower PPG values in the patient group. According to the statistical evaluation, there is strong evidence of systematic change in the patient group (RP = –0.32 [95% CI, –0.48 to –0.17), while no such systematic change was found in the control group (RP = 0.17 [95% CI, –0.05 to 0.31]). A typical PPG recording showing how the blood flow decreased during passive knee flexions is shown in Figure 4.

Figure 5 shows that the median change in patients was –26% (interquartile range, 37) from resting values, while the median change in controls was close to 0 (7%) (interquartile range, 50.5). The figure also shows that the changes in pulsatile blood flow during flexion were significantly different between the groups ($P < .0002$).

DISCUSSION

The principal finding of this study was a significant reduction of blood flow in the patella in PFPS patients compared with healthy controls after passive knee flexion to 90°.

Although some authors have found a correlation between mechanical factors within the knee joint and patellofemoral knee pain, no pain mechanism has yet been defined.[12] In the absence of biomechanical abnormalities (malalignment), biologic factors might be the main reason for the pain experienced. As long as a validated pain mechanism is not presented, several possibilities exist. The pathogenic paradigm proposed by Dye[10] focuses on mechanical overload to a joint suffering a homeostatic imbalance. The imbalance could be caused by a sudden external loading event (climbing up or down stairs, sitting in and rising from chairs, kneeling, or squatting). Even if the knee joint has a disturbed homeostasis, several pain mechanisms are possible. One possible mechanism is an increase in pain sensitivity due to an inflammatory response.[33] However, central pain mechanisms such as allodynia could represent other possible pain mechanisms not correlated to acute inflammatory reactions. The phenomenon of rest pain in PFPS (theater or movie sign) has never been satisfactorily explained and may be an example of tactile allodynia. Our results, showing that pulsatile blood flow in the patellar bone decreases when the knee is flexed, indicate that vascular problems also could be of importance in explaining the pain, even though we do not know whether the altered blood flow is causal or a consequence.

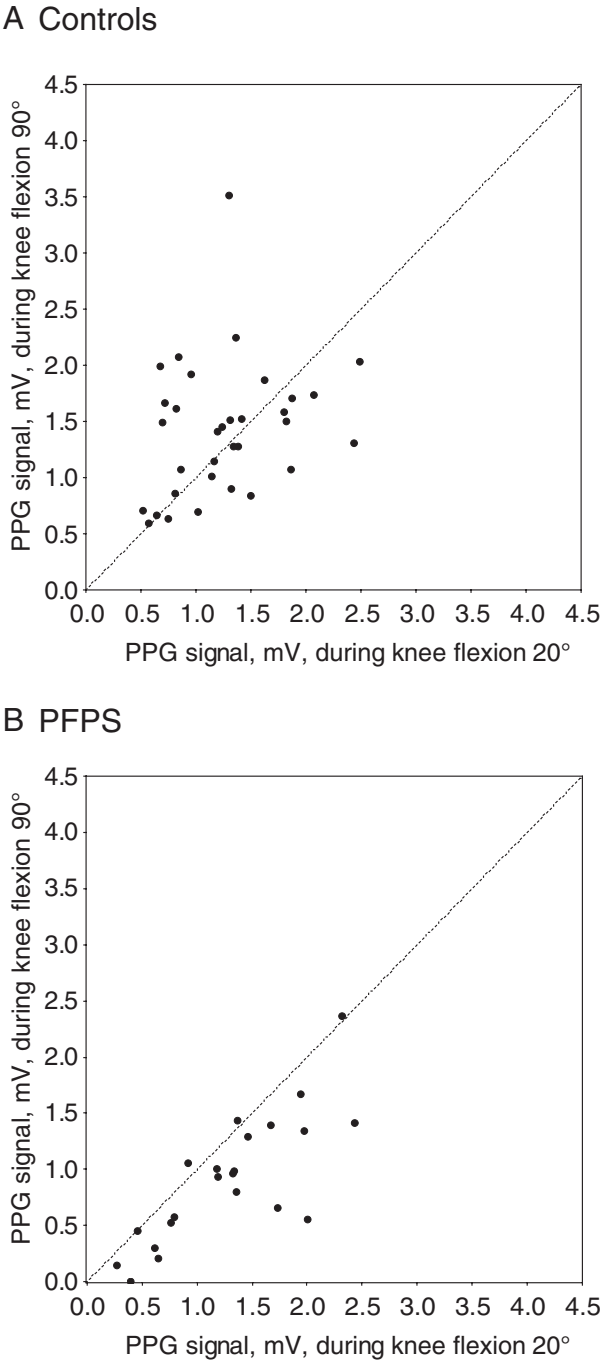

Figure 3. Paired individual data of passive knee flexion–induced changes (from passive flexion at 20° to 90°) in the photoplethysmographic (PPG) signal in controls (A) and patients with patellofemoral pain syndrome (PFPS) (B).

Patients with PFPS often show evidence of ischemia in soft tissues.[27] Sometimes they also show more bone remodeling in all bony compartments in the knee joint compared with non-PFPS patients, perhaps owing to intermittent ischemia.[22] Gelfer et al[11] used single-photon emission computed tomography (SPECT) to show that postoperative transient patellar ischemia was related to clinical patellofemoral pain. The capillary ingrowth into cartilage

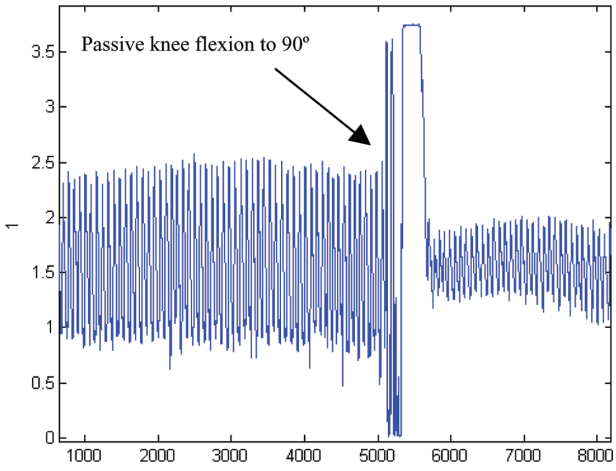

Figure 4. Photoplethysmographic recordings showing the decrease in the pulsatile patellar blood flow after passive knee flexion to 90°.

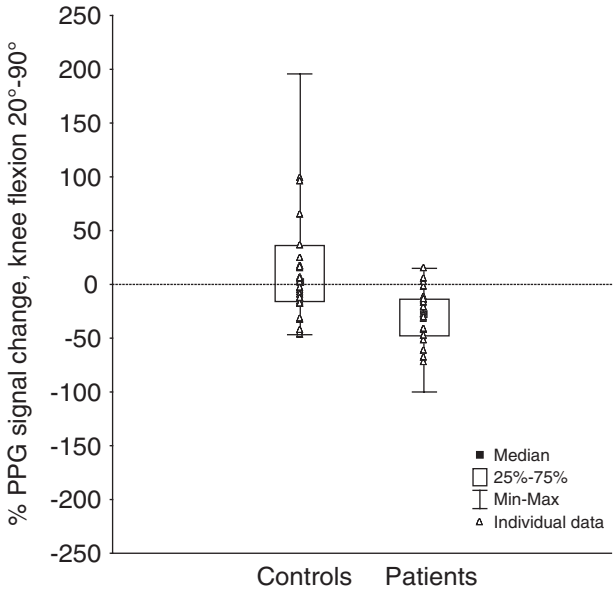

Figure 5. Changes in pulsatile blood flow in controls and patients after knee flexion from 20° to 90° expressed as a percentage of resting pulsatile blood flow. Values are expressed as median (min-max), but individual data are also shown.

at the osteochondral junction shown by Badalemente and Cherney[5] might be secondary to ischemia.

Even basic knowledge of how blood flow is regulated in bone tissue is limited. The importance of central and peripheral mechanisms for regulation is not known, and so the cause behind the decreased blood flow in PFPS shown in our study is unknown. Accordingly, care must be taken when interpreting the results of this study.

Current methods for studying blood flow and blood volume in human bone tissue have certain serious limitations. Few, if any, methods measuring blood flow are specific for bone tissue. Indirect measurements of blood flow in bone tissue have been made using bone scintigraphy,[9] SPECT,[11] the ultrasound-Doppler technique,[19] the microsphere method,[2] and positron emission tomography.[15] Direct measurements have been made using the laser Doppler technique[14] and an intravital microscope television system in combination with confocal laser-scanning optics.[18] These last techniques require surgical manipulation of the bone and may therefore introduce artifacts attributable to local manipulation of the vessels. None of the methods mentioned above allows the assessment of blood flow continuously and noninvasively during interventions resembling functional activities. This is, however, possible with the newly developed PPG technique for the patellar bone.[23] Comparing the pattern of pulsatile blood flow before and after an intervention, it is possible to assess differences between patients and controls without knowing the actual rate of blood flow. The importance of using a noninvasive instrument for measuring blood flow is clear from a number of studies on knee surgery.[6,25] The PPG technique was developed using a model in which differences between pulsatile and nonpulsatile fluid were studied. The patellar bone represents a rigid container where not only arterial but also venous blood flow is likely to have a pulsatile component. As a consequence, we have used the term pulsatile instead of arterial because we cannot rule out a venous influence.

The PFPS patients commonly complained of diffuse peripatellar pain when sitting with flexed knees for a long time (movie sign). We therefore evaluated blood flow in the patella in a resting position of 20° of flexion and after passive flexion to 90°. However, we do not know if the acclimatization period of 15 minutes of rest before the measurements was sufficient. Bone blood flow may be influenced by factors lasting for hours or even days. Our findings are in line with the ischemic explanation for PFPS, even though we cannot be certain which stressor—mechanical strain, venous occlusion, intraosseous pressure, or decreased arterial blood flow—will be most important for the altered pulsatile blood flow seen in our study. Another drawback is that we do not know if the baseline values differed; this could be of importance for the changes observed after passive knee flexion. Because no other noninvasive technique that continuously measures bone blood flow exists, the most obvious limitation is the lack of a standard method for calibration.[23] Thus, results can only be shown as a relative changes from one point in time to another.

With the present study design, it was not possible to randomize our subjects because the inclusion and exclusion criteria we used limited the number of patients. On the other hand, we have used homogeneous groups of subjects concerning the inclusion and exclusion criteria, which make the results more accurate. External control subjects were used because bilateral defects in patellar blood flow are possible, as patients often report bilateral symptoms. Thus, using the contralateral knee as an internal control would certainly have introduced bias even if only one of the knees was symptomatic.

Variations in blood flow in asymptomatic subjects have not been studied properly. As can be seen from the scatter plot (Figure 3A), some of the controls experienced decreased blood flow, even though they were pain free. This circumstance stresses the important notion that several factors may influence homeostasis. One might speculate that in some individuals, the reduction in blood flow is sufficient to create a

homeostatic reaction severe enough to cause pain (PFPS), while in others, the maintenance of homeostasis is possible without having pain as an activity regulator.[7]

Many authors have reported positive clinical effects from different exercise treatment protocols.[8] One effect correlated to muscle contractions is an increase in the nutritional blood flow. It remains to be shown if the decrease in patellar blood flow seen in our patient group will normalize after muscle contractions in the leg.

Rethinking the pathogenesis of PFPS and exploring possible pain mechanisms could ultimately lead to changes in the assessment, management, and prognosis of this pain syndrome.

CONCLUSION

This controlled study shows that patellar pulsatile blood flow was found to decrease among patients with PFPS when the knee was flexed from 20° to 90°. No such systematic change was found in the control group. Our findings support previous suggestions of an ischemic mechanism involved in the pathogenesis of PFPS.

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