Lower Limb Oedema in Patients with Proximal Femoral Fracture

A study of pathogenetic mechanisms

PhD Thesis

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LIST OF PAPERS

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S. Sajid H. Kazmi, Einar Stranden, Andries J Kroese, Carl-Erik Slagsvold, Lien M. Diep, Knut Stromsøe, and Jørgen J Jørgensen. Edema in the lower limb of patients operated on for proximal femoral fractures. J Trauma 2007;62(3):701-707.

Paper II:
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Paper III:
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Paper IV:
S Sajid H Kazmi, Stranden E. Pathophysiological aspects of lower limb oedema in patients with proximal femoral fractures. Scand J Clin Lab Invest 2009;69(7):741–747.

ABBREVIATIONS

ARS	antirotation screw
CDU	color duplex ultrasound
CFC	capillary filtration coefficient
COP_{if}	interstitial fluid colloid osmotic pressure
COP_{pl}	plasma colloid osmotic pressure
CSA	cross-sectional area
CT	computed tomography
DHS	dynamic hip screw
DVT	deep venous thrombosis
FCF	femoral cervical fracture
IL-6	interleukin 6
IL-8	interleukin 8
LIH	Lars Ingvar Hansson nail
MRI	magnetic resonance imaging
PFF	proximal femoral fracture
P_{if}	interstitial fluid hydrostatic pressure
PTF	pertrochanteric fracture
TSP	trochanter supporting plate
VOP	venous occlusion plethysmography

INTRODUCTION

Proximal femoral fracture (PFF) is one of the most frequent reasons for the hospitalization of elderly patients[1,2]. PFF is a serious, sometimes life-threatening trauma in elderly patients, and the risk of social deterioration is great[3,4]. PFF is associated with high morbidity and mortality[5-7]. The mortality rate after PFF is nearly 20% during the first year, and thereafter age-related mortality risk increases with age by approximately 20% per year[8,9]. Postoperative general complications significantly predict mortality and length of hospitalization[10]. The incidence of PFF is increasing in Western Europe[5, 11-15]. Especially in Norway, the overall incidence of PFF is 12.1 per 1000 inhabitants over 65 years of age[16,17]. The incidence of proximal femoral fractures among females is 2 to 3 times higher than the incidence of such fractures among males[18].

According to the Central Bureau of Statistics Norway, the proportion of population above 65 years of age, which is about 15% of the total population in 2009, is going to be doubled (30%) until year 2060. This increasing longevity of the population will contribute to a considerable number of patients with proximal femoral fracture in the coming years[19,20].

Under normal physiological conditions, the extracellular fluid compartment is kept relatively constant by a number of buffering mechanisms[21]. Oedema may develop if the capillary permeability is increased, or there is imbalance in the hydrostatic and colloid osmotic forces across the capillary wall, resulting in net transcapillary filtration exceeding lymph flow. The factors regulating fluid transport across the capillary wall were outlined by Starling (Starling 1896) and are described by the so-called Starling's equation[22]:

$$F = CFC\ [(P_c - P_{if}) - \sigma\ (COP_{pl} - COP_{if})] = J_l,$$

where, P_c and P_{if} are the hydrostatic pressure in the capillaries and interstitial fluid, respectively. COP_{pl} and COP_{if} are the colloid osmotic pressure of plasma and interstitial fluid, and σ is the capillary wall reflection coefficient[22,23]. In the subcutaneous tissue, σ is probably in the range 0.9-1.0[23,24]. The colloid osmotic pressures are caused by proteins, mainly albumin. If proteins are freely permeable, no osmotic pressure gradient is created and $\sigma = 0$. The capillary filtration coefficient (CFC) is a proportionality factor in the Starling equation, and represents the amount of net filtrate formed in 100g of tissue per min for each mmHg rise in net capillary filtration pressure. It is a product of capillary wall hydrodynamic conductivity per unit area and available capillary surface area. If the gaps between the endothelial cells widens, then the capillary hydraulic conductance increases. The available capillary surface area increases with an increase in the number of perfused capillaries. An increase in CFC indicates an increase in the rate of capillary filtration at a given net filtration pressure. The interstitial fluid volume is normally kept fairly constant

within narrow limits. This requires that lymph flow (J_l) balances net transcapillary filtration (Figure 1).
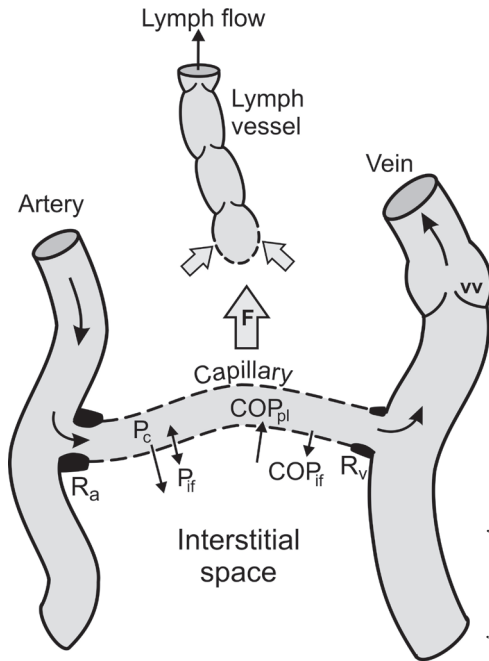
Figure 1. Schematic presentation of the factors regulating transcapillary fluid balance. The arrows indicate the direction of the forces. F represents the net capillary filtration.

Lower limb oedema in the subcutaneous tissue has been investigated thoroughly in the case of many other clinical conditions like DVT, critical limb ischaemia, lower limb oedema after arterial reconstruction[25-27]. However, despite its common observation the post-operative lower limb oedema in the patients with PFF has not been investigated thoroughly. Little is known about the pathophysiology of this type of oedema. Therefore, we planned and conducted this study to investigate the following research questions:

1. *What is the incidence of postoperative lower limb oedema in the patients operated on for PFF? (Paper I)[28]*
2. *How is the distribution of oedema in the different soft tissue compartments of the lower limb in the patients with PFF? (Paper II)[29]*
3. *Is there any difference in the magnitude of oedema in the patients with PTF and FCF and is this post-operative oedema uni- or a bilateral phenomenon in these patients? (Paper 1 and Paper II)[28,29]*

Since deep venous thrombosis (DVT) is a commonly seen complication after hip arthroplasty[30]. One may suspect DVT as a possible cause of lower limb oedema in the patients with PFF. We also posed us the question:

4. *Can DVT be the cause of this type of oedema in the patients with PFF? (Paper I,II,III)[28,29,31]*

Tissue injury may result in an increased endothelial hyperpermeability of vascular endothelium as a result of inflammatory response[32]. The list of mediators inducing endothelial hyperpermeability continues to grow. If any simultaneous/concomitant increase in the inflammatory mediators occurs during oedema development, this could probably identify inflammation as a cause of lower limb oedema in the patients operated on for PFF. Pro-inflammatory interleukins, IL6 and IL8, are well known as the mediators of acute phase reaction and hence inflammation. Other important research questions were:

5. *What changes in the plasma IL6 and IL8 levels occur immediately after the injury and after the operation for PFF? (Paper III)[31]*
6. *PTF is a more severe injury than FCF and also the operation for it is greater. Is there any difference between the plasma levels of IL6 and IL8 in the patients with PTF and FCF? (Paper III)[31]*

Oedema usually reflects the imbalance in the forces well known to prevent or limit its formation. It can be of interest to study the changes in the different factors of Starling equation to have a better understanding of the pathophysiological changes in the lower limb of patients with a PFF. Generally, oedema development can be promoted by any factor that increases the net capillary filtration or reduces lymph flow. Factors like reduced CFC, P_c, and COP_{if} or increased σ, COP_{pl}, P_{if} or L are known to have oedema-limiting effect. The activation of these oedema limiting factors does not exclude change in the interstitial fluid volume. The activation of these factors just limits larger interstitial fluid volume changes[33]. Therefore we also posed us this question:

7. *What changes in the Starling forces can be observed that limit the lower limb oedema formation in the patients with PFF? (Paper IV)[34]*

Finding answers to these research questions may provide us a better understanding of the pathophysiology of lower limb oedema development in the patients with PFF. It may also help us to optimize the treatment and prophylaxis to reduce personal sufferings and economical costs.

MAIN AIMS OF THE STUDY

The main objectives of this study were to:

1. Investigate the incidence of lower limb oedema in the patients operated on for proximal femoral fracture (I).
2. Investigate the distribution of oedema in the different soft tissue compartments of the thigh and calf (II).
3. Investigate plasma pro-inflammatory interleukins, IL-6 and IL-8, in the patients operated on for PFF to observe any correlation with the lower limb oedema (III).
4. Investigate the changes in the Starling forces regulating the transcapillary fluid balance (IV).

MATERIAL

Proximal femoral fracture (PFF)

PFF can be classified into femoral cervical fracture (FCF) and pertrochanteric fractures (PTF), where the former is an intracapsular fracture and the latter one is extracapsular fracture (Figure 2). AO/ASIF (Association for the Study of Internal Fixation) classify these fractures on the basis of localization and the degree of communition and dislocation into A1, A2 and A3 for pertrochanteric fractures and B1, B2 and B3 for FCF[35,36], where the degree of communition and dislocation increases from 1 to 3. Operative treatment of the patients comprises of reduction and fixation of the fracture with 2 or 3 LIH nails under spinal anaesthesia. In case of PTF the operation is more extensive and the reduction and fixation of fracture are achieved with dynamic hip screw (DHS) and a side plate with a varying numbers of holes. Sometimes trochanteric supporting plate, anti-rotation screw and cerclage wire have also to be used. Usually the FCF operation takes 30-60 minutes, whereas the operation for PTF may take 1-2 hours or even more.
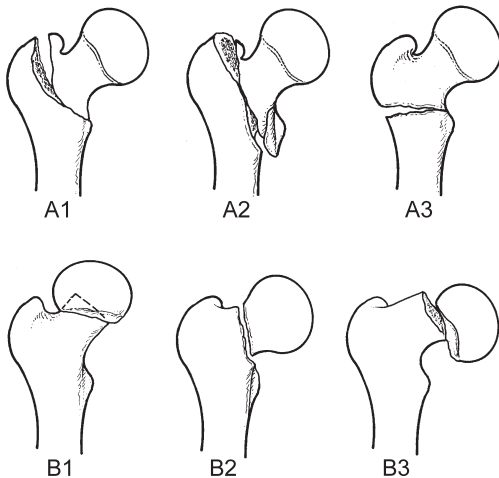
Figure 2. Type I and Type II proximal femoral fracture classification according to AO/ASIF (Association for the Study of Internal Fixation).

Either PTF or FCF, it is a common observation that the patients operated on for these types of fractures experience post-operative pain localized to the operation site as well as post operative lower limb oedema in the operated limb. Although the postoperative pain is the main hindrance in the effective mobilization of these patients, postoperative lower limb oedema has also been observed as a cause of discomfort. This post operative oedema may sometimes cause stiffness of the knee and ankle joints and hence may come in the way of an effective postoperative mobilization of these patients. Only 50% of elderly patients with PFF return to the same ambulatory state they had before injury. And 10-20% of these patients become institutionalized within a year[8,9,37,38].

DISCUSSION OF METHODS

Colloid osmotic pressure (COP)

In a normally hydrated tissue there is only small amount of free fluid containing proteins. A system for sample volume enlargement is required for the measurement of COP_{if}. Blister suction technique as described by Kiistala and Mustakallio was employed to collect interstitial fluid[39]. When a subatmospheric pressure is applied to a small area of skin, the dermis may be separated from the epidermis and a blister is formed. The applied suction increases the transcapillary filtration and could be a potential source of error. The COP_{if} obtained by this technique is lower than the true COP of resting tissue for this reason. However, Rein et al. found that the COP values in the fluid collected by this technique corresponded well to the COP value in fluid sampled by wick technique[40]. The fluid collected in the blister has to be collected in the capillary tubes immediately since the protein content of the blister fluid increase after the cessation of suction due to an inflammatory reaction. The blister suction technique is non-invasive and is easy to perform. Besides it is tolerated well by most patients.

Another technique which can be used for collection of interstitial fluid for protein analysis is the wick method. It is based on fluid equilibrium between the saline soaked thread and the surrounding interstitial fluid[41]. The COP measured from the wicks will ideally reflect the COP_{if} of the undisturbed tissue[42,43]. However, it is a relatively invasive approach as compared to the blister suction technique. The method requires application of local anaesthetics prior to the insertion of the wicks in the subcutaneous tissue. Besides the further extraction of the wick fluid and COP analysis also requires further processing.

The direct sampling of interstitial fluid by catheter can also be used for the protein analysis. But again the method is invasive as in case of wick method and the suction applied might increase net capillary filtration and thereby reduce the interstitial fluid protein concentration[23].

On the 7th post-operative day, a blister suction device with five suction cups connected by tubing to a manual pump (Blister Suction Device, E. Stranden) was applied bilaterally to the skin at the ventral surface of the thigh and calf[26]. The suction cups were made of PVC and were 20 mm wide, each with five concave holes 5 mm in diameter into which blisters were formed. A subatmospheric pressure of 200 mmHg was maintained for 60-90 minutes to obtain blisters. The interstitial fluid from the skin blisters was then transferred to unheparinised glass capillaries marked with the site and side of the limb. The samples were preserved at -70° C until analysed.

A colloid osmometer modified from Aukland and Johnsen (OncoLab, E. Stranden) was used to measure the colloid osmotic pressure[44,45]. The osmometer included a dialysing membrane with a protein cut-off at molecular weight 30000 Dalton (Biomax Ultrafiltration Membranes, Millipore Corporation, Bedford, Mass., USA,

www.millipore.com), so that proteins of greater size became osmotically active in the osmometer (Figure 3).

Blood from the median cubital vein was also drawn on the 7th post-operative day and centrifuged to obtain plasma. This plasma was then preserved at -70° C until analysed for COP_{pl} on the osmometer described above.
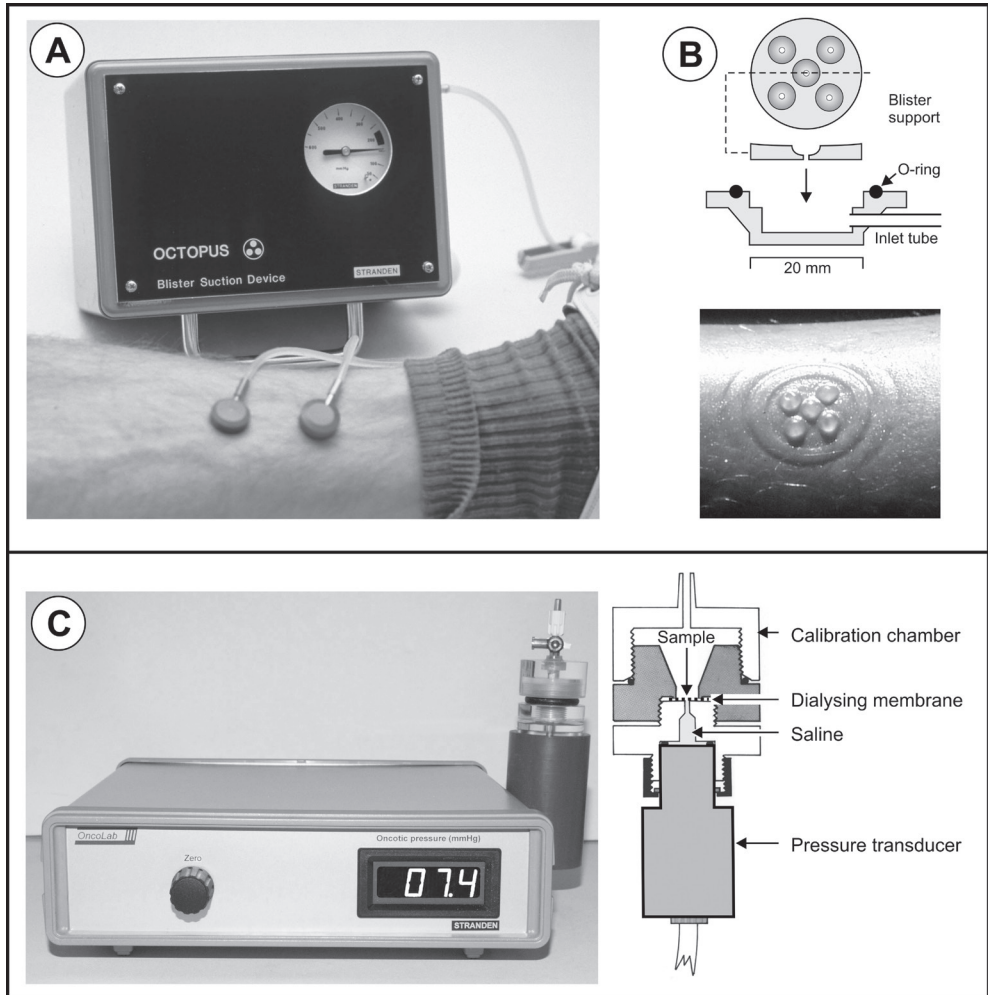

Figure 3. A: Suction cups applied to the ventral surface of leg. Suction cups are connected by tubing to a manual pump (Blister Suction Device, E. Stranden). B: Schematic illustration of the suction cup and blister support. C: Colloid osmometer (OncoLab, E. Stranden) and schematic illustration of the different parts of the osmotic pressure measuring device.

Interstitial fluid hydrostatic pressure (P_{if})

Interstitial fluid hydrostatic pressure (P_{if}) was measured in the anterior muscle compartment of the calf on the 7th post-operative day using the, "wick-in-needle" technique (WIN). The non-operated limb served as a control.

The needle (0.8 mm OD, 40 mm length) was provided with a 4 mm side-hole, approximately 7 mm from the tip, and was filled with cotton thread and sterilised by autoclaving. The thread provided a continuous water connection between tissue and needle lumen. During measurements the needle was connected to a pressure transducer with a small volume displacement (Statham P23 Db). The pressure measurements were recorded with a Graphtec Linearcorder Mark VII (Figure 4).

The system was adjusted to zero pressure by levelling the needle at the site of measurement and adjusting the pressure amplifier to zero pressure on the digital display (Pressure Monitor, E. Stranden) and on the pen recorder. After each recording, the needle was again placed at the same level to check zero level.
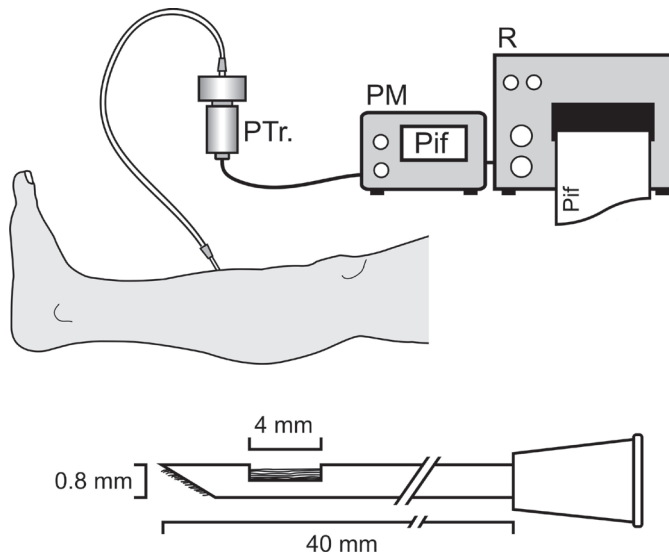
Figure 4. Interstitial fluid hydrostatic pressure (P_{if}) measurement in the anterior muscle compartment of leg using a hypodermic needle provided with a 4 mm side hole and filled with cotton threads (wick-in-needle method). The needle is connected to a pressure transducer (PTr.) with a small volume displacement. The pressure measurements were amplified in a pressure monitor (PM) and recorded with a linear recorder (R).

The method is based on fluid equilibrium with a water column between a pressure transducer and the interstitium. This basic idea of fluid equilibration is common for wicks, capsules, needles or micropipettes. The reliability of the WIN technique, described by Scholander PF et al. 1968), was outlined by Wiig and Noddeland et al.[41,46-48]. The time needed for equilibration is dependent on the degree of

tissue hydration. Wiig et al. found that the WIN technique may overestimate the P_{if} in a normally hydrated skin but the overestimation was diminished when the tissue hydration was increased[49].

Capillary filtration coefficient (CFC)

CFC is the product of the capillary hydraulic permeability per unit surface area and the available area[23]. It is usually expressed as mL of net filtrate formed in 100 g of tissue per minute for each millimetre rise in mean capillary filtration pressure (mL/min·100g of tissue·mmHg). The CFC is estimated by recording the calf volume increase over a period of a few minutes during a stepwise increase in venous pressure. The first steep rise is caused by venous filling and distension and is excluded from the calculations. In the normal human leg CFC is about 0.0012-0.0017 mL/min·100g of tissue·mmHg[50,51]. CFC is a proportionality factor in the Starling equation, therefore a rise in CFC will increase the net capillary filtration at a given net filtration pressure. In other words, despite a reduced CFC, the net filtration rate and the interstitial fluid volume may remain unchanged at a higher net filtration pressure.

Domed Filtrass Angio (Lekam Medical Limited, Devon, UK) was used to measure CFC. Filtrass Angio is a computer-assisted, mercury-free strain-gauge plethysmograph[52].

The patients were recumbent for 15 minutes before the start of measurements. The room temperature was kept at 23-25° C during the procedure. Venous occlusion cuffs were applied at the thigh level. Cushions supported both the thighs and the ankles and care was taken to keep the feet slightly above the heart level. An electromechanical strain-gauge sensor was applied bilaterally to the anterolateral aspect of the calf, at the level of largest circumference. The calf circumference was measured with a measuring tape to choose an appropriate length for the nylon thread of the transducer.

A venous occlusion pressure of 30 mmHg was applied simultaneously to both thighs for 5 minutes, and pressure was then increased to 50 mmHg and 70 mmHg at 5 and 10 minutes, respectively. CFC was calculated from the slopes of the volume curve following each periodic increase in the venous occlusion pressure (Figure 5)[51].

Since the venous outflow pressure and the postcapillary resistance were not known before the inflation, the CFC values obtained may be underestimated. However, this underestimation is of similar value bilaterally and the CFC ratio between the limbs is unchanged.

According to Stranden when tissue volume increases by x% due to oedema, the amount of filtrate formed is underestimated x% by this method of calculation of CFC[51].
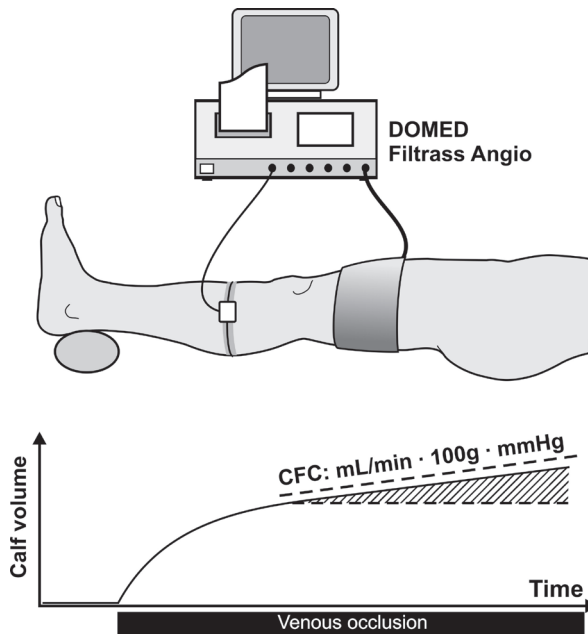
Figure 5. Measurement of capillary filtration coefficient (CFC) using a DOMED Filtrass Angio plethysmograph. Pneumatic occlusion cuff is applied to the thigh. An electromechanical strain-gauge sensor is applied to the leg for measurement of calf volume changes. The initial rise in the curve represents venous filling and distension. The calculation of CFC is based on the rate of further volume increase (hatched area).

Calf blood flow

Stranden et al. found a positive correlation between calf blood flow and CFC[51]. Venous occlusion plethysmography (Domed Filtrass Angio) was used to measure bilateral resting blood flow. The thigh venous occlusion cuffs were repeatedly (three times) inflated to 50 mmHg for 10 seconds. The concomitant rate of volume increase was then used for the automatic calculation of calf blood flow (mL/min·100g of tissue) (Figure 6). The test was carried out before the CFC measurements, and the positioning of the patients and the measuring equipment was as described above for CFC.
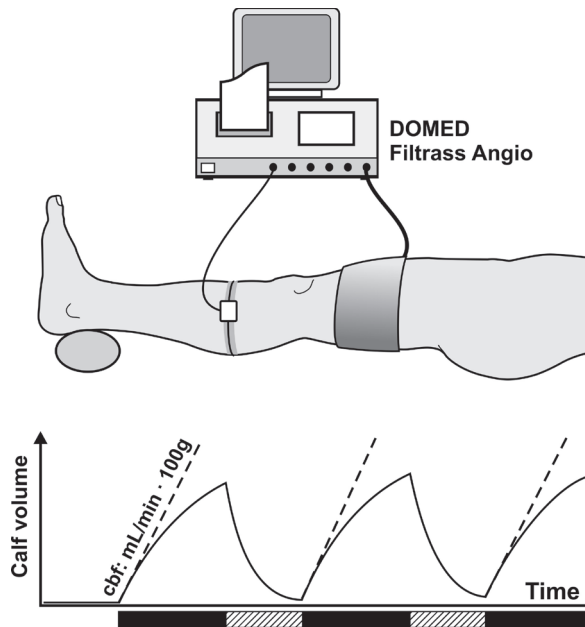
Figure 6. Calf blood flow (cbf) measured by venous occlusion plethysmography. The rise in the curves represents the increase in calf volume during repeated infla-tion (solid boxes). Calculation of cbf (mL/min·100g of tissue) is based on the initial increase in calf volume. Hatched boxes represent cuff deflation.

Inflammatory markers

Increased levels of plasma pro-inflammatory cytokines, IL6 and IL8 have been correlated with the post-traumatic inflammatory response[53-56]. In the present study, the inflammatory response to the fracture and the operation was determined by measurement of the same plasma pro-inflammatory cytokines. In all patients, immediately after inclusion in the present study, venous blood samples were obtained for measurement of the plasma IL6 and IL8. A total of eight blood samples were obtained from the common femoral vein at hospital admission, one hour before operation and postoperatively at 1, 6, 12, 24, 48 hours and on 5th post-operative day. Test tubes with EDTA were used for collection of the blood samples. The blood samples were centrifuged at 4° C for 10 minutes at 3000 rpm. Plasma samples were stored at -70° C until analysed.

IL6 and IL8 were measured by using Biotrak human interleukin enzyme linked immunosorbent assays (ELISA, Amersham Biosciences, UK). A standard curve comprising of serial dilutions of purified recombinant human IL-6 and IL-8 was constructed. The assays allow measurement of IL6 and IL8 with sensitivity of < 1 pg/mL and up to the maximum range of 400 pg/mL and 1000 pg/mL, respectively. The measurements were performed at The Hormone Laboratory, Oslo University Hospital, Aker.

Volume measurements (Frustum method)

The frustum method is based on the assumption that the thigh and the calf approximate in shape to a truncated cone, or frustum (Figure 7)[57-59]. The volume of a frustum can be calculated by measuring at the largest and smallest circumferences, C and c in figure 4, respectively. The h is the calculated length between C and c based on surface measurement of according to the formula:

$$V = (\pi/3)\, h\, (R^2 + Rr + r^2),$$

where, $h = \sqrt{h'^2 - (R - r)^2}$ and R and r are calculated from respectively C/2π and c/2π. R and r are radii at the point of measurement of the greatest and the smallest circumference, respectively. By applying these to the above formula, the leg volume V can be quantified.

The frustum method has previously been compared with water displacement volumetry, and there is a highly significant correlation between the percentage changes in the volume of the two methods of volume measurement[57]. In a control subject, the volume at calf level was measured 20 times by using frustum method and the coefficient of variation was calculated to be 0.65% by the formula:

V (coefficient of variation) = SD/mean value.
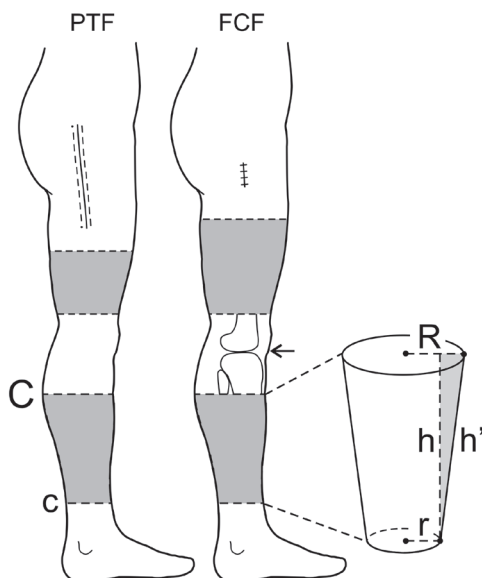
Volume of truncated cone:

$$V = \frac{\pi}{3} \cdot h \cdot (R^2 + Rr + r^2)$$

Figure 7. Volume calculation of lower limb segments by the frustum method. C and c represents the sites of circumference measurement at the largest and the smallest part of the calf- or thigh segments. h = length of the limb segment between the largest and the smallest circumferences. The formula for volume of truncated cone is used.

In the patients with the PFF we would measure volume changes in the thigh and the leg separately. The water displacement volumetry method was hence not ideal. Besides, the surface measurement method is easier and rapid to apply. The patients with PFF usually have post-operative pain and limited flexion and extension at the hip joint which could have also lead to reduced patient compliance in case the water displacement method was planned.

Colour duplex ultrasound (CDU)
To diagnose for DVT a Vingmed System Five ultrasound scanner (GE Vingmed Ultrasound A/S, Horten, Norway) with a 5- and 7.5-MHz linear array transducer was used. CDU combines B-mode tissue and colour-flow imaging (doppler) with spectral blood flow analysis by doppler ultrasound. One experienced physician at our vascular diagnostic department performed all CDU examinations on postoperative day 7. The common femoral, superficial femoral, and deep femoral veins were examined with the patient in the supine position. The popliteal vein and the three major calf veins were examined with the patient lying on the examination table with the legs tilted downwards. The venous imaging included both longitudinal and transverse planes. The criteria for diagnosis of DVT were based upon the presence of one of the following findings: (1) incompressibility of the vein, indicating the presence of thrombus; (2) visualization of the thrombus; (3) absence of flow augmentation on distal compression; and (4) absence of phasic flow with respiration[60,61]. The two first criteria are the most important, though.

Venous occlusion plethysmography (VOP)
An air plethysmograph (MacroLab, Stranden, Norway) was used to exclude any functionally significant venous outflow obstruction that might be caused by DVT[62]. The patients were examined in the supine position and the limb was supported by pillows under the thigh and foot, with the calf above the level of the sternum. The venous occlusion and recording cuffs were applied to the thigh and to the calf, respectively. Their width was approximately 70% of the circumference of the limb[63]. The pressure in the recording cuff was 6 mmHg, and a venous occlusion pressure of 50 mmHg was maintained for 1 minute. That permitted an unrestricted arterial flow into the limb while venous outflow was compromised, thus resulting in increased leg volume. On deflation of the thigh (occlusion) cuff after 1 minute, calf volume decreased rapidly if venous outflow from the lower limb was unobstructed. The changes in the leg volume were recorded on a linear recorder. The degree of decline of the plethysmographic curve on release of the thigh cuff is a measure of the venous emptying rate and indicates whether the patient has any functionally significant venous obstruction, proximal to the cuff at calf level[64,65].

CT scan
Siemens Somatom Volume Zoom was used for CT scans on the 7th and 30th postoperative days. Of the 34 patients who were examined by CT scan on the 7th post-

operative day, 26 could also be examined on the 30th post-operative day.

With the patient supine and feet first, a spiral sequence of 120 KV/100 mAs/0.5 s rotation time was used, and a 1 mm slice was taken at both thigh and calf level bilaterally (Figure 8). The sites of CT slices on the thigh and calf were determined by measuring the distance from the medial aspect of the knee joint, and were marked on the skin. The scans were taken by keeping the marked areas on both limbs at the same level. In cases where it was not possible to bring the marked areas to the same level due to differences in femur length, the CT scans were taken separately. The cross-sectional CT areas of the different tissue compartments were measured in cm^2 using display and analysis software (Dicomworks).
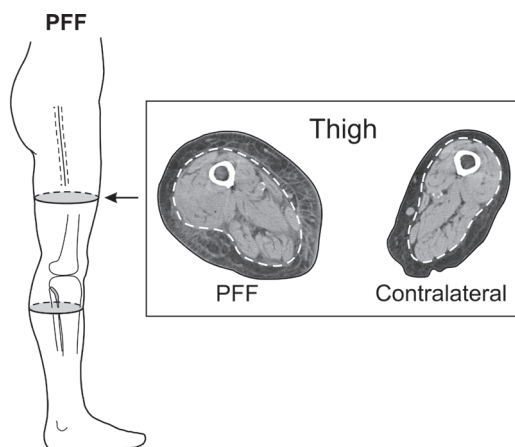
Figure 8. 1-mm CT scan slice is taken at fixed distance on the thigh (distal to the lower edge of the surgical wound) and at the calf. Oedema can be determined by the difference in measured cross-sectional area of the soft tissue compartments.

CT scan has been frequently used to analyse volume and tissue changes in patients with leg oedema of different aetiology, e.g., post reconstructive oedema, critical ischaemic oedema, leg oedema in deep venous thrombosis, etc[66-68]. The studies were based on CT scans proximal to the ankle and in calf. From these scans, at unilateral oedema, subcutaneous and intramuscular swelling could be calculated by planimetry and later by computer area measurement, as the difference between the oedematous and the contralateral extremity. However, X-ray radiation load can be an unwanted effect of CT scanning.

Magnetic resonance imaging (MRI) has also been used for the measurement of leg oedema in the patients with lymphoedema, DVT, and leg oedema after vascular reconstruction in the lower limb[69]. The T2-weighted MRI is used to analyse the oedema volume in the soft tissue compartments. Although MRI has a clear advantage of having no radiation it can be time consuming and more costly than the CT scan.

DISCUSSION OF RESULTS

All patients with PFF developed post-operative lower limb oedema in the fractured limb (paper 1). Increase in the volume of the contralateral limb was also registered but this increase was neither clinical nor statistically significant. Therefore we concluded that the patients operated on for PFF develop only oedema in the operated limb. Usually, oedema is clinically not detected until the interstitial volume has increased by over 100%, which corresponds to a 10% increase in limb size[70]. Most of the patients with PFF are elderly and a reduced nutritional state of the elderly patients is well known and sufficiently addressed in the medical literature. Hypoalbuminemia could have been a causative factor of oedema since the plasma albumin levels in the patient population was 36.6 g/L, (SD 3.8), (normal reference values 45-57 g/L). However, it was still far beyond the levels where hypoalbuminemia could have caused a general oedema (20-25 g/L)[71]. The lower plasma albumin concentration still might have contributed generally but cannot alone explain the formation of unilateral lower limb oedema in patients with PFF.

Both increase in COP_{pl} and reduction in COP_{if} have been mentioned as the most important oedema preventing factors by Fadnes and Noddeland et al.[71,72]. COP_{if} was lower in the operated limb as compared to the contralateral limb in the patients with PFF but the difference was not statistically significant. Stranden and Myhre had similar COP_{if} finding in their study in the patients with lower limb ischemia[27].

We did not have control subjects for the measurement of COP in the present study. Despite a low plasma albumin concentration the COP_{pl} in our patient groups (FCF=20.4 mmHg (SD 2.2) and PTF=19.3 mmHg (SD 1.1)) was not much different from the COP_{pl} found by Noddeland et al. for control subjects (mean 26.9 mmHg (range 20-35 mmHg). The controls in their study was however much younger than the patients in our study and therefore not readily comparable.

Noddeland et al. concluded that in the patients with nephrotic syndrome no leg oedema developed if the COP_{pl} was above 16.5 mmHg[72]. In our study in the patients with PFF a substantial amount of thigh and leg oedema developed in the operated limb even though the COP_{pl} was as high as approximately 20 mmHg. This points to a conclusion that other factor than lower plasma protein concentration per se is causing oedema development in our patients, e.g. local inflammatory process.

According to Pitkanen et al. the transcapillary colloid osmotic gradient ($\Delta COP = COP_{pl} - COP_{if}$) would be lower than normal in situations with oedema developing tendency[73]. In the patients with PTF transcapillary colloid osmotic gradient was significantly reduced as compared to the FCF (Figure 9). The PTF patients therefore had a weaker oedema limiting potential as compared to the FCF patients and perhaps therefore for this reason a more substantial development of limb oedema.

The direct methods of sampling interstitial fluid necessitate the use of suction. This may lead to erroneous increase in the net capillary filtration and hence a dilution of interstitial proteins. This freshly formed ultrafiltrate in the blisters

may give an underestimation of COP_{if}[40]. According to Adamson et al. the protein concentration in the interstitial fluid is higher than the protein concentration in the area immediately outside the cell membrane glycocalyx[74]. This subglycocalyx fluid comes into contact with the interstitial space through a narrow cleft between the endothelial cells. The protein in the interstitial fluid has to diffuse along the cleft against a fluid flow gradient to exert their osmotic effect. Under conditions of low capillary filtration 70-90% of the bulk COP_{if} may be effective in the subglycocalyx space, at heart level. In conditions with higher filtration, e.g. inflammation, the effective proportion of the bulk COP_{if} is even smaller. In the light of this information about the COP_{if} by Adamson et al. a suspected underestimation of the COP_{if} by the suction blister technique still might be even closer to the actual effective COP_{if}.
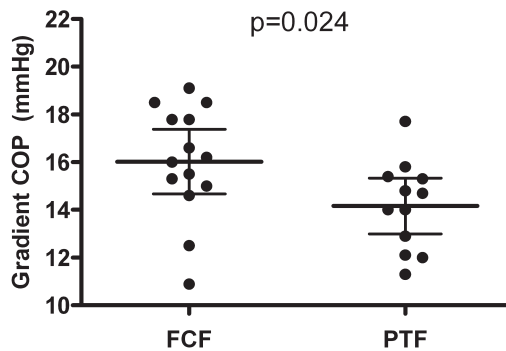

Figure 9. Colloid osmotic gradient ($\Delta COP = COP_{pl}$-COP_{if}), where COP_{pl} is the colloid osmotic pressure of the plasma and COP_{if} is the colloid osmotic pressure of the interstitial fluid, in patients with femoral column fracture (FCF) and pertro-chanteric fracture (PTF). The horizontal bold lines represent mean values and the thin lines are 95% confidence intervals.

An ongoing inflammatory process in the patients with PFF may lead to an increase in capillary pressure (P_c) that follows reduction in precapillary resistance. The P_c is determined by arterial and venous pressures (P_a and P_v) and the ratio between the pre- and post-capillary resistance, R_v/R_a, as given by the equation:

$$P_c = (P_v + P_a \cdot R_v/R_a) / (1 + (R_v/R_a))^{23,75}$$

The finding of a significantly increased level of IL6 in patients with PFF is a strong indicator of an ongoing inflammation (Figure 10). Inflammation is well known for numerous vascular events like arteriolar dilatation and increased blood flow and thereby enhances the vascular transport to macromolecules and accumulation of and infiltration of the leucocytes[76-78]. Many inflammatory mediators have been in the later years recognized as capable of disrupting the inter-endothelial junction assembly, thereby causing endothelial hyperpermeability[32]. CFC was

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significantly increased in operated limbs as compared to the contralateral limbs in both PTF and FCF groups (0.0042 vs. 0.0032 mL/min˙100g of tissue˙mmHg and 0.0032 vs. 0.0025 mL/min˙100g of tissue˙mmHg, respectively)(Figure 11).
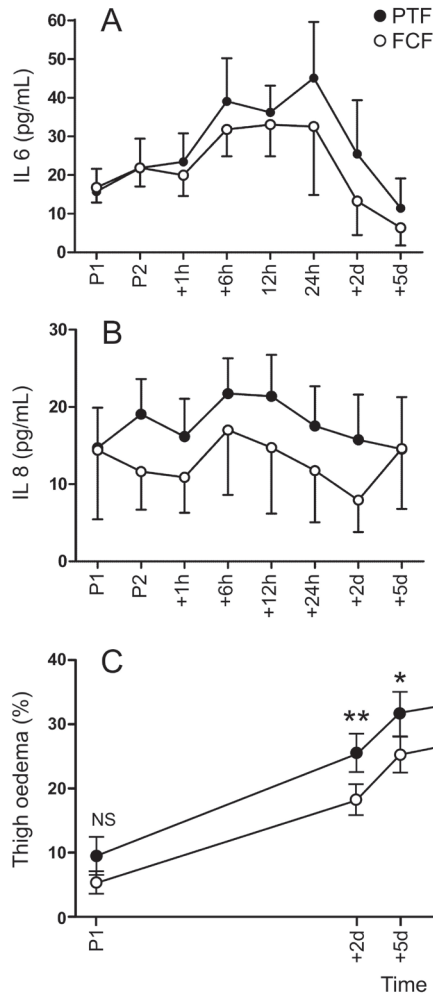
Figure 10. Graphs A and B illustrate mean plasma IL-6 and IL-8 levels at eight different time intervals in the patients with pertrochanteric- (PTF) and femoral cervical fracture (FCF). Vertical bars represent 95% confidence interval. The lower graph (C) represents the thigh oedema changes during the first 7 post-operative days in the operated limb as compared to the preoperative thigh volume in the non-fractured limb. Significant difference in the oedema volume between the patients with PTF and FCF was found at day 2, 5 and 7 post-operatively.
* denotes p<0.05 and ** p<0.01.

Since CFC is a product of hydraulic conductivity of the capillary wall and the available capillary surface area for filtration, CFC can be increased due to an increase in the capillary surface area. The significant increase in the CFC reflects an increased filtration in patients with PFF probably due to an increased hydraulic conductivity of the capillary walls and incorporation of more number of capillaries due to ongoing inflammation[79]. The hydraulic conductivity of the capillary wall can also be increased by "pore stretching" effect, described by Rippe B. et al., of the increased venous pressure[80].
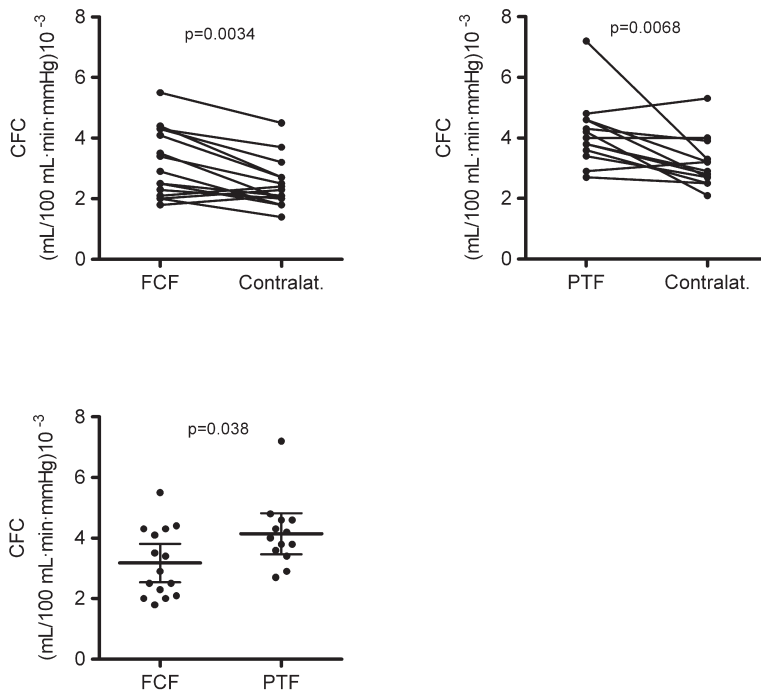
Figure 11. Capillary filtration coefficient (CFC) in patients with femoral column fracture (FCF) and pertrochanteric fracture (PTF). The upper two graphs compare CFC in the operated and the non-operated limb of patients with FCF and PTF, while the lower graph compares CFC in the two patient groups. The horizontal bold lines represent mean values and the thin lines are 95% confidence intervals.

The patients with PFF especially FCF patients cannot do proper weight bearing on the operated limb postoperatively due to the pain at the site of operation. This definitely leads to a poor calf muscle pump function in these patients. Calf muscle pump activity prevents oedema formation by reducing the ambulatory venous pressure in the leg and ultimately the increased capillary hydrostatic pressure in upright position[81]. We have not measured the venous pressure in our patients but a poor calf

muscle pump function is to be expected due to lesser mobility after operation and during the early mobilisation.

In the patients with PFF, despite an extensive postoperative lower limb oedema in the operated limb on the 7th post-operative day, P_{if} did not increase in the anterior muscle compartment of the leg. It was only in case of PTF that the P_{if} values were significantly higher than the contralateral side (1.9 mmHg vs. 0.2 mmHg, respectively, p<0.01). Since the subcutaneous tissue is known to have a higher compliance it is assumed that the P_{if} values were even lower in the subcutaneous tissue. A high compliance means that interstitial fluid can accumulate with a relatively small increase in P_{if}. We achieved the equilibrium state rapidly after needle insertion in the anterior muscle compartment of the leg which reflects the tissue was well hydrated[72]. Increase in P_{if} has been identified as an oedema-limiting factor by reducing the net filtration pressure and has especially been recognised as a factor in stimulating lymphatic uptake and drainage[72,82].

Calf muscle blood flow was significantly increased in the operated limb of the patients with PTF. This may induce increase in the capillary surface area as a result of recruitment of capillaries, and hence an increased CFC[51,83-85].

The patients with PTF and FCF had a substantial increase in the thigh volume as compared to the non-operated side on the post-operative day 7 (17.2% and 9.1%) respectively for PTF and FCF. The oedema formation in the thigh was significantly larger than in the leg in both groups. The distribution of oedema in the soft tissue compartments on the 7th post-operative day showed a significantly larger increase in the CSA of the subcutaneous tissue in only thigh region and only in the patients with PTF. There was also a significant increase in the CSA of the muscle compartment both in the thigh as well as in the leg region in both groups. The pattern of distribution of oedema was somewhat complicated (Paper II, table 1). Although the proportional changes in the CSA measured are real, it probably is not free from an erroneous extrapolation. The CT scan of a mere 1 mm thickness at just one site on the thigh or on the leg of a patient with a PFF might illustrate correctly the proportional changes in the different soft tissue area changes at that site, however it does not necessarily reflect the net soft tissue volume changes in a larger part of the extremity.

The reduction in the subcutaneous tissue volume of the calf on the 30th post-operative day may be partly explained by the use of class I elastic compression stockings. P_{if} is increased artificially by the use of such compression stockings and this can help reduce the oedema development by counteracting the net filtration pressure as well as stimulating lymphatic drainage. A significant increase in the volume of calf muscle on the 30th post-operative day could be due to a moderate compression generated by the class I elastic compression stockings (approximately 14-17 mmHg)[86]. No patients, except one, developed any functionally significant DVT. By "functionally significant" we mean a venous obstruction of a magnitude that cause increased distal venous pressure that may lead to oedema formation. However, any deep venous thrombosis in the small calf muscle veins, without any

functional effect on the venous outflow, could still have been present in the calf muscle despite a negative CDU and VOP. This could be suspected as an additional causative factor for the calf muscle CSA increase on the 30th post-operative day.

The finding of approximately 17.2% volume increase compared to contralateral limb of patients with PTF is quite considerable. This extensive volume increase may cause discomfort and a general feeling of heaviness, thus hindering mobilization and prolonging rehabilitation. The extent of injury and the operated trauma itself, in case of PTF is much larger than FCF and results in almost twice the amount of oedema of the lower limb in the patients with PTF.

MAIN CONCLUSIONS

- All patients with PFF develop lower limb oedema in the operated limb. The patients with PTF develop significantly larger lower limb oedema as compared to the patients with FCF.

- The oedema is distributed both in muscle and subcutaneous tissue.

- The patients with PFF have ongoing inflammation, most probably as a result of both fracture and the operation trauma. This increases transcapillary filtration. A reduced colloid osmotic pressure gradient, especially in PTF, also contributes to increased filtration.

- The patients are suspected to have increased capillary pressure (P_c) due to arteriolar dilatation caused by inflammation, as well as increased venous pressure (P_v) at upright position caused by a poor calf muscle pump function.

CLINICAL IMPLICATIONS

P_{if} can be artificially increased by the use of elastic compression stockings. Increased P_{if} counteracts the capillary filtration pressure and is also known to stimulate lymph flow[87]. The reduction of the subcutaneous leg oedema in patients with PFF on the 30th post-operative day was partly due to the use of Class I compression stockings. Since the P_{if} values measured in the anterior leg compartment were far lower than known for compartment syndrome, one can safely allow the patients with PFF to use Class II compression stockings when ambulant, which generates a larger compression pressure and probably can help reduce oedema development even in the muscle compartment.

Focus can also be given to the movements of the lower limb joints in the operated limb as well as weight bearing to ensure a proper calf muscle pump function. This may reduce the post-operative lower limb oedema in these patients and probably helps to a better and an earlier mobilization of the patients.

The serological markers available for the detection of inflammation are costly and the methodology is also time consuming and difficult. In future studies one may probably use other commercially available inflammation marker like hs-CRP.

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