Edema in the lower limb following arterial reconstruction for atherosclerosis.

A study of pathogenetic mechanisms.

EINAR STRANDEN
(Department of Surgery, Aker Hospital)

J. Oslo City Hosp. 1984, *34:* 3-20

CONTENTS

PREFACE

The purpose of the present investigation was to study pathogenetic mechanisms causing edema of the lower limb following arterial reconstruction for atherosclerosis. This paper is based on the following articles which will be referred to by their Roman numerals:

I *Stranden, E. and Myhre, H. O.:* Transcapillary forces in patients with lower limb ischemia. Scand J Clin Lab Invest 1983, *43:* 233-239.

II *Stranden, E.:* A comparison between surface measurements and water displacement volumetry for the quantification of leg edema. J Oslo City Hosp 1981, *31:* 153-155.

III *Stranden, E. and Enge, I.:* Computed tomography in the investigation of leg edema following arterial reconstruction. Europ J Radiol 1982, *2:* 113-116.

IV *Stranden, E. and Myhre, H. O.:* Pressure-volume recordings of human subcutaneous tissue. A study in patients with edema following arterial reconstruction for lower limb atherosclerosis. Microvasc Res 1982, *24 (3):* 241-248.

V *Stranden, E.:* Transcapillary forces in subcutaneous tissue of patients following operation for lower limb atherosclerosis. Scand J Clin Lab Invest 1983, *43:* 381-388.

VI *Standen, E. and Kramer, K.:* Lymphatic and transcapillary forces in patients with edema following operation for lower limb atherosclerosis. Lymphology 1982, *15:* 148-155.

VII *Stranden, E.:* Transcapillary fluid filtration in patients with leg edema following arterial reconstruction for lower limb atherosclerosis. VASA 1983, *12 (3):* 219-224.

VIII *Stranden, E.:* Dynamic recordings of the local vasoconstrictor response to increased venous transmural pressure. A study in patients with lower limb atherosclerosis. Acta Chir Scand (in press).

ACKNOWLEDGEMENTS

This study was carried out in the years 1979-83 when I was research fellow at the Department of Surgery, Section of Vascular Surgery, Aker Hospital, Oslo.

First and foremost I wish to express my profound gratitude to my chief, Professor *Sverre Vasli* who encouraged me to start the study. He provided excellent working facilities and guided me with friendly criticism through all stages of the project.

I am indebted to Dr. *Hans O. Myhre* who was my daily source of advice and criticism.

Some of the methods used were developed at the Institute of Physiology, University of Bergen. I wish to express my warmest thanks to Professor *Knut Aukland,* Dr. *Hans O. Fadnes,* Dr. *Harald Noddeland* and Dr. *Rolf Reed* for kindly introducting me to the methods.

I am grateful to Dr. *Andries Kroese,* Dr. *Gunnar Nicolaysen* and Dr. *Egil Seem* for helpful discussions.

Dr. *Arnfinn Engeset* and Dr. *Waldemar Olszewski* at the Norwegian Radium Hospital gave instruction in the technique of lymph vessel cannulation, performed by Dr. *Karin Kramer.*

I thank Professor *Ivar Enge,* Chief Engineer *Odvar Iversen* and Civil Engineer *Arne Grip* for excellent technical assistance.

I also want to thank Miss *Bente Finsrud,* Mrs. *Anne Marie Haraldstad* and Miss *Sigrid Huseby* for kind assistance.

The study was supported by grants from Anders Jahre's Fund for the Promotion of Science, the Norwegian Research Council for Science and the Humanities, The Norwegian Council for Cardiovascular Diseases, «Landsforeningen for Hjerte- og Lungesykes Medisinske Fond», Professor Carl Semb's Fund for Medical Scientific Research, Otto and Karen Andersen's Fund, Gotfred and Marie Lie's Fund and Joh. H. Andresens's Medical Fund.

INTRODUCTION

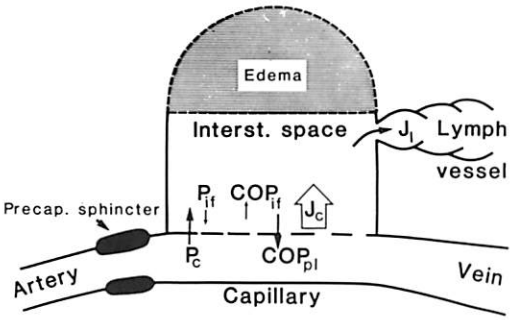
Edema of the foot and leg is a common complication after successful femoropopliteal reconstruction (*Husni* 1967) with a reported incidence ranging between 40% and 100% (*Conolly* and *Stemmer* 1970, *Vaughan* et al. 1970, *Hamer* 1972, *Koontz* and *Stansel* 1972). The edema usually appears within a few days postoperatively and may last for several months. It may worry the patient and represents a problem in the postoperative rehabilitation.

The exact mechanism for the development of post-reconstructive edema is unknown, but several causes have been proposed:

1. *Deep venous thrombosis* (*Taylor* 1962, *Ernst* et al. 1964). However, the incidence of deep venous thrombosis in patients with post-reconstructive edema is low (*Myhre* et al. 1974). This may be due to a hyperemia and concomitantly increased venous flow velocity which usually develops after vascular reconstruction (*Sumner* and *Folse* 1968, *Myhre* and *Dedichen* 1972, *Kroese* 1975). In addition anticoagulation therapy including heparin is used during the operations (*Kakkar* et al. 1971).
2. *Destruction of lymph vessels* caused by local dissection with resultant lymphedema (*Linton* and *Darling* 1962, *Vaughan* et al. 1970, *Porter* et al. 1972, *Støren* et al. 1974, *Eickhoff* and *Engell* 1982). The presence of lymph vessel disruption, visualized by lymphangiography, was not correlated with occurrence of postoperative edema (*Porter* et al. 1972). However, lymphangiography is probably an inadequate technique to study lymph vessel function in the development of edema.
3. *Increased filtration* from the capillaries which are suddenly exposed to a rise in blood pressure after prolonged adaptation to low pressure with concomitant degeneration of the arterial wall (*Simeone* and *Husni* 1959, *Husni* 1967, *Husni* and *Manion* 1967).

Fluid exchange between intra- and extravascular space takes place across the capillary wall. This structure is regarded as semipermeable: impermeable to plasma proteins and freely permeable to water and low molecular solutes. The interstitial fluid volume (IFV) is normally kept within narrow limits (*Aukland* and *Nicolaysen* 1981). A net increase in interstitial volume (Δ IFV) which is present in patients with postoperative edema, must be caused by a net capillary filtration (F) exceeding lymphatic flow (L):

$$\Delta \text{ IFV} = \int \text{F dt} - \int \text{L dt} \qquad (1)$$



$$J_c = CFC((P_c - P_{if}) - \sigma(COP_{pl} - COP_{if}))$$

Fig. 1. Factors participating in the transcapillary fluid balance. Edema occurs when net capillary filtration (F) exceeds lymphatic flow (L). σ : capillary reflection coefficient. CFC: capillary filtration coefficient. P_c and P_{if}: hydrostatic pressures in the capillaries and interstitial fluid. COP_{pl} and COP_{if}: colloid osmotic pressures of plasma and interstitial fluid.

Net capillary filtration is governed by hydrostatic and colloid osmotic pressures (Starling forces) in plasma and the interstitial fluid (Fig. 1):

$$F = CFC((P_c - P_{if}) - \sigma(COP_{pl} - COP_{if})) \quad (2)$$

where P_c and P_{if} are hydrostatic pressures in the capillaries and interstitium respectively. Capillary filtration coefficient (CFC) represents the amount of net filtrate formed in 100 g of tissue per minute for each mm Hg rise in net filtration pressure. CFC is the product of hydraulic conductivity of the capillary wall and the capillary surface area. COP_{pl} and COP_{if} are colloid osmotic pressures of plasma and interstitial fluid respectively. Sigma is the capillary reflection coefficient. In subcutaneous tissue σ is probably between 0.9 and 1.0, indicating that capillaries in this vascular bed are nearly impermeable to plasma proteins (*Pappenheimer* and *Soto-Rivera* 1948, *Renkin* et al. 1977, *Taylor* et al. 1977).

Studies on transcapillary fluid balance (Starling forces eq. 2) in patients with lower limb atherosclerosis have probably not been performed previously, mainly because of lack of suitable methods for clinical investigations. A «wick» method for collecting samples of interstitial fluid and «wick-in-needle» technique for measuring interstitial fluid pressure (*Aukland* and *Fadnes* 1973, *Fadnes* et al. 1977, *Noddeland* 1982a, 1982b) are valuable tools in the clinical investigation of transcapillary fluid balance.

In the present thesis Starling factors (eq. 2) were studied in patients with lower limb atherosclerosis before and after femoropopliteal reconstruction. The aim of the study was to gain information on the etiology of post-reconstructive edema.

The following questions were posed:

1. What is the magnitude of the Starling forces (i.e. what is the safety margin against edema formation) in patients with lower limb atherosclerosis?
2. In which compartment (subcutaneous, intramuscular) is the post-reconstructive edema located? This may have influence on the management of the edema, for example prophylactic fasciotomy.
3. To what extent does the increased volume influence interstitial fluid pressure, i.e. what is the tissue compliance?
4. Are the capillary filtration coefficient and Starling forces changed in legs with edema?
5. Does lower limb atherosclerosis affect arteriolar regulatory mechanisms?

DISCUSSION OF METHODS

Femoropopliteal arterial reconstruction

In all patients vascular surgery consisted of a femoropopliteal bypass. Usually a reversed autogenous saphenous vein was

used. If a suitable vein was not available, Dardik Biograft® (umbilical vein homograft) or Gore Tex® (expanded Teflon - PTFE) were chosen as a graft. Multiple skin incisions were made along the course of the great saphenous vein (Fig. 2A) (*Cooley* and *Wukasch* 1979). Following end-to-side anastomosis to the popliteal artery the graft was placed subfascially and anastomosed end-to-side to the common femoral artery (Fig. 2B).

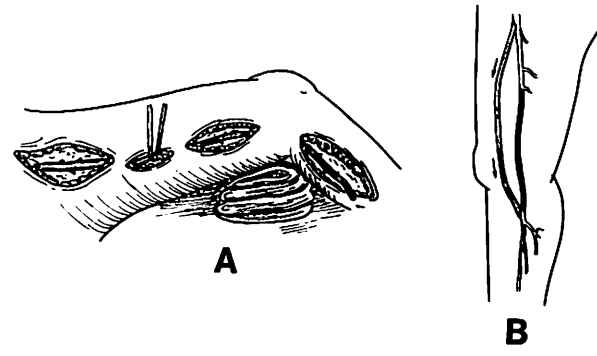


Fig. 2. Schematic illustration of a femoropopliteal bypass operation.

Intraoperative anticoagulation consisted of 3000 IE Heparin®. To avoid interferences with the Starling forces no colloids were given postoperatively. On the day of operation the patients received an average of 1000 ml of isotonic saline solution and 3000 ml of Ringer's lactate.

The patients received normal diet from the first postoperative day and were mobilized from the second. The measurements were performed with the patients in supine position in a room with an air-temperature of 23-25 degrees centigrade, after a resting period of at least 20 min.

Interstitial fluid colloid osmotic pressure (COP_{if}) measurements

Two main approaches to collect interstitial fluid for protein analysis have been used in previous investigations (*Aukland* and *Nicolaysen* 1981):

I. Direct sampling by micropipettes and catheters (*Creese* et al. 1962, *Garetto* and *Hargens* 1976, *Haljamäe* and *Fredén* 1970). However, the applied suction might increase net capillary filtration and thereby reduce interstitial fluid protein concentration (*Aukland* and *Nicolaysen* 1981).

II a. Technique based on fluid equilibrium by implantation of perforated capsules during a 4-6 weeks period (*Guyton* 1963). Use of the method in human investigation is for obvious reasons limited.

II b. In the present investigation a wick method was used (*Scholander* et al. 1968), *Aukland* and *Fadnes* 1973). In a recent study by *Noddeland* et al. (1982) similar values of COP_{if} were found in fluid collected by implanted nylon wicks, empty wick catheter (no suction) and implantable colloid osmometer. Their investigation supported the assumption that COP of the fluid collected by the wick method reflects «true» COP_{if}.

Wicks made from 0.8 mm-thick nylon thread consisting of 210 filaments were soaked in saline. They were sewn subcutaneously. Wick insertion causes an inflammatory reaction during the first half hour after implantation, with marked increase in capillary protein leakage during that period. More than 50% of albumin in the wick is derived from plasma. In the next half hour the capillary protein leakage is reduced, and the wick equilibrates osmotically with the surrounding fluid (*Fadnes* and *Aukland* 1977). Following an implantation period of one hour the wick fluid was isolated as described by *Johnsen* (1974). The sample (2-10 µl) was centrifuged and transferred to an oncometer modified from those described by *Tybjaerg Hansen* (1961) and *Aukland* and *Johnsen* (1974). For the oncometer an amplifier unit was constructed («5 µl Oncometer», Fig. 3), which permitted

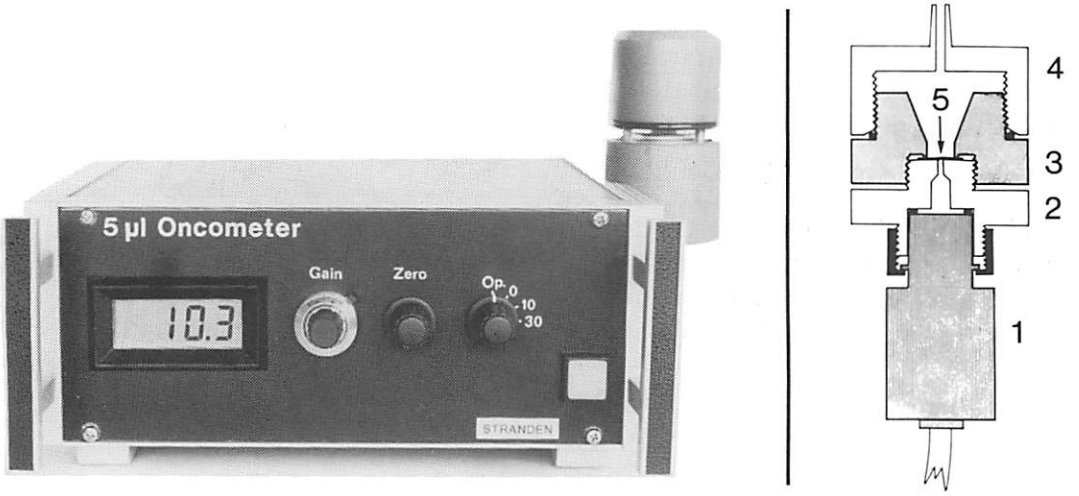


Fig. 3. «5 µl Oncometer» (1): Statham pressure transducer (P 23 Db) with low volume displacement (0.04 mm^3/100 mm Hg), (2): reference chamber filled with isotonic saline solution, (3): sample chamber, (4): calibration connector, (5): dialyzing membrane with protein cutoff at MW 30000.

easy read-out of the measured colloid osmotic pressure.

Sometimes wicks had to be discarded because of blood staining, but in most subjects at least one of the four wicks was without serious contamination. Usually one double strand was enough to obtain a sample of 3-5 µl which was needed for the oncometer. Pink wicks were included, since there is no significant difference between COP in clear and pink wicks obtained from the same person (*Noddeland* 1982b).

The wicks were introduced under local intracutaneous anesthesia (lidocain chloride, 20 mg/ml, without adrenaline). The parts of the wicks passing anesthetized areas were cut away and did not contribute to the sample.

Interstitial fluid hydrostatic pressure (P_{if}) measurements

P_{if} was measured by a «wick-in-needle» (WN) technique (*Scholander* et al. 1968, *Fadnes* et al. 1977). The method is based on fluid equilibrium, with a water column between a pressure transducer and the interstitium. Hypodermic needles (0.8 mm OD, 40 mm length) were provided with a 4-mm side-hole approximately 7 mm from the tip. The needles were filled with cotton thread and sterilized by gamma irradiation. The thread provided a continuous water connection between tissue and needle lumen. When a needle without wick is used the tip is often obstructed.

The needle was connected to a pressure transducer (Statham P 23 Db) with a polyethylene tube (Portex manometer line, 60 cm, 200/490/060) (Fig. 4). The pressure transducer had a volume displacement of 0.04 µl/100 mm Hg, and compliance of the total measuring system was 0.7 µl/100 mm Hg.

After insertion of the needle under local anesthesia a negative pressure of 10 to 20 mm Hg was usually recorded in subcutaneous tissue. This was regarded as an insertion artifact. The pressure increased rapidly and stabilized after 1-10 min. In legs with edema the plateau was reached almost instantaneously. In normally hydrated tissue the process lasted longer. The patency

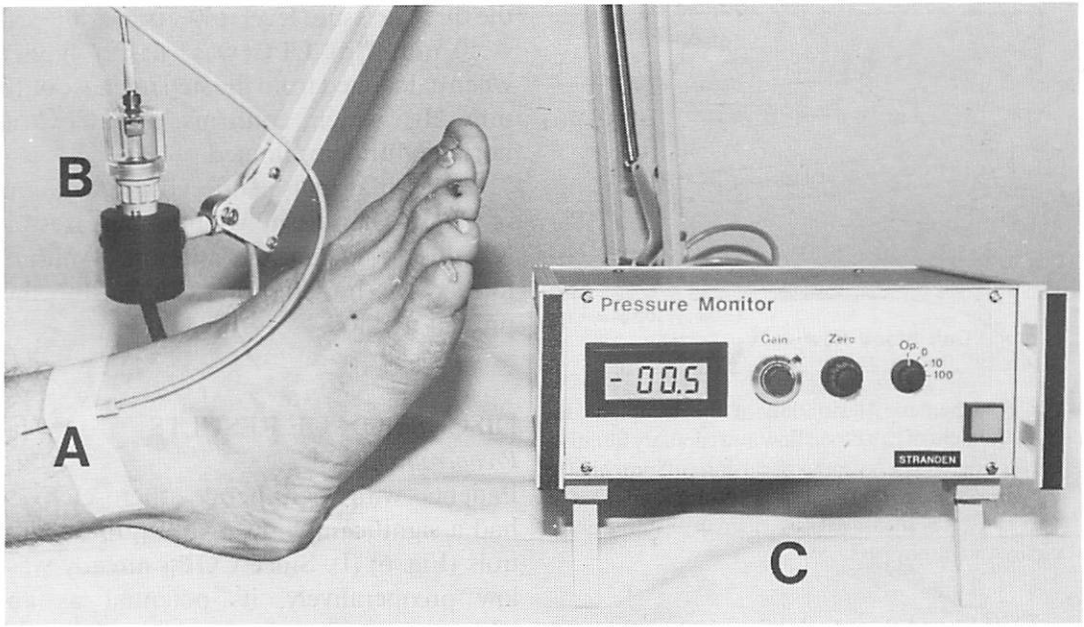


Fig. 4. Measurement of interstitial fluid pressure (P_{if}). A needle provided with a 4-mm side-hole approximately 7 mm from the tip, filled with a cotton thread (A) was connected to (B) a pressure transducer (Statham P 23 Db). (C): amplifier unit.

of the fluid phase was checked by slight compression of the polyethylene catheter by means of a screw clamp which was tightened to induce a pressure rise of approximately 5 mm Hg. Loosening the clamp gave the opposite response. The measurements were accepted only when the pressures were re-established ($\pm$ 0.5 mm Hg).

WN technique might result in erroneously high P_{if} because of traumatic exudation by the needle insertion (*Brace* 1979). However, from investigations with WN and micropuncture techniques it was concluded that inflammatory reaction does not interfere with reliable measurements of P_{if} by WN technique (*Wiig* et al. 1981).

Measurement of calf blood flow and capillary filtration coefficient.

Calf blood flow and capillary filtration coefficient (CFC) were measured by venous occlusion plethysmography (*Hillestad* 1963). A mercury strain-gauge plethysmograph with electrical calibration was used (Loosco Plethysmograph, G. L. Loos & Co., Amsterdam, Holland). The electrical calibration was compared with mechanical stretching of the strain-gauges by use of a micrometer. Mean difference between the two calibration procedures was approximately 3% which was regarded as satisfactory. Furthermore, an exact linear relationship was found between extension of the gauges and the recorded volume change.

The width of the venous occlusion cuff was approximately 1/3 of the circumference of the thigh (*Graf* 1964). The cuff was placed just proximal to the knee and inflated instantaneously to 50 mm Hg. The resulting change in leg volume was recorded by a Watanabe Mark V linear recorder (Watanabe Instruments Corp., Tokyo, Japan).

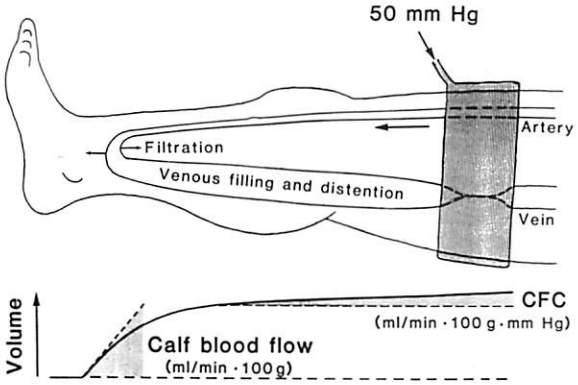


Fig. 5. Schematic illustration of the technique for measurement of calf blood flow and capillary filtration coefficient (CFC). A venous occlusion cuff proximal to the knee is inflated to 50 mm Hg. Volume changes in the calf are measured by mercury strain-gauge plethysmography.

Calf blood flow (ml/min · 100 g of tissue) was calculated from the initial slope of the volume curve (Fig. 5) and estimated as the average of 3 consecutive measurements.

CFC was calculated from the slope of the volume curve during 3-6 min following venous occlusion (Fig. 5), assuming that filtration pressure increased 50 mm Hg. This is necessarily an approximation, since venous outflow pressure before inflation and postcapillary resistance were unknown. These factors may lead to an underestimation of CFC. However, the underestimation is probably similar in both limbs and the CFC-ratio between the limbs is therefore unchanged. This hypothetical technical error was investigated in two patients in whom cuff pressure was increased in step from 40 to 50 mm Hg. The increase in filtration pressure was assumed to be 10 mm Hg in both limbs, irrespective of the individual resting capillary pressures. In both patients leg volume increased more in the edematous leg than in the contralateral when filtration pressure increased by 10 mm Hg. CFC-ratio between operated and contralateral leg was almost equal at the three pressure levels (40, 50 and 40 → 50 = 10 mm Hg). CFC was slightly higher when calculated from the step increase of 10 mm Hg, which confirms that CFC is normally underestimated.

Edema may in itself affect the calculation of CFC. When tissue volume increases by X% due to edema, the amount of filtrate formed is underestimated X% by the present method.

DISCUSSION OF RESULTS

Preoperatively

Patients with peripheral atherosclerosis had a significantly lower COP_{if} than controls (Fig. 6) (I). Since COP_{if} already was low preoperatively, its potential as an edema preventing factor was equally reduced and could predispose to postoperative edema (*Noddeland* et al. 1982).

The reduction in COP_{if} was not due to a fall in plasma protein concentration;

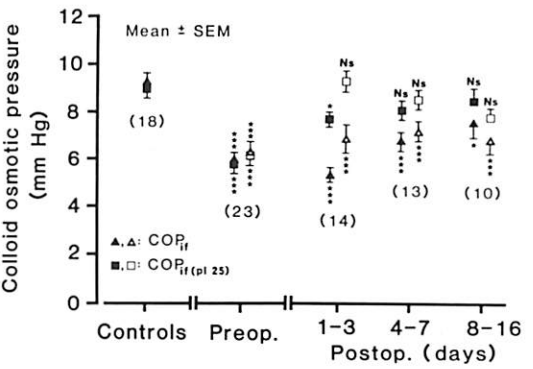


Fig. 6. Colloid osmotic pressure of interstitial fluid (COP_{if}) in controls, patients with lower limb atherosclerosis (Preop.) and after arterial reconstructiof (Postop.). Filled symbols (▲, ■) represent control legs, the most diseased leg preoperatively and the operated leg; open symbols (△, □) represent contralateral leg. $COP_{if\ (pl\ 25)}$ is the calculated interstitial fluid colloid osmotic pressure when variations in COP_{pl} are compensated for. Number of subjects in parentheses. $^{*}p<0.05$, $^{***}p<0.005$ versus controls. Ns: not statistically different from controls.

COP_{pl} was not different from controls. Neither did the patients show signs of ischemic edema (*Thulesius* and *Sivertsson* 1973). Therefore the lower COP_{if} was probably caused by a net reduction in interstitial protein mass i.e. «washout» of proteins. Since the capillary filtration coefficient was normal (VII), «washout» was probably caused by increased net filtration pressure. A reduced COP_{if} by «washout» of interstitial proteins may accompany increased venous pressure (*Fadnes* 1976, *Wiederhielm* 1979). In a recent study of patients with deep venous thrombosis and increased venous pressure of the lower limb we found a reduction in COP_{if} of 3.2 mm Hg compared to the contralateral leg (*Seem* and *Stranden* 1982). However, the condition was associated with edema, and the reduced COP_{if} could also be caused by dilution of interstitial proteins.

The mean age of patients was higher than in the control group. Age difference did not influence the measurement for COP_{if}. COP_{if} of the six oldest control subjects with a mean age compatible to the patients', was 9.5 mm Hg, not different from the other controls ($p>0.05$).

The force opposing filtration (reabsorption pressure, P_r) is defined as:

$$P_r = \sigma \cdot COP_{pl} - \sigma \cdot COP_{if} + P_{if}.$$

Assuming no net filtration across the capillary wall (i.e. filtration equals reabsorption), P_r is equal to capillary pressure (*Pappenheimer* and *Soto-Rivera* 1948, *Hargens* et al. 1981). Normally net transcapillary filtration occurs and mean P_c is higher than P_r. The difference between the pressures (i.e. net filtration pressure) is however small, probably about 0.5 mm Hg (*Aukland* and *Nicolaysen* 1981). Net filtration pressure may be defined as lymph flow divided by CFC (L/CFC) (*Aukland* and *Nicolaysen* 1981). The calculated net filtration pressure in legs where lymph vessels

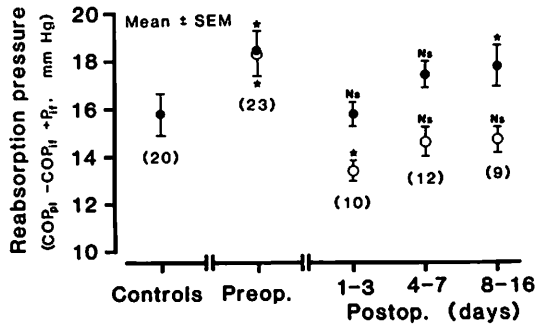


Fig. 7. Calculated reabsorption pressure (COP_{pl} - COP_{if} + P_{if}, where P_{if} is hydrostatic pressure of interstitial fluid and COP_{pl} and COP_{if} are colloid osmotic pressure of plasma and interstitial fluid) in controls, patients with lower limb atherosclerosis (Preop.) and after arterial reconstruction (Postop.). Filled symbols (●) represent control legs, the most diseased leg preoperatively and the operated leg; open symbols (○) represent contralateral leg. Number of subjects in parentheses. *$p<0.05$ versus controls. Ns: not statistically different from controls.

were cannulated (VI) was 0.5 ± 0.09 mm Hg. In this calculation it was assumed that the amount of soft tissue drained by the cannulated vessel was 100 g, and that the value of CFC did not change throughout the leg.

In patients with lower limb atherosclerosis P_r was higher than in controls (Fig. 7) (I). This finding was unexpected since we assumed that lower ankle systolic blood pressure would reduce capillary pressure.

Impaired arteriolar regulatory mechanisms seem to be among causative factors for the increased P_r in patients. This was concluded from the absence of vasoconstrictor response to increased venous distention (VIII). In atherosclerotic patients lower limb capillary pressure is thus more susceptible to increase in arterial pressure, for example in upright position.

An increased P_r, which means even higher P_c since P_c is normally higher than P_r, may explain the reduced COP_{if} in patients by causing increased filtration and

«washout» of proteins as mentioned above. Both factors (reduced COP_{if} and increased P_T) are unfavorable with respect to postoperative edema prevention.

Postoperatively

All patients had a successful operation. Venous thrombosis was not detected plethysmographically. Leg edema developed progressively during the first two weeks after surgery (V). During the first three postoperative days two out of 15 limbs became edematous. In the group studied 8-16 days postoperatively all 10 patients had edema. In the latter group the average leg volume increase was 22.5% calculated from surface measurements (II). Virtually all distally located edema (i.e. 98%) was subcutaneous (III). In the calf a relatively higher fraction of edema was intramuscular. Here the mean volume increase compared to the contralateral leg was 9.7% in the muscular compartments and 78.3% in subcutaneous tissue. This finding and registration of normal intramuscular pressure in edematous legs confirmed that prophylactic fasciotomy was not indicated in this group of patients (III).

Capillary filtration coefficient

In 15 patients with leg edema CFC in the operated limb was twice the value of the contralateral (0.0032 versus 0.0017 ml/min · 100 g · mm Hg) (VIII). Thus, at otherwise equal net filtration pressure the amount of transudate formed in the operated limb was twice as high as in the contralateral.

CFC is the product of the hydrodynamic conductivity of the capillary wall and the capillary surface area available for exchange of fluid. Both factors may contribute to the increased CFC in limbs with edema. Because of the positive correlation between CFC and calf blood flow and postoperative hyperemia, it is tempting to assume that the increased CFC was due to increased capillary surface area by recruitment of capillaries (*Kitchin* 1963, *Worm* and *Nielsen* 1981). During venous occlusion plethysmography, however, primarily closed capillaries are probably filled and opened retrogradely when venous pressure is elevated to 50 mm Hg. The capillary surface area is therefore assumed to be maximal during the measurements, irrespective of precapillary tone.

Most legs with edema had postoperative hyperemia and increased skin temperature. Increased temperature reduces plasma viscosity and hence increases the rate of fluid transfer across the capillary wall (*Curry* 1979). Capillary permeability may also be enhanced by local increase of vasoactive substances such as histamine and bradykinin due to surgical trauma. These substances may increase capillary permeability (*Boykin* et al. 1980, *Gawlowski* 1982).

Calf blood flow was calculated from the slope of the volume curve immediately after inflation of the venous occlusion cuff - before venous pressure had increased considerably. Blood flow during measurement of CFC is probably lower than the value obtained at the beginning of venous occlusion. CFC was calculated at venous pressure of 50 mm Hg, presumably enough to trigger the veno-arteriolar reflex. Consequently in that period calf blood flow may have been reduced considerably (VIII). In addition, the increased venous pressure will in itself reduce local perfusion pressure. However, these considerations do not invalidate but increase the positive correlation between CFC and calf blood flow.

Transcapillary forces

Compared to the values obtained preoperatively (I), COP_{if} of the operated limb

was slightly lower in the first period (1-3 days) after surgery and increased in the later phase (Fig. 6) (V). However, the role of COP_{if} in the transcapillary fluid balance is not determined by its absolute value, since the balance itself also depends on COP_{pl}. This was indicated by a positive correlation between COP_{if} and COP_{pl} (V). Therefore a new parameter was introduced, COP_{if} (pl 25). Each COP_{if}-recording was given a new value where deviation in COP_{pl} from a standardized plasma value of 25 mm Hg was compensated for. Two examples are given (Fig. 8). The measured COP_{if} (triangles) were moved along a parallel to the regression line of the non-operated leg to a vertical line at COP_{pl} = 25 mm Hg, to give the corrected COP_{if} (squares). The two recordings obtained quite opposite values when variations in COP_{pl} were corrected. This strongly emphasizes that the value of COP_{pl} should be considered when COP_{if} is discussed. (An alternative way is to calculate the colloid osmotic gradient, grad COP = COP_{pl} - COP_{if}, and compare this parameter).

Because mean COP_{pl} was close to 25 mm Hg in both controls and patients preoperatively, COP_{if} (pl 25) was almost identical to the measured COP_{if}. Postoperatively, however, protein concentration of plasma was reduced, causing «uphill» transposition in figure 8. As a consequence COP_{if} (pl 25) in all postoperative periods was higher than the measured COP_{if}. The corrected value was higher than in the same type of patients preoperatively ($p<0.005$). This implies that the fraction of plasma proteins in the interstitial space is increased. Impaired lymphatic drainage is the most likely cause. It may increase P_{if} (Fig. 9) which reduces net filtration by reduction in net filtration pressure. Protein transport by diffusion, depending on transcapillary concentration gradient, is however maintained.

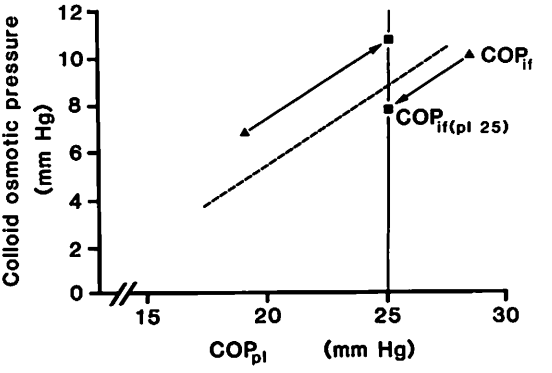


Fig. 8. Relationship between COP_{if} (▲) and COP_{if} (pl 25) (■). In the latter, variations in plasma colloid osmotic pressure (COP_{pl}) are compensated for. The measured COP_{if} was moved along a parallel to the regression line of the non-operated leg (interrupted line) to a vertical line at COP_{pl} = 25 mm Hg, to give the corrected value.

A new steady state has presumably been established, in which both P_{if} and COP_{if} are increased. Increase in COP_{if} caused by moderate lymphatic obstruction is disputable (*Olszewski* 1977). On the other hand the hypothesis is supported by measurements on patients with chronic unilateral lymph-

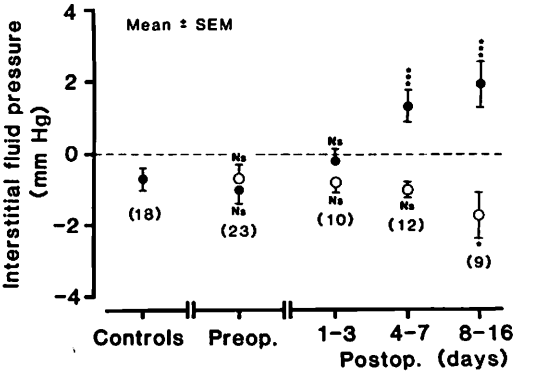


Fig. 9. Subcutaneous interstitial fluid pressure in controls, patients with lower limb atherosclerosis (Preop.) and after arterial reconstruction (Postop.). Filled symbols (●) represent control legs, the most diseased leg preoperatively and the operated leg; open symbols (O) represent contralateral leg. Number of subjects in parentheses. $^{*}p<0.05$, $^{***}p<0.005$ versus controls. Ns: not statistically different from controls.

edema of the lower limb. These patients had a mean increase in COP_{if} of 5 mm Hg in the afflicted compared to the contralateral leg (*Stranden,* unpublished).

In all patients with lymph vessel cannulation (VI), maximal (systolic) intralymphatic end pressure waves ranged between 30 and 40 mm Hg, similar to those found in healthy controls (*Olszewski* and *Engeset* 1980). Thus preoperative ischemia did not reduce the efficiency of intrinsic mechanisms for lymph propulsion.

A high lymph flow measured after cannulating lymphatic vessels at the ankle (VI) does not imply high flow before cannulation. Because the lymphatics were only cannulated in distal direction, an obstructed system may have been opened during the cannulating procedure to give an artificial high value. Lymph flow was positively correlated to both CFC and P_r, which indicated that the increased flow represented increased transcapillary filtration and not merely drainage of accumulated edema fluid.

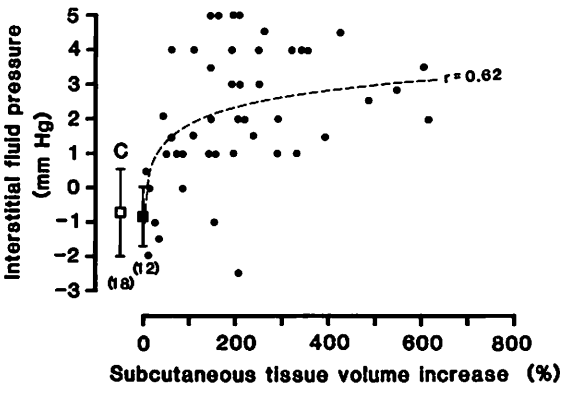


Fig. 10. Relationship between subcutaneous interstitial fluid pressure (P_{if}) and calculated subcutaneous tissue volume increase in patients following arterial reconstruction for lower limb atherosclerosis. Patients with postoperative edema are represented by ●. Mean $P_{if} \pm$ SD in patients without edema is represented by ⧳, whereas mean $P_{if} \pm$ SD of healthy controls (C) is given to the left (⧲). Number of subjects in parentheses. The interrupted line is the regression curve representing all patients, and is described by the equation: $f(z) = 0.71 \cdot \ln z - 1.4$, where $f(z) = P_{if}$ and $z\,(z>0)$ is percentage increase in subcutaneous tissue volume, $r = 0.62$, $p<0.001$.

Compliance of the subcutaneous tissue

Tissue compliance determines the change in P_{if} resulting from a change in interstitial fluid volume (IFV) and is defined as $\Delta IFV/\Delta P_{if}$. A high compliance means that interstitial fluid can accumulate with a relatively small increase in P_{if} and vice versa.

Increased P_{if} may be an edema preventing factor by reducing net filtration pressure. The magnitude of this factor depends largely on tissue compliance. Pressure-volume measurements in patients with postoperative edema showed that subcutaneous tissue compliance varied considerably at different degrees of edema (Fig. 10) (IV).

When a logarithmic curve-fitting program was applied to the data the regression curve was represented by the equation:

$$f(z) = 0.71 \cdot \ln z - 1.4, \qquad (3)$$

where $f(z) = P_{if}$ and $z\,(z>0)$ is percentage increase in subcutaneous tissue volume, $r = 0.62$, $p<0.001$. This equation is represented by the interrupted line in figure 10. The first order derivative of eq. 3 is expressed by:

$$f'(z) = df(z)/dz = \Delta P_{if}/\Delta IFV = 0.71/z, \qquad (4)$$

which is the reciprocal of compliance. Assuming that eq. 3 is representing the pressue-volume relationship of the edematous leg in these patients, the subcutaneous tissue compliance is:

$$\text{Compliance}_{(z)} = z/0.71, \qquad (5)$$

where z ($z>0$) is percentage increase in subcutaneous tissue volume. According to eq. 5 compliance increases linearly with IFV.

As an example the calculated compliance corresponding to a subcutaneous tissue volume increase of 50% was 70 ml/mm Hg · 100 g subcutaneous tissue. With extensive edema amounting to 600% the compliance was 845 ml/mm Hg · 100 g. There was a relatively large scatter in the recorded pressures, and the calculated examples must be regarded with caution.

The clinical consequence of the obtained pressure-volume curve is that *initial* accumulation of fluid in the interstitial space may be counteracted by a concomitant increase in P_{if} (the steepest part of the compliance curve). In the later phase of edema formation (>100% subcutaneous tissue volume increase) the compliance has increased considerably, permitting large quantities of fluid to transudate from the capillaries without any significant increase in P_{if}. In this state of hydration P_{if} plays only a minor role in limiting further edema formation.

Interstitial tissue compliance in humans has not previously been established. The shape of the pressure-volume curve obtained in our study (IV) is similar to what has been found in animal experiments (*Guyton* 1965, *Eliassen* et al. 1974, *Wiig* and *Reed* 1981) although compliance (according to eq. 5) did not change abruptly. The calculated compliance was much higher than in previous studies. One explanation may be that the magnitude of volume changes and composition of tissues were different.

Arteriolar regulatory mechanisms

To elucidate the arteriolar function in patients with lower limb atherosclerosis the veno-arteriolar (VA) reflex was studied (VIII). When vascular transmural pressure is increased more than 25 mm Hg (e. g. by lowering a limb) local blood flow is normally reduced (*Gaskell* and *Burton* 1953). The reduction is caused by arteriolar constriction due to a local sympathetic axon reflex triggered by venous distention (*Henriksen* 1977). In the present study (VIII) increase in transmural pressure was achieved by exposing a limb to subatmospheric pressure (limb negative pressure exposure: LNPE) of 75 mm Hg in a negative pressure chamber (*Stranden* et al. 1979).

The reflex was absent in patients with atherosclerosis studied before revascularisation. This could indicate dysfunction of the arteriolar smooth muscle cells or nerves participating in the reflex. In patients with pain at rest the peripheral resistance was probably reduced due to passive distention during LNPE. This finding indicated that *autoregulation* as well as *vasoconstrictor response* were hampered, possibly due to ischemia.

Atrophy of the vessel wall due to chronically reduced arterial pressure may be a causative factor for the longlasting postoperative hyperemia and edema (*Husni* and *Manion* 1967). However, other causes presumably play a part since the VA reflex, although absent in the immediate postoperative period, already returned one week after surgery. Accumulation of vasodilation metabolites in ischemic areas could make arteriolar smooth muscle cells less sensitive to constrictor stimuli (*Henriksen* and *Wisborg* 1975). On the other hand, although the VA reflex was normalized from the second postoperative week, postoperative hyperemia was still present in that period (VII). Therefore, a normal VA reflex does not exclude increased capillary pressure to be among the factors causing late postoperative edema.

MEASURES TO LIMIT EDEMA FORMATION

Prophylactic. Based on the assumption that lymphedema due to lymph vessel disruption is an etiological factor for post-reconstructive edema, measures may be taken to reduce surgical trauma in the inguinal and popliteal region (*Eickhoff* and *Engell* 1982). Lymph vessels may be visualized by injection of Patent Blue-Violet between first and second toe a few hours preoperatively, to save as many vessels as possible.

Symptomatic. To reduce the formation of edema postoperatively we have started compression treatment after arterial reconstruction for lower limb atherosclerosis. The compression increases P_{if} and thereby reduces net filtration pressure. Compression has been achieved by 1: Intermittent inflation of a cuff surrounding the limb (Jobst Extremity Pump®, Jobst Ireland Ltd., Thurles, Ireland) for periods of 45 min three times a day, or 2: By use of elastic stockings (T. E. D.® Anti-embolism stockings, Kendall, Boston, USA) commonly used by patients with deep venous insufficiency. The experience so far is that elastic stockings reduces edema formation most efficiently.

SUMMARY AND CONCLUSIONS

Reduced lymph flow and increased transcapillary filtration are major pathogenetic factors for lower limb edema following arterial reconstruction.

Decreased lymphatic drainage may explain the increased colloid osmotic pressure of interstitial fluid (COP_{if}) and greater fraction of plasma proteins found in interstitial fluid postoperatively. Since the intrinsic pumping mechanism in the lymphatics was normal, reduced lymph flow was probably caused by lymph vessel damage during dissection in the groin and popliteal region.

In patients with postoperative edema, the capillary filtration coefficient (CFC) was significantly greater than preoperatively. This corresponded with a subcutaneous transudate formation twice as high as in the contralateral limb at equal net filtration pressure.

Based on measurements of Starling forces, the calculated capillary pressure in the operated leg was at least 2.5 mm Hg higher than in the contralateral. This rendered the operated leg even more susceptible to edema formation.

In addition, reduced COP_{if} preoperatively may predispose to postoperative edema formation. Impaired arteriolar regulatory mechanisms in patients with atherosclerosis probably increase capillary pressure, resulting in a greater net filtration pressure. This in turn increases transcapillary filtration and «washout» of interstitial proteins.

Subcutaneous tissue compliance increased proportionally to increase in subcutaneous tissue volume. Interstitial fluid pressure (P_{if}) may *initially* serve as an important edema limiting factor. When edema has formed, its potential is reduced.

REFERENCES

Aukland, K. & Fadnes, H. O.: Protein concentration of interstitial fluid collected from rat skin by a wick method. Acta Physiol Scand 1973, *88:* 350-358.

Aukland, K. & Johnsen, H. M.: A colloid osmometer for small fluid sample. Acta Physiol Scand 1974, *90:* 485-490.

Aukland, K. & Nicolaysen, G.: Interstitial volume: Local regulatory mechanisms. Physiol Rev 1981, *61:* 556-643.

Boykin, J. V., Eriksson, E., Sholley, M. M. & Pittman, R. N.: Histamine-mediated delayed permeability response after scald burn inhibited by cimetidine or cold-water treatment. Science 1980, *209:* 815-817.

Connolly, J. E. & Stemmer, E. A.: The nonreversed saphenous vein bypass for femoral-popliteal occlusive disease. Surgery 1970, *68:* 602-609.

Cooley, D. A. & Wukasch, D. C.: Techniques in vascular

surgery. Philadelphia: W. B. Saunders Company, 1979.

Creese, R. D., D'Silva, J. L. & Shaw, D. M.: Interfibre fluid from guinea-pig muscle. J Physiol 1962, *162:* 44-53.

Curry, F. E.: The effect of temperature on the hydraulic conductivity of single capillaries of frog mesentery: the role of albumin in the perfusate. Microvasc Res 1979, *17 (3):* S82.

Eickhoff, J. H. & Engell, H. C.: Local regulation of blood flow and the occurrence of edema after reconstruction of the lower limbs. Ann Surg 1982, *195:* 474-478.

Eliassen, E., Folkow, B., Hilton, S. M., Öberg, B. & Rippe, B.: Pressure-volume characteristics of the interstitial fluid space in the skeletal muscle of the cat. Acta Physiol Scand 1974, *90:* 583-593.

Ernst, C. B., Fry, W. J., Kraft, R. O. & De Weese, M. S.: The role of low molecular weight dextran in the management of venous thrombosis. Surg Gynecol Obstet 1964, *119:* 1243-1247.

Fadnes, H. O.: Effect of increased venous pressure on the hydrostatic and colloid osmotic pressure in subcutaneous interstitial fluid in rats: edema-preventing mechanisms. Scand J Clin Lab Invest 1976, *36:* 371-377.

Fadnes, H. O. & Aukland, K.: Protein concentration and colloid osmotic pressure of interstitial fluid collected by the wick method. Analysis and evaluation of the method. Microvasc Res 1977, *14:* 11-25.

Fadnes, H. O., Reed, R. K. & Aukland, K.: Interstitial fluid pressure in rats measured with a modified wick technique. Microvasc Res 1977, *14:* 27-36.

Garetto, L. P. & Hargens, A. R.: Interstitial fluid composition as sampled by wick catheters in skeletal muscle. Physiologist 1976, *19:* 203.

Gaskell, P. & Burton, A. C.: Local postural vasomotor reflexes arising from the limb veins. Circ Res 1953, 1: 27-39.

Gawlowski, D. M., Ritter, A. B. & Duran, W. N.: Reproducibility of microvascular permeability response to successive topical applications of bradykinin in the hamster cheek pouch. Microvasc Res 1982, *24:* 354-363.

Graf, K.: Auswertung und Messfehler okklusionsplethysmografischer Durchblutungsregistrierungen. Acta Physiol Scand 1964, *60:* 120-135.

Guyton, A. C.: A concept of negative interstitial pressure based on pressures in implanted perforated capsules. Circ Res 1963, *12:* 399-414.

Guyton, A. C.: Interstitial fluid pressure: II. Pressure-volume curves of interstitial space. Circ Res 1965, *16:* 452-460.

Haljamäe, H. & Fredén, H.: Comparative analysis of the protein content of local subcutaneous tissue fluid and plasma. Microvasc Res 1970, *2:* 163-171.

Hamer, J. D.: Investigation of oedema of the lower limb following successful femoropopliteal by-pass surgery: The role of phlebography in demonstrating venous thrombosis. Brit J Surg 1972, *59:* 979-982.

Hargens, A. R., Cologne, J. B., Menninger, F. J., Hogan, J. S., Tucker, B. J. & Peters, R. M.: Normal transcapillary pressures in human skeletal muscle and subcutaneous tissue. Microvasc Res 1981, *22:* 177-189.

Henriksen, O.: Local sympathetic reflex mechanism in regulation of blood flow in human subcutaneous adipose tissue. Thesis. Acta Physiol Scand 1977, *Suppl. 450:* 1-48.

Henriksen, O. & Wisborg, K.: The effect of induced arterial hypertension upon regional blood flow in patients with arterial insufficiency of the legs. Scand J Clin Lab Invest 1975, *35:* 115-120.

Hillestad, L. K.: The peripheral blood flow in intermittent claudication. V. Plethysmographic studies. The significance of the calf blood flow at rest and in response to timed arrest of the circulation. Acta Eed Scand 1963, *174:* 23-41.

Husni, E. A.: The edema of arterial reconstruction. Circulation 1967, *35 (Suppl. 1):* 169-173.

Husni, E. A. & Manion, W. C.: Atrophy of the arterial wall incident to localized chronic hypotension. Surgery 1967, *61:* 611-618.

Johnsen, A. M.: Measurements of colloid osmotic pressures of interstitial fluid. Acta Physiol Scand 1974, *91:* 142-144.

Kakkar, V. V., Field, E. S., Nicolaides, A. N., Flute, P. T., Wessler, S. & Yin, E. T.: Low dose of heparin on prevention of deep-vein thrombosis. Lancet 1971, *1:* 669-671.

Kitchin, A. H.: Peripheral blood flow and capillary filtration rates. Br Med Bull 1963, *19:* 155-160.

Koontz, T. J. & Stansel, H. C.: Factors influencing patency of the autogenous vein femoropopliteal bypass graft: An analysis of 74 cases. Surgery 1972, *71:* 753-759.

Kroese, A.: Hyperaemia of the calf after arterial reconstruction for lower limb atherosclerosis. Acta Chir Scand 1975, *141:* 104-108.

Linton, R. R. & Darling, R. C.: Autogenous saphenous vein bypass graft in femoropopliteal obliterative arterial disease. Surgery 1962, *51:* 62-73.

Myhre, H. O. & Dedichen, H.: Haemodynamic factors in the oedema of arterial reconstructions. Scand J Thorac Cardiovasc Surg 1972, *6:* 323-326.

Myhre, H. O., Støren, E. J. & Ongre, A.: The incidence of deep venous thrombosis in patients with leg oedema after arterial reconstruction. Scand J Thorac Cardiovasc Surg 1974, *8:* 73-76.

Noddeland, H.: Influence of body posture on transcapillary pressures in human subcutaneous tissue. Scand J Clin Lab Invest 1982a, *42:* 131-138.

Noddeland, H.: Colloid osmotic pressure of human subcutaneous interstitial fluid sampled by nylon wicks: evaluation of the method. Scand J Clin Lab Invest 1982b, *42:* 123-130.

Noddeland, H., Hargens, A. R., Reed, R. K. & Aukland, K.: Interstitial colloid osmotic and hydrostatic pressures in subcutaneous tissue of human thorax. Microvasc Res 1982, *24:* 104-113.

Olszewski, W.: Patophysiological and clinical observations of obstructive lymph edema of the limbs. In «Lymph edema» (L. Clodius ed.). Stuttgart: Thieme, 1977.

Olszewski, W. & Engeset, A.: Intrinsic contractility of prenodal lymph vessels and lymph flow in human leg. Am J Physiol 1980, *239:* H775-H783.

Pappenheimer, J. R. & Soto-Rivera, A.: Effective osmotic pressure of the plasma proteins and other quantities associated with the capillary circulation in the hindlimbs of cats and dogs. Am J Physiol 1948, *152:* 471-491.

Porter, J. M., Lindell, T. D. & Larkin, P. C.: Leg edema following femoropopliteal autogenous vein bypass. Arch Surg 1972, *105:* 883-888.

Renkin, E. M., Watson, P. D., Sloop, C. H., Joyner, W. M. & Curry, F. E.: Transport pathways for fluid and large molecules in microvascular endothelium of the dog's paw. Microvasc Res 1977, *14:* 205-214.

Scholander, P. F., Hargens, A. R. & Miller, S. L.: Negative pressure in the interstitial fluid of animals. Science 1968, *161:* 321-328.

Seem, E. and Stranden, E.: Transcapillary forces in patients with deep venous thrombosis. Scand J Clin Lab Invest 1983, *43 (Suppl.):* 39.

Simeone, F. A. & Husni, E. A.: The hyperemia of reconstructive arterial surgery. Ann Surg 1959, *150:* 575-585.

Stranden, E., Kroese, A. J. & Myhre, H. O.: Mercury strain gauge plethysmography during local exposure to subatmospheric pressure. Studies of the venous circulation of the lower limb. J Oslo City Hosp 1979, *29:* 127-134.

Støren, E. J., Myhre, H. O. & Stiris, G.: Lymphangiographic findings in patients with leg oedema after arterial reconstructions. Acta Chir Scand 1974, *140:* 385-387.

Sumner, D. S. & Folse, R.: Persistent hyperemia following prolonged arterial occlusion. Ann Surg 1968, *168:* 837-843.

Taylor, G. W.: Arterial grafting for gangrene. Ann R Coll Surg Engl 1962, *31:* 168-186.

Taylor, A. E., Granger, D. N. & Brace, R. A.: Analysis of lymphatic protein flux data. I. Estimation of the reflection coefficient and permeability surface area product for total protein. Microvasc Res 1977, *13:* 297-313.

Thulesius, O. & Sivertsson, R.: Ischämishes und postischämisches Ödem. Aktuel Probl Angiol 1973, *22:* 14-20.

Tybjaerg Hansen, A.: A self-recording electronic osmometer for quick, direct measurement of colloid osmotic pressure in small samples. Acta Physiol Scand 1961, *53:* 197-213.

Vaughan, B. F., Slavotinek, A. H. & Jepson, R. P.: Edema of the lower limb after vascular operations. Surg Gynecol Obstet 1970, *131:* 282-290.

Wiederhielm, C. A.: Dynamics of capillary fluid exchange: A non linear computer simulation. Microvasc Res 1979, *18:* 48-82.

Wiig, H. & Reed, R. K.: Compliance of the interstitial space in rats. II. Studies on skin. Acta Physiol Scand 1981, *113:* 307-315.

Wiig, H. Reed, R. K. & Aukland, K.: Micropuncture measurement of interstitial fluid pressure in rat subcutis and skeletal muscle: Comparison to wick-in-needle technique. Microvasc Res 1981, *21:* 308-319.

Worm, A. - M. & Nielsen, S. L.: Increased microvascular water filtration and blood flow in extensive skin disease. J Invest Dermatol 1981, *76:* 110-112.